OLARTEMOURE
OLARTE MOURE & ASOCIADOS LTDA.

C

Carlos R. Olarte
Juan G. Moure

Alexander Agudelo
Carlos A. Parra
Juan Felipe Acosta
Andrés Rincón
Mónica Guevara
Andrés Alvarado
Ella Ponce
Líliana Galindo
María Clara Calderón
Mauricio Ávila
iro Dangond
Gina Cáceres
bella Herrera
Zaava Ravid
Felipe Porras
talina Amaya
i M. Escobar

Medellín
María Clara Múnera
Eddie Manotas
Adrián Santamaría

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES
E. S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-236624- -00001-0000
Fecha: 2013-10-07 16:40:07 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 3

Re: Expediente Nº. 13-236.624
Solicitud de patente de invención titulada: "INHIBIDORES DE QUINASA RELACIONADOS CON PIRROLO [2,3-d] PIRIMIDINA TROPOMIOSINA"
Solicitante: PFIZER LIMITED.
Nuestra Ref.: P2013/000172

MEMORIAL DE ALCANCE

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, me permito dar alcance a la solicitud de patente en referencia radicada el 4 de octubre de 2013, para aportar el recibo original No. 13-0094655 de pago por valor de $505.000 correspondientes a la tasa de nuevas solicitudes, y un CD con los documentos de la patente en formato pdf, ya que por un error involuntario se adjuntó la fotocopia y no el original del mismo.

Atentamente,

CARLOS R. OLARTE
CC. No.79.782.747 de Bogotá
T.P. 74.295

Adjunto: Lo enunciado.

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0094655

Bogotá D.C., Septiembre 20 de 2013 - 08:23:13

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	522585593	19/09/2013	7.600.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD DE INVENSION	505.000.00	505.000.00
				$505.000.00

SON: **QUINIENTOS CINCO MIL PESOS MONEDA CORRIENTE***

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

Industria y Comercio SUPERINTENDENCIA	PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA ***RELACIÓN DE ANEXOS***	
Dependencia: 2020	Fecha: 13 / 10 / 07 / AAAA MM DD	Recorrido: 3
Tipo de Radicación: Entrada: ☒ Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	*No. Radicación*	*Consecutivo*	*Item*
1	13-236624-	1	7
2			
3			
4			
5			
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7			
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10			
11			
12			
13			
14			
15			
16			
17			

Item	*Unidad de Conservación*
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	**Otro**
Item	***Soporte Documental***
X	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	**Otro**

Observaciones:

EL C.D ANEXO CONTIENE UN TOTAL DE 6 ARCHIVOS: 6 EN FORMATO P.D.F, LOS CUALES FUERON PROCESADOS.

UBICADO EN EL FOLIO 3.

CR.

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA.

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación.

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2013/000172**

SOLICITUD DE:

1

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

[X] Capítulo I. [ ] Capítulo II.

2

SOLICITANTE (71)

Nombre: PFIZER LIMITED
Dirección: Ramsgate Road, Sandwich Kent CT 13 9NJ (GB)
Nacionalidad o Domicilio: Gran Bretaña.
Lugar de Constitución Gran Bretaña.
Teléfono: **Fax:**
E-mail:

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Carrera 5 No. 34-03 Bogotá, Colombia
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número 79.782.747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA.
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

5

PCT (86)

Solicitud Internacional No. PCT/IB2012/051363 Fecha Marzo 22, 2012

Publicación Internacional No. WO 2012/137089 A1 Fecha Octubre 11,2012

6

Título (54) INHIBIDORES DE QUINASA RELACIONADOS CON PIRROLO[2,3-d]PIRIMIDINA TROPOMIOSINA

Clasificación Internacional (51) C07D 487/04, A61K 31/519, A61P 35/00 A61P 25/00

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Abril 5, 2011	61/471,758

9

Comprobante de pago No. 13- **Fecha** Octubre 2013

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica. Poderes, si fuere el caso.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones. Declaración bajo la Regla 417(ii) del PCT.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

11 **FIGURA CARACTERÍSTICA:**

12 Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA: _____

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/IB2012/051363

Mark David ANDREWS
Ramsgate Road,
Sandwich Ken CT13 9NJ
Gran Bretaña
Nacionalidad: Británico

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Ramsgate Road,
Sandwich Ken CT13 9NJ
Gran Bretaña
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Gran Bretaña
Nacionalidad: Japonés

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Nacionalidad: Belga

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Ramsgate Road,
Sandwich Ken CT13 9NJ
Gran Bretaña
Nacionalidad: Británica

Paul Anthony STUPPLE
Ramsgate Road,
Sandwich Ken CT13 9NJ
Gran Bretaña
Nacionalidad: Británico

WK 6299208

19 OCT. 2007

ESCRITURA PUBLICA NUMERO= = = = =
MIL DOSCIENTOS SESENTA Y CUATRO (1264) = = =
En la ciudad de Bogotá, Distrito Capital, República de Colombia, a los Diecinueve = = = = = (19) días del mes de Octubre = = = = del año dos mil siete (2007), ante mi, MARIA EUGENIA ROJAS DE URUETA = = = = = = = = = = NOTARIA(O) VEINTISIETE (27) DEL CIRCULO DE BOGOTA,= = = se otorgó la escritura pública que se consigna en los siguientes términos: ----------

---

CLASE(S) DE ACTO: PROTOCOLIZACION: ----------
OLARTE RAISBECK FRIERI MOURE & CASTRO LTDA "OLARTERAISBECK" - ----------
NIT 830122870-6.- ----------

Compareció **CARLOS REINALDO OLARTE GARCIA** mayor de edad, vecino de ésta ciudad, identificado con la cédula de ciudadanía número 79.782.747, obrando en nombre y representación de **OLARTE RAISBECK FRIERI MOURE & CASTRO LTDA "OLARTERAISBECK"** con número de identificación tributaria 830122870-6, sociedad legalmente constituida mediante escritura mil ciento diecinueve (1119) de la notaria treinta y nueve (39) de Bogotá de fecha diez (10) de junio de dos mil tres (2003) como lo acredita con el certificado de constitución y gerencia que presenta para su protocolización y dijo: ----------

PRIMERO.- Que presenta para su protocolización y custodia en los archivos de ésta notaría, bajo el número y lugar que a ésta escritura corresponda, en trece (13) folios autenticados, el poder y sus traducciones el cual del siguiente tenor: ----------

PODER GENERAL.- ----------

NOTARIA VEINTISIETE
María Eugenia Rojas de Uruetá

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

El suscrito PFIZER LIMITED, domiciliado en Ramsgate Road, Sándwich Kent, Ct13 9NJ, England nombramos por el presente a Olarte Raisbeck & Frieri Ltda. con oficinas en el World Trade Center- Torre A, Calle 100 No. 8A-37, piso 10, Bogotá D.C. nuestros representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia, la República de Bolivia, la República del Ecuador, la República del Perú y la República Bolivariana de Venezuela, ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado a intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la Ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses.-

01

63767910

CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

1 DE OCTUBRE DE 2007 HORA 09:28:12

02NA4100106807LR10530 HOJA : 001

* *

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS.

LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL,

CERTIFICA :

NOMBRE : OLARTE RAISBECK FRIERI MOURE & CASTRO LTDA PERO PARA TODOS LOS EFECTOS PODRA OPERAR BAJO EL NOMBRE OLARTERAISBECK
N.I.T. : 830122870-6 ADMINISTRACION: BOGOTA PERSONAS JURIDICAS, REGIMEN COMUN.
DOMICILIO : BOGOTA D.C.

CERTIFICA :

MATRICULA NO. 01284164

CERTIFICA :

CONSTITUCION : QUE POR ESCRITURA PUBLICA NO. 0001119 DE NOTARIA 39 DE BOGOTA D.C. DEL 10 DE JUNIO DE 2003 , INSCRITA EL 25 DE JUNIO DE 2003 BAJO EL NUMERO 00885810 DEL LIBRO IX, SE CONSTITUYO LA SOCIEDAD COMERCIAL DENOMINADA: OR LEGAL LTDA

CERTIFICA :

QUE POR ESCRITURA PUBLICA NO. 0001328 DE NOTARIA 39 DE BOGOTA D.C. DEL 4 DE JULIO DE 2003 , INSCRITA EL 9 DE JULIO DE 2003 BAJO EL NUMERO 00887749 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE : OR LEGAL LTDA POR EL DE : OLARTE RAISBECK & FRIERI LTDA PERO PARA TODOS LOS EFECTOS PODRA OPERAR BAJO EL NOMBRE OLARTERAISBECK

QUE POR ESCRITURA PUBLICA NO. 0000579 DE NOTARIA 27 DE BOGOTA D.C. DEL 24 DE MAYO DE 2007 , INSCRITA EL 30 DE MAYO DE 2007 BAJO EL NUMERO 01134613 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE : OLARTE RAISBECK & FRIERI LTDA PERO PARA TODOS LOS EFECTOS PODRA OPERAR BAJO EL NOMBRE OLARTERAISBECK POR EL DE : OLARTE RAISBECK FRIERI MOURE & CASTRO LTDA PERO PARA TODOS LOS EFECTOS PODRA OPERAR BAJO EL NOMBRE OLARTERAISBECK

CERTIFICA :

REFORMAS:

ESCRITURA	FECHA	NOTARIA	CIUDAD	INSCRIPCION	FECHA
0001328	2003/07/04	00039	BOGOTA D.C.	00887749	2003/07/09
0000579	2007/05/24	00027	BOGOTA D.C.	01134607	2007/05/30
0000579	2007/05/24	00027	BOGOTA D.C.	01134610	2007/05/30
0000579	2007/05/24	00027	BOGOTA D.C.	01134611	2007/05/30

CERTIFICA :

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 10 DE JUNIO DE 2103 .

CERTIFICA :

OBJETO SOCIAL : LA SOCIEDAD TENDRA POR OBJETO PRINCIPAL LA PRESTACION DE SERVICIOS DE ASESORIA EN EL AREA SOCIAL, TECNICA, COMERCIAL Y JURIDICA, DE PERSONAS NATURALES O JURIDICAS, NACIONALES O EXTRANJERAS, PUBLICAS O PRIVADAS. EN DESARROLLO DE

NOTARIA VEINTISIETE
María Eugenia Reyes de Uribe

SU OBJETO SOCIAL PODRA : A. PRESTAR ASESORIA Y EJERCER LA REPRESENTACION JUDICIAL DE PERSONAS NATURALES O JURIDICAS ANTE LAS DIFERENTES JURISDICCIONES Y PARTICIPAR EN SU NOMBRE Y REPRESENTACION EN TRIBUNALES DE ARBITRAMENTO, AMIGABLE COMPOSICION, CONCILIACION Y MEDIACION. B. CONFORMAR Y PARTICIPAR EN CENTROS DE ARBITRAJE Y CONCILIACION. C. CELEBRAR Y EJECUTAR TODAS LAS OPERACIONES DE CAMBIO Y COMERCIO EXTERIOR QUE REQUIERA EL BUEN FUNCIONAMIENTO DE LA COMPAÑIA ; D. ADQUIRIR, ENAJENAR, GRAVAR, DAR O TOMAR EN ARRENDAMIENTO TODA CLASE DE BIENES, DANDO O RECIBIENDO LAS GARANTIAS DEL CASO CUANDO HAYA LUGAR A ELLAS ; E. INTERVENIR COMO DEUDORA O ACREEDORA EN TODA CLASE DE OPERACIONES DE CREDITO, DANDO O RECIBIENDO LAS GARANTIAS DEL CASO CUANDO HAYA LUGAR A ELLAS ; F. CELEBRAR CON ESTABLECIMIENTOS DE CREDITO NACIONALES O EXTRANJEROS Y CON COMPAÑIAS ASEGURADORAS TODAS LAS OPERACIONES QUE SE RELACIONEN CON LOS NEGOCIOS Y BIENES SOCIALES. G. ABRIR, OPERAR Y CERRAR CUALQUIER TIPO DE CUENTAS BANCARIAS ; H. GIRAR, ACEPTAR, ENDOSAR, ASEGURAR, COBRAR, RECHAZAR, PROTESTAR, AVALAR GARANTIZAR Y NEGOCIAR EN GENERAL TODA CLASE DE INSTRUMENTOS NEGOCIABLES Y CUALQUIER OTRA CLASE DE TITULOS DE CREDITO ; I. ORGANIZAR, PROMOVER, FORMAR Y FINANCIAR SOCIEDADES O EMPRESAS NACIONALES O EXTRANJERAS QUE TIENDAN A FACILITAR, ENSANCHAR, O COMPLEMENTAR LOS NEGOCIOS SOCIALES DENTRO Y FUERA DEL PAIS Y SUSCRIBIR ACCIONES O CUOTAS EN ELLAS, Y EJERCER TODOS LOS DERECHOS Y OBLIGACIONES ECONOMICOS Y CORPORATIVOS QUE SURJAN DE DICHA PARTICIPACION. J. CREAR CONSORCIOS Y UNIONES TEMPORALES. K. SERVIR DE COMISIONISTA O INTERMEDIARIO COMERCIAL A TITULO DE CORRETAJE O A CUALQUIER OTRO TITULO ; I. SER CORRESPONSAL Y TENER CORRESPONSALES INTERNACIONALES ; M. EFECTUAR AVALUOS COMERCIALES DE TODA CLASE DE BIENES. N. ADQUIRIR Y CONSTRUIR TODA CLASE DE INSTALACIONES INDUSTRIALES O COMERCIALES COMO FABRICAS, TALLERES, ALMACENES DE DISTRIBUCION O VENTA ESTABLECIMIENTOS DE COMERCIO, ETC. O. DISTRIBUIR O VENDER TODO TIPO DE PRODUCTOS Y ABRIR Y ADMINISTRAR, DIRECTA O INDIRECTAMENTE, LOS ESTABLECIMIENTOS DE COMERCIO QUE SEAN NECESARIOS PARA ELLO. P. ENAJENAR, ARRENDAR, GRAVAR Y ADMINISTRAR EN GENERAL LOS BIENES QUE COMPONEN EL PATRIMONIO SOCIAL. Q. APORTAR SUS BIENES, EN TODO O EN PARTE, A OTRA U OTRAS SOCIEDADES A QUE LE CONVENGA VINCULARSE PARA UN MEJOR DESARROLLO DE SUS NEGOCIOS. R. TRANSIGIR, DESISTIR O SOMETER A DECISIONES ARBITRALES LAS CUESTIONES EN QUE TENGA INTERES FRENTE A TERCEROS. ; S. SOLICITAR, CONSEGUIR LOS REGISTROS RESPECTIVOS ANTE LA AUTORIDAD COMPETENTE Y EXPLOTAR EL DERECHO SOBRE MARCAS, NOMBRES COMERCIALES O CUALQUIER SIGNO DISTINTIVO, DIBUJOS, INSIGNIAS, PATENTES Y CUALQUIER OTRO DERECHO DE PROPIEDAD INDUSTRIAL O INTELECTUAL YA SEA A NOMBRE DE LA SOCIEDAD O DE UN TERCERO. T. HACER PUBLICACIONES Y COMUNICACIONES RELACIONADAS CON EL OBJETO SOCIAL. U. CELEBRAR Y EJECUTAR CON SU PROPIO NOMBRE Y POR CUENTA DE TERCEROS O EN PARTICIPACION CON ELLOS, ACTOS O CONTRATOS Y OPERACIONES EN GENERAL, TODO ACTO O CONTRATO QUE SEA NECESARIO O CONVENIENTE PARA CUMPLIR O FACILITAR LOS ACTOS Y OPERACIONES PREVISTAS EN LOS ESTATUTOS Y QUE DE MANERA DIRECTA SE RELACIONEN CON EL OBJETO SOCIAL, TAL COMO QUEDA DETERMINADO.

CERTIFICA :

CAPITAL Y SOCIOS : $ 120,000,000.00 DIVIDIDO EN 12,000.00 CUOTAS CON VALOR NOMINAL DE $ 10,000.00 CADA UNA, DISTRIBUIDO ASI :

- SOCIOS CAPITALISTA(S)

FRIERI DEL CASTILLO ANA MARIA C.C. 00045483209

NO. CUOTAS: 2,400.00 VALOR:$24,000,000.00
CASTRO VELEZ NATALIA C.C. 00052008577
NO. CUOTAS: 2,400.00 VALOR:$24,000,000.00
RAISBECK LLINAS JAMES IAN C.C. 00079376996
NO. CUOTAS: 2,400.00 VALOR:$24,000,000.00
OLARTE GARCIA CARLOS REINALDO C.C. 00079782747
NO. CUOTAS: 2,400.00 VALOR:$24,000,000.00
MOURE PEREZ JUAN GUILLERMO C.C. 00080412281
NO. CUOTAS: 2,400.00 VALOR:$24,000,000.00
TOTALES
NO. CUOTAS: 12,000.00 VALOR :$120,000,000.00

CERTIFICA :

REPRESENTACION LEGAL : LA SOCIEDAD TENDRA UN GERENTE GENERAL, EL CUAL TENDRA UN PRIMER SUPLENTE Y UN SEGUNDO SUPLENTE QUE LO REEMPLAZARA EN SUS FALTAS ABSOLUTAS, TEMPORALES O ACCIDENTALES, Y CUYA DESIGNACION Y REMOCION CORRESPONDERA TAMBIEN A LA JUNTA DE SOCIOS.

CERTIFICA :

** NOMBRAMIENTOS : **

QUE POR ESCRITURA PUBLICA NO. 0001119 DE NOTARIA 39 DE BOGOTA D.C. DEL 10 DE JUNIO DE 2003 , INSCRITA EL 25 DE JUNIO DE 2003 BAJO EL NUMERO 00885810 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE	IDENTIFICACION
GERENTE	
OLARTE GARCIA CARLOS REINALDO	C.C.00079782747
PRIMER SUPLENTE DEL GERENTE	
RAISBECK LLINAS JAMES IAN	C.C.00079376996
SEGUNDO SUPLENTE DEL GERENTE	
FRIERI DEL CASTILLO ANA MARIA	C.C.00045483209

CERTIFICA :

FACULTADES DEL REPRESENTANTE LEGAL : EL GERENTE GENERAL ES EL REPRESENTANTE LEGAL DE LA SOCIEDAD, Y EN CASO DE FALTA TEMPORAL O ABSOLUTA HARA SUS VECES EL PRIMER SUPLENTE O EN SU DEFECTO EL SEGUNDO SUPLENTE, TAMBIEN ELEGIDOS POR LA JUNTA DE SOCIOS. EL GERENTE REPRESENTARA Y COMPROMETERA A LA SOCIEDAD FRENTE A TERCEROS, SEAN PERSONAS O ENTIDADES PARTICULARES, OFICIALES O JUDICIALES. ASI MISMO, PODRA CELEBRAR EN SU NOMBRE CONTRATO DE ARRENDAMIENTO COMO ARRENDADOR O ARRENDATARIO. CONSTITUIR APODERADOS DE LA SOCIEDAD, DESISTIR, INTERPONER TODA CLASE DE RECURSOS RECIBIR DINERO EN MUTUO, HACER DEPOSITOS BANCARIOS O DE CUALQUIER OTRA INDOLE, FIRMAR TITULOS VALORES Y NEGOCIARLOS, TENERLOS, CONTRATARLOS, PAGARLOS, ENDOSARLOS, DESCARGARLOS, CELEBRAR CONTRATOS COMERCIALES, EJECUTAR LOS ACUERDOS DE LA JUNTA DE SOCIOS Y CONVOCARLA A REUNIONES ORDINARIAS O EXTRAORDINARIAS, SUSCRIBIR CONTRATOS LABORALES A NOMBRE DE LA SOCIEDAD, Y EN GENERAL TODAS LAS GESTIONES QUE OBEDEZCAN A LA NATURALEZA DE SU

NOTARIA VEINTISIETE
María Eugenia Pardo de Urueta

ENCARGO Y QUE SE RELACIONEN DIRECTAMENTE CON EL GIRO ORDINARIO DE LOS NEGOCIOS SOCIALES. EL GERENTE REQUERIRA APROBACION DE LA JUNTA DE SOCIOS PARA CELEBRAR ACTOS CUYA CUANTIA SEA O EXCEDA LA SUMA DE DIEZ MILLONES DE PESOS ($10,000,000) MONEDA CORRIENTE.

CERTIFICA :

** REVISOR FISCAL: **

QUE POR ACTA NO. 0000006 DE JUNTA DE SOCIOS DEL 5 DE MARZO DE 2004 , INSCRITA EL 8 DE JULIO DE 2004 BAJO EL NUMERO 00942232 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL	
LACHE NUÑEZ JOSE LUCIO	C.C.00006763005

CERTIFICA :

DIRECCION DE NOTIFICACION JUDICIAL : CLL 100 NO 8A-37 P 10 W.T.C. T A
MUNICIPIO : BOGOTA D.C.
DIRECCION COMERCIAL : CLL 100 NO 8A-37 P 10 W.T.C. T A
MUNICIPIO : BOGOTA D.C.
E-MAIL : elizabeth.barbosa@olarteraisbeck.com

CERTIFICA :

QUE LA SOCIEDAD TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS :
NOMBRE : OR LEGAL LIMITADA
MATRICULA NO. 01284255
RENOVACION DE LA MATRICULA : EL 30 DE MARZO DE 2007
ULTIMO AÑO RENOVADO : 2007

CERTIFICA :

DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

* * * EL PRESENTE CERTIFICADO NO CONSTITUYE PERMISO DE * * *
* * * FUNCIONAMIENTO EN NINGUN CASO * * *

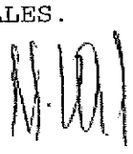
INFORMACION COMPLEMENTARIA

LOS SIGUIENTES DATOS SOBRE RIT Y PLANEACION DISTRITAL SON INFORMATIVOS
CONTRIBUYENTE INSCRITO EN EL REGISTRO RIT DE LA DIRECCION DISTRITAL DE IMPUESTOS, FECHA DE INSCRIPCION 2003/06/24
FECHA DE ENVIO DE INFORMACION A PLANEACION DISTRITAL: 10 DE JULIO DE 2004

EL SECRETARIO DE LA CAMARA DE COMERCIO,

VALOR : $ 3,000.00

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.



OLARTERAISBECK
OLARTE RAISBECK FRIERI MOURE & CASTRO LTDA.

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

On this date, 20th September 2007

The undersigned Notary Public certifies:

1. That Keith Stephen Ruddock, Senior Patent Attorney of legal age and domiciled in Ramsgate Road, Sandwich, Kent, CT13 9NJ, England. signed the foregoing document.

2. That the grantor has executed the foregoing document as of. PFIZER LIMITED

3. That PFIZER LIMITED having its principal place of business located in 2 Sandwich, Kent, England. is duly incorporated, is currently in existence, and that the purposes for which the General Power is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the General Power 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):
Power of Attorney issued on 16th August 2006. AND MINUTE EXTRACT OF A BOARD OF DIRECTORS MEETING DATED 20 SEPTEMBER 2007.

Certificación Notarial

En esta fecha, 20 DE SEPTIEMBRE DE 2007.

el Notario Público suscrito certifica:

1. Que KEITH STEPHEN RUDDOCK

mayor de edad y domiciliado EN RAMSGATE ROAD, SANDWICH, KENT, CT13 9NJ suscribió el documento que antecede.

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

4. Que PFIZER LIMITED con sede principal ubicada en SANDWICH, KENT, INGLATERRA 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 exhibición de los (del) siguiente(s) documento(s) auténtico(s):
ESCRITURA DE PODER CON FECHA 16 DE AGOSTO 2006 Y EXTRACTO DE UN ACTA DE JUNTA DE DIRECTORES CON FECHA 20 DE SEPTIEMBRE 2007

NOTARIA VEINTISIETE
María Eugenia Rojas de Orueta

NOTARY PUBLIC (Signature):

Andrew Martin Johnson B.A.
NOTARY PUBLIC
20 St George's Place
Canterbury
CT1 1UT, England
Tel: 01227 479479

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by / a été signé par **Andrew Martin Johnson**

3. Acting in the capacity of / agissant en qualité de **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de **The Said Notary Public**

5. at London/à Londres

   Certified/Attesté
6. the/le **23 September 2007**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs / par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **H531294**

9. Stamp: / timbre:

10. Signature: **R Shilton**

FOREIGN AND COMMONWEALTH OFFICE LONDON

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

OLARTERAISBECK

OLARTE RAISBECK FRIERI MOURE & CASTRO LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahín
Simón Salinas
Alexander Agudelo
Lina Mosquera
Catalina Barbastefano
Ángela Correa
Erika Rico
Carlos A. Parra
Carolina Romero

Of Counsel
Guillermo Chahín
Graciela Melo
Jacqueline Chaparro
Cruz E. de Moncaleano

General Power

The undersigned, PFIZER LIMITED

domiciled in Ramsgate Road, Sandwich Kent, CT13 9NJ, England

hereby appoint Olarte Raisbeck & Frieri Ltda. with offices in the World Trade Center – Torre A, Calle 100 No. 8A-37, Piso 10, Bogota D.C., legal representatives with faculties to receive notifications and to appoint judicial or extrajudicial agents in patent matters, who at the same time have the faculty to represent us before the administrative, judicial or police authorities of any hierarchy of the Republic of Colombia, the Republic of Bolivia, the Republic of Ecuador, the Republic of Peru, and the Bolivarian Republic of Venezuela, to initiate before said authorities all the necessary actions to accomplish said purposes and to intervene in all instances, grades and procedural levels; to file and prosecute applications, declarations, complaints, to claim, counterclaim, answer claims and counterclaims; to draw up specifications; to make amendments; oppositions and all types of objections and writings of any nature; cancellations and administrative injunction proceedings; to pay all installments and effect all other payments prescribed by law; to receive documents and monies; act as complainants as well as defendants, before the competent judges, with full powers to request preliminary injunctions of any nature, settle, make arrangements, to submit to arbitrators, to desist from claims or procedures, to accept claims, to collect, to ratify legal proceedings subscribed before the appointment and/or presentation of this Power, substitute or delegate the legal representation and other acts prescribed by law, in short, with all such further powers as may be required; to comply with all other requirements and, to take all those measures which they may deem fit for the protection of our interests.

Poder General

El suscrito,

domiciliado en

nombramos por el presente a Olarte Raisbeck & Frieri Ltda. con oficinas en el World Trade Center – Torre A, Calle 100 No. 8A-37, Piso 10, Bogotá D.C., nuestros representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia, la República de Bolivia, la República del Ecuador, la República del Perú y la República Bolivariana de Venezuela, ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses.

NOTARIA VEINTISIETE
María Eugenia [illegible] de Urueta

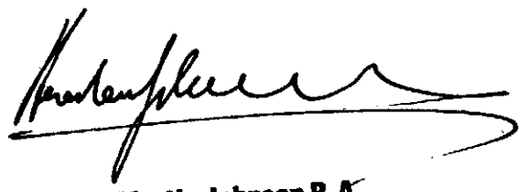
PFIZER LIMITED

Signature/Firma:

Keith Stephen Ruddock, Senior Patent Attorney

Date/Fecha: 20th September 2007

City,Country/Ciudad,País: Sandwich, Kent, England.



Andrew Martin Johnson B.A.
NOTARY PUBLIC
29 St George's Place
Canterbury
CT1 1UT, England
Tel: 01227 479479

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by **Andrew Martin Johnson**
   a été signé par

3. Acting in the capacity of **Notary Public**
   agissant en qualité de

4. Bears the seal/stamp of **The Said Notary Public**
   est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres

6. the/le **23 September 2007**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **H531296**

9. Stamp:
   timbre:

10. Signature: **R Shilton**

FOREIGN AND COMMONWEALTH OFFICE LONDON

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

Martin Johnson B.A.
NOTARY PUBLIC
George's Place
Canterbury
CT1 1UT, England
Tel: 01227 479479

POWER OF ATTORNEY

This Power of Attorney is made by way of deed this 16th day of August 2006 by Pfizer Limited, a company with limited liability, incorporated in accordance with the laws of England with registered number 526209, whose registered office is at Ramsgate Road, Sandwich, Kent, England ("the Company").

The Company hereby appoints Peter Richardson, Stéphane Drouin, Keith Stephen Ruddock, Graham Lane, Henrike Dekker and Jason Edward Rutt (being Patent Attorneys) to be true and lawful attorneys (jointly and severally) for it and in its name to do, and if necessary to join with another or others in doing, all or any of the following acts and things:-

> To approve, execute, and deliver in the name of and on behalf of the Company documents (in whatever form) relating to the applying for, obtaining, maintaining, abandoning, assigning, protecting and enforcing (by infringement or opposition proceedings or otherwise) of patents, trade-marks, design rights, and/or other intellectual property rights in any country or jurisdiction as fully and effectively as the Company could do if acting on its own behalf and to do all other acts and things as may be necessary or desirable in this regard. This includes (without affecting the generality of the foregoing) paying fees, signing registers, filing documents, receiving official documents, making declarations and appointing agents in the place of any such attorney (with or without the power to make substitutions), approving, executing and delivering such documents and doing such things, and approving, executing, and delivering assignments and any other documents or instruments that may be required in connection with such patents, trade-marks, design rights, and/or other intellectual property rights.

The Company hereby declares that all things done under and by virtue of this Power of Attorney shall be as valid and effectual as if sealed by the common seal of the Company.

This Power of Attorney (a) cancels and replaces the previous Power of Attorney dated 4 August 2006 given in respect of the above, (b) may be terminated at any time by a written instrument signed by a director of the Company or the Company secretary but shall at all times be conclusively binding on the Company in favour of third parties who have no notice of its termination, and (c) is governed by and construed in accordance with English law.

Should any of the above named Patent Attorneys cease to be employed by the Company, Pfizer Inc, or any other Affiliate of the Company then his or her authority under this Power of Attorney will cease with immediate effect. For the purposes of this Power of Attorney, "Affiliate" shall mean any entity which directly or indirectly Controls, is Controlled by or is under common Control with the Company and "Control" shall mean the ownership of more than 50% of the issued share capital, or the legal power to direct or cause the direction of the party in question and Controlled shall be construed accordingly.

This Power of Attorney is executed and delivered as a deed for and on behalf of Pfizer Limited on the date stated above.

The common seal of)
Pfizer Limited was)
affixed to this deed)
in the presence of)

Director M. FAVERBACH

~~Director~~/Secretary M. SUMNER

H:\data\My Documents\Word\legal1\patent2.doc

POR LA PRESENTE CERTIFICO QUE ESTA ES UNA FOTOCOPIA DE SU ORIGINAL QUE SE ME HA EXHIBIDO EL DÍA DE HOY.
SANDWICH A 20 DE SEPTIEMBRE 2007.

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by / a été signé par **Andrew Martin Johnson**

3. Acting in the capacity of / agissant en qualité de **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de **The Said Notary Public**

5. at London/à Londres — Certified/Attesté
6. the/le **23 September 2007**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs / par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **H531295**

9. Stamp: / timbre:

10. Signature: **R Shilton**

FOREIGN AND COMMONWEALTH OFFICE LONDON

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

Andrew Martin Johnson B.A.
NOTARY PUBLIC
29 St. George's Place
Canterbury
CT1 1UT, England
Tel: 01227 479479

[redacted]

Sandwich Laboratories
Pfizer Limited
Sandwich, Kent CT13 9NJ, UK
Telephone: +44 (0)1304 616161 Facsimile: +44 (0)1304 656221

Global Research & Development

Pfizer Limited Board Minute Extract

The following is an extract from the minutes of a Pfizer Limited board meeting held on 16 August 2006:

"The following document was submitted in triplicate and approved, and it was resolved that the common seal of the Company be affixed thereto:

> A power of attorney appointing Peter Richardson, Stéphane Drouin, Keith Stephen Ruddock, Graham Lane, Henrike Dekker and Jason Edward Rutt as true and lawful attorneys (acting jointly and severally and, if necessary, joining with another or others) to approve, execute, and deliver in the name of and on behalf of the Company documents (in whatever form) relating to the applying for, obtaining, maintaining, abandoning, assigning, protecting and enforcing (by infringement or opposition proceedings or otherwise) of patents, trade-marks, design rights, and/or other intellectual property rights in any country or jurisdiction as fully and effectively as the Company could do if acting on its own behalf and to do all other acts and things as may be necessary or desirable in this regard.

The seal was duly affixed and attested."

For and on behalf of Pfizer Limited:

M.J. Sumner
Company Secretary

Date: 20 September 2007

NOTARIA MERCANTIL SIETE
María Eugenia Rojas de Urbeta

POR LA PRESENTE CERTIFICO QUE ESTA ES UNA FOTOCOPIA DE SU ORIGINAL QUE SE ME HA EXHIBIDO EL DÍA DE HOY. SANDWICH, A 20 DE SEPTIEMBRE DE 2007.

Andrew Martin Johnson B.A.
NOTARY PUBLIC
9 St. George's Place
Canterbury
CT1 1UT, England
Tel: 01227 479479

Traducción oficial de un documento cuyo original está en ingles

Sello:

(Firmado) Andrew Martin Johnson – Notario Público

29 St. George's Place

Canterbury

CT1 1UT, England

Tel: 01227 479479.

Apostilla:

APOSTILLE

(Convention du La Haye du 5 octobre 1961)

Reino Unido de Gran Bretaña y Irlanda del Norte

1. País:	Reino Unido de Gran Bretaña y Irlanda del Norte
	El presente documento público
2. Ha sido firmado por:	Andrew Martin Johnson
3. Actuando en calidad de:	Notario Público
4. Lleva el sello / estampilla de:	Dicho Notario Público
	Certificado
5. En:	Londres
6. El:	Día 23 de Septiembre de 2007
7. Por:	Secretario de Estado Principal de su Majestad para las Relaciones Exteriores y la Commonwealth.
8. Bajo el No.	H531294
9. Sello / estampilla:	Oficina del Exterior y de la Commonwealth – Londres
10. Firma:	(Firmado) R. Shilton
	Por el Secretario de Estado

Si este documento va a ser usado en un país que no haga parte de la convención de La Haya del 5 de Octubre de 1961, debe presentarse a la sección consular de la misión que representa a ese país. Una Apostilla o certificado de legalización sólo confirma que la firma, sello o estampilla que lleva el documento es genuina. No significa que el contenido del documento sea correcto o que la Oficina de Relaciones Exteriores y de la Commonwealth apruebe el contenido.

NOTARIA VEINTISIETE
María Eugenia Reyes de Urueta

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

APOSTILLE

(Convention du La Haye du 5 octobre 1961)

Reino Unido de Gran Bretaña y Irlanda del Norte

1. Pais:	Reino Unido de Gran Bretaña y Irlanda del Norte
	El presente documento público
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NOTARIA VEINTISIETE
María Eugenia Rojas de Urueta

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Pfizer L. – Res."

Fecha: 4 de Octubre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 0791

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

MINISTERIO DE
COMUNICACIONES

1991 OCT 16 A 9:16

JEFE DE LA DIVISION
BOGOTA D.C.

JEFE DE AREA
RESPONSABLE
DEL TEMA

b72144

Jorge Sierra

JEFE DE LA DIVISION
DE FUNCIONES VINCULADAS

Traducción oficial de un documento cuyo original esta en ingles

DOCUMENTO DE PODER

El documento de Poder ha sido hecho por medio de escritura este día 16 de Agosto 16 de 2006 por Pfizer Limited, una compañía de responsabilidad limitada, constituida de acuerdo con las leyes de Inglaterra bajo el No. 526209, cuya oficina registrada queda en Ramsgate Road, Sandwich, Kent, England ("la Compañía").

La Compañía nombra por medio de este documento a Peter Richardson, Stéphane Drouin, Keith Stephen Ruddock, Graham Lane, Henrike Dekker y Jason Edward Rutt (quienes son Abogados de Patentes) para que sean apoderados, auténticos y legales (conjunta y mutuamente) de dicha empresa y hagan en su nombre y si es necesario se asocien con otro u otros para realizar todo o cualquiera de las partes de los siguientes actos y cosas:

Aprobar, ejecutar y entregar en nombre de la Compañía los documentos (en cualquier forma) relacionados con la aplicación, obtención, mantenimiento, abandono, asignación, protección e implementación (por procedimientos de contravención u oposición u otros) de patentes, marcas registradas, derechos de diseños, y/u otros derechos de propiedad intelectual en cualquier país o jurisdicción tan completa y efectivamente como pudiera hacerlo la Compañía si actuara en su propio nombre, así como realizar todas las demás acciones y cosas que puedan ser necesarias o deseables a este

NOTARIA VEINTIUNO
María Eugenia Rojas de Urueta

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

respecto. Esto incluye (si afectar la generalidad de lo anterior) pagar aranceles, firmar registros, radicar documentos, recibir documentos oficiales, hacer declaraciones y nombrar representantes en el lugar de cualquiera de dichos apoderados (con o sin la facultad de hacer sustituciones), aprobar, ejecutar y entregar dichos documentos y hacer tales cosas y aprobar, ejecutar y entregar escrituras y cualquier otro documento o instrumento que se pueda requerir con respecto a dichas patentes, marcas registradas, derechos de diseño y/u otros derechos de propiedad intelectual.

La Compañía declara por medio del presente documento que todas las cosas que se realicen según y por virtud de este Documento de Poder serán tan validas y efectivas como si estuvieran selladas con el sello común de la Compañía.

Este Documento de Poder (a) cancela y reemplaza el anterior Documento de Poder fechado el 4 de Agosto de 2006 otorgado con respecto a lo anterior, (b) puede terminarse en cualquier momento por medio de un instrumento escrito firmado por un directivo de la Compañía o el secretario de la Compañía, pero en todo momento será inequívocamente obligatorio de la Compañía a favor de terceras partes que no tienen notificación de su terminación y (c) está regido y realizado de acuerdo con la ley inglesa.

Si cualquiera de los Abogados de Patentes anteriormente nombrados deja de estar empleado por la Compañía, Pfizer Inc., o cualquier otra

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Ministerial

afiliada de la Compañía, entonces su autoridad de acuerdo con este Documento de Poder cesará inmediatamente, con propósito de este Documento de Poder, "afiliada" significará cualquier entidad que directa o indirectamente controle, esté controlada o esté bajo el control común de la Compañía y "control" significará la propiedad de más del 50% del capital de acciones emitido, o el poder legal para dirigir o causar la dirección de la parte en cuestión y "controlado" se interpretará de acuerdo con esto.

Este Documento de Poder se ejecutó y entregó como escritura para Pfizer Limited y a su nombre en la fecha antes declarada.

El sello común de Pfizer Limited fue estampado a esta escritura en presencia de:

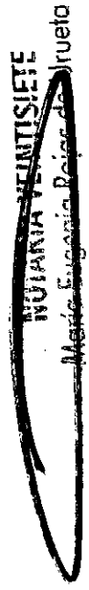
(Firmado) M. Fauerbach, Director

(Firmado) M. Summer, Secretario

Hay un sello de Pfizer Limited.

Sello: Andrew Martin Johnson – Notario (ilegible)

Apostilla:



Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

El sello fue debidamente estampado y certificado"

Por y en nombre de Pfizer Limited:

(Firmado) M.J. Summer, Secretario de la Compañía

Fecha: 20 de Septiembre de 2007

Hay un sello de Pfizer Limited.

Sello: "Andrew Martin Johnson – Notario Público

29 St. George's Place / Canterbury / CT1 1UT, England / Tel: 01227 479479".

Registrado en Inglaterra: No. 526209. Oficina Registrada: Ramsgate Road. Sandwich, Kent CT13 9NJ, UK

Apostilla:

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

Traducción oficial de un documento cuyo original está en ingles

PFIZER

Sandwich Laboratories
Pfizer Limited
Sandwich, Kent CT13 9NJ, UK
Tel: +44 (0) 1304 616161 Fax: +44 (0) 1304 656221

INVESTIGACIÓN Y DESARROLLO GLOBALES

Extracto del Acta de la Junta de Pfizer Limited

El siguiente es un estracto del Acta de una Asamblea de la Junta de Pfizer Limited, llevada a cabo el día 16 de Agosto de 2006:

"El siguiente documento fue enviado en triplicado y aprobado, y se resolvió que el sello común de la Compañía sea puesto en el mismo.

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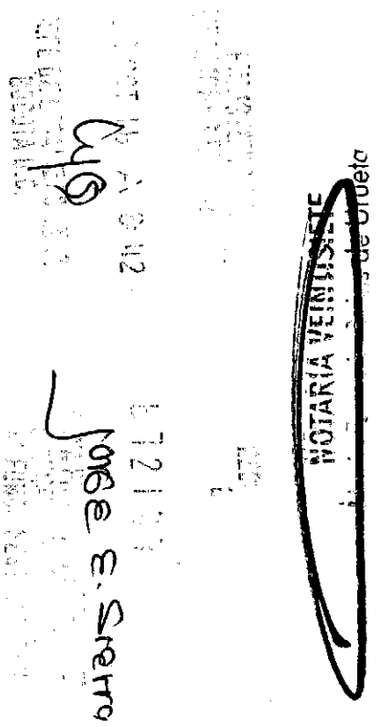
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WK 6299192

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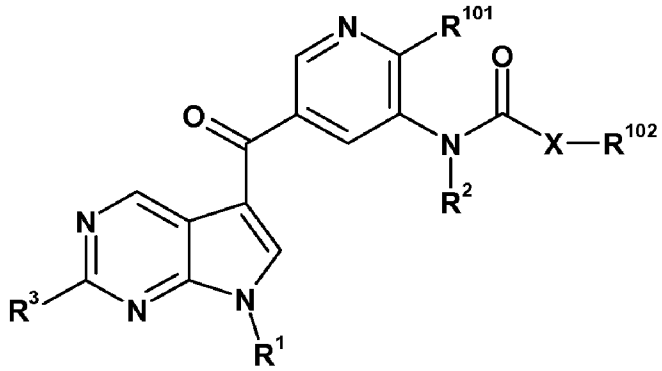
Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

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

[Continued on next page]

(54) **Title**: PYRROLO [2, 3 -D] PYRIMIDINE DERIVATIVES AS INHIBITORS OF TROPOMYOSIN- RELATED KINASES



(I)

(57) **Abstract**: The present invention relates to compounds of Formula (I) and their pharmaceutically acceptable salts, wherein the substituents are as described herein, and their use in medicine, in particular as Trk antagonists.

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

Published:

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

PYRROLO[2,3-d)PYRIMIDINE TROPOMYOSIN-RELATED KINASE INHIBITORS

The invention described herein relates to certain pyrrolo[2,3-d}pyrimidine compounds and the pharmaceutically acceptable salts of such compounds. The invention also relates to the processes for the preparation of the compounds, compositions containing the compounds, and the uses of such compounds and salts in treating diseases or conditions associated with tropomyosin-related kinase (Trk), activity. More specifically the invention relates to the compounds and their salts useful as inhibitors of Trk .

BACKGROUND

Tropomyosin-related kinases (Trks) are a family of receptor tyrosine kinases activated by neurotrophins. Trks play important roles in pain sensation as well as tumour cell growth and survival signaling. Thus, inhibitors of Trk receptor kinases might provide targeted treatments for conditions such as pain and cancer. Recent developments in this field have been reviewed by Wang *et al* in Expert Opin. Ther. Patents (2009) 19(3): 305-319 and an extract is reproduced below.

"1.1 Trk receptors

As one of the largest family of proteins encoded by the human genome, protein kinases are the central regulators of signal transduction as well as control of various complex cell processes. Receptor tyrosine kinases (RTKs) are a subfamily of protein kinases (up to 100 members) bound to the cell membrane that specifically act on the tyrosine residues of proteins. One small group within this subfamily is the Trk kinases, with three highly homologous isoforms: TrkA, TrkB, and TrkC. All three isoforms are activated by high affinity growth factors named neurotrophins (NT): i) nerve growth factor (NGF), which activates TrkA; ii) brain-derived neurotrophic factor (BDNF) and NT-4/5, which activate TrkB; and iii) NT-3, which activates TrkC. The binding of neurotrophins to the extracellular domain of Trks causes the Trk kinase to autophosphorylate at several intracellular tyrosine sites and triggers downstream signal transduction pathways. Trks and neurotrophins are well known for their effects on neuronal growth and survival.

1.2 Trks and cancer

Originally isolated from neuronal tissues, Trks were thought to mainly affect the maintenance and survival of neuronal cells. However, in the past 20 years, increasing evidence has suggested that Trks play key roles in malignant transformation, chemotaxis, metastasis, and survival signaling in human tumors. The association between Trks and cancer focused on prostate cancer in earlier years and the topic has been reviewed. For example, it was reported that malignant prostate epithelial cells secrete a series of neurotrophins and at least one Trks. In pancreatic cancer, it was proposed that paracrine and/or autocrine neurotrophin-Trk interactions may influence the invasive behavior of the cancer. TrkB was also reported to be overexpressed in metastatic human pancreatic cancer cells. Recently, there have been a number of new findings in other cancer settings. For example, a translocation leads to expression of a fusion protein derived from the *N*-terminus of the ETV6 transcription factor and the *C*-terminal kinase domain of TrkC. The resulting ETV6-TrkC fusions are oncogenic *in vitro* and appear causative in secretory breast carcinoma and some acute myelogenous leukemias (AML). Constitutively active TrkA fusions occurred in a subset of papillary thyroid cancers and colon carcinomas. In neuroblastoma, TrkB expression was

reported to be a strong predictor of aggressive tumor growth and poor prognosis, and TrkB overexpression was also associated with increased resistance to chemotherapy in neuroblastoma tumor cells *in vitro*. One report showed that a novel splice variant of TrkA called TrkAIII signaled in the absence of neurotrophins through the inositol phosphate–AKT pathway in a subset of neuroblastoma. Also, mutational analysis of the tyrosine kinome revealed that Trk mutations occurred in colorectal and lung cancers. In summary, Trks have been linked to a variety of human cancers, and discovering a Trk inhibitor and testing it clinically might provide further insight to the biological and medical hypothesis of treating cancer with targeted therapies.

1.3 Trks and pain

Besides the newly developed association with cancer, Trks are also being recognized as an important mediator of pain sensation. Congenital insensitivity to pain with anhidrosis (CIPA) is a disorder of the peripheral nerves (and normally innervated sweat glands) that prevents the patient from either being able to adequately perceive painful stimuli or to sweat. TrkA defects have been shown to cause CIPA in various ethnic groups.

Currently, non-steroidal anti-inflammatory drugs (NSAIDs) and opiates have low efficacy and/or side effects (e.g., gastrointestinal/renal and psychotropic side effects, respectively) against neuropathic pain and therefore development of novel pain treatments is highly desired. It has been recognized that NGF levels are elevated in response to chronic pain, injury and inflammation and the administration of exogenous NGF increases pain hypersensitivity. In addition, inhibition of NGF function with either anti-NGF antibodies or non-selective small molecule Trk inhibitors has been shown to have effects on pain in animal models. It appears that a selective Trk inhibitor (inhibiting at least NGF's target, the TrkA receptor) might provide clinical benefit for the treatment of pain. Excellent earlier reviews have covered targeting NGF/BDNF for the treatment of pain so this review will only focus on small molecule Trk kinase inhibitors claimed against cancer and pain. However, it is notable that the NGF antibody tanezumab was very recently reported to show good efficacy in a Phase II trial against osteoarthritic knee pain."

International Patent Application publication number WO2009/012283 refers to various fluorophenyl compounds as Trk inhibitors; International Patent Application publication numbers WO2009/152087, WO2008/080015 and WO2008/08001 and WO2009/152083 refer to various fused pyrroles as kinase modulators; International Patent Application publication numbers WO2009/143024 and WO2009/143018 refer to various pyrrolo[2,3-d]pyrimidines substituted as Trk inhibitors; International Patent Application publication numbers WO2004/056830 and WO2005/116035 describe various 4-amino-pyrrolo[2,3-d]pyrimidines as Trk inhibitors. International Patent Application publication number WO2011/133637 describes various pyrrolo[2,3-d]pyrimidines and pyrrolo[2,3-b]pyridines as inhibitors of various kinases.

US provisional application US61/471758 was filed 5th April 2012 and the whole contents of that application in it's entirety are herewith included by reference thereto.

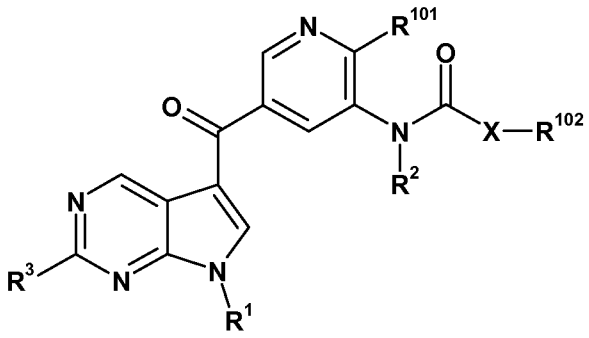
Thus Trk inhibitors have a wide variety of potential medical uses. There is a need to provide new Trk inhibitors that are good drug candidates. In particular, compounds should preferably bind potently to the

Trk receptors in a selective manner compared to other receptors, whilst showing little affinity for other receptors, including other kinase and / or GPC receptors, and show functional activity as Trk receptor antagonists. They should be non-toxic and demonstrate few side-effects. Furthermore, the ideal drug candidate will exist in a physical form that is stable, non-hygroscopic and easily formulated. They should preferably be e.g. well absorbed from the gastrointestinal tract, and / or be injectable directly into the bloodstream, muscle, or subcutaneously, and / or be metabolically stable and possess favourable pharmacokinetic properties.

Among the aims of this invention are to provide orally-active, efficacious, compounds and salts which can be used as active drug substances, particularly Trk antagonists, i.e. that block the intracellular kinase activity of the Trk, e.g. TrkA (NGF) receptor. Other desirable features include good HLM/hepatocyte stability, oral bioavailability, metabolic stability, absorption, selectivity over other types of kinase, dofetilide selectivity. Preferable compounds and salts will show a lack of CYP inhibition/induction, and be CNS-sparing.

SUMMARY

The present invention provides compounds of Formula I:



(I)

and pharmaceutically acceptable salts thereof wherein the subsituents are defined below.

The invention also comprises pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The invention is also directed to a method of treating a disease or condition indicated for treatment with a Trk antagonist, in a subject, by administering to a subject in need thereof a therapeutically effective amount of one or more of the compounds herein, or a pharmaceutically acceptable salt thereof.

Other aspects of the invention will be apparent from the remaining description and claims.

Preferably, the compounds of the present invention are potent antagonists at Trk receptors, and have a suitable PK profile to enable once daily dosing.

The compounds of the present invention are potentially useful in the treatment of a range of disorders where a Trk antagonist is indicated, particularly pain indications. Depending on the disease and condition of the patient, the term "treatment" as used herein may include one or more of curative, palliative and prophylactic treatment.

According to the invention a compound of the present invention may be useful to treat any physiological pain such as inflammatory pain, nociceptive pain, neuropathic pain, acute pain, chronic pain, musculo-skeletal pain, on-going pain, central pain, heart and vascular pain, head pain, orofacial pain. Other pain conditions which may be treated include intense acute pain and chronic pain conditions which may involve the same pain pathways driven by pathophysiological processes and as such cease to provide a protective mechanism and instead contribute to debilitating symptoms associated with a wide range of disease states.

Pain is a feature of many trauma and disease states. When a substantial injury, via disease or trauma, to body tissue occurs the characteristics of nociceptor activation are altered, this leads to hypersensitivity at the site of damage and in nearby normal tissue. In acute pain the sensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is normally due to nervous system injury due to maladaptation of the afferent fibres (Woolf & Salter 2000 Science 288: 1765-1768). Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. There are a number of typical pain subtypes: 1) spontaneous pain which may be dull, burning, or stabbing; 2) pain responses to noxious stimuli are exaggerated (hyperalgesia); 3) pain is produced by normally innocuous stimuli (allodynia) (Meyer et al., 1994 Textbook of Pain 13-44). Pain can be divided into a number of different areas because of differing pathophysiology, these include nociceptive, inflammatory, neuropathic pain among others. It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. Back pain, Cancer pain have both nociceptive and neuropathic components.

NOCICEPTIVE PAIN

Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and sensitise the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994 Textbook of Pain 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmit rapidly and are responsible for the sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey the dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of, but is not limited to pain from strains/sprains, post-operative pain (pain following any type of surgical procedure),

posttraumatic pain, burns, myocardial infarction, acute pancreatitis, and renal colic. Also cancer related acute pain syndromes commonly due to therapeutic interactions such as chemotherapy toxicity, immunotherapy, hormonal therapy and radiotherapy. Moderate to severe acute nociceptive pain is a prominent feature of, but is not limited to, cancer pain which may be tumour related pain, (e.g. bone pain, headache and facial pain, viscera pain) or associated with cancer therapy (e.g. postchemotherapy syndromes, chronic postsurgical pain syndromes, post radiation syndromes), back pain which may be due to herniated or ruptured intervertabral discs or abnormalities of the lumbar facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament.

NEUROPATHIC PAIN

According to the invention a compound of the present invention can potentially be used to treat neuropathic pain and the symptoms of neuropathic pain including hyperalgesia, allodynia and ongoing pain. Neuropathic pain is defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system (IASP definition). Nerve damage can be caused by trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include but are not limited to, Diabetic neuropathy, Post herpetic neuralgia, Back pain, Cancer neuropathy, HIV neuropathy, Phantom limb pain, Carpal Tunnel Syndrome, chronic alcoholism, hypothyroidism, trigeminal neuralgia, uremia, or vitamin deficiencies. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patients quality of life (Woolf and Mannion 1999 Lancet 353: 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf & Decosterd 1999 Pain Supp. 6: S141-S147; Woolf and Mannion 1999 Lancet 353: 1959-1964). They include spontaneous pain, which can be continuous, or paroxysmal and abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

INTENSE ACUTE PAIN AND CHRONIC PAIN

Intense acute pain and chronic pain may involve the same pathways driven by pathophysiological processes and as such cease to provide a protective mechanism and instead contribute to debilitating symptoms associated with a wide range of disease states. Pain is a feature of many trauma and disease states. When a substantial injury, via disease or trauma, to body tissue occurs the characteristics of nociceptor activation are altered. There is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. This leads to hypersensitivity at the site of damage and in nearby normal tissue. In acute pain these mechanisms can be useful and allow for the repair processes to take place and the hypersensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is normally due to nervous system injury. This injury often leads to maladaptation of the afferent fibres (Woolf & Salter 2000 Science 288: 1765-1768). Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. There are a number of typical pain subtypes: 1) spontaneous pain which may be dull, burning,

or stabbing; 2) exaggerated pain responses to noxious stimuli (hyperalgesia); 3) pain is produced by normally innocuous stimuli (allodynia) (Meyer et al., 1994 Textbook of Pain 13-44). Although patients with back pain, arthritis pain, CNS trauma, or neuropathic pain may have similar symptoms, the underlying mechanisms are different and, therefore, may require different treatment strategies.

CHRONIC PAIN

Chronic pain comprises one or more of, chronic nociceptive pain, chronic neuropathic pain, chronic inflammatory pain, breakthrough pain, persistent pain hyperalgesia, allodynia, central sensitisation, peripheral sensitisation, disinhibition and augmented facilitation.

Chronic pain includes cancer pain, e.g. cancer pain arising from malignancy, adenocarcinoma in glandular tissue, blastoma in embryonic tissue of organs, carcinoma in epithelial tissue, leukemia in tissues that form blood cells, lymphoma in lymphatic tissue, myeloma in bone marrow, sarcoma in connective or supportive tissue, adrenal cancer, AIDS-related lymphoma, anemia, bladder cancer, bone cancer, brain cancer, breast cancer, carcinoid tumour s, cervical cancer, chemotherapy, colon cancer, cytopenia, , endometrial cancer, esophageal cancer, gastric cancer, head cancer, neck cancer, hepatobiliary cancer, kidney cancer, leukemia, liver cancer, lung cancer, lymphoma, Hodgkin's disease, lymphoma, non-Hodgkin's, nervous system tumours, oral cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, thyroid cancer, urethral cancer, bone cancer, sarcomas cancer of the connective tissue, cancer of bone tissue, cancer of blood-forming cells, cancer of bone marrow, multiple myeloma, leukaemia, primary or secondary bone cancer, tumours that metastasize to the bone, tumours infiltrating the nerve and hollow viscus, tumours near neural structures. Cancer pain also comprises visceral pain, e.g. visceral pain which arises from pancreatic cancer and/or metastases in the abdomen, somatic pain, e.g. somatic pain due to one or more of bone cancer, metastasis in the bone, postsurgical pain, sarcomas cancer of the connective tissue, cancer of bone tissue, cancer of blood-forming cells of the bone marrow, multiple myeloma, leukaemia, primary or secondary bone cancer.

INFLAMMATORY PAIN

Inflammatory conditions include acute inflammation, persistent acute inflammation, chronic inflammation, and combined acute and chronic inflammation.

Inflammatory pain includes acute inflammatory pain and/or chronic inflammatory pain wherein the chronic inflammatory pain can be pain involving both peripheral and central sensitisation and/or mixed etiology pain involving both inflammatory pain and neuropathic pain or nociceptive pain components. Inflammatory pain also comprises hyperalgesia, e.g. primary and/or secondary hyperalgesia. Additionally or alternatively the inflammatory pain can include allodynia. Inflammatory pain also comprises pain that persists beyond resolution of an underlying disorder or inflammatory condition or healing of an injury.

Inflammatory pain is pain resulting an inflammatory condition. e.g. in response to acute tissue injury due to trauma, disease e.g. an inflammatory disease, immune reaction, the presence of foreign substances,

chemicals or infective particles for example micro-organisms. Inflammatory conditions can be either acute or chronic inflammation or both.

Inflammatory pain can result from an inflammatory condition due to an inflammatory disease such as inflammatory joint diseases, inflammatory connective tissue diseases, inflammatory autoimmune diseases, inflammatory myopathies, inflammatory digestive system diseases, inflammatory air way diseases, cellular immune inflammation diseases, hypersensitivities and allergies, vasular inflammation diseases, non-immune inflammatory disease, synovitis, villonodular synovitis, arthralgias, ankylosing spondylitis, spondyloarthritis, spondyloarthropathy, gout, Pagets disease, periarticular disorders such as bursitis, rheumatoid disease, rheumatoid arthritis and osteoarthritis, rheumatoid arthritis or osteoarthritis. Rheumatoid arthritis in particular, represents ongoing inflammation associated with severe pain. Arthritic pain is a form of inflammatory pain and arises from inflammation in a joint which causes both peripheral sensitization and central sensitization. Under inflammatory conditions the nociceptive system is activated by normally innocuous and nonpainful mechanical stimuli. Additionally when the joint is at rest pain is present and appears as spontaneous pain and hyperalgesia (augmented pain response on noxious stimulation and pain on normally nonpainful stimulation). Inflammatory processes in peripheral tissues lead to central sensitization in the spinal cord, which contributes to hyperalgesia and allodynia typically associated with inflammatory pain. Other types of inflammatory pain include inflammatory bowel diseases (IBD).

OTHER TYPES OF PAIN

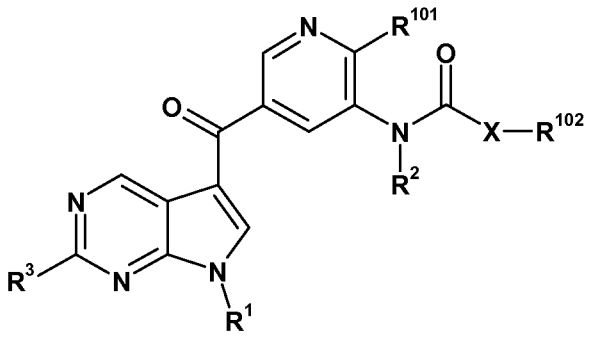
Other types of pain include but are not limited to:

- Musculo-skeletal disorders including but not limited to myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, Glycogenolysis, polymyositis, pyomyositis;
- Central pain or 'thalamic pain' as defined by pain caused by lesion or dysfunction of the nervous system including but not limited to central post-stroke pain, multiple sclerosis, spinal cord injury, Parkinson's disease and epilepsy;
- Heart and vascular pain including but not limited to angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma, scleredoma, skeletal muscle ischemia;
- Visceral pain, and gastrointestinal disorders. The viscera encompasses the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders include the functional bowel disorders (FBD) and the inflammatory bowel diseases (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including – for FBD, gastro-esophageal reflux, dyspepsia, the irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and – for IBD, Crohn's disease, ileitis, and ulcerative colitis, which all regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, pelvic pain, cystitis and pancreatitis;

Head pain including but not limited to migraine, migraine with aura, migraine without aura cluster headache, tension-type headache. Orofacial pain including but not limited to dental pain, temporomandibular myofascial pain, tinnitus, hot flushes, restless leg syndrome and blocking development of abuse potential. Further pain conditions may include, back pain (e.g. chronic lower back pain), cancer pain, complex regional syndrome, HIV-related neuropathic pain, post-operative induced neuropathic pain, post-stroke pain, spinal cord injury pain, traumatic nerve injury pain, diabetic peripheral neuropathy, moderate / severe interstitial cystitis pain, irritable bowel syndrome pain, moderate / severe endometriosis pain, moderate / severe pelvic pain, moderate / severe prostatitis pain, moderate / severe osteoarthritis pain,post-herpetic neuralgia, rheumatoid arthritis pain, dysmenorrhea pain, pre-emptive post-operative pain, trigeminal neuralgia, bursitis, dental pain, fibromyalgia or myofacial pain, menstrual pain, migraine, neuropathic pain (including painful diabetic neuropathy), pain associated with post-herpetic neuralgia, post-operative pain, referred pain, trigeminal neuralgia, visceral pain (including interstitial cystitis and IBS) and pain associated with AIDS, allodynia, burns, cancer, hyperalgesia, hypersensitisation, spinal trauma and/or degeneration and stroke.

DETAILED DESCRIPTION

Emodiment 1 of the invention is a compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is

H, or

C_{1-5} alkyl optionally substituted by up to 3 substituents independently selected from OH, $CON(R^5R^6)$, SO_2R^7, SR^7, OR^7, CH_2OH, CO_2R^5, $SONR^7R^7$, $NR^7SO_2R^5$, CN, NO_2 and R^8 , or

a ring system selected from C_{3-5} cycloalkyl, propellanyl, or a 4-6 membered saturated heterocyclyl ring, which ring system has up to 3 ring hetero-atoms selected from N, O and S, and which ring system is optionally substituted by up to 3 substituents independently selected from methyl, OH, $CON(R^5R^6)$, SO_2R^7, OR^7, CH_2OH, CO_2R^5, $SONR^7R^7$, $NR^7SO_2R^5$, CN, NO_2 and R^8;

R^2 is H or methyl;

R^3 is H, NH_2 or NH(C_{1-3} alkyl optionally substituted with up to 3 substituents independently selected from OH and O(C_{1-3} alkyl));

R^{101} is H, OH, methyl, cyclopropyl, methoxy, ethyl, ethoxy or CN,

X is a bond, O, $(CH\text{-}R^4)_n$, NR^{104}, OCH_2 or CH_2O;

R^4 is independently H, CH_3, CH_2OH, CH_2OCH_3, OH, NH_2, $NHCH_3$, $N(CH_3)_2$, CH_2NH_2, CH_2NHCH_3,or $CH_2N(CH_3)_2$;

R^{104} is H, C_{1-3} alkyl or a C_{4-6} saturated carbocycle, each of which is optionally substituted by up to 3 substituents independently selected from C_{1-3} alkyl, CH_2OH and NH_2;

n is 1 or 2;

R^{102} is a ring system which is a 3-7 membered monocyclic carbocyclic or heterocyclic system, or an 8-14-membered bicyclic system, which ring system may be saturated or partially or fully unsaturated, wherein the heterocyclic ring system may have up to 5 ring hetero-atoms selected from N, S, and O,
wherein the bicyclic ring system can be 2 rings (carbocyclic-carbocyclic, carbocyclic-heterocyclic, heterocyclic-carbocyclic or heterocyclic-heterocyclic) fused or linked by a single bond,
which ring system is optionally substituted by up to 3 substituents independently selected from, where possible -
halo, CN, NR^5R^6, SO_2R^7, SR^7, C_{1-4} alkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{1-3} alkyl substituted by up to 3 halogen, OH, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, O(C_{1-3} alkyl substituted by up to 3 halogen), O(C_{1-3} alkyl substituted by up to 3 OH and/or C_{1-3} alkoxy groups), $NR^5SO_2R^7$, =O, R^8, $C(O)R^8$, NO_2, $NR^5CO_2R^7$, NR^5COR^7,OR^8, $S(O)R^7$, and CH_2R^8;

R^5 and R^6 are each independently
H, or
C_{1-5} alkyl optionally substituted by up to 3 substituents independently selected from OH, $CONR^7R^7$, SO_2R^7, OR^7, CH_2OH, CO_2R^7, $SONR^7R^7$, $NR^7SO_2R^7$, CN, NO_2 and R^9 ,
or
a ring system selected from C_{3-5} cycloalkyl, propellanyl, or a 4-6 membered saturated heterocyclyl ring, which ring system is optionally substituted by up to 3 substituents independently selected from OH, $CON(R^7R^7)$, SO_2R^7, CO_2R^7, $SONR^7R^7$, $NR^7SO_2R^7$, CN, NO_2, halo, NR^7R^7,SR^7,C_{1-4} alkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{1-3} alkyl substituted by 1 to 3 halogen, O(C_{3-6} cycloalkyl optionally substituted

by up to 3 OH and/or C_{1-3} alkoxy groups, O(C_{1-3} alkyl substituted by up to 3 halogen, O(C_{1-3} alkyl substituted by up to 3 OH and/or C_{1-3} alkoxy, $NR^7SO_2R^7$,=O,NO_2,$NR^7CO_2R^7$, and $S(O)R^7$
or R^5 and R^6 together with the N to which they are attached can be a 4-7 membered ring optionally including up to 2 further ring hetero-atoms independently selected from N, O, S, which ring is optionally substituted by C_{1-3} alkoxy and / or C_{1-3} alkyl;

R^7 is H, C_{1-5} alkyl or C_{1-5} alkoxy,
which C_{1-5} alkyl or C_{1-5} alkoxy is optionally substituted by up to 3 substituents independently selected from halogen;

R^8 is a is a ring system which is a 3-7 membered monocyclic carbocyclic or heterocyclic system, or an 8-14-membered bicyclic system, which ring system may be saturated or partially or fully unsaturated, wherein the heterocyclic ring system may have up to 5 ring hetero-atoms selected from N, S, and O, wherein the bicyclic ring system can be 2 rings (carbocyclic-carbocyclic, carbocyclic-heterocyclic, heterocyclic-carbocyclic or heterocyclic-heterocyclic) fused or linked by a single bond,
which ring system is optionally substituted by up to 3 substituents independently selected from, where possible -
halo, CN, NR^5R^6, SO_2R^7, SR^7, C_{1-4} alkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{1-3} alkyl substituted by 1 to 3 halogen, OH, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, O(C_{1-3} alkyl substituted by up to 3 halogen, O(C_{1-3} alkyl substituted by up to 3 OH and/or C_{1-3} alkoxy, $NR^5SO_2R^7$, =O, NO_2, NR^7COR^7,$NR^5CO_2R^7$, and $S(O)R^7$;

R^9 is a is a ring system which is a 3-7 membered monocyclic carbocyclic or heterocyclic system, or an 8-14-membered bicyclic system, which ring system may be saturated or partially or fully unsaturated, wherein the heterocyclic ring system may have up to 5 ring hetero-atoms selected from N, S, and O, wherein the bicyclic ring system can be 2 rings (carbocyclic-carbocyclic, carbocyclic-heterocyclic, heterocyclic-carbocyclic or heterocyclic-heterocyclic) fused or linked by a single bond,
which ring system is optionally substituted by up to 3 substituents independently selected from, where possible -
halo, CN, NR^7R^7, SO_2R^7, SR^7, C_{1-4} alkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{1-3} alkyl substituted by 1 to 3 halogen, OH, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, O(C_{1-3} alkyl substituted by up to 3 halogen, O(C_{1-3} alkyl substituted by up to 3 OH and/or C_{1-3} alkoxy, $NR^7SO_2R^7$, =O, NO_2, $NR^7CO_2R^7$, NR^7COR^7,and $S(O)R^7$;

wherein each CH moiety can be replaced by a CF moiety.

Embodiment 2 of the invention is a compound or salt according to embodiment 1 wherein R^1 is H, C_{1-5} alkyl optionally substituted by up to 2 OH,

or R^1 is C_{1-5} alkyl substituted by $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2H, CO_2CH_3, OCH_3, SCH_3, SO_2CH_3, or R^1 is a ring system selected from C_{3-5} cycloalkyl, propellanyl, or oxetanyl, which ring system is optionally substituted by methyl, OH or CH_2OH.

Embodiment 3 of the invention is a compound or salt according to any one of embodiments 1 or 2 wherein R^1 is t-butyl, hydroxy-t-butyl, dihdyroxy-t-butyl, 1-hydroxyprop-2-yl or 1,3-dihydroxyprop-2-yl.

Embodiemnt 4 of the invention is a compound or salt according to any one of embodiments 1 to 3 wherein R^2 is H.

Embodiemt 5 of the invention is a compound or salt according to any one of embodiments 1 to 4 wherein R^3 is H or NH_2.

Embodiment 6 of the invention is a compound or salt according to any one of embodiments 1 to 5 wherein R^3 is NH_2.

Embodiment 7 of the invention is a compound or salt according to any one of embodiments 1 to 5 wherein R^3 is H.

Embodiment 8 of the invention is a compound or salt according to any one of embodiments 1 to 7 wherein R^{101} is H.

Embodiment 9 of the invention is a compound or salt according to any one of embodiments 1 to 7 wherein R^{101} is OH.

Embodiment 10 of the invention is a compound or salt according to any one of embodiments 1 to 9 wherein X is a bond, O, CH_2, C_2H_4, $CH(CH_3)CH_2$, $CH(CH_3)$, $CH(CH_2OH)$, CH_2O, $CH(NH_2)$, CH(OH) or NH.

Embodiment 11 of the invention is a compound or salt according to any one of embodiments 1 to 10 wherein X is CH_2.

Embodiment 12 of the invention is a compound or salt according to any one of embodiments 1 to 11 wherein R^{102} is an optionally substituted nitrogen-containing ring system which is linked to the X moiety via a nitrogen ring atom.

Embodiment 13 of the invention is a compound or salt according to any one of embodiments 1 to 11 wherein R^{102} is an optionally substituted ring system where the ring system is selected from - benzimidazolyl, benzisoxazolyl, benzofuranyl, benzoxazolyl, benzotriazolyl, biphenyl, bipyrazolyl, cinnolinyl, cyclobutylimidazolyl, cyclobutylpyrazolyl, cyclobutylthiazolyl, cyclopentyltriazolyl, cyclopropylisoxazolyl, cyclopropyloxazolyl, cyclopropylpyrazolyl, cyclopropyltriazolyl, diazirenylphenyl, dihydronaphthyridinyl, dihydropyrrolopyrazolyl, dioxinopyridinyl, furazanyl, furopyridinyl, furopyrrolyl,

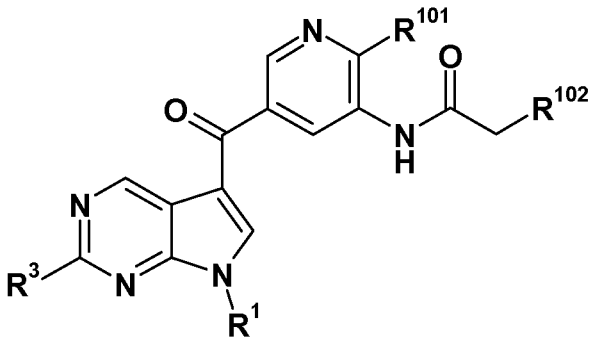
imidazolyl, imidazopyrazinyl, imidazopyridazinyl, imidazopyridinyl, imidazopyrimidinyl, imidazothiadiazolyl, imidazothiazolyl, indanyl, indazolyl, indolyl, isoindolyl, isoxazolopyridinyl, isoxazolyl, isoquinolinyl, naphthyridinyl, oxazolyl, phenyl, phenylcyclopropyl, phenylimidazolyl, phenylpyrazolyl, phenylpyrrolyl, phenyltetrazolyl, phthalazinyl, purinyl, pyrazinyl, pyrazolyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolotriazinyl, pyridinyl, pyridazinyl, pyridinyltriazolyl, pyrimidinyl, pyrroloimidazolyl, pyrrolopyrazinyl, pyrrolopyrimidinyl, pyrrolopyridinyl, pyrrolyl, quinolinyl, quinazolyl, quinoxalinyl, tetrahydrobenzisoxazolyl, tetrahydrocyclopentapyrazolyl, tetrahydrotriazolopyridinyl, tetrazolopyridazinyl, tetrazolopyridinyl, thiazolyl, thiazolopyridinyl, thiazolopyrimidinyl, thienylpyrazolyl, thienopyridinyl, triazolopyridinyl and triazolyl,

Embodiment 14 of the invention is a compound or salt according to embodiment 13 where the optional substituents are independently selected from, where possible -
halo, methyl, ethyl, propyl, isopropyl, cyclopropyl, CF_3, CHF_2, CH_2F, CH_2OCH_3, CN, CH_2OH, OCH_3, =O, NH_2, SCH_3, SO_2CH_3, phenoxy, fluorophenoxy, benzyl, SCF_3, OCF_3, SO_2CF_3, $NHSO_2CH_3$, $NHSO_2CF_3$, $C(O)CF_3$, $C(O)CH_3$, benzoyl, azetidinylmethyl, fluoroazetidinylmethyl and morpholinomethyl.

Embodiment 15 of the invention is a compound or salt according to any one of embodiments 1 to 11, 13 or 14, wherein R^{102} is selected from phenyl, pyrazol-1-yl, 1,2,3-triazol-1-yl, benzotriazol-2-yl, pyridin-2-yl, pyridin-3-yl and pyridin-4-yl,
each of which is optionally substituted by halo, methyl, ethyl, propyl, isopropyl, cyclopropyl, CF_3, CHF_2, CH_2F, CH_2OCH_3, CN, CH_2OH, OCH_3, =O, NH_2, SCH_3, SO_2CH_3, phenoxy, fluorophenoxy, benzyl, SCF_3, OCF_3, SO_2CF_3, $NHSO_2CH_3$, $NHSO_2CF_3$, $C(O)CF_3$, $C(O)CH_3$, benzoyl, azetidinylmethyl, fluoroazetidinylmethyl and/or morpholinomethyl.

Embodiment 16 of the invention is a compound or salt according to any one of embodiments 1 to 15 with R^5 and R^6 groups present, wherein R^5 and R^6 are each independently H, C_{1-3} alkyl optionally substituted by C_{1-3} alkoxy, C_{3-5} cycloalkyl, propellanyl, oxetanyl, tetrahydrofuranyl or pyranyl,
or R^5 and R^6 together with the N to which they are attached can be an azetidine, pyrrolidine, piperidine, piperazine or morpholine ring, which ring is optionally substituted by C_{1-3} alkoxy and / or C_{1-3} alkyl.

Embodiment 17 of the invention is a compound according to embodiment 1 of the Formula IA:



(IA)

or a pharmaceutically acceptable salt thereof, wherein

R^3 is H or NH_2;

R^1 is C_{2-4} alkyl optionally substituted by 1 or 2 OH groups;

R^{101} is H or OH;

and R^{102} is phenyl or an aromatic or partially unsaturated 5- or 6-membered heterocycle, which heterocycle is optionally fused to a further phenyl or 5-7 membered aromatic or partially unsaturated heterocyclic ring, wherein each heterocycle has from 1 to 3 ring heteroatoms selected from N, O and S, and which ring system is optionally substituted by up to 3 substituents independently selected from halo, CF_3, C_{1-4} alkyl and C_{3-5} cycloalkyl.

Embodiment 18 of the invention is a compound or salt according to embodiment 17 wherein R^{101} is H.

Embodiment 19 of the invention is a compound or salt according to embodiment 18 wherein

R^1 is t-butyl, hydroxy-t-butyl or 1-hydroxyprop-2-yl;

and R^{102} is 4-trifluromethylphenyl, 4-chlorophenyl, 2,4-difluorophenyl, 5-chloropyridin-2-yl, 5-fluoropyridin-2-yl, 3-trifluromethylpyrazolyl-1-yl, 4-trifluromethylpyrazol-1-yl, 3-trifluromethyl-5-methylpyrazol-1-yl, 3-cyclopropylpyrazol-1-yl, 4-cyclopropylpyrazol-1-yl, 4-trifluromethyl (1,2,3-triazol-1-yl), 4-cyclopropyl-(1,2,3-triazol-1-yl), or benzotriazol-2-yl.

Embodiment 20 of the invention is a compound according to embodiment 1, selected from:

N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-chlorophenyl)acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(5-fluoropyridin-2-yl)acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(3-cyclopropyl-1H-pyrazol-1-yl)acetamide;

N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide;

N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide;

N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-chloropyridin-2-yl)acetamide;

N-(5-{[2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(5-chloropyridin-2-yl)acetamide;

N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide;

2-(4-chlorophenyl)-N-[5-({7-[(1S)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide

N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

N-[5-({7-[(1S)-2-Hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[4-(trifluoromethyl)phenyl]acetamide;

N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[4-(trifluoromethyl)phenyl]acetamide;

2-(4-chlorophenyl)-N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide;

N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

2-(5-chloropyridin-2-yl)-N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide;

N-(5-{[2-Amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-chlorophenyl)acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-chlorophenyl)acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide;

N-(5-{[2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

and
N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide;
or a pharmaceutically acceptable salt thereof.

Embodiment 21 of the invention is a pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of the preceding embodiments 1 to 20, and a pharmaceutically acceptable carrier.

Embodiment 22 of the invention is a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of embodiments 1 to 20, for use as a medicament.

Embodiment 23 of the invention is a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of embodiments 1 to 20 for use in the treatment of a disease for which an Trk receptor antagonist is indicated

Embodiment 24 of the invention is a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of embodiments 1 to 20 for use in the treatment of pain.

Embodiment 25 of the invention is the use of a compound of the formula (I) or a pharmaceutically acceptable salt or composition thereof, as defined in any one of embodiments 1 to 20, for the manufacture of a medicament to treat a disease for which a Trk receptor antagonist is indicated

Embodiment 26 of the invention is the use of a compound of the formula (I) or a pharmaceutically acceptable salt or composition thereof, as defined in any one of embodiments 1 to 20, for the manufacture of a medicament to treat pain.

Embodiment 27 of the invention is a method of treatment of a mammal, to treat a disease for which an Trk receptor antagonist is indicated, comprising treating said mammal with an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of embodiments 1 to 20.

Embodiment 28 of the invention is a method of treatment of pain in a mammal, comprising treating said mammal with an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of embodiments 1 to 20.

Embodiment 29 of the invention is compound or salt according to any one of embodiments 1 to 20 for use in a medical treatment in combination with a further drug susbtance.

Further embodiments of the invention include:

Compounds or salts of formula (I) where R^1 has a value as exemplified in the Examples below;
Compounds or salts of formula (I) where X has a value as exemplified in the Examples below;
Compounds or salts of formula (I) where R^{102} has a value as exemplified in the Examples below;
Compounds or salts of formula (I) where R^1, R^2, R^3, R^{101}, X and R^{102} have a value as exemplified in the Examples below;
A compound selected from any one of the Examples below or a pharmaceutically acceptable salt thereof; and
any novel intermediate compound herein disclosed.
Other embodiments may be envisaged based on the description below.

"Halogen" means a fluoro, chloro, bromo or iodo group.
"Alkyl" groups, containing the requisite number of carbon atoms, can be unbranched or branched.
Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl.

"Pharmaceutically acceptable salts" of the compounds of formula I include the acid addition and base addition salts (including disalts, hemisalts, etc.) thereof.
Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.
Suitable base addition salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.
For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

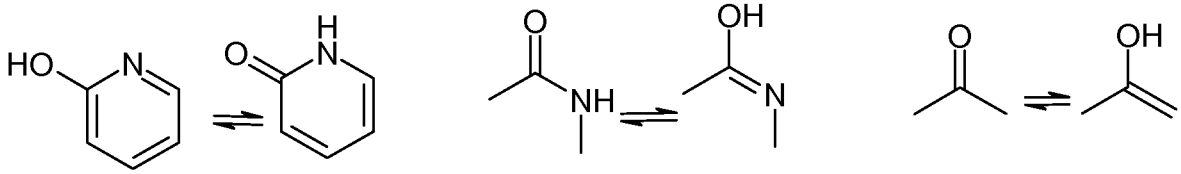
The compounds of the invention include compounds of formula I and salts thereof as hereinbefore defined, polymorphs, and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labelled compounds of formula I.

Unless otherwise specified, compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains for example, a keto or guanidine group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the claimed compounds of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting

more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base addition salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Examples of types of potential tautomerisms shown by the compounds of the invention include hydroxypyridine ⇔ pyridone; amide ⇔ hydroxyl-imine and keto ⇔ enol tautomersims:



Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or other derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on a resin with an asymmetric stationary phase and with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Mixtures of stereoisomers may be separated by conventional techniques known to those skilled in the art. [see, for example, “Stereochemistry of Organic Compounds” by E L Eliel (Wiley, New York, 1994).]

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labelled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labelled reagents in place of the non-labelled reagent previously employed.

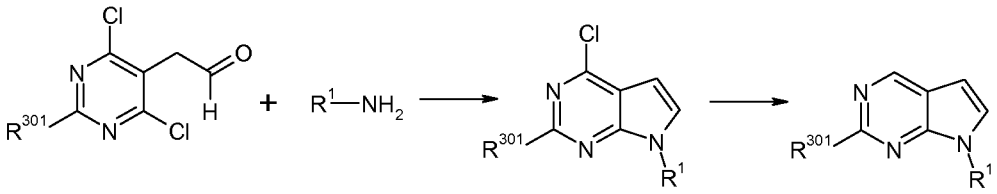
The routes below, including those mentioned in the Examples and Preparations, illustrate methods of synthesising compounds of formula (**I**). The skilled person will appreciate that the compounds of the invention, and intermediates thereto, could be made by methods other than those specifically described herein, for example by adaptation of the methods described herein, for example by methods known in the art. Suitable guides to synthesis, functional group interconversions, use of protecting groups, etc., are for example:"Comprehensive Organic Transformations" by RC Larock, VCH Publishers Inc. (1989); Advanced Organic Chemistry" by J. March, Wiley Interscience (1985); "Designing Organic Synthesis" by S Warren, Wiley Interscience (1978); "Organic Synthesis – The Disconnection Approach" by S Warren, Wiley Interscience (1982); "Guidebook to Organic Synthesis" by RK Mackie and DM Smith, Longman (1982); "Protective Groups in Organic Synthesis" by TW Greene and PGM Wuts, John Wiley and Sons, Inc. (1999); and "Protecting Groups" by PJ, Kocienski, Georg Thieme Verlag (1994); and any updated versions of said standard works.

In the general synthetic methods below, unless otherwise specified, the substituents are as defined above with reference to the compounds of formula (**I**) above. R^{1011} is the same as R^{101} or a suitably protected version thereof.

Scheme 1 illustrates the preparation of the intermediates of general formula (**Int 1**), where they can be made from amine (**Int3**) where, in those cases where R^1 contains an alcohol, a protected form of R^1 where a suitable hydroxyl protecting group (PG) is used. Any suitable oxygen protecting group may be used (as described in "Protecting Groups in Organic Synthesis" 3rd edition T.W. Greene and P.G. Wuts, Wiley-Interscience, 1999). Common oxygen protecting groups suitable for use herein include tert-butyldimethylsilyl (TBDMS), tetrahydropyranyl (THP) and tertbutylsilyl (TBS).

Compounds of formula (Int 1) can be prepared from compounds of formula (Int 2) as illustrated in Scheme 1.

Scheme 1



Int 4 **Int 3** **Int 2** **Int 1**

Wherein R^{301} can be H or halogen, typically chlorine.

Compounds of formula (Int 1) may be prepared from amine (**Int 3**) and (**Int4**) in a cyclisation step followed by a dechlorination step. Typical conditions employed involve stirring the amine of general formula (**Int 3**) and the aldehyde (**Int 4**) together, preferably in ethanol at a temperature from room temperature up to 80°C.

e.g. as exemplified in Preps. 1-5

The intermediate chloride (**Int 2**) is reduced using standard literature conditions, for example hydrogenation using a suitable catalyst such as palladium on carbon and an additive such as ammonia in a suitable solvent such as ethanol. Alternatively the chloride may be removed by displacing the chloro with methane thiol followed by Raney Nickel removal of the SMe intermediate.

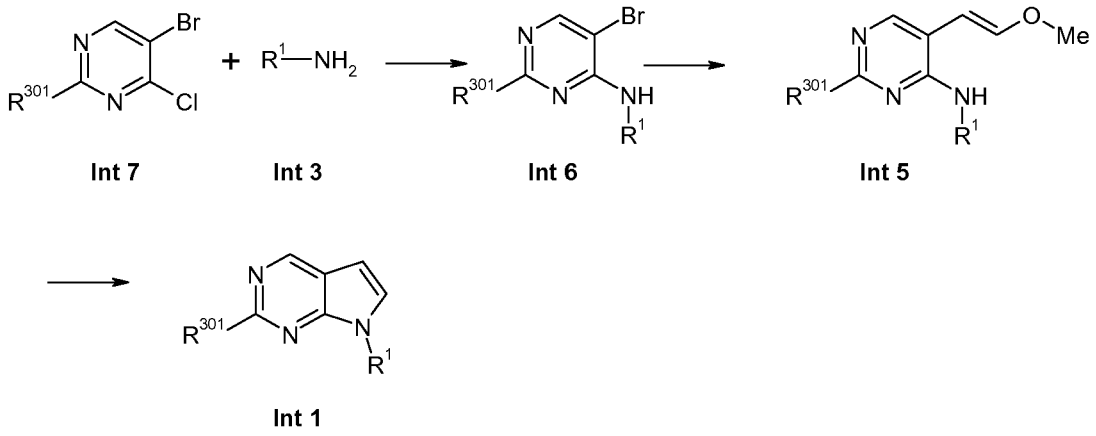
e.g. as exemplified in Preps. 8-13

In those cases where R^1 contains one or more alcohols, a protected form of R^1 with a suitable hydroxyl protecting group (PG) can be used. Any suitable oxygen protecting group protection/deprotection system may be used (as described in "Protecting Groups in Organic Synthesis" 3rd edition T.W. Greene and P.G. Wuts, Wiley-Interscience, 1999). Common oxygen protecting groups suitable for use herein include tert-butyldimethylsilyl (TBDMS) and tetrahydropyranyl (THP).

Intermediates of general formula (**Int 3**) and (**Int 4**) are either commercially available or will be well-known to those skilled in the art with reference to literature precedents and/or the preparations herein.

Compounds of formula (**Int 1**) can be prepared from compounds of formula (**Int 7**) as illustrated in Scheme 2.

Scheme 2



.

Compounds of formula (**Int 1**) wherein R^3 can be H or halogen, typically chlorine, may also be prepared from compounds of formula (**Int 7**) through displacement of a halogen, typically chlorine, with amines of formula (**Int 3**), in a palladium catalysed Suzuki reaction followed by an acidic cyclisation.

Typical conditions comprise stirring the amine of general formula (**Int 3**) and the intermediate of general formula (**Int 7**) together with a suitable base, such as triethylamine, in a solvent such as acetonitrile or dichloromethane, to provide compounds of general formula (**Int 6**).

The vinyl ether can be introduced by reacting intermediate (**Int 6**) with a suitable boronic ester and a suitable base, such as sodium hydroxide and a suitable catalyst such as tetrakis(triphenylphosphine)palladium (0) in a solvent such as THF at a temperature from room temperature up to 70°C.

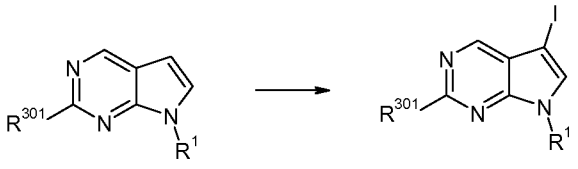
Intermediates of formula (**Int 1**) can be made by treatment of intermediate (**Int 5**) with an acid such as hydrogen chloride in an organic solvent such as isopropanol at a temperature from room temperature up to 70°C.

e.g. as exemplified in Preps. 60-62

Intermediates of general formula (**Int 3**) and (**Int 7**) are either commercially available or will be well-known to those skilled in the art with reference to literature precedents and/or the preparations herein.

Compounds of formula (**Int 8**) can be prepared from compounds of formula (**Int 1**) as illustrated in Scheme 3.

Scheme 3

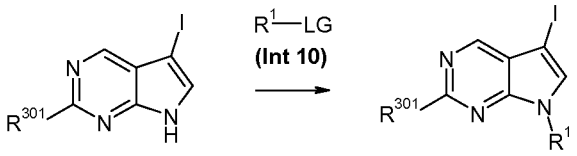


Wherein R^{301} is H or halogen, typically chlorine;

Compounds of formula (**Int 8**) are typically prepared by iodination of the pyrrolopyrimidine intermediates (**Int 1**).Typical conditions employed involve stirring the intermediate of general formula (**XI**) with an iodinating reagent such as N-iodosuccinimide in a suitable solvent, such as DMF or acetonitrile.
e.g. as exemplified in Preps. 14-19, 40, 63.

Compounds of formula (**Int 8**) can also be prepared from compounds of formula (**Int 9**) as illustrated in Scheme 4.

Scheme 4

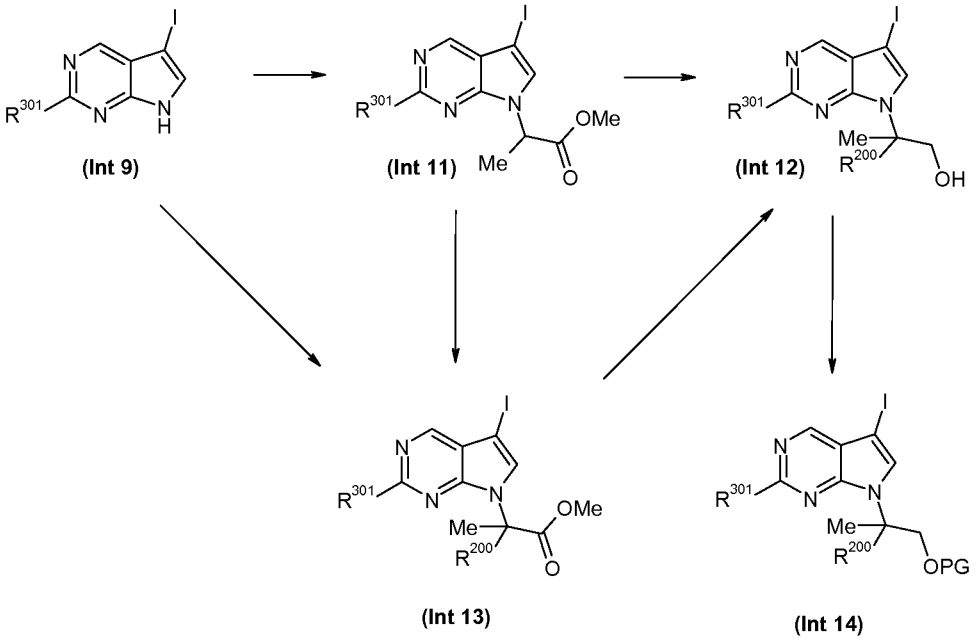


(Int 9) **(Int 8)**

Wherein R^{301} is H or halogen, typically chlorine; LG is halogen or tosylate, triflate or mesylate;
Alternatively intermediates of general formula (**Int 8**) can be prepared by alkylation of the pyrrolopyrimidine intermediates (**Int 9**), with compounds of formula (**Int 10**) using a suitable base such as caesium carbonate or potassium carbonate in an organic solvent. A suitable alternative is to use an additive (such as potassium iodide) as well as a base. Preferred conditions comprise cesium carbonate in DMF at room temperature.
In those cases where R^1 contains one or more alcohols, a protected form of R^1 can be used as described in Scheme 1.
E.g. as exemplified in Preparation 20.

Compounds of formula (**Int 12**) can be prepared from compounds of formula (**Int 11**) as illustrated in Scheme 5.

Scheme 5



Wherein R^{301} is H or halogen, typically chlorine;

Intermediates of general formula (**Int 9**) are reacted in an alkylation reaction to provide an ester intermediate (**Int 11**) or (**Int 13**), from which the ester group can be reduced and protected to furnish a compound of general formula (**Int 14**), where R^{200} is a H or methyl group. As previously mentioned in Scheme 1 the hydroxy group can be protected with a suitable oxygen protecting group (PG), where the preferred protecting groups are TBDMS, TBS and THP.

Typical conditions employed for the alkylation involve stirring the compound of general formula (**Int 9**) with the appropriate halide together with a suitable base, as described in Scheme 4. Compounds of general formula (**Int 11**) where R^{200} is H can be converted to intermediates (**Int 13**) where R^{200} is methyl by a further alkylation, typically involving a suitable alkylating agent such as methyl iodide and a suitable base such as potassium t-butoxide in an organic solvent such as THF.

e.g. as exemplified in Preps. 20, 21, 41, 53

Reduction of the ester intermediates (**Int 11**) and (**Int 13**) can be done by using a suitable reducing reagent such as lithium borohydride, lithium alumninium hydride or diisobutylalumnium hydride in a suitable solvent such as ethanol or THF. Alternatively intermediates of general formula (**Int 12**) can be made in a two step reaction by hydrolysing the ester of formula (**Int 11**) or (**Int 13**) to the appropriate acid using a suitable base such as aqueous lithium hydroxide in a suitable organic solvent such as THF then activating the acid using a suitable reagent such as isobutyl chloroformate and using a suitable reducing agent such as sodium borohydride.

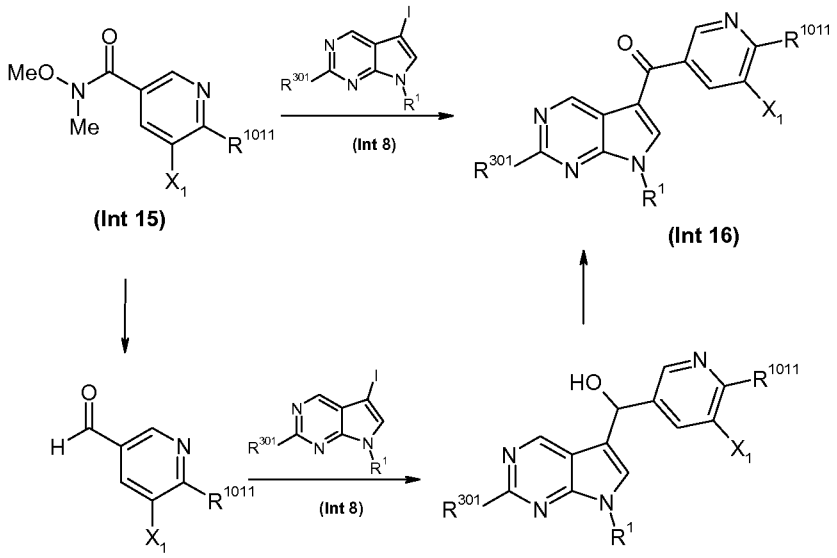
e.g. as exemplified in Preps. 22, 42, 43, 54

Compounds of general formula (**Int 14**) can be made by protection of the hydroxy group of intermediates (**Int 12**) with a suitable oxygen protecting group (PG), where the preferred protecting groups are TBDMS and THP,as described in Scheme 1.

e.g. as exemplified in Preps. 44, 45, 55.

Compounds of formula (**Int 16**) can be prepared from compounds of formula (**Int 8**) as illustrated in Scheme 6.

Scheme 6



Wherein R^{301} is H or halogen, typically chlorine; and X_1 is a suitable halogen, typically bromine or iodine;

Compounds of formula (**Int 16**) can be prepared from compounds of formula (**Int 8**) and (**Int 15**) through a metallation of intermediate (**Int 8**) (using a suitable organometallic reagent such as butyllithium or isopropylmagnesium chloride) and reacting with the Weinreb amide intermediate (**Int 15**) at a temperature from -78°C up to room temperature.

e.g. as exemplified in Preps. 26, 27, 46, 47, 56, 58, 64

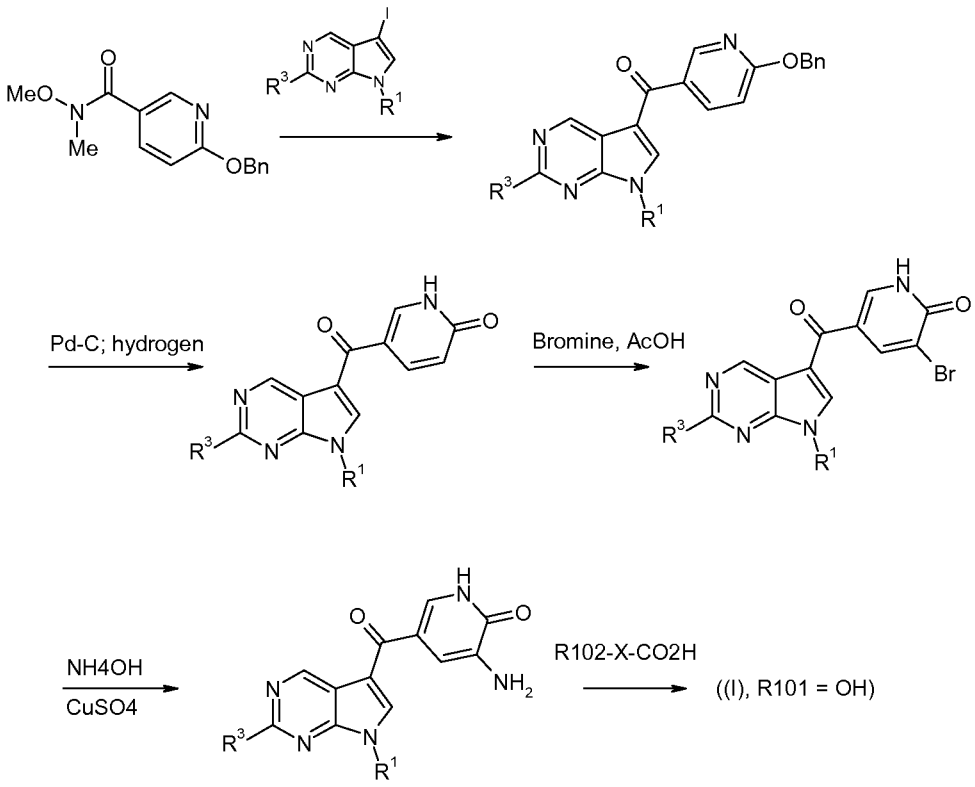
Alternatively compounds of formula (**Int 15**) may be converted into aldehydes of formula (**Int 17**) by reduction of the Weinreb amide intermediate using a suitable reducing agent. Preferred conditions comprise diisopropylaluminium hydride in THF at -78°C, exemplified in Preparation 106.

Compounds of formula (**Int 17**) may then be reacted with compounds of formula (**Int 8**) according to the same metallation procedure described above. The intermediate alcohol (**Int 18**) may then be oxidised to the ketone (**Int 16**). Typical oxidation conditions involve using an oxidising reagent such as the Dess-Martin reagent in DCM or 2-iodoxybenzoic acid in a suitable solvent such as ethyl acetate at a temperature from room temperature to reflux temperature.

e.g. as exemplified in Preps. 29, 30

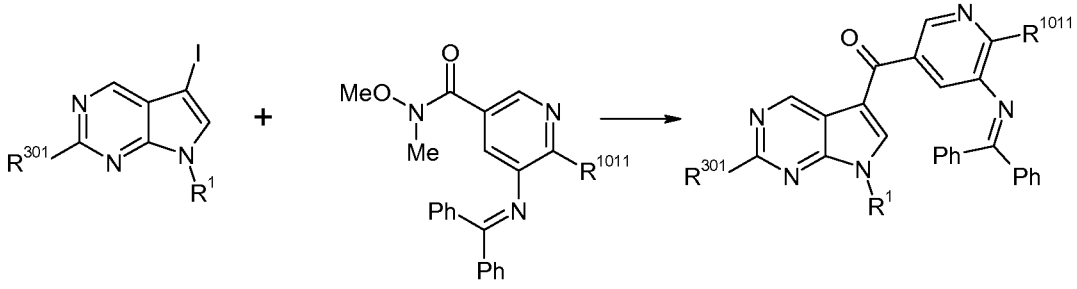
Intermediates of general formula (**Int 15**) and (**Int 17**) are either commercially available or will be well-known to those skilled in the art with reference to literature precedents and/or the preparations herein.

Corresponding intermediates and compounds of formula (I) where R^{101} is OH are considered as tautormers of pyridones and can be made using an analogous methodology using a benzyl protecting group for the Weinreb amide step, viz R^{1011} is benzyloxy (OBn), e.g. as illustrated below:



Compounds of formula (**Int 20**) can be prepared from compounds of formula (**Int 8**) as illustrated in Scheme 7.

Scheme 7



(Int 8) **(Int 19)** **(Int 20)**

Wherein R^{301} is H or halogen, typically chlorine;

Compounds of formula (**Int 20**) may be prepared from compounds of formulae (**Int 8**) and (**Int 19**) according to a metallation procedure as described in Scheme 6 above.

Typical conditions employed involve metallation of the intermediate halide (**Int 8**) (using a suitable organometallic reagent such as butyllithium or isopropylmagnesium chloride) and reacting with the

Weinreb amide intermediate (**Int 19**) at a temperature from -78°C up to room temperature in a suitable solvent such as THF.

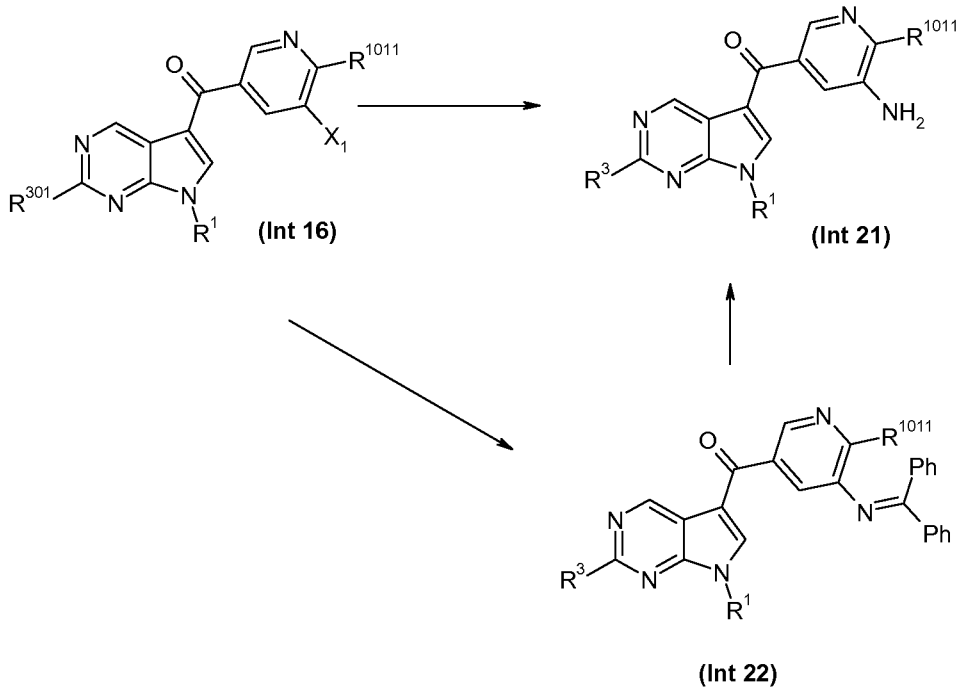
e.g. as exemplified in Preps. 24, 25, 28, 50

Intermediates (**Int 19**) will be well-known to those skilled in the art with reference to literature precedents and/or the preparations herein.

e.g. as exemplified in Prep. 23

Compounds of formula (**Int 21**) can be prepared from compounds of formula (**Int 16**) as illustrated in Scheme 8.

Scheme 8



Wherein X_1 is bromine or iodine;

Compounds of formula (**Int 21**) may be prepared from compounds of formula (**Int 16**) through direct amination of the halide using standard literature conditions. For example, amine (**Int 21**) is typically prepared using ammonia with a suitable copper catalyst such as copper (II) sulphate or copper (I) oxide in suitable solvent such as NMP in a sealed vessel at a temperature between room temperature and 140°C. Where R^{301} is Cl this is also displaced by ammonia under the same conditions to provide amines of general formula (**Int 21**) where R^3 is NH_2.

e.g. as exemplified in Preps. 31, 32, 36, 48, 49, 57, 59, 65

De-protection of a hydroxyl protecting group on R^1 (if present) can also occur under these conditions. In these cases, either the protecting group can be reapplied as previously described in Scheme 5 or the amine of general formula (**Int 21**) can be used directly.

Alternatively compounds of general formula (**Int 21**) where R3 is H, can be made by converting intermediates of general formula (**Int 16**) where R^{301} is H, via compounds (**Int 22**). Typical conditions

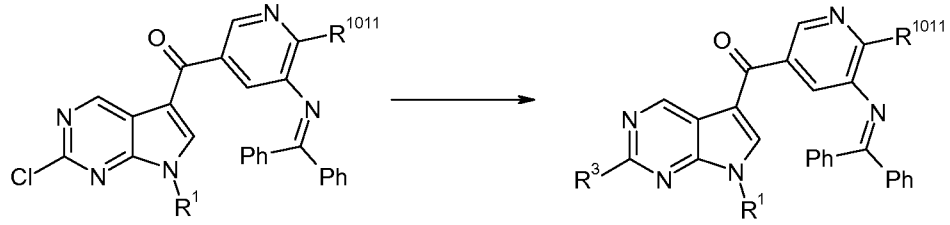
employed involve stirring the halide of general formula (**Int 16**), where R^{301} is H, with benzophenone imine, a suitable base such as potassium phosphate, a suitable ligand such as 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl and a suitable catalyst such as tris(dibenzylideneacetone)dipalladium in an organic solvent such as 1,2-dimethoxyethane at a temperature from room temperature up to the boiling point of the solvent.

Intermediate (**Int 22**) can be deprotected to furnish the amines of general formula (**Int 21**). Typical conditions employ treatment with an aqueous acid such as hydrogen chloride or citric acid in an organic solvent such as THF.

e.g. as exemplified in Preps. 33, 37-39

Compounds of formula (**Int 20**) can be prepared from compounds of formula (**Int 22 where R^{301} is Cl**) as illustrated in Scheme 9.

Scheme 9



(Int 22) Where R^{301} is Cl) **(Int 20)**

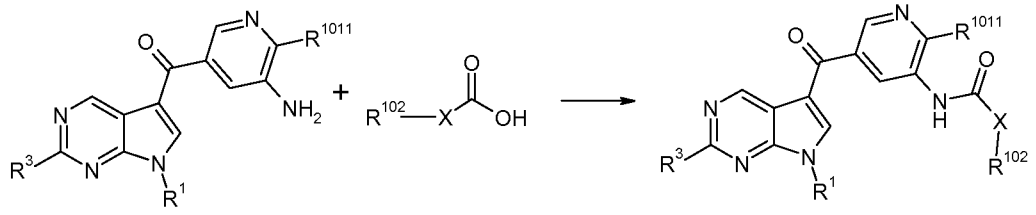
Compounds of formula (**Int 20**) may be prepared from compounds of formula (Int 22) where R^{301} is chloro through an amination reaction as decribed above. Wherein the chlorine is is reacted with 2,4-dimethoxybenzylamine and the amine can be deprotected as previously.

Typical conditions employed involve stirring the chloro-pyrimidine of general formula (**Int 22**), where R^{301} is Cl, with 2,4-dimethoxybenzylamine and a suitable additive such as 4-dimethylaminopyridine in a suitable solvent such as 1,4 dioxane at a temperature from room temperature up to reflux temperature.

e.g. as exemplified in Prep. 51

Compounds of formula (**I**) can be prepared from compounds of formula (**Int 21**) and (**Int 23**) as illustrated in Scheme 10.

Scheme 10



(Int 21) **(Int 23)** **(I)**

Compounds of formula (I) may be prepared from compounds of formula (**Int 21**) and (**Int 23**) via amide formation, if necessary adding a suitable base (such as DIPEA) and/or additive (such as DMAP), and a suitable solvent (such as pyridine).

Typical conditions employed involve stirring the amine of general formula (**Int 21**) and the acid of general formula (**Int 23**) together with a suitable coupling reagent such as HATU or 1-propylphosphonic acid cyclic anhydride, if necessary adding a suitable base such as NMM, DIPEA or TEA in a suitable solvent such as pyridine, THF, DMF or DMA at a temperature from room temperature up to 50°C. A suitable alternative is to use an additive (such as 4-dimethylaminopyridine) as well as a base. Any suitable solvent may be used in place of those mentioned above. At least one equivalent of the acid (**Int 23**) and at least one equivalent of the coupling reagent should be used and an excess of one or both may be used if desired.

e.g. as exemplified in Examples 1-8, 34-45,48-53, 57-64, Preps. 34, 35, 52, 66-78

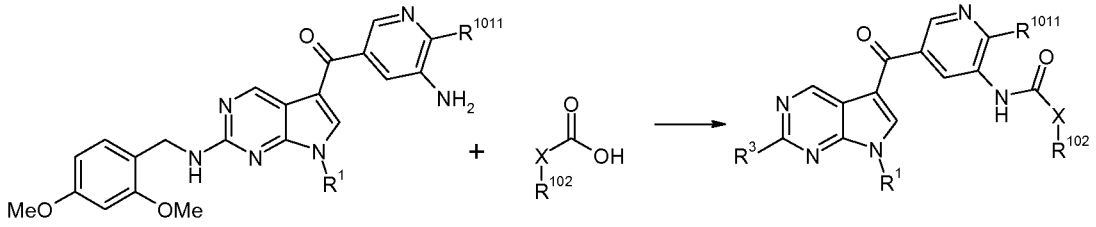
Where R^1 contains a suitable hydroxyl protecting group in intermediate (**Int 21**), removal of the protecting group (PG) can be done in situ or as an additional step, adding a suitable acid and organic solvent to the crude residue after the amide formation has taken place. Common protecting groups to use include TBDMS, which is readily removed by treatment with an acid such as aqueous hydrogen chloride or aqueous citric acid in an organic solvent such as THF or by treatment with a fluoride source such as tetrabutylammonium fluoride in an organic solvent such as THF, and THP, which is also readily removed by treatment with an acid such as aqueous hydrogen chloride in an organic solvent such as THF.

e.g. as exemplified in Examples 9-33, 54-56,

Intermediates of general formula (**Int 23**) are either commercially available or will be well-known to those skilled in the art with reference to literature precedents and/or the preparations herein.

Compounds of formula (**I**) where R^3 is NH_2 can be prepared from compounds of formula (**Int 20**) as illustrated in Scheme 11.

Scheme 11



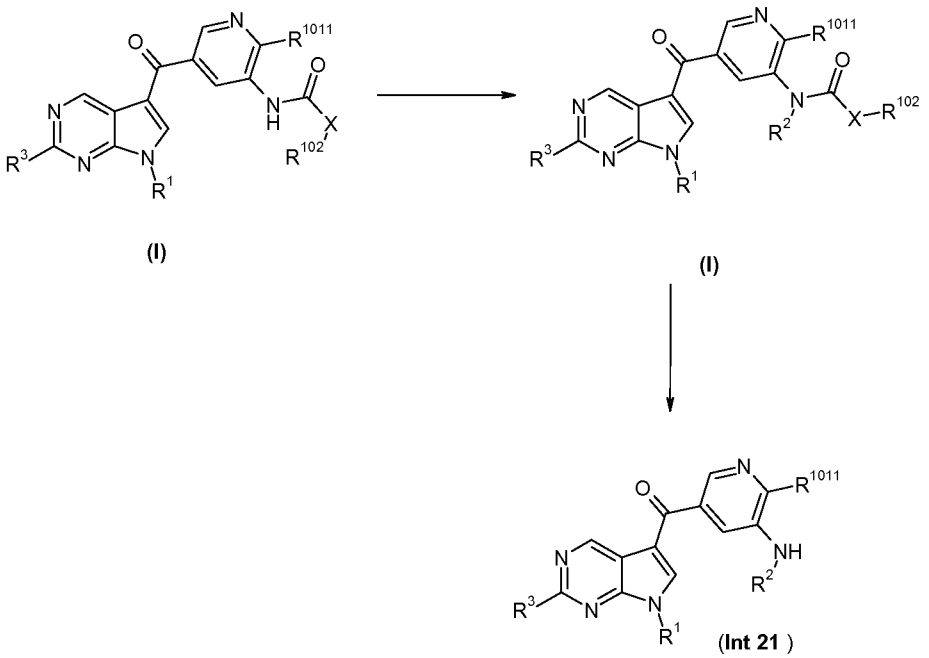
(Int 24) (Int 23) (I)

Compounds of formula (I) can be prepared from compounds of formula (**Int 24**) via amide bond formation as previously described in Scheme 10 followed by removal of the dimethoxbenzylamine group in situ, by adding a suitable acid and organic solvent to the crude residue after the amide formation has taken place. Suitable acids for this de-protection include hydrogen choride or trifluoroacetic acid in an organic solvent such as THF.

e.g. as exemplified in Examples 46-47

Compounds of formula (**I**) where R^2 is methyl can be prepared from compounds of formula (**I**) where R^2 is H as illustrated in Scheme 12.

Scheme 12

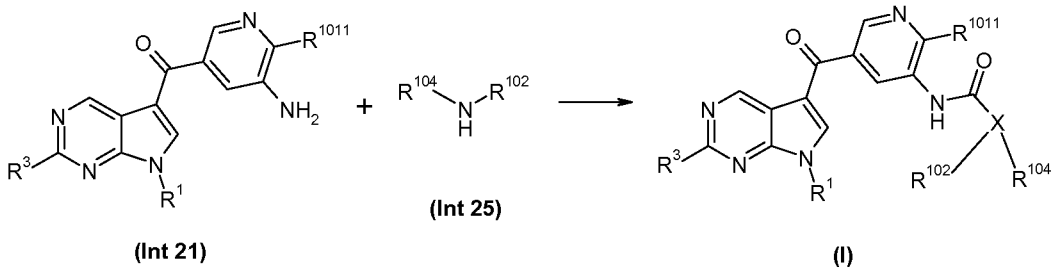


Compounds of formula (I) where R^2 is methyl can be prepared from compounds of formula (**I**) where R^2 is H according to an alkylation reaction with methyl iodide as described in Scheme 4.

When XR^{102} is boc, this can be deprotected using standard protecting group conditions to provide intermediate (**Int 21**).

Compounds of formula (**I**) where X is NR^{104} can be prepared from compounds of formula (**Int 21**) as illustrated in Scheme 13.

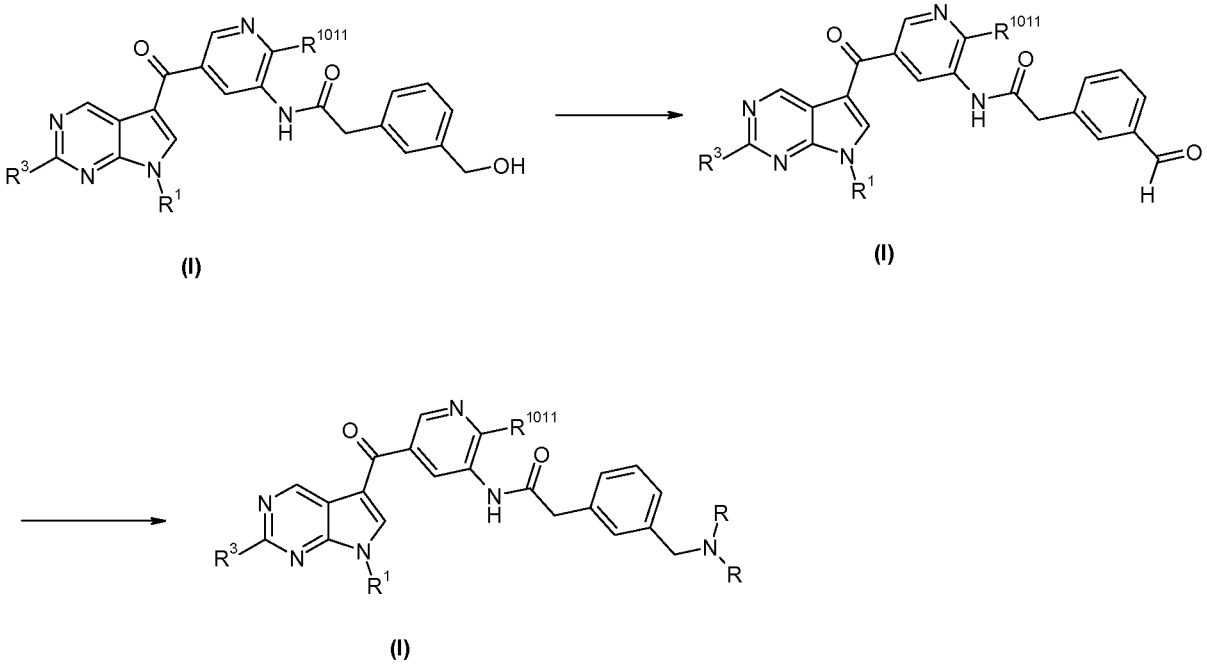
Scheme 13



Compounds of formula (I) where X is NR^{104} may be prepared from compounds of formula (**Int 21**), (**Int 25**) and phenylchloroformate. Typical conditions comprise phenyl chloroformate and compounds of formula (Int 24) with pyridine in THF from 0 to 100°C, as exemplified in **Example 526**.

Compounds of formula (**I**) where a substituent on the ring(s) of R^{102} is an aminomethyl CH_2NR_2 group may be prepared from compounds of formula (**1**) as illustrated in Scheme 14.

Scheme 14



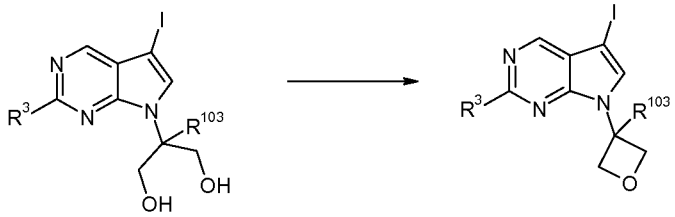
(I) **(I)**

(I)

Compounds of formula (I) where a primary alcohol exists may be oxidised to the aldehyde using Dess Martin periodinane in DCM at room temperature followed by a reductive amination with a suitable amine HNR_2 using sodium triacetoxyborohydride and acetic acid in DCM.

Compounds of formula (**Int 26**) can be prepared from compounds of formula (**Int 27**) as illustrated in Scheme 15.

Scheme 15



Int 27 **Int 26**

Wherein R^{103} is Me or CH_2OH;

Compounds of formula (**Int 26**) can be prepared from compounds of formula (**Int 27**) through conversion of an alcohol into a suitable leaving group followed by cyclisation under basic conditions. Preferred conditions comprise tosyl chloride with n-butyl lithium in THF.

According to a further embodiment the present invention provides novel intermediate compounds.

Pharmaceutically acceptable salts of a compound of formula (I) may be readily prepared by mixing together solutions of the compound of formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised.

The compounds of the invention intended for pharmaceutical use may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drug agent (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any biologically inactive ingredient other than the compounds and salts of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. For example, a compound of the formula I, or a pharmaceutically acceptable salt or solvate thereof, as defined above, may be administered simultaneously (e.g. as a fixed dose combination), sequentially or separately in combination with one or more other drug agent.

Exemplary additional agents could be selected from one or more of:

- a Nav1.7 channel modulator, such as a compound disclosed in WO 2009/012242 or WO2010/079443;
- an alternative sodium channel modulator, such as a Nav1.3 modulator (e.g. as disclosed in WO2008/118758); or a Nav1.8 modulator (e.g. as disclosed in WO 2008/135826, more particularly N-[6-Amino-5-(2-chloro-5-methoxyphenyl)pyridin-2-yl]-1-methyl-1H-pyrazole-5-carboxamide);
- an inhibitor of nerve growth factor signaling, such as: an agent that binds to NGF and inhibits NGF biological activity and/or downstream pathway(s) mediated by NGF signaling (e.g. tanezumab), a TrkA antagonist or a p75 antagoinsist;
- a compound which increases the levels of endocannabinoid, such as a compound with fatty acid amid hydrolase inhibitory (FAAH) activity, in particular those disclosed in WO 2008/047229 (e.g. N-pyridazin-3-yl-4-(3-{[5-(trifluoromethyl)pyridine-2-yl]oxy}benzylidene)piperidene-1-carboxamide);
- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;
- a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal or thiopental;

- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H_1 antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphrenadine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®, a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (–)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone;
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- an anticonvulsant, e.g. carbamazepine, lamotrigine, topiratmate or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);
- a muscarinic antagonist, e.g oxybutynin, tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine and ipratropium;
- a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;
- a coal-tar analgesic, in particular paracetamol;
- a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonepiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;
- a vanilloid receptor agonist (e.g. resinferatoxin) or antagonist (e.g. capsazepine);
- a beta-adrenergic such as propranolol;
- a local anaesthetic such as mexiletine;
- a corticosteroid such as dexamethasone;

- a 5-HT receptor agonist or antagonist, particularly a 5-$HT_{1B/1D}$ agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
- a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);
- a 5-HT_3 antagonist, such as ondansetron
- a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) or nicotine;
- Tramadol®;
- a PDEV inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;
- an alpha-2-delta ligand such as gabapentin, pregabalin, 3-methylgabapentin, (1α,3α,5α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;
- metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;
- a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;
- a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, buproprion, buproprion metabolite hydroxybuproprion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;

- a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
- an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[(1R,3S)-3-amino-4- hydroxy-1-(5-thiazolyl)-butyl]thio]-5-chloro-3-pyridinecarbonitrile; 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3 pyridinecarbonitrile, 2-[[(1R,3S)-3- amino-4-hydroxy- 1 -(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, or guanidinoethyldisulfide;
- an acetylcholinesterase inhibitor such as donepezil;
- a prostaglandin E_2 subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(1*S*)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;
- a microsomal prostaglandin E synthase type 1 (mPGES-1) inhibitor;
- a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870,

a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl),1,4-benzoquinone (CV-6504).

Pharmaceutical compositions suitable for the delivery of compounds and salts of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

Compounds and salts of the invention intended for pharmaceutical use may be prepared and administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

Oral Administration

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations, such as tablets, capsules containing particulates, liquids, or powders; lozenges (including liquid-filled), chews; multi- and nano-particulates; gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight% to 80 weight% of the dosage form, more typically from 5 weight% to 60 weight% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight% to 25 weight%, preferably from 5 weight% to 20 weight% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight% of the tablet, and glidants may comprise from 0.2 weight% to 1 weight% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight% to 10 weight%, preferably from 0.5 weight% to 3 weight% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavoring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight% to about 90 weight% binder, from about 0 weight% to about 85 weight% diluent, from about 2 weight% to about 10 weight% disintegrant, and from about 0.25 weight% to about 10 weight% lubricant. [Make sure these specific ranges are relevant]

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

The foregoing formulations for the various types of administration discussed above may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

Parenteral Administration

The compounds and salts of the invention may be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) and salts used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Thus, compounds and salts of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. An example of such formulations include drug-coated stents.

Topical Administration

The compounds and salts of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated [see, for example, Finnin and Morgan, J Pharm Sci, 88 (10), 955-958 (October 1999).] Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

Inhaled/Intranasal Administration

The compounds and salts of the invention may also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

A pressurised container, pump, spray, atomizer, or nebuliser may contain a solution or suspension of the compound(s) or salt(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound or salt of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound or salt of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I) or salt thereof, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by a prefilled capsule, blister or pocket or by a system that utilises a gravimetrically fed dosing chamber . Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1 to 5000 µg of the compound or salt. The overall daily dose will typically be in the range 1 µg to 20 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

Rectal/Intravaginal Administration

The compounds and salts of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various well known alternatives may be used as appropriate.

Ocular and Aural Administration

The compounds and salts of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid; a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose; or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Other Technologies

The compounds and salts of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

For administration to human patients, the total daily dose of the compounds and salts of the invention is typically in the range 0.1 mg to 200 mg depending, of course, on the mode of administration, preferred in the range 1 mg to 100 mg and more preferred in the range 1 mg to 50 mg. The total daily dose may be administered in single or divided doses.

These dosages are based on an average human subject having a weight of about 65kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

For the above-mentioned therapeutic uses, the dosage administered will, of course, vary with the compound or salt employed, the mode of administration, the treatment desired and the disorder indicated. The total daily dosage of the compound of formula (I)/salt/solvate (active ingredient) will, generally, be in the range from 1 mg to 1 gram, preferably 1 mg to 250 mg, more preferably 10 mg to 100 mg. The total

daily dose may be administered in single or divided doses. The present invention also encompasses sustained release compositions.

The pharmaceutical composition may, for example, be in a form suitable for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefor, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Dosage regimens may be adjusted to provide the optimum desired response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form, as used herein, refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the chemotherapeutic agent and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

Thus, the skilled artisan would appreciate, based upon the disclosure provided herein, that the dose and dosing regimen is adjusted in accordance with methods well-known in the therapeutic arts. That is, the maximum tolerable dose can be readily established, and the effective amount providing a detectable therapeutic benefit to a patient may also be determined, as can the temporal requirements for administering each agent to provide a detectable therapeutic benefit to the patient. Accordingly, while certain dose and administration regimens are exemplified herein, these examples in no way limit the dose and administration regimen that may be provided to a patient in practicing the present invention.

It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated, and may include single or multiple doses. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. For example, doses may be adjusted based on pharmacokinetic or pharmacodynamic parameters, which may include clinical effects such as toxic effects and/or laboratory values. Thus, the present invention encompasses intra-patient dose-escalation as determined by the skilled artisan. Determining appropriate dosages and regiments for administration of the chemotherapeutic agent are well-known in the relevant art and would be understood to be encompassed by the skilled artisan once provided the teachings disclosed herein.

A pharmaceutical composition of the invention may be prepared, packaged, or sold in bulk, as a single unit dose, or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

For parenteral dosages, this may conveniently be prepared as a solution or as a dry powder requiring dissolution by a pharmacist, medical practitioner or the patient. It may be provided in a bottle or sterile syringe. For example it may be provided as a powder in a multicompartment syringe which allows the dry powder and solvent to be mixed just prior to administration (to aid long-term stability and storage). Syringes could be used which allow multiple doses to be administered from a single device.

The relative amounts of the active ingredient, the pharmaceutically acceptable carrier, and any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

In addition to the active ingredient, a pharmaceutical composition of the invention may further comprise one or more additional pharmaceutically active agents.
Controlled- or sustained-release formulations of a pharmaceutical composition of the invention may be made using conventional technology.

As used herein, "parenteral administration" of a pharmaceutical composition includes any route of administration characterized by physical breaching of a tissue of a subject and administration of the pharmaceutical composition through the breach in the tissue. Parenteral administration thus includes, but is not limited to, administration of a pharmaceutical composition by injection of the composition, by application of the composition through a surgical incision, by application of the composition through a tissue-penetrating non-surgical wound, and the like. In particular, parenteral administration is contemplated to include, but is not limited to, subcutaneous, intraperitoneal, intramuscular, intrasternal injection, and kidney dialytic infusion techniques.

Formulations of a pharmaceutical composition suitable for parenteral administration comprise the active ingredient combined with a pharmaceutically acceptable carrier, such as sterile water or sterile isotonic saline. Such formulations may be prepared, packaged, or sold in a form suitable for bolus administration or for continuous administration. Injectable formulations may be prepared, packaged, or sold in unit dosage form, such as in ampules or in multi-dose containers containing a preservative. Formulations for parenteral administration include, but are not limited to, suspensions, solutions, emulsions in oily or aqueous vehicles, pastes, and implantable sustained-release or biodegradable formulations as discussed below. Such formulations may further comprise one or more additional ingredients including, but not limited to, suspending, stabilizing, or dispersing agents. In one embodiment of a formulation for parenteral administration, the active ingredient is provided in dry (i.e. powder or granular) form for reconstitution with a suitable vehicle (e.g. sterile pyrogen-free water) prior to parenteral administration of the reconstituted composition.

A composition of the present invention can be administered by a variety of methods known in the art. The route and/or mode of administration vary depending upon the desired results. The active compounds can be prepared with carriers that protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are described by e.g., Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, (1978). Pharmaceutical compositions are preferably manufactured under GMP conditions.

The pharmaceutical compositions may be prepared, packaged, or sold in the form of a sterile injectable aqueous or oily suspension or solution. This suspension or solution may be formulated according to the known art, and may comprise, in addition to the active ingredient, additional ingredients such as the

dispersing agents, wetting agents, or suspending agents described herein. Such sterile injectable formulations may be prepared using a non-toxic parenterally-acceptable diluent or solvent, such as water or 1,3-butane diol, for example. Other acceptable diluents and solvents include, but are not limited to, Ringer's solution, isotonic sodium chloride solution, and fixed oils such as synthetic mono- or di-glycerides. Other parentally-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form, in a liposomal preparation, or as a component of a biodegradable polymer system. Compositions for sustained release or implantation may comprise pharmaceutically acceptable polymeric or hydrophobic materials such as an emulsion, an ion exchange resin, a sparingly soluble polymer, or a sparingly soluble salt.

The precise dosage administered of each active ingredient will vary depending upon any number of factors, including but not limited to, the type of animal and type of disease state being treated, the age of the animal, and the route(s) of administration.

The following non-limiting Preparations and Examples illustrate the preparation of compounds and salts of the present invention.

GENERAL EXPERIMENTAL

The Preparations and Examples that follow illustrate the invention but do not limit the invention in any way. All starting materials are available commercially or described in the literature. All temperatures are in ^{0}C. Flash column chromatography was carried out using Merck silica gel 60 (9385). Thin layer chromatography (TLC) was carried out on Merck silica gel 60 plates (5729). "R_f" represents the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate. Melting points were determined using a Gallenkamp MPD350 apparatus and are uncorrected. NMR was carried out using a Varian-Unity Inova 400MHz NMR spectrometer or a Varian Mercury 400MHz NMR spectrometer. Mass spectroscopy was carried out using a Finnigan Navigator single quadrupole electrospray mass spectrometer or a Finnigan aQa APCI mass spectrometer.

Where it is stated that compounds were prepared in the manner described for an earlier Preparation or Example, the skilled person will appreciate that reaction times, number of equivalents of reagents and reaction temperatures may be modified for each specific reaction, and that it may nevertheless be necessary or desirable to employ different work-up or purification conditions.

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

The Preparations and Examples that follow illustrate the invention but do not limit the invention in any way. All starting materials are available commercially or described in the literature. All temperature are in °C. Flash column chromatography was carried out using Merck silica gel 60 (9385) or Redisep silica. NMR was carried out using a Varian Mercury 400MHz NMR spectrometer or a Jeol ECX 400MHz NMR.

The mass spectra were obtained using:
Waters ZQ ESCI
Applied Biosystem's API-2000 5 min LC-MS
Waters Alliance 2795 with ZQ2000 (ESI)
Aglient 110 HPLC 5 min (System 5)
Waters ZQ ESCI 8min LC-MS
Waters Alliance 2695 with ZQ2000 (ESI) 25 min
HP 1100 HPLC with Waters Micromass ZQ mass detector 12.5 min LC-MS
UPLC mass spectra were obtained using a Waters Acquity ZQD (ESI) 1.5 min LC-MS
WATERS ACQUITY UPLC/WATERS 3100 MSD/PL-ELS 2100 ICE ELSD

Where singleton compounds have been analysed by LCMS, there are six methods used. These are illustrated below.

System 1

6 minute LC-MS gradient and instrument conditions
A: 0.1 % formic acid in water
B: 0.1 % formic acid in acetonitrile
Column: C18 phase Waters Sunfire 50 x 4.6 mm with 5 micron particle size
Gradient: 95-5% A over 3 min, 1 min hold, 2 min re-equilibration, 1.5mL/min flow rate
UV: 210nm - 450nm DAD
Temperature: 50°C

System 2

2 minute LC-MS gradient and instrument conditions
A: 0.1 % formic acid in water
B: 0.1 % formic acid in acetonitrile
Column: C18 phase Phenomenex 20 x 4.0 mm with 3 micron particle size
Gradient: 70-2% A over 1.5min, 0.3 min hold, 0.2 re-equilbration, 1.8mL/min flow rate
UV: 210nm - 450nm DAD
Temperature: 75°C

System 3

5 minute LC-MS gradient and instrument conditions
A: 0.1 % formic acid in water
B: 0.1 % formic acid in acetonitrile
Column: C18 phase Waters Sunfire 50 x 4.6 mm with 5 micron particle size
Gradient: 95-5% A over 3 min, 1 min hold, 1 min re-equilibration, 1.5mL/min flow rate
UV: 225nm – ELSD - MS
Temperature: ambient

System 4

5 minute LC-MS gradient and instrument conditions
A: 0.1 % ammonium hydroxide in water

B: 0.1 % ammonium hydroxide in acetonitrile

Column: C18 phase XTerra 50 x 4.6 mm with 5 micron particle size

Gradient: 95-5% A over 3 min, 1 min hold, 1 min re-equilibration, 1.5mL/min flow rate

UV: 225nm – ELSD - MS

Temperature: ambient

System 5

5 minute LC-MS gradient and instrument conditions

A: 0.0375 % TFA in water

B: 0.01875 % TFA in acetonitrile

Column: C18 phase Welch XB 50 x 2.1 mm with 5 micron particle size

Gradient: 99-0% A over 4 min, 0.70 min re-equilibration, 0.8 mL/min flow rate

UV: 225nm – ELSD - MS

Temperature: 50°C

System 6

5 minute LC-MS gradient and instrument conditions

A: 0.0375 % TFA in water

B: 0.01875 % TFA in acetonitrile

Column: C18 phase Welch XB 50 x 2.1 mm with 5 micron particle size

Gradient: 90-0% A over 4 min, 0.70 min re-equilibration, 0.8 mL/min flow rate

UV: 225nm – ELSD - MS

Temperature: 50°C

System 7

25 minute LC-MS gradient and instrument conditions

A: 10 mmol ammonium bicarbonate in water

B: acetonitrile

Column: C18 phase XBridge 150 x 3.0 mm with 5 micron particle size

Gradient: 95-5% A over 15 min, 10 min hold, 2 min re-equilibration, 0.5mL/min flow rate

UV: 200nm - 350nm DAD

Temperature: 30°C

System 8

3 minute LC-MS gradient and instrument conditions

A: 0.05% formic acid in water

B: acetonitrile

Column: C18 phase Restek 30 x 2.1 mm with 3 micron particle size

Gradient: 98-2% A over 2 min, 0.25 min hold, 0.75 min re-equilibration, 1.5mL/min flow rate

UV: 200nm - 350nm DAD

Temperature: 50°C

System 9

5 minute LC-MS gradient and instrument conditions

A: 0.05% formic acid in water

B: acetonitrile
Column: C18 phase XBridge 50 x 4.6 mm with 5 micron particle size
Gradient: 90-10% A over 3 min, 1 min hold, 1min re-equilibration, 1.2mL/min flow rate
UV: 200nm - 260nm DAD
Temperature: 25°C

System 10

5 minute LC-MS gradient and instrument conditions
A: 10 mM ammonium acetate in water
B: acetonitrile
Column: C18 phase Gemini NX 50 x 4.6 mm with 5 micron particle size
Gradient: 90-10% A over 3 min, 1 min hold, 1min re-equilibration, 1.2mL/min flow rate
UV: 200nm - 260nm DAD
Temperature: 25°C

Where singleton compounds have been purified by High Performance Liquid Chromatography, unless otherwise stated, one of four methods were used, and these are shown below.
Waters Purification Systems with mass spec or UV detection

Prep system 1

10 minute prep LC-MS gradient and instrument conditions
A: 0.1% formic acid in water
B: 0.1% formic acid in acetonitrile
Column: C18 phase Sunfire 100 x 19.0 mm
Gradient: 95-2% A over 7 min, 2 min hold, 1 min re-equilibration, 18 mL/min flow rate
Temperature: ambient

Prep system 2

10 minute prep LC-MS gradient and instrument conditions
A: 0.1% DEA in water
B: 0.1% DEA in acetonitrile
Column: C18 phase Xterra 100 x 19.0 mm
Gradient: 95-2% A over 7 min, 2 min hold, 1 min re-equilibration, 18 mL/min flow rate
Temperature: ambient

Prep system 3

7 minute prep LC-MS gradient and instrument conditions
A: 0.05% ammonia in water
B: acetonitrile
Column: C18 phase Xbridge 50 x 19.0 mm
Gradient: 90-20% A over 7 min, 20 mL/min flow rate
Temperature: ambient

Prep system 4

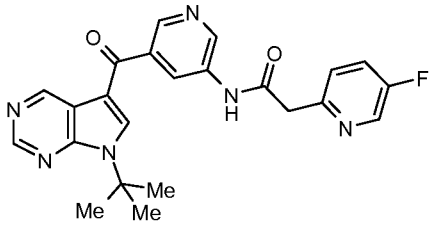
8 minute prep LC-MS gradient and instrument conditions

A: 0.1% TFA in water
B: acetonitrile
Column: C18 phase Sepax BR 100 x 21.2 mm
Gradient: 96-33% A over 8 min, 30 mL/min flow rate
Temperature: ambient

Where it is stated that compounds were prepared in the manner described for an earlier Preparation or Example, the skilled person will appreciate that reaction times, number of equivalents of reagents and reaction temperatures may have been modified for each specific reaction, and that it may nevertheless be necessary, or desirable, to employ different work-up or purification conditions. The invention is illustrated by the following non-limiting Examples in which the following abbreviations and definitions are used: AcOH – acetic acid; APCI - atmospheric pressure chemical ionization; Arbocel is a filter agent; br s – broad singlet; BINAP – 2,2'-bis(diphenylphosphino)-1,1'-binapthyl; nBuLi – n-Butyllithium; $CDCl_3$ – deuterated chloroform; Cs_2CO_3 is caesium carbonate; CuI is copper (I) iodide; $Cu(OAc)_2$ is copper (II) acetate; δ – chemical shift; d – doublet; DAD – diode array detector; DCE – 1,2-dichloroethane DCM – dichloromethane; DEA – diethylamine; DIBAL – Diisobutylaluminium hydride; DIPEA – diisopropylethylamine; DMAP – 4-dimethylaminopyridine; DME – dimethoxyethane; DMF – N,N-dimethylformamide; DMF-DMA - N,N-dimethylformamide-dimethylacetal; DMSO – dimethylsulphoxide DPPF – 1,1'-bis(diphenylphosphino)ferrocene; ELSD – evaporative light scattering detector; ESI - electrospray ionization; Et_2O – diethylether; EtOAc/EA – ethyl acetate; EtOH – ethanol; g – gram; HATU - 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HBTU is O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate; HCl is hydrochloric acid;HOBT is N-hydroxybenzotriazole hydrate; HPLC – high pressure liquid chromatography; IPA – isopropyl alcohol; K_2CO_3 is potassium carbonate; $KHSO_4$ is potassium hydrogen sulphate; KOAc is potassium acetate; KOH is potassium hydroxide; K_3PO_4 is potassium phosphate tribasic; KF - potassium fluoride; L is litre; LCMS – liquid chromatography mass spectrometry; LiHMDS – Lithium hexamethyldisilazide; m – multiplet; mg – milligram; mL – millilitre; M/Z – Mass Spectrum Peak; MeCN – acetonitrile; MeOH – methanol; 2-MeTHF – 2-methyltetrahydrofuran; $MgSO_4$ is magnesium sulphate; MnO_2 – manganese dioxide; $NaClO_2$ – sodium chlorite; NaH - sodium hydride; $NaHCO_3$ - sodium hydrogencarbonate; Na_2CO_3 - sodium carbonate; NaH_2PO_4- sodium phosphate; $NaHSO_3$ - sodium bisulphite; $NaHSO_4$ - sodium hydrogensulphate; NaOH - sodium hydroxide; Na_2SO_4 - sodium sulphate; NH_3 – ammonia; NH_4Cl – ammonium chloride; NMM – N-MethylMorpholine; NMR – nuclear magnetic resonance; Pd/C – palladium on carbon; $PdCl_2$ – palladium dichloride; $Pd_2(dba)_3$ is tris(dibenzylideneacetone)dipalladium(0); $Pd(PPh_3)_4$ - palladium tetrakis(triphenylphosphine); $Pd(OAc)_2$ – palladium acetate; PTSA – para-toluenesulfonic acid; Prep – preparation; R_t – retention time; q – quartet; s – singlet; TBDMS – tertbutyldimethylsilyl; TBME – tertbutyldimethylether; TCP – 1-propylphosphonic acid cyclic anhydride; TEA – triethylamine; TFA – trifluoroacetic acid; THF – tetrahydrofuran; TLC – thin layer chromatography; (R, S) – racemic mixture; WSCDI - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

For the avoidance of doubt, named compounds used herein have been named using IUAPC, Chemdraw and/or Name Pro ACD Labs Name Software v7.11™ or using other standard nomenclature. NMR spectra were measured in deuterated solvents and were consistent with the names/structures given below.

Example 1: N-{5-[(7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-fluoropyridin-2-yl)acetamide



2-(5-Fluoropyridin-2-yl)acetic acid (23.1 mg, 0.149 mmol) (see **Preparation 92**) was added to (5-aminopyridin-3-yl)(7-*tert*-butyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanone (40 mg, 0.135 mmol) (see **Preparation 31**), 1-propylphosphonic acid cyclic anhydride (0.2 mL, 0.338 mmol, 50% in EtOAc) and triethylamine (0.65 mL, 0.474 mmol) in THF (3 mL). The mixture was stirred at 25°C for 18 hours, evaporated *in vacuo* and partitioned between saturated aqueous sodium bicarbonate (5 mL) and ethyl acetate (5 mL). The organic phase was dried over sodium sulfate, evaporated *in vacuo* and the residue was triturated with pentane:diethyl ether (3:1, 1 mL) to afford the title compound as an off white solid in 65% yield, 38 mg.

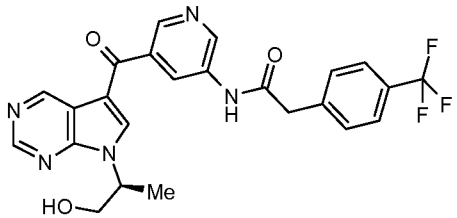
^{1}H NMR (400 MHz, DMSO) δ*:* 1.79 (s, 9H), 3.95 (s, 2H), 7.50 (m, 1H), 7.72 (m, 1H), 8.21 (s, 1H), 8.50 (d, 1H), 8.76 (d, 1H), 8.95 (d, 1H), 9.00 (s, 1H), 9.48 (s, 1H), 10.72 (s, 1H); LCMS (System 4): R_t = 2.86 min; m/z 433 $[M+H]^+$.

Examples 2 to 8 were prepared according to the method described above for Example **1**, starting from (5-aminopyridin-3-yl)(7-*tert*-butyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanone (see **Preparation 31)** and the appropriate acids.

Example	Name	Data
2	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide	LCMS (system 4): R_t = 3.26 min; m/z 473 $[M+H]^+$
3	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(3-cyclopropyl-1H-pyrazol-1-yl)acetamide	LCMS (system 4): R_t = 3.04 min; m/z 444 $[M+H]^+$
4	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide	LCMS (system 4): R_t = 2.75 min; m/z 445 $[M+H]^+$
5	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 4): R_t = 3.04 min; m/z 472 $[M+H]^+$

6	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-chloropyridin-2-yl)acetamide	LCMS (system 4): R_t = 2.92 min; m/z 449 $[M+H]^+$
7	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-cyclopropyl-1H-pyrazol-1-yl)acetamide	LCMS (system 4): R_t = 2.96 min; m/z 443 $[M+H]^+$
8	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS(system 4) : R_t = 3.00 min; m/z 472 $[M+H]^+$

Example 9: N-[5-({7-[(1S)-2-Hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[4-(trifluoromethyl)phenyl]acetamide

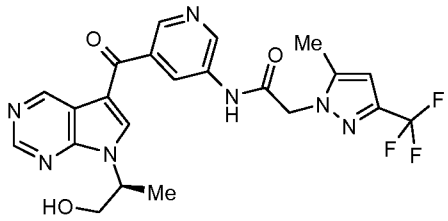


4-(Trifluoromethyl)phenylacetic acid (33.6 g, 165 mmol) was added to (5-aminopyridin-3-yl){7-[(1S)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (45.2 g, 110 mmol) (see **Preparation 37**), 1-propylphosphonic acid cyclic anhydride (194 mL, 329 mmol, 50% solution in EtOAc) and triethylamine (53.6 mL, 384 mmol) in THF (400 mL). The mixture was stirred at 25°C for 2 hours then saturated aqueous sodium bicarbonate (250 mL) was added and the organic layer was separated. The aqueous phase was extracted with EtOAc (2 x 200 mL) and all organic phases were combined and dried over sodium sulfate then evaporated *in vacuo*.

The residue brown solid was dissolved in THF (400 mL) and aqueous HCl (200 mL, 2M) was added. The mixture was stirred at room temperature for 2 hours then cooled to 0°C and sodium hydroxide (28 g) was added. The mixture was stirred for 3 hours then water (100 mL) was added. The organic layer was separated and the aqueous phase was extracted with EtOAc (2 x 300 mL) and all organic phases were combined and dried over sodium sulfate then evaporated *in vacuo*. The crude solid was recrystallised using ethyl acetate (150 mL) to afford the title compound as a white solid in 63% yield, 33.4 g.

^{1}H NMR (400 MHz, DMSO) δ*:* 1.51 (d, 3H), 3.68-3.79 (m, 1H), 3.81-3.93 (m, 3H), 4.93-5.06 (m, 2H), 7.55-7.63 (m, 2H), 7.67-7.75 (m, 2H), 8.41-8.49 (m, 2H), 8.73 (d, 1H), 8.98 (s, 1H), 9.00 (d, 1H), 9.44 (s, 1H), 10.72 (s, 1H); LCMS (System 1): Rt = 4.53 min; m/z 484 $[M+H]^+$.

Example 10: N-[5-({7-[(1S)-2-Hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide



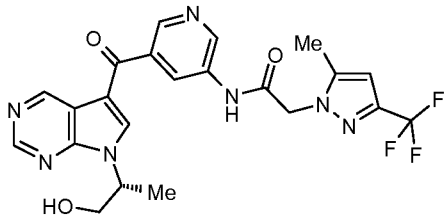
10% Hydrochloric acid in 1,4- dioxane (0.2 mL) was added to **Preparation 66** (59 mg, 0.098 mmol) in THF (2 mL) and the mixture was stirred at room temperature for 18 hours. The mixture was evaporated *in vacuo* and triturated with pentane:diethyl ether (3:1, 1 mL) to afford the title compound as an off white solid in 86% yield, 41 mg.

LCMS (system 4): Rt = 2.85 min; m/z 488.2 $[M+H]^+$.

Examples 11 to 16 were prepared according to the method described above for **Example 10**, starting from the appropriate protected alcohol.

Example	Name	Data
11	2-(4-chlorophenyl)-N-[5-({7-[(1S)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	LCMS (system 4): Rt = 2.89 min; m/z 450 $[M+H]^+$
12	N-[5-({7-[(1S)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 4): Rt = 2.88 min; m/z 474 $[M+H]^+$
13	N-[5-({7-[(1S)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide	LCMS (system 4): Rt = 2.68 min; m/z 475 $[M+H]^+$
14	2-(5-chloropyridin-2-yl)-N-[5-({7-[(1S)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	LCMS (system 4): Rt = 2.72 min; m/z 451 $[M+H]^+$
15	2-(2H-benzotriazol-2-yl)-N-[5-({7-[(1S)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	LCMS (system 4): Rt = 2.64 min; m/z 457 $[M+H]^+$
16	2-(2,4-difluorophenyl)-N-[5-({7-[(1S)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	LCMS (system 4) Rt = 2.74 min; m/z 452 $[M+H]^+$

Example 17: N-[5-({7-[(1R)-2-Hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide



(5-Methyl-3-trifluoromethyl-pyrazol-1-yl)acetic acid (46.8 mg, 0.225 mmol) was added to (R,S) (5-aminopyridin-3-yl){7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (66 mg, 0.173 mmol) (see **Preparation 36**), 1-propylphosphonic acid cyclic anhydride

(0.31 mL, 0.519 mmol) and DIPEA (0.09mL, 0.606 mmol) in THF (5 mL). The mixture was heated at reflux for 48 hours, evaporated *in vacuo* and partitioned between saturated aqueous sodium bicarbonate (5 mL) and ethyl acetate (5 mL). The organic phase was dried over sodium sulfate, evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (gradient of EtOAc: Hexane 85: 15) to afford the intermediate as an off white solid in 53% yield, 52 mg.

10% Hydrochloric acid in 1,4- dioxane (0.4 mL) was added to the intermediate (52 mg, 0.091 mmol) in THF (2 mL) and the mixture was stirred at room temperature for 1.5 hours. The mixture was evaporated *in vacuo* and triturated with pentane:diethyl ether (3:1, 1 mL) to afford the title compound as an off white solid in 94% yield, 42 mg.

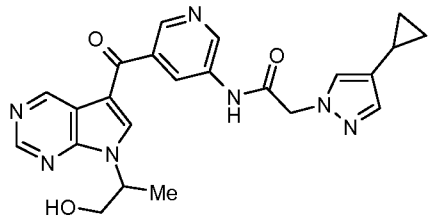
^{1}H NMR (400 MHz, DMSO) δ*:* 1.49 (d, 3H), 2.32 (d, 3H), 3.56 (m, 1H), 5.00 (m, 1H), 5.20 (s, 2H), 6.56 (s, 1H), 8.45 (s, 1H), 8.54 (s, 1H), 8.79 (s, 1H), 9.02 (s, 2H), 9.48 (s, 1H), 11.05 (s, 1H);

LCMS(system 4): R_t = 2.86 min; m/z 488 $[M+H]^+$.

Examples 18 to 24 were prepared according to the method described above for **Example 17**, starting from (5-aminopyridin-3-yl){7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (see **Preparation 36**).

Example	Name	Data
18	2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	LCMS (system 4): Rt = 2.21 min; m/z 474 $[M+H]^+$
19	2-(5-fluoropyridin-2-yl)-N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	LCMS (system 4): Rt = 2.24 min; m/z 435 $[M+H]^+$
20	N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[4-(trifluoromethyl)phenyl]acetamide	LCMS (system 4): Rt = 2.98 min; m/z 484 $[M+H]^+$
21	N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide	LCMS (system 4): Rt = 2.70 min; m/z 475 $[M+H]^+$
22	N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 4): Rt = 2.80 min; m/z 474 $[M+H]^+$
23	2-(5-chloropyridin-2-yl)-N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	LCMS (system 4): R_t = 2.49 min; m/z 451 $[M+H]^+$
24	2-(4-chlorophenyl)-N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	LCMS (System 2): R_t = 1.01 min; m/z 450 $[M+H]^+$

Example 25: (R,S) 2-(4-Cyclopropyl-1H-pyrazol-1-yl)-N-(5-{[7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide



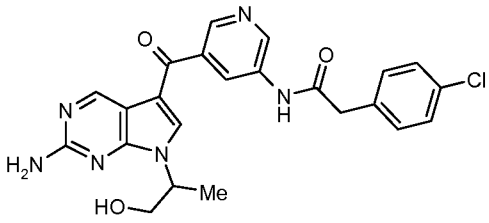
The title compound was prepared according to the method described for **Example 9** using (R,S) (5-aminopyridin-3-yl){7-[2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (see **Preparation 39**) and (4-cyclopropyl-1*H*-pyrazol-1-yl)acetic acid (see **Preparation 88**) to afford the title compound as a white solid in 14% yield, 20 mg.

^{1}H NMR (400 MHz, DMSO) δ*:* 0.46 (d, 2H), 0.79 (d, 2H), 1.49 (d, 3H), 1.70 (m, 1H), 3.73 (m, 1H), 3.87 (m, 1H), 5.00 (s, 4H), 7.26 (s, 1H), 7.54 (s, 1H), 8.40 (s, 1H), 8.47 (s, 1H), 8.75 (d, 1H), 8.98 (s, 1H), 9.00 (d, 1H), 9.44 (s, 1H), 10.75 (s, 1H); LCMS (system 4): R_t = 2.53 min; m/z 445 $[M+H]^+$.

Examples 26 to 33 were prepared according to the method described above for **Example 10**, starting from the appropriate protected alcohol TBDMS ether.

Example	Name	Data
26	N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 4): R_t = 2.89 min; m/z 502 $[M+H]^+$
27	N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide	LCMS (system 4): R_t = 3.03 min; m/z 498 $[M+H]^+$
28	2-(4-chlorophenyl)-N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide	^{1}H NMR (400 MHz, DMSO) δ*:* 1.73 (s, 6H), 3.75 (s, 2H), 3.96 (s, 2H), 7.39 (s, 4H), 8.22 (s, 1H), 8.51 (s, LCMS (system 4): R_t = 3.02 min; m/z 464.1 $[M+H]^+$
29	2-(5-chloropyridin-2-yl)-N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide	LCMS (system 4): R_t = 2.72 min; m/z 465 $[M+H]^+$
30	N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 4): R_t = 2.80 min; m/z 488 $[M+H]^+$
31	2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide	LCMS (system 4): R_t = 2.47 min; m/z 461 $[M+H]^+$
32	N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide	LCMS (system 4): R_t = 2.78 min; m/z 489 $[M+H]^+$
33	2-(4-cyclopropyl-1H-pyrazol-1-yl)-N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide	LCMS(system 4): R_t = 2.68 min; m/z 460 $[M+H]^+$

Example 34: N-(5-{[2-Amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-chlorophenyl)acetamide *(enantiomer 1)*



4-Chlorophenylacetic acid (25 mg, 0.14 mmol) was added to [2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl](5-aminopyridin-3-yl)methanone (50 mg, 0.16 mmol) (see **Preparation 57**) and HATU (91 mg, 0.24 mmol) in pyridine (2 mL). The mixture was stirred at room temperature for 16 hours. Saturated aqueous sodium bicarbonate (5 mL) was added then extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with brine (5 mL) then dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by preparative TLC (95:5 DCM:MeOH) to afford the title compound as a yellow solid in 48% yield, 32 mg.

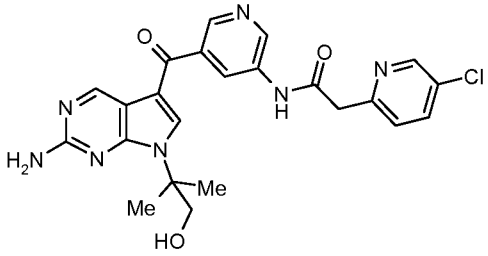
LCMS (system 5): Rt = 2.90 min; m/z 465 $[M+H]^+$.

Examples 35 to 45 were prepared according to the method described above for **Example 34**, starting from [2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl](5-aminopyridin-3-yl)methanone (see **Preparation 57, enantiomer 1 or Preparation 59, enantiomer 2**) and the appropriate acids.

Example	Name	Data
35	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(5-chloropyridin-2-yl)acetamide	Enantiomer 1 LCMS (system 5): Rt = 2.63 min; m/z 466 $[M+H]^+$
36	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide	Enantiomer 1 LCMS (system 5): Rt = 2.88 min; m/z 499 $[M+H]^+$
37	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(5-fluoropyridin-2-yl)acetamide	Enantiomer 1 LCMS (system 5): Rt = 2.25 min; m/z 450 $[M+H]^+$
38	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	Enantiomer 1 LCMS (system 4): Rt = 2.39 min; m/z 489 $[M+H]^+$
39	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide	Enantiomer 1 LCMS (system 5): Rt = 2.61 min; m/z 490 $[M+H]^+$
40	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(5-fluoropyridin-2-yl)acetamide	Enantiomer 2 LCMS (system 4): Rt = 1.89 min; m/z 450 $[M+H]^+$
41	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(5-chloropyridin-2-yl)acetamide	Enantiomer 2 LCMS (system 4): Rt = 2.16 min; m/z 466 $[M+H]^+$
42	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-chlorophenyl)acetamide	Enantiomer 2 LCMS (system 4): Rt = 2.63 min; m/z 465 $[M+H]^+$

43	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide	Enantiomer 2 LCMS (system 4): Rt = 2.73 min; m/z 499 $[M+H]^+$
44	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	Enantiomer 2 LCMS (system 4): Rt = 2.38 min; m/z 489 $[M+H]^+$
45	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide	Enantiomer 2 LCMS (system 5): Rt = 2.60 min; m/z 490 $[M+H]^+$

Example 46: N-(5-{[2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(5-chloropyridin-2-yl)acetamide



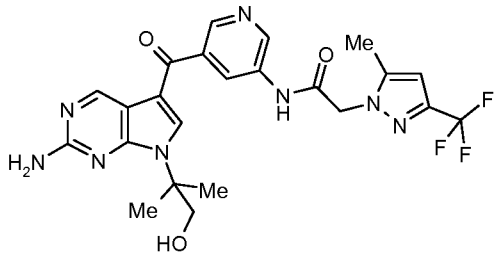
(5-Chloropyridin-2-yl)acetic acid (26.1 g, 152 mmol) (see **Preparation 90**) was added to (5-aminopyridin-3-yl){7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-[(2,4-dimethoxybenzyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (75.0 g, 130 mmol) (see **Preparation 51**), 1-propylphosphonic acid cyclic anhydride (187 mL, 317 mmol, 50% solution in EtOAc) and triethylamine (61.9 mL, 444 mmol) in THF (423 mL). The mixture was stirred at 25°C for 2 hours then saturated aqueous sodium bicarbonate (400 mL) was added and the organic layer was separated. The aqueous phase was extracted with EtOAc (400 mL) and all organic phases were combined and dried over sodium sulfate then evaporated *in vacuo*.

The residue brown solid was dissolved in trifluoroacetic acid (300 mL) and the solution was stirred at 50°C for 3 hours then evaporated *in vacuo*. Methanol (1800 mL) was added to the residue and the mixture was filtered. The filtrate was evaporated *in vacuo* and azeotroped with ethanol (3 x 200 mL).

Potassium carbonate (87.7 g, mmol) was added to the crude trifluoroacetamide in methanol (300 mL) and the mixture was stirred at room temperature for 16 hours. The mixture was poured into water (2000 mL) and filtered. The solid was washed with water (200 mL) then triturated with ethanol (2 x 200 mL at room temperature then 380 mL at 50°C) to afford the title compound as a yellow solid in 48% yield, 29.9 g.

^{1}H NMR (400 MHz, DMSO-*d6*) δ: 1.64 (s, 6H), 3.90 (d, 2H), 3.95 (s, 2H), 5.05 (t, 1H), 6.54 (br s, 2H), 7.49 (d, 1H), 7.69 (s, 1H), 7.92 (dd, 1H), 8.40 (m, 1H), 8.56 (m, 1H), 8.64 (d, 1H), 8.94 (d, 1H), 8.96 (s, 1H), 10.71 (s, 1H); LCMS (System 3): R_t = 9.92 min; m/z 480 $[M+H]^+$.

Example 47: N-(5-{[2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide

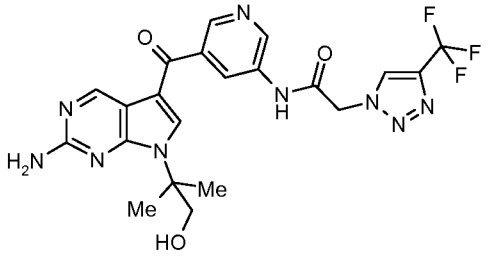


The title compound was prepared according to the method described for **Example 46** using (5-aminopyridin-3-yl){7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-[(2,4-dimethoxybenzyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (see **Preparation 51**) and (5-methyl-3-trifluoromethyl-pyrazol-1-yl)acetic acid (46.8 mg, 0.225 mmol) to afford the title compound as a brown solid in 79% yield, 82 mg. LCMS (System 1): R_t = 2.83 min; m/z 517 $[M+H]^+$.

Examples 48 to 53 were prepared according to the method described above for **Example 34**, starting from [2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl](5-aminopyridin-3-yl)methanone (see **Preparation 48**) and the appropriate acids.

Example	Name	Data
48	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide	LCMS (system 5): R_t = 3.12 min; m/z 513 $[M+H]^+$
49	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-chlorophenyl)acetamide	LCMS (system 5): R_t = 2.89 min; m/z 479 $[M+H]^+$
50	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(2,4-difluorophenyl)acetamide	MS (ESCI): m/z 481 $[M+H]^+$
51	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(5-fluoropyridin-2-yl)acetamide	LCMS (system 5): R_t = 2.42 min; m/z 464 $[M+H]^+$
52	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 4): R_t = 2.54 min; m/z 503 $[M+H]^+$
53	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(3-cyclopropyl-1H-pyrazol-1-yl)acetamide	LCMS (system 4) R_t = 2.23 min; m/z 475 $[M+H]^+$

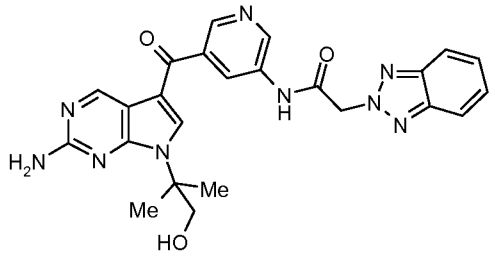
Example 54: N-(5-{[2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide



The title compound was prepared according to the method described for **Example 9** using [7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-amino-7H-pyrrolo[2,3-d]pyrimidin-5-yl]{5-aminopyridin-3-yl}methanone (see **Preparation 48a**) and [4-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]acetic acid (see **Preparation 81**) to afford the title compound as a brown solid in 85% yield, 62 mg.

^{1}H NMR (400 MHz, DMSO-*d6*) δ: 1.63 (s, 6H), 3.89 (d, 2H), 5.01 (br, 1H), 5.56 (s, 2H), 6.67 (br s, 2H), 7.72 (s, 1H), 8.36 (s, 1H), 8.70 (s, 1H), 8.94-8.96 (m, 3H), 11.05 (s, 1H); LCMS (system 5): R_t = 2.71 min; m/z 502 $[M-H]^+$.

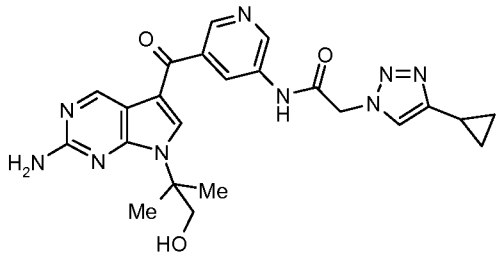
Example 55: N-(5-{[2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(2H-benzotriazol-2-yl)acetamide



The title compound was prepared according to the method described for **Example 9** using {2-amino-7-[1,1-dimethyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}(5-aminopyridin-3-yl)methanone (see **Preparation 49**) to afford the title compound as a brown solid in 46% yield, 20 mg.

^{1}H NMR (400 MHz, DMSO-*d6*) δ: 1.63 (s, 6H), 3.88 (d, 2H), 5.04 (t, 1H), 5.80 (s, 2H), 6.54 (s, 2H), 7.46-7.49 (m, 2H), 7.69 (s, 1H), 7.95-7.97 (m, 2H), 8.35 (s, 1H), 8.69 (s, 1H), 8.96 (s, 1H), 8.98 (s, 1H), 11.06 (s, 1H); MS (ESCI): m/z 486 $[M+H]^+$.

Example 56: N-(5-{[2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide



The title compound was prepared according to the method described for **Example 10** using N-[5-({2-amino-7-[1,1-dimethyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide (see **Preparation 52**) to afford the title compound as a yellow solid in 24% yield, 14 mg.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 0.71-0.72 (m, 2H), 0.89-0.91 (m, 2H), 1.64 (s, 6H), 1.94-1.99 (m, 1H), 3.89 (d, 2H), 5.07 (t, 1H), 5.31 (s, 2H), 6.53 (s, 2H), 7.69 (s, 1H), 7.86 (s, 1H), 8.35 (s, 1H), 8.65 (s, 1H), 8.95 (m, 2H), 11.04 (s, 1H); LCMS (system 5): R_t = 2.42 min; m/z 476 $[M+H]^+$.

Examples 57 to 64 were prepared according to the method described above for Example **1**, starting from (2-amino-7-*tert*-butyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)(5-aminopyridin-3-yl)methanone (see **Preparation 65**) and the appropriate acids.

Example	**Name**	**Data**
57	N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(3-cyclopropyl-1H-pyrazol-1-yl)acetamide	LCMS (system 5): R_t = 2.90 min; m/z 459 $[M+H]^+$
58	N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide	LCMS (system 5, 12 min run): R_t = 6.13 min; m/z 460 $[M+H]^+$
59	N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-fluoropyridin-2-yl)acetamide	LCMS (system 4): R_t = 2.60 min; m/z 448 $[M+H]^+$
60	N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 5): R_t = 2.99 min; m/z 487 $[M+H]^+$
61	N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide	LCMS (system 5): R_t = 3.04 min; m/z 488 $[M+H]^+$
62	N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 5): R_t = 3.09 min; m/z 487 $[M+H]^+$
63	N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-chloropyridin-2-yl)acetamide	LCMS (system 5): R_t = 2.95 min; m/z 464 $[M+H]^+$
64	N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 5): R_t = 3.09 min; m/z 501 $[M+H]^+$

The following Examples were prepared according to Method a (**Example 34** at 50°C) or Method b (**Example 1** using DIPEA) as described above starting from (5-Aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 95**) and the appropriate acid.

Example	Name	Data
65	2-(4-fluorophenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 1): R_t = 2.73 min; m/z 418 $[M+H]^+$.
66	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(trifluoromethyl)phenyl]acetamide	LCMS (system 9): R_t = 3.22 min; m/z 468 $[M+H]^+$.
67	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)phenyl]acetamide	LCMS (system 9): R_t = 3.22 min; m/z 468 $[M+H]^+$.
68	2-(3,4-dichlorophenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 7): R_t = 11.34 min; m/z 468 $[M+H]^+$

69	2-(4-chlorophenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	m/z 434 $[M+H]^+$
70	2-[2-(cyclopropyloxy)phenyl]-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 4): R_t = 3.13 min; m/z 456 $[M+H]^+$ Prep HPLC (method 2) Using [2-(cyclopropyloxy)phenyl]acetic acid (**Preparation 160**).
71	2-(4-cyanophenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 2): R_t = 1.16 min; m/z 425 $[M+H]^+$
72	2-[4-cyano-3-(trifluoromethyl)phenyl]-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 1): R_t = 2.82 min; m/z 493 $[M+H]^+$ Using [4-cyano-3-(trifluoromethyl)phenyl]acetic acid (**Preparation 164**).
73	2-[4-(cyclopropyloxy)phenyl]-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 3) R_t = 3.05 min; m/z 456 $[M+H]^+$ Using [4-(cyclopropyloxy)phenyl]acetic acid (**Preparation 161**). Prep method 2
74	2-[3-(cyclopropyloxy)phenyl]-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 1) R_t = 2.52 min; m/z 456 $[M+H]^+$ Using [3-(cyclopropyloxy)phenyl]acetic acid (**Preparation 162**).
75	2-[3-(hydroxymethyl)phenyl]-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 2): R_t = 1.3 min; m/z 430 $[M+H]^+$
76	2-(4-cyano-3-fluorophenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 2): R_t = 1.5 min; m/z 443 $[M+H]^+$
77	2-(4-cyano-3-methoxyphenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 2): R_t = 1.3 min; m/z 455 $[M+H]^+$
78	2-(6-fluoro-1-oxo-1,3-dihydro-2H-isoindol-2-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 2): R_t = 1.5 min; m/z 473 $[M+H]^+$
79	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(3-pyridin-2-yl-1H-pyrazol-1-yl)acetamide	LCMS (System 2): R_t = 1.2 min; m/z 467 [M+H]+.
80	2-(1H-benzimidazol-5-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 2): R_t = 1.0 min; m/z 440 $[M+H]^+$
81	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-quinoxalin-6-ylacetamide	LCMS (System 2): R_t = 1.1 min; m/z 452 $[M+H]^+$
82	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(1,5-naphthyridin-3-yl)acetamide	LCMS (System 9): R_t = 2.63 min; m/z 452 $[M+H]^+$ Using 1,5-naphthyridin-3-ylacetic acid (**Preparation 188**).

83	2-(3-amino-1,2-benzisoxazol-5-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 9): R_t = 2.76 min; m/z 456 $[M+H]^+$ using (3-amino-benzo[d]isoxazol-5-yl)-acetic acid ethyl ester (**Preparation 129**)
84	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[2-(trifluoromethyl)-1H-benzimidazol-5-yl]acetamide	LCMS (System 9): R_t = 2.90 min; m/z 508 $[M+H]^+$
85	2-imidazo[1,2-a]pyridin-7-yl-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 10): R_t = 2.57 min; m/z 440 $[M+H]^+$ using imidazo[1,2-a]pyridin-7-yl-acetic acid (**Preparation 132**)
86	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(1H-pyrazolo[4,3-b]pyridin-1-yl)acetamide	LCMS (System 9): R_t = 2.54 min; m/z 441 $[M+H]^+$ Using 1H-pyrazolo[4,3-b]pyridin-1-yl)acetic acid (**Preparation 190**).
87	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(methylsulfonyl)phenyl]acetamide	LCMS (System 9): R_t = 2.74 min; m/z 478 $[M+H]^+$
88	2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 9): R_t = 2.68 min; m/z 431 $[M+H]^+$. Using 4-cyclopropyl-1H-1,2,3-triazol-1-ylacetic acid (**Preparation 83**).
89	2-(1,3-benzoxazol-5-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 9): R_t = 2.79 min; m/z 441.1 $[M+H]^+$
90	2-(3-cyclopropyl-1H-pyrazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 9): R_t = 2.75 min; m/z 430 $[M+H]^+$ (3-cyclopropyl-1H-pyrazol-1-yl)acetic acid (**Preparation 80**).
91	2-[5-(cyclopropyloxy)pyridin-3-yl]-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 3) R_t = 2.36 min; m/z 457 $[M+H]^+$ Prep method 2 Using [5-(cyclopropyloxy)pyridin-3-yl]acetic acid (**Preparation 163**).
92	2-(2,3-dihydro-1-benzofuran-5-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 3): R_t = 2.91 min; m/z 442 $[M+H]^+$ Prep HPLC (method 1)
93	2-(2H-indazol-2-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 3): R_t = 2.74 min; m/z 440 $[M+H]^+$ Prep HPLC (method 1)
94	2-(5-fluoro-2H-indazol-2-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 9): R_t = 2.96 min; m/z 458 $[M+H]^+$ Using -(5-fluoro-2H-indazol-2-yl)acetic acid (**Preparation 174**).

95	2-(5-fluoro-1H-indazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 9): R_t = 2.97 min; m/z 458 $[M+H]^+$ Using (5-fluoro-1H-indazol-1-yl)acetic acid (**Preparation 172**).
96	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 8): R_t = 1.62 min; m/z 472 $[M+H]^+$
97	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 3): R_t = 2.97 min; m/z 458 $[M+H]^+$ Prep HPLC (method 1)
98	2-(5-chloropyridin-2-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 9): R_t = 2.86 min; m/z 435 $[M+H]^+$ Using (5-chloropyridin-2-yl)acetic acid (**Preparation 90**).
99	2-(1H-indazol-6-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	m/z 440 $[M+H]^+$ Using 1H-indazol-6-ylacetic acid (**Preparation 182**).
100	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-quinolin-7-ylacetamide	LCMS (system 7): R_t = 8.73 min; m/z 451 $[M+H]^+$
101	2-(7-fluoro-2H-indazol-2-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 9): R_t = 2.95 min; m/z 458 $[M+H]^+$ Using (7-fluoro-2H-indazol-2-yl)acetic acid (**Preparation 178**).
102	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(1H-pyrazolo[3,4-b]pyridin-1-yl)acetamide	LCMS (system 9): R_t = 2.72 min; m/z 441 $[M+H]^+$ Using 1H-pyrazolo[3,4-b]pyridin-1-yl)acetic acid (**Preparation 180**).
103	2-(1H-indazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 3): R_t = 2.82 min; m/z 440 $[M+H]^+$ Prep HPLC (method 1)
104	2-(3-isopropyl-5-methyl-1H-pyrazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.65 min; m/z 446 $[M+H]^+$ Using (3-isopropyl-5-methyl-1H-pyrazol-1-yl)acetic acid (**Preparation 167**).
105	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-isopropyl-1H-1,2,3-triazol-1-yl)acetamide	LCMS (system 8): R_t = 1.52 min; m/z 433 $[M+H]^+$
106	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide	LCMS (system 9): R_t = 2.98 min; m/z 459 $[M+H]^+$ Using [4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetic acid (**Preparation 81**).
107	2-(7-fluoro-1H-indazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 9): R_t = 2.96 min; m/z 458 $[M+H]^+$ Using (7-fluoro-1H-indazol-1-yl)acetic acid (**Preparation 176**).
108	2-(2H-benzotriazol-2-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.57 min; m/z 441 $[M+H]^+$

109	2-(7-fluoro-2-methyl-1H-indol-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.64 min; m/z 471 $[M+H]^+$
110	2-(5-chloro-2-methyl-1H-indol-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.69 min; m/z 487 $[M+H]^+$
111	2-(1H-indol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.66 min; m/z 439 $[M+H]^+$
112	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[1-isopropyl-5-(trifluoromethyl)-1H-pyrazol-4-yl]acetamide	LCMS (system 9): R_t = 3.13 min; m/z 500 $[M+H]^+$ Using 1-isopropyl-5-(trifluoromethyl)-1H-pyrazol-4-yl]acetic acid (**Preparation 185**).
113	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(3-methyl-1H-pyrazol-1-yl)acetamide	LCMS (system 8): R_t = 1.50 min; m/z 404 $[M+H]^+$
114	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(1H-pyrazol-1-yl)acetamide	LCMS (system 8): R_t = 1.45 min; m/z 390 $[M+H]^+$
115	2-(3,5-dimethyl-1H-pyrazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.55 min; m/z 418 $[M+H]^+$
116	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(2-methyl-1H-indol-3-yl)acetamide	LCMS (system 8): R_t = 1.62 min; m/z 453 $[M+H]^+$
117	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-methoxy-1H-indol-3-yl)acetamide	LCMS (system 8): R_t = 1.57 min; m/z 469 $[M+H]^+$
118	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-pyridin-3-ylacetamide	LCMS (system 8): R_t = 1.35 min; m/z 401 $[M+H]^+$
119	2-(5-chloro-1H-benzotriazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.61 min; m/z 475 $[M+H]^+$
120	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(2-thienyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 8): R_t = 1.61 min; m/z 472 $[M+H]^+$
121	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(7-methylimidazo[1,2-a]pyrimidin-2-yl)acetamide	LCMS (system 8): R_t = 1.37 min; m/z 455 $[M+H]^+$
122	2-(2,6-dimethyl-9H-purin-9-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.43 min; m/z 470 $[M+H]^+$

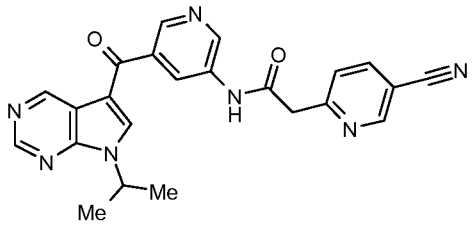
123	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(6-nitro-1H-indazol-1-yl)acetamide	LCMS (system 8): R_t = 1.60 min; m/z 485 $[M+H]^+$
124	2-(5-chloro-1-methyl-1H-indazol-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.73 min; m/z 488 $[M+H]^+$ J. Med Chem. 1992, 35, 2155-2165
125	2-(5-fluoro-2-methyl-1H-indol-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.63 min; m/z 471 $[M+H]^+$
126	2-(6-chloroimidazo[1,2-a]pyridin-2-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.45 min; m/z 474 $[M+H]^+$
127	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(2-methyl-1H-benzimidazol-1-yl)acetamide	LCMS (system 8): R_t = 1.36 min; m/z 454 $[M+H]^+$
128	2-imidazo[1,2-a]pyridin-2-yl-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.31 min; m/z 440 $[M+H]^+$
129	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-1-yl)acetamide	LCMS (system 8): R_t = 1.49 min; m/z 470 $[M+H]^+$
130	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-methyl-1H-pyrazol-1-yl)acetamide	LCMS (system 8): R_t = 1.49 min; m/z 404 $[M+H]^+$
131	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(7-methyl-1H-benzimidazol-1-yl)acetamide	LCMS (system 8): R_t = 1.43 min; m/z 454 $[M+H]^+$
132	2-(1H-indol-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.59 min; m/z 439 $[M+H]^+$
133	2-(1H-benzimidazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.40 min; m/z 440 $[M+H]^+$
134	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(3-methyl-1H-pyrazol-5-yl)acetamide	LCMS (system 8): R_t = 1.45 min; m/z 404 $[M+H]^+$
135	2-(1H-benzotriazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.52 min; m/z 441 $[M+H]^+$
136	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(1-methyl-1H-indol-3-yl)acetamide	LCMS (system 8): R_t = 1.68 min; m/z 453 $[M+H]^+$
137	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-phenyl-1H-pyrrol-	LCMS (system 8): R_t = 1.66 min; m/z 465 $[M+H]^+$

	2-yl)acetamide	
138	2-(2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.49 min; m/z 469 $[M+H]^+$
139	2-(5-chloro-1H-indol-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.67 min; m/z 473 $[M+H]^+$
140	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(1-phenyl-1H-pyrrol-3-yl)acetamide	LCMS (system 8): R_t = 1.71 min; m/z 465 $[M+H]^+$ Can be prepared by a similar method to Harrak, Y. et al. Bioorganic & Medicinal Chemistry (2007), 15(14), 4876-4890.
141	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-methyl-1H-indol-3-yl)acetamide	LCMS (system 8): R_t = 1.63 min; m/z 453 $[M+H]^+$
142	2-(2-ethyl-1H-benzimidazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.37 min; m/z 468 $[M+H]^+$
	2-imidazo[1,2-a]pyrimidin-2-yl-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.38 min; m/z 441 $[M+H]^+$
144	2-(1H-indazol-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.55 min; m/z 440 $[M+H]^+$
145	2-(5-fluoro-7-methoxy-1H-indol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.67 min; m/z 487 $[M+H]^+$
146	2-(1-benzyl-1H-1,2,3-triazol-4-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.57 min; m/z 481 $[M+H]^+$
147	2-(6-chloro-1-methyl-1H-indazol-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.72 min; m/z 488 $[M+H]^+$ Using -(6-chloro-1-methyl-1H-indazol-3-yl)acetic acid (**Preparation 170**).
148	2-(7-chloro-1H-indol-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.67 min; m/z 473 $[M+H]^+$
149	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-methyl-4-phenyl-1H-pyrazol-1-yl)acetamide	LCMS (system 8): R_t = 1.68 min; m/z 480 $[M+H]^+$
150	2-(5-bromopyridin-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.60 min; m/z 479 $[M+H]^+$
151	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-pyridin-2-	LCMS (system 8): R_t = 1.41 min; m/z 401 $[M+H]^+$

	ylacetamide	
152	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(6-methoxypyridin-3-yl)acetamide	LCMS (system 8): R_t = 1.55 min; m/z 431 $[M+H]^+$
153	2-(2,5-dimethyl-1H-indol-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.67 min; m/z 467 $[M+H]^+$
154	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(6-methylpyridin-3-yl)acetamide	LCMS (system 8): R_t = 1.33 min; m/z 415 $[M+H]^+$
155	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(2-methylquinolin-7-yl)acetamide	LCMS (system 8): R_t = 1.40 min; m/z 465 $[M+H]^+$ Using (2-methylquinolin-7-yl)acetic acid (**Preparation 165**).
156	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-methoxy-2-methyl-1H-indol-3-yl)acetamide	LCMS (system 8): R_t = 1.60 min; m/z 483 $[M+H]^+$
157	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-tetrazolo[1,5-b]pyridazin-6-ylacetamide	LCMS (system 8): R_t = 1.46 min; m/z 443 $[M+H]^+$. (can be prepared via a similar method to WO2010/129379, 11 Nov 2010)
158	2-(5-hydroxy-1H-indol-3-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.45 min; m/z 455 $[M+H]^+$
159	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5H-pyrrolo[2,3-b]pyrazin-7-yl)acetamide	LCMS (system 8): R_t = 1.47 min; m/z 441 $[M+H]^+$
160	2-(5,6-dimethyl-1H-benzimidazol-1-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 8): R_t = 1.43 min; m/z 468 $[M+H]^+$
161	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-pyridin-2-yl-1H-1,2,3-triazol-1-yl)acetamide	LCMS (system 8): R_t = 1.48 min; m/z 468 $[M+H]^+$
162	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-methyl-1H-1,2,3-triazol-1-yl)acetamide	LCMS (system 8): R_t = 1.43 min; m/z 405 $[M+H]^+$
163	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-methyl-3-phenyl-1H-pyrazol-4-yl)acetamide	LCMS (system 8): R_t = 1.55 min; m/z 480 $[M+H]^+$
164	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[2-(methylthio)pyrimidin-5-yl]acetamide	LCMS (system 8): R_t = 1.55 min; m/z 448 $[M+H]^+$ can be prepared via a similar method to Smrz, R. et al. Collection of Czechoslovak Chemical Communications (1976), 41(9), 2771-87

165	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-pyrimidin-2-ylacetamide	LCMS (system 8): R_t = 1.44 min; m/z 402 $[M+H]^+$

Example 166: 2-(5-Cyanopyridin-2-yl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide

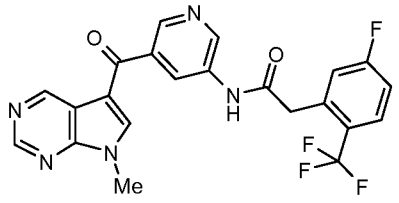


Zinc cyanide (28 mg, 0.23 mmol) was added to 2-(5-Bromo-pyridin-2-yl)-N-[5-(7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide (**Example 317**, 75 mg, 0.16 mmol) in DMF (2 mL) and the mixture was degassed with argon for 10 minutes. Then tris(dibenzylideneacetone)dipalladium (3 mg, 0.003 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (7 mg, 0.012 mmol) were added and the mixture was heated at 100°C for 40 mins under microwave irradiation. The mixture was diluted with EtOAc (5 mL) and washed with water (2 mL), brine (2 mL) and dried over sodium sulphate. The filtrate was evaporated *in vacuo* and purified by preparative TLC (3% MeOH in DCM) to afford the title compound as a light brown solid in 18% yield, 12 mg.

^{1}H NMR (400 MHz, DMSO) δ*:* 1.55 (d, 6H), 4.07 (s, 2H), 5.09 (m, 1H), 7.67 (d, 1H), 8.30 (m, 1H), 8.44 (s, 1H), 8.52 (s, 1H), 8.74 (d, 1H), 8.98-8.99 (m, 3H), 9.44 (s, 1H), 10.79 (s, 1H);

LCMS (System 9): R_t = 2.75 min; m/z 426 $[M+H]^+$.

Example 167: 2-[5-Fluoro-2-(trifluoromethyl)phenyl]-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide



1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide HCl (150 µL, 0.5M in DMF) was added to 5-fluoro-2-(trifluoromethyl)phenylacetic acid (90 µmol), N-methylmorpholine (25 µL, 150 µmol), 1-hydroxybenzotriazole (15 µmol, 0.05M in DMF) and (5-aminopyridin-3-yl)(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 110**, 75 µmol, 0.25 M in DMF). The mixture was stirred at 50°C for 2 hours and then evaporated *in vacuo* and purified by prep-HPLC (method 4) to afford the title compound.

LCMS (system 5): R_t = 2.66 min; m/z 458 $[M+H]^+$

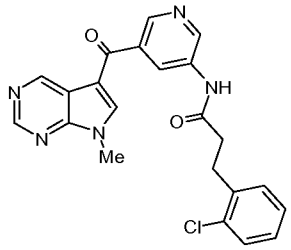
The following Examples were prepared according to the method described above for **Example 167** starting from (5-aminopyridin-3-yl)(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 110)** and the appropriate acid.

Example	Name	Data
168	2-(3-methylphenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 5): R_t = 2.53 min; m/z 386 $[M+H]^+$
169	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[2-(trifluoromethyl)phenyl]acetamide	LCMS (system 5): R_t = 2.61 min; m/z 440 $[M+H]^+$
170	2-(3,5-difluorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 5): R_t = 2.52 min; m/z 408 $[M+H]^+$
171	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(2,4,6-trifluorophenyl)acetamide	LCMS (system 5): R_t = 2.50 min; m/z 426 $[M+H]^+$
172	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(2,3,6-trifluorophenyl)acetamide	LCMS (system 5): R_t = 2.49 min; m/z 426 $[M+H]^+$
173	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(methylsulfonyl)phenyl]acetamide	LCMS (system 5): R_t = 2.13 min; m/z 450 $[M+H]^+$
174	2-[3-fluoro-4-(trifluoromethyl)phenyl]-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 5): R_t = 2.77 min; m/z 458 $[M+H]^+$
175	2-(3-methoxyphenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS: R_t = 2.34 min; m/z 402 $[M+H]^+$
176	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(trifluoromethoxy)phenyl]acetamide	LCMS (system 5): R_t = 2.76 min; m/z 456 $[M+H]^+$
177	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(2,3,5-trifluorophenyl)acetamide	LCMS (system 5): R_t = 2.54 min; m/z 426 $[M+H]^+$
178	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(2-methylquinolin-7-yl)acetamide	LCMS (system 5): R_t = 1.95 min; m/z 437 $[M+H]^+$ Using (2-methylquinolin-7-yl)acetic acid (**Preparation 165**).
179	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-phenylacetamide	LCMS (system 5): R_t = 2.37 min; m/z 372 $[M+H]^+$
180	2-(2-chloro-6-fluorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 5): R_t = 2.51 min; m/z 424 $[M+H]^+$
181	2-(4-methoxyphenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS: R_t = 2.22 min; m/z 402 $[M+H]^+$

182	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-{4-[(trifluoromethyl)thio]phenyl}acetamide	LCMS (system 5): R_t = 2.90 min; m/z 472 $[M+H]^+$
183	2-biphenyl-4-yl-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 6): R_t = 2.67 min; m/z 448 $[M+H]^+$
184	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(2,4,5-trifluorophenyl)acetamide	LCMS (system 5): R_t = 2.54 min; m/z 426 $[M+H]^+$
185	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-{3-[(trifluoromethyl)thio]phenyl}acetamide	LCMS (system 5): R_t = 2.86 min; m/z 472 $[M+H]^+$
186	2-(4-methylphenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 5): R_t = 2.53 min; m/z 386 $[M+H]^+$
187	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(3,4,5-trifluorophenyl)acetamide	LCMS (system 5): R_t = 2.62 min; m/z 426 $[M+H]^+$
188	2-(2,4-dimethylphenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 5): R_t = 2.64 min; m/z 400 $[M+H]^+$
189	2-(2,3-dihydro-1-benzofuran-5-yl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 5): R_t = 2.37 min; m/z 414 $[M+H]^+$
190	2-(2,5-difluorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 5): R_t = 2.44 min; m/z 408 $[M+H]^+$
191	2-(2,4-difluorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 5): R_t = 2.46 min; m/z 408 $[M+H]^+$
192	2-[2-fluoro-3-(trifluoromethyl)phenyl]-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 5): R_t = 2.72 min; m/z 458 $[M+H]^+$
193	2-(2,6-difluorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin -3-yl}acetamide	LCMS (system 5): R_t = 2.41 min; m/z 408 $[M+H]^+$
194	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(trifluoromethyl)phenyl]acetamide	LCMS (System 2): Rt = 1.6 min; m/z 440 $[M+H]^+$
195	2-(3,4-difluorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]yridine-3-yl}acetamide	LCMS (System 2): Rt = 1.5 min; m/z 408 $[M+H]^+$
196	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]yridine-3-yl}-2-[4-(trifluoromethoxy)phenyl]acetamide	LCMS (System 2): Rt = 1.6 min; m/z 456 $[M+H]^+$

197	2-(3-chlorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]yridine-3-yl}acetamide	LCMS (System 2): R_t = 1.5 min; m/z 406 $[M+H]^+$

Example 198: 3-(2-chlorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}propanamide



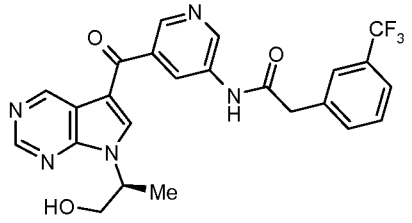
The title compound was prepared according to the method described above for **Example 167** starting from (5-aminopyridin-3-yl)(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone **(Preparation 110)** and 3-(2-chlorophenyl)propanoic acid.

LCMS (system 5): R_t = 2.66 min; m/z 420 $[M+H]^+$

The following Examples were prepared according to Method b (**Example 1** using DIPEA) as described above starting from (5-aminopyridin-3-yl)(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 31**) and the appropriate acids.

Example	Name	Data
199	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(2-cyclopropyl-1,3-oxazol-4-yl)acetamide	LCMS (system 9): R_t = 3.16 min; m/z 445 $[M+H]^+$ using (2-cyclopropyl-1,3-oxazol-4-yl)acetic acid (**Preparation 155**).
200	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(methylsulfonyl)phenyl]acetamide	LCMS (system 9): R_t = 2.87 min; m/z 492 $[M+H]^+$
201	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(1,3-dimethyl-1H-pyrazol-4-yl)acetamide	LCMS (system 9): R_t = 2.76 min; m/z 432$[M+H]^+$
202	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(1-methyl-1H-pyrazol-4-yl)acetamide	LCMS (system 9): R_t = 2.73 min; m/z 418$[M+H]^+$
203	N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(3-cyclopropyl-1-methyl-1H-pyrazol-4-yl)acetamide	LCMS (system 9): R_t = 2.80 min; m/z 458 $[M+H]^+$ using (3-Cyclopropyl-1-methyl-1H-pyrazol-4-yl)-acetic acid (**Preparation 125**)

Example 204: N-[5-({7-[(1S)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)phenyl]acetamide



10% Hydrochloric acid in 1,4- dioxane (0.2 mL) was added to N-(5-{7-[(S)-2-(tert-Butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-7H-pyr
rolo[2,3-d]pyrimidine-5-carbonyl}-pyridin-3-yl)-2-(3-trifluoromethyl-phenyl)-acetamide (**Preparation 105,** 59 mg, 0.098 mmol) in THF (2 mL) and the mixture was stirred at room temperature for 18 hours. The mixture was evaporated *in vacuo* and triturated with ether-pentane to afford the title compound as an off white solid in 86% yield, 41 mg.

LCMS (system 9): Rt = 2.97 min; m/z 484 $[M+H]^+$.

The following Examples were prepared according to the method described above for **Example 204** using the appropriate preparations as described.

Example	Name	Data
205	N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)phenyl]acetamide	LCMS (system 9): Rt = 2.89 min; m/z 484 $[M+H]^+$ Using (**Preparation 142**).
206	N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-(4-isopropyl-1H-1,2,3-triazol-1-yl)acetamide	LCMS (system 9): Rt = 2.52 min; m/z 449 $[M+H]^+$ Using (**Preparation 144**).
207	N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[1-isopropyl-5-(trifluoromethyl)-1H-pyrazol-4-yl]acetamide	LCMS (system 9): Rt = 2.87 min; m/z 516 $[M+H]^+$ Using (**Preparation 150**).
208	2-(4-cyanophenyl)-N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	LCMS (system 9): Rt = 2.68 min; m/z 441 $[M+H]^+$ Using (**Preparation 151**).
209	N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(methylsulfonyl)phenyl]acetamide	LCMS (system 9): Rt = 2.57 min; m/z 494 $[M+H]^+$ Using (**Preparation 152**).
210	N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-quinolin-7-ylacetamide	LCMS (system 9): Rt = 1.96 min; m/z 467 $[M+H]^+$ Using (**Preparation 153**).

The following Examples were prepared according to the method described above for **Example 34** at 50°C, starting from [2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl](5-aminopyridin-3-yl)methanone (*enantiomer 1,* **Preparation 57**) and the appropriate acids.

Example	Name	Data
211	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-quinolin-7-ylacetamide	LCMS (system 10): Rt = 2.48 min; m/z 482 $[M+H]^+$
212	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-cyanophenyl)acetamide	LCMS (system 10): Rt = 2.57 min; m/z 456 $[M+H]^+$
213	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	LCMS (system 10): Rt = 2.87 min; m/z 499 $[M+H]^+$

The following Examples were prepared according to the method described above for **Example 34** at 50°C, starting from [2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl](5-aminopyridin-3-yl)methanone (*enantiomer 2,* **Preparation 59**) and the appropriate acids.

Example	Name	Data
214	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-cyanophenyl)acetamide	LCMS (system 9): Rt = 2.26 min; m/z 456 $[M+H]^+$
215	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	LCMS (system 9): Rt = 2.72 min; m/z 499 $[M+H]^+$
216	N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-quinolin-7-ylacetamide	LCMS (system 9): Rt = 1.62 min; m/z 482 $[M+H]^+$

The following Examples were prepared according to the method described above for **Example 34** at 50°C starting from (5-aminopyridin-3-yl)(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 100**) and the appropriate acid.

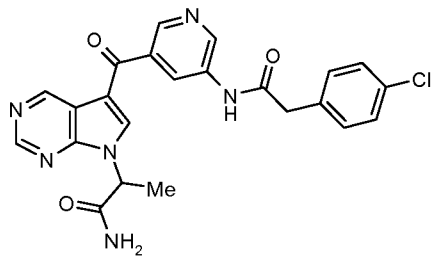
Example	Name	Data
217	2-(3,4-dichlorophenyl)-N-{5-[(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (system 3): R_t = 3.04 min; m/z 482 $[M+H]^+$

218	2-(4-cyanophenyl)-N-{5-[(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 2): Rt = 1.3 min; m/z 439 $[M+H]^+$
219	2-(4-chlorophenyl)-N-{5-[(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 2): Rt = 1.5 min; m/z 448 $[M+H]^+$
220	2-(3-chlorophenyl)-N-{5-[(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 2): Rt = 1.5 min; m/z 448 $[M+H]^+$
221	2-(3-cyanophenyl)-N-{5-[(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 2): Rt = 1.3 min; m/z 439 $[M+H]^+$
222	N-{5-[(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-quinolin-7-ylacetamide	LCMS (System 2): Rt = 1.0 min; m/z 465 $[M+H]^+$
223	2-(6-chloroimidazo[1,2-a]pyridin-2-yl)-N-{5-[(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS (System 2): Rt = 1.0 min; m/z 488 $[M+H]^+$
224	N-{5-[(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(1-oxo-1,3-dihydro-2H-isoindol-2-yl)acetamide	LCMS (System 2): Rt = 1.3 min; m/z 469 $[M+H]^+$

The following Examples were prepared according to the method described above for **Example 204**, using the preparations as described.

Example	Name	data
225	2-(4-cyanophenyl)-N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide	LCMS (System 9): R_t = 2.74 min; m/z 455.4 $[M+H]^+$ **Using Preparation 131**
226	N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	LCMS (System 9): R_t = 2.99 min; m/z 498 $[M+H]^+$ **Using Preparation 136**
227	N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-isopropyl-1H-1,2,3-triazol-1-yl)acetamide	^{1}H NMR (400 MHz, DMSO) δ: 1.22 (d, 6H), 1.71 (s, 6H), 2.96 (m, 2H), 3.94 (s, 2H), 5.35 (s, 2H), 7.87 (s, 1H), 8.20 (s, 1H), 8.44 (s, 1H), 8.75 (s, 1H), 8.98 (m, 2H), 9.46 (s, 1H), 11 (s, 1H) **Using Preparation 144**
228	N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-quinolin-7-ylacetamide	LCMS (System 9): R_t = 2.61 min; m/z 481 $[M+H]^+$ **Using Preparation 140**

Example 229: racemic 2-{5-[(5-{[(4-Chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}propanamide



2-bromopropionamide (46.5 mg, 0.31 mmol) was added to a mixture of 2-(4-chlorophenyl)-N-[5-(7H-pyrrolo[2,3-d]pyrimidin-5-ylcarbonyl)pyridin-3-yl]acetamide (**Example 308**, 100 mg, 0.26 mmol) and cesium carbonate (150 mg, 0.46 mmol) in DMF (1.3 mL). The mixture was stirred at 60°C for 3 hours. The reaction mixture was cooled and water (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic phases were passed through a phase separator and evaporated *in vacuo.* Purification by preparative HPLC gave the title compound as a white solid in 34% yield, 15 mg.

LCMS (System 3): R_t = 2.13 min; m/z 463 $[M+H]^+$.

Example 230: racemic 2-{5-[(5-{[(4-Chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}-N,N-dimethylpropanamide

The title compound was prepared according to the method described for **Example 34** at 50°C using racemic 2-{5-[(5-{[(4-chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}propanoic acid (**Example 354**) and dimethylamine. Purification was accomplished by preparative HPLC (method 1) to afford the title compound.

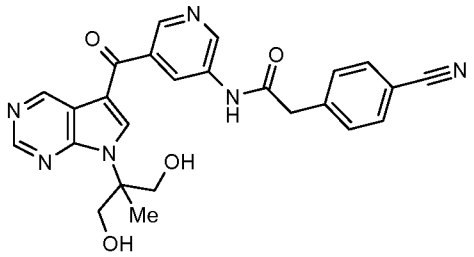
LCMS (system 3): R_t = 2.39 min; m/z 491 $[M+H]^+$.

Example 231: racemic 2-{5-[(5-{[(4-Chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}-N-methylpropanamide

The title compound was prepared according to the method described for **Example 34** at 50°C using 2-{5-[(5-{[(4-chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}propanoic acid (**Example 354**) and methylamine. Purification was accomplished by preparative HPLC (method 1) to afford the title compound.

LCMS (system 3): R_t = 2.31 min; m/z 477 $[M+H]^+$.

Example 232: 2-(4-Cyanophenyl)-N-[5-({7-[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide



4-Cyanophenylacetic acid (19 mg, 0.10 mmol) was added to (5-aminopyridin-3-yl){7-[2-{[tert-butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (**Preparation 116**, 54 mg, 0.97 mmol), 1-propylphosphonic acid cyclic anhydride (0.17 mL, 0.291 mmol) and triethylamine (0.047 mL, 0.291 mmol) in tetrahydrofuran (3 mL). The mixture was stirred at 50°C for 16 hours. Saturated aqueous sodium bicarbonate (5 mL) was added then extracted with dichloromethane (3 x 7 mL). The combined organic phases were dried over magnesium sulphate and evaporated *in vacuo*.

The residue was dissolved in tetrahydrofuran (3 mL) and a tetrabutylammonium fluoride solution in THF (1 mL of a1M solution, 1 mmol) was added and the solution was stirred for 1 hour. Saturated aqueous sodium bicarbonate (5 mL) was added then extracted with dichloromethane (3 x 5 mL). The combined organic phases were dried over magnesium sulphate, evaporated *in vacuo* and purified by preparative HPLC (method 2).

LCMS (system 4): R_t = 2.52 min; m/z 471 $[M+H]^+$

The following Examples were prepared according to the method described above for **Example 232** starting from (5-aminopyridin-3-yl){7-[2-{[tert-butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (**Preparation 116**) and the appropriate acids.

Example	Name	Data
233	N-[5-({7-[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-quinolin-7-ylacetamide	LCMS (system 4) Rt = 2.52 min; m/z 497 $[M+H]^+$ Prep method 1
234	N-[5-({7-[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 4) Rt = 2.69 min; m/z 518 $[M+H]^+$ Prep method 1
235	2-(4-chlorophenyl)-N-[5-({7-[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	LCMS (system 4) Rt = 2.83 min; m/z 480 $[M+H]^+$ Prep method 1
236	N-[5-({7-[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[4-(trifluoromethyl)phenyl]acetamide	LCMS (system 4) Rt = 2.81 min; m/z 514 $[M+H]^+$ Prep method 1
237	2-(5-chloropyridin-2-yl)-N-[5-({7-[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]-7H-pyrrolo[2,3-	LCMS (system 3) Rt = 2.37 min; m/z 481 $[M+H]^+$

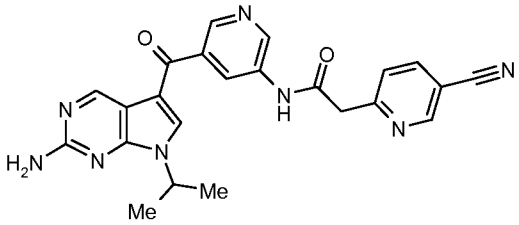
	d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	Prep method 1 Using (5-chloropyridin-2-yl)acetic acid (**Preparation 90**).
238	N-[5-({7-[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)phenyl]acetamide	LCMS (system 4) Rt = 2.84 min; m/z 514 $[M+H]^+$ Prep method 1
239	N-[5-({7-[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (system 3) Rt = 2.59 min; m/z 504 $[M+H]^+$ Prep method 2

The following Examples were prepared according to the method described above for **Example 1** using DIPEA and purification by preparative HPLC, starting from (2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(5-aminopyridin-3-yl)methanone (**Preparation 122**) and the appropriate acids.

Example	Name	Data
240	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide	LCMS (System 9): R_t = 2.57 min; m/z 474 $[M+H]^+$ Using 4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetic acid (**Preparation 81**).
241	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-cyanophenyl)acetamide	LCMS (System 9): R_t = 2.56 min; m/z 440 $[M+H]^+$
242	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-chloropyridin-2-yl)acetamide	LCMS (System 9): R_t = 2.46 min; m/z 450 $[M+H]^+$ Using -(5-chloropyridin-2-yl)acetic acid (**Preparation 90**).
243	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-fluoropyridin-2-yl)acetamide	LCMS (System 9): R_t = 2.20 min; m/z 434 $[M+H]^+$ Using (5-fluoropyridin-2-yl)acetic acid (**Preparation 92**).
244	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)phenyl]acetamide	LCMS (System 10): R_t = 3.22 min; m/z 483 $[M+H]^+$
245	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(trifluoromethyl)phenyl]acetamide	LCMS (System 10): R_t = 3.22 min; m/z 483 $[M+H]^+$
246	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(1,3-benzoxazol-5-yl)acetamide	LCMS (System 9): R_t = 2.22 min; m/z 456 $[M+H]^+$
247	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(methylsulfonyl)phenyl]acetamide	LCMS (System 9): R_t = 2.15 min; m/z 493 $[M+H]^+$
248	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-isopropyl-1H-1,2,3-triazol-1-yl)acetamide	LCMS (System 9): R_t = 2.16 min; m/z 448 $[M+H]^+$

249	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide	LCMS (System 9): R_t = 2.01 min; m/z 446 $[M+H]^+$ Using **Preparation 83**
250	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-chlorophenyl)acetamide	LCMS (System 10): R_t = 3.03 min; m/z 449 $[M+H]^+$
251	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[1-isopropyl-5-(trifluoromethyl)-1H-pyrazol-4-yl]acetamide	LCMS (System 10): R_t = 3.03 min; m/z 515 $[M+H]^+$ Using **Prep 185**
252	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (System 10): R_t = 2.92 min; m/z 473 $[M+H]^+$
253	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(3-cyclopropyl-1H-pyrazol-1-yl)acetamide	LCMS (System 9) R_t 2.46 min; m/z 445 $[M+H]^+$
254	N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[1-isopropyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]acetamide	LCMS (System 9): R_t = 2.77 min; m/z 515 $[M+H]^+$

Example 255: N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-cyanopyridin-2-yl)acetamide



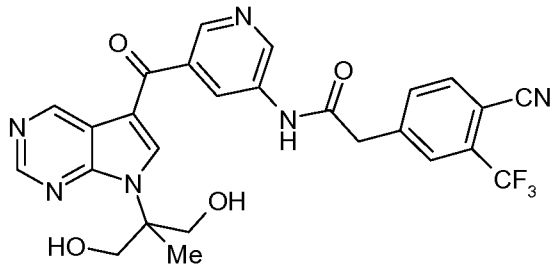
The title compound was prepared according to the method described for **Example 166** using N-{5-[(2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-bromopyridin-2-yl)acetamide (**Example 318**) to afford the title compound in 45% yield, 30 mg. ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 1.45 (d, 6H), 4.06 (s, 2H), 4.84 (m, 1H), 6.62 (s, 2H), 7.66 (d, 1H), 7.97 (s, 1H), 8.29 (dd, 1H), 8.37 (t, 1H), 8.66 (d, 1H), 8.92 (s, 1H), 8.95-8.98 (m, 2H), 10.75 (s, 1H);LCMS (System 10): R_t = 2.49 min; m/z 441 $[M+H]^+$.

The following Examples were prepared according to the method described above for **Example 34** at 50°C starting from [2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl](5-aminopyridin-3-yl)methanone (**Preparation 48**) and the appropriate acids.

Example	Name	Data
256	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	LCMS (System 10): R_t = 2.91 min; m/z 513 $[M+H]^+$
257	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-	LCMS (System 10): R_t = 2.48

	pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(1,3-benzoxazol-5-yl)acetamide	min; m/z 486 $[M+H]^+$
258	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(methylsulfonyl)phenyl]acetamide	LCMS (System 10): R_t = 2.50 min; m/z 523 $[M+H]^+$
259	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-cyanophenyl)acetamide	LCMS (System 10): R_t = 2.62 min; m/z 470 $[M+H]^+$
260	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[1-isopropyl-5-(trifluoromethyl)-1H-pyrazol-4-yl]acetamide	LCMS (System 10): R_t = 2.89 min; m/z 545 $[M+H]^+$ Using **Prep 185**

Example 261: 4-cyano-3-(trifluoromethyl)phenyl)-N-(5-(7-(1,3-dihydroxy-2-methylpropan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)acetamide



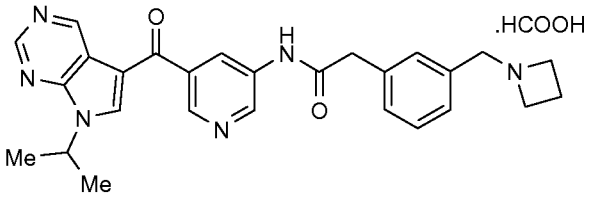
2-(4-cyano-3-(trifluoromethyl)phenyl)acetic acid (**Preparation 164**, 29.8 mg, 0.13 mmol) was added to a stirred solution of (5-aminopyridin-3-yl){7-[2-{[tert-butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-yl)methanone (**Preparation 116**, 55.6 mg, 0.10 mmol) and 2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (57 mg, 0.15 mmol) in pyridine (0.5 mL). The mixture was stirred at 50°C for 16 hours, then cooled to room temperature and partitioned between saturated aqueous sodium bicarbonate (5 mL) and DCM (5 mL). The organic phase was separated and concentrated *in vacuo* to provide a residue that was dissolved in 3 mL of THF and then treated with 3 mL of a 1N aqueous solution of HCl. The mixture was stirred rapidly for 4 hours at room temperature and then basified by the addition of 4 mL of a 1N aqueous NaOH solution. The mixture was extracted with three separate 5 mL portions of a 95/5 DCM/MeOH mixture. The combined organic extracts were dried by passage through a phase separator and then concentrated *in vacuo* to obtain a crude residue. This residue was dissolved in 1 mL DMSO and purified by preparative HPLC to afford the title compound as an off white solid in 56% yield, 30 mg. ^{1}H NMR (400 MHz, DMSO) δ*:* 1.68 (s, 3H), 3.83 (m, 2H), 4.01 (s, 2H), 4.19 (m, 2H), 5.00 (m, 2H), 7.82 (m, 1H), 8.01 (d, 1H), 8.18 (m, 1H), 8.21 (s, 1H), 8.66 (s, 1H), 8.97 (m, 2H), 9.40 (s, 1H), 10.78 (s, 1H). LCMS (System 2): R_t = 0.90 min; m/z 539 $[M+H]^+$.

The following Examples were prepared according to the method described above for **Example 261**, starting from ((5-aminopyridin-3-yl){7-[2-{[tert-butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-yl)methanone (**Preparation 116**) and the appropriate acids followed by silyl group deprotection.

Example	Name	Data

262	*N*-(5-(7-(1,3-dihydroxy-2-methylpropan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonyl)pyridin-3-yl)-2-(3-trifluoromethoxy)phenyl)acetamide	LCMS (system 2): R_t = 0.96 min; m/z 516 $[M+H]^+$
263	*N*-(5-(7-(1,3-dihydroxy-2-methylpropan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonyl)pyridin-3-yl)-2-(4-fluoro-3-(trifluoromethyl)phenyl)acetamide	LCMS (system 2): R_t = 1.05 min; m/z 532 $[M+H]^+$
264	*N*-(5-(7-(1,3-dihydroxy-2-methylpropan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonyl)pyridin-3-yl)-3-(trifluoromethyl)benzamide	LCMS (system 2): R_t = 1.04 min; m/z 500 $[M+H]^+$
265	*N*-(5-(7-(1,3-dihydroxy-2-methylpropan-2-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonyl)pyridin-3-yl)-3-fluoro-4-(trifluoromethyl)benzamide	LCMS (system 2): R_t = 1.09 min; m/z 532 $[M+H]^+$

Example 266: 2-[3-(azetidin-1-ylmethyl)phenyl]-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide formate salt.



Azetidine hydrochloride (10 mg, 0.11 mmol) was added to a stirred solution of 2-(3-formylphenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide (**Preparation 192**, 23 mg, 0.05 mmol) in DCM (1 mL) and acetic acid (0.04 mL, 0.60 mmol). The reaction mixture was stirred for 30 min at room temperature before addition of sodium triacetoxyborohydride (29 mg, 0.14 mmol) and stirring continued for 3 hours. Water (1 mL) was added and the mixture concentrated *in vacuo* (with toluene azeotroping). The residue was purified by preparative HPLC to afford the title compound as a formate salt in 12% yield, 3.4 mg.

LCMS: R_t = 2.95 min; m/z 469 $[M+H]^+$.

Example 267: 2-{3-[(3-fluoroazetidin-1-yl)methyl]phenyl}-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide

The title compound was prepared according to the method described for **Example 266** using 2-(3-formylphenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide (**Preparation 192**, 60 mg, 0.14 mmol) and 3-fluoroazetidine to afford the title compound in 16% yield, 11 mg.

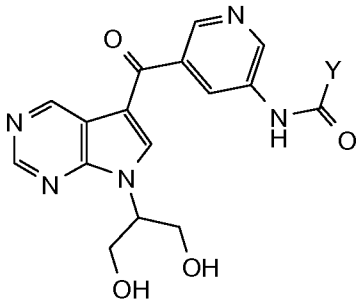
LCMS: R_t = 2.75 min; m/z 487 $[M+H]^+$.

Example 268: N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[3-(morpholin-4-ylmethyl)phenyl]acetamide formate salt

The title compound was prepared according to the method described for **Example 266** using 2-(3-formylphenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide (**Preparation 192**, 60 mg, 0.14 mmol) and morpholine to afford the title compound as a formate salt in 30% yield, 21 mg.

LCMS: R_t = 2.70 min; m/z 499 $[M+H]^+$

Examples 269-283 General method:



The mixture of (5-aminopyridin-3-yl)(7-(2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 196**, 54.2 mg, 0.10 mmol), HATU (57 mg, 0.15 mmol) and the requisite carboxylic acid (0.13 mmol) in pyridine (0.5 mL) were stirred at 50 °C for 16 hours. After cooling to room temperature, saturated sodium bicarbonate solution (5 mL) was added and the mixture was extracted with DCM (5 mL). The organic layer was passed through a phase separator and concentrated *in vacuo*. The resulting residue was dissolved in THF (2 mL) and 1 N aqueous HCl (2 mL) added to the solution. The reaction mixture was stirred for 2 hours at room temperature and quenched with 1 N aqueous NaOH (3 mL). The mixture was then treated according to one of the following methods:

Method A

The mixture was extracted with a mixture of DCM/MeOH (95/5, 5 mL x 3), the combined organic layers passed through a phase separator and concentrated *in vacuo* to obtain a crude residue. This residue was dissolved in DMSO (1 mL) and purified via HPLC to yield the desired compound.

Method B

The mixture was suspended in DCM/MeOH (95/5, 5 mL), the solid filtered and washed with water (5 mL) and DCM (5 mL) and dried *in vacuo* to yield the desired compound.

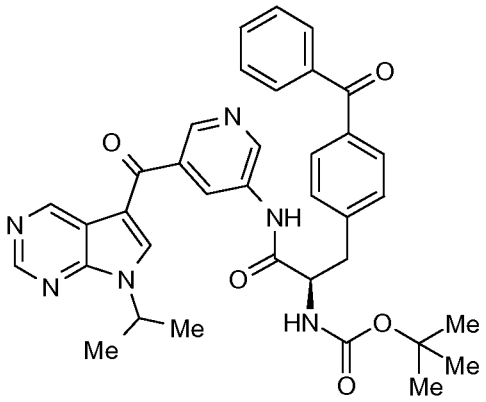
Method C

The mixture was extracted with a mixture of EtOAc/MeOH (95:5, 5 mL x 3), the combined organic layers passed through a phase separator and concentrated *in vacuo* to obtain a crude residue. This residue was dissolved in DMSO (1 mL) and purified via preparative HPLC to yield the desired compound.

Example	Name	Data
269	N-(5-(7-(1,3-dihydroxypropan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)-3-(trifluoromethyl)benzamide	LCMS: R_t = 2.69 min; m/z 486 $[M+H]^+$
270	2-(4-chlorophenyl)-N-(5-(7-(1,3-dihydroxypropan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)acetamide	LCMS: R_t = 2.63 min; m/z 466 $[M+H]^+$
271	N-(5-(7-(1,3-dihydroxypropan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-	LCMS: R_t = 2.68

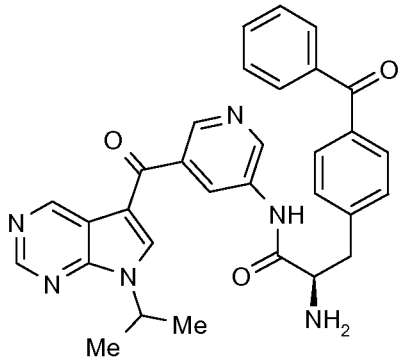
	carbonyl)pyridin-3-yl)-3-(trifluoromethoxy)benzamide	min; m/z 502 $[M+H]^+$
272	N-(5-(7-(1,3-dihydroxypropan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)-2-(quinolin-7-yl)acetamide	LCMS: R_t = 1.27 min; m/z 483 $[M+H]^+$
273	N-(5-(7-(1,3-dihydroxypropan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)-2-(4-(trifluoromethyl)phenyl)acetamide	LCMS: R_t = 2.69 min; m/z 500 $[M+H]^+$
274	N-(5-(7-(1,3-dihydroxypropan-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)-2-(3-(trifluoromethyl)phenyl)acetamide	m/z 500 $[M+H]^+$
275	N-[5-({7-[2-hydroxy-1-(hydroxymethyl)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-(2-methylquinolin-7-yl)acetamide	m/z 497 $[M+H]^+$ **Preparation 165**
276	2-(3,4-dichlorophenyl)-N-[5-({7-[2-hydroxy-1-(hydroxymethyl)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	m/z 500 $[M+H]^+$
277	2-[3-fluoro-4-(trifluoromethyl)phenyl]-N-[5-({7-[2-hydroxy-1-(hydroxymethyl)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	m/z 518 $[M+H]^+$
278	2-(2,4-dichlorophenyl)-N-[5-({7-[2-hydroxy-1-(hydroxymethyl)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	m/z 500 $[M+H]^+$
279	N-[5-({7-[2-hydroxy-1-(hydroxymethyl)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethoxy)phenyl]acetamide	m/z 516 $[M+H]^+$
280	N-[5-({7-[2-hydroxy-1-(hydroxymethyl)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[4-(trifluoromethoxy)phenyl]acetamide	m/z 516 $[M+H]^+$
281	3-fluoro-N-[5-({7-[2-hydroxy-1-(hydroxymethyl)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-5-(trifluoromethyl)benzamide	m/z 504 $[M+H]^+$
282	2-(5-chloropyridin-2-yl)-N-[5-({7-[2-hydroxy-1-(hydroxymethyl)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide	LCMS: R_t = 0.90 min, m/z 467 $[M+H]^+$
283	N-[5-({7-[2-hydroxy-1-(hydroxymethyl)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS: Rt = 1.81 min, m/z 490 $[M+H]^+$

Example 284: 4-benzoyl-N-*alpha*-(tert-butoxycarbonyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-L-phenylalaninamide



(5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (20 mg, 0.07 mmol) (see **Preparation 95**) was dissolved in pyridine (1mL) and 4-benzoyl-N-(tert-butoxycarbonyl)-D-phenylalanine was added (26 mg, 0.07 mmol) followed by HATU (27 mg, 0.07 mmol). The mixture was stirred at 50 °C for 5 hours and then cooled, evaporated *in vacuo* and the crude material was purified by column chromatography on silica gel (gradient of DCM:Methanol 100:0 to 95:5) to afford the title compound as a yellow solid in 52% yield, 23 mg.

Example 285: 4-benzoyl-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-D-phenylalaninamide



4-benzoyl-Nalpha-(tert-butoxycarbonyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-D-phenylalaninamide (**Example 284**, 20 mg, 0.03 mmol) was stirred with 10% hydrochloric acid in 1,4-dioxane (5 mL) at room temperature for 1 hour. The mixture was evaporated *in vacuo* and purified by preparative HPLC to afford the title compound as a gum in 56% yield, 9 mg.

LCMS (system 5): R_t = 2.89 min; m/z 533 $[M+H]^+$.

Example 286 :4-benzoyl-N-*alpha*-(tert-butoxycarbonyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-L-phenylalaninamide

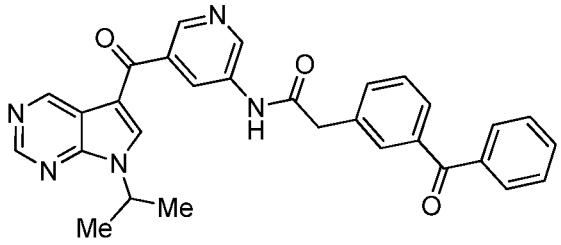
The title compound was prepared according to **Example 284** using (5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 95**) and 4-benzoyl-N-(tert-butoxycarbonyl)-L-phenylalanine

Example 287: 4-benzoyl-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-L-phenylalaninamide

The title compound was prepared according to the method described for **Example 285** using 4-benzoyl-Nalpha-(tert-butoxycarbonyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-L-phenylalaninamide (**Example 286**) to afford the title compound in 36% yield, 5 mg.

LCMS (system 4): R_t = 2.30 min; m/z 533 $[M+H]^+$.

Example 288: 2-(3-benzoylphenyl)-N-(5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)acetamide



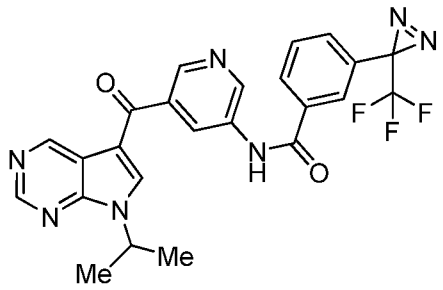
The title compound was prepared according to the method described for **Example 34** starting from (5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 95**) and 2-(3-benzoylphenyl)acetic acid to afford the title compound in 86% yield, 31 mg.

LCMS (system 3): R_t = 3.05 min; m/z 504 $[M+H]^+$.

Example 289 2-(4-benzoylphenyl)-N-(5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)acetamide

The title compound was prepared according to the method described for **Example 34** starting from (5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 95**) and 2-(4-benzoylphenyl)acetic acid (JOC, 1961, 1635) to afford the title compound in 94% yield, 34 mg. LCMS (system 3): R_t = 3.12 min; m/z 504 $[M+H]^+$.

Example 290: N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-3-[3-(trifluoromethyl)-3H-diaziren-3-yl]benzamide



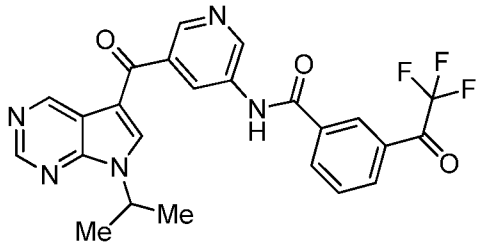
The title compound was prepared according to the method described for Example 34 starting from (5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 95**) and 3-[3-(trifluoromethyl)-3H-diaziren-3-yl]benzoic acid (**Preparation 197**) to afford the title compound as a white solid in 36% yield, 23 mg.

^{1}H NMR (400 MHz, d4-MeOH) δ:1.65 (s, 6H), 5.20 (m, 1H), 7.52-7.61 (m, 4H), 7.79 (s, 1H), 8.07 (m, 1H), 8.29 (s, 1H), 8.94 (s, 1H), 8.81 (m, 1H), 9.55 (s, 1H).

Example 291: N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-4-[3-(trifluoromethyl)-3H-diaziren-3-yl]benzamide

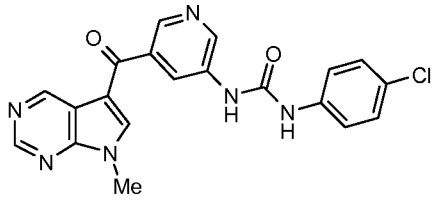
The title compound was prepared according to the method described for **Example 34** starting from (5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 95**) and 4-[3-(trifluoromethyl)-3H-diaziren-3-yl]benzoic acid to afford the title compound as a white solid in 4% yield, 2 mg. LCMS (system 3): R_t = 3.64 min; m/z 494 $[M+H]^+$.

Example 292: N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-3-(trifluoroacetyl)benzamide



The title compound was prepared according to the method described for **Example 34** starting from (5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 95**) and 3-(trifluoroacetyl)benzoic acid (**Preparation 200**) to afford the title compound as a white solid in 80% yield, 41 mg. LCMS (system 3): R_t = 2.52 min; m/z 482 $[M+H]^+$.

Example 293: 1-(4-chlorophenyl)-3-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}urea



1-chloro-4-isocyanatobenzene (24 mg, 0.15 mmol) was added to (5-aminopyridin-3-yl)(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (30 mg, 0.12 mmol) (**Preparation 232**) in pyridine (1.0 mL). The mixture was stirred at room temperature overnight then evaporated *in vacuo* to yield the product as a crude residue. The crude residue was purified by preparative HPLC to afford the title compound in 49% yield, 24 mg.

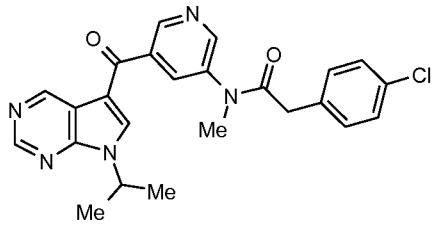
LCMS: R_t = 1.58 min; m/z 407 $[M+H]^+$

The following Examples were prepared according to the method described above for **Example 293**, starting from (5-aminopyridin-3-yl)(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 232**) and the appropriate isocyanates.

Example	Name	Data
294	1-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-3-[4-(trifluoromethyl)phenyl]urea	LCMS: R_t = 1.64 min; m/z 441 $[M+H]^+$
295	1-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-3-[3-(trifluoromethyl)phenyl]urea	LCMS: Rt = 1.64 min; m/z 441

		$[M+H]^+$
296	1-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-3-[4-(trifluoromethoxy)phenyl]urea	LCMS: Rt = 1.67 min; m/z 457 $[M+H]^+$

Example 297: 2-(4-chlorophenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-N-methylacetamide



(4-chlorophenyl)acetic acid (22 mg, 0.13 mmol) was added to a stirring mixture of (7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)[5-(methylamino)pyridin-3-yl]methanone (30 mg, 0.10 mmol) (**Preparation 149**) andN-[(dimethylamino)(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methylene]-N-methylmethanaminium hexafluorophosphate (57 mg, 0.15 mmol) in pyridine (1.0 mL). The mixture was heated to 50 °C for 16 hours, evaporated *in vacuo* and partitioned between saturated aqueous sodium bicarbonate (10 mL) and EtOAc (10 mL). The aqueous layer was washed with further EtOAc (2 x 10 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* and purified by preparative HPLC to afford the title compound 43% yield, 19 mg,

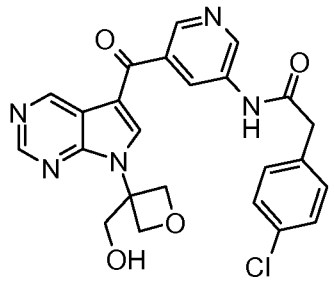
^{1}H NMR (400 MHz, DMSO) δ*:* 1.52 (d, 6H), 3.40 (br. s, 3H), 3.59 (s, 2H), 5.00-5.18 (m, 1H), 7.00-7.42 (m, 4H), 8.21 (s, 1H), 8.50 (s, 1H), 8.86 (s, 1H), 8.90-9.12 (m, 2H), 9.48 (s, 1H);

LCMS: R_t = 2.99 min; m/z 448 $[M+H]^+$

The following Example was prepared according to the method described above for **Example 297**, starting from (7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)[5-(methylamino)pyridin-3-yl]methanone (**Preparation 149**) and the appropriate acid.

Example	**Name**	**Data**
298	2-(4-cyanophenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-N-methylacetamide	LCMS: R_t = 2.86 min; m/z 439 $[M+H]^+$

Example 299: 2-(4-Chloro-phenyl)-N-{5-[7-(3-hydroxymethyl-oxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide



N-(5-{7-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-pyridin-3-yl)-2-(4-chloro-phenyl)-acetamide (**Preparation 203** 35 mg, 0.059 mmol) was dissolved in dry THF (0.5 mL) and tetrabutylammonium fluoride (0.065 mL of a 1M solution in THF, 0.065 mmoL) was added. The reaction was stirred for 30 min at room temperature. The mixture was partitioned between water and EtOAc. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were concentrated and purified by preparative HPLC to give the title compound in quantitative yield 28 mg.

LCMS (System 4): R_t = 3.03 min; m/z 478 $[M+H]^+$

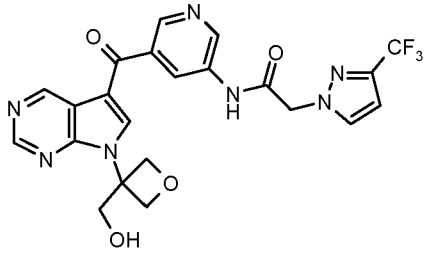
Example 300: N-{5-[7-(3-Hydroxymethyl-oxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-trifluoromethyl-phenyl)-acetamide:

The title compound was prepared according to the method described for **Example 299** starting from N-(5-{7-[3-(tert-butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-pyridin-3-yl)-2-(4-trifluoromethyl-phenyl)-acetamide (**Preparation 204)** to afford the title compound as a white solid in quantitative yield, 30 mg. LCMS: R_t = 2.74 min; m/z 512 $[M+H]^+$.

Example 301: 2-(5-chloropyridin-2-yl)-N-[5-({7-[3-(hydroxymethyl)oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide

The title compound was prepared according to the method described for **Example 299** starting from N-[5-({7-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-(5-chloropyridin-2-yl)acetamide (**Preparation 223**) to afford the title compound as a pale yellow liquid in 87% yield, 23 mg. LCMS (System 4): R_t = 1.57 min; m/z 479 $[M+H]^+$.

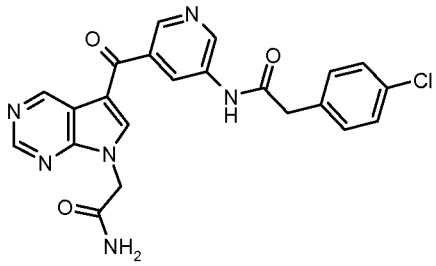
Example 302: N-[5-({7-[3-(hydroxymethyl)oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide



The title compound was prepared according to the method described for **Example 299** starting from N-[5-({7-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide (34 mg, 0.055 mmol) (**Preparation 224**) to give the the title compound in 63% yield, 17.7mg.

LCMS (System 5) R_t = 1.57 min; m/z 502 $[M+H]^+$.

Example 303: N-(5-{[7-(2-amino-2-oxoethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-chlorophenyl)acetamide



To a stirred solution of 2-(4-chlorophenyl)-N-[5-(7H-pyrrolo[2,3-d]pyrimidin-5-ylcarbonyl)pyridin-3-yl]acetamide (**Example 308,** 50 mg, 0.13 mmol) in DMF (1 ml) was added Cs_2CO_3 (75mg, 0.23 mmol) followed by 2-bromoacetamide (21.3mg, 0.154 mmol). The reaction was then stirred at room temperature overnight. The reaction was quenched with water (5 mL) and extracted with EtOAc (3 x 5 mL). The organics were combined, washed with water (5 mL) then brine (5 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by preparative HPLC gave the title compound in 59% yield, 34mg.

LCMS (System 4): R_t = 1.56 min; m/z 449 $[M+H]^+$.

Example 304: 2-{5-[(5-{[(4-chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}-N,N-dimethylacetamide

{5-[(5-{[(4-chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}acetic acid potassium salt (**Example 307**, 50 mg, 0.102 mmol) was added to a stirred solution of dimethyl amine HCl (12.5 mg, 0.153 mmol) and HATU (58.2mg, 0.153 mmol) in pyridine (2 mL) and the resultant solution was stirred at 50°C (reactivial) for 14 hours. The reaction was cooled to 25°C, diluted with DCM (5 mL) then quenched with saturated $NaHCO_3$ (aq) (5 mL) and extracted with further DCM (3 x 5 mL). The organics were combined, washed with saturated brine (5 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by preparative HPLC gave the title compound in 55% yield, 26.6mg.

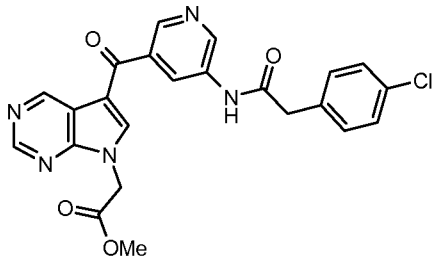
LCMS: R_t = 1.86 min; m/z 477 $[M+H]^+$.

Example 305: 2-(4-chlorophenyl)-N-[5-({7-[2-(methylamino)-2-oxoethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide

{5-[(5-{[(4-chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}acetic acid potassium salt (**Example 307**, 50 mg, 0.102 mmol) was added to a stirred solution of methyl amine hydrochloride (10.3 mg, 0.153 mmol) and HATU (58.2mg, 0.153 mmol) in pyridine (2 mL) . The resultant solution was stirred at 50 °C (reactivial) for 14 hours. The reaction was cooled to 25 °C, diluted with DCM (5 mL) then quenched with saturated $NaHCO_3$ (aq) (5 mL) and extracted with further DCM (3 x 5 mL). The organics were combined, washed with saturated brine (5 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo.* Purification by preparative HPLC gave the title compound in 65% yield, 30.5mg.

LCMS: R_t = 2.63 min; m/z 463 $[M+H]^+$.

Example 306 Methyl {5-[(5-{[(4-chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}acetate



To a stirred solution of 2-(4-chlorophenyl)-N-[5-(7H-pyrrolo[2,3-d]pyrimidin-5-ylcarbonyl)pyridin-3-yl]acetamide (**Example 308**, 250mg, 0.638 mmol) in DMF (4 mL) was added Cs_2CO_3 (374mg, 1.15 mmol) followed by methyl bromoacetate (73uL, 0.766 mmol). The reaction was stirred at 25 °C for 3 hours and then quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). The organics were combined, washed with water (10 mL) and saturated brine (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give a pale yellow oil (356mg) which solidified on standing. Purification by column chromatography on silica gel (gradient of 0-100% 90:10:1 DCM/MeOH/NH3 in DCM) gave the title compound as a pale yellow solid in 70% yield, 208 mg. ^{1}HNMR (400MHz, $CDCl_3$) δ 3.78 (s, 2H), 3.81 (s, 3H), 5.15 (s, 2H), 7.29-7.41 (m, 4H), 7.51 (s, 1H), 7.88 (s, 1H), 8.46 (m, 1H), 8.78-8.82 (m, 2H), 9.04 (s, 1H), 9.65 (s, 1H). LCMS (System 4): R_t = 2.07 min; m/z 464 $[M+H]^+$.

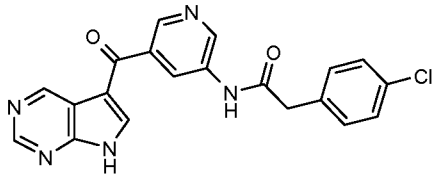
Example 307 {5-[(5-{[(4-chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}acetic acid potassium salt

To a suspension of methyl {5-[(5-{[(4-chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}acetate (**Example 306**, 197 mg, 0.425 mmol) in MeOH (4 mL) was added an aqueous solution of KOH (0.425 mL of a 1M solution, 0.425 mmol) and then further MeOH (4 mL) was added. The reaction was stirred for 2 hours at room temperature. The reaction was concentrated in vacuo to give the title compound as a light brown solid in 99% yield, 205 mg.

LCMS (System 4): R_t = 1.76 min; m/z 450 $[M+H]^+$.

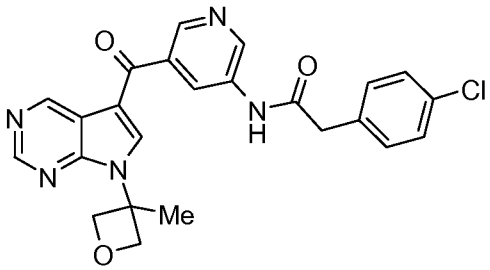
Example 308 : 2-(4-Chlorophenyl)-N-[5-(7H-pyrrolo[2,3-d]pyrimidin-5-ylcarbonyl)pyridin-3-yl]acetamide

The title compound was prepared according to the method described for **Example 46** to afford the title compound as a white solid in 87% yield, 930 mg.



^{1}H NMR (400 MHz, DMSO) ä: 3.74 (s, 2H), 7.38 (m, 4H), 8.34 (s, 1H), 8.46 (s, 1H), 8.71 (s, 1H), 8.94 (s, 1H), 8.97 (s, 1H), 9.45 (s, 1H), 10.66 (s, 1H), 13.14 (s, 1H);LCMS (system 9): R_t = 2.87 min; m/z 392 $[M+H]^+$.

Example 309: 2-(4-chlorophenyl)-N-(5-{[7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide



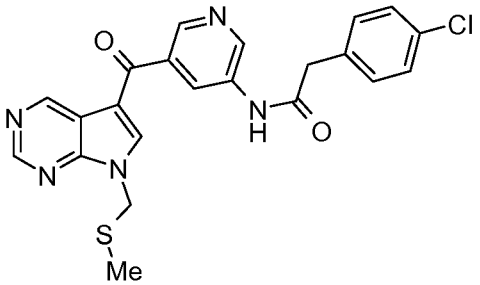
(5-aminopyridin-3-yl)[7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**Preparation 222,** 15.5 mg, 0.05 mmol) was added to a stirring mixture of 4-chlorophenylacetic acid (11.1mg, 0.065 mmol) and HATU (28.5 mg, 0.075 mmol) in pyridine (0.25 mL). The mixture was heated to 50 °C and stirred for 16 hours. The mixture was allowed to cool to room temperature and saturated sodium bicarbonate solution (5 mL) was added. The mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic fractions were washed with brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure to obtain the crude product which was autopurified.

LCMS (system 4): R_t = 3.08 min; m/z 462$[M+H]^+$.

The following Examples were prepared according to the method described above for **Example 309** starting from 5-aminopyridin-3-yl)[7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**Preparation 222**) and the appropriate acids.

Example	Name	Data
310	2-(5-chloropyridin-2-yl)-N-(5-{[7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide	LCMS (System 2): R_t = 0.88 min; m/z 463 $[M+H]^+$ Using **Preparation 90**
311	N-(5-{[7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide	LCMS (System 2): R_t = 0.97 min; m/z 486 $[M+H]^+$
312	N-(5-{[7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide	LCMS (System 2): R_t = 0.92 min; m/z 487 $[M+H]^+$ Using **Preparation 85**

Example 313: 2-(4-chlorophenyl)-N-[5-({7-[(methylthio)methyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide



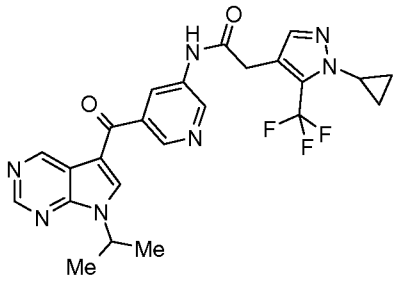
Potassium carbonate (38 mg, 0.275 mmol) was added to a stirring solution of 2-(4-chlorophenyl)-N-[5-(7H-pyrrolo[2,3-d]pyrimidin-5-ylcarbonyl)pyridin-3-yl]acetamide (**Example 308**, 60.0 mg, 0.153 mmol) in DMF (1.0 mL) at room temperature. After 10 min, chloromethyl methyl sulfide (19 µL, 0.23 mmol) was added to the mixture and the reaction was stirred for 24 hours at room temperature. Water (3 mL) was added to the mixture and it was extracted with EtOAc (3 x 5 mL). The combined organic fractions were washed with water (5 mL), brine (5 mL), dried over magnesium sulfate and concentrated under reduced pressure to give a pale yellow oil. The crude material was purified by column chromatography on silica gel (gradient of 100% DCM to 90:10:1 DCM/MeOH/NH_3) to give the title compound as a pale yellow solid in 36% yield, 25 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.13 (s, 3H), 3.79 (s, 2H), 5.39 (s, 2H), 7.30-7.34 (m, 3H), 7.40-7.43 (m, 2H), 8.02 (s, 1H), 8.52 (m, 1H), 8.74-8.75 (d, 1H), 8.82-8.83 (d, 1H), 9.05 (s,1H), 9.65 (s, 1H); LCMS (system 4): R_t = 1.97 min; m/z 452; 454 $[M+H]^+$.

Example 314 : 2-(4-chlorophenyl)-N-[5-({7-[(methylsulfonyl)methyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide

Potassium peroxomonosulfate (Oxone, 67.2 mg, 0.110 mmol) was added to a stirring solution of 2-(4-chlorophenyl)-N-[5-({7-[(methylthio)methyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide (**Example 313**, 25.0 mg, 0.055 mmol) in methanol (1.0 mL) and water (0.25 mL) at 0 °C. After 1 hour, the reaction was allowed to warm to room temperature and stirred for 24 hours. The reaction mixture was cooled to 0 °C and sodium metabisulfite (0.5M, 1ml) was added. The reaction mixture was evaporated under reduced pressure to remove the methanol. Water (3 mL) was added to the mixture and it was extracted with EtOAc (3 x 5 mL). The combined organic fractions were washed with water (5 mL), brine (5 mL), dried over magnesium sulfate the solvent was removed under reduced pressure to give the crude product as an off-white solid. The crude material was purified by column chromatography on silica gel (gradient of 100% DCM to 90:10:1 DCM/MeOH/NH_3) to give the title compound as a pale yellow solid in 17% yield, 27 mg. LCMS (system 4): R_t = 1.91 min; m/z 484; 486 $[M+H]^+$.

Example 315: 2-(1-Cyclopropyl-5-trifluoromethyl-1H-pyrazol-4-yl)-N-[5-(7-isopropyl-7H-pyrrolo [2, 3-d] pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide



To a solution of (5-Amino-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 95**, 50 mg, 0.17 mmol), (1-Cyclopropyl-5-trifluoromethyl-1H-pyrazol-4-yl)-acetic acid (**Preparation 141**, 47.1 mg, 0.21 mmol) and TEA (0.08 mL, 0.62 mmol) in THF (1 mL), 1-propylphosphonic acid cyclic anhydride (50% solution in EtOAc, 0.26 mL, 0.44 mmol) was added and the mixture was stirred at room temperature for 14 hours. The reaction mixture was evaporated under reduced pressure and the residue partitioned between water and ethyl acetate. The organic layer was

washed with saturated sodium bicarbonate solution and dried (Na_2SO_4) and evaporated *in vacuo*. Purification by column chromatography on silica gel (gradient of EtOAc:Hexane 0:100 to 80:20) gave the title compound as a white solid in 76 % yield, 67 mg. ^{1}H NMR (400 MHz, DMSO-D6) δ*:* 1.05-1.07 (m, 2H), 1.08-1.15 (m, 2H), 1.54 (d, 6H), 3.73-3.76 (m, 3H), 5.06-5.13 (m, 1H), 7.55 (s, 1H), 8.44 (s, 1H), 8.51 (s, 1H), 8.73 (s, 1H), 8.94 (d, 1H), 8.99 (s, 1H), 9.44 (s, 1H), 10.61 (s, 1H).LCMS (System 10): R_t = 3.03 min m/z 498 $[M+H]^+$

Example 316: N-(5-{[2-amino-7-(1-hydroxy-2-methylpropan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(5-bromopyridin-2-yl)acetamide

The title compound was prepared according to the method described for **Example 34** at 50°C using [2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl](5-aminopyridin-3-yl)methanone (**Preparation 48**) and (5-bromopyridin-2-yl)acetic acid to afford the title compound as a yellow solid in 60% yield, 75 mg. LCMS (System 10): R_t = 2.69 min; m/z 524 $[M+H]^+$

Example 317: 2-(5-bromopyridin-2-yl)-N-(5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide

The title compound was prepared according to the method described for Example 1 with DIPEA using (5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (Preparation 95) and (5-bromopyridin-2-yl)acetic acid to afford the title compound as a yellow solid in 45% yield, 75 mg. LCMS (System 9): R_t = 2.97 min; m/z 479 $[M+H]^+$.

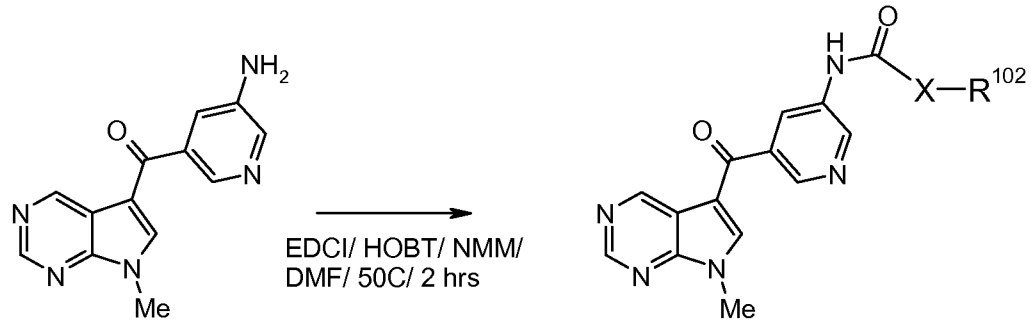
Example 318 : N-{5-[(2-Amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-bromopyridin-2-yl)acetamide

The title compound was prepared according to the method described for **Example 1** with DIPEA using (2-amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(5-aminopyridin-3-yl)methanone (**Preparation 122**) and (5-bromopyridin-2-yl)acetic acid to afford the title compound as a colourless oil in 57% yield, 75 mg.

LCMS (System 10): R_t = 2.81 min; m/z 494 $[M+H]^+$.

Library Protocol 1

The compounds below were prepared in parallel in the following manner.

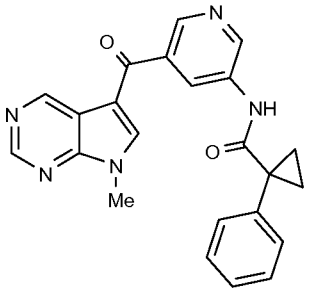


A 0.25 M stock solution of (5-amino-pyridin-3-yl)-(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 110**) in anhydrous DMF was prepared. Stock solutions (0.30 M) of each acid monomer was prepared in anhydrous DMF. A stock solution of EDCI (0.5 M) and HOBT (0.05 M) in anhydrous DMF

were prepared. 300µl (90 µmol,) of each acid monomer solution was dispensed to 8 mL vials, followed by 300 µl (75 umol) of (5-amino-pyridin-3-yl)-(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone solution. N-methyl morpholine (150 µmol, 2.0 eq), 300 µl EDCI solution (150 µmol) and HOBT (15µmol) were added to each vial. The vials were capped and shaken at 50 °C for 2 hours. The solvent was removed using a Speedvac, and the final product purified by HPLC under the conditions listed to provide the final compounds.

Example	Name	Data
319	2-(4-chlorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS: R_t = 2.59 min; m/z 406 $[M+H]^+$
320	3-(4-chlorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}propanamide	LCMS: R_t = 2.70 min; m/z 420 $[M+H]^+$
321	3-(3-methylphenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}propanamide	LCMS: R_t = 2.69 min; m/z 400 $[M+H]^+$
322	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-3-(pyridin-3-yl)propanamide	LCMS: R_t = 1.80 min; m/z 387 $[M+H]^+$
323	3-(3-chlorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}propanamide	LCMS: R_t = 2.69 min; m/z 420 $[M+H]^+$
324	3-(3-fluorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}propanamide	LCMS: R_t = 2.56 min; m/z 404 $[M+H]^+$
325	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[2-(trifluoromethoxy)phenoxy]acetamide	LCMS: R_t = 2.80 min; m/z 472 $[M+H]^+$
326	3-(2-methylphenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}propanamide	LCMS:R_t = 2.63 min; m/z 400 $[M+H]^+$
327	3-(2-fluorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}propanamide	LCMS: R_t = 2.53 min; m/z 404 $[M+H]^+$
328	3-(4-fluorophenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}propanamide	LCMS: R_t = 2.55 min; m/z 404 $[M+H]^+$
329	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-3-phenylpropanamide	LCMS:R_t = 2.50 min; m/z 386 $[M+H]^+$
330	3-(4-methylphenyl)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}propanamide	LCMS:R_t = 2.65 min; m/z 400 $[M+H]^+$
331	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-{[(trifluoromethyl)sulfonyl]amino}phenyl)acetamide	LCMS: R_t = 2.60 min; m/z 519 $[M+H]^+$
332	N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-phenoxyacetamide	LCMS: R_t = 2.53 min; m/z 388 $[M+H]^+$
333	2-[4-(methoxymethyl)phenyl]-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS: R_t = 2.31 min; m/z 416 $[M+H]^+$
334	2-(4-fluorophenoxy)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide	LCMS: R_t = 2.44 min; m/z 406 $[M+H]^+$

Example 336: N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-1-phenylcyclopropanecarboxamide



The title compound was prepared according to the method described for **Library protocol 1** starting from (5-amino-pyridin-3-yl)-(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 110**) and 1-phenylcyclopropanecarboxylic acid to afford the title compound. LCMS: R_t = 2.61 min; m/z 398 $[M+H]^{+\cdot}$

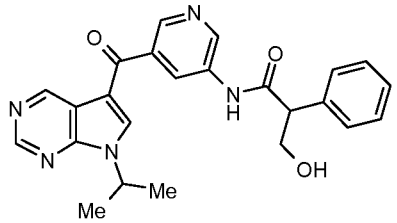
Example 337: N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}indane-2-carboxamide

The title compound was prepared according to the method described for **Library protocol 1** starting from (5-amino-pyridin-3-yl)-(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 110**) and indane-2-carboxylic acid to afford the title compound. LCMS: R_t = 2.58 min; m/z 398 $[M+H]^{+\cdot}$

Example 338: (2R)-N-{5-[(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-phenylpropanamide

The title compound was prepared according to the method described for **Library protocol 1** starting from (5-amino-pyridin-3-yl)-(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 110**) and (2R)-2-phenylpropanoic acid to afford the title compound. LCMS: R_t = 2.52 min; m/z 386 $[M+H]^{+\cdot}$

Example 339: 3-hydroxy-2-phenyl-N-(5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)propanamide



The title compound was prepared according to the method described for **Example 167** using (5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 95**) and tropic acid to afford the title compound as a yellow solid in 7% yield, 15 mg.

^{1}H NMR (400 MHz, DMSO-*d6*) δ: 1.57 (d, 6H), 3.16-3.22 (m, 1H), 3.37-3.41 (m, 1H), 3.60-3.64 (m, 1H), 5.10 (m, 1H), 6.30 (t, 1H), 7.10 (t, 1H), 7.20 (t, 2H), 7.30-7.32 (m, 3H), 8.12 (s, 1H), 8.15 (d, 1H), 8.61 (s, 1H), 8.96 (s, 1H), 9.44 (s, 1H).

LCMS (system 10): R_t = 2.36 min; m/z 430 $[M+H]^+$.

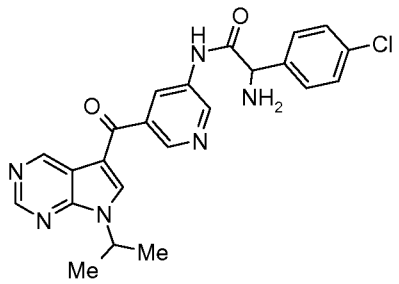
The following Example was prepared according to **Examples 1** and **34** for Methods a and b as described above.

Example	Name	Data
340	N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]-pyridin-3-yl}-2-(5-methoxy-1H-indol-1-yl)acetamide	LCMS (system 8): R_t = 1.63 min; m/z 469 $[M+H]^+$

The following examples were prepared according to **Example 356** using (5-amino-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 95**) and the appropriate acid.

Example	Name	Data
343	3-chloro-N-(5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)benzamide	LCMS R_t = 2.95 min; m/z 420 $[M+H]^+$.
344	4-chloro-N-(5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)benzamide	LCMS R_t = 2.93 min; m/z 420 $[M+H]^+$.
345	N-(5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-4-(trifluoromethyl)benzamide	LCMS R_t = 2.99 min; m/z 454 $[M+H]^+$.
346	N-(5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-4-(trifluoromethoxy)benzamide	LCMS R_t = 3.05 min; m/z 470 $[M+H]^+$.
347	2-(2-cyanophenoxy)-N-(5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide	LCMS R_t = 0.67 min; m/z 441 $[M+H]^+$.
348	N-(5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethoxy)phenoxy]acetamide	LCMS R_t = 3.01 min; m/z 500 $[M+H]^+$.

Example 350 : 2-amino-2-(4-chlorophenyl)-N-(5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)acetamide

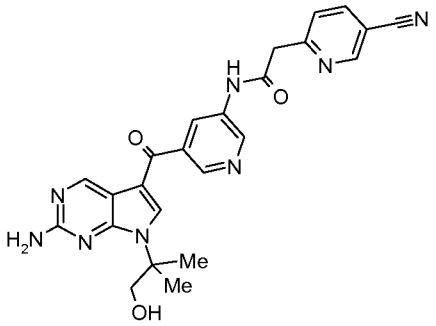


To tert-butyl (1-(4-chlorophenyl)-2-((5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)amino)-2-oxoethyl)carbamate (**Preparation 299**, 64 mg, 0.11 mmol) was added 4M HCl/dioxane (5 mL) and the reaction stirred at room temperature for 18 hours. The mixture was evaporated *in vacuo* and purified by preparative reverse phase HPLC to give the title compound as a beige solid in 8% yield, 4 mg.

^{1}H NMR (400 MHz, MeOD) δ: 1.59 (d, 6H), 4.63 (s, 1H), 5.16 (m, 1H), 7.35 (d, 2H), 7.47 (d, 2H), 8.33 (s, 1H), 8.62 (s, 1H), 8.69 (s, 1H), 8.88 (s, 1H), 8.92 (s, 1H), 9.47 (s, 1H).

LCMS R_t = 2.81 min; MS m/z 449 $[M+H]^+$

Example 351: N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(5-cyano-pyridin-2-yl)-acetamide

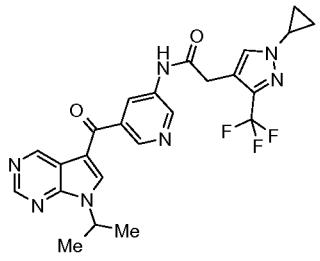


To a solution of N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(5-bromo-pyridin-2-yl)-acetamide (**Example 316**, 75 mg, 0.143 mmol) in DMF (2 mL) was added $Zn(CN)_2$ (25 mg, 0.215 mmol) and the reaction mixture was degassed with argon for 10 minutes. $Pd_2(dba)_3$ (3 mg, 0.002 mmol) and 1,1'-bis(diphenylphosphino)ferrocene 6 mg, 0.011 mmol) were then added and the resultant reaction mixture was heated at 100^{0}C for 40 minutes under microwave irradiation. The reaction mixture was diluted with EtOAc (20 mL) and washed with water (2 x 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by preparative TLC (7% MeOH in DCM) to afford the title compound as yellow solid in 31% yield, 21 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.63 (s, 6H), 3.89 (d, 2H), 4.06 (s, 2H), 5.04 (t, 1H), 6.53 (s, 2H), 7.65-7.68 (m, 2H), 8.29 (dd, 1H), 8.40 (s, 1H), 8.64 (d, 1H), 8.93-8.97 (m, 3H), 10.75 (s, 1H).

LCMS (system 10): R_t = 2.50 min MS m/z 471$[M+H]^+$

Example 352: 2-(1-Cyclopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-N-[5-(7-isopropyl-7H-pyrrolo [2, 3-d] pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide



To a solution of (5-Amino-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 95**, 50 mg, 0.17 mmol), (1-Cyclopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-acetic acid (**Preparation 148**, 47.1 mg, 0.21 mmol) and TEA (0.08 mL, 0.62 mmol) in THF (1mL), 1-propylphosphonic acid cyclic anhydride (50% solution in EtOAc, 0.26 mL, 0.44 mmol) was added and the mixture was stirred at room temperature for 18 hours. The reaction mixture was evaporated under reduced pressure and the residue partitioned between water and EtOAc. The organic layer was washed with saturated sodium bicarbonate solution, dried (Na_2SO_4) and evaporated *in vacuo*. Purification by

column chromatography on silica gel (EtOAc) gave the title compound as a white solid in 77 % yield, 68 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.00-1.01 (m, 2H), 1.06-1.14 (m, 2H), 1.54 (d, 6H), 3.70 (s, 2H), 3.84 (m, 1H), 5.08-5.12 (m, 1H), 7.98 (s, 1H), 8.45 (s, 1H), 8.51 (s, 1H), 8.74 (s, 1H), 8.96 (d, 1H), 8.99 (s, 1H), 9.44 (s, 1H), 10.60 (s, 1H).

LCMS (system 10): R_t = 3.02 min MS m/z 498 $[M+H]^+$.

Example 353: racemic Methyl 2-{5-[(5-{[(4-chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}propanoate

The title compound was prepared according to the method described for **Example 229** using 2-(4-chlorophenyl)-N-[5-(7H-pyrrolo[2,3-d]pyrimidin-5-ylcarbonyl)pyridin-3-yl]acetamide (**Example 308**), methyl 2-bromopropionate and cesium carbonate. Purified using preparative HPLC (method 1) to afford the title compound.

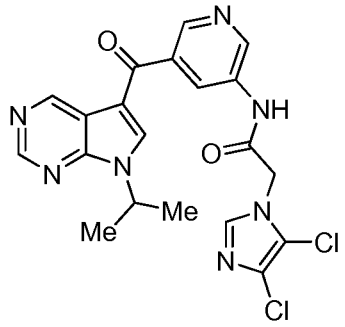
LCMS (system 2): R_t = 1.42 min MS m/z 478 $[M+H]^+$

Example 354: racemic 2-{5-[(5-{[(4-Chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}propanoic acid

The title compound was prepared according to the method described for **Preparation 155** using methyl 2-{5-[(5-{[(4-chlorophenyl)acetyl]amino}pyridin-3-yl)carbonyl]-7H-pyrrolo[2,3-d]pyrimidin-7-yl}propanoate (**Example 353**) to afford the title compound as a white solid in 100% yield, 97 mg.

LCMS (system 2): R_t = 1.40 min; m/z 464 $[M+H]^+$.

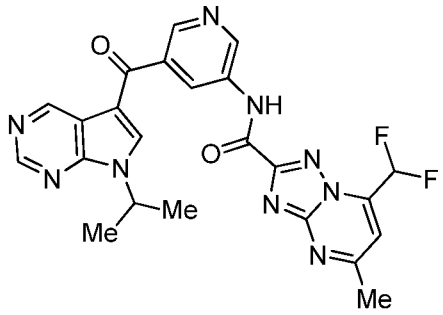
Example 355: 2-(4,5-Dichloro-imidazol-1-yl)-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide (method d)



(4,5-Dichloro-imidazol-1-yl)-aceticacid (25.2 mg, 0.130 mmol) was added to (5-amino-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (28.1 mg, 0.1 mmol), HATU (49.4 mg, 0.130 mmol) and DIPEA (51.7 uL, 0.300 mmol) in anhydrous DMF (1 mL). The mixture was stirred at 50°C for 16 hours and then evaporated *in vacuo* and purified by prep-HPLC (method 5) to afford the title compound in 46% yield, 21.2 mg.

LCMS (system 8): R_t = 1.55 min; m/z 458 [M+H]

Example 356: 7-Difluoromethyl-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide (method e)



7-Difluoromethyl-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carboxylic acid (29.64 mg, 0.130 mmol) was added to (5-amino-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (28.1 mg, 0.1 mmol), HATU (49.42 mg, 0.130 mmol) and DIPEA (22.4 uL, 0.13 mmol) in anhydrous DMF (1 mL). The mixture was stirred at 50°C for 16 hours and then evaporated *in vacuo* and purified by prep-HPLC (method 5) to afford the title compound in 12 % yield, 6.1 mg.
LCMS (system 8): R_t = 1.56 min; m/z 492 $[M+H]^+$

The following Examples were prepared according to one of the methods for **Examples 355** (Method d) and **356** (Method e) using (5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 95**).

Example	Name	Data
357	2-(4,5-Dichloro-imidazol-1-yl)-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.55 min; m/z 458 $[M+H]^+$. Prep HPLC (method 5)
358	2-(3,5-Dimethyl-1,2,4-triazol-1-yl)-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.43 min; m/z 419 $[M+H]^+$. Prep HPLC (method 5)
359	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(2-methyl-imidazol-1-yl)-acetamide	LCMS (system 8): R_t = 1.27 min; m/z 404 $[M+H]^+$. Prep HPLC (method 5)
360	2-Imidazo[2,1-b]thiazol-6-yl-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.42 min; m/z 446 $[M+H]^+$. Prep HPLC (method 5)
361	2-(4-Hydroxy-phthalazin-1-yl)-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.46 min; m/z 468 $[M+H]^+$. Prep HPLC (method 5)

362	2-(2,3-Dimethyl-imidazo[2,1-b]thiazol-6-yl)-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.48 min; m/z 474 $[M+H]^+$. Prep HPLC (method 5)
363	2-[4-(1-Hydroxy-cyclopentyl)-1,2,3-triazol-1-yl]-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.44 min; m/z 475 $[M+H]^+$. Prep HPLC (method 5) (From Prep 294)
364	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(5-m-tolyl-tetrazol-1-yl)-acetamide	LCMS (system 8): R_t = 1.57 min; m/z 482 $[M+H]^+$. Prep HPLC (method 5)
365	2-[4-(4-Fluoro-phenyl)-imidazol-1-yl]-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.45 min; m/z 484 $[M+H]^+$. Prep HPLC (method 5)
366	2-(5-Isopropyl-pyrazol-1-yl)-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.60 min; m/z 432 $[M+H]^+$. Prep HPLC (method 5) (Acid can be prepared in an analogus to method given in WO03/072572)
367	2-(2-Ethyl-imidazo[2,1-b]-1,3,4-thiadiazol-6-yl)-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.60 min; m/z 475 $[M+H]^+$. Prep HPLC (method 5)
368	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(2-methyl-imidazo[2,1-b]thiazol-6-yl)-acetamide	LCMS (system 8): R_t = 1.45 min; m/z 460 $[M+H]^+$. Prep HPLC (method 5) (from Prep 289)
369	2-(3-Chloro-5-methyl-1,2,4-triazol-1-yl)-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.48 min; m/z 439 $[M+H]^+$. Prep HPLC (method 5)
370	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(2-phenyl-imidazol-1-yl)-acetamide	LCMS (system 8): R_t = 1.34 min; m/z 466 $[M+H]^+$. Prep HPLC (method 5)

371	2-(2-Chloro-imidazo[2,1-b]thiazol-6-yl)-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.59 min; m/z 480 $[M+H]^+$. Prep HPLC (method 5)
372	2-Imidazol-1-yl-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.26 min; m/z 390 $[M+H]^+$. Prep HPLC (method 5)
373	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(3-methyl-imidazo[2,1-b]thiazol-6-yl)-acetamide	LCMS (system 8): R_t = 1.46 min; m/z 460 $[M+H]^+$. Prep HPLC (method 5)
374	2-[1-(4-Hydroxy-phenyl)-1H-pyrrol-3-yl]-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.57 min; m/z 481 $[M+H]^+$. Prep HPLC (method 5)
375	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl-acetamide	LCMS (system 8): R_t = 1.41 min; m/z 442 $[M+H]^+$. Prep HPLC (method 5)
376	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-pyrazin-2-yl-acetamide	LCMS (system 8): R_t = 1.44 min; m/z 402 $[M+H]^+$. Prep HPLC (method 5)
377	2-[4-(3-Hydroxy-phenyl)-1,2,3-triazol-1-yl]-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide	LCMS (system 8): R_t = 1.48 min; m/z 483 $[M+H]^+$. Prep HPLC (method 5) (from Prep 292)
378	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(5-phenyl-tetrazol-1-yl)-acetamide	LCMS (system 8): R_t = 1.63 min; m/z 468 $[M+H]^+$. Prep HPLC (method 5)

5

379	7-Difluoromethyl-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.56 min; m/z 492 $[M+H]^+$. Prep HPLC (method 5)
380	Furo[3,2-c]pyridine-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.73 min; m/z 427 $[M+H]^+$. Prep HPLC (method 5)
381	4-Methyl-furazan-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.61 min; m/z 392 $[M+H]^+$. Prep HPLC (method 5)
382	1-Methyl-1H-indazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.75 min; m/z 440 $[M+H]^+$. Prep HPLC (method 5)
383	1H-Indole-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.67 min; m/z 425 $[M+H]^+$. Prep HPLC (method 5)
384	2-Methyl-4-trifluoromethyl-thiazole-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.62 min; m/z 475 $[M+H]^+$. Prep HPLC (method 5)
385	5-Cyclopropyl-oxazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.67 min; m/z 417 $[M+H]^+$. Prep HPLC (method 5)
386	Pyridazine-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.52 min; m/z 388 $[M+H]^+$. Prep HPLC (method 5)
387	3-Methyl-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.53 min; m/z 458 $[M+H]^+$. Prep HPLC (method 5) (Acid from prep 290)

388	4-Methyl-pyridine-2-carboxylic acid[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.70 min; m/z 401 [M+H]+. Prep HPLC (method 5)
389	3-Cyclobutyl-1H-pyrazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.59 min; m/z 430 [M+H]+. Prep HPLC (method 5)
390	Oxazole-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.46 min; m/z 377 [M+H]+. Prep HPLC (method 5)
391	4-Methyl-1H-imidazole-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.52 min; m/z 390 [M+H]+. Prep HPLC (method 5)
392	1H-Pyrrolo[2,3-c]pyridine-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.56 min; m/z 426 [M+H]+. Prep HPLC (method 5) (Acid: Synthesis, 1993, 295-297)
393	5-Methyl-pyrazine-2-carboxylic acid[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.58 min; m/z 402 [M+H]+. Prep HPLC (method 5)
394	1,3-Dimethyl-1H-pyrazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.53 min; m/z 404 [M+H]+. Prep HPLC (method 6)
395	1H-Pyrazolo[4,3-b]pyridine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.46 min; m/z 427 [M+H]+. Prep HPLC (method 5) (Acid: see US 20110111046)
396	5-Ethyl-isoxazole-3-carboxylic acid[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.63 min; m/z 405 [M+H]+. Prep HPLC (method 5)

397	2-Methyl-2H-pyrazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.54 min; m/z 390 [M+H]+. Prep HPLC (method 5)
398	Quinoline-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.66 min; m/z 437 [M+H]+. Prep HPLC (method 5)
399	5-Fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.61 min; m/z 444 [M+H]+. Prep HPLC (method 5) (Acid: WO2008/107543)
400	1,5-Dimethyl-1H-pyrazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.57 min; m/z 404 [M+H]+. Prep HPLC (method 5)
401	2-Cyclopropyl-oxazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.64 min; m/z 417 [M+H]+. Prep HPLC (method 5)
402	4-Trifluoromethyl-thiazole-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.58 min; m/z 461 [M+H]+. Prep HPLC (method 5)
403	6,7-Dihydro-5H-pyrrolo[1,2-c]imidazole-1-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.51 min; m/z 416 [M+H]+. Prep HPLC (method 5) (Acid can be preparaed by oxidation of aldehyde described in Tetrahedron, 1999, 8111)
404	Thieno[3,2-c]pyridine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.77 min; m/z 443 [M+H]+. Prep HPLC (method 5)
405	1-Methyl-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.60 min; m/z 458 [M+H]+. Prep HPLC (method 5)

406	Imidazo[1,5-a]pyridine-7-carboxylicacid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.47 min; m/z 426 [M+H]+. Prep HPLC (method 5)
407	1H-Pyrrolo[2,3-b]pyridine-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.54 min; m/z 426 [M+H]+. Prep HPLC (method 5)
408	3-Ethyl-isoxazole-5-carboxylic acid[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.60 min; m/z 405 [M+H]+. Prep HPLC (method 5)
409	4-Methoxy-pyridine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.67 min; m/z 417 [M+H]+. Prep HPLC (method 5)
410	Pyrimidine-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.46 min; m/z 388 [M+H]+. Prep HPLC (method 5)
411	3-Methyl-1H-pyrazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.46 min; m/z 390 [M+H]+. Prep HPLC (method 5)
412	5-Methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.54 min; m/z 440 [M+H]+. Prep HPLC (method 5)
413	5-Methyl-pyrimidine-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.60 min; m/z 402 [M+H]+. Prep HPLC (method 5)
414	Thieno[3,2-b]pyridine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.64 min; m/z 443 [M+H]+. Prep HPLC (method 5)

415	Pyrazolo[1,5-a]pyrimidine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.54 min; m/z 427 [M+H]+. Prep HPLC (method 5)
416	4,5,6,7-Tetrahydro-1,2-benzisoxazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.75 min; m/z 431 [M+H]+. Prep HPLC (method 5)
417	Imidazo[1,5-a]pyridine-3-carboxylicacid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.75 min; m/z 426 [M+H]+. Prep HPLC (method 5)
418	1H-Pyrrolo[2,3-b]pyridine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.65 min; m/z 426 [M+H]+. Prep HPLC (method 5)
419	1,4,5,6-Tetrahydro-cyclopentapyrazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.59 min; m/z 416 [M+H]+. Prep HPLC (method 5)
420	4-Amino-pyrimidine-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.41 min; m/z 403 [M+H]+. Prep HPLC (method 5)
421	1H-Pyrrolo[2,3-c]pyridine-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.32 min; m/z 426 [M+H]+. Prep HPLC (method 5)
422	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-methyl-isonicotinamide	LCMS (system 8): Rt = 1.51 min; m/z 401 [M+H]+. Prep HPLC (method 5)
423	Imidazo[1,2-a]pyridine-6-carboxylicacid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.33 min; m/z 426 [M+H]+. Prep HPLC (method 5)

424	1H-1,2,4-Triazole-3-carboxylic acid[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.38 min; m/z 377 [M+H]+. Prep HPLC (method 7)
425	5-Methoxy-pyridine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.66 min; m/z 417 [M+H]+. Prep HPLC (method 5)
426	Cinnoline-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.57 min; m/z 438 [M+H]+. Prep HPLC (method 5)
427	[1,2,4]Triazolo[1,5-a]pyridine-7-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.51 min; m/z 427 [M+H]+. Prep HPLC (method 5)
428	Pyrazolo[1,5-a]pyrimidine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.54 min; m/z 427 [M+H]+. Prep HPLC (method 5)
429	Pyridine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): Rt = 1.62 min; m/z 387 [M+H]+. Prep HPLC (method 5)
430	5-Chloro-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-nicotinamide	LCMS (system 8): Rt = 1.62 min; m/z 421 [M+H]+. Prep HPLC (method 5)
431	4H-Furo[3,2-b]pyrrole-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo1[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.59 min; m/z 415 $[M+H]^+$. Prep HPLC (method 5)
432	Imidazo[1,2-a]pyridine-7-carboxylicacid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.34 min; m/z 426 $[M+H]^+$. Prep HPLC (method 5)

433	1-Ethyl-1H-pyrazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.52 min; m/z 404 $[M+H]^+$. Prep HPLC (method 5)
434	1-Isopropyl-1H-imidazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.58 min; m/z 418 $[M+H]^+$. Prep HPLC (method 5) (Acid :WO2010/009062
435	8-Methoxy-imidazo[1,2-a]pyrazine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.62 min; m/z 457 $[M+H]^+$. Prep HPLC (method 5) (Acid can be prepared by carbonylation of the bromide e.g. WO2010/078408)
436	1H-Pyrrolo[2,3-b]pyridine-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.55 min; m/z 426 $[M+H]^+$. Prep HPLC (method 5)
437	2-Methyl-5-propyl-2H-pyrazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.69 min; m/z 432 $[M+H]^+$. Prep HPLC (method 5)
438	4-Isopropyl-thiazole-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.79 min; m/z 435 $[M+H]^+$. Prep HPLC (method 5) (Acid: WO2007/017144
439	3-Methyl-furo[2,3-c]pyridine-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.77 min; m/z 441 $[M+H]^+$. Prep HPLC (method 5) (Acid: WO04052348)
440	6-Methyl-pyridine-2-carboxylic acid[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.69 min; m/z 401 $[M+H]^+$. Prep HPLC (method 5)
441	5-Chloro-1-methyl-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.63 min; m/z 492 $[M+H]^+$. Prep HPLC (method 5)

442	5-Methoxy-1H-benzimidazole-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.63 min; m/z 456 $[M+H]^+$. Prep HPLC (method 5) (Acid: US2007/017144)
443	4-Chloro-1,5-dimethyl-1H-pyrazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.65 min; m/z 438 $[M+H]^+$. Prep HPLC (method 5)
444	1H-Pyrrolo[3,2-c]pyridine-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.58 min; m/z 426 $[M+H]^+$. Prep HPLC (method 5)
445	4-Ethyl-pyridine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.76 min; m/z 415 $[M+H]^+$. Prep HPLC (method 5) (Acid: JOC, 1990, 55, 738-741)
446	2,3-Dihydro-1,4-dioxino[2,3-b]pyridine-7-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.54 min; m/z 445 $[M+H]^+$. Prep HPLC (method 5)
447	1H-Pyrrolo[3,2-b]pyridine-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.58 min; m/z 426 $[M+H]^+$. Prep HPLC (method 5)
448	Pyrazolo[1,5-a]pyridine-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.59 min; m/z 426 $[M+H]^+$. Prep HPLC (method 5) (Acid: J. Med. Chem. (2007), 45(21), 4594-4597)
449	6-Methoxy-quinoline-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.68 min; m/z 467 $[M+H]^+$. Prep HPLC (method 5)
450	5-Methyl-2-(2,2,2-trifluoro-ethyl)-2H-pyrazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.66 min; m/z 472 $[M+H]^+$. Prep HPLC (method 5) (Acid: WO 2008/016192)

451	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-4-trifluoromethyl-nicotinamide	LCMS (system 8): R_t = 1.58 min; m/z 455 $[M+H]^+$. Prep HPLC (method 5)
452	1-(2-Cyano-ethyl)-1H-pyrazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.46 min; m/z 429 $[M+H]^+$. Prep HPLC (method 5)
453	Furo[3,2-c]pyridine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.45 min; m/z 427 $[M+H]^+$. Prep HPLC (method 5) (Acid: J.Het.Chem. (1987),24(2), 373-6)
454	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.32 min; m/z 426 [M+H]+. Prep HPLC (method 5)
455	Furo[3,2-c]pyridine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.70 min; m/z 427 $[M+H]^+$. Prep HPLC (method 5)
456	2,4-Dimethyl-oxazole-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.58 min; m/z 405 $[M+H]^+$. Prep HPLC (method 5)
457	1-Methyl-1H-pyrrolo[2,3-c]pyridine-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.32 min; m/z 440 $[M+H]^+$. Prep HPLC (method 5) (Acid: WO07017144)
458	5,6-Dihydro-4H-pyrrolo[1,2-b]pyrazole-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.59 min; m/z 416 $[M+H]^+$. Prep HPLC (method 5)
459	2-Cyclobutyl-thiazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.79 min; m/z 447 $[M+H]^+$. Prep HPLC (method 5) (Acid: WO2009098448)

460	3-Fluoro-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-isonicotinamide	LCMS (system 8): R_t = 1.53 min; m/z 405 $[M+H]^+$. Prep HPLC (method 5)
461	2-Methyl-imidazo[1,2-a]pyrimidine-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.52 min; m/z 441 $[M+H]^+$. Prep HPLC (method 5)
462	5-Methyl-isoxazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.57 min; m/z 391 $[M+H]^+$. Prep HPLC (method 5)
463	4,6-Dimethoxy-pyrimidine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.62 min; m/z 448 $[M+H]^+$. Prep HPLC (method 5)
464	6-Methyl-pyrazine-2-carboxylic acid[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.58 min; m/z 402 $[M+H]^+$. Prep HPLC (method 5)
465	1-Methyl-1H-imidazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.49 min; m/z 390 $[M+H]^+$. Prep HPLC (method 5)
466	5-Chloro-pyridine-2-carboxylic acid[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.71 min; m/z 421 $[M+H]^+$. Prep HPLC (method 5)
467	1,8-Naphthyridine-2-carboxylic acid[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.68 min; m/z 438 $[M+H]^+$. Prep HPLC (method 5)
468	1-Methyl-1H-imidazole-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.59 min; m/z 390 $[M+H]^+$. Prep HPLC (method 5)

469	5-Methoxymethyl-isoxazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.56 min; m/z 421 $[M+H]^+$. Prep HPLC (method 5)
470	Phthalazine-1-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.67 min; m/z 438 $[M+H]^+$. Prep HPLC (method 5)
471	5,6-Dihydro-4H-pyrrolo[1,2-b]pyrazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.55 min; m/z 416 $[M+H]^+$. Prep HPLC (method 5)
472	5-Bromo-pyrimidine-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.58 min; m/z 467 $[M+H]^+$. Prep HPLC (method 5)
473	6-Cyano-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-nicotinamide	LCMS (system 8): R_t = 1.55 min; m/z 412 $[M+H]^+$. Prep HPLC (method 5)
474	Pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.58 min; m/z 427 $[M+H]^+$. Prep HPLC (method 5)
475	3-Methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.53 min; m/z 441 $[M+H]^+$. Prep HPLC (method 5)
476	7-Methyl-pyrazolo[1,5-a]pyridine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.73 min; m/z 440 $[M+H]^+$. Prep HPLC (method 5)
477	5-Methyl-oxazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.59 min; m/z 391 $[M+H]^+$. Prep HPLC (method 5)

478	Thieno[3,4-c]pyridine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.74 min; m/z 443 $[M+H]^+$. Prep HPLC (method 5) (Acid: WO 2002100857)
479	2,6-Dimethyl-pyrimidine-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.65 min; m/z 416 $[M+H]^+$. Prep HPLC (method 5)
480	4-Cyano-pyridine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.62 min; m/z 412 $[M+H]^+$. Prep HPLC (method 5).
481	5-Methoxymethyl-1-methyl-1H-pyrazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.56 min; m/z 434 $[M+H]^+$. Prep HPLC (method 5). (Acid: Prep 299)
482	4,5-Dichloro-1H-imidazole-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.68 min; m/z 444 $[M+H]^+$. Prep HPLC (method 5). (Acid: Angewandte Chemie, 1988, 1417-1418)
483	4-Methoxy-8-methyl-1,7-naphthyridine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.78 min; m/z 482 $[M+H]^+$. Prep HPLC (method 5) (Acid: can be prepared using chemistry outlined in WO07011811)
484	2-Ethyl-4-methyl-oxazole-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.63 min; m/z 419 $[M+H]^+$. Prep HPLC (method 5)
485	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-5-methoxy-nicotinamide	LCMS (system 8): R_t = 1.57 min; m/z 417 $[M+H]^+$. Prep HPLC (method 5)
486	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.49 min; m/z 427 $[M+H]^+$. Prep HPLC (method 5)

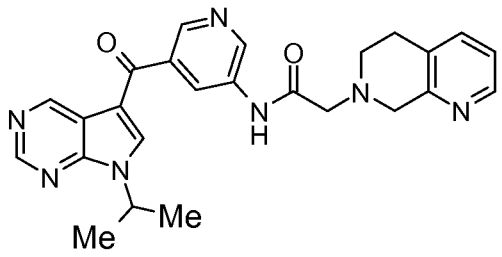
487	3H-Imidazo[4,5-b]pyridine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.44 min; m/z 427 $[M+H]^+$. Prep HPLC (method 5)
488	8-Methoxy-imidazo[1,2-a]pyrazine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.61 min; m/z 457 $[M+H]^+$. Prep HPLC (method 5) (Acid: can be made from the appropriate halo derivative e.g. WO07028051)
489	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-isonicotinamide	LCMS (system 8): R_t = 1.51 min; m/z 387 $[M+H]^+$. Prep HPLC (method 5)
490	3-Methyl-pyridine-2-carboxylic acid[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.70 min; m/z 401 $[M+H]^+$. Prep HPLC (method 5)
491	Furo[2,3-b]pyridine-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.59 min; m/z 427 $[M+H]^+$. Prep HPLC (method 5) (Acid: WO 9516688)
492	3-Isopropyl-1,2,4-triazolo[4,3-a]pyridine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.57 min; m/z 469 $[M+H]^+$. Prep HPLC (method 5)
493	Oxazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.50 min; m/z 377 $[M+H]^+$. Prep HPLC (method 5)
494	3-Chloro-pyridine-2-carboxylic acid[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.62 min; m/z 421 $[M+H]^+$. Prep HPLC (method 5)
495	Imidazo[1,2-a]pyrimidine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.44 min; m/z 427 $[M+H]^+$. Prep HPLC (method 5) (Acid – Prep 300)

496	5-Cyclopropyl-isoxazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.67 min; m/z 417 $[M+H]^+$. Prep HPLC (method 5)
497	5-Cyclopropyl-2H-pyrazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.58 min; m/z 416 $[M+H]^+$. Prep HPLC (method 5)
498	4,7-Dimethyl-pyrazolo[5,1-c][1,2,4]triazine-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.69 min; m/z 456 $[M+H]^+$. Prep HPLC (method 5)
499	N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-4-methyl-nicotinamide	LCMS (system 8): R_t = 1.51 min; m/z 401 $[M+H]^+$. Prep HPLC (method 5)
500	1-Cyclobutyl-1H-imidazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.64 min; m/z 430 $[M+H]^+$. Prep HPLC (method 5) (Acid – Prep 288)
501	Pyrazolo[1,5-a]pyridine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.65 min; m/z 426 $[M+H]^+$. Prep HPLC (method 5)
502	Tetrazolo[1,5-a]pyridine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.51 min; m/z 428 $[M+H]^+$. Prep HPLC (method 5) Commercial
503	5,6,7,8-Tetrahydro-1,2,4-triazolo[4,3-a]pyridine-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.60 min; m/z 431 $[M+H]^+$. Prep HPLC (method 5) Commercial
504	2-Methyl-5-trifluoromethyl-oxazole-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.69 min; m/z 459 $[M+H]^+$. Prep HPLC (method 5)

505	1H-Pyrrolo[3,2-b]pyridine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.36 min; m/z 426 $[M+H]^+$. Prep HPLC (method 5)
506	Pyrazolo[3,4-b]pyridine-6-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.57 min; m/z 427 $[M+H]^+$. Prep HPLC (method 5)
507	2H-Indazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.65 min; m/z 426 $[M+H]^+$. Prep HPLC (method 5)
508	3-Methyl-isoxazolo[5,4-b]pyridine-5-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.58 min; m/z 442 $[M+H]^+$. Prep HPLC (method 5) (Acid - Synthesis, 2009, 1858-1864)
509	Pyridazine-4-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.45 min; m/z 388 $[M+H]^+$. Prep HPLC (method 5)
510	2,3-Dihydro-1,4-dioxino[2,3-c]pyridine-7-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.66 min; m/z 445 $[M+H]^+$. Prep HPLC (method 5) (Acid: WO 2010/067332)
511	1H-Pyrazolo[3,4-b]pyridine-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.58 min; m/z 427 $[M+H]^+$. Prep HPLC (method 5) (Acid: WO 2011/084486)
512	5-Fluoro-1H-indazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.68 min; m/z 444 $[M+H]^+$. Prep HPLC (method 5)
513	2,5-Dimethyl-2H-pyrazole-3-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.59 min; m/z 404 $[M+H]^+$. Prep HPLC (method 5)

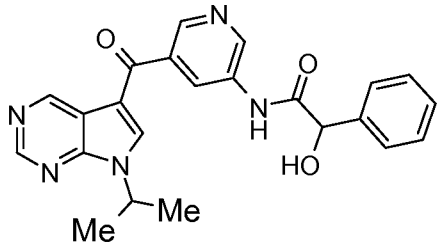
514	Thiazolo[4,5-b]pyridine-7-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.56 min; m/z 444 $[M+H]^+$. Prep HPLC (method 5)
515	6-Chloro-imidazo[1,2-b]pyridazine-2-carboxylic acid [5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-amide	LCMS (system 8): R_t = 1.68 min; m/z 461 $[M+H]^+$. Prep HPLC (method 5)

Example 517: 2-(5,8-Dihydro-6H-[1,7]naphthyridin-7-yl)-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide



To a DMF solution of (5,8-Dihydro-6H-[1,7]naphthyridin-7-yl)-acetic acid hydrochloride (**Preparation 235**) (34.2 mg, 0.18 mmol) were added (5-Amino-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 95**) (50 mg, 0.18 mmol), HATU (136.4 mg, 0.36 mmol) and Hunig's base (0.092 ml, 0.54 mmol). The mixture was heated at 50°C for 20 hours and then diluted with ethyl acetate, washed with water, brine, dried over sodium sulphate and evaporated to dryness *in vacuo*. The crude solid was purified over preparative TLC eluting with 5% MeOH/EtOAc to afford the title compound as off white solid in 26% yield, 21 mg. ^{1}H NMR (400 MHz, DMSO-D6) δ*:* 1.55 (d, 6H), 2.85-2.92 (m, 4H), 3.45 (s, 2H), 3.80 (s, 2H), 5.10 (m, 1H), 7.19 (dd, 1H), 7.56 (d, 1H), 8.32 (d, 1H), 8.53 (s, 1H), 8.56 (t, 1H), 8.73 (d, 1H), 8.99 (s, 1H), 9.07 (d, 1H), 9.45 (s, 1H), 10.31 (s, 1H); LCMS (system 9): R_t = 1.77 min; m/z 456 $[M+H]^+$.

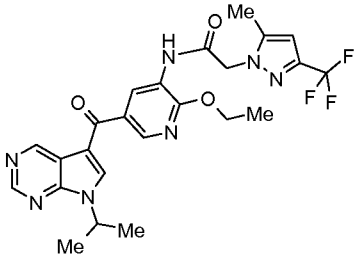
Example 518: 2-Hydroxy-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-phenyl-acetamide



To stirred solution of N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-phenyl-2-(tetrahydro-pyran-2-yloxy)-acetamide (60 mg, 0.12 mmol) (**Preparation 237**) in dioxane (1 mL) was added dioxane-HCl (1 mL of a 4N solution) at 0°C. The mixture was stirred at room temperature for 2 hours. All the volatiles were removed *in vacuo* and the solid obtained was triturated with diethyl ether to afford the title compound as a yellowish solid in 78% yield, 42 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.55 (d, 6H), 5.08-5.12 (m, 1H), 5.19 (s, 1H), 7.30 (t, 1H), 7.37 (t, 2H), 7.53 (d, 2H), 8.56 (s, 1H), 8.63 (s, 1H), 8.76 (br s, 1H), 9.05 (s, 1H), 9.17 (br s, 1H), 9.48 (br s, 1H), 10.56 (s, 1H); LCMS (system 10): R_t = 2.81 min; m/z 416 $[M+H]^+$.

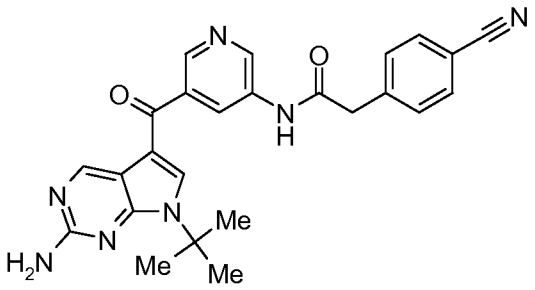
Example 519: N-[2-Ethoxy-5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(5-methyl-3-trifluoromethyl-pyrazol-1-yl)-acetamide



The title compound was prepared according to the method described for **Example 1** using (5-Amino-6-ethoxy-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 242**) and (5-Methyl-3-trifluoromethyl-pyrazol-1-yl)-acetic acid to afford the title compound as off white solid in 50% yield, 40 mg.

^{1}H NMR (400 MHz, CDCl3) δ: 1.38 (t, 3H), 1.60 (d, 6H), 2.38 (s, 3H), 4.50 (q, 2H), 4.95 (s, 2H), 5.14-5.22 (m, 1H), 6.44 (s, 1H), 7.93 (s, 1H), 8.41 (s, 1H), 8.44 (s, 1H), 8.99 (s, 1H), 9.04 (s, 1H), 9.57 (s, 1H); LCMS (system 10): R_t = 3.48 min; m/z 516 $[M+H]^+$.

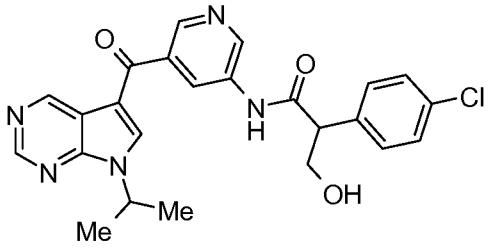
Example 520: N-[5-(2-Amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(4-cyano-phenyl)-acetamide



The title compound was prepared according to the method described for **Example 1** using (2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-(5-amino-pyridin-3-yl)-methanone (see **Preparation 65**) and 4-cyano phenyl acetic acid to afford the title compound as off white solid in 58%, 23 mg.

LCMS (system 10): R_t = 2.78 min; m/z 454 $[M+H]^+$.

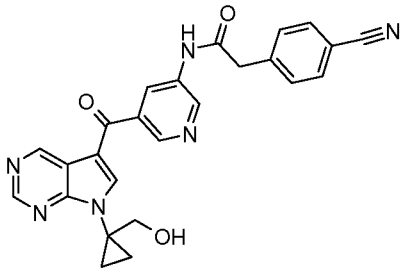
Example 521: 2-(4-Chloro-phenyl)-3-hydroxy-N-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-propionamide



2-(4-Chloro-phenyl)-3-hydroxy-propionic acid (570 mg, 2.84 mmol) (**Preparation 244**) was added to a solution of (5-Amino-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (200 mg, 0.71 mmol) (**Preparation 95**) in THF (5 mL). Di-isopropyl ethylamine (0.64 mL, 3.56 mmol), EDCI.HCl (273 mg, 1.42 mmol) and HOBT (193 mg, 1.42 mmol) were added and the mixture was stirred at 25°C for 48 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (2 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was washed with water (5mL), brine (5 mL), dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by preparative TLC (dichloromethane: methanol 93:7) to afford the title compound as a yellow solid in 3% yield, 10 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.55 (d, 6H), 3.58-3.61 (m, 1H), 3.88-3.91 (m, 1H), 4.04 (t, 1H), 5.07-5.13 (m, 2H), 7.41 (s, 4H), 8.47 (s, 1H), 8.50 (s, 1H), 8.72 (s, 1H), 8.99 (s, 2H), 9.43 (s, 1H), 10.65 (s, 1H); LCMS (system 10): R_t = 2.99 min; m/z 464 $[M+H]^+$.

Example 522: 2-(4-Cyano-phenyl)-N-{5-[7-(1-hydroxymethyl-cyclopropyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide



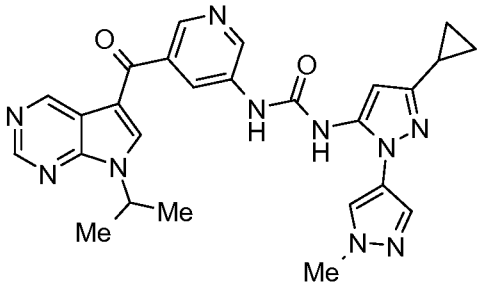
(4-Cyano-phenyl)-acetic acid (6.1 mg, 0.04 mmol) was added to a solution of (5-Amino-pyridin-3-yl)-{7-[1-(tetrahydro-pyran-2-yloxymethyl)-cyclopropyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone (15 mg, 0.04 mmol) (**Preparation 251**) in THF (1 mL). Then 1-propylphosphonic acid cyclic anhydride (0.07 mL, 0.11 mmol) and triethylamine (0.02 mL, 0.13 mmol) were added and the mixture was stirred at 25°C for 4 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (2 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layer was washed with water (5mL), brine (5 mL), dried over sodium sulphate and evaporated *in vacuo*. The crude was dissolved in methanol (1 mL), PTSA (5 mg) was added and stirred at room temperature for 16 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (2 mL) and extracted with dichloromethane (5 x 5 mL). The combined organic layer was washed with brine (5 mL), dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by preparative TLC (dichloromethane: methanol 95:5) to afford the title compound as a white solid in 58% yield, 10 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.13-1.15 (m, 2H), 1.27-1.29 (m, 2H), 3.66 (d, 2H), 3.87 (s, 2H), 5.00 (t, 1H), 7.56 (d, 2H), 7.82 (d, 2H), 8.22 (s, 1H), 8.45 (s, 1H), 8.74 (s, 1H), 8.96 (s, 1H), 9.00 (s, 1H), 9.44 (s, 1H), 10.73 (s, 1H); LCMS (system 10): R_t = 2.57 min; m/z 453 $[M+H]^+$.

The following Examples were prepared according to the method described above for **Example 522** starting from (5-Amino-pyridin-3-yl)-[7-(3-methyl-oxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone (**Preparation 251**) and the appropriate acids.

Example	Name	Data
523	2-(5-Chloro-pyridin-2-yl)-N-{5-[7-(1-hydroxymethyl-cyclopropyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide	LCMS (system 10): Rt = 2.53 min; m/z 463 [M+H]+
524	N-{5-[7-(1-Hydroxymethyl-cyclopropyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-trifluoromethyl-phenyl)-acetamide	LCMS (system 10): R_t = 2.89 min; m/z 496 $[M+H]^+$.
525	N-{5-[7-(1-Hydroxymethyl-cyclopropyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(3-trifluoromethyl-pyrazol-1-yl)-acetamide	LCMS (system 9): R_t = 2.71 min; m/z 486 $[M+H]^+$.

Example 526: 1-(3-Cyclopropyl-1'-methyl-1'H-[1,4']bipyrazolyl-5-yl)-3-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-urea



Phenyl chloroformate (0.03 mL, 0.24 mmol) was added slowly to a solution of 3-Cyclopropyl-1'-methyl-1'H-[1,4']bipyrazolyl-5-ylamine (Preparation 297, 40 mg, 0.19 mmol) and pyridine (0.03 mL) in THF (2 mL) at 0°C and the mixture was stirred at room temperature for 4 hours. A solution of (5-Amino-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 95**) (55.4 mg, 0.19 mmol) in DMF (1 mL) and was then added and the reaction mixture heated at 100°C for 16 hours. The mixture was cooled and diluted with ethyl acetate (15 mL), and washed with aqueous saturated $NaHCO_3$ solution (2 x 10 mL), water (10 mL), brine (10 mL), dried over sodium sulphate and evaporated to dryness *in vacuo*. The crude material was purified over preparative TLC plate (eluting with 5% methanol in DCM) to afford the title compound as off white solid in 15% yield, 15 mg. ^{1}H NMR (400 MHz, DMSO-d6) δ: 0.64-0.65 (m, 2H), 0.85-0.88 (m, 2H), 1.56 (d, 6H), 1.82-1.85 (m, 1H), 3.89 (s, 3H), 5.09-5.12 (m, 1H), 6.10 (s, 1H), 7.66 (s, 1H), 8.05 (s, 1H), 8.36 (s, 1H), 8.52 (s, 1H), 8.61 (br s, 1H), 8.65 (s, 1H), 8.78 (s, 1H), 8.99 (s, 1H), 9.45 (s, 2H); LCMS (system 10): R_t = 2.75 min; m/z 511 $[M+H]^+$.

Example 527: 1-(3-tert-Butyl-1'-methyl-1'H-[1,4']bipyrazolyl-5-yl)-3-[5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-urea

The title compound was prepared according to the method described for **Example 526** using (5-Amino-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 95**) and 3-tert-Butyl-1'-methyl-1'H-[1,4']bipyrazolyl-5-ylamine (**Preparation 296**) to afford the title compound as yellow solid in 35% yield, 17 mg.LCMS (system 10): R_t = 3.01 min; m/z 527 $[M+H]^+$.

The following **Examples** were prepared according to the method described above for **Example 1**, starting from (2-amino-7-*tert*-butyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)(5-aminopyridin-3-yl)methanone (**Preparation 65**) and the appropriate acids.

Example	Name	Data
528	N-[5-(2-Amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(1H-benzoimidazol-2-yl)-acetamide	LCMS (system 10): Rt = 2.79 min; m/z 469 [M+H]+.
529	N-[5-(2-Amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(5-bromo-pyridin-2-yl)-acetamide	LCMS (system 10): R_t = 2.94 min; m/z 508 $[M+H]^+$
530	N-[5-(2-Amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(5-cyano-pyridin-2-yl)-acetamide	LCMS (system 10): R_t = 2.78 min; m/z 455 $[M+H]^+$ (acid can be prepared by cyanation of an appropriate bromo derivative

The following Examples were prepared according to the method described for **Example 522** using (5-Amino-pyridin-3-yl)-{7-[(S)-1-methyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone (**Preparation 33**) and the appropriate acid.

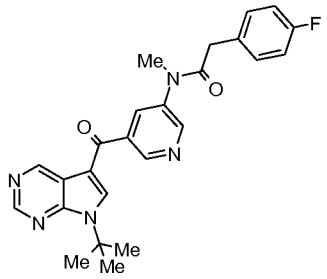
Example	Name	Data
531	2-(4-Difluoromethoxy-phenyl)-N-{5-[7-((S)-2-hydroxy-1-methyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide	LCMS (system 9): R_t = 2.80 min; m/z 482 $[M+H]^+$
532	N-{5-[7-((S)-2-Hydroxy-1-methyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-indazol-2-yl-acetamide	LCMS (system 9): Rt = 2.58 min; m/z 456 $[M+H]^+$
533	2-(1H-Benzoimidazol-2-yl)-N-{5-[7-((S)-2-hydroxy-1-methyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide	LCMS (system 10): Rt = 2.42 min; m/z 456 [M+H]+.
534	N-{5-[7-((S)-2-Hydroxy-1-methyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-trifluoromethoxy-phenyl)-acetamide	LCMS (system 9): Rt = 2.99 min; m/z 500 $[M+H]^+$
535	2-(3,4-Difluoro-phenyl)-N-{5-[7-((S)-2-hydroxy-1-methyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide	LCMS (system 9): Rt = 2.75 min; m/z 452 $[M+H]^+$

The following Examples were prepared according to the Method described for d]pyrimidin-5-yl]methanone (**Preparation 186**) and the appropriate acid.

Example	Name	Data

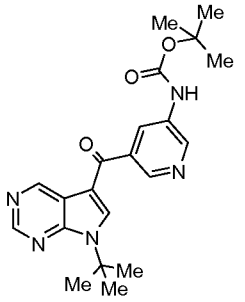
536	2-(5-Chloro-pyridin-2-yl)-N-{5-[7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide	LCMS (system 10): R_t = 2.92 min; m/z 479 $[M+H]^+$
537	2-(5-Fluoro-pyridin-2-yl)-N-{5-[7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide	LCMS (system 10): R_t = 2.79 min; m/z 463 $[M+H]^+$.
538	2-(3-Cyclopropyl-pyrazol-1-yl)-N-{5-[7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide	LCMS (system 10): R_t = 2.89 min; m/z 474 $[M+H]^+$.
539	2-(4-Fluoro-phenyl)-N-{5-[7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide	LCMS (system 10): R_t = 3.03 min; m/z 462 $[M+H]^+$.

Example 540: N-[5-(7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(4-fluoro-phenyl)-N-methyl-acetamide



To a stirred solution of N-[5-(7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(4-fluoro-phenyl)-acetamide (**Example 546**, 115 mg, 0.27 mmol) in anhydrous THF (4.5 mL), was added NaH (60% in paraffin oil, 10.7 mg, 0.27 mmol) at 0°C under nitrogen and the resulting mixture stirred for 10 min. MeI (0.017 mL, 0.27 mmol) was then added and the reaction mixture was stirred at room temperature for 1 hour. Aqueous saturated ammonium chloride (5 mL) was added and the mixture extracted with ethyl acetate (2 x 10 mL). The organic phase was washed with water (10 mL), brine (10 mL), dried over sodium sulphate and evaporated to dryness *in vacuo*. The crude material was purified via preparative TLC (eluting with 5% methanol in DCM) to afford the title compound as off white solid in 46% yield, 55 mg. ^{1}H NMR (400 MHz, DMSO-D6) δ: 1.79 (s, 9H), 3.28 (s, 3H), 3.58 (br, 2H), 7.08-7.20 (m, 4H), 8.20 (s, 1H), 8.32 (s, 1H), 8.83 (s, 1H), 8.97 (br, 1H), 9.01 (s, 1H), 9.50 (s, 1H); LCMS (system 10): R_t = 3.08 min; m/z 446 $[M+H]^+$.

Example 541: [5-(7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-carbamic acid tert-butyl ester

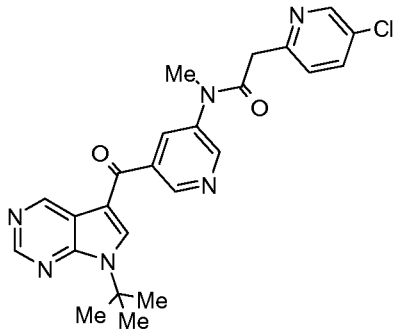


To a stirred solution of (5-Amino-pyridin-3-yl)-(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 31**) (200 mg, 0.68 mmol) in DCM (4 mL) was added boc-anhydride (0.155 mL, 0.68 mmol) and Hunig's base (0.24 mL, 1.36 mmol) and the reaction mixture was stirred at room temperature for 16 hours. It was diluted with DCM (15 mL) and washed with water (2 x 10 mL), brine (10 mL), dried over sodium sulphate and evaporated to dryness *in vacuo*. The crude material was purified by column chromatography on silica gel (Methanol:DCM 2:98) to afford the title compound as light brown gum in 41% yield, 110 mg. LCMS (system 10): R_t = 3.16 min; m/z 396 $[M+H]^+$.

Example 542: [5-(7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-methyl-carbamic acid tert-butyl ester

The title compound was prepared according to the method described for **Example 540** using [5-(7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-carbamic acid tert-butyl ester (**Example 541**) to afford the title compound as yellow solid in 79% yield, 90 mg. LCMS (system 10): R_t = 3.83 min; m/z 410 $[M+H]^+$.

Example 543: N-[5-(7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(5-chloro-pyridin-2-yl)-N-methyl-acetamide



The title compound was prepared according to the method described for **Example 1** using (7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-(5-methylamino-pyridin-3-yl)-methanone (**Preparation 187**) and (5-chloro-pyridin-2-yl)-acetic acid(see **Preparation 90**) to afford the title compound as off white solid in 21% yield, 25 mg. ^{1}H NMR (400 MHz, DMSO-D6) δ*:* 1.78 (s, 9H), 3.32 (s, 3H), 3.77 (brs, 2H), 7.26 (br, 1H), 7.83 (br, 1H), 8.21 (s, 1H), 8.32 (s, 1H), 8.48 (s, 1H), 8.85 (s, 1H), 8.97 (s, 1H), 9.02 (s, 1H), 9.51 (s, 1H); LCMS (system 10): R_t = 3.29 min; m/z 463.2 $[M+H]^+$.

Example 544: N-[5-(7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(4-chloro-phenyl)-N-methyl-acetamide

The title compound was prepared according to the method described for **Example 1** using (7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-(5-methylamino-pyridin-3-yl)-methanone (**Preparation 187**) and (4-chloro-phenyl)-acetic acid to afford the title compound as off white solid in 45% yield, 21 mg.
LCMS (system 10): R_t = 3.28 min; m/z 462 $[M+H]^+$.

The following Examples were prepared according to the method described above for **Example 1**, starting from (5-aminopyridin-3-yl)(7-*tert*-butyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanone (**Preparation 31)** and the appropriate acids.

Example	Name	Data
545	N-[5-(7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(4-chloro-phenyl)-acetamide	LCMS (system 10): R_t = 3.18 min; m/z 448 $[M+H]^+$.
546	N-[5-(7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(4-fluoro-phenyl)-acetamide	LCMS (system 10): R_t = 3.08 min; m/z 432 $[M+H]^+$.

The following Examples were prepared according to the method described for **Example 1** starting from [2-Amino-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-(5-amino-pyridin-3-yl)-methanone (**Preparation 261**) and the appropriate acid.

Example	Name	Data
547	N-{5-[2-Amino-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(5-chloro-pyridin-2-yl)-acetamide	LCMS (system 10): R_t = 2.85 min; m/z 494 $[M+H]^+$. (Acid: Prep 90)
548	N-{5-[2-Amino-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(5-fluoro-pyridin-2-yl)-acetamide	LCMS (system 10): R_t = 2.77 min; m/z 478 $[M+H]^+$. (Acid Prep 92)
549	N-{5-[2-Amino-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(3-trifluoromethyl-pyrazol-1-yl)-acetamide	LCMS (system 10): R_t = 3.02 min; m/z 517 $[M+H]^+$. (Acid Prep 85)
550	N-{5-[2-Amino-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-trifluoromethyl-[1,2,3]triazol-1-yl)-acetamide	LCMS (system 10): R_t = 2.93 min; m/z 518 $[M+H]^+$. (Acid Prep 81)
551	N-{5-[2-Amino-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-trifluoromethyl-pyrazol-1-yl)-acetamide	LCMS (system 10): R_t = 3.01 min; m/z 517 $[M+H]^+$. (Acid Prep 85)
552	N-{5-[2-Amino-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-cyclopropyl-[1,2,3]triazol-1-yl)-acetamide	LCMS (system 10): R_t = 2.69 min; m/z 490 $[M+H]^+$. (Acid Prep 83)

The following **Examples** were prepared according to the method described for **Example 522** using (5-Amino-pyridin-3-yl)-{7-[(S)-1-methyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone (**Preparation 49**) and the appropriate acid.

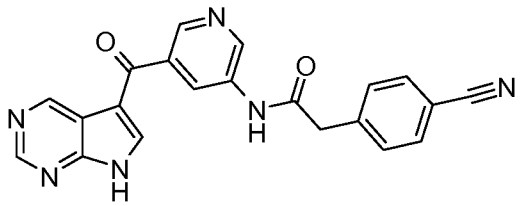
Example	Name	Data
553	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-indazol-2-yl-acetamide	LCMS (system 10): R_t = 2.67 min; m/z 485 $[M+H]^+$.
554	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-oxo-4H-quinazolin-3-yl)-acetamide	LCMS (system 10): R_t = 2.52 min; m/z 513 $[M+H]^+$.
555	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(3,5-difluoro-pyridin-2-yl)-acetamide	LCMS (system 9): R_t = 2.07 min; m/z 482 $[M+H]^+$. Acid Prep 265)
556	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(5-methyl-pyridin-2-yl)-acetamide	LCMS (system 9): R_t = 1.36 min; m/z 460 $[M+H]^+$. Acid Prep 274
557	N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-{4-[methyl(methylsulfonyl)amino]phenyl}-acetamide	LCMS (system 9): R_t = 2.19 min; m/z 552 $[M+H]^+$. Acid Prep 271
558	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(1H-benzoimidazol-2-yl)-acetamide	LCMS (system 9): R_t = 1.42 min; m/z 485 $[M+H]^+$.
559	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(2-oxo-5-trifluoromethyl-2H-pyridin-1-yl)-acetamide	LCMS (system 9): R_t = 2.18 min; m/z 530 $[M+H]^+$.
560	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(5-chloro-3-fluoro-pyridin-2-yl)-acetamide	LCMS (system 9): R_t = 2.23 min; m/z 498 $[M+H]^+$.
561	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(5-ethoxy-pyridin-2-yl)-acetamide	LCMS (system 10): R_t = 2.64 min; m/z 490 $[M+H]^+$ (acid can be prepared from the appropriate bromide using the method in WO2011/114271)
562	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(5-trifluoromethyl-pyridin-2-yl)-acetamide	LCMS (system 9): R_t = 2.40 min; m/z 514 $[M+H]^+$.
563	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-trifluoromethyl-pyrazol-1-yl)-acetamide	LCMS (system 9): R_t = 2.39 min; m/z 503 $[M+H]^+$. Acid prep 85
564	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-	LCMS (system 9) R_t = 4.47 min (12 min run); m/z 538 $[M+H]^+$.

	yl}-2-(4-methanesulfonylamino-phenyl)-acetamide	

The following Examples were prepared according to the method described for **Examples 73-87** using (5-Amino-pyridin-3-yl)-{7-[(S)-1-methyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone (**Preparation 49**) and the appropriate acid.

Example	Name	Data
565	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-difluoromethoxy-phenyl)-acetamide	LCMS (system 9): R_t = 2.56 min; m/z 511 $[M+H]^+$.
567	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-trifluoromethoxy-phenyl)-acetamide	LCMS (system 9): R_t = 2.74 min; m/z 529 $[M+H]^+$.
568	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(3,4-difluoro-phenyl)-acetamide	LCMS (system 9): R_t = 2.50 min; m/z 481 $[M+H]^+$.
569	N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(5-chloro-pyrimidin-2-yl)-acetamide	LCMS (system 10): R_t = 2.35 min; m/z 481 $[M+H]^+$ (acid can be prepared by oxidation of the appropriate aldehyde WO04110453)

Example 570: 2-(4-Cyano-phenyl)-N-[5-(7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-acetamide



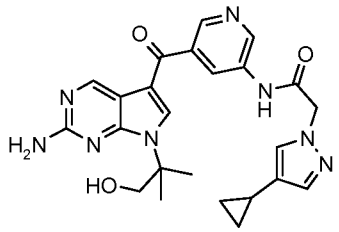
The title compound was prepared according to the method described for **Example 343** using 2-(4-Cyano-phenyl)-N-{5-[7-(2-trimethylsilanyl-ethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide (**Preparation 277**) to afford the title compound as a white solid in 99% yield, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.87 (s, 2H), 7.55 (d, 2H), 7.81 (d, 2H), 8.36 (s, 1H), 8.47 (s, 1H), 8.72 (s, 1H), 8.97 (m, 2H), 9.47 (s, 1H), 10.66 (s, 1H), 13.14 (s, 1H); LCMS (System 10): R_t = 2.48 min; m/z 383 $[M+H]^+$.

The following Examples were prepared according to the method described above for **Example 1**, starting from (5-Amino-pyridin-3-yl)-[7-(3-methyl-oxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone (**Preparation 222**) and the appropriate acid.

Example	Name	Data
571	N-{5-[7-(3-Methyl-oxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-trifluoromethyl-phenyl)-acetamide	LCMS (System 10): R_t = 3.02 min; m/z 496 $[M+H]^+$

572	N-{5-[7-(3-Methyl-oxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(3-trifluoromethyl-phenyl)-acetamide	LCMS (System 10): Rt = 2.98 min; m/z 496 $[M+H]^+$.
573	2-(3-Fluoro-4-trifluoromethyl-phenyl)-N-{5-[7-(3-methyl-oxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide	LCMS (System 10): Rt = 3.01 min; m/z 514 $[M+H]^+$.
574	N-{5-[7-(3-Methyl-oxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-3-trifluoromethyl-benzamide	LCMS (System 10): Rt = 3.00 min; m/z 482 $[M+H]^+$.
575	N-{5-[7-(3-Methyl-oxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-3-trifluoromethoxy-benzamide	LCMS (System 10): Rt = 3.05 min; m/z 498 $[M+H]^+$

Example 576: N-{5-[2-Amino-7-(2-hydroxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-2-(4-cyclopropyl-pyrazol-1-yl)-acetamide



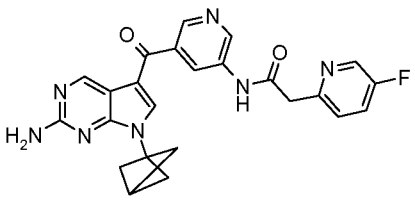
The title compound was prepared according to the method described for **Example 1** using {2-amino-7-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-(5-amino-pyridin-3-yl)-methanone (**Preparation 49)** and (4-Cyclopropyl-pyrazol-1-yl)-acetic acid to afford the title compound as a white solid in 72 % yield, 16.5 mg.

LCMS (System 10): R_t = 2.62 min; m/z 475 $[M+H]^+$.

Example 577: N-[5-(2-Amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(4-cyclopropyl-pyrazol-1-yl)-acetamide

The title compound was prepared according to the method described for **Example 1** using (2-Amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-(5-amino-pyridin-3-yl)-methanone (see **Preparation 65**) and (4-cyclopropyl-pyrazol-1-yl)-acetic acid to afford the title compound as a pale yellow solid in 16 % yield, 12 mg.LCMS (System 10) : R_t = 2.80 min; m/z 459 $[M+H]^+$.

Example 578: N-[5-(2-Amino-7-bicyclo[1.1.1]pent-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(5-fluoro-pyridin-2-yl)-acetamide

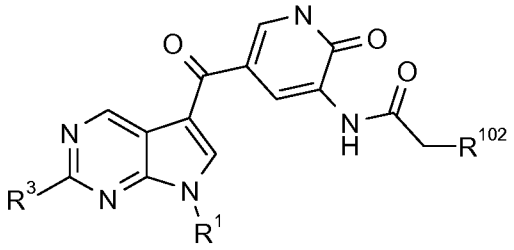


To a solution of (5-amino-pyridin-3-yl)-[7-bicyclo[1.1.1]pent-1-yl-2-(4-methoxy-benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone (**Preparation 287**) (50 mg, 0.11 mmol) in THF (5 mL) at room temperature was added 5-fluoro pyridine-2-yl acetic acid (27 mg, 0.17 mmol), TEA (0.08 mL, 0.56 mmol) and 1-propylphosphonic acid cyclic anhydride (50% solution in EtOAc, 0.20 mL, 0.34 mmol). The resulting mixture was before stirred for 18 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between saturated sodium bicarbonate solution (10 mL) and ethyl acetate (25 mL). The organic phase was dried over sodium sulphate and concentrated under reduced pressure. TFA (1.5 mL) was added and the resulting mixture stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure and the residue partitioned between saturated sodium bicarbonate (10 mL) and ethyl acetate (30 mL). The organic phase was dried over sodium sulphate, concentrated under reduced pressure purified by Preparative TLC (MeOH:DCM 5: 95) to afford the title compound as off white solid in 31% yield, 16 mg. ^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 2.32 (s, 6H), 2.66 (s, 1H), 3.94 (s, 2H), 6.57 (s, 2H), 7.49 (m, 1H), 7.69-7.73 (m, 2H), 8.38 (s, 1H), 8.50 (d, 1H), 8.65 (d, 1H), 8.92 (s, 1H), 8.96 (d, 1H), 10.67 (s, 1H); LCMS (System 10): R_t = 2.85 min; m/z 458 $[M+H]^+$.

The following Examples were prepared according to the method described above for **Example 578** starting from ((5-Amino-pyridin-3-yl)-[7-bicyclo[1.1.1]pent-1-yl-2-(4-methoxy-benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone (**Preparation 287**) and the appropriate acid.

Example	Name	Data
579	N-[5-(2-Amino-7-bicyclo[1.1.1]pent-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(3-methanesulfonyl-phenyl)-acetamide	LCMS (System 10): Rt = 2.87 min; m/z 517 $[M+H]^+$.
580	N-[5-(2-Amino-7-bicyclo[1.1.1]pent-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(3-trifluoromethyl-pyrazol-1-yl)-acetamide	LCMS (System 10): Rt = 2.92 min; m/z 497 $[M+H]^+$.
581	N-[5-(2-Amino-7-bicyclo[1.1.1]pent-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(4-trifluoromethyl-[1,2,3]triazol-1-yl)-acetamide	LCMS (System 10): Rt = 2.89 min; m/z 498 $[M+H]^+$. (Acid : Prep 81)
582	N-[5-(2-Amino-7-bicyclo[1.1.1]pent-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(4-cyano-phenyl)-acetamide	LCMS (System 10): Rt = 2.94 min; m/z 464 $[M+H]^+$.
583	N-[5-(2-Amino-7-bicyclo[1.1.1]pent-1-yl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-(5-chloro-pyridin-2-yl)-acetamide	LCMS (system 9) : Rt = 6.28 min; m/z 474 $[M+H]^+$. (Acid Prep 90)

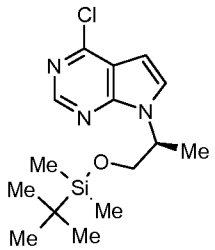
Examples 584-5923 illustrate compounds of general formula :



that fall into general formula (I) by virtue of pyridone tautomerism.

Example	Name	Data
584	2-(4-cyanophenyl)-N-(2-oxo-5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}-1,2-dihydropyridin-3-yl)acetamide	LCMS Rt = 5.25 min; m/z 441 [M+H]+
585	N-(2-oxo-5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}-1,2-dihydropyridin-3-yl)-2-[2-(trifluoromethoxy)phenoxy]acetamide	LCMS Rt = 4.04 min; m/z 516 [M+H]+
586	2-(2-cyclopropyl-1,3-oxazol-4-yl)-N-(2-oxo-5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}-1,2-dihydropyridin-3-yl)acetamide	LCMS Rt = 3.39 min; m/z 447 [M+H]+
587	2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2-oxo-5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}-1,2-dihydropyridin-3-yl)acetamide	LCMS Rt = 3.51 min; m/z 488 [M+H]+
588	N-(2-oxo-5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}-1,2-dihydropyridin-3-yl)-2-(quinolin-7-yl)acetamide	LCMS Rt = 3.51 min; m/z 485 [M+H]+
589	2-(4-chlorophenyl)-N-(2-oxo-5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}-1,2-dihydropyridin-3-yl)acetamide	LCMS Rt = 3.82 min; m/z 450 [M+H]+
590	2-(5-chloropyridin-2-yl)-N-(2-oxo-5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}-1,2-dihydropyridin-3-yl)acetamide	LCMS Rt = 3.22 min; m/z 451 [M+H]+
591	N-(2-oxo-5-{[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}-1,2-dihydropyridin-3-yl)-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide	LCMS Rt = 3.31 min; m/z 475 [M+H]+
592	N-(5-{[2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}-2-oxo-pyridin-3-yl)-2-(5-chloropyridin-2-yl))acetamide	
593	N-[5-({7-[(1S)-2-Hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)-2-oxo-pyridin-3-yl]-2-[4-(trifluoromethyl)phenyl]acetamide	m/z 500, RT 4.94

Preparation 1: 7-[(1S)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl]-4-chloro-7H-pyrrolo[2,3-d]pyrimidine

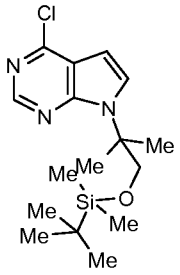


(S)-2-*tert*-Butyldimethylsilyloxy-1-methylethylamine (120 g, 636 mmol) was added to (4,6-dichloropyrimidin-5-yl)acetaldehyde (52.8 g, 276 mmol) in ethanol (500 mL). The mixture was heated to

reflux for 45 minutes. The reaction mixture was evaporated *in vacuo* then the residue was diluted with water (400 mL) and extracted with ethyl acetate (600 mL). The organic extract was evaporated *in vacuo* and the crude material was purified by column chromatography on silica gel (gradient of pentane:EtOAc 90:10 to 80:20) to afford the title compound as a yellow liquid in 67% yield, 60.4 g.

^{1}H NMR (400 MHz, CDCl3) δ: -0.92 (s, 6H), 0.80 (s, 9H), 1.58 (d, 3H), 3.86 (m, 2H), 5.04 (m, 1H), 6.59 (d, 1H), 7.40 (d, 1H), 8.60 (s, 1H).

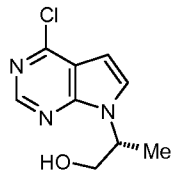
Preparation 2: 7-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-4-chloro-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 1** using (4,6-dichloropyrimidin-5-yl)acetaldehyde and 1-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylpropan-2-amine to afford the title compound as a yellow oil in 38% yield, 377 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.00 (s, 6H), 0.94 (s, 9H), 1.97 (s, 6H), 4.28 (s, 2H), 6.78 (d, 1H), 7.66 (d, 1H), 8.83 (s, 1H).

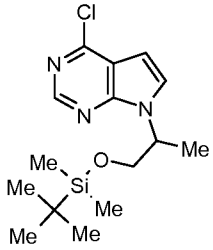
Preparation 3: (2R)-2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propan-1-ol



The title compound was prepared according to the method described for **Preparation 1** using (4,6-dichloropyrimidin-5-yl)acetaldehyde and (R)-2-amino-1-propanol to afford the title compound as a yellow solid in 100% yield, 11.12 g.

LCMS (system 2): R_t = 0.89 min; m/z 212 $[M+H]^+$.

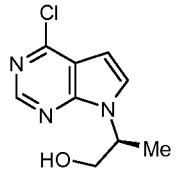
Preparation DL3: (R,S) 7-[2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl]-4-chloro-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 1** using (4,6-dichloropyrimidin-5-yl)acetaldehyde and 2-*tert*-butyldimethylsilyloxy-1-methylethylamine to afford the title compound as an orange oil in 77% yield, 4.08 g.

^{1}H NMR (400 MHz, CDCl3) δ*:* -0.90 (s, 6H), 0.82 (s, 9H), 1.58 (d, 3H), 3.84 (m, 2H), 5.05 (m, 1H), 6.59 (d, 1H), 7.42 (d, 1H), 8.60 (s, 1H).

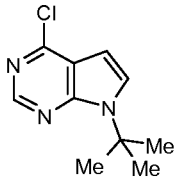
Preparation 4: (2S)-2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propan-1-ol



The title compound was prepared according to the method described for **Preparation 1** using (4,6-dichloropyrimidin-5-yl)acetaldehyde and (S)-2-amino-1-propanol to afford the title compound as a cream solid in 98% yield, 10.9 g.

^{1}H NMR (400 MHz, DMSO-D6) δ*:* 1.42 (d, 3H), 3.72 (m, 2H), 4.89 (m, 1H), 6.63 (d, 1H), 7.83 (d, 1H), 8.59 (s, 1H).

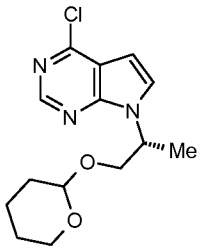
Preparation 5: 7-*tert*-Butyl-4-chloro-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 1** using (4,6-dichloropyrimidin-5-yl)acetaldehyde and *tert*-butylamine to afford the title compound as a yellow liquid in 77% yield, 1.61 g.

^{1}H NMR (400 MHz, DMSO-D6) δ*:* 1.75 (s, 9H), 6.60 (d, 1H), 7.79 (d, 1H), 8.63 (s, 1H).

Preparation 6: 4-Chloro-7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine

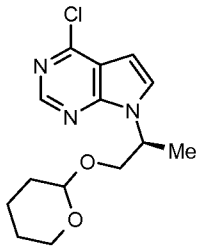


2,3-Dihydropyran (25.0 mL, 270 mmol) was added to (2R)-2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propan-1-ol (11.00 g, 51.97 mmol) (see **Preparation 3**) and pyridinium toluene-4-sulphonate (3.92 g,

15.6 mmol) in DCM (150 mL). The reaction mixture was washed with water (200 mL) and the aqueous phase was extracted with DCM (2 x 150 mL). The combined organic phases were dried over magnesium sulfate and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of heptane:EtOAc 100:0 to 70:30) to afford the title compound as a yellow oil in 100% yield, 15.65 g.

LCMS (system 2): R_t = 1.30 min; m/z 296 $[M+H]^+$.

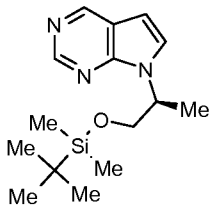
Preparation 7: 4-Chloro-7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 6** using (2S)-2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propan-1-ol (see **Preparation 4**) to afford the title compound as a yellow oil in 87% yield, 11.5 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43-1.71 (m, 9H), 3.42 (m, 1H), 3.57 (m, 1H), 3.69 (m, 1H), 4.00 (m, 1H), 4.52 (m, 1H), 5.19 (m, 1H), 6.60 (d, 1H), 7.44 (d, 1H), 8.61 (s, 1H).

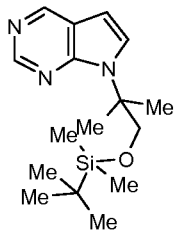
Preparation 8: 7-[(1S)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidine



Palladium (10% on carbon, 18 g) was added to 7-[(1S)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl]-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (182 g, 558 mmol) (see **Preparation 1**) in ethanol (900 mL) and concentrated ammonia solution (100 mL) and hydrogenated (60 psi, 20°C) for 18 hours. The reaction mixture was filtered through Arbocel™ and the filtrate was evaporated *in vacuo*. Diethyl ether (300 mL) was added to the residue and the mixture was filtered. The filtrate was evaporated *in vacuo* to afford the title compound as an orange oil in 94% yield, 162.7 g.

^{1}H NMR (400 MHz, CDCl3) δ: -0.90 (s, 3H), 0.80 (s, 9H), 1.58 (d, 3H), 3.86 (m, 2H), 5.06 (m, 1H), 6.53 (d, 1H), 7.40 (d, 1H), 8.83 (s, 1H), 8.96 (s, 1H).

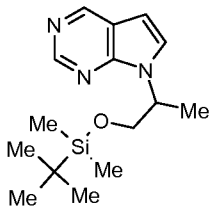
Preparation 9: 7-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 8** using 7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 2**) to afford the title compound as a white solid in 97% yield, 327 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 0.01 (s, 6H), 0.94 (s, 9H), 2.02 (s, 6H), 4.30 (s, 2H), 6.92 (d, 1H), 7.84 (d, 1H), 9.13 (s, 1H), 9.21 (s, 1H).

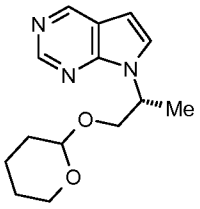
Preparation 10: (R,S) 7-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 8** using (R,S) 7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation DL3**) to afford the title compound as a brown liquid in 78% yield, 1.12 g.

^{1}H NMR (400 MHz, DMSO-D6) δ*:* 0.01 (s, 6H), 0.88 (s, 9H), 1.69 (d, 3H), 4.09 (m, 2H), 5.20 (m, 1H), 6.84 (d, 1H), 7.92 (d, 1H), 8.96 (s, 1H), 9.18 (s, 1H).

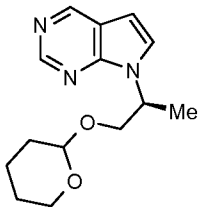
Preparation 11: 7-[(1R)-1-Methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 8** using 4-chloro-7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 6**) to afford the title compound as a yellow oil in 100% yield, 13.78 g.

LCMS (system 2): R_t = 0.73 min; m/z 262 $[M+H]^+$.

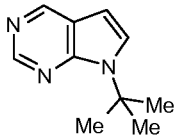
Preparation 12: 7-[(1S)-1-Methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 8** using 4-chloro-7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 7**) to afford the title compound as a colourless oil in 90% yield, 9.18 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 1.44-1.69 (m, 9H), 3.42 (m, 1H), 3.57 (m, 1H), 3.69 (m, 1H), 4.02 (m, 1H), 4.54 (m, 1H), 5.27 (m, 1H), 6.69 (d, 1H), 7.57 (d, 1H), 8.91 (s, 1H), 8.99 (s, 1H).

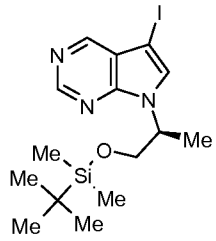
Preparation 13: 7-*tert*-Butyl-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 8** using 7-*tert*-butyl-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 5**) to afford the title compound as a yellow liquid in 94% yield, 1.27 g.

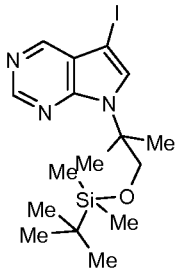
^{1}H NMR (400 MHz, DMSO-D6) δ*:* 1.75 (s, 9H), 6.57 (d, 1H), 7.66 (d, 1H), 8.78 (s, 1H), 8.98 (s, 1H).

Preparation 14: 7-[(1S)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl]-5-iodo-7H-pyrrolo[2,3-d]pyrimidine



N-Iodosuccinimide (124 g, 553 mmol) was added to 7-[(1S)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidine (153.4 g, 526 mmol) (see **Preparation 8**) in acetonitrile (700 mL). The mixture was stirred at room temperature for 16 hours then saturated aqueous sodium thiosulfate (700 mL) was added. The mixture was extracted with EtOAc (800 mL) then the organic extract was dried over magnesium sulfate and evaporated *in vacuo.* The crude material was purified by column chromatography on silica gel (gradient of pentane:EtOAc 90:10 to 80:20) to afford the title compound as a yellow solid in 66% yield, 145 g. ^{1}H NMR (400 MHz, $CDCl_3$) δ*:* -0.90 (d, 6H) 0.80 (s, 9H) 1.58 (d, 3H) 3.84 (m, 2H) 5.07 (m, 1H) 7.48 (s, 1H) 8.73 (s, 1H) 8.86 (s, 1H).

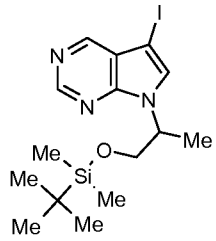
Preparation 15: 7-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-5-iodo-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 14** using 7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 9**) to afford the title compound as a brown oil in 59% yield, 270 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 0.01 (s, 6H), 0.92 (s, 9H), 2.00 (s, 6H), 4.20 (s, 2H), 7.95 (s, 1H), 9.02 (s, 1H), 9.16 (s, 1H).

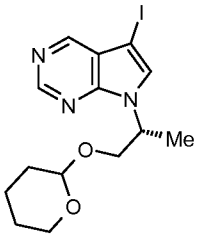
Preparation 16: (R,S) 7-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-5-iodo-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 14** using (R,S) 7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 10**) to afford the title compound as a yellow liquid in 74% yield, 1.18 g.

LCMS (system 1): R_t = 4.03 min; m/z 418 $[M+H]^+$.

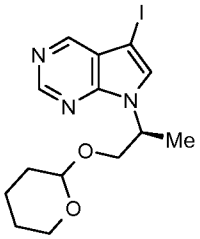
Preparation 17: 5-Iodo-7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 14** using 7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 11**) to afford the title compound as a brown oil in 34% yield, 7.50 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 1.43-1.74 (m, 9H), 3.42 (m, 1H), 3.54 (m, 1H), 3.67 (m, 1H), 3.99 (m, 1H), 4.54 (m, 1H), 5.23 (m, 1H), 7.51 (s, 1H), 8.74 (s, 1H), 8.88 (s, 1H).

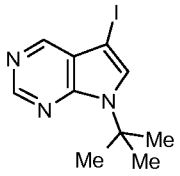
Preparation 18: 5-Iodo-7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 14** using 7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 12**) to afford the title compound as a brown oil in 71% yield, 9.68 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44-1.65 (m, 9H), 3.45 (m, 1H), 3.56 (m, 1H), 3.67 (m, 1H), 3.99 (m, 1H), 4.54 (m, 1H), 5.24 (m, 1H), 7.51 (s, 1H), 8.76 (s, 1H), 8.89 (s, 1H).

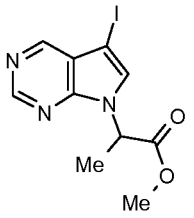
Preparation 19: 7-*tert*-Butyl-5-iodo-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 14** using 7-*tert*-butyl-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 13**) to afford the title compound as a yellow solid in 71% yield, 1.55 g.

LCMS (system 1): R_t = 3.12 min; m/z 302 $[M+H]^+$.

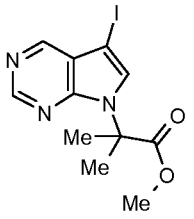
Preparation 20: (R,S) Methyl 2-(5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propanoate



Methyl-2-bromopropionate (6.83 mL, 61.2 mmol) was added to a mixture of 5-iodo-7H-pyrrolo[2,3-d]pyrimidine (15.0 g, 61.0 mmol) and cesium carbonate (35.9 g, 110.0 mmol) in DMF (75 mL). The mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with water (250 mL) and extracted with diethyl ether (100 mL). The organic layer was washed with brine (70 mL), dried over magnesium sulfate and evaporated *in vacuo* to afford the title compound as an off-white solid in 83% yield, 16.87 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.82 (d, 3H), 3.76 (s, 3H), 5.72 (q, 1H), 7.48 (s, 1H), 8.76 (s, 1H), 8.89 (s, 1H).

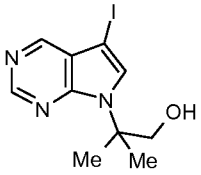
Preparation 21: Methyl 2-(5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropanoate



Potassium *t*-butoxide (71.3 mL, 71.3 mmol, 1.0 M in THF) was added to (R,S) methyl 2-(5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propanoate (16.9 g, 50.9 mmol) (see **Preparation 20)** and iodomethane (4.44 mL, 71.3 mmol) in THF (100 mL). The mixture was stirred at room temperature for 15 minutes then water (20 mL) and aqueous HCl (0.3 mL, 2M) was added. THF was removed by evaporation *in vacuo* then the aqueous residue was extracted with EtOAc (250 mL). The organic phase was dried over magnesium sulfate and evaporated *in vacuo.* The crude solid was purified by column chromatography on silica gel (80:20 pentane:EtOAc) to afford the title compound as a white solid in 51% yield, 8.92 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 1.93 (s, 6H), 3.68 (s, 3H), 7.43 (s, 1H), 8.75 (s, 1H), 8.85 (s, 1H).

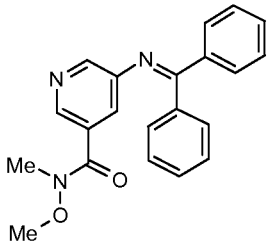
Preparation 22: 2-(5-Iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropan-1-ol



Lithium borohydride (32.3 mL, 64.6 mmol, 2.0 M in THF) was added to methyl 2-(5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropanoate (8.92 g, 25.9 mmol) (see **Preparation 21**) in ethanol (70 mL). The mixture was stirred at room temperature for 17 hours then water (70 mL) was added. The mixture was evaporated *in vacuo* then the residue was partitioned between DCM (250 mL) and water (50 mL). The aqueous phase was extracted with DCM:MeOH (90:10, 2 x 250 mL) and the combined organic phases were dried over magnesium sulfate and evaporated *in vacuo* to afford the title compound as an off- white solid in 100% yield, 8.20 g.

^{1}H NMR (400 MHz, DMSO-d6) δ*:* 1.65 (s, 6H), 3.16 (d, 2H), 7.77 (s, 1H), 8.67 (s, 1H), 8.80 (s, 1H).

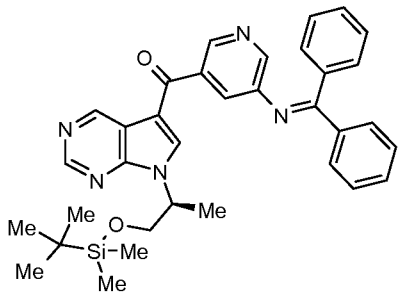
Preparation 23: 5-[(Diphenylmethylene)amino]-N-methoxy-N-methylnicotinamide



Benzophenone imine (205 mL, 1.22 mol) was added to 5-bromo-N-methoxy-N-methylisonicotinamide (250 g, 1.02 mol), tris(dibenzylideneacetone)dipalladium (28.0 g, 31.0 mmol), 2-di-*tert*-butylphosphino-

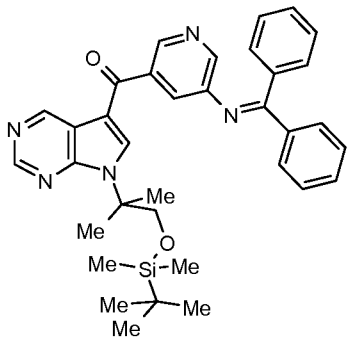
2′,4′,6′-triisopropylbiphenyl (34.7 g, 82.0 mmol) and freshly ground potassium phosphate tribasic (541 g, 2.55 mol) in 1,2-dimethoxyethane (2500 mL). The mixture was stirred at 50°C for 17 hours. The reaction mixture was filtered through Arbocel™ and the pad was washed with EtOAc (500 mL). The filtrate was evaporated *in vacuo* and the crude material was purified by column chromatography on silica gel (gradient of heptane:EtOAc 70:30 to 0:100) to afford the title compound as an orange gum in 51% yield, 180.0 g.
^{1}H NMR (400 MHz, DMSO-D6) δ*:* 3.19 (s, 3H), 3.37 (s, 3H), 7.18-7.23 (m, 2H), 7.29 (m, 1H), 7.32-7.39 (m, 3H), 7.46-7.53 (m, 2H), 7.57 (m, 1H), 7.67-7.73 (m, 2H), 8.09 (d, 1H), 8.27 (d, 1H).

Preparation 24: {7-[(1S)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone



Isopropyl magnesium chloride (68.8 mL, 138 mmol, 2.0 M in THF) was added to 7-[(1S)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl]-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (52.2 g, 125 mmol) (see **Preparation 14**) in THF (400 mL) at 0°C, under nitrogen. The mixture was stirred at 0°C for 1 hour then a solution of 5-[(diphenylmethylene)amino]-N-methoxy-N-methylnicotinamide (47.5 g, 138 mmol) (see **Preparation 23**) in THF (100 mL) was added dropwise at 0°C. The mixture was warmed to room temperature and stirred at this temperature for 16 hours. The reaction mixture was quenched with 10% aqueous ammonium chloride (250 mL) and extracted with ethyl acetate (2 x 250 mL). The combined organic extracts were washed with brine (250 mL), dried over sodium sulfate, evaporated *in vacuo* and the crude material was purified by column chromatography on silica gel (gradient of EtOAc:pentane 10:90 to 60:40) to afford the title compound as a colourless gum in 88% yield, 63.2 g.
R_t = 7.94 min; m/z 576 $[M+H]^+$.

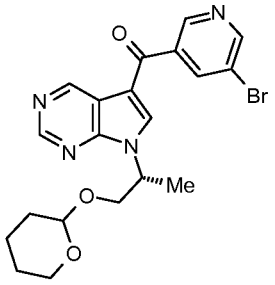
Preparation 25: [7-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone



The title compound was prepared according to the method described for **Preparation 24** using 7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 15**) and 5-[(diphenylmethylene)amino]-N-methoxy-N-methylnicotinamide (see **Preparation 23**) to afford the title compound as a colourless gum in 56% yield, 1.49 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.21 (s, 6H), 0.67 (s, 9H), 1.80 (s, 6H), 4.10 (s, 2H), 7.14 (d, 2H), 7.33 (m, 3H), 7.45 (m, 2H), 7.54 (m, 1H), 7.58 (t, 1H), 7.79 (d, 2H), 7.89 (s, 1H), 8.18 (d, 1H), 8.58 (d, 1H), 9.01 (s, 1H), 9.60 (s, 1H).

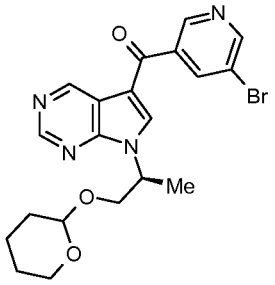
Preparation 26: (5-Bromopyridin-3-yl){7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone



The title compound was prepared according to the method described for **Preparation 24** using 5-iodo-7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 17**) and 5-bromo-N-methoxy-N-methylnicotinamide to afford the title compound as a brown oil in 66% yield, 215 mg.

LCMS (system 2): R_t = 1.27 min; m/z 447 $[M+H]^+$.

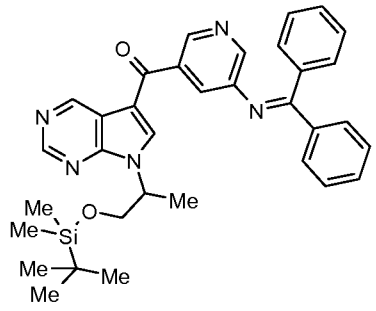
Preparation 27: (5-Bromopyridin-3-yl){7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone



The title compound was prepared according to the method described for **Preparation 24** using 5-iodo-7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 18**) and 5-bromo-N-methoxy-N-methylnicotinamide to afford the title compound as a colourless oil in 32% yield, 181 mg.

LCMS (system 2): R_t = 1.27 min; m/z 447 $[M+H]^+$.

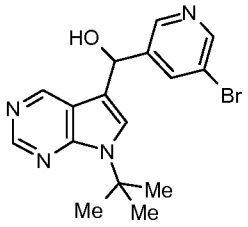
Preparation 28: (R,S) {7-[2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone



^{n}Butyllithium (0.57 mL, 1.31 mmol, 2.3 M in hexanes) was added to (R,S) 7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (500 mg, 1.19 mmol) (see **Preparation 16**) in dry ether (20 mL) at -78°C and the reaction mixture was stirred for 30 minutes. Then 5-[(diphenylmethylene)amino]-N-methoxy-N-methylnicotinamide (372 mg, 1.07 mmol) (see **Preparation 23)** in dry ether (25mL) was added drop wise at the same temperature. After 15 minutes the mixture was quenched with saturated aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (70 mL). The organic extract was dried over sodium sulfate, evaporated *in vacuo* and purified by column chromatography on silica gel (hexane:EtOAc 70: 30) to afford the title compound as an off-white solid in 19% yield, 134 mg.

LCMS (System 4): R_t = 4.53 min; m/z 576 $[M+H]^+$.

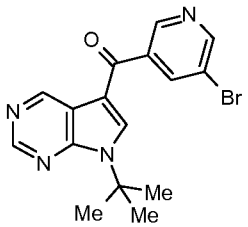
Preparation 29: (R,S) (5-Bromopyridin-3-yl)(7-*tert*-butyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanol



The title compound was prepared according to the method described for **Preparation 28** using 7-*tert*-butyl-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 19**) and 5-bromo-pyridine-3-carbaldehyde to afford the title compound as a colourless oil in 37% yield, 486 mg.

LCMS (System 4): R_t = 2.94 min; m/z 362 $[M+H]^+$.

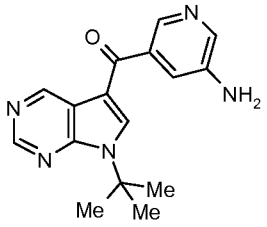
Preparation 30: (5-Bromopyridin-3-yl)(7-*tert*-butyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanone



2-Iodoxybenzoic acid (909 mg, 3.25 mmol) was added to (R,S) (5-bromopyridin-3-yl)(7-*tert*-butyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanol (405 mg, 1.34 mmol) (see **Preparation 29**) in ethyl acetate (30mL) and the mixture was refluxed for 4 hours. The mixture was filtered and the filtrate was evaporated *in vacuo* to afford the title compound as a white solid in 95% yield, 554 mg.

LCMS (system 4): R_t = 3.28 min; m/z 360 $[M+H]^+$.

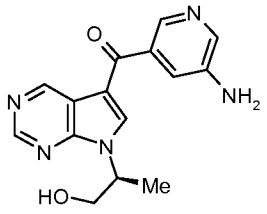
Preparation 31: (5-Aminopyridin-3-yl)(7-*tert*-butyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanone



Copper sulfate pentahydrate (55 mg, 0.24 mmol) was added to (5-bromopyridin-3-yl)(7-*tert*-butyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanone (292 mg, 0.81 mmol) (see **Preparation 30**) and concentrated ammonia solution (20 mL). The mixture was heated in a sealed vessel at 140°C for 17 hours. The reaction mixture was evaporated *in vacuo* and the residue was stirred in aqueous hydrochloric acid (10 mL, 2M) at room temperature for 17 hours. The reaction mixture was basified to pH 9 using saturated aqueous sodium carbonate then extracted with DCM (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate and evaporated *in vacuo* to afford the title compound as a white solid in 49% yield, 240 mg.

LCMS (System 4): R_t = 2.68 min; m/z 296 $[M+H]^+$.

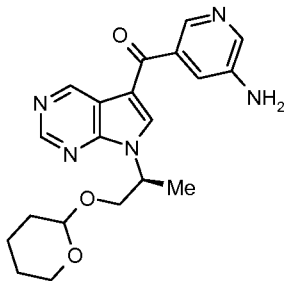
Preparation 32: (5-Aminopyridin-3-yl){7-[(1S)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone



The title compound was prepared according to the method described for **Preparation 31** using (5-bromopyridin-3-yl){7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (see **Preparation 27**) to afford the title compound as a white solid in 10% yield, 134 mg.

LCMS (system 2): R_t = 0.59 min; m/z 298 $[M+H]^+$.

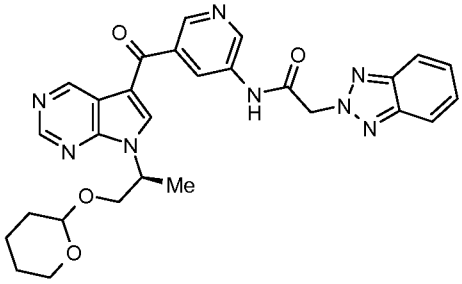
Preparation 33: (5-Aminopyridin-3-yl){7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone



Benzophenone imine (0.40 mL, 2.4 mmol) was added to (5-bromopyridin-3-yl){7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (891 mg, 2.0 mmol) (see **Preparation 27**), tris(dibenzylideneacetone)dipalladium (55 mg, 0.06 mmol), 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (68 mg, 0.16 mmol) and freshly ground potassium phosphate tribasic (1.06 g, 5.0 mmol) in 1,2-dimethoxyethane (4 mL). The mixture was stirred at 50°C for 17 hours. The reaction mixture diluted with DCM (10 mL), filtered through Arbocel™ and the pad was washed with DCM (5 mL). The filtrate was evaporated *in vacuo* and the crude material was dissolved in THF (10 mL). Aqueous citric acid (5 mL, 2M) was added and the mixture was stirred at room temperature for 16 hours. Water (40 mL) was added then sodium hydroxide was added to basify the mixture. The mixture was extracted with EtOAc (3 x 40 mL) and the combined organic extracts were dried over magnesium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (gradient of EtOAc:MeOH 100:0 to 80:20) to afford the title compound as a white solid in 70% yield, 506 mg.

LCMS (system 1): R_t = 3.27 min; m/z 382 $[M+H]^+$.

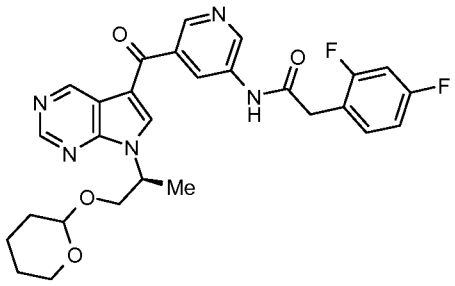
Preparation 34: 2-(2H-Benzotriazol-2-yl)-N-[5-({7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide



The title compound was prepared according to the method described for **Example 1** using (5-aminopyridin-3-yl){7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (see **Preparation 33**) and benzotriazol-2-yl-acetic acid to afford the title compound as a yellow solid in 72% yield, 70 mg.

LCMS (system 5): R_t = 2.98min, m/z 541 $[M+H]^+$.

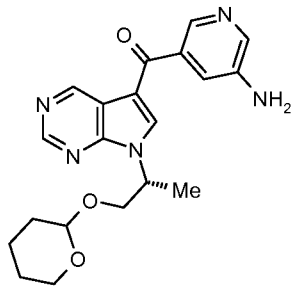
Preparation 35: 2-(2,4-Difluorophenyl)-N-[5-({7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide



The title compound was prepared according to the method described for **Example 1** using (5-aminopyridin-3-yl){7-[(1S)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (see **Preparation 33**) and 2,5-difluorophenylacetic acid to afford the title compound as a yellow solid in 75% yield, 75 mg.

LCMS (system 5): R_t = 3.08min, m/z 536 $[M+H]^+$.

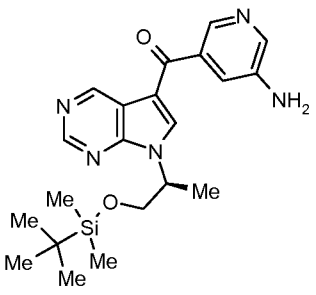
Preparation 36: (5-Aminopyridin-3-yl){7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone



Copper (I) oxide (9.2 mg, 0.06 mmol) was added to (5-bromopyridin-3-yl){7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (285 mg, 0.64 mmol) (see **Preparation 26**) and concentrated ammonia solution (2 mL) in 1-methyl-2-pyrrolidinone (0.5 mL). The mixture was heated in a sealed vessel at 80°C for 17 hours. Ethyl acetate (5 mL) and water (5 mL) were added to the reaction mixture and then filtered through a glass fibre filter. The organic phase was dried over magnesium sulfate and evaporated *in vacuo*. The crude solid was purified by column chromatography on silica gel (gradient of EtOAc:MeOH:cNH3 100:0:0 to 95:5:0.5) to afford the title compound as a colourless oil in 70% yield, 171 mg.

LCMS (system 2): R_t = 0.78 min; m/z 382 $[M+H]^+$.

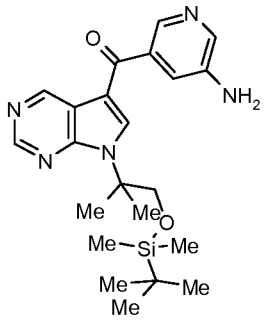
Preparation 37: (5-Aminopyridin-3-yl){7-[(1S)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone



Aqueous citric acid (120 mL, 2.0 M) was added to {7-[(1S)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone (63.2 g, 110 mmol) (see **Preparation 24**) in THF (274 mL) and the mixture was stirred at room temperature for 17 hours. The mixture was cooled to 0°C, water (200 mL) added and the mixture was basified using sodium hydroxide (28 g). The mixture was extracted with ethyl acetate (150 mL) then the aqueous phase was extracted with ethyl acetate (2 x 200 mL). The combined organic phases were washed with brine (600 mL), dried over sodium sulfate and evaporated *in vacuo* to afford the title compound as a semi-solid in quantitative yield, 45.2 g.

LCMS (system 2): R_t = 1.16 min; m/z 412 $[M+H]^+$.

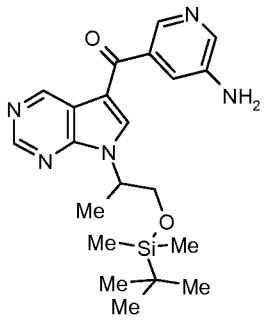
Preparation 38: (5-Aminopyridin-3-yl)[7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone



The title compound was prepared according to the method described for **Preparation 37** using [7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone (see **Preparation 25**) to afford the title compound as a white solid in 81% yield, 872 mg.

^{1}H NMR (400 MHz, DMSO-d6) δ: 0.22 (s, 6H), 0.63 (s, 9H), 1.66 (s, 6H), 4.12 (s, 2H), 5.65 (s, 2H), 7.27 (dd, 1H), 8.08 (s, 1H), 8.14-8.17 (m, 2H), 8.97 (s, 1H), 9.45 (s, 1H).

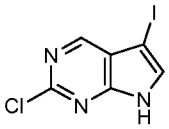
Preparation 39: (R,S) (5-Aminopyridin-3-yl){7-[2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone



The title compound was prepared according to the method described for **Preparation 37** using (R,S) {7-[2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone (see **Preparation 28**) to afford the title compound as a white solid in 89% yield, 86 mg.

LCMS (System 4): R_t =1.37 min; m/z 412 $[M+H]^+$.

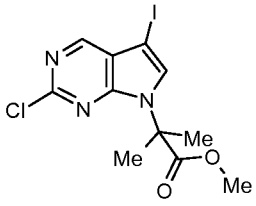
Preparation 40: 2-Chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine



N-Iodosuccinimide (742 g, 3.30 mol) was added to 2-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (482.5 g, 3.14 mol) in acetonitrile (2500 mL) at 12°C. The mixture was stirred at room temperature for 1 hour then sodium metabisulphite (650 g in 4500 mL of water) was added. The mixture was stirred for 1 hour then filtered to afford the title compound as a orange solid in 82% yield, 716.2 g.

^{1}H NMR (400 MHz, DMSO-D6) δ*:* 7.83 (s, 1H), 8.63 (s, 1H), 12.73 (s, 1H).

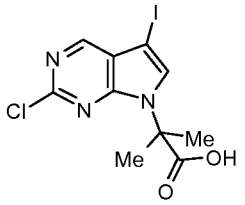
Preparation 41: Methyl 2-(2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropanoate



Methyl 2-bromo-2-methylpropanoate (663 mL, 5.13 mmol) was added to 2-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (358.1 g, 1.28 mol) (see **Preparation 40**), potassium iodide (21.3 g, 128 mmol) and cesium carbonate (1670 g, 5.13 mol) in DMF (7162 mL). The mixture was heated at 60°C for 19 hours. The reaction mixture was diluted with water (7000 mL) and stirred at room temperature for 42 hours. The mixture was filtered and the solid was washed with water (500 mL) to afford the title compound as a beige solid in 92% yield, 445.8 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.89 (s, 6H), 3.65 (s, 3H), 7.39 (s, 1H), 8.56 (s, 1H).

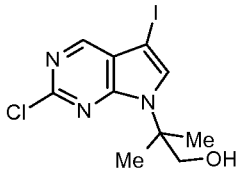
Preparation 42: 2-(2-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropanoic acid



Lithium hydroxide monohydrate (4.08 g, 97.5 mmol) was added to methyl 2-(2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropanoate (18.5 g, 48.7 mmol) (see **Preparation 41**) in THF (185 mL) and water (45 mL). The mixture was stirred at 60°C for 3 hours then the reaction mixture volume was reduced to one third by evaporation *in vacuo*. The aqueous residue was acidified using aqueous HCl (2.0 M) then extracted with EtOAc (4 x 200 mL). The organic phase was evaporated *in vacuo* and the crude material was triturated with hexane (100 mL) to afford the title compound as a white solid in 90% yield, 16.0 g.

LCMS (system 5) R_t = 2.24 min; m/z 366 $[M+H]^+$.

Preparation 43: 2-(2-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropan-1-ol



Route a

Isobutyl chloroformate (6.6 mL, 50.02 mmol) was added to 2-(2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropanoic acid (16.6 g, 45.48 mmol) (see **Preparation 42**) and triethylamine (12.64 mL, 90.9 mmol) in THF (300 mL) at 0°C under nitrogen. The mixture was stirred at room temperature for 3 hours then filtered through a short plug of Celite™. The filtrate was cooled to 0°C and sodium borohydride (8.6 g, 227.6 mmol) in water (300 mL) was added. The mixture was stirred for 10 minutes at 0°C, extracted with ethyl acetate (3 x 150 mL) then the organic extract was washed with brine (150 mL) and dried over sodium sulfate. The solution was evaporated *in vacuo* and the residue was triturated with hexane to afford the title compound as a white solid in 63% yield, 10.0 g.

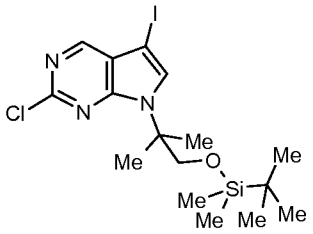
^{1}H NMR (400 MHz, DMSO-D_6) δ: 1.64 (s, 6H), 3.85 (d, 2H), 4.99 (t, 1H), 7.82 (s, 1H), 8.63 (s, 1H).

Route b

Diisobutylaluminium hydride (300 mL, 300 mmol, 1M in THF) was added dropwise to methyl 2-(2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropanoate (51.8 g, 136 mmol) (see **Preparation 41**) in THF (150 mL) at 0°C. The mixture was stirred for 90 minutes then methanol (27.9 mL) and aqueous HCl (20 mL, 2M) was added. Water (100 mL), aqueous HCl (280 mL, 2M) and EtOAc (150 mL) were added and the mixture was stirred at room temperature for 30 minutes. The mixture was filtered and the solid was washed with water (150 mL) and *tert*butylmethyl ether (150 mL) to afford the title compound as a white solid in 56% yield, 26.8 g.

LCMS (System 1) R_t = 4.88 min; m/z 352 $[M+H]^+$.

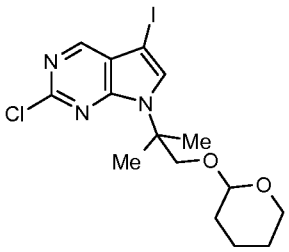
Preparation 44: 7-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine



t-Butyldimethylsilyl chloride (78.8 g, 518 mmol) was added to 2-(2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropan-1-ol (140 g, 398 mmol) (see **Preparation 43**) and imidazole (67.8 g, 996 mmol) in DMF (996 mL) at 0°C. The mixture was stirred at room temperature for 16 hours. The mixture was poured into saturated aqueous sodium bicarbonate (1500 mL) and extracted with heptane:EtOAc (1:1, 1500 mL). The organic extract was washed with brine (2 x 900 mL) then dried over magnesium sulfate and evaporated *in vacuo* to afford the title compound as a brown gum in 96% yield, 178.2 g.

LCMS (System 1) R_t = 8.32 min; m/z 466 $[M+H]^+$.

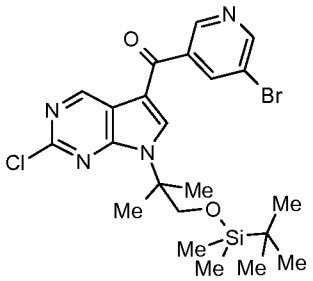
Preparation 45: 2-Chloro-7-[1,1-dimethyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-5-iodo-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 6** using 2-(2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropan-1-ol (see **Preparation 43**) to afford the title compound as a yellow oil in 74% yield, 7.3 g.

LCMS (system 5) R_t = 4.01 min; m/z 436 $[M+H]^+$.

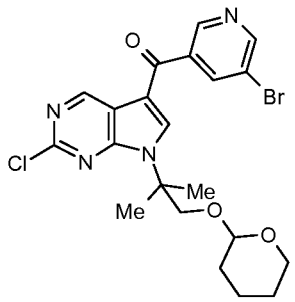
Preparation 46: (5-Bromopyridin-3-yl)[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone



The title compound was prepared according to the method described for **Preparation 28** using 7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 44**) and 5-bromo-N-methoxy-N-methylnicotinamide to afford the title compound as a yellow solid in 42% yield, 1.40 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: -0.18 (s, 6 H), 0.63 (s, 9 H), 1.72 (s, 6H), 4.09 (s, 2H), 8.24 (s, 1H), 8.39 (s, 1H), 8.95 (s, 1H), 8.99 (d, 1H), 9.36 (s, 1H).

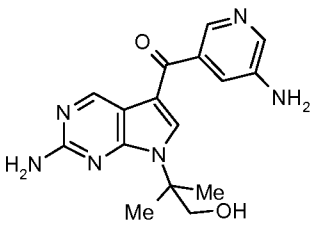
Preparation 47: (5-Bromopyridin-3-yl){2-chloro-7-[1,1-dimethyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone



The title compound was prepared according to the method described for **Preparation 28** using 2-chloro-7-[1,1-dimethyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 45**) and 5-bromo-N-methoxy-N-methylnicotinamide to afford the title compound as a yellow solid in 41% yield, 3.0 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42-1.62 (m, 6H), 1.83 (s, 6H), 3.35-3.39 (m, 1H), 3.53-3.56 (m, 1H), 3.85 (d, 1H), 4.22 (d, 1H), 4.47 (m, 1H), 7.98 (s, 1H), 8.25 (s, 1H), 8.87 (s, 1H), 8.94 (s, 1H), 9.45 (s, 1H).

Preparation 48: [2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl](5-aminopyridin-3-yl)methanone



The title compound was prepared according to the method described for **Preparation 36**

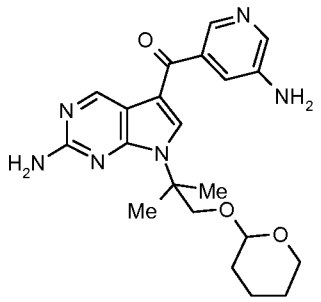
using (5-bromopyridin-3-yl)[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (see **Preparation 46**) to afford the title compound as a yellow solid in 48% yield, 300 mg.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 1.64 (s, 6H), 3.90 (d, 2H), 5.07 (t, 1H), 5.60 (s, 2H), 6.50 (s, 2H), 7.23 (s, 1H), 7.61 (s, 1H), 8.11 (m, 2H), 8.93 (s, 1H).

[7-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-amino-7H-pyrrolo[2,3-d]pyrimidin-5-yl]{5-aminopyridin-3-yl}methanone (**Preparation 48a**) was also isolated from the reaction mixture.

^{1}H NMR (400 MHz, DMSO) δ*:* -0.18 (s, 6H), 0.66 (s, 9H), 1.67 (s, 6H), 4.05 (s, 2H), 5.59 (s, 2H), 6.51 (s, 2H), 7.19 (s, 1H), 7.57 (s, 1H), 8.07 (s, 1H), 8.10 (s, 1H), 8.93 (s, 1H).

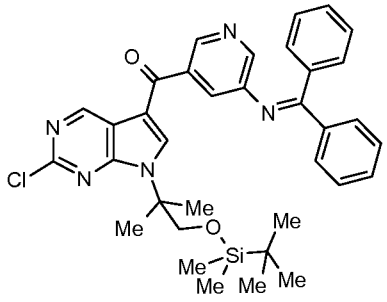
Preparation 49: {2-Amino-7-[1,1-dimethyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}(5-aminopyridin-3-yl)methanone



The title compound was prepared according to the method described for **Preparation 36** using (5-bromopyridin-3-yl){2-chloro-7-[1,1-dimethyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (see **Preparation 47**) to afford the title compound as a yellow solid in 52% yield, 1.3 g.

LCMS (system 5) R_t = 2.72 min; m/z 411 $[M+H]^+$.

Preparation 50: [7-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl]{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone

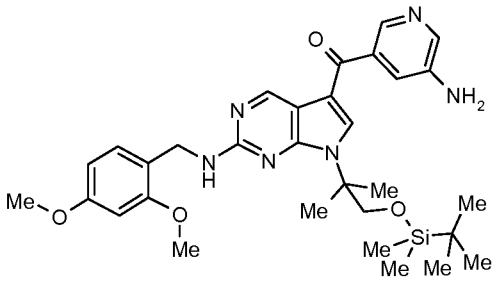


Isopropyl magnesium chloride (105 mL, 210 mmol, 2.0 M in THF) was added to 7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (89.0 g, 190 mmol) (see **Preparation 44**) in THF (450 mL) at 0°C, under nitrogen. The mixture was stirred at 0°C for 1 hour then a solution of 5-[(diphenylmethylene)amino]-N-methoxy-N-methylnicotinamide (72.6 g, 210 mmol)

(see **Preparation 23**) in THF (200 mL) was added dropwise at 0°C. The mixture was warmed to room temperature and stirred at this temperature for 16 hours. The reaction mixture was quenched with 10% aqueous ammonium chloride (500 mL) and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (2 x 300 mL). The combined organic extracts were washed with brine (400 mL), dried over sodium sulfate, evaporated *in vacuo* and the crude material was purified by column chromatography on silica gel (gradient of heptane:EtOAc 100:0 to 60:40) to afford the title compound as a colourless gum in 66% yield, 78.9 g.

LCMS (System 1) R_t = 8.60 min; m/z 624 $[M+H]^+$.

Preparation 51: (5-Aminopyridin-3-yl){7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-[(2,4-dimethoxybenzyl)amino]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone

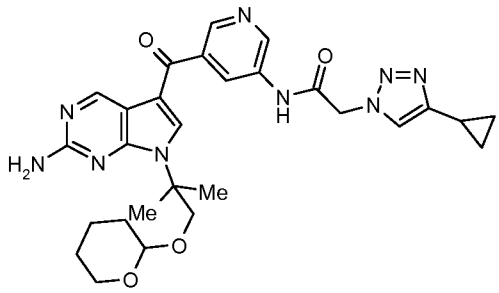


2,4-Dimethoxybenzylamine (99.4 g, 594 mmol) was added to [7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl]{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone (53.0 g, 85 mmol) (see **Preparation 50**) and 4-dimethylaminopyridine (2.07 g, 17.0 mmol) in 1,4-dioxane (170 mL). The mixture was heated to reflux for 2 days then cooled to room temperature and filtered. The filtrate was evaporated *in vacuo*, the residue was dissolved in EtOAc (300 mL) and washed with saturated aqueous ammonium chloride (500 mL). The organic phase was dried over magnesium sulfate and evaporated *in vacuo.*

The crude residue was dissolved in THF (200 mL) and aqueous citric acid (200 mL, 2M) was added. The mixture was stirred at room temperature for 5 hours then diluted with water (200 mL). The mixture was extracted with EtOAc (300 mL) and the organic extract was washed with aqueous potassium carbonate (300 mL, 2M). The organic phase was dried over magnesium sulfate, evaporated *in vacuo* and the residue was purified by column chromatography on silica (gradient of pentane: EtOAc 100:0 to 0:100, followed by EtOAc:MeOH 95:5) to afford the title compound as a colourless oil in 78% yield, 39.0 g.

LCMS (System 1) R_t = 5.97 min; m/z 591 $[M+H]^+$.

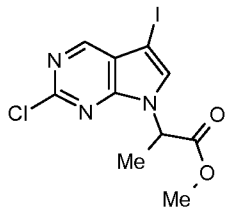
Preparation 52: N-[5-({2-Amino-7-[1,1-dimethyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide



The title compound was prepared according to the method described for **Example 1** using {2-amino-7-[1,1-dimethyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}(5-aminopyridin-3-yl)methanone (see **Preparation 49**) and (4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)acetic acid (see **Preparation 83**) to afford the title compound as a yellow solid in 86% yield, 70 mg.

LCMS (system 5): R_t = 2.87 min; m/z 560 $[M+H]^+$.

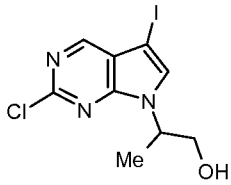
Preparation 53: (R,S) Methyl 2-(2-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propanoate



The title compound was prepared according to the method described for **Preparation 20** using 2-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (see **Preparation 40**) to afford the title compound as a brown solid in 62% yield, 18.0 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.77 (d, 3H), 3.75 (s, 3H), 5.67 (q, 1H), 7.46 (s, 1H), 8.58 (s, 1H).

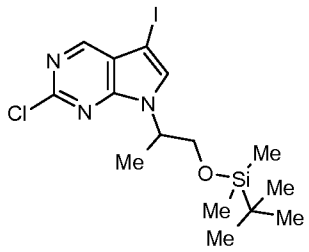
Preparation 54: (R,S) 2-(2-Chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propan-1-ol



The title compound was prepared according to the method described for **Preparation 22** using (R,S) methyl 2-(2-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propanoate (see **Preparation 53**) to afford the title compound as a yellow solid in 75% yield, 11.0 g.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 1.40 (d, 3H), 3.62-3.74 (m, 2H), 4.83 (m, 1H), 4.98 (t, 1H), 8.03 (s, 1H), 8.64 (s, 1H).

Preparation 55: 7-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 44** using 2-(2-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)propan-1-ol (see **Preparation 54**) to afford the title compound as a yellow solid in 89% yield, 12.50 g.

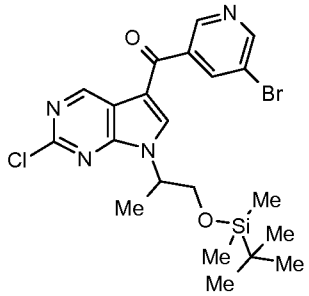
^{1}H NMR (400 MHz, $CDCl_3$) δ: -0.09 (s, 6H), 0.80 (s, 9H), 1.53 (d, 3H), 3.80 (d, 2H), 5.04 (m, 1H), 7.46 (s, 1H), 8.55 (s, 1H).

The enantiomers were separated using a Chiralpak IC 20 x 250 mm, 98:2:0.1 heptane:IPA:diethylamine (flow rate – 18.0 mL/minute).

Enantiomer 1 Yield 5.2 g, 99% e.e. (first eluting peak at 7.10 mins)

Enantiomer 2 Yield 5.0 g, 99% e.e. (second eluting peak at 7.64 mins)

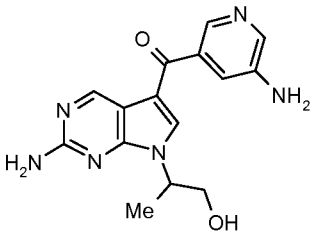
Preparation 56: (5-Bromopyridin-3-yl)[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone *(enantiomer 1)*



The title compound was prepared according to the method described for **Preparation 28** using 7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 55, enantiomer 1**) and 5-bromo-N-methoxy-N-methylnicotinamide to afford the title compound as a yellow solid in 30% yield, 1.0 g.

^{1}H NMR (400 MHz, DMSO-D_6) δ: -0.14 (s, 6H), 0.61 (s, 9H), 1.52 (d, 3H), 3.91-3.96 (m, 2H), 5.00 (m, 1H), 8.37 (s, 1H), 8.58 (s, 1H), 8.95 (s, 1H), 9.00 (s, 1H), 9.33 (s, 1H).

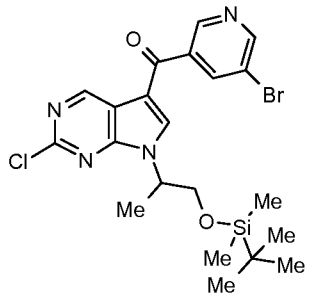
Preparation 57: [2-Amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl](5-aminopyridin-3-yl)methanone *(enantiomer 1)*



The title compound was prepared according to the method described for **Preparation 36** using (5-bromopyridin-3-yl)[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (see **Preparation 56**) to afford the title compound as a yellow solid in 51% yield, 450 mg.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 1.41 (d, 3H), 3.66 (m, 2H), 4.74 (m, 1H), 5.01 (t, 1H), 5.59 (s, 2H), 6.55 (s, 2H), 7.22 (s, 1H), 7.83 (s, 1H), 8.11-8.13 (m, 2H), 8.91 (s, 1H); LCMS (system 5) R_t = 1.72 min; m/z 313 $[M+H]^+$.

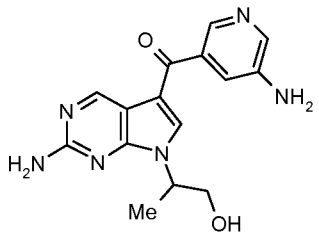
Preparation 58 : (5-Bromopyridin-3-yl)[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone *(enantiomer 2)*



The title compound was prepared according to the method described for **Preparation 28** using 7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (see **Preparation 55, enantiomer 2**) and 5-bromo-N-methoxy-N-methylnicotinamide to afford the title compound as a yellow solid in 30% yield, 1.4 g.

^{1}H NMR (400 MHz, DMSO-D_6) δ: -0.14 (s, 6H), 0.61 (s, 9H), 1.52 (d, 3H), 3.91-3.96 (m, 2H), 5.00 (m, 1H), 8.37 (s, 1H), 8.58 (s, 1H), 8.95 (s, 1H), 9.00 (s, 1H), 9.33 (s, 1H).

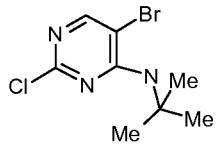
Preparation 59: [2-Amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl](5-aminopyridin-3-yl)methanone *(enantiomer 2)*



The title compound was prepared according to the method described for **Preparation 36** using (5-bromopyridin-3-yl)[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1-methylethyl)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (see **Preparation 58**) to afford the title compound as a yellow solid in 51% yield, 450 mg.

LCMS (system 5) R_t = 1.70 min; m/z 313 $[M+H]^+$.

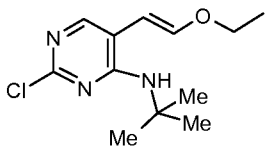
Preparation 60: 5-Bromo-*N*-*tert*-butyl-2-chloropyrimidin-4-amine



tert-Butylamine (5.28 g, 72 mmol) was added to 5-bromo-2,4-dichloropyrimidine (15 g, 66 mmol) and triethylamine (19.9 g, 197 mmol) in acetonitrile (450 mL) at room temperature and the mixture was stirred at room temperature for 16 hours. Then the mixture was evaporated *in vacuo* and the crude residue was partitioned between EtOAc (450 mL) and water (400 mL). The organic layer was separated, washed with brine (400 mL) then dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:EtOAc 88:12) to afford the title compound as a yellow oil in 52% yield, 8.8 g.

LCMS (system 5): R_t = 3.46 min; m/z 265 $[M+H]^+$.

Preparation 61: *N*-*tert*-Butyl-2-chloro-5-[(*E*)-2-ethoxyvinyl]pyrimidin-4-amine

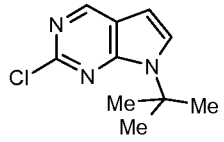


Catecholborane (7.8 g, 65.4 mmol) in THF (50 mL) was added dropwise to a solution of 40% ethoxyacetylene in hexane (12.8 mL, 72.5 mmol) under nitrogen at 0-5ºC. The mixture was stirred for 2 hours at room temperature then heated at 70ºC for 2 hours. The mixture was then cooled to room temperature and a solution of 5-bromo-*N*-*tert*-butyl-2-chloropyrimidin-4-amine (10 g, 37.8 mmol) (see **Preparation 60**) in THF (50 mL) was added. The solution was degassed with argon for about 25 minutes

followed by the addition of $Pd(PPh_3)_4$ (1.3 g, 1.13 mmol) and powdered sodium hydroxide (4.53 g, 113 mmol). The mixture was heated at 70°C for 16 hours and then cooled to room temperature. EtOAc (200 mL) was added and the mixture was filtered through a Celite™ pad. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (gradient of hexane:EtOAc 93:7 to 90:10) to afford the title compound as a yellow oil in 55% yield, 5.3 g.

LCMS (system 5): R_t = 3.65 min; m/z 256 $[M+H]^+$.

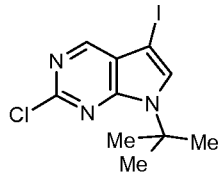
Preparation 62: 7-*tert*-Butyl-2-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine



Concentrated HCl (25 mL) was added to *N*-*tert*-butyl-2-chloro-5-[(*E*)-2-ethoxyvinyl]pyrimidin-4-amine (5.3 g, 20.72 mmol) (see **Preparation 61**) in isopropanol (210 mL) and the mixture was heated at reflux for 4 hours. The reaction mixture was then evaporated *in vacuo* and the residue was basified with saturated aqueous $NaHCO_3$ and extracted with EtOAc (200 mL). The organic extract was dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (gradient of hexane:EtOAc 93:7 to 90:10) to afford the title compound as a yellow oil in 85% yield, 3.7 g.

LCMS (system 5): R_t = 3.42 min; m/z 210 $[M+H]^+$.

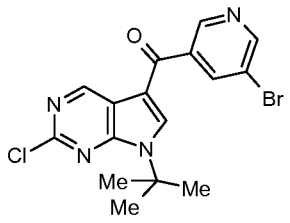
Preparation 63: 7-*tert*-Butyl-2-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine



The title compound was prepared according to the method described for **Preparation 14** using 7-*tert*-butyl-2-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (see **Preparation 62**) to afford the title compound as a brown solid in 87% yield, 4.7 g.

^1H NMR (400 MHz, $CDCl_3$) δ: 1.55 (s, 9H), 7.39 (s, 1H), 8.54 (s, 1H).

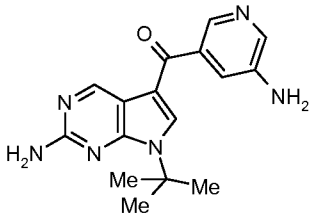
Preparation 64: (5-Bromopyridin-3-yl)(7-*tert*-butyl-2-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanone



The title compound was prepared according to the method described for **Preparation 28** using 7-*tert*-butyl-2-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (see **Preparation 63**) and 5-bromo-N-methoxy-N-methylnicotinamide to afford the title compound as a brown oil in 36% yield, 2.1 g.

^{1}H NMR (400 MHz, CDCl3) δ: 1.82 (s, 9H), 7.78 (s, 1H), 8.25 (s, 1H), 8.88 (s, 1H), 8.92 (s, 1H), 9.44 (s, 1H).

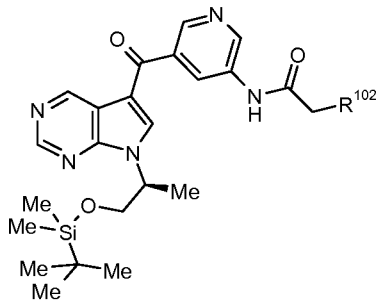
Preparation 65: (2-Amino-7-*tert*-butyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)(5-aminopyridin-3-yl)methanone

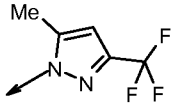
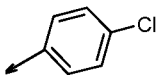
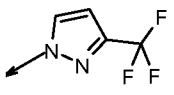


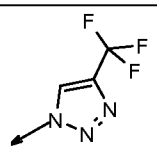
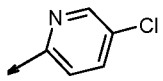
The title compound was prepared according to the method described for **Preparation 36** using (5-bromopyridin-3-yl)(7-*tert*-butyl-2-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanone (see **Preparation 64**) to afford the title compound as a white solid in 55% yield, 870 mg.

LCMS (system 5): R_t = 2.42 min; m/z 311 $[M+H]^+$.

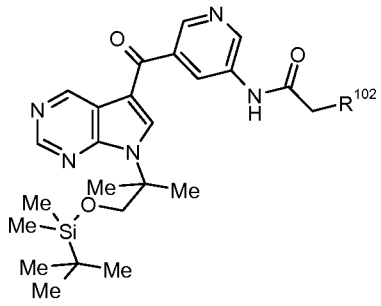
Preparations 66 to 70 were prepared according to Example **1**, starting from (5-aminopyridin-3-yl){7-[(1S)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (see **Preparation 37**) and the appropriate acids of formula :

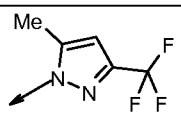
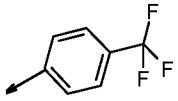
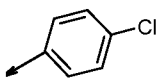
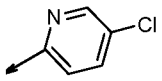
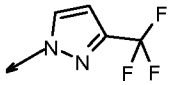
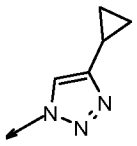
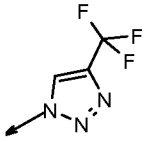


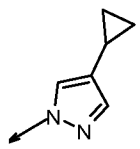
Preparation	R^{102}	Data
66		LCMS(system 4): R_t = 3.73min, m/z 602 $[M+H]^+$
67		LCMS(system 4): R_t = 3.87min, m/z 563 $[M+H]^+$
68		LCMS(system 4): R_t = 1.71min, m/z 588 $[M+H]^+$

69		LCMS (system 4): R_t = 3.51min, m/z 589 $[M+H]^+$
70		LCMS(system 4): R_t = 3.55min, m/z 565 $[M+H]^+$

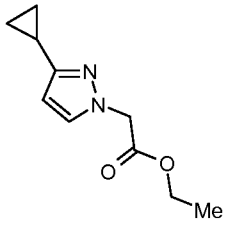
Preparations 71 to78 were prepared according to the method described above for Example **1**, starting from (5-aminopyridin-3-yl)[7-(2-{[*tert*-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (see **Preparation 38**) and the appropriate acids of formula :



Preparation	**R^{102}**	**Data**
71		LCMS(system 4): R_t = 3.88 min; m/z 616 $[M+H]^+$
72		LCMS (system 4): R_t = 4.09 min; m/z 612 $[M+H]^+$
73		LCMS(system 4): R_t = 4.07 min; m/z 578 $[M+H]^+$
74		LCMS(system 4): R_t = 3.81 min; m/z 579 $[M+H]^+$
75		LCMS(system 4): R_t = 3.79 min; m/z 602 $[M+H]^+$
76		LCMS(system 4): R_t = 3.58 min; m/z 575 $[M+H]^+$
77		LCMS(system 4): R_t = 3.74 min; m/z 603 $[M+H]^+$

78		LCMS (system 4): R_t = 3.78 min; m/z 573 $[M+H]^+$

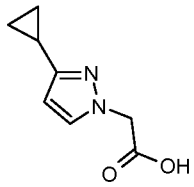
Preparation 79: Ethyl (3-cyclopropyl-1H-pyrazol-1-yl) acetate



Potassium carbonate (7.67 g, 55.56 mmol) was added to 3-cyclopropyl-1H-pyrazole (2.0 g, 18.52 mmol) in dry DMF (20 mL) at 25°C and the mixture was stirred for 20 minutes. Ethyl bromoacetate (2.06 mL, 18.52 mmol) was added then the mixture was stirred for 2 days at room temperature. The reaction mixture was neutralized with aqueous HCl (1.0 M), extracted with ether (40 mL) and the organic extract was washed with brine (30 mL), dried over sodium sulfate then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:EtOAc 88:12) to afford the title compound as a yellow oil in 42% yield, 1.50 g.

^{1}H NMR (400 MHz, DMSO) δ*:* 0.59 (d, 2H), 0.83 (d, 2H), 1.19 (t, 3H), 1.83 (m, 1H), 4.13 (q, 2H), 4.91 (s, 2H), 5.94 (d, 1H), 7.54 (d, 1H).

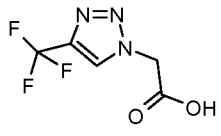
Preparation 80: (3-Cyclopropyl-1H-pyrazol-1-yl)acetic acid



The title compound was prepared according to the method described for **Preparation 42** using ethyl (3-cyclopropyl-1H-pyrazol-1-yl) acetate (see **Preparation 79**) to afford the title compound as a white solid in 83% yield, 4.06 g.

LCMS(system 4): R_t = 1.16 min; m/z 167 $[M+H]^+$.

Preparation 81: [4-(Trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]acetic acid



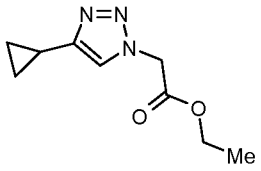
Trifluoromethyl acetylene (22.0 g, 0.234 mol) in THF (210 mL) was added to sodium ascorbate (2.77 g, 14.0 mmol), ethyl azidoacetate (27.1 g, 0.210 mol) and copper sulfate (4.76 mL, 0.3 M in water) in water

(105 mL). The mixture was stirred at room temperature for 240 hours then evaporated *in vacuo*. The residue was extracted with EtOAc (500 mL) and the organic phase was dried over magnesium sulfate then evaporated *in vacuo*.

Sodium hydroxide (7.32 g, 0.183 mol) in water (30 mL) was added to the residue (32.7 g, 0.146 mol) in methanol (50 mL) and the mixture was stirred at room temperature for 17 hours. The methanol was evaporated *in vacuo* and the residue was diluted with water (10 mL). Potassium hydrogen sulfate (26.6 g, 0.195 mol) in water (70 mL) was added. The solution was evaporated *in vacuo* and the crude solid was purified by crystallisation using water to afford the title compound as a white solid in 75% yield, 25.8 g.

^{1}H NMR (400 MHz, DMSO-d6) δ*:* 5.40 (s, 2H), 8.85 (s, 1H), 13.50 (br s, 1H).

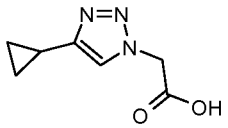
Preparation 82: Ethyl (4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)acetate



Cyclopropylacetyene (15 g, 0.116 mol), ethyl azidoacetate (11.5 g, 0.174 mol), triethylamine (0.32 mL, 2.33 mmol) and copper iodide (442 mg, 2.33 mmol) in acetonitrile (100 mL) were stirred at 25°C for 18 hours. The mixture was evaporated *in vacuo* and the residue was partitioned between water (100 mL) and ethyl acetate (100 mL). The organic phase was dried over sodium sulfate, evaporated *in vacuo* and purified by column chromatography on silica gel (EtOAc: Hexane 40: 60) to afford the title compound as a colorless liquid in 95% yield, 21.6 g.

^{1}H NMR (400 MHz, DMSO) δ*:* 0.68 (m, 2H), 0.90 (m, 2H), 1.21 (t, 3H), 1.95 (m, 1H), 4.17 (q, 2H), 5.29 (s, 2H), 7.81 (s, 1H).

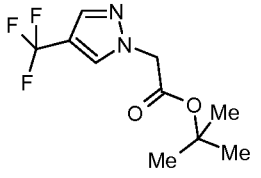
Preparation 83: (4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)acetic acid



The title compound was prepared according to the method described for **Preparation 42** using ethyl (4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)acetate (see **Preparation 82**) to afford the title compound as a yellow solid in 63% yield, 13.0 g.

LCMS (system 4): R_t = 1.86 min; m/z 186$[M+H]^+$.

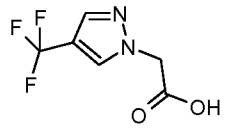
Preparation 84: *tert*-Butyl [4-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetate



The title compound was prepared according to the method described for **Preparation 79** using 4-(trifluoromethyl)-1H-pyrazole and *tert* butyl bromoacetate to afford the title compound as a yellow solid in 24% yield, 1.32 g.

LCMS(system 4): R_t =3.64min; m/z 251 $[M+H]^+$.

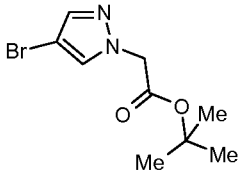
Preparation 85: [4-(Trifluoromethyl)-1*H*-pyrazol-1-yl]acetic acid



Trifluoroacetic acid (10 mL) was added to *tert*-butyl [4-(trifluoromethyl)-1*H*-pyrazol-1-yl]acetate (1.3 g, 5.2 mmol) (see **Preparation 84**) in dry DCM (10 mL) and the mixture was stirred for 18 hours at 25°C. Then the mixture was evaporated *in vacuo* and the residue was purified by trituration with diethyl ether:pentane (1:9, 2 mL) to afford the title compound as a white solid in 79% yield, 800 mg.

LCMS(system 4): R_t = 1.39min; m/z 193 $[M+H]^+$.

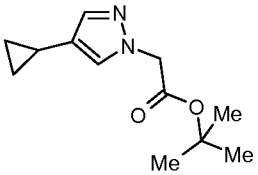
Preparation 86: *tert*-Butyl [4-bromo-1*H*-pyrazol-1-yl]acetate



The title compound was prepared according to the method described for **Preparation 79** using 4-bromo-1H-pyrazole and *tert* butyl bromoacetate to afford the title compound as a yellow solid in 34% yield, 48.0 g.

^{1}H NMR (400 MHz, CDCl3) δ*:* 1.42 (s, 9H), 4.70 (s, 2H), 7.40 (s, 2H).

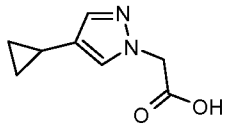
Preparation 87: *tert*-Butyl (4-cyclopropyl-1*H*-pyrazol-1-yl)acetate



Palladium acetate (215 mg, 0.957 mmol) was added to *tert*-butyl [4-bromo-1*H*-pyrazol-1-yl]acetate (5 g, 19.14 mmol) (see **Preparation 86**), cyclopropyl boronic acid (8.22 g, 95.74 mmol), potassium phosphate (8.12 g, 38.29 mmol) and tricyclohexylphosphine (537 mg, 1.91 mmol) in toluene: water (60mL:15mL). The mixture was degassed for 20 minutes then refluxed for 18 hours. The reaction mixture was filtered through Celite™, the filtrate was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel (gradient of EtOAc: hexane 15: 85) to afford the title cpompound as an off white solid in 21% yield, 1.3 g.

LCMS (System 4): R_t =3.17min; m/z 223$[M+H]^+$.

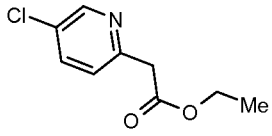
Preparation 88: (4-Cyclopropyl-1*H*-pyrazol-1-yl)acetic acid



The title compound was prepared according to the method described for **Preparation 85** using *tert*-butyl (4-cyclopropyl-1*H*-pyrazol-1-yl)acetate (see **Preparation 87**) to afford the title compound as a yellow solid in 75% yield, 1.0 g.

LCMS (system 4): R_t=1.13min; m/z 165$[M+H]^+$.

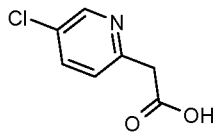
Preparation 89: Ethyl (5-chloropyridin-2-yl)acetate



Cesium carbonate (71 g, 218 mmol) was added to 2-bromo-5-chloropyridine (14 g, 73 mmol) and diethyl malonate (22 mL, 145 mmol) in dry 1,4-dioxane (280 mL) and the solution was degassed with argon for 30 minutes. Then copper (I) oxide (2.8 g, 14.55 mmol) and picolinic acid (3.6 g, 29 mmol) were added and the mixture was stirred in a sealed vessel at 130°C for 24 hours. The mixture was cooled to room temperature, quenched with water (100 mL) and extracted with EtOAc (3 x 100 ml). The organic extracts were washed with water (200 mL), brine (200 mL), dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc: Hexane 92: 8) to afford the title compound as a yellow oil in 54% yield, 8.0 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 1.17 (t, 3H), 3.85 (s, 2H), 4.08 (q, 2H), 7.42 (d, 1H), 7.90 (dd, 1H), 8.54 (d, 1H).

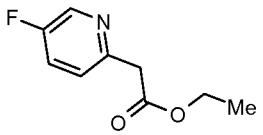
Preparation 90: (5-Chloropyridin-2-yl)acetic acid



The title compound was prepared according to the method described for **Preparation 42** using ethyl (5-chloropyridin-2-yl)acetate (see **Preparation 89**) to afford the title compound as a brown solid in 51% yield, 3.5 g.

LCMS (system 4): R_t = 1.00 min; m/z 172 $[M+H]^+$.

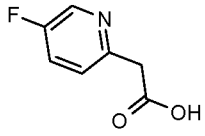
Preparation 91: Ethyl (5-fluoropyridin-2-yl)acetate



The title compound was prepared according to the method described for **Preparation 89** using 2-bromo-5-fluoropyridine to afford the title compound as a yellow oil in 20% yield, 5 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.17 (t, 3H), 3.84 (s, 2H), 4.08 (q, 2H), 7.42-7.45 (m, 1H), 7.67-7.72 (m, 1H), 8.48 (d, 1H).

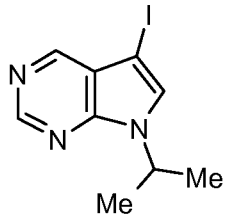
Preparation 92: (5-Fluoropyridin-2-yl)acetic acid



The title compound was prepared according to the method described for **Preparation 42** using ethyl (5-fluoropyridin-2-yl)acetate (see **Preparation 91**) to afford the title compound as a brown solid in 57% yield, 2.4 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.75 (s, 2H), 7.41-7.44 (m, 1H), 7.65-7.70 (m, 1H), 8.47 (d, 1H), 12.50 (br s, 1H).

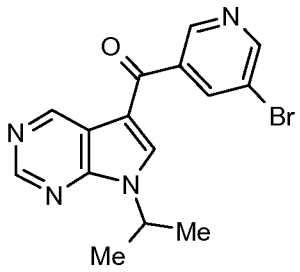
Preparation 93: 5-Iodo-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine



To a mixture of 5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 201**, 2.90 g, 12.0 mmol) and cesium carbonate (5.78 g, 17.8 mmol) in DMF (45 mL) was added 2-iodopropane (1.78 mL, 17.8 mmol). The mixture was stirred at room temperature for 3 hours. The reaction mixture was then poured onto saturated aqueous ammonium chloride (500 mL) and a solid precipitated. The solid was collected by filtration, rinsed with water (200 mL) and dried under reduced pressure for 17 hours to afford the title compound as a brown solid in 77% yield, 2.61 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (d, 6H), 5.15 (m, 1H), 7.40 (s, 1H), 8.73 (s, 1H), 8.88 (s, 1H); LCMS (system 2): R_t = 1.02 min; m/z 288 $[M+H]^+$.

Preparation 94: (5-Bromopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone

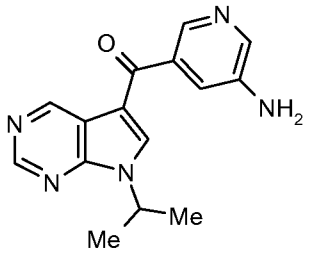


To a stirred solution of 5-iodo-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 93**, 4.85 g, 16.9 mmol) in THF (90 mL) at 0°C, under nitrogen was added isopropyl magnesium chloride (9.28 mL, 18.6

mmol, 2.0 M in diethyl ether). The mixture was stirred at 0 °C for 1 hour then a solution of 5-bromo-N-methoxy-N-methylnicotinamide (**Preparation 227**, 4.55 g, 18.6 mmol) in THF (10 mL) was added dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organics were concentrated under reduced pressure and purified by silica gel column chromatography eluting with gradient of EtOAc:DCM 95:5 to 50:50 to afford a light brown oil. The crude material was recrystallised using EtOAc:heptane (15:200 mL) to afford the title compound as a white solid in 33% yield, 2.16 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60 (d, 6H), 5.20 (m, 1H), 7.79 (s, 1H), 8.28 (dd, 1H), 8.90 (d, 1H), 8.95 (d, 1H), 9.03 (s, 1H), 9.59 (s, 1H); LCMS (system 2): R_t = 1.36 min; m/z 346 $[M+H]^+$.

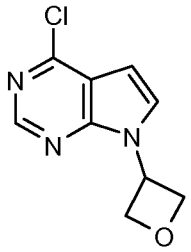
Preparation 95: (5-Aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone



The title compound was prepared according to the method described for **Preparation 31** using (5-bromopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 94**) to afford the title compound as a white solid in 69% yield, 1.20 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58 (d, 6H), 3.98 (br s, 2H), 5.18 (m, 1H), 7.39 (dd, 1H), 7.89 (s, 1H), 8.29 (br s, 1H), 8.43 (br s, 1H), 9.01 (s, 1H), 9.59 (s, 1H); LCMS (system 2): R_t = 0.50 min; m/z 282 $[M+H]^+$.

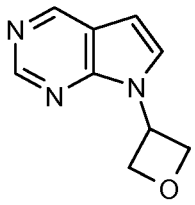
Preparation 96: 4-Chloro-7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 1** using (4,6-dichloropyrimidin-5-yl)acetaldehyde (**Preparation 208**) and oxetan-3-amine to afford the title compound as a yellow solid in 67% yield, 2.81 g.

LCMS (system 1): R_t = 1.92 min; m/z 210, 212 $[M+H]^+$.

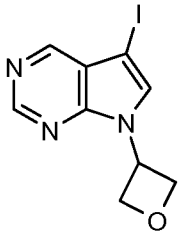
Preparation 97: 7-Oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 8** using 4-chloro-7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 96**) to afford the title compound as a white solid in 90% yield, 1.20 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.97-5.06 (m, 4H), 5.96 (m, 1H), 6.74 (d, 1H), 8.04 (d, 1H), 8.80 (s, 1H), 9.03 (s, 1H).

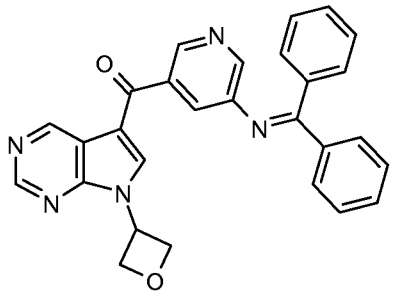
Preparation 98: 5-Iodo-7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 14** using 7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 97**) to afford the title compound as a white solid in 49% yield, 999 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.92-5.08 (m, 4H), 5.94 (m, 1H), 8.28 (s, 1H), 8.75 (s, 1H), 8.85 (s, 1H).

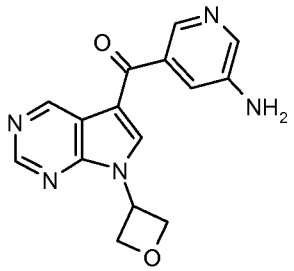
Preparation 99: {5-[(Diphenylmethylene)amino]pyridin-3-yl}(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone



The title compound was prepared according to the method described for **Preparation 94** using 5-iodo-7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 98**) and 5-[(diphenylmethylene)amino]-N-methoxy-N-methylnicotinamide (**Preparation 23**) to afford the title compound as a yellow solid in 55% yield, 253 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.95-5.06 (m, 2H), 5.15-5.24 (m, 2H), 5.96 (m, 1H), 7.21-7.80 (m, 11H), 8.22 (d, 1H), 8.52 (s, 1H), 8.62 (m, 1H), 9.01 (s, 1H), 9.44 (s, 1H).

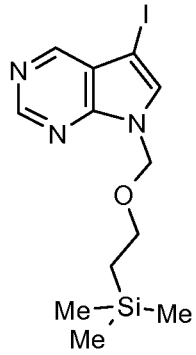
Preparation 100: (5-Aminopyridin-3-yl)(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone



The title compound was prepared according to the method described for **Preparation 37** using {5-[(diphenylmethylene)amino]pyridin-3-yl}(7-oxetan-3-yl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 99**) to afford the title compound as a yellow solid in 96% yield, 128 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.95-5.04 (m, 2H), 5.14-5.22 (m, 2H), 5.66 (br s, 2H), 5.97 (m, 1H), 7.33 (m, 1H), 8.19 (d, 1H), 8.25 (d, 1H), 8.62 (s, 1H), 9.00 (s, 1H), 9.46 (s, 1H).

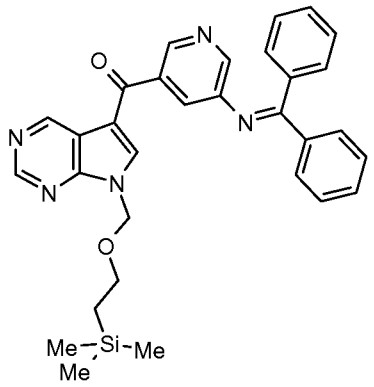
Preparation 101: 5-Iodo-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine



To a stirred solution of 5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 201**, 735 mg, 3.00 mmol) in DMF (5 mL) at 0 °C was added to sodium hydride (132 mg, 3.30 mmol, 60% in oil). The mixture was stirred at room temperature for 30 minutes, cooled to -20 °C and 2-(trimethylsilyl)ethoxymethyl chloride (0.58 mL, 3.30 mmol) added. The reaction mixture was stirred at -20°C for 3 hours then water (30 mL) was added. The mixture was extracted with EtOAc (2 x 50 mL) and the combined organic phases were dried over magnesium sulphate and evaporated under reduced pressure. The crude solid was purified by column chromatography on silica gel, eluting with a gradient of heptane:EtOAc 100:0 to 50:50), to afford the title compound as a white solid in 61% yield, 691 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: -0.11 (s, 9H), 0.81 (t, 2H), 3.51 (t, 2H), 5.61 (s, 2H), 8.01 (s, 1H), 8.77 (s, 1H), 8.89 (s, 1H).

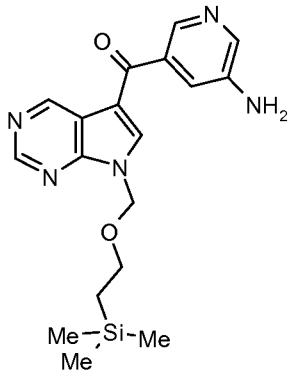
Preparation 102: {5-[(Diphenylmethylene)amino]pyridin-3-yl}(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone



The title compound was prepared according to the method described for **Preparation 28** using 5-iodo-7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 101**) and 5-[(diphenylmethylene)amino]-N-methoxy-N-methylnicotinamide (**Preparation 23**) to afford the title compound as a yellow oil in 32% yield, 460 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: -0.11 (s, 9H), 0.84 (m, 2H), 3.59 (m, 2H), 5.71 (s, 2H), 7.27 (m, 2H), 7.37 (m, 3H), 7.51 (m, 2H), 7.59 (m, 2H), 7.73 (d, 2H), 8.22 (d, 1H), 8.38 (s, 1H), 8.56 (d, 1H), 9.00 (s, 1H), 9.45 (s, 1H); LCMS (system 9): R_t = 2.36 min; m/z 534 $[M+H]^+$.

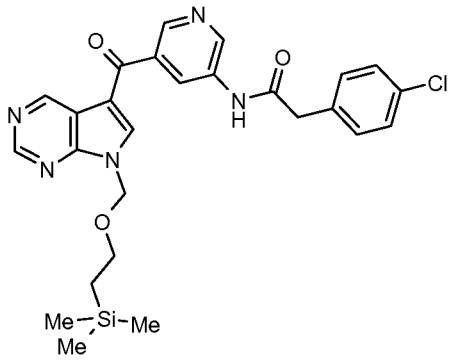
Preparation 103: (5-Aminopyridin-3-yl)(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone



The title compound was prepared according to the method described for **Preparation 37** using {5-[(diphenylmethylene)amino]pyridin-3-yl}(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 102**) to afford the title compound as a colourless oil in 73% yield, 2.10 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.09 (s, 9H), 0.84 (t, 2H), 3.60 (t, 2H), 5.66 (m, 4H), 7.30 (s, 1H), 8.18 (s, 2H), 8.55 (s, 1H), 9.02 (s, 1H), 9.47 (s, 1H); LCMS(system 9): R_t = 3.25 min; m/z 370 $[M+H]^+$.

Preparation 104: 2-(4-chlorophenyl)-N-(5-(7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)acetamide

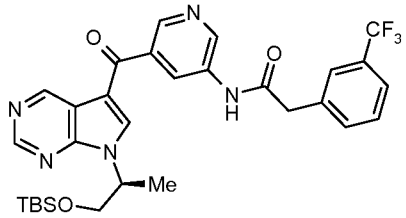


The title compound was prepared according to the method described for **Examples 73-87** using (5-aminopyridin-3-yl)(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 103**) and 4-chlorophenylacetic acid to afford the title compound as a white solid in 66% yield, 223 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: -0.11 (s, 9H), 0.82 (t, 3H), 3.60 (t, 2H), 3.74 (s, 2H), 5.70 (s, 2H), 7.37 (t, 4H), 8.47 (s, 1H), 8.60 (s, 2H), 8.72 (s, 1H), 8.98 (s, 1H), 9.03 (s, 1H), 9.48 (s, 1H);

LCMS (system 9): R_t = 3.50 min; m/z 522 $[M+H]^+$.

Preparation 105: N-[5-({7-[(1S)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)phenyl]acetamide

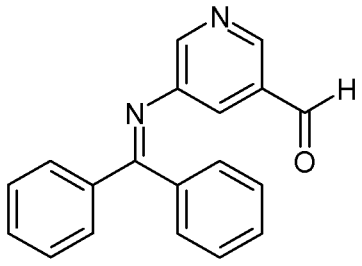


Prepared according to **Example 1**, using (S) (5-aminopyridin-3-yl){2-{[tert-butyl(dimethyl)silyl]oxy}-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (**Preparation 37**) and 3-trifluoromethylphenylacetic acid with DIPEA as base.

^{1}H NMR (400 MHz, DMSO) δ: -0.24 (s, 3H), -0.18 (s, 3H), 0.56 (s, 9H), 1.52 (d, 3H), 3.86 (m,3H), 3.94 (m, 1H), 5.06 (m, 1H), 7.58 (t, 1H), 7.63 (t,2H), 7.72 (s, 1H), 8.45 (s, 1H), 8.50 (s, 1H), 8.67 (d, 1H), 8.93 (d, 1H), 8.98 (s,1H), 9.45 (s,1H), 10.73 (s,1H).

LCMS (System 9): R_t = 3.89min; m/z 598 $[M+H]^+$.

Preparation 106: 5-[(Diphenylmethylene)amino]nicotinaldehyde



To a stirred solution of 5-[(diphenylmethylene)amino]-N-methoxy-N-methylnicotinamide (Preparation 23, 7.50 g, 0.021 mol) in THF (150 mL) at -70°C was added diisopropylaluminium hydride (42 mL, 0.042 mol,

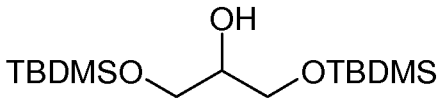
1.0 M in THF) and the resulting mixture stirred at -70°C for 2 hours. Water (20 mL) and ethyl acetate (100 mL) were added. The organic phase was separated, concentrated under reduced pressure and purified by silica gel column chromatography eluting with EtOAc: petroleum ether 1:10 to afford the title compound as a brown solid in 65% yield, 4 g.

The title compound can also be prepared according to the following process:

A mixture of 5-bromonicotinaldehyde (2790 mg, 15.0 mmol), diphenylmethanimine (3.01 mL, 18 mmol), $Pd_2(dba)_3$ (412 mg, 0.45 mmol), di-tert-butyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (510 mg, 1.2 mmol) and K_3PO_4 (7960 mg, 37.5 mmol) in DME (30.0 mL) was stirred at 50 °C for 16 hours. After cooling to room temperature, the reaction was diluted with DCM (50 mL) and the mixture filtered through a pad of arbocel. The filter cake was washed with DCM (50 mL) and the filtrate concentrated under reduced pressure. The crude material was recrystallized from ethyl acetate/heptane to give the desired compound as a solid in 78% yield, 3341 mg.

1H NMR (400 MHz, DMSO-d_6) δ: 7.18-7.26 (m, 2H), 7.30-7.39 (m, 3H), 7.47-7.54 (m, 2H), 7.55-7.62 (m, 2H), 7.68-7.75 (m, 2H), 8.25 (d, 1H), 8.63 (d, 1H), 10.00 (s, 1H).

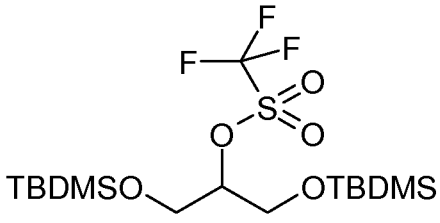
Preparation 107: 2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol



To a stirred solution of glycerol (4.01 mL, 55 mmol) and imidazole (18.7 g, 275 mmol) in DMF (150 mL) at 0 °C was added tert-butyldimethylsilyl chloride (17.2 g, 113 mmol) in DMF (33 mL). The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. Water (500 mL) was added to the reaction mixture and the resulting mixture extracted with heptane (500 mL x 3). The combined organic layers were washed with water (300 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography with a gradient elutant of heptane:EtOAc 100:0 to 80:20 to afford the title compound as a colorless oil in 68% yield, 11.9 g.

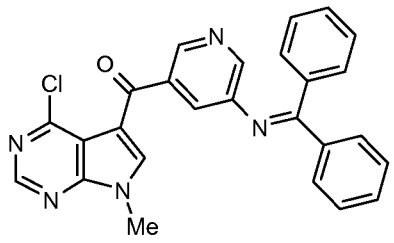
1H NMR (400 MHz, DMSO-d_6) δ: 0.03 (s, 12H), 0.86 (s, 18H), 3.40-3.59 (m, 5H), 4.58 (d, 1H).

Preparation 108: 2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl trifluoromethanesulfonate



To a stirred solution of 2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol (**Preparation 107**, 6410 mg, 20 mmol) and pyridine (2.42 mL, 30 mmol) in DCM (40 mL) at -50 °C was added trifluoromethanesulfonic anhydride (5.05 mL, 30 mmol) and the reaction stirred at -30 °C for 2 hours. Aqueous 1 N HCl (40 mL) was added to the reaction and the mixture was extracted with DCM (40 mL x 3). The combined organic layers were concentrated under reduced pressure to obtain a colourless oil which was used in the next step (**Preparation 196**) without further purification.

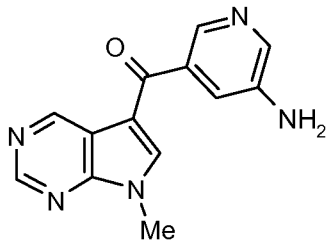
Preparation 109: 4-Chloro-[7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone



The title compound was prepared according to the method described for **Preparation 28** followed by **Preparation 30** using 4-chloro-5-iodo-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**Preparation 226**) and 5-[(diphenylmethylene)amino]nicotinaldehyde (**Preparation 106**) to afford the title compound as a yellow solid (11.0 g, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 3.87 (s, 3H), 7.06 (m, 2H), 7.28 (m, 2H), 7.37 (m, 2H), 7.45 (m, 3H), 7.70 (m, 3H), 8.15 (d, 1H), 8.49 (d, 1H), 8.69 (s, 1H).

Preparation 110 :(5-Aminopyridin-3-yl)(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone



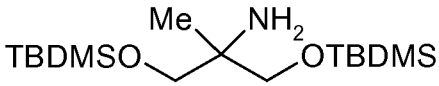
Citric acid (2 M, 200 mL) was added to 4-chloro-[7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl]{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone (**Preparation 109**, 30 g, 0.066 mol) in THF (200 mL) and the mixture was stirred at room temperature for 30 minutes. Ether (200 mL) was added and the phases were separated. The aqueous layer was neutralised with aqueous sodium carbonate then the solid was collected by filtration and dried under vacuum to give (5-aminopyridin-3-yl)(4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone as a brown solid, 18 g, 95%

Methanethiol sodium salt (15.5 g, 0.22 mol) was added to 5-aminopyridin-3-yl)(4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (21 g, 0.073 mol) in methanol (300 mL) and the mixture was stirred at room temperature for 7 hours. The reaction mixture was poured into ice-water (200 mL) and the precipitate was filtered. The filter cake was washed with water (100 mL) then acetone (20 mL) to afford the (5-aminopyridin-3-yl)[7-methyl-4-(methylthio)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone as a brown solid, 15 g, 69%

Raney nickel (10 g) was added to (5-aminopyridin-3-yl)[7-methyl-4-(methylthio)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (1.5 g, 5.0 mmol) and conc ammonia (150 mL) in 1,4 dioxane (150 mL). The mixture was refluxed for 6 hours then filtered. The filtrate was evaporated *in vacuo* and purified by prep HPLC (method 4) to afford the title compound as a brown solid in 100% yield, 1.9 g.

^{1}H NMR (400 MHz, DMSO-D6) δ*:* 3.88 (s, 3H), 5.63 (s, 2H), 7.27 (m, 1H), 8.14-8.18 (m, 2H), 8.40 (s, 1H), 8.97 (s, 1H), 9.42 (s, 1H).

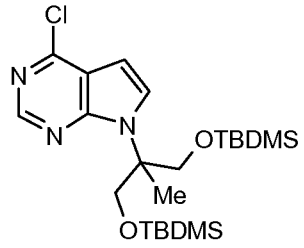
Preparation 111: 2,2,3,3,6,9,9,10,10-Nonamethyl-4,8-dioxa-3,9-disilaundecan-6-amine



The title compound was prepared according to the method described for **Preparation 44** using 2-amino-2-methyl-1,3-propanediol to afford the title compound as a colourless oil in 100% yield, 23.0 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.05 (s, 12H), 0.87-0.99 (m, 21H), 3.36-3.42 (m, 4H).

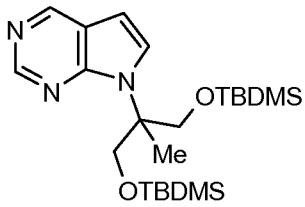
Preparation 112: 7-[2-{[tert-Butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-4-chloro-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 1** using 2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecan-6-amine (**Preparation 111**) to afford the title compound as a colourless gum in 75% yield, 8.91 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.09-0.11 (m, 12H), 0.78-0.79 (m, 18H), 1.74 (s, 3H), 4.06-4.09 (m, 2H), 4.29-4.31 (m, 2H), 6.52 (m, 1H), 7.44-7.45 (m, 1H), 8.56 (m, 1H).

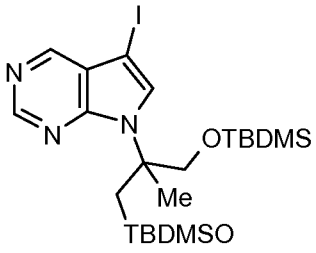
Preparation 113: 7-[2-{[tert-Butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 8** using 7-[2-{[tert-butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 112**) to afford the title compound as a yellow oil in 99% yield, 8.14 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: -0.13 (s,6H), -0.10 (s,6H), 0.78 (s,18H), 1.75 (s, 3H), 4.11 (d, 2H), 4.33 (d, 2H), 6.45 (d, 1H), 7.41 (d, 1H), 8.78 (s,1H), 8.90 (s, 1H).

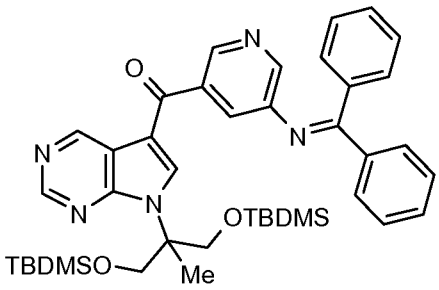
Preparation 114: 7-[2-{[tert-Butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-5-iodo-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 14** using 7-[2-{[tert-butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 113**) to afford the title compound as a yellow oil in 88% yield, 7.98 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: -0.10 (s, 12H), 0.79 (s, 18H), 1.75 (s, 3H), 4.07 (d, 2H), 4.27 (d, 2H), 7.49 (s, 1H), 8.70 (s, 1H), 8.82 (s, 1H).

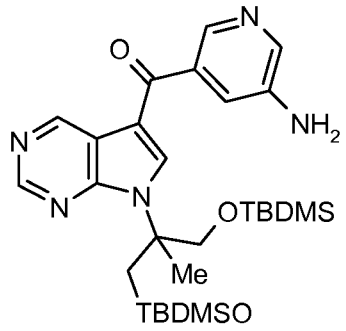
Preparation 115: {7-[2-{[tert-Butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone



The title compound was prepared according to the method described for **Preparation 28** using 7-[2-{[tert-butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 114**) and 5-[(diphenylmethylene)amino]-N-methoxy-N-methylnicotinamide (**Preparation 23**) to afford the title compound as a yellow foam in 69% yield, 1.76 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.10-0.12 (m, 12H), 0.73-0.76 (m, 18H), 1.77 (s, 3H), 4.06-4.09 (m, 2H), 4.34-4.36 (m, 2H), 7.11-7.16 (m, 2H), 7.28-7.33 (m, 3H), 7.42-7.47 (m, 2H), 7.50-7.54 (m, 2H), 7.78-7.80 (m, 2H), 7.93 (s, 1H), 8.15-8.16 (m, 1H), 8.56 (m, 1H), 8.94 (s, 1H), 9.58 (s, 1H).

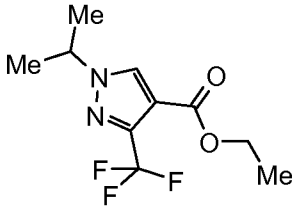
Preparation 116: (5-Aminopyridin-3-yl){7-[2-{[tert-butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone



The title compound was prepared according to the method described for **Preparation 37** using {7-[2-{[tert-butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}{5-[(diphenylmethylene)amino]pyridin-3-yl}methanone (**Preparation 115**) to afford the title compound as a yellow foam in 85% yield, 1.15 g.

LCMS (System 1): R_t = 4.01 min; m/z 556 $[M+H]^+$.

Preparation 117: 1-Isopropyl-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester

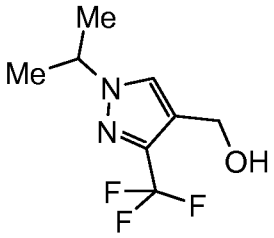


To a suspension of 5-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (13 g, 62.5 mmol) and cesium carbonate (61.1 g, 187.5 mmol) in DMF (70 mL) was added 2-iodo-propane (6.86 mL, 68.75 mmol) and the resulting mixture allowed to stir at room temperature for 16 hours. The crude reaction mixture was poured onto water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organics were washed with water (50 mL x 2), brine (50 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to afford the title compound as an off-white solid in 65% yield, 10.2 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (t, 3H), 1.53 (d, 6H), 4.30 (q, 2H), 4.50-4.57 (m, 1H), 8.00 (s, 1H);

LCMS (system 9): R_t = 3.55 min; m/z 251 $[M+H]^+$.

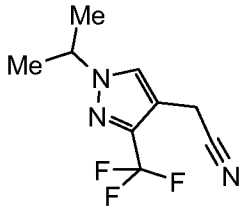
Preparation 118: (1-Isopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-methanol



The title compound was prepared according to the method described for **Preparation 183** using 1-isopropyl-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (**Preparation 117**) to afford the title compound an off-white solid in 97% yield, 8.3 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (d, 6H), 1.72 (t, 1H), 4.47-4.54 (m, 1H), 4.65 (d, 2H), 7.50 (s, 1H); LCMS (system 9): R_t = 2.77 min; m/z 209 $[M+H]^+$.

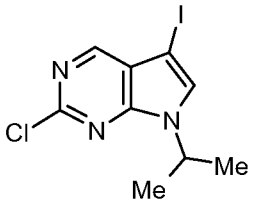
Preparation 119: (1-Isopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-acetonitrile



The title compound was prepared according to the method described for **Preparation 184** using (1-isopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-methanol (**Preparation 118**) to afford the title compound as an off-white solid in 58% yield, 5 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.42 (d, 6H), 3.92 (s, 2H), 4.56-4.63 (m, 1H), 8.06 (s, 1H).

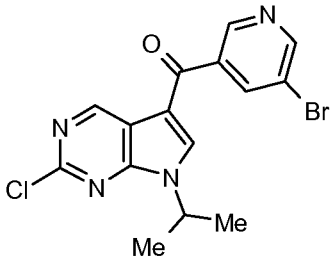
Preparation 120: 2-Chloro-5-iodo-7-isopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidine



The title compound was prepared according to the method described for **Preparation 93** using 2-chloro-5-iodo-7-isopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**Preparation 40**) to afford the title compound as a white solid in 87% yield, 5.5 g.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.50 (d, 6H), 5.10 (m, 1H), 7.36 (s, 1H), 8.55 (s, 1H); LCMS (System 10) R_t = 3.6 min; m/z 322 $[M+H]^+$.

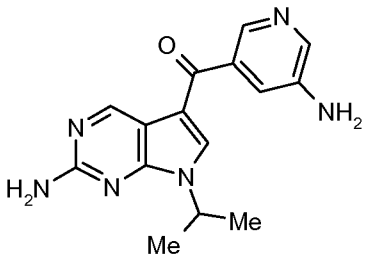
Preparation 121: (5-Bromopyridin-3-yl)(2-chloro-7-isopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanone



The title compound was prepared according to the method described for **Preparation 28** using 2-chloro-5-iodo-7-isopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**Preparation 120**) and 5-bromo-N-methoxy-N-methylnicotinamide to afford the title compound as a yellow solid in 41% yield, 1.2 g.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 1.54 (d, 6H), 5.02 (m, 1H), 8.41 (d, 1H), 8.63 (s, 1H), 9.0 (m, 2H), 9.33 (s, 1H).

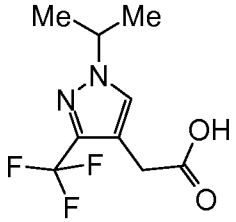
Preparation 122: (2-Amino-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(5-aminopyridin-3-yl)methanone



The title compound was prepared according to the method described for **Preparation 31** using (5-bromopyridin-3-yl)(2-chloro-7-isopropyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)methanone (**Preparation 121**) to afford the title compound as a yellow solid in 58% yield, 500 mg.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 1.47 (d, 6H), 4.82-4.86 (m, 1H), 5.60 (s, 2H), 6.58 (s, 2H), 7.23 (s, 1H), 7.88 (s, 1H), 8.12 (m, 2H), 8.91 (s, 1H); LCMS (System 9) R_t = 0.99 min; m/z 297 $[M+H]^+$.

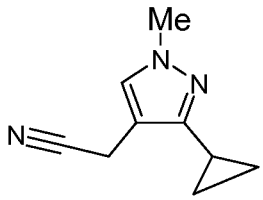
Preparation123: (1-Isopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-acetic acid



The title compound was prepared according to the method described for **Preparation 185** using (1-isopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-acetonitrile (**Preparation 119**) to afford the title compound as off-white solid in 82% yield, 4.5 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.41 (d, 6H), 3.50 (s, 2H), 4.52-4.58 (m, 1H), 7.89 (s, 1H), 12.35 (br, 1H); LCMS (system 10): R_t = 1.56 min; m/z 235 $[M-H]^-$.

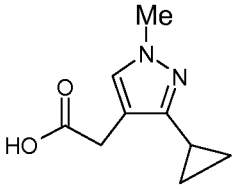
Preparation 124: (3-Cyclopropyl-1-methyl-1H-pyrazol-4-yl)-acetonitrile



To a suspension of potassium tert-butoxide (8.95 g, 79.9 mmol) in DME (250 mL) -78 ^{0}C under nitrogen was added a solution of 1-(isocyanomethyl sulfonyl)-4-methyl benzene (9.36 g, 47.94 mmol) in DME (50 ml). After stirring for 10 minutes, a solution of 3-cyclopropyl-1-methyl-1H-pyrazole-4-carbaldehyde (6 g, 39.95 mmol) in DME (100 mL) was added. The resulting mixture was allowed to stir at -78 ^{0}C for 1 hour and then at room temperature for 1hour. Methanol (50 mL) was added and the resulting mixture refluxed for 1 hour. The reaction mixture was quenched with saturated ammonium chloride solution (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with hexane:EtOAc 90:10 to afford the title compound an off-white solid in 67% yield, 4.3 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.67-0.7 (m, 2H), 0.79-0.83 (m, 2H), 1.75-1.80 (m, 1H), 3.68 (s, 3H), 3.79 (s, 2H), 7.54 (s, 1H); LCMS (system 9): R_t = 2.53 min; m/z 162 $[M+H]^+$.

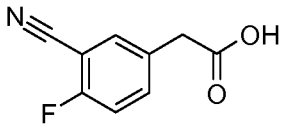
Preparation 125: (3-Cyclopropyl-1-methyl-1H-pyrazol-4-yl)-acetic acid



The title compound was prepared according to the method described for **Preparation 141** using (3-Cyclopropyl-1-methyl-1H-pyrazol-4-yl)-acetonitrile (**Preparation 124**) to afford the title compound as solid in 83% yield, 4 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.62-0.66 (m, 2H), 0.73-0.77 (m, 2H), 1.67-1.74 (m, 1H), 3.38 (s, 2H), 3.66 (s, 3H), 7.40 (s, 1H), 12.22 (br, 1H); LCMS (system 9): R_t = 1.97 min; m/z 181 $[M+H]^+$.

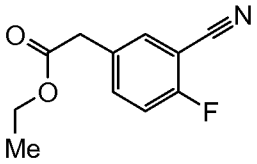
Preparation 126: (3-Cyano-4-fluoro-phenyl)-acetic acid



To a solution of (3-bromo-4-fluoro-phenyl)-acetic acid (10 g, 42.9 mmol) in DMF (65 mL) was added copper (I) cyanide (7.7 g, 85.8 mmol) and heated at 130 °C for 24 hrs. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (250 mL). The organic layer was washed with water (5 x 50 mL), brine (50 mL), dried over sodium filtered and concentrated under reduced pressure. The crude material was re-crystallized from diethyl ether and hexane to afford the title compound as a yellow solid in 65% yield, 5 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.68 (s, 2H), 7.48 (t, 1H), 7.66-7.71 (m, 1H), 7.82 (dd, 1H), 12.53 (br s, 1H); LCMS (system 10): R_t = 1.39 min; m/z 178 $[M-H]^-$.

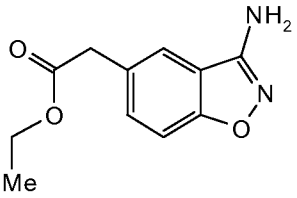
Preparation 127: (3-Cyano-4-fluoro-phenyl)-acetic acid ethyl ester



To a suspension of (3-cyano-4-fluoro-phenyl)-acetic acid (500 mg, 2.79 mmol) (**Preparation 126**) and potassium carbonate (770 mg, 5.58 mmol) in DMF (5 mL) was added ethyl iodide (0.89 mL, 11.16 mmol) and the reaction mixture stirred at room temperature for 4 hours. The crude reaction mixture was poured onto water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with water (5 x 10 mL), brine (10 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure to afford the title compound as an off-white solid in 87% yield, 500 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (t, 3H), 3.61 (s, 2H), 4.16 (q, 2H), 7.17 (t, 1H), 7.49-7.55 (m, 2H).

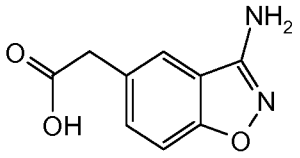
Preparation 128: (3-Amino-benzo[d]isoxazol-5-yl)-acetic acid ethyl ester



To a solution of (3-cyano-4-fluoro-phenyl)-acetic acid ethyl ester (**Preparation 127**, 400 mg, 1.93 mmol) and acetohydroxamic acid (362 mg, 4.83 mmol) in DMF (40 mL) and water (15 mL) was added potassium carbonate (1.6 g, 11.58 mmol) and the reaction mixture stirred at room temperature for 12 hours. The reaction mixture was diluted with water (100 mL) and the resulting white precipitate and collected by filtration. The crude material was purified by silica gel column chromatography eluting with a gradient of dichloromethane: methanol 100:0 to 97:3 to afford the title compound as an off-white solid in 59% yield, 250 mg.

LCMS (system 9): R_t = 2.87 min; m/z 221 $[M+H]^+$.

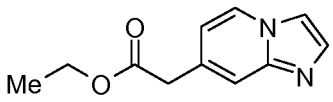
Preparation 129: (3-Amino-benzo[d]isoxazol-5-yl)-acetic acid



The title compound was prepared according to the method described for **Preparation 141** using (3-amino-benzo[d]isoxazol-5-yl)-acetic acid ethyl ester (**Preparation 128**) to afford the title compound as an off-white solid in 69% yield, 30 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.65 (s, 2H), 6.36 (br s, 2H), 7.36-7.42 (m, 2H), 7.69 (s, 1H), 12.37 (br s, 1 H); LCMS (system 10): R_t = 1.65 min; m/z 193 $[M+H]^+$.

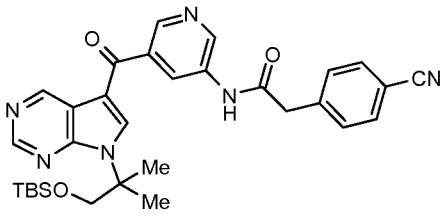
Preparation 130: Imidazo[1,2-a]pyridin-7-yl-acetic acid ethyl ester



To a stirred solution of 7-bromo-imidazo[1,2-a]pyridine (600 mg, 3.0 mmol) and diethyl malonate (0.93 mL, 6.1 mmol) in dry dioxane (15 mL) was added cesium carbonate (3 gm, 9.1 mmol). Argon was bubbled through the mixture for 10 minutes and then copper (I) iodide (116 mg, 0.61 mmol) and picolinic acid (150 mg, 1.22 mmol) were added. The resultant mixture was heated in a sealed tube at 130 ^{0}C for 24 hours. The reaction mixture was cooled to room temperature, quenched with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (2 x 10 mL), brine (10 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with a gradient of dichloromethane: methanol 100:0 to 98:2 to afford the title compound as an off-white gum in 29% yield, 180 mg.

LCMS (system 10): R_t = 2.61 min; m/z 205 $[M+H]^+$.

Preparation 131: N-(5-{[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-cyanophenyl)acetamide

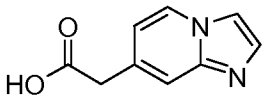


Prepared according to the method described for Example 1 using (5-aminopyridin-3-yl)[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**Preparation 38**), and 4-cyanophenylacetic acid with DIPEA.

^{1}H NMR (400 MHz, DMSO) δ: -0.26 (s, 6H), 0.58 (s, 9H), 1.75 (s, 6H), 3.86 (s, 2H), 4.10 (s, 2H), 7.54 (d, 2H), 7.82 (d, 2H), 8.16 (s, 1H), 8.51 (s, 1H), 8.68 (s, 1H), 8.88 (s, 1H), 8.98 (s, 1H), 9.47 (s, 1H), 10.73 (s, 1H);

LCMS (System 9): R_t = 3.80 min; m/z 569 $[M+H]^+$.

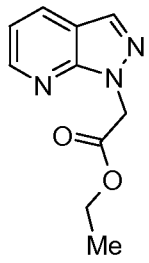
Preparation 132: Imidazo[1,2-a]pyridin-7-yl-acetic acid



To a solution of imidazo[1,2-a]pyridin-7-yl-acetic acid ethyl ester (180 mg, 0.65 mmol) (**Preparation 130**) in dioxane (4 mL) at 0 ^{0}C was added 2 N aqueous sodium hydroxide solution (4 mL). Then reaction mixture was heated at 90^{0}C for 6 hours. After cooling to 0 ^{0}C, the mixture was acidified to pH 4 with with 2 N aqueous hydrochoric acid and extracted with 20% isopropanol in dichoromethane (8 x 10 mL). The combined organics were dried over sodium sulfate and concentrated under reduced pressure to afford the title compound as an off-white solid in 70% yield, 80 mg.

LCMS (system 10): R_t = 1.40 min; m/z 177 $[M+H]^+$.

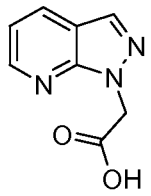
Preparation 133: Pyrazolo[3,4-b]pyridin-1-yl-acetic acid ethyl ester



To a solution of 7-aza indazole (250 mg, 2.1 mmol) and ethyl bromoacetate (0.47 mL, 4.2 mmol) in DMF (8 mL) was added K_2CO_3 (1.16 gm, 8.4 mmol) and the resulting mixture stirred at 70 °C for 16 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). The organic layer was washed with water (2 x 5 mL), brine (5 mL), dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude material was purified using silica gel column chromatography eluting with EtOAc:hexane 10:90 to afford the title compound as an off-white solid in 49% yield, 210 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.19 (t, 3H), 4.14 (q, 2H), 5.35 (s, 2H), 7.25-7.28 (m, 1H), 8.22 (s, 1H), 8.29 (d, 1H), 8.55 (d, 1H).

Preparation 134: Pyrazolo[3,4-b]pyridin-1-yl-acetic acid



To a stirred solution of pyrazolo[3,4-b]pyridin-1-yl-acetic acid ethyl ester (210 mg, 1.02 mmol) (**Preparation 133**) in THF (4 mL) and water (1 mL) at 0 °C was added LiOH.H_2O (129 mg, 3.06 mmol). The reaction mixture was stirred at room temperature for 2 hours. The pH was of the mixture was adjusted to pH 4 with 2 N aqueous hydrochoric acid and extracted with 20% isopropanol in dichloromethane (8 x 5 mL). The combined organics were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford the title compound as an off-white solid in 40% yield, 70 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.22 (s, 2H), 7.25 (dd, 1H), 8.19 (s, 1H), 8.27 (dd, 1H), 8.55 (dd, 1H), 13.15 (brs, 1H); LCMS (system 9): R_t = 1.93 min; m/z 178 $[M+H]^+$.

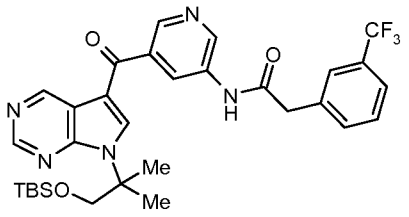
Preparation 135: 1-Cyclopropyl-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester



4,4,4-Trifluoro-3-oxo-butyric acid ethyl ester (16 g, 86.4 mmol) was dissolved in acetic anhydride (33.6 g, 329.6 mmol) and triethyl orthoformate (38.4 g, 260 mmol) was added to the mixture. The resultant mixture was refluxed for 18 hours. The mixture was concentrated under reduced pressure to obtain 20 g of 2-[1-Ethoxy-meth-(E)-ylidene]-4,4,4-trifluoro-3-oxo-butyric acid ethyl ester as crude. This was taken in EtOH (50 mL) and added to a suspension of cyclopropyl hydrazine hydrochloride (9.95 g, 91.7 mmol) and DIPEA (28.3 ml, 166.7 mmol) in EtOH (150 mL) at -20°C. The resultant mixture was slowly warmed to room temperature and stirred for 16 hours. The mixture was concentrated under reduced pressure and residue formed was partitioned between EtOAc (50 mL) and water (50 mL). The organic layer was washed with 2N HCl (25 mL), water (25 mL), brine (25 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (EtOAc:Hexane 5:95) to afford the title compound as off white sticky solid in 7% yield, 1.4 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.10-1.21 (m, 4H), 1.26 (t, 3H), 3.90 (m, 1H), 4.26 (q, 2H), 7.98 (s, 1H).

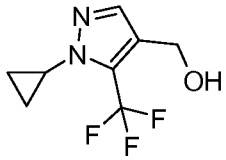
Preparation 136: N-(5-{[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide



Prepared according to the method described for **Example 1** using (5-aminopyridin-3-yl)[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**Preparation 38**), and 3-trifluoromethylphenylacetic acid with DIPEA.

^{1}H NMR (400 MHz, DMSO) δ*:* -0.27 (s, 6H), 0.56 (s, 9H), 1.75 (s, 6H), 3.87 (s, 2H), 4.09 (s, 2H), 7.57-7.64

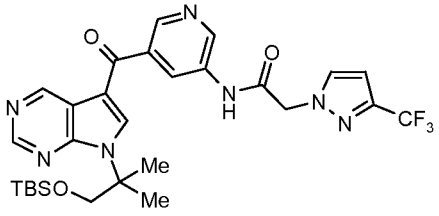
Preparation 137: (1-Cyclopropyl-5-trifluoromethyl-1H-pyrazol-4-yl)-methanol



A solution of 1-Cyclopropyl-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (**Preparation 135**, 1.4 g, 5.64 mmol) in dry toluene (25 mL) was cooled to -78°C and DIBAL-H (11.8 mL of 1.2 M solution in toluene, 14.1 mmol) was added dropwise to it. The reaction mixture was stirred at -78°C for 2 hours and poured into 2N HCl (10 mL). This was stirred for a further 4 hours at room temperature followed by extraction with EtOAc (2 x 25 mL) and the combined organic layers were washed with water (2 x 10 mL), brine (10 mL) dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as off white solid in 100% yield, 1.2 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.03-1.17 (m, 4H), 3.68-3.73 (m, 1H), 4.42 (d, 2H), 5.15 (t, 1H), 7.51 (s, 1H); LCMS (system 10): R_t = 2.68 min; m/z 207 $[M+H]^+$

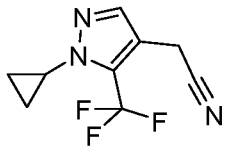
Preparation 138: N-(5-{[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-isopropyl-1H-1,2,3-triazol-1-yl)acetamide.



Prepared according to the method described for **Example 1** using (5-aminopyridin-3-yl)[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**Preparation 38**), and [4-(trifluoromethyl)-1H-pyrazol-1-yl]acetic acid (**Preparation 85**) with DIPEA as base.

LCMS (System 9): R_t = 3.67 min; m/z 577 $[M+H]^+$.

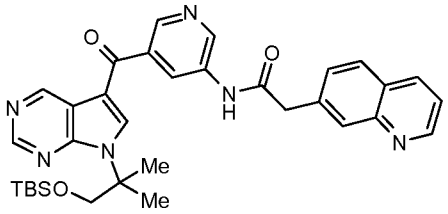
Preparation 139: (1-Cyclopropyl-5-trifluoromethyl-1H-pyrazol-4-yl)-acetonitrile



A solution of (1-Cyclopropyl-5-trifluoromethyl-1H-pyrazol-4-yl)-methanol (**Preparation 137**, 1.2 g, 5.82 mmol) in DCM (15 mL) was cooled to 0°C and thionyl chloride (0.85 mL, 11.7 mmol) was added. The reaction mixture was stirred at 0°C for 2 hours and diluted with DCM. The organic layer was washed with water, brine and dried (Na_2SO_4) and evaporated *in vacuo*. The crude residue obtained was dissolved in dioxane (25 mL) and water (25 mL) and tetrabutyl ammonium bromide (1.38 g, 4.28 mmol) was added. The reaction mixture was stirred for 10 mins followed by the addition of KCN (1.28 g, 19.82 mmol) and resultant mixture was stirred for a further 16 hours at room temperature. The mixture was diluted with EtOAc (50 mL) and washed with water (1 x 10 mL), brine (1 x 10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (Hexane:EtOAc 10:90) to afford the title compound as light yellow solid in 56% yield, 700 mg.

^{1}H NMR (400 MHz, CDCl3) δ: 1.06-1.13 (m, 2H), 1.24-1.29 (m, 2H), 3.61-3.62 (m, 1H), 3.66 (s, 2H), 7.49 (s, 1H).

Preparation 140: N-(5-{[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-quinolin-7-ylacetamide

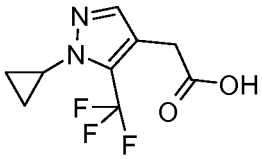


Prepared according to the method described for **Example 1** using (5-aminopyridin-3-yl)[7-(2-{[tert-butyl(dimethyl)silyl]oxy}-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone (**Preparation 38**), and 2-quinolin-7-ylacetic acid with DIPEA as base.

^{1}H NMR (400 MHz, DMSO) δ: -0.28 (s, 6H), 0.55 (s, 9H), 1.74 (s, 6H), 3.98 (s, 2H), 4.09 (s, 2H), 7.51 (m, 1H), 7.60 (m, 1H), 7.94 (m, 1H), 8.00 (s, 1H), 8.16 (s, 1H), 8.33 (m, 1H), 8.54 (m, 1H), 8.67 (s, 1H), 8.84 (m, 1H), 8.91 (s, 1H), 8.98 (s, 1H), 9.47 (s, 1H), 10.77 (s, 1H);

LCMS (System 9): R_t = 3.72 min; m/z 595 $[M+H]^+$.

Preparation 141: (1-Cyclopropyl-5-trifluoromethyl-1H-pyrazol-4-yl)-acetic acid

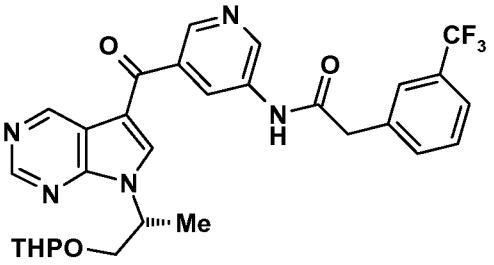


To a solution of (1-Cyclopropyl-5-trifluoromethyl-1H-pyrazol-4-yl)-acetonitrile (**Preparation 139**, 700 mg, 3.25 mmol) in EtOH (15 mL) was added aqueous 1N NaOH (15 mL). The resulting solution was heated at 60°C for 16 hours. The mixture was concentrated and the residue was dissolved in water (10 mL) and

washed with EtOAc. The pH of aqueous layer was adjusted to 5 using 1N HCl and extracted with 10% IPA in DCM (4 x 30 mL). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a solid in 85% yield, 650 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.04-1.07 (m, 2H), 1.11-1.16 (m, 2H), 3.55 (s, 2H), 3.69-3.73 (m, 1H), 7.47 (s, 1H), 12.45 (br, 1H); LCMS (system 10): R_t = 1.50 min; m/z 233 $[M-H]^+$.

Preparation 142 N-[5-({7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)phenyl]acetamide

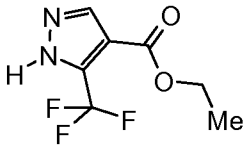


Prepared according to the method described above for **Example 1**, using (5-aminopyridin-3-yl){7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (**Preparation 36**) and 3-trifluoromethylphenylacetic acid with DIPEA as base.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.29-1.42 (m, 5H), 1.54 (d, 3H), 3.50 (m, 1H), 3.71 (m, 1H), 3.86 (s, 2H), 3.93 (m, 1H), 4.05 (m, 1H), 4.44 (s, 1H), 4.58 (s, 1H), 5.17 (m, 1H), 7.56 (m, 1H), 7.63 (m, 2H), 7.72 (s, 1H), 8.47 (m, 2H), 8.70 (s, 1H), 8.96 (m, 2H), 9.45 (s, 1H), 10.72 (s, 1H);

LCMS (System 9): R_t = 3.56 min; m/z 568 $[M+H]^+$.

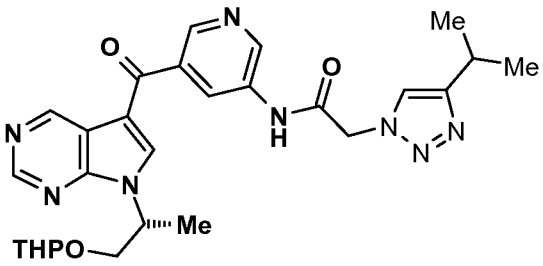
Preparation 143: 5-Trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester



To a suspension of hydrazine hydrochloride (10 g, 147 mmol) in EtOH (500 mL), DIPEA (45.3 mL, 267 mmol) was added slowly at -20^{0}C and stirred for 10 mins. Then 2-[1-Ethoxy-meth-(E)-ylidene]-4,4,4-trifluoro-3-oxo-butyric acid ethyl ester (**Preparation 135**, 32 g, 133.33 mmol) was added to above solution and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure and residue was partitioned between EtOAc (200 mL) and water (50 mL). The organic layer was washed with water (25 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (Hexane:EtOAc 90:10) to afford the title compound as off white solid in 43% yield, 13 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.26 (t, 3H), 4.25 (q, 2H), 8.57 (s, 1H), 14.10 (br s, 1H).

Preparation 144: N-[5-({7-[(1R)- 1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-(4-isopropyl-1H-1,2,3-triazol-1-yl)acetamide

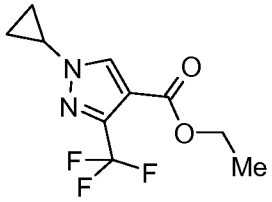


Prepared according to the method described above for **Example 1**, using (5-aminopyridin-3-yl){7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (**Preparation 36**) and (4-isopropyl-1H-1,2,3-triazol-1-yl)acetic acid with DIPEA as base.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.22 (6H, d), 1.23-1.30 (m, 5H), 1.54(d, 3H), 3.4 (1H, m), 3.72 (m, 1H), 3.88 (m, 1H), 3.95 (m, 1H), 4.10 (m, 1H), 4.45 (s, 1H), 4.59 (s, 1H), 5.20 (1H, m), 5.36 (s, 2H), 7.88 (s, 1H), 8.43 (m, 1H), 8.53 (d, 1H), 8.75 (s, 1H), 8.97 (m, 2H), 9.45 (s, 1H), 10.96 (s, 1H);

LCMS (System 9): R_t = 2.86 min; m/z 533 $[M+H]^+$.

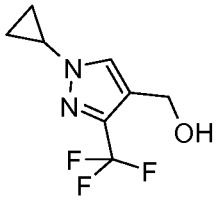
Preparation 145: 1-Cyclopropyl-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester



Cyclopropyl boronic acid (11 g, 127 mmol), Copper acetate (17.4 g, 95.7 mmol), Pyridine (17.7 g, 223 mmol) and triethylamine (22.4 mL, 160 mmol) were added successively to a solution of 5-Trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (**Preparation 143**, 6.63 g, 31.9 mmol) in THF (70 mL) and the resulting mixture was allowed to stir at 60^{0}C for 36 hours. The reaction mixture was filtered over a celite bed and filtrate was concentrated *in vacuo* and diluted with EtOAc (200 mL). The organic layer was washed with 1N HCl (1 x 25 mL), brine (1 x 25 mL) and dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (Hexane:EtOAc 85:15) to afford the title compound as brown solid in 29% yield, 2.3 g.

^{1}H NMR (400 MHz, CDCl3) δ: 1.08-1.14 (m, 2H), 1.17-1.21 (m, 2H), 1.33 (t, 3H), 3.62-3.67 (m, 1H), 4.30 (q, 2H), 8.01 (s, 1H); LCMS (system 10): R_t = 3.39 min; m/z 249 $[M+H]^+$.

Preparation 146: (1-Cyclopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-methanol

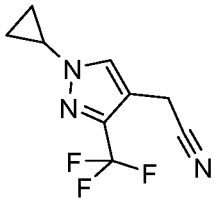


A solution of 1-Cyclopropyl-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (**Preparation 145,** 3.5 g, 14.11 mmol) in dry toluene (70 mL) was cooled to -78°C and DIBAL-H (29.4 mL of a 1.2 M solution in toluene, 35.3 mmol) was added dropwise to it. The reaction mixture was stirred at -78°C for 2 hours and then poured into 2N HCl (25 mL) followed by further stirring for 2 hours at room temperature. The mixture

was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with water (2 x 15 mL), brine (15 mL) and dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as off white solid in 100% yield, 3 g.

^{1}H NMR (400 MHz, CDCl3) δ: 1.02-1.07 (m, 2H), 1.11-1.16 (m, 2H), 1.68 (t, 1H), 3.57-3.63 (m, 1H), 4.64 (d, 2H), 7.53 (s, 1H); LCMS (system 10): R_t = 2.57 min; m/z 207 $[M+H]^+$.

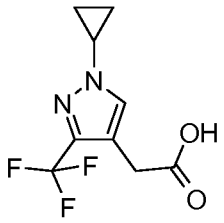
Preparation 147: (1-Cyclopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-acetonitrile



The title compound was prepared according to the method described for **Preparation 139** using (1-Cyclopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-methanol (**Preparation 146**) to afford the title compound as yellow solid in 70% yield, 2.2 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 0.98-1.03 (m, 2H), 1.06-1.11 (m, 2H), 3.83-3.88 (m, 1H), 3.91 (s, 2H), 8.08 (s, 1H); LCMS (system 10): R_t = 3.10 min; m/z 216 $[M+H]^+$.

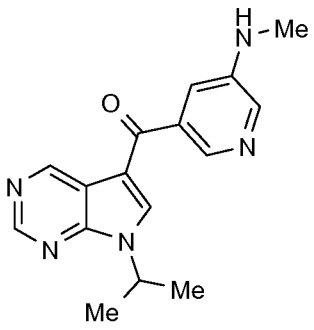
Preparation 148: (1-Cyclopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-acetic acid



The title compound was prepared according to the method described for **Preparation 141** using (1-Cyclopropyl-3-trifluoromethyl-1H-pyrazol-4-yl)-acetonitrile (**Preparation 147**) to afford the title compound as a solid in 79% yield, 1.9 g.

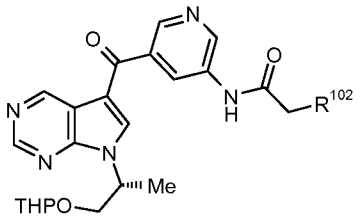
^{1}H NMR (400 MHz, DMSO-D6) δ: 0.96-1.07 (m, 4H), 3.49 (s, 2H), 3.76-3.84 (m, 1H), 7.91 (s, 1H), 12.27 (br, 1H); LCMS (system 10): R_t = 1.41 min; m/z 233 $[M-H]^+$.

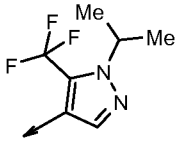
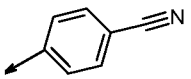
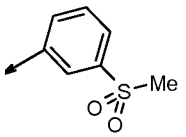
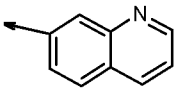
Preparation 149: (7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)[5-(methylamino)pyridin-3-yl]methanone



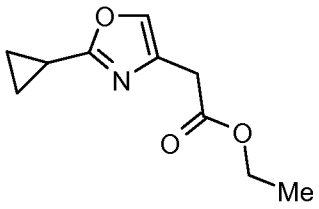
The title compound was prepared according to the method described for **Preparation 31** using (5-bromopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 94**) and methylamine (20 mL) in 13% yield, 78 mg.
LCMS (system 2): R_t = 0.91 min; m/z 296 $[M+H]^+$

The following Preparations were prepared according to the method described above for **Example 1**, using (5-aminopyridin-3-yl){7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone (**Preparation 36**) and the corresponding carboxylic acid with DIPEA. All carboxylic acids are commercially available unless otherwise mentioned.



Preparation	Name	R^{102}	Data
150	N-[5-({7-[(1R)- 1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[1-isopropyl-5-(trifluoromethyl)-1H-pyrazol-4-yl]acetamide		LCMS (System 9): R_t = 3.24 min; m/z 600 $[M+H]^+$ Using (**Prep 185**).
151	2-(4-cyanophenyl)-N-[5-({7-[(1R)-1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide		LCMS (System 9): R_t = 2.94 min; m/z 525 $[M+H]^+$.
152	N-[5-({7-[(1R)- 1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(methylsulfonyl)phenyl]acetamide		LCMS (System 9): R_t = 2.82 min; m/z 578 $[M+H]^+$
153	N-[5-({7-[(1R)- 1-methyl-2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-quinolin-7-ylacetamide		LCMS (System 9): R_t = 2.97 min; m/z 551 $[M+H]^+$.

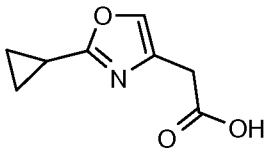
Preparation 154: Ethyl (2-cyclopropyl-1,3-oxazol-4-yl)acetate



Ethyl 4-chloroacetoacetate (20.0 g, 122.0 mmol) was added to cyclopropanecarboxamide (3.52 g, 41.5 mmol) in toluene (100 mL) and 1,4-dioxane (100 mL). The mixture was refluxed at 120°C for 17 hours then evaporated *in vacuo*. The crude solid was purified by column chromatography on silica gel (80:20 petroleum ether: EtOAc) to afford the title compound as a white solid in 50% yield, 4.00 g.

^{1}H NMR (300 MHz, DMSO-d_6) δ*:* 0.80-1.00 (m, 4H), 1.20 (t, 3H), 2.10 (m, 1H), 3.50 (s, 2H), 4.10 (q, 2H), 7.80 (s, 1H).

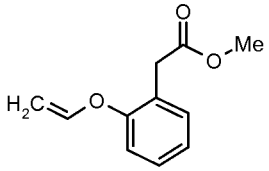
Preparation 155: **(2-Cyclopropyl-1,3-oxazol-4-yl)acetic acid**



Lithium hydroxide monohydrate (7.83 g, 186.7 mmol) was added to ethyl (2-cyclopropyl-1,3-oxazol-4-yl)acetate (**Preparation 154,** 7.00 g, 35.9 mmol) in THF (200 mL) and water (100 mL). The mixture was stirred at room temperature for 2 hours then the reaction mixture volume was reduced to one third by evaporation *in vacuo*. The aqueous residue was acidified using aqueous HCl (1.0 M) then extracted with EtOAc (200 mL). The organic phase was evaporated *in vacuo* and the crude material was triturated with diethyl ether (100 mL) to afford the title compound as a white solid in 66% yield, 4.00 g.

^{1}H NMR (300 MHz, $CDCl_3$) δ*:* 1.05 (m, 4H), 2.10 (m, 1H), 3.60 (s, 2H), 7.40 (s, 1H), 10.00 (br s, 1H).

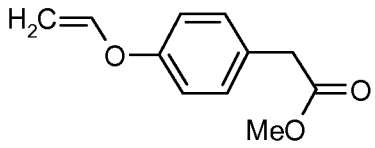
Preparation 156: Methyl [2-(vinyloxy)phenyl]acetate



Copper acetate (1.42 g, 7.82 mmol) was added to DCM (6 mL) and stirred for 20 minutes, with a drying tube attached. Trivinylcycloboroxane (1.24 g, 5.16 mmol), cesium carbonate (2.55 g, 7.82 mmol) and methyl 2-hydroxyphenyl acetate (1.30 g, 7.82 mmol) were added and the mixture stirred at room temperature for 17 hours. Saturated aqueous sodium bicarbonate (25 mL) was added and the mixture was extracted with DCM (20 mL). The organic phase was filtered, dried over magnesium sulphate and evaporated *in vacuo* to afford the title compound as a black oil in 52% yield, 784 mg. This material was used crude in subsequent steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.67 (s, 2H), 3.39 (s, 3H), 4.40 (dd, 1H), 4.69 (dd, 1H), 6.59 (dd, 1H), 6.97-7.08 (m, 2H), 7.23-7.28 (m, 2H).

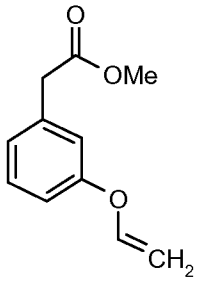
Preparation 157: Methyl [4-(vinyloxy)phenyl]acetate



The title compound was prepared according to the method described for **Preparation 156** using methyl 4-hydroxyphenyl acetate to afford the title compound as a colourless oil in 70% yield, 914 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.58 (s, 2H), 3.39 (s, 3H), 4.42 (m, 1H), 4.75 (m, 1H), 6.62 (m, 1H), 6.94-6.97 (m, 2H), 7.21-7.24 (m, 2H).

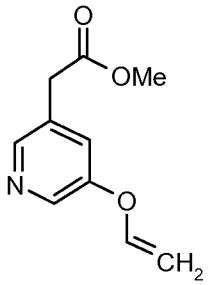
Preparation 158: **Methyl [3-(vinyloxy)phenyl]acetate**



The title compound was prepared according to the method described for **Preparation 156** using methyl 3-hydroxyphenyl acetate to afford the title compound as a colourless oil in 56% yield, 835 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.61 (s, 2H), 3.70 (s, 3H), 4.44 (m, 1H), 4.78 (m, 1H), 6.63 (m, 1H), 6.89-6.94 (m, 2H), 7.00 (m, 1H), 7.27 (m, 1H).

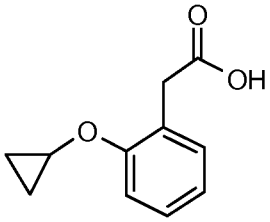
Preparation 159: Methyl [5-(vinyloxy)pyridin-3-yl]acetate



The title compound was prepared according to the method described for **Preparation 156** using methyl (5-hydroxypyridin-3-yl)acetate to afford the title compound as a yellow oil in 25% yield, 76 mg.

LCMS (system 2): R_t = 0.85 min; m/z 194 $[M+H]^+$.

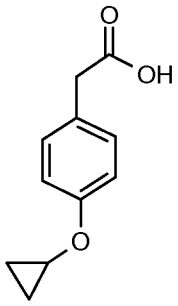
Preparation 160: [2-(Cyclopropyloxy)phenyl]acetic acid



Diethyl zinc (2.34 mL, 2.34 mmol, 1M in heptane) was cooled to 0°C under nitrogen then chloroiodomethane (0.35 mL, 4.68 mmol) in DCE (1 mL) was added drop-wise. The mixture was stirred under nitrogen at 0°C for 20 minutes then methyl [2-(vinyloxy)phenyl]acetate (**Preparation 156**, 150 mg, 0.78 mmol) in DCE (1 mL) was added. The reaction mixture was stirred at 0°C for 30 minutes then stirred at room temperature for 17 hours. Saturated aqueous ammonium chloride (10 mL) was added and the mixture was extracted with DCM (4 x 8 mL). The combined organic phases were dried over magnesium sulphate and evaporated *in vacuo*. Sodium hydroxide (3.28 mL, 3.28 mmol, 1 M) was added to the residue in THF (3 mL). The mixture was heated at 80°C for 17 hours then evaporated *in vacuo*. Hydrochloric acid (10 mL, 1M) was added to the residue then extracted with EtOAc (10 mL). The organic phase was evaporated *in vacuo* to afford the title compound as a yellow oil in 53% yield, 83 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 0.65-0.71 (m, 4H), 3.54 (s, 2H), 3.71 (m, 1H), 6.82-6.87 (m, 2H), 7.05-7.23 (m, 2H).

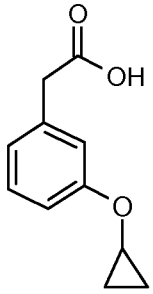
Preparation 161: [4-(Cyclopropyloxy)phenyl]acetic acid



Prepared according to the method described for **Preparation 160** using methyl [4-(vinyloxy)phenyl]acetate (**Preparation 157**) to afford the title compound as a colourless oil in 44% yield, 360 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 0.65-0.71 (m, 4H), 3.59 (s, 2H), 3.71 (m, 1H), 6.99-7.02 (m, 2H), 7.16-7.20 (m, 2H).

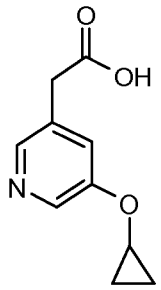
Preparation 162: [3-(Cyclopropyloxy)phenyl]acetic acid



The title compound was prepared according to the method described for **Preparation 160** using methyl [3-(vinyloxy)phenyl]acetate (**Preparation 158**) to afford the title compound as a colourless oil in 33% yield, 50 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.74–0.81 (m, 4H), 3.57–3.67 (m, 2H), 3.72 (m, 1H), 6.74-7.03 (m, 3H), 7.22 (m, 1H).

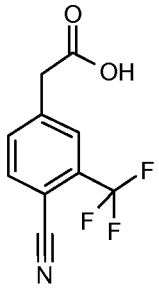
Preparation 163: [5-(Cyclopropyloxy)pyridin-3-yl]acetic acid



The title compound was prepared according to the method described for **Preparation 160** using methyl [5-(vinyloxy)pyridin-3-yl]acetate (**Preparation 159**) to afford the title compound as a yellow oil in 38% yield, 28 mg.

LCMS (system 2): R_t = 0.55 min; m/z 194 $[M+H]^+$.

Preparation 164: [4-Cyano-3-(trifluoromethyl)phenyl]acetic acid

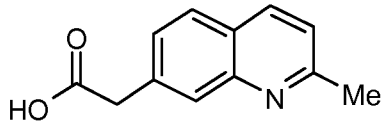


Lithium diisopropylamide (13.8 mL, 24.8 mmol, 1.8M in THF) was added to 4-methyl-2-(trifluoromethyl)benzonitrile (2.30 g, 12.4 mmol) in THF (20 mL) at -78°C and stirred for 5 minutes at -78°C. Excess solid carbon dioxide was added then the mixture was stirred at room temperature for 17 hours. Saturated aqueous ammonium chloride (10.5 mL) and EtOAc (20 mL) were added then the

aqueous layer was acidified with HCl acid solution (1 M). This was extracted with EtOAc (3 x 15 mL) and the combined organic phases were dried over sodium sulphate and evaporated *in vacuo* to afford the title compound as a brown oil in 88% yield, 2.52 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 3.81 (s, 2H), 7.62 (d, 1H), 7.73 (s, 1H), 7.83 (d, 1H).

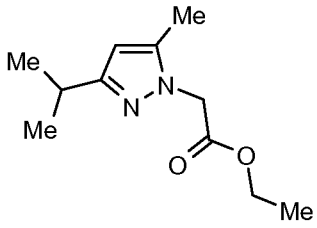
Preparation 165: (2-Methylquinolin-7-yl)acetic acid



Crotonic aldehyde (33.0 mL, 0.40 mol) was added to 3-aminophenylacetic acid (30.0 g, 0.20 mmol) in concentrated hydrochloric acid (400 mL) and toluene (100 mL) at 110°C. The mixture was heated at 110°C for 90 minutes. The aqueous layer was separated, washed with diethyl ether (350 mL) then neutralised with aqueous ammonia. The aqueous solution was washed with chloroform (3 x 500 mL) and the organic phase was evaporated *in vacuo*. The solid residue was refluxed with chloroform (900 mL) and methanol (100 mL) then the solution was decanted and purified by column chromatography on silica gel (gradient of chloroform:MeOH 9:1 to 4:1) to afford a mixture of isomeric acids. This was purified by fractional crystallisation using isopropanol to afford the title compound as a white solid in 12% yield, 4.90 g.

^{1}H NMR (400 MHz, DMSO-d6) δ*:* 2.64 (s, 3H), 3.78 (s, 2H), 7.37 (d, 1H), 7.44 (dd, 1H), 7.80 (s, 1H), 7.84 (d, 1H), 8.19 (d, 1H), 12.40 (br s, 1H).

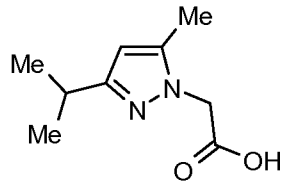
Preparation 166: Ethyl (3-isopropyl-5-methyl-1*H*-pyrazol-1-yl)acetate



Ethyl bromoacetate (1.00 mL, 9.03 mmol) was added to 5-isopropyl-3-methyl-1*H*-pyrazole (1.07 g, 8.60 mmol) and potassium carbonate (3.57 g, 25.9 mol) in DMF (10 mL). The mixture was stirred at room temperature for 17 hours then EtOAc (20 mL) and aqueous HCl (20 mL, 1 M) were added. The organic phase was dried over magnesium sulphate then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:EtOAc 4:1) to afford the title compound as a yellow oil in 34% yield, 607 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 1.26 (m, 9H), 2.03 (s, 3H), 2.96 (m, 1H), 4.21 (q, 2H), 4.78 (s, 2H), 7.13 (s, 1H).

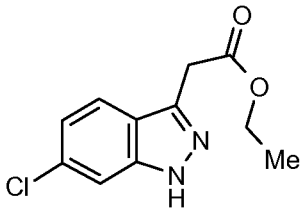
Preparation 167: (3-Isopropyl-5-methyl-1*H*-pyrazol-1-yl)acetic acid



Lithium hydroxide (342 mg, 8.15 mmol) in water (4 mL) was added to ethyl (3-isopropyl-5-methyl-1*H*-pyrazol-1-yl)acetate (**Preparation 166**, 571 mg, 2.72 mmol) in methanol (4 mL) and the mixture was stirred at room temperature for 30 minutes. Aqueous hydrochloric acid (2 M) was added to acidify the mixture then the solution was extracted with EtOAc (10 mL). The organic phase was dried over magnesium sulphate and evaporated *in vacuo* to afford the title compound as a cream solid in 66% yield, 328 mg.

m/z 183 $[M+H]^+$.

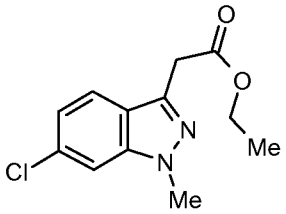
Preparation 168: Ethyl (6-chloro-1*H*-indazol-3-yl)acetate



Concentrated sulphuric acid (0.25 mL) was added to a solution of 2-(6-chloro-1H-indazol-3-yl)acetic acid (2.024 g, 9.60 mmol) in EtOH (10 mL). The mixture was heated at 80°C for 4 hours then evaporated *in vacuo*. The residue was partitioned between EtOAc (30 mL) and 5% aqueous sodium bicarbonate (30 mL). The organic phase was dried over sodium sulphate, evaporated *in vacuo* and purified by column chromatography on silica gel (DCM:MeOH 99:1) to afford the compound **3** as a white solid in 83% yield, 1.90 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 1.17 (t, 3H), 4.00 (s, 2H), 4.10 (q, 2H), 7.11 (d, 1H), 7.56 (s, 1H), 7.74 (d, 1H), 13.00 (s, 1H).

Preparation 169: Ethyl (6-chloro-1-methyl-1*H*-indazol-3-yl)acetate



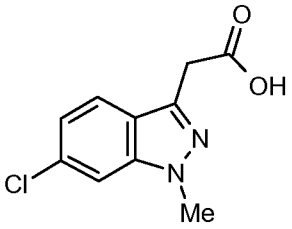
Sodium hydride (24 mg, 0.602 mmol, 60% in oil) was added to ethyl (6-chloro-1*H*-indazol-3-yl)acetate (**Preparation 168**, 120 mg, 0.502 mmol) in THF (4 mL) at 0°C and the mixture was stirred for 30 minutes. Then iodomethane (0.09 mL, 1.508 mmol) was added. The mixture was stirred at room temperature for 30 mins then water (4 mL) was added. The mixture was evaporated *in vacuo* and the aqueous residue was acidified with aqueous HCl (6 M). This was extracted with ethyl acetate (10 mL) and the organic phase

was dried over sodium sulphate and evaporated *in vacuo* to afford the title compound as a white solid in 100% yield, 150 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 1.18 (t, 3H), 3.89 (s, 3H), 4.07 (s, 2H), 4.13 (q, 2H), 7.15 (d, 1H), 7.56 (s, 1H), 7.74 (d, 1H);

LCMS (System 9): R_t =3.48 min; m/z 253 $[M+H]^+$.

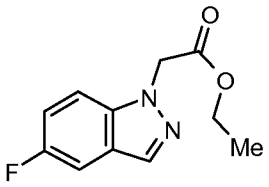
Preparation 170: (6-Chloro-1-methyl-1*H*-indazol-3-yl)acetic acid



Aqueous potasium hydroxide (5.93 mL, 10%) was added to ethyl (6-chloro-1-methyl-1*H*-indazol-3-yl)acetate (**Preparation 169**, 1.78 g, 0.704 mol) in MeOH (30 mL). The mixture was stirred for 1 hour at 25°C then the methanol was evaporated *in vacuo*. The aqueous residue was washed with diethyl ether (30 mL) then acidified with aqueous HCl (6 M). The mixture was extracted with ethyl acetate (30 mL) and the organic phase was dried over sodium sulphate, evaporated *in vacuo* and purified by column chromatography on silica gel (DCM:MeOH 95: 5) to afford the title compound as a white solid in 56% yield, 865 mg.

^{1}H NMR (400 MHz, DMSO-d6) δ*:* 3.79 (s, 2H), 4.14 (s, 3H), 7.12 (d, 1H), 7.73 (d, 1H), 7.83 (s, 1H). 12.51 (s, 1H).

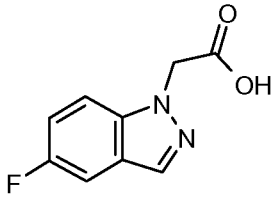
Preparation 171: Ethyl (5-fluoro-1*H*-indazol-1-yl)acetate



The title compound was prepared according to the method described for **Preparation 93** using 5-fluoro-1*H*-indazole and ethyl bromoacetate to afford the title compound as an off- white solid in 53% yield, 260 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 1.24 (t, 3H), 4.22 (q, 2H), 5.13 (s, 2H), 7.17 (m, 1H), 7.28 (m, 1H), 7.37 (d, 1H), 7.99 (s, 1H); LCMS (System 9): R_t = 3.14 min; m/z 223 $[M+H]^+$.

Preparation 172: (5-Fluoro-1H-indazol-1-yl)acetic acid

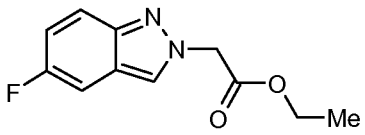


The title compound was prepared according to the method described for **Preparation 155** using ethyl (5-fluoro-1H-indazol-1-yl)acetate (**Preparation 171**) to afford the title compound as a yellow solid in 62% yield, 140 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.26 (s, 2H), 7.28 (m, 1H), 7.54 (dd, 1H), 7.68 (dd, 1H), 8.06 (s, 1H), 13.11 (br s, 1H).

LCMS (System 9): R_t = 1.49 min; m/z 193 $[M-H]^-$

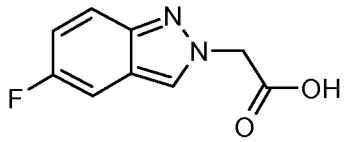
Preparation 173: Ethyl (5-fluoro-2*H*-indazol-2-yl)acetate



The title compound was prepared according to the method described for **Preparation 93** using 5-fluoro-1*H*-indazole and ethyl bromoacetate to afford the title compound as an off- white solid in 27% yield, 130 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (t, 3H), 4.25 (q, 2H), 5.17 (s, 2H), 7.06-7.11 (m, 1H), 7.21-7.24 (m, 1H), 7.64-7.68 (m, 1H), 7.96 (s, 1H); LCMS (System 9): R_t = 3.04 min; m/z 223 $[M+H]^+$

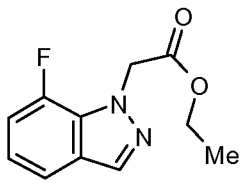
Preparation 174:(5-Fluoro-2H-indazol-2-yl)acetic acid



The title compound was prepared according to the method described for **Preparation 155** using ethyl (5-fluoro-2*H*-indazol-2-yl)acetate (**Preparation 173**) to afford the title compound as a yellow solid in 100% yield, 160 mg.

LCMS (System 9): R_t = 1.49 min; m/z 193 $[M-H]^-$

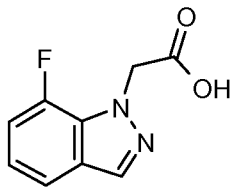
Preparation 175: Ethyl (7-fluoro-1*H*-indazol-1-yl)acetate



The title compound was prepared according to the method described for **Preparation 93** using 7-fluoro-1*H*-indazole and ethyl bromoacetate to afford the title compound as an off- white solid in 41% yield, 200 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (t, 3H), 4.22 (q, 2H), 5.28 (s, 2H), 6.98-7.07 (m, 2H), 7.49 (m, 1H), 8.02 (d, 1H).

Preparation 176: (7-Fluoro-1H-indazol-1-yl)acetic acid

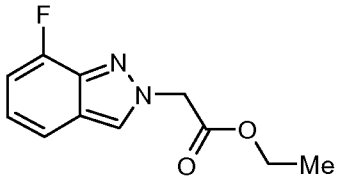


The title compound was prepared according to the method described for **Preparation 155** using ethyl (7-fluoro-1*H*-indazol-1-yl)acetate (**Preparation 175**) to afford the title compound as a yellow solid in 68% yield, 120 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 5.27 (s, 2H), 7.12 (m, 1H), 7.23 (m, 1H), 7.60 (d, 1H), 8.17 (d, 1H), 13.18 (br s, 1H); LCMS (System 9):

R_t = 1.38 min; m/z 195 $[M+H]^+$

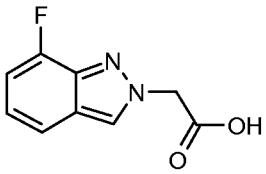
Preparation 177: Ethyl (7-fluoro-2*H*-indazol-2-yl)acetate



The title compound was prepared according to the method described for **Preparation 93** using 7-fluoro-1*H*-indazole and ethyl bromoacetate to afford the title compound as an off- white solid in 35% yield, 175 mg.

^{1}H NMR (400 MHz, CDCl3) δ*:* 1.28 (t, 3H), 4.25 (q, 2H), 5.28 (s, 2H), 6.93 (m, 1H), 6.99 (m, 1H), 7.43 (d, 1H), 8.06 (d, 1H).

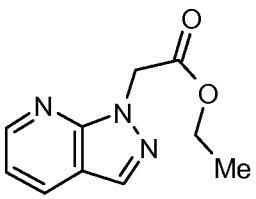
Preparation 178: (7-Fluoro-2H-indazol-2-yl)acetic acid



The title compound was prepared according to the method described for **Preparation 155** using ethyl (7-fluoro-2*H*-indazol-2-yl)acetate (**Preparation 177**) to afford the title compound as a yellow solid in 75% yield, 110 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 5.34 (s, 2H), 6.97-7.05 (m, 2H), 7.56 (d, 1H), 8.50 (d, 1H), 13.30 (br s, 1H); LCMS (System 9): R_t = 1.40 min; m/z 195 $[M+H]^+$

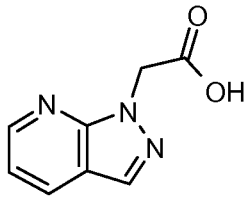
Preparation 179: Ethyl 1*H*-pyrazolo[3,4-*b*]pyridin-1-ylacetate



The title compound was prepared according to the method described for **Preparation 93** using 1*H*-pyrazolo[3,4-*b*]pyridine and ethyl bromoacetate to afford the title compound as an off- white solid in 49% yield, 210 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 1.19 (t, 3H), 4.14 (q, 2H), 5.35 (s, 2H), 7.27 (m, 1H), 8.27 (s, 1H), 8.29 (d, 1H), 8.55 (d, 1H).

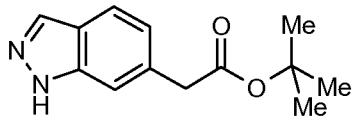
Preparation 180: 1*H*-Pyrazolo[3,4-*b*]pyridin-1-ylacetic acid



The title compound was prepared according to the method described for **Preparation 155** using ethyl 1*H*-pyrazolo[3,4-*b*]pyridin-1-ylacetate (see **Preparation 179**) to afford the title compound as a yellow solid in 40% yield, 70 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 5.22 (s, 2H), 7.25 (dd, 1H), 8.19 (s, 1H), 8.27 (dd, 1H), 8.55 (dd, 1H), 13.15 (br s, 1H).

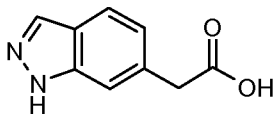
Preparation 181: *tert*-Butyl 1*H*-indazol-6-ylacetate



6-Bromo-1H-indazole (1.3 g, 6.6 mmol) and *t*-butylacetate (1.33 mL, 9.9 mmol) in toluene (20 mL) were degassed with argon for 15 mins. Then the mixture was cooled to 0°C and LiHMDS (16.5 mL, 16.5 mmol, 1M in hexane) was added dropwise. Bis(dibenzylideneacetone)palladium (380 mg, 0.66 mmol) and tri-*t*-butyl phosphine tetrafluoroborate (383 mg, 1.32 mmol) were added and the mixture was stirred at 10°C for 2 hours. The mixture was quenched with water (10 mL) then extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with water (2 x 10 mL), brine (10 mL) and dried over sodium sulphate (Na_2SO_4). The filtrate was evaporated *in vacuo* and purified by column chromatography on silica gel (hexane:EtOAc 80:20) to afford the title compound as a white solid (65%, 1.00 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 1.43 (s, 9H), 3.64 (s, 2H), 7.08 (dd, 1H), 7.39 (s, 1H), 7.69 (d, 1H), 8.03 (s, 1H), 10.05 (br s, 1H).

Preparation 182: 1*H*-Indazol-6-ylacetic acid

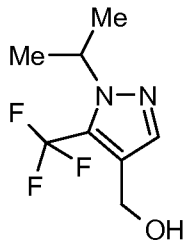


Hydrochloric acid (10 mL, 4 M in 1.4 dioxane) was added to *tert*-butyl 1*H*-indazol-6-ylacetate (**Preparation 181**, 1.00 g, 4.3 mmol) in 1,4 dioxane (5 mL) at 0°C and the mixture was stirred at room

temperature for 16 hours. The mixture was evaporated *in vacuo* and the residue was triturated with dry ether to afford the title compound as a white solid in 100% yield, 800 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 3.69 (s, 2H), 7.00 (d, 1H), 7.41 (s, 1H), 7.67 (d, 1H), 8.02 (s, 1H), 12.81 (br s, 1H).

Preparation 183: [1-Isopropyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]methanol

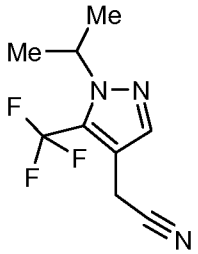


Diisobutylaluminium hydride (99 mL, 120 mmol, 1.2 M solution in toluene) was added to ethyl 1-isopropyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (WO 2007071900, 12 g, 48 mmol) in toluene (220 mL) at -78°C . The reaction mixture was stirred at -78°C for 2 hours then poured into aqueous HCl (100 mL, 2 M). The mixture was stirred for 4 hours at room temperature then extracted with EtOAc (400 mL). The organic phase was washed with water (200 mL), brine (200 mL) and dried over sodium sulphate. The filtrate was evaporated *in vacuo* to afford the title compound as a colourless oil in 100% yield, 10.5 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 1.51 (d, 6H), 4.57-4.66 (m, 3H), 7.58 (s, 1H).

^{1}H NMR (400 MHz, CDCl3) δ: 1.26 (s, 4H), 3.83 (s, 2H), 6.47 (d, 1H), 7.26 (d, 1H), 8.83 (s, 1H), 8.88 (s, 1H); LCMS (system 10): R_t = 1.67 min; m/z 189.9 $[M+H]^+$.

Preparation 184: [1-Isopropyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]acetonitrile



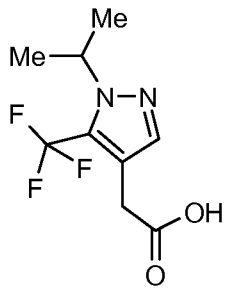
Thionyl chloride (5.26 mL, 72 mmol) was added to [1-isopropyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]methanol (**Preparation 183**, 7.5 g, 36 mmol) in DCM (75 mL) at 0 °C and the mixture was stirred for 2 hours. The mixture was diluted with DCM (30 mL) and the organic phase was washed with water (75 mL), brine (75 mL) and dried over sodium sulphate. The filtrate was evaporated *in vacuo* to afford 4-(chloromethyl)-1-isopropyl-5-(trifluoromethyl)-1*H*-pyrazole in 86% yield, 7 g.

Tetrabutyl ammonium bromide (7.95 gm, 24.7 mmol) was added to 4-(chloromethyl)-1-isopropyl-5-(trifluoromethyl)-1*H*-pyrazole (7 g, 31 mmol) in dioxane (75 mL) and water (75 mL) and the mixture was stirred for 10 min. Potassium cyanide (7.42 g, 114 mmol) was added and the mixture was stirred for 16 hours at room temperature. The mixture was diluted with EtOAc (100 mL) then the organic phase was washed with water (100 mL), brine (100 mL) and dried over sodium sulphate. The filtrate was evaporated

in vacuo and purified by column chromatography on silica gel (hexane:EtOAc 90:10) to afford the title compound as a white solid in 100% yield, 7.00 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.43 (d, 6H), 3.99 (s, 2H), 4.61 (m, 1H), 7.71 (s, 1H).

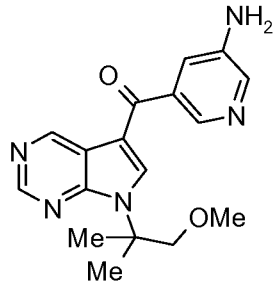
Preparation 185: [1-Isopropyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]acetic acid



Aqueous sodium hydroxide (150 mL of a 1 M solution) was added to [1-isopropyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl]acetonitrile (**Preparation 184**, 6.2 g, 28.6 mmol) in EtOH (150 mL) and the mixture was heated at 60 °C for 16 hours. The mixture was evaporated *in vacuo* and the residue was dissolved in water (50 mL) then washed with EtOAc (100 mL). The aqueous phase was acidified to pH 5 using 1N HCl and extracted with 10% IPA in DCM (4 x 100 mL). The combined organic phases were dried over sodium sulphate and evaporated in vacuo to afford the title compound as a white solid in 75% yield, 5.0 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.42 (d, 6H), 3.56 (s, 2H), 4.58 (m, 1H), 7.57 (s, 1H), 12.28 (br s, 1H).

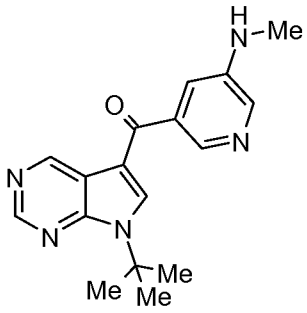
Preparation 186: (5-Amino-pyridin-3-yl)-[7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone



The title compound was prepared according to the method described for **Preparation 65** using (5-Bromo-pyridin-3-yl)-[7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone (**Preparation 263**) to afford the title compound as off white solid in 41% yield, 650 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ 1.76 (s, 6H), 3.19 (s, 3H), 3.96 (s, 2H), 5.65 (s, 2H), 7.30 (s, 1H), 8.05 (s, 1H), 8.16 (s, 2H), 8.97 (s, 1H), 9.44 (s, 1H); LCMS (system 10): R_t = 2.56 min; m/z 327 $[M+H]^+$.

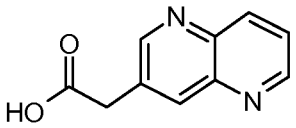
Preparation 187: (7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-(5-methylamino-pyridin-3-yl)-methanone



[5-(7-tert-Butyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-methyl-carbamic acid tert-butyl ester (**Example 542**) was treated with 4N HCl in Dioxane at room temperature for 2 hours. The solvent was removed *in vacuo* and the solid obtained was triturated with diethyl ether to afford the title compound as white solid in 100% yield, 76 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.80 (s, 9H), 2.84 (s, 3H), 7.27 (br s, 1 H), 8.21 (d, 1H), 8.29 (s, 1H), 8.41 (s, 1H), 9.03 (s, 1H), 9.49 (s, 1H); LCMS (system 10): R_t = 2.74 min; m/z 310 $[M+H]^+$.

Preparation 188: 1,5-naphthyridin-3-ylacetic acid

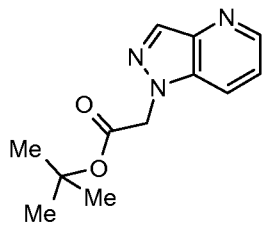


A mixture of 3-bromo-1,5-naphthyridine (540 mg, 2.58 mmol), diethylmalonate (0.8 mL, 5.17 mmol) and cesium carbonate (2.53 g, 7.75 mmol) in 1,4-dioxane (6 mL) was degassed with argon for 15 min then picolinic acid (64 mg, 0.517 mmol) and CuI (50 mg, 0.258 mmol) was added. The mixture was heated in a sealed tube at 110 °C for 24 hours then cooled to room temperature, diluted with ethyl acetate (10 mL), washed with water (10 mL) and brine (10 mL). The organic phase was dried over sodium sulphate then evaporated *in vacuo* and purified by column chromatography on silica gel (hexane:EtOAc 70:30) to afford 450 mg of ethyl 1,5-naphthyridin-3-ylacetate.

Sodium hydroxide (10 mL, 2.0 M) was added to ethyl 1,5-naphthyridin-3-ylacetate in 1,4-dioxane (10 mL) and the mixture was heated at 100 °C for 6 hours. The reaction mixture was cooled to room temperature and acidified to pH 4 using aqueous 2M HCl and then evaporated *in vacuo*. The residue was azeotroped with toluene (2 x 15 mL) then dissolved in THF (50 mL) and stirred at 40 °C for 30 min. The mixture was filtered, the filtrate was evaporated *in vacuo* and the residue was triturated with diethyl ether to afford the title compound as an off white solid, 200 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.94 (s, 2H), 7.76 (m, 1H), 8.31 (s, 1H), 8.42 (d, 1H), 8.91 (d, 1H), 8.99 (dd, 1H), 12.65 (br s, 1H); LCMS (System 10): R_t = 1.49 min; m/z 187 $[M-H]^+$

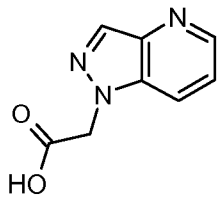
Preparation 189: Tert-butyl 1H-pyrazolo[4,3-*b*]pyridin-1-ylacetate



Tert-butyl bromoacetate (0.55 mL, 3.69 mmol) was added to 1H-pyrazolo[4,3-*b*]pyridine (220 mg, 1.85 mmol) and Cs_2CO_3 (723mg, 2.22 mmol) in anhydrous DMF (7 mL). The mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water (3 x 30 mL), brine (30 mL), dried over sodium sulphate, evaporated *in vacuo* and purified by column chromatography on silica gel (hexane:EtOAc 80:20) to afford a colourless gum in 51% yield, 220mg.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 1.39 (s, 9H), 5.32 (s, 2H), 7.42 (dd, 1H), 8.14 (d, 1H), 8.32 (s, 1H), 8.55 (d, 1H).

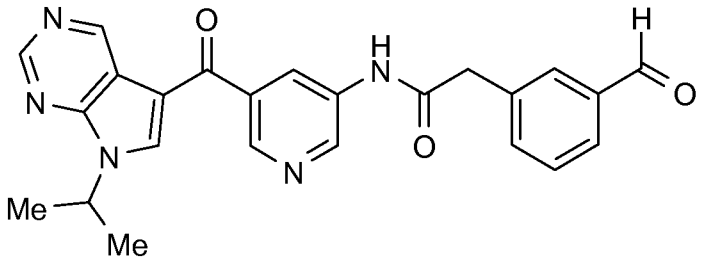
Preparation 190: 1*H*-Pyrazolo[4,3-*b*]pyridin-1-ylacetic acid



Tert-butyl 1H-pyrazolo[4,3,b]pyridin-1-ylacetate (**Preparation 189**, 220 mg, 0.944 mmol) was dissolved in HCl (4 mL, 4.0 M in 1,4 dioxane) and stirred under nitrogen at room temperature for 4 hours. The mixture was evaporated *in vacuo* and the residue was triturated with anhydrous diethyl ether to afford the title compound as an off white solid in 60% yield, 120mg.

^{1}H NMR (400 MHz, DMSO-D_6) δ: 5.36 (s, 2H), 7.51 (dd, 1H), 8.30 (d, 1H), 8.36 (s, 1H), 8.62 (d, 1H); LCMS (System 10): R_t = 1.39 min; m/z 176 [M-H]$^+$.

Preparation 192: 2-(3-formylphenyl)-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide

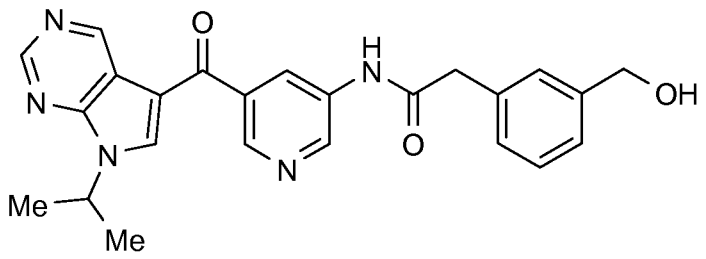


Dess Martin Periodinane (392 mg, 0.93 mmol) was added to a solution of (2-[3-(hydroxymethyl)phenyl]-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide (**Preparation 193**, 265 mg, 0.62 mmol) in dichloromethane (15 mL) and the mixture was stirred at room temperature for 18 hours. Water (10 mL) was added and the aqueous layer extracted with a 95:5 mixture of dichloromethane/methanol (3 x 10 mL). The combined organic layers were dried over magnesium sulfate

and concentrated *in vacuo*. The residue was purified by column chromatography using silica gel (gradient of dichloromethane to dichloromethane/methanol (10:1 to 9:1) to afford the title compound as a brown solid in 80% yield, 211 mg.

LCMS (System 4): R_t = 2.11 min; m/z 428 $[M+H]^+$.

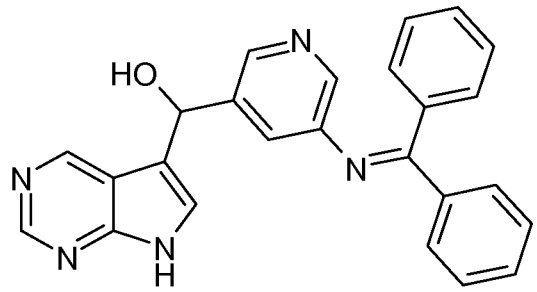
Preparation 193: 2-[3-(hydroxymethyl)phenyl]-N-{5-[(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}acetamide



A mixture of (5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 95**, 250 mg, 0.89 mmol), [4-(hydroxymethyl)phenyl]acetic acid (177 mg, 1.06 mmol) and HATU (505 mg, 1.33 mmol) in pyridine (7 mL) was stirred at 50 °C for 3 hours, then at room temperature for 18 hours. The mixture was concentrated *in vacuo* and azeotroped with toluene. The residue was purified by column chromatography using silica gel (gradient of dichloromethane to dichloromethane/methanol (10:1 to 9:1) to afford the title compound as a gum. This material was dissolved in a 9:1 mixture of dichloromethane/methanol (1.5 mL) and added dropwise to diethyl ether (100 mL), the resulting precipitate was filtered off and dried *in vacuo* to afford the title compound as a white solid, 412 mg, which was used crude in subsequent reactions.

LCMS (System 2): R_t = 1.33 min; m/z 430 $[M+H]^+$.

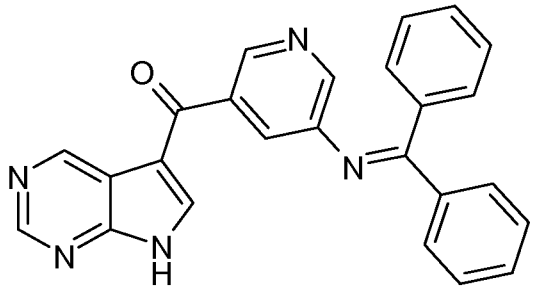
Preparation 194: (5-((Diphenylmethylene)amino)pyridin-3-yl)(7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanol



A mixture of 7H-pyrrolo[2,3-d]pyrimidine (**Preparation 202**, 953 mg, 8.0 mmol), 5-[(diphenylmethylene)amino]nicotinaldehyde (**Preparation 106**, 3340 mg, 11.7 mmol) and KOH (1350 mg, 24 mmol) in MeOH (16 mL) was stirred for 16 hours at room temperature. The reaction was neutralized with saturated aqueous ammonium chloride solution and the mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to obtain a crude residue. The crude material was purified by column chromatography on silica gel (EtOAc:MeOH = 100:0 to 80:20,) to give the desired compound as a solid in 62% yield, 2003 mg.

1H NMR (400 MHz, DMSO-d6) δ: 5.88-5.99 (m, 2H), 6.96-6.99 (m, 1H), 7.04-7.14 (m, 3H), 7.16-7.27 (m, 3H), 7.43-7.51 (m, 2H), 7.51-7.58 (m, 1H), 7.64-7.69 (m,2H), 7.89 (d, 1H), 8.21 (d, 1H), 8.72 (s, 1H), 8.73 (s, 1H), 11.92 (br s, 1H)

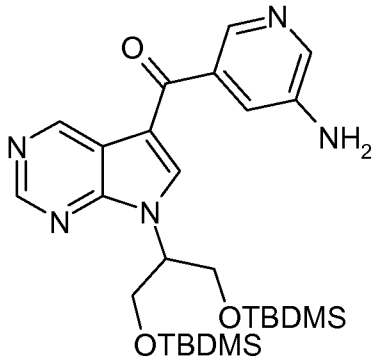
Preparation 195: (5-((Diphenylmethylene)amino)pyridin-3-yl)(7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone



To a stirred solution of (5-((Diphenylmethylene)amino)pyridin-3-yl)(7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanol (**Preparation 194,** 1820 mg, 4.5 mmol) in MeCN (45 mL) was added MnO_2 (1960 mg, 22.5 mmol) portionwise and the resulting mixture stirred at 50 °C overnight. Another portion of MnO_2 (1960 mg, 22.5 mmol) was added to the reaction and the mixture heated to reflux for 5 hr. After cooling to room temperature, the reaction mixture was filtered through a pad of arbocel, the filter cake rinsed with DCM (100 mL) and the resulting filtrate concentrated in vacuo. The resulting material was purified by column chromatography on silica gel (gradient of EtOAc:MeOH 100:0 to 90:10) to give the desired compound as a solid in 61% yield, 1120 mg.

1H NMR (400 MHz, DMSO-d6) δ: 7.24-7.33 (m, 2H), 7.37-7.64 (m, 7H), 7.64-7.78 (m, 3H), 8.28 (d, 1H), 8.53 (d, 1H), 8.94 (s, 1H), 9.41 (s, 1H), 13.09 (br s, 1H)

Preparation 196: (5-aminopyridin-3-yl){7-[2-{[tert-butyl(dimethyl)silyl]oxy}-1-({[tert-butyl(dimethyl)silyl]oxy}methyl)ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}methanone



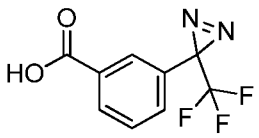
A mixture of (5-((Diphenylmethylene)amino)pyridin-3-yl)(7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 195**, 1120 mg, 2.77 mmol) and Cs_2CO_3 (2710 mg, 8.31 mmol) in DMF (10 mL) was stirred at room temperature for 30 min. A solution of crude 2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl trifluoromethanesulfonate (**Preparation 108**) in DMF (3.8 mL) was then added to the reaction and the resulting mixture stirred at room temperature for 16 hours. The reaction was quenched with saturated aqueous ammonium chloride solution (100 mL) and the mixture extracted with EtOAc (100

mLx3). The combined organic layers were washed with water (200 mL), dried over sodium sulfate and concentrated *in vacuo*. The resulting material was purified by column chromatography on silica gel (gradient of heptane:EtOAc 100:0 to 50:50) to provide (5-((diphenylmethylene)amino)pyridin-3-yl)(7-(2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone.

The above material was dissolved in THF (20 mL) and aqueous 1N citric acid (20 mL) was added to the solution. The reaction mixture was stirred for 4 hours at room temperature, diluted with water (100 mL) and basified with NaOH to pH 7. The resulting mixture was extracted with EtOAc (3 x 150 mL), the combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo. The resulting material was purified by column chromatography on silica gel (heptane:EtOAc = 40:60 to 0:100) to give the desired compound as a white solid in 49% yield, 739 mg.

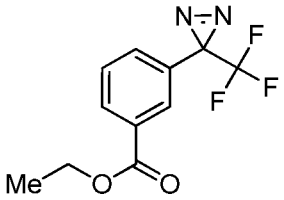
1H NMR (400 MHz, DMSO-d6) δ: -0.11 (s, 6H), -0.07 (s, 6H), 0.68 (s, 18H), 3.99-4.16 (m, 4H), 5.01-5.11 (m, 1H), 5.65 (br s, 2H), 7.21-7.26 (m, 1H), 8.13 (d, 1H), 8.17 (d, 1H), 8.38 (s, 1H), 8.98 (s, 1H), 9.44 (s, 1H).

Preparation 197: 3-(3-(trifluoromethyl)-3H-diazirin-3-yl)benzoic acid



Ethyl 3-(3-(trifluoromethyl)-3H-diazirin-3-yl)benzoate (**Preparation 198**, 60 mg, 0.23 mmol) was stirred in a 2:1 mixture of THF:water (2mL). Lithium hydroxide (5 mg. 0.23 mmol) was added and the mixture stirred at 25° C for 18 hours. The reaction mixture was acidified to pH 1 using 6M aqueous hydrochloric acid and then extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over magnesium sulfate and evaporated *in vacuo* to afford the title compound as a solid in 75% yield, 40 mg. This material was used in the next step without further purification.

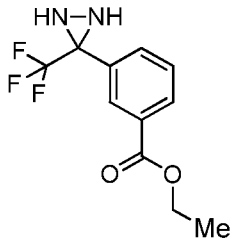
Preparation 198 Methyl 3-(3-(trifluoromethyl)-3H-diazirin-3-yl)benzoate



Ethyl 3-(3-(trifluoromethyl)diaziridin-3-yl)benzoate (**Preparation 199**, 226 mg, 0.87 mmol) was stirred in methanol (10mL) with triethylamine (0.36 mL, 2.61 mmol). Iodine (662 mg, 2.61 mmol) was dissolved in 2 mL methanol and added portion-wise until an orange-brown colour persisted. The reaction mixture was evaporated *in vacuo* and the residue was diluted with 1M aq. NaOH (30 mL) and then extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to afford the title compound as a gum in 27% yield, 60 mg. This material was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (t, 3H), 4.38 (q, 2H), 7.46-7.51 (m, 2H), 7.83 (s, 1H), 8.08 (d, 1H).

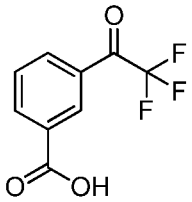
Preparation 199: Ethyl 3-(3-(trifluoromethyl)diaziridin-3-yl)benzoate



To a solution of ethyl 3-(2,2,2-trifluoroacetyl)benzoate (500 mg, 2.15 mmol) in ethanol was added pyridine (5 mL) and hydroxylamine hydrochloride (500 mg, 7.2 mmol) and the resulting mixture stirred at 57°C for 3 hours. The reaction mixture was cooled and passed through an ion exhange column eluting with methanol (30 mL). The methanol solution was evaporated *in vacuo* to give (E)-ethyl 3-(2,2,2-trifluoro-1-(hydroxyimino)ethyl)benzoate as an oil in 71% yield, 401 mg which was used in the next step without further purification. To a stirred solution of (E)-ethyl 3-(2,2,2-trifluoro-1-(hydroxyimino)ethyl)benzoate (401 mg, 1.54 mmol) in dichloromethane (10 mL) was added DMAP (17 mg, 0.14 mmol) and the mixture cooled to 0°C. 4-methylbenzene-1-sulfonyl chloride (331 mg, 1.74 mmol) was added portion-wise as a solution in dichloromethane (5 mL). The reaction mixture was then left to stand at room temperature for 18 hours. The mixture was diluted with water (10 mL) and the organic layer separated, dried over magnesium sulfate and evaporated *in vacuo* to afford (*E*)-ethyl 3-(2,2,2-trifluoro-1-((tosyloxy)imino)ethyl)benzoate as an oil in 78% yield, 500 mg. This material was used in the next step without further purification. A mixture of (*E*)-ethyl 3-(2,2,2-trifluoro-1-((tosyloxy)imino)ethyl)benzoate (500 mg, 1.2 mmol) in diethylether (5 mL) in a 3-necked flask equipped with an internal thermometer and condensor was cooled to -78°C. Ammonia gas was introduced for 5 min and then stirring continued for 45 min. The reaction mixture was warmed to -33°C and stirred for 2 hours after which it was allowed to warm to room temperature overnight with stirring. The mixture was evaporated *in vacuo* and the crude material purified by column chromatography on silica gel (gradient of dichloromethane:ethyl acetate 100:0 to 90:10) to afford the title compound as a gum in 76% yield, 240mg.

^{1}H NMR (400 MHz,$CDCl_3$) δ: 1.31 (t, 3H), 4.31 (q, 2H), 7.40-7.44 (m, 1H), 7.74 (d, 1H), 8.02 (d, 1H), 8.20 (s, 1H).

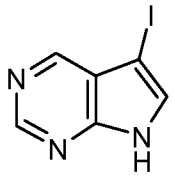
Preparation 200: 3-(2,2,2-trifluoroacetyl)benzoic acid



The title compound was prepared according to the method described for **Preparation 42** starting from ethyl 3-(2,2,2-trifluoroacetyl)benzoate to afford the title compound as a white solid in 26% yield, 23 mg.

^{1}H NMR (400 MHz,$CDCl_3$) δ: 7.71 (t, 1H), 8.32 (d, 1H), 8.45 (d, 1H), 8.80 (s, 1H).

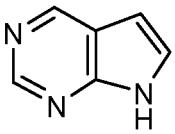
Preparation 201: 5-iodo-7H-pyrrolo[2,3-d]pyrimidine



A mixture of 7H-pyrrolo[2,3-d]pyrimidine (**Preparation 202**, 28.0 g, 235 mmol) and N-iodosuccinimide (55.4 g, 246 mmol) in acetonitrile (470 mL) was stirred at room temperature for 16 hours. The solids were filtered, rinsed with acetonitrile (150 mL) and dried *in vacuo*. The solid was dissolved in 1.5 L of 1N aqueous sodium hydroxide solution and to it was added 2N aqueous hydrogen chloride solution until ~pH 9. The resulting precipitate was filtered, rinsed with water (300 mL), and dried *in vacuo* for 16 hours at 70 °C, ~10 mbar, to afford the title compound in 81% yield, 46.84 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.82 (s, 1H), 8.73 (s, 1H), 8.80 (s, 1H), 12.56 (br s, 1H); LCMS (system 1): R_t = 0.87 min; m/z 246 $[M+H]^+$.

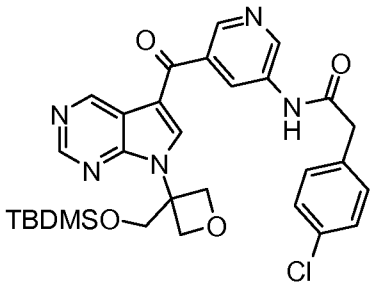
Preparation 202: 7H-pyrrolo[2,3-d]pyrimidine



In each of four separate reaction vessels, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (50.0 g, 260 mmol) was suspended in ethanol (1.4 L) and concentrated ammonium hydroxide solution (140 mL). 10% palladium on carbon (2.5 g) was added to each vessel and the mixture was pressurized to 20 psi hydrogen and stirred at room temperature overnight. Those reactions still containing starting material were charged with another 1 g of 10% palladium on carbon, pressurized to 20 psi hydrogen and stirred until the starting material had been consumed. The reaction mixture was filtered over Arbocel, washed with ethanol, and the filtrate was evaporated to obtain a white solid. The four crude reaction products were combined, suspended in 500 mL water and extracted with ethyl acetate (3 x 500 mL). The organic layers were combined, dried over magnesium sulfate, filtered and the filtrate was concentrated *in vacuo* to obtain 122 g of a white solid. The aqueous layer was further extracted with 5% methanol in ethyl acetate (3 x 500 mL), the organic layers combined, dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo* to obtain another 30 g of white solid. The solids were combined to obtain the title compound in 98% yield, 152 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.63 (dd, 1H), 7.43 (dd, 1H), 8.96 (s, 1H), 9.07 (s, 1H), 11.65 (br. s., 1 H).

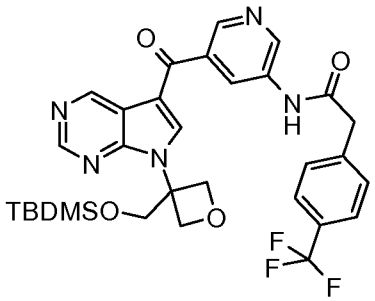
Preparation 203: N-(5-{7-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-pyridin-3-yl)-2-(4-chloro-phenyl) acetamide:



(5-Amino-pyridin-3-yl)-{7-[3-(tert-butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone (**Preparation 216**, 30 mg, 0.068 mmol) was dissolved in dry pyridine (2 mL) under nitrogen and to this was added (4-chloro-phenyl)-acetic acid (17 mg, 0.102 mmol), followed by HATU (39 mg, 0.102 mmol). The reaction was heated to 50˚C and stirred overnight. The reaction was cooled to room temperature, diluted with dichloromethane and saturated aqueous sodium bicarbonate was added. The phases were separated and the aqueous layer was extracted with dichloromethane (3 x 5mL). The combined organics were concentrated to dryness to afford N-(5-{7-[3-(tert-butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-pyridin-3-yl)-2-(4-chloro-phenyl)-acetamide as a pale yellow solid 35 mg, 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ-0.23 (s, 6 H) 0.65 (s, 9 H) 3.77 (s, 2 H) 4.26 (s, 2 H) 4.89 (d, *J*=7.6 Hz, 2 H) 5.27 (d, *J*=7.8 Hz, 2 H) 7.30 (d, *J*=8.6 Hz, 2 H) 7.37 - 7.44 (m, 2 H) 7.72 (s, 1 H) 8.49 (s, 1 H) 8.70 (d, *J*=2.3 Hz, 1 H) 8.78 (s, 1 H) 8.94 (s, 1 H) 9.64 (s, 1 H).

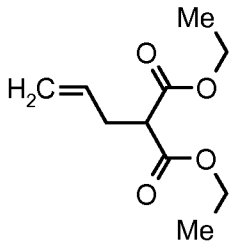
Preparation 204: N-(5-{7-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-pyridin-3-yl)-2-(4-trifluoromethyl-phenyl)-acetamide:



(5-Amino-pyridin-3-yl)-{7-[3-(tert-butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone (**Preparation 216**, 30 mg, 0.068 mmol) was dissolved in dry pyridine (2 mL) under nitrogen and to this was added (4-trifluoromethyl-phenyl)-acetic acid (21 mg, 0.102 mmol), followed by HATU (39 mg, 0.102 mmol). The reaction mixture was heated to 50˚C and stirred overnight. The reaction was then cooled to room temperature, diluted with dichloromethane (5 mL) and saturated aqueous sodium bicarbonate was added (5 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (3 x 5mL). The combined organics were concentrated to dryness to afford N-(5-{7-[3-(tert-butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-pyridin-3-yl)-2-(4-trifluoromethyl-phenyl)-acetamide as a pale yellow solid 39 mg, 92% yield.

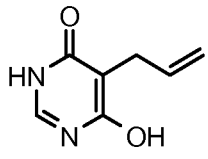
^{1}H NMR (400 MHz, DMSO-d_6) δ-0.29 (s, 6 H) 0.58 (s, 9 H) 3.84 (s, 2 H) 4.16 (s, 2 H) 4.77 (d, *J*=7.4 Hz, 2 H) 5.21 (d, *J*=7.4 Hz, 2 H) 7.56 (d, *J*=7.8 Hz, 2 H) 7.68 (d, *J*=7.8 Hz, 2 H) 8.28 (s, 1 H) 8.46 (t, *J*=2.1 Hz, 1 H) 8.69 (d, *J*=2.0 Hz, 1 H) 8.91 - 8.95 (m, 2 H) 9.46 (s, 1 H) 10.71 (s, 1 H).

Preparation 205: 2-Allyl-malonic acid diethyl ester



Malonic acid diethyl ester (100 g, 0.625 mol) was added dropwise at 0°C to a mixture of sodium ethoxide (46.8 g, 0.688 mol) in ethanol (1 L). The reaction mixture was stirred for 4 hours. 3-Bromo-propene (83.2 g, 0.688 moles) was added dropwise to the mixture at 0°C. After addition, the mixture was warmed to reflux and stirred overnight. The mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo* to afford the title compound in 86% yield, 100 g which was used for the next step without further purification.

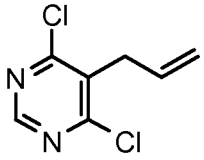
Preparation 206: 5-Allyl-6-hydroxy-3H-pyrimidin-4-one



2-Allyl-malonic acid diethyl ester (**Preparation 205,** 100 g, 0.5 mol) was added dropwise to a mixture of sodium methoxide (27 g, 0.5 mol) in ethanol (1 L) at 0-5°C and the mixture was stirred at this temperature for 10 min. Formamidine acetate (51.9 g, 0.5 mol) was added and the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, and aqueous hydrochloric acid (36.5%) and water were added to adjust the pH to approximately 3 at 0-20°C. The resulting mixture was filtered to afford the title compound as a colorless solid in 57% yield, 87.12 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.96 (d, 1H), 4.89 (m, 2H), 5.76 (m, 1H), 7.89 (s, 1H).

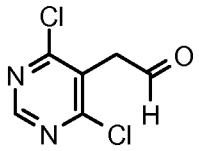
Preparation 207: 5-Allyl-4,6-dichloro-pyrimidine



5-Allyl-6-hydroxy-3H-pyrimidin-4-one (**Preparation 206**, 40 g, 0.263 mol) was added to $POCl_3$ (100 mL) at room temperature. The solution was stirred and warmed to reflux for 8 hours. The mixture was evaporated *in vacuo* to remove most of the $POCl_3$. The residue was poured slowly onto ice-water, which was extracted with ethyl acetate (500 mL x 4), washed with brine (300 mL), dried over sodium sulfate and evaporated *in vacuo* to afford the title compound as a yellow oil in 59% yield, 31 g.

^{1}H NMR (400 MHz,$CDCl_3$) δ: 3.59 (m, 2H), 5.09 (m, 2H), 5.79 (m, 1H), 8.59 (s, 1H).

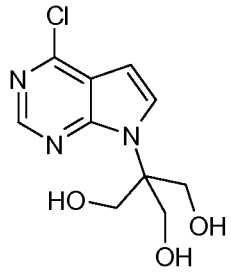
Preparation 208: (4,6-Dichloro-pyrimidin-5-yl)-acetaldehyde



To a stirred solution of 5-Allyl-4,6-dichloro-pyrimidine (**Preparation 207**, 30 g, 0.159 mole) in dry dichloromethane (400 mL) was bubbled ozone at -70°C for 30 min. After excess ozone was purged by nitrogen gas, dimethyl sulfide (10 mL) was added at -5°C, and the reaction was stirred for 2 hours. The mixture was washed with water, brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude material was purified by trituration from pentane-diethyl ether to afford the title compound as a colorless solid in 84% yield, 10 g.

^{1}H NMR (400 MHz,$CDCl_3$) δ: 4.15 (s, 2H), 8.74 (s, 1H), 9.80 (s, 1H).

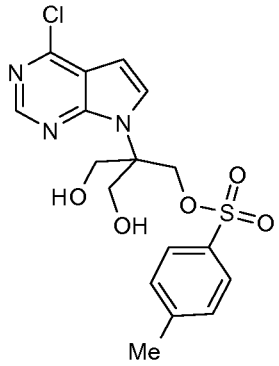
Preparation 209: 2-(4-Chloro-pyrrolo[2,3-d]pyrimidin-7-yl)-2-hydroxymethyl-propane-1,3-diol



Trisamine (1.27 g, 10.5 mmol) was added to 4,6-Dichloro-pyrimidin-5-yl)-acetaldehyde (**Preparation 208**, 1.0 g, 5.2 mmol) in ethanol (40 mL) and stirred at reflux temperature for 16 hours. The reaction mixture was evaporated *in vacuo* and partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The separated aqueous phase was extracted with dichloromethane twice more and the combined organics were washed with saturated brine and evaporated *in vacuo* to afford the title compound as a pale yellow foam in 74% yield, 1.0 g.

^{1}H NMR (400 MHz,$CDCl_3$) δ ppm 2.97 (br. s, 1H), 3.09 - 3.27 (m, 2H), 3.51 (d, *J*=9.18 Hz, 1H), 3.83 - 4.00 (m, 4H), 4.06 (d, *J*=11.13 Hz, 1H), 5.43 (dd, *J*=6.44, 1.76 Hz, 1H), 6.16 (dd, *J*=10.74, 4.69 Hz, 1H), 8.40 (s, 1H); LCMS (System 2): R_t = 1.04 min; m/z 258 $[M+H]^+$.

Preparation 210: Toluene-4-sulfonic acid 2-(4-chloro-pyrrolo[2,3-d]pyrimidin-7-yl)-3-hydroxy-2-hydroxymethyl-propyl ester

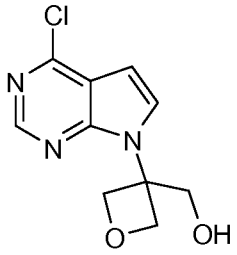


Triethylamine (0.879 mL, 6.31 mmol) and trimethylamine hydrochloride (253 mg, 2.65 mmol) were added to a solution of 2-(4-chloro-pyrrolo[2,3-d]pyrimidin-7-yl)-2-hydroxymethyl-propane-1,3-diol (**Preparation**

209, 650 mg, 2.52 mmol) in dichloromethane (20 mL) at 0°C. The mixture was treated portion-wise with tosyl chloride (505 mg, 2.65 mmol) and stirred at 0°C for 16 hours. The reaction mixture was treated with water and stirred for 10 min. The resulting mixture was washed with citric acid, saturated aqueous sodium bicarbonate, and saturated brine, then evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel (gradient of EtOAc:DCM 0:100 to 30:70) to afford the title compound as a colorless solid in 55% yield, 570 mg.

LCMS (system 2): R_t = 1.28 min; m/z 412 $[M+H]^+$.

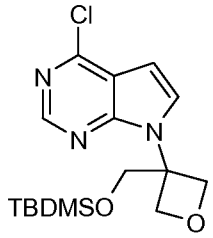
Preparation 211: [3-(4-Chloro-pyrrolo[2,3-d]pyrimidin-7-yl)-oxetan-3-yl]-methanol



^{n}Butyllithium (12.2 mL, 30.6 mmol, 2.5 M in hexanes) was added to toluene-4-sulfonic acid 2-(4-chloro-pyrrolo[2,3-d]pyrimidin-7-yl)-3-hydroxy-2-hydroxymethyl-propyl ester (**Preparation 210**, 5.73 g, 13.9 mmol) in THF (100 mL) at 0°C and stirred for 5 min. The reaction mixture was then warmed to room temperature and stirred for 16 hours, at which point it was quenched with saturated aqueous ammonium chloride. The resulting mixture was extracted with ethyl acetate (100mL x3) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was triturated with dichloromethane and filtered to afford the title compound in 36% yield, 1.2 g.

^{1}H NMR (400 MHz, MeOH-d_4) δ: 4.15 (s, 2H), 4.92 (d, *J*=7.22 Hz, 2H), 5.22 (d, *J*=7.03 Hz, 2 H), 6.69 (d, *J*=3.51 Hz, 1H), 7.51 (d, *J*=3.71 Hz, 1H), 8.51 (s, 1H).

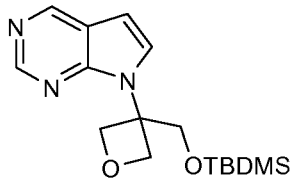
Preparation 212: 7-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-4-chloro-7H-pyrrolo[2,3-d]pyrimidine



Imidazole (277 mg, 4.07 mmol) was added to [3-(4-Chloro-pyrrolo[2,3-d]pyrimidin-7-yl)-oxetan-3-yl]-methanol (**Preparation 211**, 650 mg, 2.71 mmol) in dicloromethane (10 mL), and this mixture was treated with a solution of *t*-butyldimethylsilyl chloride (495 mg, 3.25 mmol) in dichloromethane (5 mL). The resulting mixture was stirred at room temperature for 16 hours, then quenched with water (50 mL). The mixture was extracted with dichloromethane (3 x 50mL), and the combined organic phases were washed with water and saturated brine, and evaporated *in vacuo* to afford the title compound as a pale brown oil in 91% yield, 875 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: -0.21 (s, 6H), 0.77 (s, 9H), 4.22 (s, 2H), 4.88 (d, *J*=7.22 Hz, 2H), 5.19 (d, *J*=7.03 Hz, 2H), 6.61 (d, *J*=3.71 Hz, 1H), 7.11 (d, *J*=3.71 Hz, 1H), 8.55 (s, 1H); LCMS (system 2): R_t = 1.82 min; m/z 354 $[M+H]^+$.

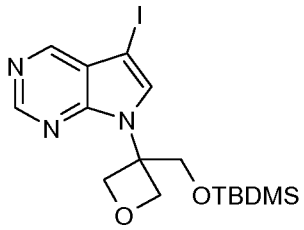
Preparation 213: 7-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 8** using 7-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 212**) to afford the title compound as a brown oil in 82% yield, 650 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: -0.24 (s, 6H), 0.76 (s, 9H), 4.24 (s, 2H), 4.91 (d, *J*=7.03 Hz, 2H), 5.22 (d, *J*=7.03 Hz, 2H), 6.55 (d, *J*=3.51 Hz, 1H), 7.08 (d, *J*=3.71 Hz, 1H), 8.78 (s, 1H), 8.97 (s, 1H); LCMS (system 2): R_t = 0.90 min; m/z 320 $[M+H]^+$.

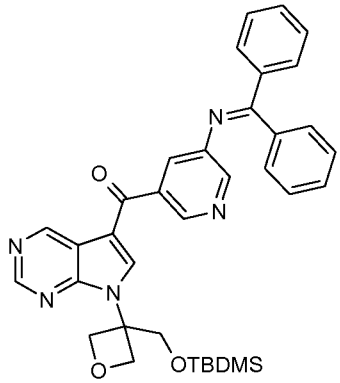
Preparation 214: 7-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-5-iodo-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 14** using 7-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 213**) and DMF to afford the title compound as a brown solid in 75% yield, 675 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: -0.24 (s, 6H), 0.77 (s, 9H), 4.20 (s, 2H), 4.88 (d, *J*=7.22 Hz, 2H), 5.21 (d, *J*=7.03 Hz, 2H), 7.17 (s, 1H), 8.77 (s, 1H), 8.81 (s, 1H); LCMS (system 2): R_t = 1.55 min; m/z 446 $[M+H]^+$.

Preparation 215: (7-(3-(((tert-Butyldimethylsilyl)oxy)methyl)oxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(5-((diphenylmethylene)amino)pyridin-3-yl)methanone

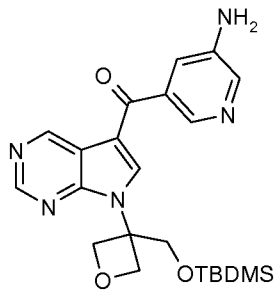


The title compound was prepared according to the method described for **Preparation 24** using 7-[3-(tert-butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 214**) and 5-

[(Diphenylmethylene)amino]-N-methoxy-N-methylnicotinamide (**Preparation 23**) to afford the title compound as a purple solid in 51% yield, 240 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.20 (s, 6H), 0.70 (s, 9H), 4.28 (s, 2H), 4.89 (d, *J*=7.22 Hz, 2H), 5.20 (d, *J*=7.22 Hz, 2H), 7.11 - 7.18 (m, 2H), 7.33 (m, 3H), 7.40 - 7.48 (m, 2H), 7.49 - 7.57 (m, 3H), 7.79 (d, *J*=7.42 Hz, 2H), 8.18 (d, *J*=2.54 Hz, 1H), 8.60 (d, *J*=1.95 Hz, 1H), 8.93 (s, 1H), 9.60 (s, 1H).

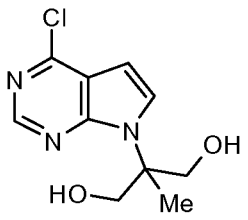
Preparation 216: (5-Amino-pyridin-3-yl)-{7-[3-(tert-butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone



The title compound was prepared according to the method described for **Preparation 37** using (7-(3-(((tert-butyldimethylsilyl)oxy)methyl)oxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(5-((diphenylmethylene)amino)pyridin-3-yl)methanone (**Preparation 215**) to afford the title compound as a colourless solid in 76% yield, 132 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.01 (s, 6H), 0.88 (s, 9H), 4.11 (br. s, 2H), 4.45 (s, 2H), 5.17 (m, 2H), 5.40 (m, 2H), 7.58 (s, 1H), 7.80 (s, 1H), 8.45 (s, 1H), 8.61 (s, 1H), 9.15 (s, 1H), 9.83 (s, 1H).

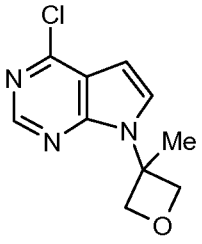
Preparation 217: 2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropane-1,3-diol



The title compound was prepared according to the method described for **Preparation 1** using (4,6-dichloropyrimidin-5-yl)acetaldehyde (**Preparation 208**) and 2-amino-2-methylpropane-1,3-diol to afford the title compound as a yellow liquid in 79% yield, 3.88 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.66 (s, 3H), 3.86 (dd, 2H), 4.13 (dd, 2H), 4.92 (t, 2H), 6.58 (d, 1H), 7.73 (d, 1H), 8.59 (s, 1H).

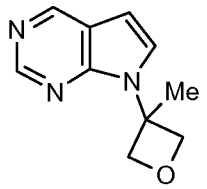
Preparation 218: 4-chloro-7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine



n-BuLi (6.6 mL of a 2.5 M solution in hexane, 16.5 mmol) was added to a solution of 2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methylpropane-1,3-diol (**Preparation 217**, 3.63 g, 15.0 mmol), in THF (80 mL) at -78 °C. The reaction mixture was allowed to warm to -50 °C in 2 hours and TsCl (3.15 mg, 16.5 mmol) in THF (20 mL) was added to the reaction. The reaction was allowed to warm to 0 °C in 3 hours and additional n-BuLi (6.6 mL of a 2.5 M solution in hexane solution, 16.5 mmol) was slowly added to the reaction mixture. The mixture was stirred for 1 hour at 0 °C and stirred at 60 °C for 16 hours. After cooling to room temperature, the reaction was quenched by 50 mL of saturated aqueous NH_4Cl solution and 100 mL of water, and the mixture was extracted with EtOAc (3x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatogranhy on silica gel (gradient of EtOAc:heptane 20:80 to 70:30) to give a solid in 55% yield, 1.87 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 1.79 (s, 3H) 4.72 (d, 2H) 5.15 (d, 2H) 6.69 (d, 1H) 7.78 (d, 1H) 8.59 (s, 1H).

Preparation 219: 7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine



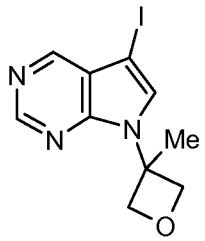
The title compound was prepared according to the method described for **Preparation 8** using 4-chloro-7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 218**) to afford the title compound as a yellow liquid in 22% yield, 0.341 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 1.81 (s, 3H), 4.72-4.77 (m, 2H), 5.16-5.21 (m, 2H), 6.69 (d, 1H), 7.66 (d, 1H), 8.76 (s, 1H), 9.02 (s, 1H).

The title compound may also be prepared according to the following method:

LiHMDS (14.5 mL of a 1M solution in THF, 14.5 mmol) was added slowly to a solution of 2-Methyl-2-pyrrolo[2,3-d]pyrimidin-7-yl-propane-1,3-diol (**Preparation 278**, 3 g, 14.5 mmol) in anhydrous THF (200 mL) over a period of 2 hours (using a syringe pump) under nitrogen at 0°C. After completion of the addition, the reaction mixture was stirred for an additional 40 min before TsCl (2.76 g, 14.5 mmol) as a solution in THF (50 mL) was slowly added. The mixture was stirred for another 1 hour at 0°C. TLC showed consumption of starting material and another equivalent of LiHMDS (14.5 mL, 14.5 mmol) was added to the mixture and it was heated at 60° for 16 hours. Sat. aq. NH_4Cl solution (200 mL) was then added and the mixture then extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of EtOAc:Hexane 3:7 to 2:3) to afford the title compound as a colourless gum in 37% yield, 1 g.

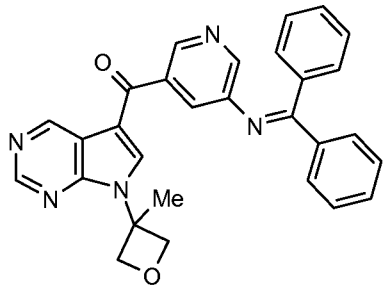
Preparation 220: 5-iodo-7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 14** using 7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 219**) to afford the title compound as a yellow solid in 78% yield, 0.44 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.80 (s, 3H), 4.71 (d, 2H), 5.18 (d, 2H), 7.94 (s, 1H), 8.76 (s, 1H), 8.82 (s, 1H).

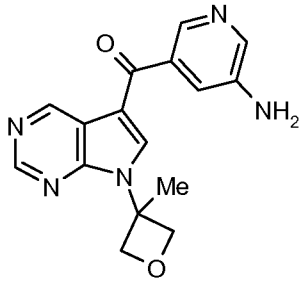
Preparation 221: (5-((diphenylmethylene)amino)pyridin-3-yl)(7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone



The title compound was prepared according to the method described for **Preparation 24** using 5-iodo-7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 220**) to afford the title compound.

LCMS (system 2): R_t = 1.24 min; m/z 474 $[M+H]^+$.

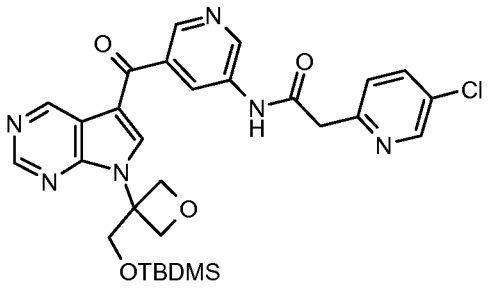
Preparation 222: (5-aminopyridin-3-yl)[7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]methanone



The title compound was prepared according to the method described for **Preparation 37** using (5-((diphenylmethylene)amino)pyridin-3-yl)(7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 221**) to afford the title compound as a white solid in 14% yield over two steps, 64 mg.

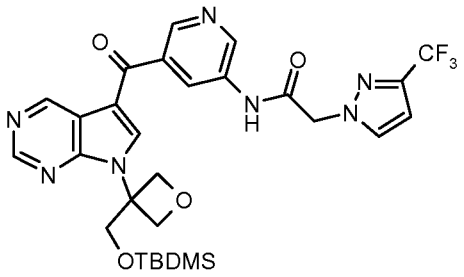
^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.89 (s, 3H), 4.75 (d, 2H), 5.23 (d, 2H), 5.64 (br s, 2H), 7.29-7.36 (m, 1H), 8.17 (d, 1H), 8.24 (d, 1H), 8.41 (s, 1H), 8.95 (s, 1H), 9.46 (s, 1H); LCMS (System 4): R_t = 2.30 min; m/z 310 $[M+H]^+$.

Preparation 223: N-[5-({7-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-(5-chloropyridin-2-yl)acetamide



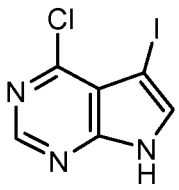
(5-Amino-pyridin-3-yl)-{7-[3-(tert-butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone (**Preparation 216,** 30 mg, 0.068 mmol) was added to a stirred mixture of (5-chloropyridin-2-yl)acetic acid (17.5 mg, 0.102 mmol) and HATU (38.8 mg, 0.102 mmol) in pyridine (2 ml). The reaction mixture was warmed to 50°C and stirred at this temperature for 14 hours. The reaction was then cooled and a further portion of HATU (38.8 mg, 0.102 mmol) was added. The reaction was warmed to 50°C and stirred at this temperature for 8 hours and then allowed to cool to room temperature and stirred for a further 60 hours. The reaction mixture was then diluted with DCM (20ml) and the resultant solution quenched with saturated $NaHCO_3$ (20 ml). The layers were separated and the aqueous layer extracted with DCM (3x 20 ml). The combined organic layers were washed with brine (20ml) and then concentrated *in vacuo* to give the crude product as a pale yellow oil (35 mg) which was taken forward for use in the preparation of **Example 238**.

Preparation 224: N-[5-({7-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide



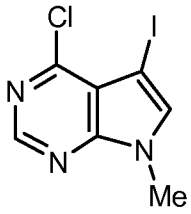
(5-Amino-pyridin-3-yl)-{7-[3-(tert-butyl-dimethyl-silanyloxymethyl)-oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone (**Preparation 216**, 30 mg, 0.068 mmol) was added to a stirred mixture of [3-(trifluoromethyl)-1H-pyrazol-1-yl]acetic acid (19.8 mg, 0.102 mmol) and HATU (38.8 mg, 0.102 mmol) in pyridine (2 ml). The reaction mixture was warmed to 50°C and stirred at this temperature for 14 hours. The reaction mixture was then cooled to room temperature and diluted with DCM (20ml) and the resultant solution quenched with saturated $NaHCO_3$ (20 ml). The layers were separated and the aqueous layer extracted with DCM (3x 20 ml). The combined organic layers were washed with saturated brine (20ml) and then concentrated *in vacuo* to give the crude product as a pale yellow solid (44 mg) which was taken forward crude for use in the preparation of **Example 239**.

Preparation 225: 4-Chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine



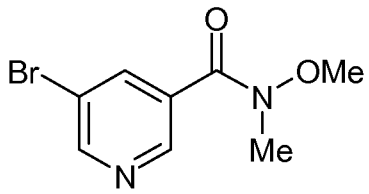
To a suspension of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (70.5 g, 0.45 mol) in DCM (1.8 L) was added N-iodosuccinimide (120 g, 0.54 mol) in portions. After addition, the mixture was stirred at room temperature overnight. The solid was filtered and washed with water (250 mL), MeOH (280 mL) and CH_2Cl_2 (280 mL) sequentially. The solid was dried under vacuum to afford 4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine as a brown solid in 79% yield, 107g.

Preparation 226: 4-Chloro-5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidine



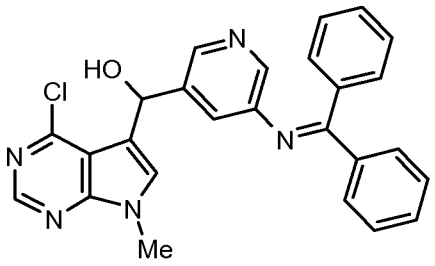
To a mixture of 4-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 225**, 30 g, 0.1 mol), Cs_2CO_3 (50 g, 0.15 mol) in DMF (150 mL), MeI (28.4 g, 0.2 mol) was added dropwise at 0ºC. After addition, the mixture was stirred at room temperature for 10 hours. The reaction mixture was cooled to 0ºC and quenched by the addition of water (500 mL). Then the solid was collected by filtration and washed with Et_2O (100 mL) to afford 4-chloro-5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidine as a brown solid in 61% yield, 20g.

Preparation 227: 5-Bromo-N-methoxy-N-methyl-nicotinamide



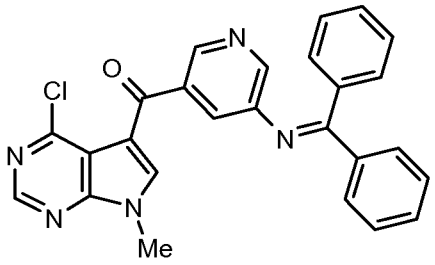
To a solution of 5-bromo-nicotinic acid (100 g, 0.5 mol) in THF (2 L) at 0ºC, $(COCl)_2$ (95 g, 0.74 mol) was added. After stirring for 0.5 h, Et_3N (152 g, 1.5 mol) and O, N-dimethyl hydroxylamine.HCl (140 g, 1.5 mol) were added. The reaction mixture was stirred at room temperature for 2.5 hours and then water (200 mL) and EtOAc (500 mL) were added. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to afford 5-the title compound as a brown oil in 82% yield, 100%.

Preparation 228: (4-Chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(5-((diphenylmethylene)amino)pyridin-3-yl)methanol



To stirred solution of 4-chloro-5-iodo-7-methyl-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 226**, 6.6 g, 22.7 mmol) in THF (130 mL) was added n-BuLi (18.2 mL of a 2.5M solution in hexane, 45 mmol) at -75 ºC under N_2, and the mixture was stirred for 50 min. A solution of 5-((diphenylmethylene)amino)nicotinaldehyde (**Preparation 106**, 6.5 g, 22.7 mmol) in dry THF (50 mL) was added and the mixture was stirred at -70 ºC for 80 min. The mixture was quenched with sat. aq. NH_4Cl solution and extracted with EtOAc (300 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a brown solid in 48% yield, 5.2g.

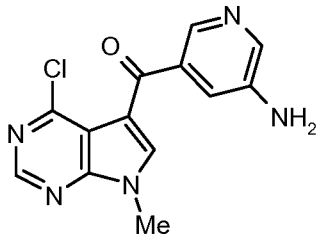
Preparation 229: (4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(5-((diphenylmethylene)amino)pyridin-3-yl)methanone



To a solution of (4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)(5-((diphenylmethylene)amino)pyridin-3-yl)methanol (**Preparation 228**, 11.4 g, 25 mmol) in CH_2Cl_2 (150 mL), Dess-Martin periodinane (15.9 g, 37 mmol) was added in portions. The reaction mixture was stirred at room temperature for 10 hours and then aqueous NaOH (30 mL) was added. The mixture was stirred for a further 0.5 hours. The mixture was then separated and the aqueous layer was exacted by CH_2Cl_2 (100 mL × 2). The combined organic layers were concentrated and washed with ether to provide the title compound as a brown solid in 99% yield, 11g.

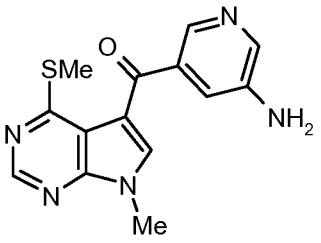
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 7.06 (m, 2H), 7.27 (m, 3H), 7.37 (m, 2H), 7.45 (m, 3H), 7.71 (m, 2H), 8.15 (d, J=2.4,1H), 8.49 (d, J=1.2,1H), 8.68 (s, 1H).

Preparation 230: (5-Amino-pyridin-3-yl)-(4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone



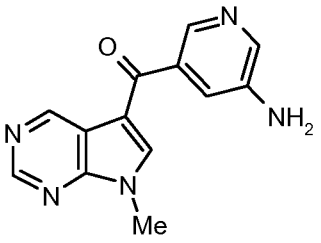
A solution of [5-(benzhydrylidene-amino)pyridin-3-yl]-(4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 229**, 30 g, 0.066 mol) in THF (200 mL) was added aq. citric acid (200 mL), the mixture was stirred for 30 min at room temperature. Ether was added and the layers were separated. The aqueous layer was adjusted to pH7 by aqueous Na_2CO_3. Then the mixture was filtered. The filter cake was evaporated with toluene and the residue was washed with EtOAc (200 mL) to give the title compound as a brown solid in 95% yield, 18g.

Preparation 231: (5-Amino-pyridin-3-yl)-(7-methyl-4-methylsulfanyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone



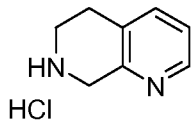
To a solution of (5-amino-pyridin-3-yl)-(4-chloro-7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 230**, 21 g, 0.073 mol) in MeOH (300 mL) was added CH_3SNa (15.5 g, 0.22 mol). The resulting mixture was stirred for 7 hours at room temperature. The mixture was poured into ice-water (200 mL), the precipitate was filtered, the filter cake was washed with water (100 mL) then acetone (20 mL) to give (5-amino-pyridin-3-yl)-(7-methyl-4-methylsulfanyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone as a brown solid in 69% yield, 15g.

Preparation 232: (5-Amino-pyridin-3-yl)-(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone



A mixture of (5-amino-pyridin-3-yl)-(7-methyl-4-methylsulfanyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 231**, 1.5 g, 5 mmol), Raney Ni (10 g) and NH_3H_2O (150 mL) in dioxane (150 mL) was refluxed for 6 hours. The mixture was filtered and the filtrate was concentrated. The residue was purified via preparative HPLC to give (5-amino-pyridin-3-yl)-(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone as a brown solid in 15% yield, 0.19g. ^{1}H NMR (400 MHz DMSO-d_6) 3.88 (s, 3H), 5.63 (s, 2H), 7.27-7.28 (m, 1H), 8.15-8.18 (m, 2H), 8.40 (s, 1H), 8.97 (s, 1H), 9.42 (s, 1H).

Preparation 233: 5,6,7,8-Tetrahydro-[1,7]naphthyridine hydrochloride

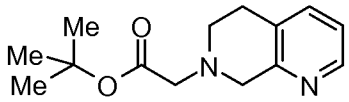


A methanolic solution (25 mL) of 7-Benzyl-5,6,7,8-tetrahydro-[1,7]naphthyridine (J. Het. Chem. 2001, 38, 535) (1.5g, 6.69 mmol) was degassed with argon for 20 min followed by the addition of 4N HCl in dioxane (2 mL) and Pd/C (300 mg, 20 wt%) and stirred under 50 psi hydrogen pressure at room

temperature for 24h. After completion of the reaction the mixture was filtered on a short pad of celite and washed with methanol (4 x 25 mL). The filtrate was evaporated to dryness *in vacuo* and crystallized from methanol to afford the title compound as yellowish solid in 65% yield (calculated as 2HCl salt), 900 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ*:* 3.10 (t, 2H), 3.40 (q, 2H), 4.36 (s, 2H), 7.50 (dd, 1H), 7.91 (d, 1H), 8.55 (d, 1H), 9.96 (brs, 2H); LCMS (system 10): R_t = 1.56 min; m/z 135.2 $[M+H]^+$.

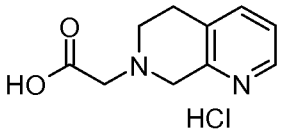
Preparation 234: (5,8-Dihydro-6H-[1,7]naphthyridin-7-yl)-acetic acid tert-butyl ester



A DMF solution (8 mL) of 5,6,7,8-Tetrahydro-[1,7]naphthyridinehydrochloride (**Preparation 233**, 400 mg, 1.93 mmol), bromo-acetic acid tert-butyl ester (414.1 mg, 2.12 mmol) and triethylamine (1.64 mL, 11.92 mmol) was heated at 80°C for 16 hours. The reaction mixture was diluted with EtOAc (40 mL), washed with water (3 x 25 mL), brine (20 mL), dried over Na_2SO_4 and evaporated to dryness *in vacuo* to afford the title compound as colorless sticky solid in 100% yield, 480 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ*:* 1.43 (s, 9H), 2.81 (s, 4H), 3.34 (s, 2H), 3.72 (s, 2H), 7.16 (dd, 1H), 7.51 (d, 1H), 8.29 (d, 1H); LCMS (system 10): R_t = 3.02 min; m/z 249.4 $[M+H]^+$.

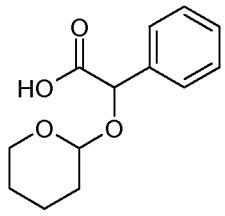
Preparation 235: (5,8-Dihydro-6H-[1,7]naphthyridin-7-yl)-acetic acid hydrochloride



(5,8-Dihydro-6H-[1,7]naphthyridin-7-yl)-acetic acid tert-butyl ester (**Preparation 234,** 1.25 g, 5.03 mmol) was treated with 4N HCl in dioxane (25 ml) at room temperature for 2 hours. The mixture was evaporated to dryness *in vacuo* and the solid residue was triturated with diethyl ether to afford the title compound as white solid in 78% yield (calculated as HCl salt), 900 mg.

^{1}H NMR (400 MHz, MeOD) δ*:* 3.38 (t, 2H), 3.79 (t, 2H), 4.38 (s, 2H), 4.84 (s, 2H), 7.79 (dd, 1H), 8.25 (d, 1H), 8.70 (d, 1H).

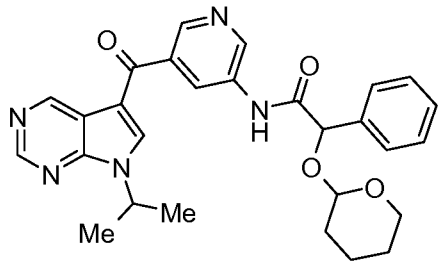
Preparation 236: Phenyl-[(tetrahydro-pyran-2-yloxy)]-acetic acid



To a stirred solution of hydroxy-phenyl-acetic acid (2 g, 13.4 mmol) in DCM (30 mL) was added PTSA (51.2 mg, 0.27 mmol) at 0°C followed by the addition of 3,4-dihydro-2H-pyran (1.55 g, 18.4 mmol). The mixture was stirred at 0°C for another 15 min and then gradually warmed up to room temperature and stirred for a further 1.5 hours. The reaction mixture was diluted with DCM (100 mL). The organic phase was washed with saturated aq. Na_2CO_3 (2 x 20 mL), water (20 mL), brine (20 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel

(EtOAc:petroleum ether 2:5) to afford the title compound as a yellow sticky solid in 48% yield, 1.5 g. LCMS (system 10): R_t = 1.82 min; m/z 237 $[M+H]^+$.

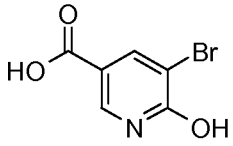
Preparation 237: N-[5-(7-Isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)-pyridin-3-yl]-2-phenyl-2-(tetrahydro-pyran-2-yloxy)-acetamide



The title compound was prepared according to the method described for **Example 1** using phenyl-[(tetrahydro-pyran-2-yloxy)]-acetic acid (**Preparation 236**) and (5-Amino-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 95**) to afford the title compound as a yellow solid in 68% yield, 60 mg.

LCMS (system 10): R_t = 3.56 min; m/z 500.2 $[M+H]^+$.

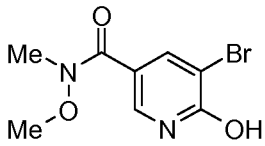
Preparation 238: 5-Bromo-6-hydroxy-nicotinic acid



Bromine (3.6 mL, 70.5 mmol) was added dropwise to a suspension of 6-Hydroxy-nicotinic acid (7 g, 50.32 mmol) in water (70 mL) at 0°C and the mixture was stirred at room temperature for 4 hours. The precipitated solid was filtered, washed with cold water and dried to get the title compound as off white solid in 82% yield, 9 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 8.03 (d, 1H), 8.14 (d, 1H), 12.57 (br s, 1H).

Preparation 239: 5-Bromo-6-hydroxy-N-methoxy-N-methyl-nicotinamide

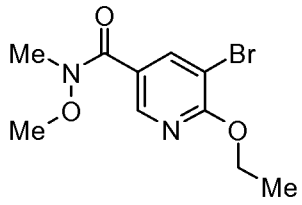


5-Bromo-6-hydroxy-nicotinic acid (**Preparation 238**, 4 g, 18.4 mmol), HATU (13.95 g, 36.71 mmol), O,N-Dimethyl-hydroxylamine hydrochloride (2.15 g, 22.02 mmol) and DIPEA (15.82 mL, 91.75 mmol) were taken in anhydrous DMF (30 mL). The mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with EtOAc (150 mL), washed with saturated aq. Na_2CO_3 (2 x 50 mL), water (4 x 30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (gradient of EtOAc:Hex 4:6 to 6:4) to afford the title compound as light yellow sticky solid in 38%, 1.8 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 3.22 (s, 3H), 3.61 (s, 3H), 7.95 (d, 1H), 8.14 (d, 1H), 12.45 (br s, 1H);

LCMS (system 10): R_t = 1.67 min; m/z 261, 263 $[M+H]^+$.

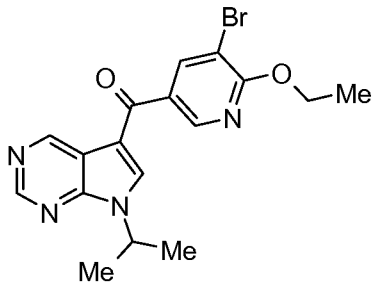
Preparation 240: 5-Bromo-6-ethoxy-N-methoxy-N-methyl-nicotinamide



A mixture of 5-bromo-6-hydroxy-N-methoxy-N-methyl-nicotinamide (**Preparation 239,** 1.80 g, 6.90 mmol), ethyl iodide (2.8 mL, 34.5 mmol) and silver carbonate (3.8 g, 13.8 mmol) in DCM (10 mL) was stirred at room temperature for 40 hours. The reaction mixture was diluted with DCM (50 mL), washed with water (2 x 30 mL), brine (20 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (EtOAc:petroleum ether 2:5) to afford the title compound as a yellow sticky solid in 30% yield, 600 mg.

^{1}H NMR (400 MHz, CDCl3) δ*:* 1.44 (t, 3H), 3.35 (s, 3H), 3.57 (s, 3H), 4.47 (q, 2H), 8.23 (d, 1H), 8.54 (d, 1H).

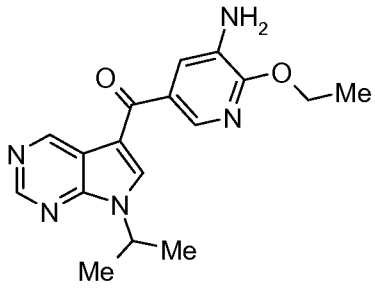
Preparation 241: (5-Bromo-6-ethoxy-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone



A solution of 5-Iodo-7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 93**, 530 mg, 1.85 mmol) in anhydrous diethyl ether (8 mL) was cooled to -78°C under nitrogen and n-BuLi (1 mL of a 2.03M solution in Hexane, 2.03 mmol) was added drop wise over a period of 10 min. Just after the completion of addition of n-BuLi, a solution of 5-Bromo-6-ethoxy-N-methoxy-N-methyl-nicotinamide (**Preparation 240**) in anhydrous diethyl ether (7 mL) was added slowly to the mixture and it was stirred at the same temperature for another 1 hour. The reaction mixture was warmed to room temperature and allowed to stir for another hour before being quenched with sat. aq. NH_4Cl (15 mL). The mixture was extracted with EtOAc (3 x 15 mL), washed with water (20 mL), brine (15 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (EtOAc:petroleum ether 2:10) to afford the title compound as a yellow gum in 49% yield, 350 mg.

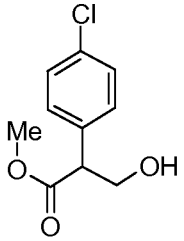
^{1}H NMR (400 MHz, CDCl3) δ*:* 1.50 (t, 3H), 1.60 (d, 6H), 4.55 (q, 2H), 5.15-5.20 (m, 1H), 7.82 (s, 1H), 8.32 (d, 1H), 8.57 (d, 1H), 9.00 (s, 1H), 9.53 (s, 1H).

Preparation 242: (5-Amino-6-ethoxy-pyridin-3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone



Copper(I) oxide (38.6 mg, 0.27 mmol) was added to (5-Bromo-6-ethoxy-pyridin3-yl)-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-methanone (**Preparation 241,** 350 mg, 0.89 mmol) in concentrated ammonia solution (6 mL) and NMP (1 mL). The mixture was heated in a sealed vessel at 130°C for 17 hours. The reaction mixture was cooled to room temperature and diluted with water (10 ml). It was extracted with 20% i-PrOH in DCM (6 x 50 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (MeOH:DCM 5:95) to afford the title compound as a yellow solid in 24% yield, 70 mg. LCMS (system 10): R_t = 2.99 min; m/z 326 $[M+H]^+$.

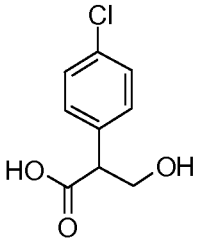
Preparation 243: 2-(4-Chloro-phenyl)-3-hydroxy-propionic acid methyl ester



To a stirred solution of (4-Chloro-phenyl)-acetic acid methyl ester (2 g, 10.8 mmol) in DMSO (22 mL) was added sodium methoxide (29.2 mg, 0.54 mmol) at 0ºC. Paraformaldehyde (342 mg, 11.4 mmol) was then added and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with EtOAc (100 mL), washed with water (3 x 20 mL), brine (20 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of hexane:EtOAc 100:0 to 84:16) to afford the title compound as a colourless gum in 52% yield, 1.2 g.

^{1}H NMR (400 MHz, CDCl3) δ: 2.23 (t, 1H), 3.70 (s, 3H), 3.79-3.83 (m, 2H), 4.05-4.12 (m, 1H), 7.20 (d, 2H), 7.30 (d, 2H); LCMS (system 10): R_t = 3.03 min; m/z 215 $[M+H]^+$.

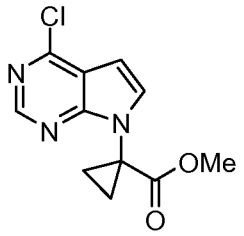
Preparation 244: 2-(4-Chloro-phenyl)-3-hydroxy-propionic acid



To a stirred solution of 2-(4-Chloro-phenyl)-3-hydroxy-propionic acid methyl ester (**Preparation 243**, 500 mg, 2.33 mmol) in THF (7 mL) was added a solution of lithium hydroxide monohydrate (244 mg, 5.82 mmol) in water (2 mL) dropwise at 0ºC and the resulting mixture stirred at room temperature for 1 hour. The reaction mixture was acidified (pH~3) with 2N hydrochloric acid and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a white solid in 90% yield, 420 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 3.58 (dd, 1H), 3.66 (t, 1H), 3.87 (t, 1H), 7.32 (d, 2H), 7.38 (d, 2H), 12.36 (br, 1H).

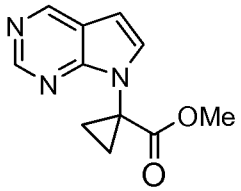
Preparation 245: 1-(4-Chloro-pyrrolo[2,3-d]pyrimidin-7-yl)-cyclopropanecarboxylic acid methyl ester



To a stirred solution of (4,6-dichloro-pyrimidin-5-yl)acetaldehyde (**Preparation 208**, 2 g, 10.5 mmol) and 1-Amino-cyclopropane-carboxylicacidmethylester hydrochloride (1.33 g, 11.6 mmol) in ethanol (30 mL) was added triethylamine (4.4 mL, 31.6 mmol) and the mixture heated in a sealed tube at 100ºC for 10 hours. Acetic acid (1.21 mL, 21.1 mmol) was then added and the mixture heated at 100ºC for additional 16 hours. The reaction mixture was cooled to room temperature and diluted with DCM (200 mL). The organic layer was washed with water (2 x 50 mL), brine (50 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of hexane:EtOAc 100:0 to 90:10) to afford the title compound as a solid in 35% yield, 900 mg.

^{1}H NMR (400 MHz, CDCl3) δ: 1.63-1.66 (m, 2H), 1.96-1.99 (m, 2H), 3.63 (s, 3H), 6.60 (d, 1H), 7.23 (d, 1H), 8.65 (s, 1H); LCMS (system 10): R_t = 2.89 min; m/z 252.1 $[M+H]^+$.

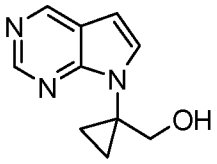
Preparation 246: 1-Pyrrolo[2,3-d]pyrimidin-7-yl-cyclopropanecarboxylic acid methyl ester



A solution of 1-(4-chloro-pyrrolo [2,3-d]pyrimidin-7-yl)-cyclopropanecarboxylic acid methyl ester (**Preparation 245**, 920 mg, 3.65 mmol) in ethanol (20 mL) was degassed with argon for 15 min. Ammonium hydroxide (4 mL) and 10% palladium on charcoal were added and the reaction mixture was stirred at room temperature under hydrogen (balloon pressure) for 5 hours. The reaction mixture was filtered on a celite bed, washed with ethanol (2 x 10 mL) and the filtrate was evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of DCM:methanol 100:0 to 98:2) to afford the title compound as a gum in 59% yield, 470 mg.

^{1}H NMR (400 MHz, CDCl3) δ: 1.63-1.66 (m, 2H), 1.95-1.99 (m, 2H), 3.63 (s, 3H), 6.55 (d, 1H), 7.20 (d, 1H), 8.90 (s, 1H), 8.94 (s, 1H); LCMS (system 10): R_t = 2.22 min; m/z 218.2 $[M+H]^+$.

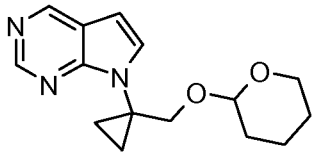
Preparation 247: (1-Pyrrolo[2,3-d]pyrimidin-7-yl-cyclopropyl)-methanol



To a stirred solution of 1-Pyrrolo[2,3-d]pyrimidin-7-yl-cyclopropanecarboxylic acid methyl ester (**Preparation 246**, 610 mg, 2.80 mmol) in ethanol (15 mL) was added sodium borohydride (318.7 mg, 8.42 mmol) and the mixture heated to reflux for 16 hours. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of DCM:methanol 100:0 to 98:2) to afford the title compound as a light yellow solid in 47% yield, 250 mg.

^{1}H NMR (400 MHz, CDCl3) δ: 1.26 (s, 4H), 3.83 (s, 2H), 6.47 (d, 1H), 7.26 (d, 1H), 8.83 (s, 1H), 8.88 (s, 1H); LCMS (system 10): R_t = 1.67 min; m/z 189.9 $[M+H]^+$.

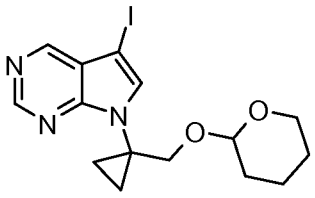
Preparation 248: 7-[1-(Tetrahydro-pyran-2-yloxymethyl)-cyclopropyl]-7H-pyrrolo[2,3-d]pyrimidine



To a stirred solution of (1-Pyrrolo[2,3-d]pyrimidin-7-yl-cyclopropyl)-methanol (**Preparation 247**, 240 mg, 1.27 mmol) in THF (12 mL) was added 3,4-dihydro-2H-pyran (0.46 mL, 5.07 mmol) followed by addition of PTSA (24 mg, 0.13 mmol). The reaction mixture was stirred at 60ºC for 4 hours. The reaction mixture was cooled to room temperature, quenched with saturated aqueous sodium bicarbonate solution (15 mL) and extracted with dichloromethane (3 x 25 mL). The combined organic layer was washed with brine (10 mL), dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of dichloromethane:methanol 100:0 to 98:2) to afford the title compound as a light brown gum in 90% yield, 320 mg.

^{1}H NMR (400 MHz, CDCl3) δ: 1.18-1.26 (m, 4H), 1.31-1.55 (m, 5H), 1.67-1.69 (m, 1H), 3.28-3.31 (m, 1H), 3.44 (t, 1H), 3.68 (d, 1H), 3.88 (d, 1H), 4.46 (s, 1H), 6.45 (d, 1H), 7.33 (d, 1H), 8.88-8.90 (m, 2H); LCMS (system 10): R_t = 2.82 min; m/z 274.6 $[M+H]^+$.

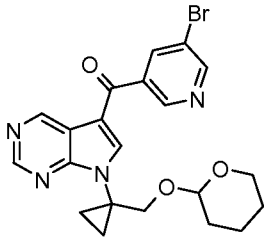
Preparation 249: 5-Iodo-7-[1-(tetrahydro-pyran-2-yloxymethyl)-cyclopropyl]-7H-pyrrolo[2,3-d]pyrimidine



To a stirred solution of 7-[1-(Tetrahydro-pyran-2-yloxymethyl)-cyclopropyl]-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 248**, 390 mg, 1.43 mmol) in DMF (8 mL) was added N-iodosuccinimide (481.5 mg, 2.14 mmol) and stirred at room temperature for 4 hours. The reaction mixture was quenched with water (8 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with water (5 x 15 mL), brine (10 mL), dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of dichloromethane:methanol 100:0 to 99:1) to afford the title compound as a solid in 79% yield, 450 mg.

^{1}H NMR (400 MHz, CDCl3) δ: 1.18-1.70 (m, 10H), 3.28-3.32 (m, 1H), 3.42 (t, 1H), 3.65 (d, 1H), 3.87 (d, 1H), 4.47 (s, 1H), 7.44 (s, 1H), 8.70 (s, 1H), 8.90 (s, 1H); LCMS (system 10): R_t = 3.28 min; m/z 400.2 $[M+H]^+$.

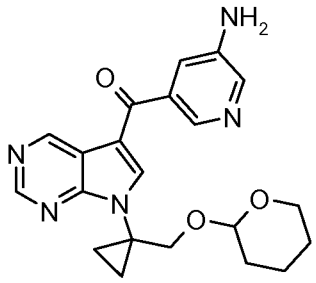
Preparation 250: (5-Bromo-pyridin-3-yl)-{7-[1-(tetrahydro-pyran-2-yloxymethyl)-cyclopropyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone



To a stirred solution of 5-Iodo-7-[1-(tetrahydro-pyran-2-yloxymethyl)-cyclopropyl]-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 249**, 450 mg, 1.13 mmol) in diethyl ether (6 mL) was added n-butyl lithium (2M in hexane, 0.62 mL, 1.24 mmol) drop wise at -70°C. Then a solution of 5-Bromo-N-methoxy-N-methyl-nicotinamide (304 mg, 1.24 mmol) in diethyl ether (2.5 mL) was added drop wise at -70°C and stirred at same temperature for another 30 minutes. The reaction was allowed to warm to room temperature slowly. The reaction was quenched with saturated aqueous ammonium chloride solution (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with water (20 mL), brine (20 mL), dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of dichloromethane:methanol 100:0 to 98:2) to afford the title compound as a light brown sticky solid in 35% yield, 250 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.25-1.57 (m, 10H), 3.17-3.28 (m, 2H), 3.64 (d, 1H), 3.95 (d, 1H), 4.57 (s, 1H), 8.36 (s, 1H), 8.40 (s, 1H), 8.96 (s, 1H), 8.99 (s, 1H), 9.02 (s, 1H), 9.45 (s, 1H); LCMS (system 10): R_t = 3.17 min; m/z 456.8, 459 $[M+H]^+$.

Preparation 251: (5-Amino-pyridin-3-yl)-{7-[1-(tetrahydro-pyran-2-yloxymethyl)-cyclopropyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone

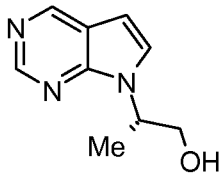


To a stirred solution of (5-Bromo-pyridin-3-yl)-{7-[1-(tetrahydro-pyran-2-yloxymethyl)-cyclopropyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone (**Preparation 250**, 200 mg, 0.45 mmol) in 1-Methyl-pyrrolidin-2-one (1.5 mL) was added ammonium hydroxide (15 mL). Then copper (I) oxide (3 mg, 0.02 mmol) was added and the reaction mixture was heated in a sealed tube at 130°C for 16 hours. The reaction mixture was cooled to room temperature, extracted with 10% methanol in dichloromethane (5 x 25 mL). The combined organic layer was dried over sodium sulphate and evaporated *in vacuo*. The crude material was

purified by column chromatography on silica gel (gradient of dichloromethane:methanol 100:0 to 96:4) to afford the title compound as a white sticky solid in 45% yield, 80 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.17-1.53 (m, 10H), 3.17-3.28 (m, 2H), 3.63 (d, 1H), 3.94 (d, 1H), 4.55 (s, 1H), 5.64 (s, 2H), 7.27 (s, 1H), 8.18-8.20 (m, 3H), 8.99 (s, 1H), 9.42 (s, 1H); LCMS (system 10): R_t = 2.59 min; m/z 394.1 $[M+H]^+$.

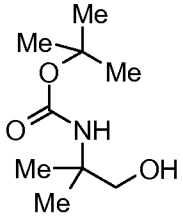
Preparation 252: (S)-2-Pyrrolo[2,3-d]pyrimidin-7-yl-propan-1-ol



The title compound was prepared according to the method described for **Preparation 8** using (2S)-2-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)propan-1-ol (**Preparation 4**) to afford the title compound as a white solid in 100% yield, 2.8 g.

^{1}H NMR (400 MHz, DMSO-d6) δ: 1.43 (d, 3H), 3.68-3.79 (m, 2H), 4.89-4.94 (m, 1H), 4.97 (t, 1H), 6.61 (d, 1H), 7.71 (d, 1H), 8.75 (s, 1H), 8.97 (s, 1H).

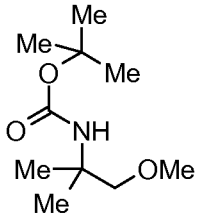
Preparation 253: (2-Hydroxy-1,1-dimethyl-ethyl)-carbamic acid tert-butyl ester



To a mixture of 2-Amino-2-methyl-propan-1-ol (2 g, 22.43 mmol) and triethyl amine (3.12 mL, 22.43 mmol) in THF was added boc-anhydride (4.89 g, 22.43 mmol) slowly at 0°C and was stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate, washed with water, brine, dried over sodium sulphate and evaporated *in vacuo* to afford the title compound as colourless oil in 92% yield, 3.9 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (s, 6H), 1.42 (s, 9H), 3.56-3.58 (d, 2H), 4.00 (brs, 1H), 4.62 (brs, 1H).

Preparation 254: (2-Methoxy-1,1-dimethyl-ethyl)-carbamic acid tert-butyl ester

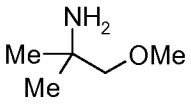


KOH (3.47 g, 61.82 mmol) was added to a solution of (2-Hydroxy-1,1-dimethyl-ethyl)-carbamic acid tert-butyl ester (**Preparation 253**, 3.9 g, 20.6 mmol) in 1,4-dioxane (30 mL) followed by the slow addition of dimethyl sulphate at room temperature. The mixture was further allowed to stir at room temperature for 48 hours. Reaction mass was filtered through a short pad of celite, washed with DCM (3 x 50 mL). The

combined filtrate was washed with water (2 x 50 mL), brine (30 mL), dried over sodium sulphate and evaporated *in vacuo* to afford the title compound as yellow oil in 88% yield, 3.7 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (s, 6H), 1.41 (s, 9H), 3.29 (s, 2H), 3.35 (s, 3H), 4.73 (brs, 1H).

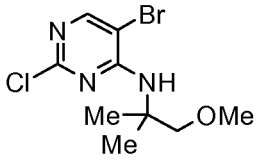
Preparation 255: 2-Methoxy-1,1-dimethyl-ethylamine



TFA (5.8 mL, 78.7 mmol) was added slowly to a DCM (25 mL) solution of (2-Methoxy-1,1-dimethyl-ethyl)-carbamic acid tert-butyl ester (**Preparation 254,** 3.2 g, 15.74 mmol) at 0°C. The mixture was allowed to stir at room temperature for another 3 hours and then all the volatiles were removed *in vacuo*. The residue was treated with aqueous saturated $NaHCO_3$ solution (50 mL) and extracted with a mixture of IPA/DCM (1:4) (4 x 50 mL). The combined organics was dried over sodium sulphate and evaporated to dryness *in vacuo* to afford the title compound as light brown oil in 100% yield, 1.6 g.

1H NMR (400 MHz, CDCl3) δ: 1.32 (s, 6H), 3.30 (s, 2H), 3.35 (s, 3H), 7.80 (brs, 2H).

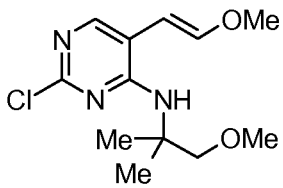
Preparation 256: (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-methoxy-1,1-dimethyl-ethyl)-amine



Triethyl amine (73.1 mL, 526.6 mmol) was added slowly to a solution of 5-Bromo-2,4-dichloro-pyrimidine (40 g, 175.5 mmol) in acetonitrile (400 mL) at 0°C and then 2-Methoxy-1,1-dimethyl-ethylamine (**Preparation 255**, 23.4 g, 263.3 mmol) was added to the mixture portion wise. The reaction mixture was stirred for another 16 hours at room temperature. TLC showed the presence of unreacted starting pyrimidine, but the reaction was not continued further. All the volatiles were removed *in vacuo* and the residue was taken in ethyl acetate, washed with water, brine, dried over sodium sulphate and evaporated to dryness *in vacuo*. The crude material was purified by column chromatography on silica gel (100-200 mesh, gradient of ethyl acetate:hexane 1:9 to 2:4) to afford the title compound as white solid in 23% yield (10 g of starting pyrimidine was recovered), 12 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.40 (s, 6H), 3.32 (s, 3H), 3.48 (s, 2H), 6.19 (s, 1H), 8.29 (s, 1H); LCMS (system 10): R_t = 3.56 min; m/z 294, 296 $[M+H]^+$.

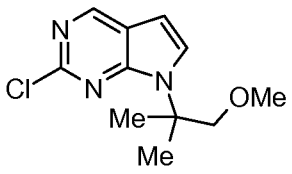
Preparation 257: [2-Chloro-5-((E)-2-ethoxy-vinyl)-pyrimidin-4-yl]-(2-methoxy-1,1-dimethyl-ethyl)-amine



The title compound was prepared according to the method described for **Preparation 61** using (5-Bromo-2-chloro-pyrimidin-4-yl)-(2-methoxy-1,1-dimethyl-ethyl)-amine (**Preparation 256**), catechol borane and ethoxyacetylene (40% in hexane) to afford the title compound as light brown gum in 44% yield, 2.6 g.

1H NMR (400 MHz, DMSO-D6) δ: 1.25 (t, 3H), 1.37 (s, 6H), 3.26 (s, 3H), 3.56 (s, 2H), 3.92 (q, 2 H), 5.74 (d, 1H), 6.12 (s, 1H), 6.94 (d, 1H), 7.88 (s, 1H); LCMS (system 10): R_t = 3.65 min; m/z 286.3 $[M+H]^+$.

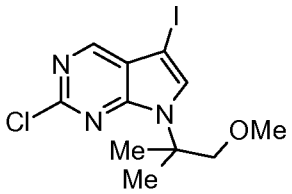
Preparation 258: 2-Chloro-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 62** using [2-Chloro-5-((E)-2-ethoxy-vinyl)-pyrimidin-4-yl]-(2-methoxy-1,1-dimethyl-ethyl)-amine (**Preparation 257**) to afford the title compound as off white solid in 91% yield, 2g.

^{1}H NMR (400 MHz, DMSO-D6) δ 1.68 (s, 6H), 3.17 (s, 3H), 3.85 (s, 2H), 6.62 (d, 1H), 7.63 (d, 1H), 8.90 (s, 1H); LCMS (system 10): R_t = 3.29 min; m/z 240 $[M+H]^+$.

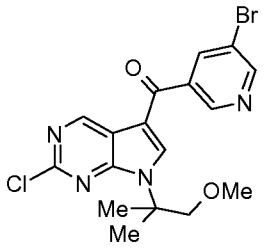
Preparation 259: 2-Chloro-5-iodo-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 63** using 2-Chloro-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 258**) to afford the title compound as yellowish solid in 75% yield, 2.3 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.67 (s, 6H), 3.17 (s, 3H), 3.83 (s, 2H), 7.81 (s, 1H), 8.64 (s, 1H); LCMS (system 10): R_t = 3.65 min; m/z 365.8 $[M+H]^+$.

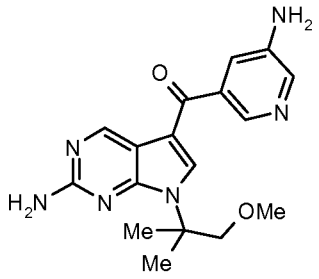
Preparation 260: (5-Bromo-pyridin-3-yl)-[2-chloro-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone



The title compound was prepared according to the method described for **Preparation 64** using 2-Chloro-5-iodo-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 259**) and 5-Bromo-N-methoxy-N-methyl-nicotinamide to afford the title compound as yellow gum in 34% yield, 900 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.73 (s, 6H), 3.21 (s, 3H), 3.90 (s, 2H), 8.22 (s, 1H), 8.42 (t, 1H), 8.98 (t, 2H), 9.35 (s, 1H).

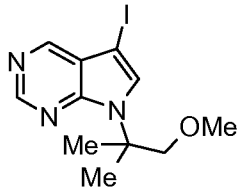
Preparation 261: [2-Amino-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-(5-amino-pyridin-3-yl)-methanone



The title compound was prepared according to the method described for **Preparation 65** using (5-Bromo-pyridin-3-yl)-[2-chloro-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone (**Preparation 260**) to afford the title compound as yellow solid in 41% yield, 300 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.68 (s, 6H), 3.19 (s, 3H), 3.89 (s, 2H), 5.61 (s, 2H), 6.54 (s, 2H), 7.23 (s, 1H), 7.55 (s, 1H), 8.11 (dd, 2H), 8.93 (s, 1H); LCMS (system 10): R_t = 2.40 min; m/z 341.2 $[M+H]^+$.

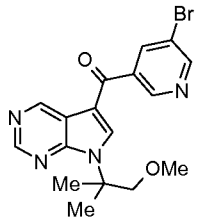
Preparation 262: 5-Iodo-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine



An anhydrous THF (100 mL) solution of 2-(5-Iodo-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methyl-propan-1-ol (**Preparation 22**) (32 g, 100.91 mmol) was added slowly to a suspension of NaH (60% in paraffin oil, 2.98 g, 121.13 mmol) in anhydrous THF (200 mL) at 0°C under nitrogen. The mixture was warmed to room temperature and stirred for another 30 minutes and again cooled to 0°C and methyl iodide (19 mL, 302.82 mmol) was added drop wise. The reaction mixture was stirred at room temperature for 2 hours,quenched with aqueous saturated ammonium chloride, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and evaporated to dryness *in vacuo*. The crude material was purified by column chromatography on silica (100-200 mesh, gradient of hexane:EtOAc 100:0 to 70:30) to afford the title compound as a yellow sticky solid in 22% yield, 7.5 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.70 (s, 6H), 3.15 (s, 3H), 3.89 (s, 2H), 7.77 (s, 1H), 8.70 (s, 1H), 8.82 (s, 1H); LCMS (system 10): R_t = 3.42 min; m/z 331.6 $[M+H]^+$.

Preparation 263: (5-Bromo-pyridin-3-yl)-[7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone



The title compound was prepared according to the method described for **Preparation 64** using 5-Iodo-7-(2-methoxy-1,1-dimethyl-ethyl)-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 262**) and 5-Bromo-N-methoxy-N-methyl-nicotinamide to afford the title compound as light brown gum in 51% yield, 3g.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.76 (s, 6H), 3.19 (s, 3H), 3.96 (s, 2H), 8.17 (s, 1H), 8.42 (t, 1H), 8.98 (brs, 2H), 9.00 (s, 1H), 9.47 (s, 1H); LCMS (system 10): R_t = 3.13 min; m/z 388.6, 390.6 $[M+H]^+$.

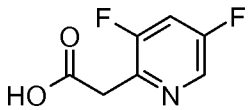
Preparation 264: 2-(3,5-Difluoro-pyridin-2-yl)-malonic acid diethyl ester



To a stirred solution of 2,3,5-trifluoro-pyridine (2 g, 15.02 mmol) in dimethyl sulfoxide (20 mL) was added diethyl malonate (4.60 g, 28.72 mmol). Then cesium carbonate (9.35 g, 28.72 mmol) was added and the reaction mixture was heated to 110ºC for 16 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (100 mL). The organic layer was washed with water (2 x 25 mL), brine (25 mL), dried over sodium sulphate and evaporated *in vacuo* to afford the title compound as oil in 85% yield, 3.5 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25-1.30 (m, 6 H), 4.20-4.29 (m, 4 H), 4.88 (s, 1 H), 7.77-7.81 (m, 1 H), 8.01 (s, 1 H).

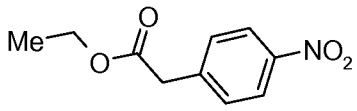
Preparation 265: (3,5-Difluoro-pyridin-2-yl)-acetic acid



To a stirred solution of 2-(3,5-difluoro-pyridin-2-yl)-malonic acid diethyl ester (1 g, 3.56 mmol) (**Preparation 264**) in THF (15 mL) was added a solution of lithium hydroxide monohydrate (462 mg, 10.4 mmol) in water (4 mL) dropwise at 0ºC and the mixture heated to reflux for 2 hours. The reaction mixture was cooled to room temperature, acidified (pH ~3) with 2N hydrochloric acid and extracted with 20% isopropanol-dichloromethane (5 x 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of DCM: MeOH 100:0 to 95:5) to afford the title compound as a solid in 53% yield, 336 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ 3.32 (s, 2H), 7.74-7.79 (m, 1H), 7.99 (t, 1H); LCMS (system 10): R_t = 0.65 min; m/z 174 $[M+H]^+$.

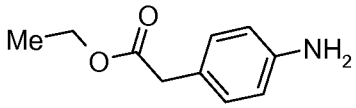
Preparation 266: (4-Nitro-phenyl)-acetic acid ethyl ester



To a stirred solution of (4-nitro-phenyl)-acetic acid (3 g, 16.4 mmol) in ethanol (30 mL) was added sulphuric acid (1 mL) and the reaction mixture was heated to reflux for 16 hours. The reaction mixture was neutralized with 2N aq. NaOH solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a light yellow oil in 98% yield, 3.4 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (t, 3H), 3.71 (s, 2H), 4.16 (q, 2H), 7.45 (d, 2H), 8.18 (d, 2H).

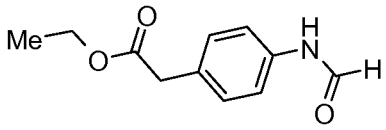
Preparation 267: (4-Amino-phenyl)-acetic acid ethyl ester



A solution of (4-nitro-phenyl)-acetic acid ethyl ester (**Preparation 266**, 3.4 g, 16.1 mmol) in methanol (100 mL) was degassed with argon for 15 min, treated with 10% palladium on charcoal (700 mg), and then stirred at room temperature under hydrogen (balloon pressure) for 16 hours. The reaction mixture was filtered through celite, washed with methanol (2 x 20 mL) and the filtrate was evaporated *in vacuo* to afford the title compound as an oil in 96% yield, 2.8 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, 3H), 3.47 (s, 2H), 3.60 (br s, 2H), 4.11 (q, 2 H), 6.63 (d, 2H), 7.05 (d, 2H).

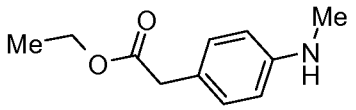
Preparation 268: (4-Formylamino-phenyl)-acetic acid ethyl ester



A mixture of acetic anhydride (0.33 mL, 3.57 mmol) and formic acid (0.17 mL, 4.46 mmol) was heated at 60ºC for 2 hours. The reaction mixture was cooled to 0ºC, a solution of (4-amino-phenyl)-acetic acid ethyl ester (**Preparation 267**, 500 mg, 2.79 mmol) in THF (10 mL) was added slowly to the reaction mixture and the reaction was allowed to stir at room temperature for 16 hours. The reaction mixture was neutralized with sat. aq. Na_2CO_3 solution and extracted with diethyl ether (2 x 25 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of DCM:MeOH 100:0 to 98:2) to afford the title compound as an oil in 93% yield, 500 mg.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.17 (t, 3H), 3.59 (s, 2H), 4.05 (q, 2H), 7.20 (d, 2H), 7.52 (d, 2H), 8.25 (d, 1H), 10.15 (s, 1H).

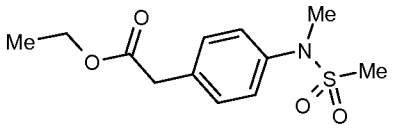
Preparation 269: (4-Methylamino-phenyl)-acetic acid ethyl ester



To a stirred solution of (4-formylamino-phenyl)-acetic acid ethyl ester (**Preparation 268**, 500 mg, 2.41 mmol) in THF (10 mL) was added borane-dimethyl sulphide complex (0.3 mL, 3.13 mmol) at 0ºC and the mixture stirred at room temperature for 1 hour. The reaction mixture was quenched with MeOH (5 mL) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of hexane:EtOAc 100:0 to 75:25) to afford the title compound as an oil in 91% yield, 460 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, 3H), 2.81 (s, 3H), 3.48 (s, 2H), 3.66 (br s, 1 H), 4.11 (q, 2H), 6.56 (d, 2H), 7.09 (d, 2 H).

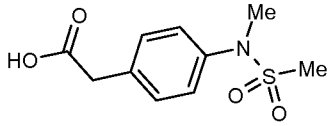
Preparation 270: [4-(Methanesulfonyl-methyl-amino)-phenyl]-acetic acid ethyl ester



To a stirred solution of (4-methylamino-phenyl)-acetic acid ethyl ester (**Preparation 269**, 418 mg, 2.16 mmol) in pyridine (4 mL) was added methanesulfonyl chloride (0.25 mL, 3.24 mmol) and the mixture stirred at room temperature for 3 hours. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as a gum in 78% yield, 460 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (t, 3H), 2.82 (s, 3H), 3.30 (s, 3H), 3.59 (s, 2H), 4.14 (q, 2H), 7.28-7.33 (m, 4H).

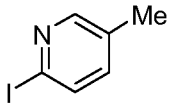
Preparation 271: [4-(Methanesulfonyl-methyl-amino)-phenyl]-acetic acid



The title compound was prepared according to the method described for **Preparation 265** using [4-(methanesulfonyl-methyl-amino)-phenyl]-acetic acid ethyl ester (**Preparation 270**) to afford the title compound as a solid in 85% yield, 350 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 2.92 (s, 3H), 3.21 (s, 3H), 3.55 (s, 2H), 7.28 (d, 2H), 7.33 (d, 2H); LCMS (system 10): R_t = 1.05 min; m/z 244 $[M+H]^+$.

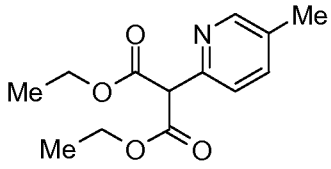
Preparation 272: 2-Iodo-5-methyl-pyridine



To a stirred solution of 2-bromo-5-methyl-pyridine (2 g, 11.6 mmol) in acetonitrile (25 mL) was added sodium iodide (6.97 g, 46.5 mmol) and the mixture heated to reflux. Acetyl chloride (1.24 mL, 17.44 mmol) was added dropwise under reflux conditions and the reaction mixture was heated to reflux for 16 hours. The reaction mixture was cooled to room temperature, quenched with sat. aq. Na_2CO_3 solution (15 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound as an oil in 55% yield, 1.4 g.

LCMS (system 10): R_t = 3.10 min; m/z 220 $[M+H]^+$.

Preparation 273: 2-(5-Methyl-pyridin-2-yl)-malonic acid diethyl ester

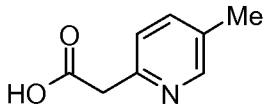


To a stirred solution of 2-Iodo-5-methyl-pyridine (**Preparation 272**, 1 g, 4.57 mmol) and diethyl malonate (2.08 mL, 13.70 mmol) in anhydrous dioxane (12 mL) was added cesium carbonate (4.46 gm, 13.7 mmol)

and the solution was degassed with argon for 30 min. CuI (174 mg, 0.91 mmol) and picolinic acid (225 mg, 1.83 mmol) were added and the resultant mixture was heated in a sealed tube at 100°C for 16 hours. The reaction mixture was cooled to room temperature, quenched with water (25 mL) and extracted with EtOAc (3 x 25 ml). The combined organic layers were washed with water (2 x 10 mL) and brine (10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (gradient of hexane:EtOAc 100:0 to 90:10) to afford the title compound as an oil in 23% yield, 300 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.15-1.18 (m, 6H), 2.29 (s, 3H), 4.12-4.17 (m, 4H), 5.01 (s, 1H), 7.30 (d, 1H), 7.62 (dd, 1H), 8.34 (s, 1H).

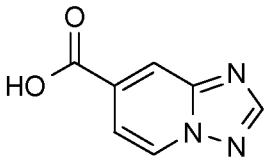
Preparation 274: (5-Methyl-pyridin-2-yl)-acetic acid



The title compound was prepared according to the method described for **Preparation 265** using 2-(5-methyl-pyridin-2-yl)-malonic acid diethyl ester (**Preparation 273**) to afford the title compound as a solid in 83% yield, 100 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 2.26 (s, 3H), 3.64 (s, 2H), 7.21 (d, 1H), 7.53 (d, 1H), 8.29 (s, 1H); LCMS (system 10): R_t = 0.73 min; m/z 152 $[M+H]^+$.

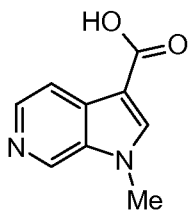
Preparation 275: [1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid



To a solution of methyl 2-aminoisonicotinate (28.8 g, 191 mmol) in DMF (97.5 mL) was added DMF-DMA (70.6 mL, 496 mmol) and the mixture heated to 130 °C for 12 hours. The mixture was then concentrated to give a residue. To the residue was added MeOH (381 mL), followed by NH_2OHSO_4 (31.9 g, 248 mmol) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated to give methyl [1,2,4]triazolo[1,5-a]pyridine-7-carboxylate in 18% yield, 6g. To a solution of methyl [1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (3 g, 16 mmol) in methanol was added 1M aq. LiOH (70 mL) and the resulting mixture stirred for 10 hours at room temperature. The pH was adjusted to 5-6 using aq. HCl and the whole mixture extracted with EtOAc (30 mL×3).The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a white solid in 38% yield, 1.05 g

1H NMR (400 MHz, DMSO-d6) δ: 7.56-7.58 (m, 1H), 8.32 (m, 1H), 8.66 (m, 1H), 9.04-9.06 (m, 1H), 13.5-14.0 (s, 1H).

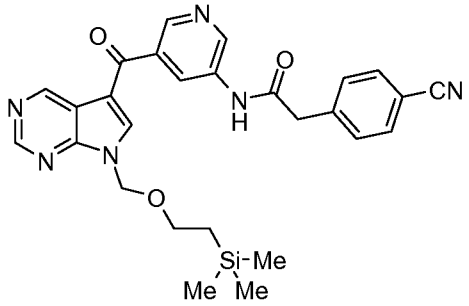
Preparation 276: 1-methyl-1H-pyrrolo[2,3-c]pyridine-3-carboxylic acid



1-methyl-1H-pyrrolo[2,3-c]pyridine-3-carbaldehyde (WO 05066132) (6.5 g, 40.6 mmol) was dissolved in a mixture of THF (120 mL) and tert-butyl alcohol (40 mL) under nitrogen. 2-Methyl-2-butene (120 mL of a 2M solution in THF, 46 mmol) was added followed by a solution of $NaClO_2$ (11.0 g, 122 mmol) and NaH_2PO_4 (21.9 g, 183 mmol) in water (30 mL). The reaction mixture was stirred at room temperature overnight under nitrogen. The reaction mixture was concentrated *in vacuo* to remove organic solvents, and the residue was filtered. The precipitate contained the title compound as a white solid in 57% yield, 4.1 g.

1H NMR (400MHz, DMSO-d6) δ: 3.96 (S, 3H), 7.87-7.89 (d, 1H), 8.23 (s, 1H), 8.28 (d, 1H), 8.91 (s, 1H), 12.3 (s, 1H).

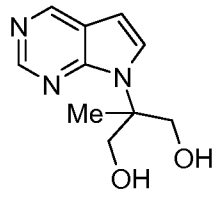
Preparation 277: 2-(4-Cyano-phenyl)-N-{5-[7-(2-trimethylsilanyl-ethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl]-pyridin-3-yl}-acetamide



The title compound was prepared according to the method described for **Example 1** using (5-Amino-pyridin-3-yl)-[7-(2-trimethylsilanyl-ethoxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone (**Preparation 103**) and 4-cyanophenylacetic acid to afford the title compound as an off-white solid in 71% yield, 235 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: -0.11 (s, 9H), 0.82 (t, 2H), 3.59 (t, 2H), 3.87 (s, 2H), 5.70 (s, 2H), 7.55 (d, 2H), 7.82 (d, 2H), 8.47 (s, 1H), 8.61 (s, 1H), 8.73 (s, 1H), 8.98 (s, 1H), 9.04 (s, 1H), 9.48 (s, 1H), 10.75 (s, 1H); LCMS (System 10): R_t = 3.25 min; m/z 513 $[M+H]^+$.

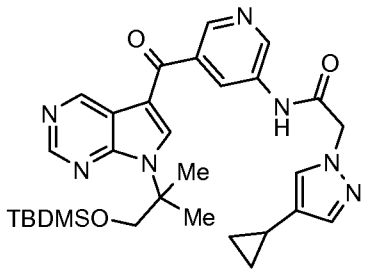
Preparation 278: 2-Methyl-2-pyrrolo[2,3-d]pyrimidin-7-yl-propane-1,3-diol



The title compound was prepared according to the method described for **Preparation 246** using 2-(4-Chloro-pyrrolo[2,3-d]pyrimidin-7-yl)-2-methyl-propane-1,3-diol (**Preparation 217**) to afford the title compound as an off-white solid in 93% yield, 800 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.65 (s, 3H), 3.87-3.91 (m, 2H), 4.10-4.14 (m, 2H), 4.94 (t, 2H), 6.55 (d, 1H), 7.63 (d, 1H), 8.72 (s, 1H), 8.95 (s, 1H).

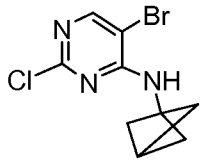
Preparation 279: N-(5-{7-[2-(tert-Butyl-dimethyl-silanyloxy)-1,1-dimethyl-ethyl]-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl}-pyridin-3-yl)-2-(4-cyclopropyl-pyrazol-1-yl)-acetamide



The title compound was prepared according to the method described for **Example 1** using (5-Amino-pyridin-3-yl)-{7-[2-(tert-butyl-dimethyl-silanyloxy)-1,1-dimethyl-ethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}-methanone (**Preparation 38**) and (4-Cyclopropyl-1*H*-pyrazol-1-yl)acetic acid (**Preparation 88**) to afford the title compound as an an off-white solid in 41% yield, 55 mg.

^{1}H NMR (400 MHz, DMSO-D6) δ*:* -0.24 (s, 6H), 0.46 (m, 2H), 0.60 (s, 9H), 0.79 (m, 2H), 1.67 (m, 1H), 1.75 (s, 6H), 4.11 (s, 2H), 4.98 (s, 2H), 7.26 (s, 1H), 7.52 (s, 1H), 8.16 (s, 1H), 8.46 (s, 1H), 8.71 (d, 1H), 8.91 (d, 1H), 8.99 (s, 1H), 9.47 (s, 1H), 10.75 (s, 1H); LCMS (System 10): R_t = 3.78 min; m/z 574 $[M+H]^+$.

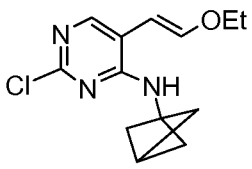
Preparation 280: Bicyclo[1.1.1]pent-1-yl-(5-bromo-2-chloro-pyrimidin-4-yl)-amine



To a solution of 5-Bromo-2,4-dichloro-pyrimidine (6 g, 26.3 mmol) and bicyclo[1.1.1]pent-1-ylamine (4.7 g, 39.5 mmol) in acetonitrile (60 mL), was added TEA (16.5 mL, 118 mmol), and the mixture was stirred at 25°C for 18 hours. The volatiles were removed *in vacuo* and the residue partitioned between water and EtOAc. The organic phase was dried (Na_2SO_4) and evaporated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:Hexane 1:99) afforded the title compound as a white solid in 82% yield, 4.8 g.

^{1}H NMR (400 MHz, DMSO-D6) δ*:* 2.10 (d, 6H), 2.48-2.50 (m, 1H), 8.26 (d, 2H); LCMS (System 10) : R_t = 3.64 min; m/z 276 $[M+H]^+$.

Preparation 281: Bicyclo[1.1.1]pent-1-yl-[2-chloro-5-((Z)-2-ethoxy-vinyl)-pyrimidin-4-yl]-amine

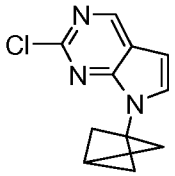


To a stirred solution of Bicyclo[1.1.1]pent-1-yl-(5-bromo-2-chloro-pyrimidin-4-yl)-amine (**Preparation 280,** 2 g, 7.29 mmol) in dry toluene (70 mL) was added (Z)-1-ethoxy-2-(tributylstannyl)ethene (2.7 mL, 8.03 mmol). The reaction mixture was purged with N_2 for 20 min and then $Pd(PPh_3)_4$ (421 mg, 0.36 mmol) was added, followed by degassing for another 20 min and heating to 110° C under N_2 overnight. The reaction was cooled to room temperature, quenched with a 2M solution of KF and filtered through a pad of Celite. The filtrate was partitioned between water (50 mL) and EtOAc (200 mL). The organic phase was washed with brine (2 x 25 mL), dried (Na_2SO_4) and evaporated *in vacuo*.The crude residue was purified by column

chromatography on silica gel (EtOAc: Hexane 18: 82) to afford the title compound as a pale green solid in 77% yield, 1.5 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 1.24 (t, 3H), 2.08 (d, 6H), 2.47 (m, 1H), 3.99 (q, 2H), 5.17 (d, 1H), 6.55 (d, 1H), 7.90 (s, 1H), 8.39 (s, 1H); LCMS (System 10): R_t = 3.54 min; m/z 266 $[M+H]^+$.

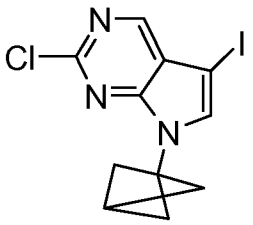
Preparation 282: 7-Bicyclo[1.1.1]pent-1-yl-2-chloro-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 62** using bicyclo[1.1.1]pent-1-yl-[2-chloro-5-((Z)-2-ethoxy-vinyl)-pyrimidin-4-yl]-amine (**Preparation 281**) to afford the title compound as an off-white solid in 89% yield, 1.4 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 2.41 (d, 6H), 2.69 (m, 1H), 6.67 (d, 1H), 7.61 (d, 1H), 8.92 (s, 1H); LCMS (System 10): R_t = 3.45 min; m/z 220 $[M+H]^+$.

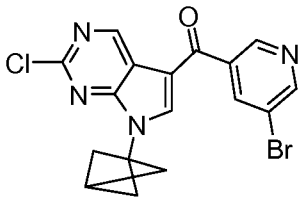
Preparation 283: 7-Bicyclo[1.1.1]pent-1-yl-2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine



The title compound was prepared according to the method described for **Preparation 63** using 7-bicyclo[1.1.1]pent-1-yl-2-chloro-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 282**) to afford the title compound as a brown solid in 72% yield, 1.3g .

^{1}H NMR (400 MHz, DMSO-D6) δ: 2.40 (d, 6H), 2.68 (m, 1H), 7.90 (s, 1H), 8.67 (s, 1H); LCMS (System 10): R_t = 3.89 min; m/z 346 $[M+H]^+$.

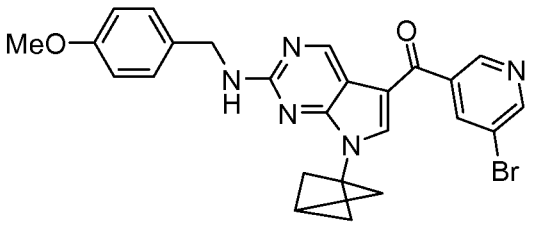
Preparation 284: (7-Bicyclo[1.1.1]pent-1-yl-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-(5-bromo-pyridin-3-yl)-methanone



The title compound was prepared according to the method described for **Preparation 64** using 7-bicyclo[1.1.1]pent-1-yl-2-chloro-5-iodo-7H-pyrrolo[2,3-d]pyrimidine (**Preparation 283**) to afford the title compound as an off-white solid in 58% yield, 1.1 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 2.47 (d, 6H), 2.72 (m, 1H), 8.40-8.42 (m, 2H), 8.99-9.00 (m, 2H), 9.33 (s, 1H); LCMS (System 10): R_t = 3.73 min; m/z 405 $[M+H]^+$.

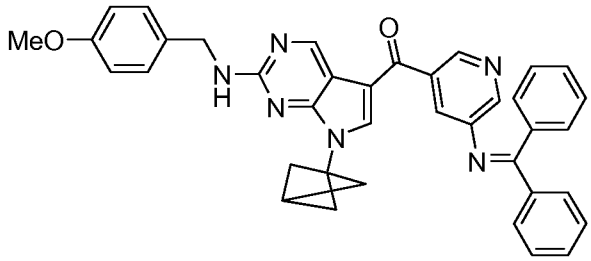
Preparation 285: [7-Bicyclo[1.1.1]pent-1-yl-2-(4-methoxy-benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-(5-bromo-pyridin-3-yl)-methanone



To a solution of (7-Bicyclo[1.1.1]pent-1-yl-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-(5-bromo-pyridin-3-yl)-methanone (**Preparation 284**, 1.1 g, 2.72 mmol) and 4-methoxy benzyl amine (1.06 mL, 8.16 mmol) in dioxane (40 mL), DIPEA (1.7 mL, 10.8 mmol) was added and mixture was heated at 110°C under microwave irradiation for 6 hours. The volatiles were removed *in vacuo* and the residue was partitioned between water (50 mL) ethyl acetate (150 mL). Organic phase was dried over sodium sulphate, evaporated *in vacuo* and purified by column chromatography on silica gel (gradient of EA: Hexane 25: 75) to afford the title compound as off white solid in 84 % yield, 1.15 g.

^{1}H NMR (400 MHz, DMSO-D6) δ: 2.35 (d, 6H), 2.64 (m, 1H), 3.70 (s, 3H), 4.45 (d, 2H), 6.85 (d, 2H), 7.27 (d, 2H), 7.75 (s, 2H), 8.32 (m, 1H), 8.91-8.94 (m, 2H); LCMS (System 10): R_t = 3.81 min; m/z 504.2 $[M+H]^+$.

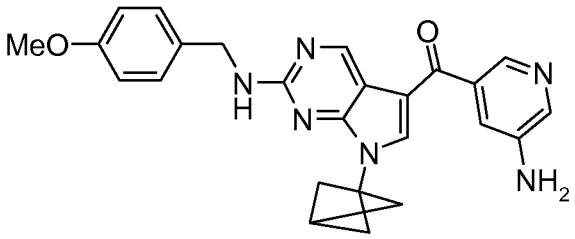
Preparation 286: [5-(Benzhydrylidene-amino)-pyridin-3-yl]-[7-bicyclo[1.1.1]pent-1-yl-2-(4-methoxy-benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone



To a stirred solution of [7-Bicyclo[1.1.1]pent-1-yl-2-(4-methoxy-benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-(5-bromo-pyridin-3-yl)-methanone (**Preparation 285**, 1.18 g, 2 mmol) and benzophenoneimine (0.50 mL, 3 mmol) in dry toluene (50 mL), cesium carbonate (3.2 g, 10 mmol) was added and the reaction mixture was purged under N_2 for 20 min and then $Pd(OAc)_2$ (45 mg, 0.2 mmol) and BINAP (125 mg, 0.2 mmol) were added followed by degassing for another 10 min and refluxing overnight. The reaction mass was cooled to room temperature and filtered through a pad of Celite. The filtrate was partitioned between water (25 mL) and EtOAc (100 mL). The organic phase was washed with brine (10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by column chromatography on silica gel (EtOAc:Hexane 25:75) afforded the title compound as a yellow solid in 85 % yield, 1.1g .

^{1}H NMR (400 MHz, DMSO-D6) δ: 2.36 (d, 6H), 2.65 (m, 1H), 3.70 (s, 3H), 4.44 (d, 2H), 6.84 (d, 2H), 7.24-7.29 (m, 4H), 7.36-7.37 (m, 3H), 7.50-7.52 (m, 4H), 7.58 (m, 1H), 7.70-7.72 (m, 3H), 8.15 (d, 1H), 8.48 (d, 1H), 8.89 (s, 1H); LCMS (System 9): R_t = 4.02 min; m/z 605 $[M+H]^+$.

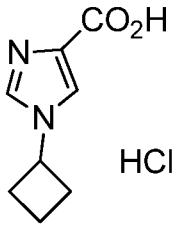
Preparation 287: (5-Amino-pyridin-3-yl)-[7-bicyclo[1.1.1]pent-1-yl-2-(4-methoxy-benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone



To a solution of [5-(Benzhydrylidene-amino)-pyridin-3-yl]-[7-bicyclo[1.1.1]pent-1-yl-2-(4-methoxy-benzylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-methanone (**Preparation 286**, 475 mg, 0.78 mmol) in THF (15 mL), citric acid (15 mL of a 1N aq. solution) was added at room temperature and the reaction mixture stirred for 2 hours. The reaction was then quenched with sat. aq. Na_2CO_3 solution and extracted with EtOAc (2 x 25 mL). The combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo*. Purification by column chromatography on neutral alumina (Methanol:DCM 3: 97) to afford the title compound as a pale yellow solid in 92 % yield, 320 mg.

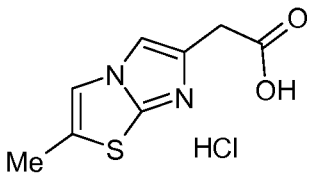
^{1}H NMR (400 MHz, DMSO-D6) δ: 2.36 (d, 6H), 2.64 (m, 1H), 3.70 (s, 3H), 4.45 (d, 2H), 5.59 (s, 2H), 6.84 (d, 2H), 7.22 (m, 1H), 7.28 (d, 2H), 7.57 (s, 1H), 7.72 (br s, 1H), 8.10-8.12 (m, 2H), 8.92 (s, 1H); LCMS (System 10): R_t = 3.10 min; m/z 441 $[M+H]^+$.

Preparation 288: 1-Cyclobutyl-1H-imidazole-4-carboxylic acid hydrochloride



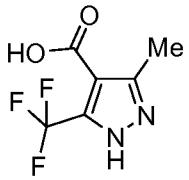
Ethyl 3-(dimethylamino)-2-isocyanoacrylate (WO 2007042545) (45 g, 0.27 mol) was added to cyclobutylamine (50 g, 0.70 mol) and heated to reflux for 2 hours. The solution was then cooled and concentrated. The residue was purified by column chromatography over silica gel (3:1 EtOAc:Heptane). The oily residue was triturated with TBME:heptane (1:1) and the resulting solid was collected and dried, giving 1-cyclobutyl-1H-imidazole-4-carboxylic acid ethyl ester (35 g, 67%, second crop not harvested). 1-Cyclobutyl-1H-imidazole-4-carboxylic acid ethyl ester (35 g, 0.21 mol) was dissolved in 6 N HCl (300 mL) and refluxed for 1 day. The solution was concentrated to dryness *in vacuo*. The solid was azeotroped with toluene, triturated with toluene and then dried under vacuum, giving the title compound 88% yield, 37.2 g, m/z 167 $[M+H]^+$.

Preparation 289: (2-Methylimidazo[2,1-b][1,3]thiazol-6-yl)acetic Acid Hydrochloride



Ethyl 4-bromo-3-oxobutanoate (92 g, 0.35 mol) was added to a solution of 5-methylthiazol-2-amine (40 g, 0.35 mol) in acetone (400 mL). The mixture was left to stand overnight and then evaporated to give 2-amino-3-(4-ethoxy-2,4-dioxobutyl)-5-methylthiazol-3-ium bromide in 82% yield, 101 g. 2-amino-3-(4-ethoxy-2,4-dioxobutyl)-5-methylthiazol-3-ium bromide (101 g, 0.28 mol) was then refluxed in ethanol (250 mL) for 2 hours. The solvent was then evaporated to give ethyl 2-(2-methylimidazo[2,1-b]thiazol-6-yl)acetate hydrobromide as yellow crystals in 97% yield, 85 g. Solid K_2CO_3 was added to a solution of ethyl 2-(2-methylimidazo[2,1-b]thiazol-6-yl)acetate hydrobromide (85 g, 0.28 mol) in water (300 mL) to pH ~8. The product was extracted with chloroform (3 × 100 mL), and the combined extracts were dried over Na_2SO_4 and evaporated to give ethyl 2-(2-methylimidazo[2,1-b]thiazol-6-yl)acetate in 84% yield 52 g. Ethyl 2-(2-methylimidazo[2,1-b]thiazol-6-yl)acetate (52 g, 0.23 mol) was refluxed in 10% aqueous HCl (150 mL) for 2 hours. The solution was evaporated to dryness to give the title compound as brown crystals in 59% yield 32.3 g; m/z 197 $[M+H]^+$.

Preparation 290: 3-Methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid



To a solution of benzyl acetoacetate (57.6 g, 300 mmol) in MeOH (50 mL) in a 350 mL pressure vessel was added H_2NMe (150 mL of a 2M solution in MeOH, 300 mmol) and acetic acid (2 mL). The capped vessel was placed in an oil bath at 70 °C and the reaction mixture was stirred for 16 hours. After the mixture had cooled to room temperature, the solvent was evaporated *in vacuo* leaving a yellow emulsion, which was dissolved in EtOAc (500 mL) and $MgSO_4$ was added to remove water. The drying agent was filtered off, and the solvent evaporated *in vacuo* to give benzyl 3-(Methylamino)but-2-enoate as a viscous yellow oil in quantitative yield 60 g which was used without further purification.

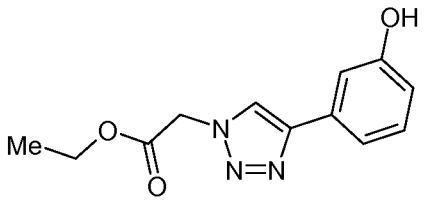
To a solution of benzyl 3-(methylamino)but-2-enoate (60 g, 300 mmol) and pyridine (27 mL, 330 mmol) in THF (500 mL), cooled to –20 °C, was added triflic anhydride (45 mL, 315 mmol) over a 30 min period. During the addition, the temperature was kept below -10 °C. The reaction mixture was allowed to warm to room temperature overnight resulting in a yellow clear reaction mixture. The solvent was evaporated *in vacuo* and the orange residue was taken up in water (1L) and Et_2O (1L). Upon shaking the mixture well in a 3-L separatory funnel, all solid material dissolved. The organic layer was separated and washed with water (3 × 500 mL), brine (500 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* provided benzyl 3-(Methylamino)-2-(trifluoroacetyl)but-2-enoate as an off-white solid in 97% yield, 90 g that was used without additional purification.

To a solution of benzyl 3-(methylamino)-2-(trifluoroacetyl)but-2-enoate (90 g, 300 mmol) in a mixture of THF (900 mL) and acetic acid (100 mL) was added hydrazine monohydrate (14.6 mL, 300 mmol) over a 5 min period. The reaction mixture was heated to reflux for 3 hours, allowed to cool to room temperature and the solvents were evaporated *in vacuo* to afford a bright yellow mass. The mass was dissolved in EtOAc (1L) and water (1L) with gentle heating, allowed to cool to room temperature and the aqueous layer was neutralized to pH 7-8 with $NaHCO_3$. This mixture was transferred to a 3-L separating funnel, the

layers were mixed vigorously, separated and the organic layer was washed with water (3 × 500 mL) dried ($MgSO_4$), filtered and evaporated *in vacuo* to give benzyl 3-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate as an off-white solid in 89% yield 74 g that was used without further purification.

A mixture of benzyl 3-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (74 g, 285 mmol), Pd/C (45 g, 10% on C) and EtOAc (1L) was treated in a Parr apparatus at room temperature with H_2 (15 psi) for 5 hours. The catalyst was filtered off over Celite and the solvent was removed *in vacuo*. Et_2O (1L) and water (200 mL) were added and the aqueous layer was made slightly basic (pH 8-9) with Na_2CO_3. The layers were separated and the aqueous layer was extracted with Et_2O (5 × 200 mL). To the aqueous layer was added dropwise conc. HCl until pH 4-5 and followed by extraction with Et_2O (3 × 500 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated *in vacuo* to give the title compound in 74% yield 7.4 g; m.p. 308-310 °C (dec.) m/z 195 $[M+H]^+$

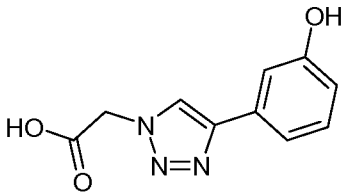
Preparation 291: Ethyl [4-(3-Hydroxyphenyl)-1*H*-1,2,3-triazol-1-yl]acetate



Ethyl azidoacetate (14.9 g, 115 mmol) was dissolved in *tert*-butanol (200 mL), and 95% 3-hydroxybenzonitrile (13.7 g, 110 mmol) was added. A solution of sodium ascorbate (2.18 g, 11 mmol) in water (100 mL) was added, followed by a 0.3 M solution of copper sulfate under argon. The mixture was stirred at room temperature for 12 hours. The solution was evaporated to dryness *in vacuo*, the residue was dissolved in EtOAc (100 mL), dried ($MgSO_4$), filtered, evaporated *in vacuo* to give the title compound as brown crystals in ~100% (27.7 g) yield.

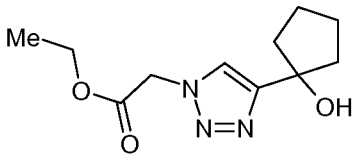
MS m/z 246 $[M-H]^-$

Preparation 292 : [4-(3-Hydroxyphenyl)-1*H*-1,2,3-triazol-1-yl]acetic Acid Hydrate



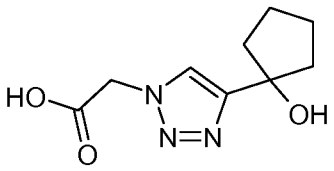
Ethyl [4-(3-Hydroxyphenyl)-1*H*-1,2,3-triazol-1-yl]acetate (Preparation 291, 27.2 g, 0.110 mol) was dissolved in methanol (200 mL), and a solution of NaOH (4.84 g, 121 mmol) in water (40 mL) was added. The solution was kept at room temperature for 24 hours. Methanol was evaporated *in vacuo*, water (120 mL) was added, and the solution was refluxed with activated charcoal. The mixture was filtered, and 11 M HCl was added to the filtrate. The mixture was dissolved by addition of water (120 mL) and cooled to carry out the crystallization. The crystals were filtered, washed with water (2 x 25 mL), and evaporated to dryness to afford the title compound as brown crystals (mp 186.3-188.7 °C) in 99.0% yield 23.9 g. MS m/z 218 $[M-H]^-$

Preparation 293: Ethyl [4-(1-hydroxycyclopentyl)-1H-1,2,3-triazol-1-yl]acetate



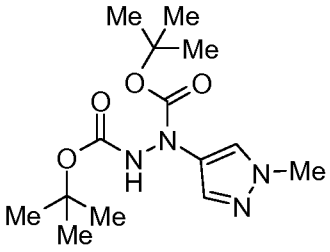
Ethyl azidoacetate (2.58 g, 20 mmol) was dissolved in *tert*-butanol (15 mL), and 1-hydroxycyclopentanecarbonitrile (2.20 g, 20 mmol) was added. A solution of sodium ascorbate (0.792 g, 4 mmol) in water (10 mL) followed by a 0.3 M solution of copper sulfate (0.67 mL) was added to the mixture, and stirring continued at room temperature for a further 48 hours. The solution was evaporated to dryness *in vacuo* and the residue was dissolved in EtOAc (50 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford the title compound as green-yellow crystals in 98% yield, 4.69 g.
MS m/z 238 $[M-H]^-$

Preparation 294: [4-(1-hydroxycyclopentyl)-1H-1,2,3-triazol-1-yl]acetic acid



To a solution of ethyl [4-(1-hydroxycyclopentyl)-1H-1,2,3-triazol-1-yl]acetate (Preparation 293, 36.4 g, 151 mmol) in water (50 mL), was added a solution of NaOH (7.60 g, 190 mmol) in water (25 mL). The solution was refluxed with activated charcoal, filtered through Celite, and $NaHSO_4$ (25.8 g, 190 mmol) added. EtOAc (50 mL) was added to the filtrate. The formed precipitate was separated by filtration, dissolved in EtOAc (100 mL), and the solution was filtered. The water layer was extracted with EtOAc (10 × 50 mL), and the combined extracts were evaporated to a volume of 100 mL. The precipitate was filtered, washed with ethyl acetate (2 x 50 mL), and concentrated under reduced pressure to afford the title compound as a colorless crystalline substance in 87% yield, 27.8 g. mp 124.0-126.0 °C; MS m/z 212 $[M+H]^+$

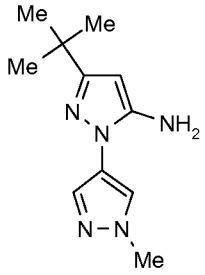
Preparation 295: Di-tert-butyl 1-(1-methyl-1H-pyrazol-4-yl)hydrazine-1,2-dicarboxylate



To a solution of 4-iodo-1-methyl-1H-pyrazole (21 g, 0.12 mol) in dry ether (200 mL) at -78 °C was added n-BuLi (84.5 mL of a 2.5 M solution in hexane, 0.18 mol) over a period of 30 min and the mixture stirred for a further 30 min. A solution of di-tert-butyl (Z)-diazene-1,2-dicarboxylate (30.4 g, 0.12 mol) in ether (100 ml) was added to the reaction mixture over a period of 10 min and the resultant mixture stirred at -78°C for 1 hour. The reaction was warmed to 0 °C and quenched with ice-water and extracted with ether (3 x 100mL). The organic layer was separated, dried (Na_2SO_4) and evaporated *in vacuo*. The crude material was washed with hexane and then dried under vacuum to give the title compound in 30% yield, 11.2 g.

^{1}H NMR (400 MHz, DMSO-d6): d 9.60 (s, 1 H), 7.62 (s, 1 H), 7.25 (s, 1 H), 3.76 (s, 3 H), 1.44 (m, 18 H).
LCMS: 313 (M+H) +

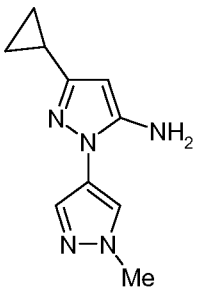
Preparation 296: 3-tert-butyl-1'-methyl-1'H-1,4'-bipyrazol-5-amine



A mixture of di-tert-butyl 1-(1-methyl-1H-pyrazol-4-yl)hydrazine-1,2-dicarboxylate (**Preparation 295** ,12.3 g, 0.039 mol) and 4,4-dimethyl-3-oxopentanenitrile (5.4 g, 0.043 mol) was dissolved in MeOH (36 mL) and HCl (12 mL) was added slowly. The reaction mixture was stirred at 65 °C for 16 hours. The reaction was distilled to remove MeOH and basified with sat. aq. $NaHCO_3$ solution to pH~8 followed by extraction with DCM. The organic layer was separated, dried (Na_2SO_4) followed by concentration *in vacuo*. The crude mixture was purified by column chromatography on silica gel (hexane:EtOAc 50:50) to give the title compound in 41% yield, 7.2 g.

^{1}H NMR (400 MHz, DMSO-d6) d 7.91 (s, 1 H), 7.58 (s, 1 H), 5.28 (s, 1 H), 5.04 (s, 2 H), 3.81 (s, 3 H), 1.21 (s, 9 H); LCMS: m/z 220 $[M+H]^+$.

Preparation 297: 3-cyclopropyl-1'-methyl-1'H-1,4'-bipyrazol-5-amine

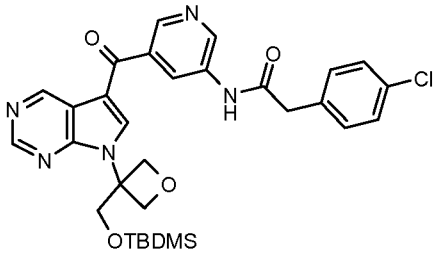


The title compound was prepared according to the method described for **Preparation 296**: using di-tert-butyl 1-(1-methyl-1H-pyrazol-4-yl)hydrazine-1,2-dicarboxylate (**Preparation 295)** and 3-cyclopropyl-3-oxopropanenitrile to afford the title compound in 48% yield, 1.7g.

^{1}HNMR (400 MHZ, DMSO-d6): 0.55-0.57 (m, 2H), 0.75-0.80 (m, 2H), 1.68-1.72 (m, 1H), 3.83(s, 3H), 5.08-5.09 (m, 3H), 7.57(s, 1H), 7.90(s, 1H).

LCMS: $[M+H]^+$ 204

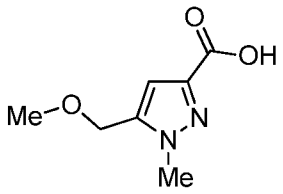
Preparation 298: N-[5-({7-[3-({[tert-butyl(dimethyl)silyl]oxy}methyl)oxetan-3-yl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-(4-chlorophenyl)acetamide



The title compound was prepared according to the method described for **Preparation 223** using (5-aminopyridin-3-yl)(7-(3-methyloxetan-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (**Preparation 222**) to afford the title compound as a white solid in 87% yield, 35 mg.

LCMS (System 2): R_t = 1.49 min; m/z 592 $[M+H]^+$.

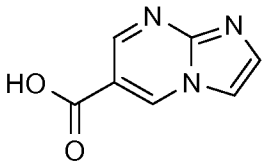
Preparation 299: 5-(methoxymethyl)-1-methyl-1H-pyrazole-3-carboxylic acid



To a solution of ethyl 5-(methoxymethyl)-1-methyl-1H-pyrazole-3-carboxylate (WO9743277) (177 mg, 0.893 mmol) in MeOH, a 0.5 M solution of LiOH was added (5.3 mL, 2.68 mmol). The reaction was stirred at room temperature overnight. The solution was evaporated to dryness and the residue was adjusted to pH5 with a 2 N HCl solution. The aqueous solution was extracted with EtOAc and the organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to give the title compound as a white solid 95%, 145mg.

^{1}H NMR (400MHz, methanol-d4) 6.68 (s, 1 H), 4.44 (s, 2 H), 3.84 (s, 3 H), 3.29 (s, 3 H). MS m/z 171 $[M+H]^+$

Preparation 300: Imidazo[1,2-a]pyrimidine-6-carboxylic acid

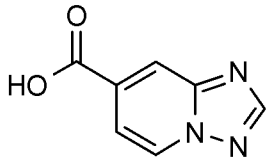


A mixture of 6-bromoimidazo[1,2-a]pyrimidine (1.17 g, 6 mmol), BINAP (18 mg, 0.06 mmol), PdCl2 (6 mg) in MeOH (30 mL) and triethylamine (1.8 mL) was heated to 80°C under CO (50 psi) for 12 hours in DMF

(97.5 mL). DMF-DMA (70.6 mL, 495.8 mmol) was added and the mixture heated to 130 °C for 12 hours. The mixture was filtered and concentrated to give methyl imidazo[1,2-a]pyrimidine-6-carboxylate (365 mg, 35%) as a yellow solid which was used in the next step without further purification. To a solution of methyl imidazo[1,2-a]pyrimidine-6-carboxylate (365 mg, 2.1 mmol) in methanol was added 1M aq. LiOH (9.0 mL) and the resulting mixture was stirred for 10 hours at room temperature. The pH was adjusted to 5-6 using aq. HCl and the whole mixture extracted with EtOAc (3x30mL).The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give the title compound as white solid in 39% yield, 133 mg

^{1}H NMR (400 MHz, DMSO-d6): δ9.15 (m, 1H), 8.8 (m, 1H), 7.9 (m, 1H), 7.65 (m, 1H),

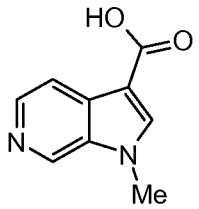
Preparation 301: [1,2,4]triazolo[1,5-a]pyridine-7-carboxylic acid



To a solution of methyl 2-aminoisonicotinate (28.8 g, 191 mmol) in DMF (97.5 mL) was added DMF-DMA (70.6 mL, 496 mmol) and the mixture heated to 130 °C for 12 hours. The mixture was then concentrated to give a residue. To the residue was added methanol (381 mL), followed by NH2OHSO4 (31.9 g, 248 mmol) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated to give methyl [1,2,4]triazolo[1,5-a]pyridine-7-carboxylate in 18% yield, 6g. To a solution of methyl [1,2,4]triazolo[1,5-a]pyridine-7-carboxylate (3 g, 16 mmol) in methanol was added 1M aq. LiOH (70 mL) and the resulting mixture stirred for 10 hours at room temperature. The pH was adjusted to 5-6 using aq. HCl and the whole mixture extracted with EtOAc (30 mL×3).The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as white solid in 38% yield, 1.05 g

1H NMR (400 MHz, DMSO-d6): δ13.5-14.0 (s, 1H), 9.04-9.06 (m, 1H), 8.66 (m, 1H), 8.32 (m, 1H), δ7.56-7.58 (m, 1H).

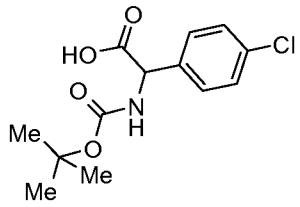
Preparation 302: 1-methyl-1H-pyrrolo[2,3-c]pyridine-3-carboxylic acid



1-methyl-1H-pyrrolo[2,3-c]pyridine-3-carbaldehyde (WO 05066132) (6.5 g, 40.6 mmol) was dissolved in a mixture solvent of THF (120 mL) and t-butyl alcohol (40 mL) under nitrogen. A 2M 2-methyl-2-butene solution in THF (120 mL, 46 mmol) was added followed by a solution of $NaClO_2$ (11.02 g, 122 mmol) and NaH_2PO_4 (21.9 g, 183 mmol) in water (30 mL). The reaction mixture was stirred at room temperature overnight under nitrogen. The reaction mixture was concentrated *in vacuo* to remove organic solvents, and the residue was filtered. The precipitate contained the title compound as white solid in 57% yield, 4.1 g.

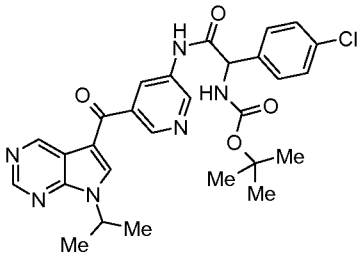
1H NMR: DMSO-d6 400MHz: δ 3.96 (S, 3 H), 7.87-7.89 (d, 1 H), 8.23 (s, 1 H), 8.28 (d, 1 H), 8.91 (s, 1 H), 12.3 (s, 1 H).

Preparation 303: 2-((tert-butoxycarbonyl)amino)-2-(4-chlorophenyl)acetic acid



To 4-chlorophenylglycine (1.50 g, 8.08 mmol) and sodium hydroxide (0.65 g, 16.2 mmol) in water (20 mL) was added di-*tert*-butyl dicarbonate (1.76 g, 8.08 mmol) in acetonitrile (15 mL) and the mixture was stirred at room temperature for 18 hours. The mixture was then washed with DCM (20 mL) and acidified using 2N HCl. The resulting aqueous layer was extracted with DCM (2 x 25 mL) and the combined organic layers were washed with brine before being dried over $MgSO_4$, filtered and evaporated *in vacuo* to give the title compound as a colourless oil in 87% yield, 2.00 g.

Preparation 304: tert-Butyl (1-(4-chlorophenyl)-2-((5-(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidine-5-carbonyl)pyridin-3-yl)amino)-2-oxoethyl)carbamate



To pyridine (4 mL) in a sealed vessel was added 2-((tert-butoxycarbonyl)amino)-2-(4-chlorophenyl)acetic acid (67 mg, 0.24 mmol) (see **Preparation 303**), (5-aminopyridin-3-yl)(7-isopropyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)methanone (52 mg, 0.18 mmol) (see **Preparation 95**) and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (105 mg, 0.28 mmol). The reaction was heated at 50°C for 18 hours and then evaporated *in vacuo* and purified by column chromatography (gradient of 100:0 to 88:12 DCM:MeOH) to give the title compound in 49% yield, 64 mg. LCMS (basic): R_t = 0.81 min; m/z 549 $[M+H]^+$.

Biological Activity

Isolated TRK Enzyme assays use the HTRF KinEASE-TK kit (Cisbio Cat# 62TK0PEJ) with recombinant His-tagged cytoplasmic domains of each TRK receptor sourced from Invitrogen (see table below). This activity-assay measures the phosphorylation of tyrosine residues within a substrate from the HTRF kit which has been validated by Cisbio for a variety of tyrosine kinases including the TRK receptors.

Assay details:

Target	Invitrogen Cat#	Amino acids	FAC enzyme	FAC ATP	Assay Reaction Time
TRKA	PV3144 (NTRK1)	aa 441-796	4nM	40uM	35min
TRKB	PV3616 (NTRK2)	aa 526-838	1nM	1.4uM	40min
TRKC	PV3617 (NTRK3)	aa 510-825	10nM	15uM	30min

0.5mM stock solutions of test compounds are prepared and serially diluted in 100% DMSO. A standard curve using the compound of Example 135 disclosed in WO2005/116035 of 150uM is also prepared on each test plate. High percentage effect (HPE) is defined by 150uM PF-00593157-00 and 0% effect (ZPE) is defined by 100% DMSO. Greiner low volume black plates containing 0.2ul of serially diluted compound, standard and HPE/ZPE are created using the Bravo nanolitre dispenser.

1X enzyme buffer is prepared from 5X Enzymatic Buffer from the Cisbio KinEASE TK kit using MilliQ water. The buffer is then supplemented with 10mM MgCl and 2mM DTT (both from Sigma). In the case of TRKB, the buffer is also supplemented with 125nM Supplement Enzymatic Buffer (SEB) from the Cisbio kit.

2X FAC of enzyme and 2X FAC ATP diluted in 1X complete enzyme buffer is incubated at room temperature for 20minutes to preactivate the enzyme. Following this preactivation step, 5ul/well of enzyme + ATP mix is added using a Multidrop Micro to the assay plate, spotted with 0.2ul 100% DMSO compound. This is left for 20mins at room temperature before adding 5ul of 2uM TK-substrate-Biotin (from the Cisbio kit) diluted in 1X enzyme buffer (1uM FAC) using the Multidrop Micro. The reaction is incubated at room temperature for the optimized assay reaction time (see table). The reaction is stopped by adding 10ul/well HTRF Detection Buffer containing 0.25uM Streptavidin-XL665 (0.125uM FAC) and 1:200 TK Antibody-Cryptate using a Multidrop.

After the Detection Reagent addition, plates are covered and incubated at room temperature for 60 minutes. HTRF signal is read using an Envision reader, measured as a ratio of emissions at two different wavelengths, 620nm and 665nm. Any compound that inhibits the action of the TRK kinase will have a lower fluorescence ratio value 665/620nM than compounds which do not inhibit theTRK kinase. Test compound data are expressed as percentage inhibition defined by HPE and ZPE values for each plate. Percentage inhibition in the presence of test compound is plotted against compound concentration on a log scale to determine an IC_{50} from the resultant sigmoid curve.

Cell Based Assays were carried out using Cell lines from DiscoveRx utilising their PathHunter technology and reagents in an antagonist assay:

Target	DiscoveRx cell line Cat#	Cognate Neurotrophin
TRKA	93-0462C3	NGF
TRKA co expressed with p75	93-0529C3	NGF

TRKB	93-0463C3	BDNF
TRKB co expressed with p75	93-0530C3	BDNF
TRKC	93-0464C3	NT3
TRKC co expressed with p75	93-0531C3	NT3

The assays are based upon DiscoveRx's proprietary Enzyme Fragment Complementation (EFC) technology. In the case of the TRK cell lines, the enzyme acceptor (EA) protein is fused to a SH2 protein and the TRK receptor of interest has been tagged with a Prolink tag.

Upon neurotrophin binding, the TRK receptor becomes phosphorylated, and the tagged SH2 protein binds. This results in functional complementation and restored β-Galactosidase activity which is can be measured using the luminescent Galacton Star substrate within the PathHunter reagent kits.

Generally, small molecule inhibitors bind to the kinase domain so are not competing with the neurotrophin (agonist) which binds to an extracellular site. This means that the IC_{50} is a good measure of affinity and should be unaffected by concentration neurotrophin stimulant.

Cryopreserved PathHunter cells are used from either in-house produced batches or bulk batches bought directly from DiscoveRx. Cryopreserved cells are resuscitated, spun 1000rpm for 4min to remove freezing media, and resuspended in MEM + 0.5% horse serum (both Invitrogen) to $5e^5$cells/ml. The cells are then plated using a Multidrop into Greiner white tissue culture treated plates at 20ul/well and incubated for 24h at 37°C, 5% CO_2, high humidity. On the day of the assay, the cell plates are allowed to cool to room temperature for 30min prior to the assay.

4mM stock solutions of test compounds are prepared and serially diluted in 100% DMSO. A standard curve using the compound of Example 135, WO2005/116035 at a top concentration of 150uM is also prepared on each test plate. High percentage effect (HPE) is defined by 150uM of the compound of Example 135, WO2005/116035 and 0% effect (ZPE) is defined by 100% DMSO. Plates containing 1ul of serially diluted compound, standard and HPE/ZPE are diluted 1/66 in assay buffer (PBS minus Ca^{2+}, minus Mg^{2+} with 0.05% pluronic F127) using a Wellmate. Using a Platemate Plus, 5ul of 1/66 diluted test compounds is then transferred to the cell plate and allowed to reach equilibrium by incubating for 30min at room temperature before addition of agonist stimulus: 10ul/well of 2nM (0.571nM FAC) of the cognate neurotrophin (Peprotech) diluted in agonist buffer (HBSS with 0.25% BSA). Final assay concentration of the test compounds is 8.66μM, (the compound of Example 135, WO2005/116035 FAC is 0.325uM). The plates are left at room temperature for a further 2hours before addition of 10ul of the DiscoveRx PathHunter detection reagent (made up by adding 1 part Galacton Star, 5 parts Emerald II and 19 parts Cell Assay Buffer as per the manufacturer's instructions).

After reagent addition, plates are covered and incubated at room temperature for 60 minutes. Luminescence signal is read using an Envision. Test compound data are expressed as percentage inhibition defined by HPE and ZPE values for each plate. Percentage inhibition in the presence of test

compound is plotted against compound concentration on a log scale to determine an IC_{50} from the resultant sigmoid curve.

Brain Penetration Assays

In Vitro

MDCK-BCRP: MDCK-BCRP data were collected according to the method described in "A 96-Well Efflux Assay To Identify ABCG2 Substrates Using a Stably Transfected MDCK II Cell Line" http://pubs.acs.org/doi/full/10.1021/mp050088t

Yongling Xiao, Ralph Davidson, Arthur Smith, Dennis Pereira, Sabrina Zhao, John Soglia, David Gebhard, Sonia de Morais, and David B. Duignan, *Mol. Pharm.* , **2006**, *3* (1), pp 45–54.

MDCK-MDR1: MDCK-MDR1 data were collected according to the method described in "Are MDCK Cells Transfected with the Human *MDR1* Gene a Good Model of the Human Intestinal Mucosa? " http://www.springerlink.com/content/qfhqlqbr4fnp3khf/fulltext.pdf

Fuxing Tang, Kazutoshi Horie, and Ronald T. Borchardt, *Pharmaceutical Research,* Vol. 19, No. 6, June 2002.

In Vivo

Brain penetration was measured according to the method described in "Assessing brain free fraction in early drug discovery". Read, K; Braggio, S., Expert Opinion Drug Metab Toxicol. (2010) 6 (3) 337- 344.

Example number	TrkA enzyme potency (nM)	TrkB enzyme potency (nM)	TrkA cell potency (nM)	TrkB cell potency (nM)	TrkC cell potency (nM)	MDCK MDR1 Papp AB (x10-6 cm/sec)	MDCK MDR1 Papp BA (x10-6 cm/sec)	RRCK BCRP Papp AB (x10-6 cm/sec)	RRCK BCRP Papp BA (x10-6 cm/sec)
1	3.7		9.5	1.5		5.5	14		
2	8.4	113	5.3	3.9	1.1	<1	15		
3	4.1		5.1	1.8		8.7	20		
4	3.9	162	5.7	6.5	4.4	<1	13	12	39
5	2.6	73	3.5	3.6	2.0	1.5	14		
6	2.5		2.0	1.3		6.9	16		
7	11	41	2.1	0.8		5.6	20		
8	2.4	15	1.9	2.0	2.3	1.8	15		
9	3.7	94	13	6.6	5.9	<1	20	9	43
10	5.7	78	30	18	18	<1	14		
11	3.3	197	17	11	6.6	<1	23		
12	9.2	547	68	22		<1	3.1		
13	20	449	1130	184		<1	1.0		
14	13	773	41	15	4.8	<1	21		
15	17	514	143	40		<1	15		
16	16	445	99	15					
17	23		103	45		<1	13		
18	128		>8660	5300		<1	<1		
19	249	5480	1840	206		<1	8.5		
20	14	635	22	19		<1	17		
21	71		5740	1770		<1	1.3		
22	25		596	190		<1	6.9		
23	26		93	52		<1	31		
24	125	427	37	27	8.9	<1	10		
25	24	433	65	19		<1	13		
26	3.5	30	14	5.9	8.6	<1	16	7.5	32
27	2.8	55	3.9	5.4	3.2	<1	17		
28	4.9	75	2.7	1.9		<1	20		
29	2.8	68	5.8	4.0		1.3	23		
30	4.0	98	11	7.5		<1	15		
31	18		401	198		<1	2.6		
32	9.0	423	87	59	18	<1	3.4		
33	5.7	96	2.0	1.6		1.0	24		
34	3.6	200	23	25	13	<1	11		
35	8.9	223	103	37		<1	5.3		
36	4.5	303	11	13	13	<1	12		
37	67		2250	571					
38	7.2		1060	589		<1	2.1		
39	24		>8660	4710		<1	<1		
40	67		2580	506		<1	2.4		
41	7.6		203	70		<1	6.3		
42	3.8	191	44	27	13	<1	9.5		
43	5.1	136	17	19	11	<1	13		
44	12		996	554		<1	1.6		
45	25		>8660	3790		<1	<1		
46	3.2	94	6.0	4.2	0.9	<1	18	7	31
47	25	27	35	13		<1	21		
48	1.7	40	2.9	3.6	2.5	<1	12		
49	2.1	37	3.1	2.1	2.1	<1	17		
50	6.6	143	10.0	2.1		<1	24		
51	7.8	198	35	7.5	9.9	<1	11		
52	3.1	103	22	16	8.1	<1	9.1		
53	4.0	163	16	5.0	8.6	<1	13		
54	6.7		368	174		<1	1.3		
55	7.0	179	12	4.5		<1	20		
56	9.5	962	451	517		1.1	1.0		
57	1.2	40	4.0	2.5		5.1	26		
58	2.1	315	11	11		1.2	54		
59	4.6	110	3.4	2.4		5.7	24		
60	1.8	13	1.6	0.9		<1	18		
61	4.5	100	13	8.4	1.4	<1	39		
62	1.8	41	1.9	2.7		5	99		
63	1.2	25	2.6	1.8	0.4	5.6	20		
64	1.5	19	2.0	1.4		<1	4.2		

Example	Trka enzyme (IC50)	Example	Trka enzyme (IC50)	Example	Trka enzyme (IC50)
65	55.6	109	65.1	153	71.5
66	3.55	110	36.5	154	94.1
67	4.15	111	46.2	155	49.1
68	12.1	112	57.8	156	133
69	10.9	113	300	157	174
70	22.8	114	976	158	230
71	135	115	102	159	234
72	63.3	116	103	160	1080
73	283	117	68.4	161	6270
74	1210	118	2550	162	324
75	567	119	233	163	1840
76	173	120	53	164	133
77	64.3	121	5200	165	3400
78	203	122	5840	166	110
79	1580	123	143	167	3470
80	392	124	244	168	702
81	197	125	148	169	3100
82	908	126	95.7	170	3100
83	355	127	1330	171	1280
84	2860	128	206	172	3840
85	70.8	129	3860	173	9810
86	95.5	130	284	174	210
87	63.2	131	831	175	2590
88	56.6	132	131	176	165
89	21.7	133	681	177	3100
90	8.81	134	330	178	3100
91	1030	135	312	179	3080
92	41.5	136	334	180	3100
93	12.4	137	496	181	3100
94	54.8	138	8310	182	543
95	3.95	139	65.7	183	1850
96	5.45	140	219	184	579
97	4.86	141	59.5	185	67.4
98	5.16	142	1380	186	719
99	19.5	143	4730	187	2630
100	25.6	144	71.5	188	277
101	204	145	37.4	189	836
102	42.9	146	573	190	820
103	41.7	147	76.4	191	873
104	20	148	93.4	192	173
105	25.6	149	3570	193	3570
106	14.8	150	51	194	101
107	12.3	151	232	195	835
108	7.63	152	82.5	196	791

Example	Trka enzyme (IC50)	Example	Trka enzyme (IC50)	Example	Trka enzyme (IC50)
197	430	242	8.71	287	4350
198	2350	243	38.4	288	43.1
199	22.1	244	4.69	289	1370
200	10.1	245	4.7	290	167
201	482	246	35.6	291	3230
202	412	247	71	292	37.7
203	316	248	23.7	293	20.2
204	4.24	249	35.8	294	61.4
205	12.2	250	3.48	295	31.9
206	123	251	33.1	296	47.7
207	110	252	5.18	297	299
208	129	253	3.92	298	1460
209	272	254	52.6	299	539
210	185	255	42.7	300	52.2
211	34.9	256	1.09	301	428
212	59	257	12.2	302	156
213	3.03	258	11.8	303	1220
214	65.9	259	8.62	304	3900
215	4.4	260	16.8	305	2640
216	31.6	261	128	306	N/D
217	83.3	262	32.3	307	N/D
218	1210	263	73.6	308	592
219	286	264	84.8	309	53.9
220	462	265	69	310	98.4
221	3100	266	2950	311	238
222	692	267	2120	312	166
223	1660	268	579	313	N/D
224	3100	269	557	314	835
225	27.7	270	343	315	39.1
226	3.61	271	39	316	N/D
227	12.5	272	697	317	N/D
228	14.9	273	342	318	N/D
229	138	274	38.6	319	188
230	63.7	275	5100	320	3100
231	N/D	276	295	321	3100
232	274	277	434	322	9800
233	96.5	278	54.3	323	3100
234	84.9	279	439	324	3100
235	70.5	280	498	325	111
236	25.2	281	161	326	2980
237	73.9	282	1010	327	3100
238	9.36	283	297	328	3100
239	22.6	284	2020	329	9810
240	19.2	285	7820	330	3100
241	45.3	286	19.5	331	9810

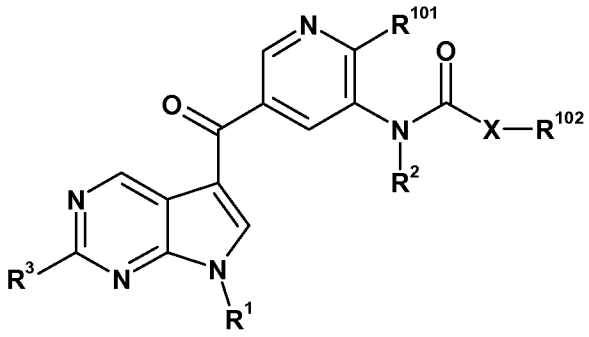
Example	Trka enzyme (IC50)	Example	Trka enzyme (IC50)	Example	Trka enzyme (IC50)
332	2180	381	2780	426	228
333	9800	382	45.7	427	93.4
334	1550	383	130	428	960
336	9800	384	4770	429	2740
337	4280	385	81.6	430	297
338	2730	386	9800	431	235
339	251	387	6880	432	2790
340	451	388	165	433	246
343	53.9	389	84.3	434	99.9
344	326	390	9800	435	5490
345	362	391	246	436	205
346	253	392	135	437	107
347	155	393	1360	438	31.2
348	36.6	394	7120	439	22.5
350	153	395	1350	440	676
351	21.1	396	177	441	8390
352	62.6	397	9800	442	36.6
353	N/D	398	138	443	47.7
354	N/D	399	153	444	496
355	302	400	593	445	5.51
356	56.3	401	132	446	812
357	302	402	9800	447	919
358	9800	403	1220	448	272
359	9800	404	118	449	155
360	956	405	1630	450	3150
361	7640	406	2640	451	7170
362	1910	407	2600	452	542
363	1030	408	654	453	634
364	5040	409	70.4	454	633
365	2040	410	9800	455	1070
366	354	411	9800	456	6960
367	5640	412	5.18	457	674
368	753	413	9800	458	213
369	3000	414	158	459	4.06
370	3540	415	2590	460	9800
371	97	416	52	461	9800
372	9800	417	71.2	462	1320
373	813	418	40.2	463	186
374	224	419	15.1	464	3010
375	9800	420	9800	465	2130
376	5100	421	1730	466	400
377	2630	422	451	467	538
378	716	423	1330	468	5100
379	56.3	424	4310	469	523
380	422	425	796	470	166

Example	Trka enzyme (IC50)	Example	Trka enzyme (IC50)	Example	Trka enzyme (IC50)
471	751	517	4390	562	3.75
472	1720	518	7.3	563	3.11
473	7280	519	47.9	564	1.57
474	4420	520	4.57	565	17.9
475	643	521	92.7	567	20.8
476	65	522	43.7	568	12.1
477	3030	523	11.4	569	34.4
478	587	524	4.53	570	6970
479	2160	525	9.48	571	2.92
480	531	526	1.51	572	9.5
481	313	527	4.64	573	17.9
482	6860	528	2.25	574	14.2
483	118	529	3.93	575	3.09
484	192	530	5.9	576	296
485	20	531	52.4	577	1.9
486	805	532	11.1	578	6.07
487	9800	533	31.3	579	8.11
488	64.6	534	20.3	580	0.825
489	9800	535	51.2	581	3.21
490	9800	536	1.57	582	9.79
491	1410	537	10.6	583	0.681
492	1690	538	1.51	584	581
493	848	539	4.08	585	36.7
494	2570	540	153	586	1000
495	9.80E+03	541	N/D	587	20.5
496	199	542	N/D	588	334
497	43.5	543	50	589	31.3
498	2340	544	31.6	590	71.2
499	9.80E+09	545	2.95	591	142
500	25.8	546	5.34		
501	201	547	3.88		
502	6280	548	21.2		
503	963	549	3.22		
504	1020	550	16.1		
505	1630	551	2.78		
506	67	552	7.62		
507	5.45	553	4.4		
508	1630	554	270		
509	9800	555	150		
510	249	556	3.16		
511	144	557	9.47		
512	12.6	558	5.56		
513	1890	559	374		
514	9800	560	1610		
515	1140	561	112		

All publications cited in this application are each herein incorporated by reference in their entirety. Although the invention has been described above with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

CLAIMS

1. A compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is

H, or

C_{1-5} alkyl optionally substituted by up to 3 substituents independently selected from OH, $CON(R^5R^6)$, SO_2R^7, SR^7, OR^7, CH_2OH, CO_2R^5, $SONR^7R^7$, $NR^7SO_2R^5$, CN, NO_2 and R^8, or

a ring system selected from C_{3-5} cycloalkyl, propellanyl, or a 4-6 membered saturated heterocyclyl ring, which ring system has up to 3 ring hetero-atoms selected from N, O and S, and which ring system is optionally substituted by up to 3 substituents independently selected from methyl, OH, $CON(R^5R^6)$, SO_2R^7, OR^7, CH_2OH, CO_2R^5, $SONR^7R^7$, $NR^7SO_2R^5$, CN, NO_2 and R^8;

R^2 is H or methyl;

R^3 is H, NH_2 or $NH(C_{1-3}$ alkyl optionally substituted with up to 3 substituents independently selected from OH and $O(C_{1-3}$ alkyl));

R^{101} is H, OH, methyl, cyclopropyl, methoxy, ethyl, ethoxy or CN,

X is a bond, O, $(CH\text{-}R^4)_n$, NR^{104}, OCH_2 or CH_2O;

R^4 is independently H, CH_3, CH_2OH, CH_2OCH_3, OH, NH_2, $NHCH_3$, $N(CH_3)_2$, CH_2NH_2, CH_2NHCH_3,or $CH_2N(CH_3)_2$;

R^{104} is H, C_{1-3} alkyl or a C_{4-6} saturated carbocycle, each of which is optionally substituted by up to 3 substituents independently selected from C_{1-3} alkyl, CH_2OH and NH_2;

n is 1 or 2;

R^{102} is a ring system which is a 3-7 membered monocyclic carbocyclic or heterocyclic system, or an 8-14-membered bicyclic system, which ring system may be saturated or partially or fully unsaturated, wherein the heterocyclic ring system may have up to 5 ring hetero-atoms selected from N, S, and O, wherein the bicyclic ring system can be 2 rings (carbocyclic-carbocyclic, carbocyclic-heterocyclic, heterocyclic-carbocyclic or heterocyclic-heterocyclic) fused or linked by a single bond, which ring system is optionally substituted by up to 3 substituents independently selected from, where possible -

halo, CN, NR^5R^6, SO_2R^7, SR^7, C_{1-4} alkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{1-3} alkyl substituted by up to 3 halogen, OH, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, O(C_{1-3} alkyl substituted by up to 3 halogen), O(C_{1-3} alkyl substituted by up to 3 OH and/or C_{1-3} alkoxy groups), $NR^5SO_2R^7$, =O, R^8, $C(O)R^8$, NO_2, $NR^5CO_2R^7$, NR^5COR^7,OR^8, $S(O)R^7$, and CH_2R^8;

R^5 and R^6 are each independently

H, or

C_{1-5} alkyl optionally substituted by up to 3 substituents independently selected from OH, $CONR^7R^7$, SO_2R^7, OR^7, CH_2OH, CO_2R^7, $SONR^7R^7$, $NR^7SO_2R^7$, CN, NO_2 and R^9 ,

or

a ring system selected from C_{3-5} cycloalkyl, propellanyl, or a 4-6 membered saturated heterocyclyl ring, which ring system is optionally substituted by up to 3 substituents independently selected from OH, $CON(R^7R^7)$, SO_2R^7, CO_2R^7, $SONR^7R^7$, $NR^7SO_2R^7$, CN, NO_2, halo, NR^7R^7,SR^7,C_{1-4} alkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{1-3} alkyl substituted by 1 to 3 halogen, O(C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, O(C_{1-3} alkyl substituted by up to 3 halogen, O(C_{1-3} alkyl substituted by up to 3 OH and/or C_{1-3} alkoxy, $NR^7SO_2R^7$,=O,NO_2,$NR^7CO_2R^7$, and $S(O)R^7$,

or R^5 and R^6 together with the N to which they are attached can be a 4-7 membered ring optionally including up to 2 further ring hetero-atoms independently selected from N, O, S, which ring is optionally substituted by C_{1-3} alkoxy and / or C_{1-3} alkyl;

R^7 is H, C_{1-5} alkyl or C_{1-5} alkoxy,

which C_{1-5} alkyl or C_{1-5} alkoxy is optionally substituted by up to 3 substituents independently selected from halogen;

R^8 is a is a ring system which is a 3-7 membered monocyclic carbocyclic or heterocyclic system, or an 8-14-membered bicyclic system, which ring system may be saturated or partially or fully unsaturated, wherein the heterocyclic ring system may have up to 5 ring hetero-atoms selected from N, S, and O, wherein the bicyclic ring system can be 2 rings (carbocyclic-carbocyclic, carbocyclic-heterocyclic, heterocyclic-carbocyclic or heterocyclic-heterocyclic) fused or linked by a single bond,

which ring system is optionally substituted by up to 3 substituents independently selected from, where possible -
halo, CN, NR^5R^6, SO_2R^7, SR^7, C_{1-4} alkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{1-3} alkyl substituted by 1 to 3 halogen, OH, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, O(C_{1-3} alkyl substituted by up to 3 halogen, O(C_{1-3} alkyl substituted by up to 3 OH and/or C_{1-3} alkoxy, $NR^5SO_2R^7$, =O, NO_2, NR^7COR^7,$NR^5CO_2R^7$, and S(O)R^7;

R^9 is a is a ring system which is a 3-7 membered monocyclic carbocyclic or heterocyclic system, or an 8-14-membered bicyclic system, which ring system may be saturated or partially or fully unsaturated, wherein the heterocyclic ring system may have up to 5 ring hetero-atoms selected from N, S, and O, wherein the bicyclic ring system can be 2 rings (carbocyclic-carbocyclic, carbocyclic-heterocyclic, heterocyclic-carbocyclic or heterocyclic-heterocyclic) fused or linked by a single bond,
which ring system is optionally substituted by up to 3 substituents independently selected from, where possible -
halo, CN, NR^7R^7, SO_2R^7, SR^7, C_{1-4} alkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, C_{1-3} alkyl substituted by 1 to 3 halogen, OH, O(C_{1-3} alkyl), O(C_{3-6} cycloalkyl optionally substituted by up to 3 OH and/or C_{1-3} alkoxy groups, O(C_{1-3} alkyl substituted by up to 3 halogen, O(C_{1-3} alkyl substituted by up to 3 OH and/or C_{1-3} alkoxy, $NR^7SO_2R^7$, =O, NO_2, $NR^7CO_2R^7$, NR^7COR^7,and S(O)R^7;

wherein each CH moiety can be replaced by a CF moiety.

2. A compound or salt according to claim 1 wherein R^1 is H, C_{1-5} alkyl optionally substituted by up to 2 OH,
or R^1 is C_{1-5} alkyl substituted by $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2H, CO_2CH_3, OCH_3, SCH_3, SO_2CH_3, or R^1 is a ring system selected from C_{3-5} cycloalkyl, propellanyl, or oxetanyl, which ring system is optionally substituted by methyl, OH or CH_2OH.

3. A compound or salt according to any one of claims 1 or 2 wherein R^1 is t-butyl, hydroxy-t-butyl, dihdyroxy-t-butyl, 1-hydroxyprop-2-yl or 1,3-dihydroxyprop-2-yl.

4. A compound or salt according to any one of claims 1 to 3 wherein R^2 is H.

5. A compound or salt according to any one of claims 1 to 4 wherein R^3 is H or NH_2.

6. A compound or salt according to any one of claims 1 to 5 wherein R^3 is NH_2.

7. A compound or salt according to any one of claims 1 to 5 wherein R^3 is H.

8. A compound or salt according to any one of claims 1 to 7 wherein R^{101} is H.

9. A compound or salt according to any one of claims 1 to 7 wherein R^{101} is OH.

10. A compound or salt according to any one of claims 1 to 9 wherein X is a bond, O, CH_2, C_2H_4, $CH(CH_3)CH_2$, $CH(CH_3)$, $CH(CH_2OH)$, CH_2O, $CH(NH_2)$, CH(OH) or NH.

11. A compound or salt according to any one of claims 1 to 10 wherein X is CH_2.

12. A compound or salt according to any one of claims 1 to 11 wherein R^{102} is an optionally substituted nitrogen-containing ring system which is linked to the X moiety via a nitrogen ring atom.

13. A compound or salt according to any one of claims 1 to 11 wherein R^{102} is an optionally substituted ring system where the ring system is selected from -

benzimidazolyl, benzisoxazolyl, benzofuranyl, benzoxazolyl, benzotriazolyl, biphenyl, bipyrazolyl, cinnolinyl, cyclobutylimidazolyl, cyclobutylpyrazolyl, cyclobutylthiazolyl, cyclopentyltriazolyl, cyclopropylisoxazolyl, cyclopropyloxazolyl, cyclopropylpyrazolyl, cyclopropyltriazolyl, diazirenylphenyl, dihydronaphthyridinyl, dihydropyrrolopyrazolyl, dioxinopyridinyl, furazanyl, furopyridinyl, furopyrrolyl, imidazolyl, imidazopyrazinyl, imidazopyridazinyl, imidazopyridinyl, imidazopyrimidinyl, imidazothiadiazolyl, imidazothiazolyl, indanyl, indazolyl, indolyl, isoindolyl, isoxazolopyridinyl, isoxazolyl, isoquinolinyl, naphthyridinyl, oxazolyl, phenyl, phenylcyclopropyl, phenylimidazolyl, phenylpyrazolyl, phenylpyrrolyl, phenyltetrazolyl, phthalazinyl, purinyl, pyrazinyl, pyrazolyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolotriazinyl, pyridinyl, pyridazinyl, pyridinyltriazolyl, pyrimidinyl, pyrroloimidazolyl, pyrrolopyrazinyl, pyrrolopyrimidinyl, pyrrolopyridinyl, pyrrolyl, quinolinyl, quinazolyl, quinoxalinyl, tetrahydrobenzisoxazolyl, tetrahydrocyclopentapyrazolyl, tetrahydrotriazolopyridinyl, tetrazolopyridazinyl, tetrazolopyridinyl, thiazolyl, thiazolopyridinyl, thiazolopyrimidinyl, thienylpyrazolyl, thienopyridinyl, triazolopyridinyl and triazolyl,

14. A compound or salt according to claim 13 where the optional substituents are independently selected from, where possible -

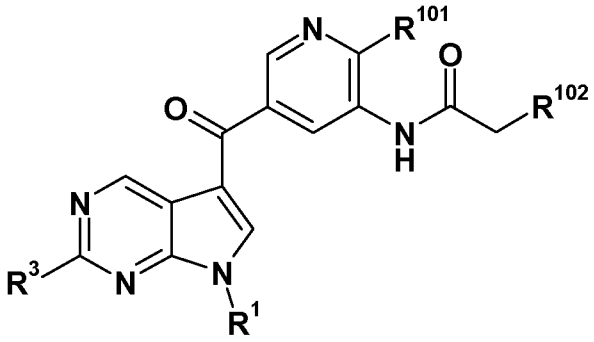
halo, methyl, ethyl, propyl, isopropyl, cyclopropyl, CF_3, CHF_2, CH_2F, CH_2OCH_3, CN, CH_2OH, OCH_3, =O, NH_2, SCH_3, SO_2CH_3, phenoxy, fluorophenoxy, benzyl, SCF_3, OCF_3, SO_2CF_3, $NHSO_2CH_3$, $NHSO_2CF_3$, $C(O)CF_3$, $C(O)CH_3$, benzoyl, azetidinylmethyl, fluoroazetidinylmethyl and morpholinomethyl.

15. A compound or salt according to any one of claims 1 to 11, 13 or 14, wherein R^{102} is selected from phenyl, pyrazol-1-yl, 1,2,3-triazol-1-yl, benzotriazol-2-yl, pyridin-2-yl, pyridin-3-yl and pyridin-4-yl, each of which is optionally substituted by halo, methyl, ethyl, propyl, isopropyl, cyclopropyl, CF_3, CHF_2, CH_2F, CH_2OCH_3, CN, CH_2OH, OCH_3, =O, NH_2, SCH_3, SO_2CH_3, phenoxy, fluorophenoxy, benzyl, SCF_3, OCF_3, SO_2CF_3, $NHSO_2CH_3$, $NHSO_2CF_3$, $C(O)CF_3$, $C(O)CH_3$, benzoyl, azetidinylmethyl, fluoroazetidinylmethyl and/or morpholinomethyl.

16. A compound or salt according to any one of claims 1 to 15 with R^5 and R^6 groups present, wherein R^5 and R^6 are each independently H, C_{1-3} alkyl optionally substituted by C_{1-3} alkoxy, C_{3-5} cycloalkyl, propellanyl, oxetanyl, tetrahydrofuranyl or pyranyl,

or R^5 and R^6 together with the N to which they are attached can be an azetidine, pyrrolidine, piperidine, piperazine or morpholine ring, which ring is optionally substituted by C_{1-3} alkoxy and / or C_{1-3} alkyl.

17. A compound according to claim 1 of the Formula IA:



(IA)

or a pharmaceutically acceptable salt thereof, wherein

R^3 is H or NH_2;

R^1 is C_{2-4} alkyl optionally substituted by 1 or 2 OH groups;

R^{101} is H or OH;

and R^{102} is phenyl or an aromatic or partially unsaturated 5- or 6-membered heterocycle, which heterocycle is optionally fused to a further phenyl or 5-7 membered aromatic or partially unsaturated heterocyclic ring, wherein each heterocycle has from 1 to 3 ring heteroatoms selected from N, O and S, and which ring system is optionally substituted by up to 3 substituents independently selected from halo, CF_3, C_{1-4} alkyl and C_{3-5} cycloalkyl.

18. A compound or salt according to claim 17 wherein R^{101} is H.

19. A compound or salt according to claim 18 wherein

R^1 is t-butyl, hydroxy-t-butyl or 1-hydroxyprop-2-yl;

and R^{102} is 4-trifluromethylphenyl, 4-chlorophenyl, 2,4-difluorophenyl, 5-chloropyridin-2-yl, 5-fluoropyridin-2-yl, 3-trifluromethylpyrazolyl-1-yl, 4-trifluromethylpyrazol-1-yl, 3-trifluromethyl-5-methylpyrazol-1-yl, 3-cyclopropylpyrazol-1-yl, 4-cyclopropylpyrazol-1-yl, 4-trifluromethyl (1,2,3-triazol-1-yl), 4-cyclopropyl-(1,2,3-triazol-1-yl), or benzotriazol-2-yl.

20. A compound according to claim 1, selected from:

N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-chlorophenyl)acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(5-fluoropyridin-2-yl)acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(3-cyclopropyl-1H-pyrazol-1-yl)acetamide;

N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide;

N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide;

N-{5-[(2-amino-7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(5-chloropyridin-2-yl)acetamide;

N-(5-{[2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(5-chloropyridin-2-yl)acetamide;

N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetamide;

2-(4-chlorophenyl)-N-[5-({7-[(1S)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide

N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

N-[5-({7-[(1S)-2-Hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[4-(trifluoromethyl)phenyl]acetamide;

N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]-2-[4-(trifluoromethyl)phenyl]acetamide;

2-(4-chlorophenyl)-N-[5-({7-[(1R)-2-hydroxy-1-methylethyl]-7H-pyrrolo[2,3-d]pyrimidin-5-yl}carbonyl)pyridin-3-yl]acetamide;

N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

2-(5-chloropyridin-2-yl)-N-(5-{[7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)acetamide;

N-(5-{[2-Amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-chlorophenyl)acetamide;

N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide;
N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-(4-chlorophenyl)acetamide;
N-(5-{[2-amino-7-(2-hydroxy-1-methylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[4-(trifluoromethyl)phenyl]acetamide;
N-(5-{[2-Amino-7-(2-hydroxy-1,1-dimethylethyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]carbonyl}pyridin-3-yl)-2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
and
N-{5-[(7-tert-butyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)carbonyl]pyridin-3-yl}-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetamide;
or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of the preceding claims 1 to 20, and a pharmaceutically acceptable carrier.

22. A compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20, for use as a medicament.

23. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20 for use in the treatment of a disease for which an Trk receptor antagonist is indicated

24. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20 for use in the treatment of pain.

25. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or composition thereof, as defined in any one of claims 1 to 20, for the manufacture of a medicament to treat a disease for which an Trk receptor antagonist is indicated

26. The use of a compound of the formula (I) or a pharmaceutically acceptable salt or composition thereof, as defined in any one of claims 1 to 20, for the manufacture of a medicament to treat pain.

27. A method of treatment of a mammal, to treat a disease for which an Trk receptor antagonist is indicated, comprising treating said mammal with an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20.

28. A method of treatment of pain in a mammal, comprising treating said mammal with an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 20.

29. A compound or salt according to any one of claims 1 to 20 for use in a medical treatment in combination with a further drug susbtance.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/051363

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P35/00 A61P25/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/116035 A1 (PFIZER PROD INC [US]; MARX MATTHEW ARNOLD [US]; LA GRECA SUSAN DEBORAH) 8 December 2005 (2005-12-08) the whole document	1-29
A,P	WO 2011/093672 A2 (HANMI PHARM IND CO LTD [KR]; KOREA INST SCI & TECH [KR]; JUNG SEUNG HY) 4 August 2011 (2011-08-04) the whole document	1-29

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 April 2012	07/05/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fritz, Martin

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/051363

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005116035 A1	08-12-2005	BR PI0511512 A	26-12-2007
		CA 2566160 A1	08-12-2005
		EP 1773836 A1	18-04-2007
		JP 4842929 B2	21-12-2011
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		US 2006035912 A1	16-02-2006
		WO 2005116035 A1	08-12-2005
WO 2011093672 A2	04-08-2011	KR 20110088960 A	04-08-2011
		WO 2011093672 A2	04-08-2011

PC71681A

INHIBIDORES DE QUINASA RELACIONADOS CON PIRROLO[2,3-d]PIRIMIDINA TROPOMIOSINA

La invención que se describe en la presente se refiere a cierto compuestos de pirrolo[2,3-d]pirimidina y las sales aceptables desde el punto de vista farmacéutico de estos compuestos. La invención además se refiere a los procesos para la preparación de los compuestos, las composiciones que contienen los compuestos, y los usos de estos compuestos y sales para tratar enfermedades y afecciones asociadas con la actividad de la quinasa relacionada con tropomiosina (Trk). En forma más específica la invención se refiere a los compuestos y sus sales útiles como inhibidores de Trk.

ANTECEDENTES

Las quinasas relacionadas con tropomiosina (Trks) son una familia del receptor de las tirosina quinasas activadas por neurotrofinas. Las Trks cumplen importantes funciones en la sensación del dolor como también en el desarrollo de las células tumorales y la señalización de la supervivencia. De este modo, los inhibidores de las quinasas del receptor Trk podrían proporcionar tratamientos focalizados para las afecciones tales como el dolor y el cáncer. Recientes desarrollos en este campo han sido revisados por Wang *et al* in Expert Opin. Ther. Patents (2009) 19(3): 305-319 y un extracto se reproduce a continuación.

"1,1 Receptores Trk

Cómo una de las familias más grandes de proteínas codificadas por el genoma humano, las proteína quinasas son los reguladores centrales de la transducción de señal como también el control varios procesos celulares complejos. Los receptores tirosina quinasas (RTKs) son una subfamilia de las proteína quinasas (hasta 100 miembros) unidas a la membrana celular que actúan específicamente sobre los residuos de tirosina de las proteínas. Un pequeño grupo dentro de esta subfamilia es las Trk quinasas, con tres isoformas muy homólogas: TrkA, TrkB, y TrkC. Las tres isoformas se activan mediante los factores de crecimiento de alta afinidad denominadas neurotrofinas (NT). i) factor de crecimiento nervioso (NGF), que activa la TrkA; ii) factor neurotrófico derivado del cerebro (BDNF) y NT-4/5, que activan la TrkB; y iii) NT-3, que activa la TrkC. La unión de las neurotrofinas al dominio extracelular de las Trks hace que la Trk quinasa autofosforile en varios sitios tirosina intracelular y dispara las vías de transducción de señal corriente abajo. Las Trks y las neurotrofinas

son bien conocidas por sus efectos sobre el desarrollo y la supervivencia neuronal.

1,2 Trks y cáncer

Aisladas originalmente de los tejidos neuronales, se pensó que las Trks afectan principalmente el mantenimiento y la supervivencia de las células neuronales. Sin embargo, en los últimos 20 años, una creciente evidencia ha sugerido que las Trks cumplen importantes funciones en la transformación maligna, la quimiotaxis, la metástasis, y la señalización de supervivencia en tumores humanos. En los años recientes la asociación entre las Trks y el cáncer se enfocó sobre el cáncer de próstata y el tópico ha sido revisado. Por ejemplo, se informó que las células epiteliales de próstata malignas secretan una serie de neurotrofinas y al menos una Trk. En el cáncer pancreático, se propuso que las interacciones de la Trk y la neurotrofina en forma parácrina y/o autocrina pueden influir en el comportamiento invasivo del cáncer. Además se informó que la TrkB se sobreexpresa en las células cancerígenas pancreáticas humanas metastásicas. Recientemente, ha habido un número de nuevos hallazgos en otros escenarios cancerígenos. Por ejemplo, una traslocación conduce a la expresión de una proteína de fusión que deriva del N-terminal del factor de transcripción ETV6 y el dominio quinasa del C-Terminal de la TrkC. Las fusiones de ETV6-TrkC resultantes son oncogénicas in vitro y parecen ser la causa del carcinoma de pecho secretor y algunas leucemias mielógenas agudas (AML). Las fusiones de TrkA constitutivamente activas se producen en un subconjunto de cánceres de tiroides papilar y carcinomas de colon. En el neuroblastoma, se informó que la expresión de la TrkB es un predictor fuerte del crecimiento tumoral agresivo y un pobre pronóstico, y la sobreexpresión de la TrkB además estaba asociada con el aumento de resistencia a la quimioterapia en las células tumorales del neuroblastoma *in vitro*. Un informe mostró que una variante de corte novedosa de la TrkA denominada TrkAIII señalizada en ausencia de neurotrofinas a través de la vía inositol fosfato-AKT en un subconjunto de neuroblastoma. Además, el análisis mutacional de la tirosina kinoma reveló que las mutaciones de Trk se producían en los cánceres colorrectales y de pulmón. En síntesis, las Trks han sido conectadas con una variedad de cánceres humanos, el descubrimiento de un inhibidor de Trk y su ensayo clínico podrían aportar más conocimiento a la hipótesis biológica y médica del tratamiento de cáncer con terapias focalizadas.

1,3 Trks y dolor

Además de la asociación recientemente desarrollada con el cáncer, las Trks se reconocen como un importante mediador de la sensación del dolor. La insensibilidad congénita al dolor con la anhidrosis (CIPA) es un trastorno de los nervios periféricos (y las glándulas sudoríparas normalmente estimuladas) que evitan que el paciente pueda percibir en forma adecuada el estímulo doloroso o transpirar. Los defectos de la TrkA han demostrado originar la CIPA en varios grupos étnicos.

Actualmente, los fármacos no esteroidales antiinflamatorios (NSAIDs) y los opiáceos tienen baja eficacia y/o efectos colaterales (por ej., efectos colaterales gastrointestinales/renales, respectivamente) contra el dolor neuropático y por lo tanto el desarrollo de novedosos tratamientos del dolor es muy deseado. Se ha reconocido que los niveles de NGF son elevados en respuesta al dolor crónico, la lesión y la inflamación y la administración NGF exógeno aumenta la hipersensibilidad del dolor. Además, la inhibición de la función del NGF con anticuerpos antiNGF o inhibidores de la Trk de pequeñas moléculas no selectivas ha demostrado tener efectos sobre el dolor en modelos animales. Parece que un inhibidor de Trk selectivo (que inhibe al menos la diana del NGF, el receptor TrkA) podría proporcionar un beneficio clínico para el tratamiento del dolor. Revisiones anteriores excelentes han cubierto la focalización del NGF/BDNF para el tratamiento del dolor de modo que esta revisión sólo hará énfasis sobre los inhibidores de Trk quinasa de pequeñas moléculas contra el cáncer y el dolor. Sin embargo, es notable como se informó recientemente que el anticuerpo NGF tanezumab mostró buena eficacia en un ensayo de Fase II contra el dolor de rodilla osteoartrítico."

La Publicación de Solicitud de Patente Internacional número WO2009/012283 se refiere a varios compuestos de fluorofenilo como inhibidores de Trk; las Publicaciones de Solicitudes de Patentes Internacionales números WO2009/152087, WO2008/080015 y WO2008/08001 y WO2009/152083 se refieren a varios pirroles fusionados como moduladores de quinasa; las Publicaciones de Solicitudes de Patentes Internacionales números WO2009/143024 y WO2009/143018 se refieren a varios pirrolo[2,3-d]pirimidinas como inhibidores de Trk; las Publicaciones de Solicitudes de Patentes Internacionales números WO2004/056830 y WO2005/116035 describen varios 4-amino-pirrolo[2,3-d]pirimidinas como inhibidores de Trk. La Publicación de Solicitud de Patente Internacional número WO2011/133637 describe varios pirrolo[2,3-d]pirimidinas y pirrolo[2,3-b]pirimidinas como inhibidores de varias quinasas.

La solicitud provisoria estadounidense US61/471758 se presentó el 5 de abril

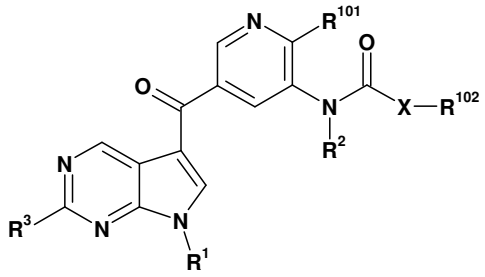
de 2012 y el contenido completo de esa solicitud en su totalidad se incluye en la presente con referencia a la misma.

De este modo los inhibidores de Trk tienen una amplia variedad de usos médicos potenciales. Existe la necesidad de proporcionar nuevos inhibidores de Trk que son buenos candidatos farmacéuticos. En particular, los compuestos deben unirse preferente y potencialmente a los receptores de Trk de manera selectiva en comparación con otros receptores, mientras que muestran poca afinidad para otros receptores, que incluyen otros receptores de quinasa y/o GPC, y muestra actividad funcional como antagonistas del receptor de Trk. Deben ser no tóxicos y muestras pocos efectos colaterales. Más aún, el candidato farmacéutico ideal existirá en una forma física que es estable, no higroscópica y de fácil formulación. Preferentemente debe ser, por ej., bien absorbido desde el tracto gastrointestinal, y/o ser inyectable directamente en el flujo sanguíneo, el músculo, o por vía subcutánea, y/o metabólicamente estable y posee propiedades farmacocinéticas favorables.

Entre los objetivos de esta invención se encuentra el de proporcionar compuestos y sales eficaces, activos por vía oral que se pueden utilizar como sustancias farmacéuticas, en particular, antagonistas de Trk, es decir, que bloquean la actividad de la quinasa intracelular de la Trk, por ej., receptor de TrkA (NGF). Otras características deseables incluyen buena estabilidad de HLM/hepatocrito, biodisponibilidad oral, estabilidad metabólica, absorción, selectividad sobre otros tipos de quinasa, selectividad de dofetilida. Los compuestos y las sales preferidas mostrarán una falta de inhibición /inducción de CYP, y son escasos en CNS.

SÍNTESIS

La presente invención proporciona compuestos de Fórmula I:



(I)

y sus sales aceptables para uso farmacéutico donde los sustituyentes se definen a continuación.

La invención además comprende composiciones farmacéuticas que

comprenden una cantidad terapéuticamente eficaz de un compuesto de fórmula I como se define en la presente, o su sal aceptable para uso farmacéutico, y un vehículo aceptable desde el punto de vista farmacéutico.

La invención además está dirigida a un método para tratar una enfermedad o afección indicada para el tratamiento con un antagonista Trk, en un sujeto, administrando a un sujeto que lo necesita una cantidad terapéuticamente eficaz de uno o más de los compuestos en la presente, o su sal aceptable para uso farmacéutico.

Otros aspectos de la invención serán evidentes a partir de la descripción restante y las reivindicaciones.

Con preferencia, los compuestos de la presente invención son antagonistas potentes en los receptores Trk, y tienen un perfil PK adecuado para permitir la dosificación diaria una vez.

Los compuestos de la presente invención son potencialmente útiles en el tratamiento de un rango de trastornos donde se indica un antagonista de Trk, en particular indicaciones de dolor. Dependiendo de la enfermedad y la afección del paciente, el término "tratamiento" tal como se usa en la presente, puede incluir uno o más tratamientos curativos, paliativos y profilácticos.

De acuerdo con la invención un compuesto de la presente invención puede ser útil para tratar cualquier dolor fisiológico tal como dolor inflamatorio, dolor nociceptivo, dolor neuropático, dolor agudo, dolor crónico, dolor músculo-esqueletal, dolor creciente, dolor central, dolor cardiaco y vascular, migraña, dolor orofacial. Otras afecciones de dolor que se pueden tratar incluyen dolor agudo intenso y afecciones de dolor crónico que pueden involucrar las mismas vías del dolor accionados por los procesos patofisiológicos y como tal cesan para proporcionar un mecanismo protector y en su lugar contribuyen a debilitar los síntomas asociados con un amplio rango de estados de enfermedad.

El dolor es un rasgo de muchos estados traumáticos y de enfermedad. Cuando se produce una lesión sustancial, a través de la enfermedad o traumatismo, al tejido corporal las características de la actividad nociceptora se alteran, esto conduce a la hipersensibilidad en el sitio de la lesión y en el tejido normal cercano. En el dolor agudo la sensibilidad retorna a normal una vez que la lesión ha cicatrizado. Sin embargo, en muchos estados de dolor crónico, la hipersensibilidad supera al proceso de cicatrización y normalmente se debe a la lesión del sistema nervioso debido a la mala adaptación de las fibras aferentes Woolf & Salter 2000 Science 288 1765-1768).

El dolor clínico está presente cuando el rasgo de molestia y sensibilidad anormal aparece entre los síntomas del paciente. Hay un número de subtipos de dolor típicos: 1) dolor espontáneo que puede ser apagado, ardiente, o punzante; 2) las respuestas de dolor al estímulo nocivo son exageradas (hiperalgesia); 3) el dolor se produce por el estímulo normalmente inocuo (alodinia) (Meyer et al., 1994 Textbook of Pain 13-44). El dolor puede dividirse en un número de diferentes áreas debido a diferente patofisiología, estos incluyen dolor nociceptivo, inflamatorio, neuropático entre otros. Debe observarse que algunos tipos de dolor tienen múltiples etiologías y de este se pueden clasificar en más de un área, por ej., el dolor de espalda, el dolor por cáncer tienen ambos componentes nociceptivos y neuropáticos.

Dolor nociceptivo

El dolor nociceptivo es inducido por la lesión del tejido o por un intenso estímulo con el potencial de causar lesión. Los aferentes del dolor se activan por la transducción del estímulo por nociceptores en el sitio de la lesión y sensibilizan la médula espinal en el nivel de su terminación. Posteriormente esto se transmite desde los tractos espinales al cerebro donde se percibe el dolor (Meyer et al., 1994 Textbook of Pain 13-44). La activación de los nociceptores activa dos tipos de fibras nerviosas aferentes. Las fibras A-delta mielinadas transmiten rápidamente y son responsables de las sensaciones de dolor agudas y punzantes, mientras que las fibras C desmielinadas transmiten a una velocidad inferior y transportan el dolor apagado o doloroso. El dolor nociceptivo moderado a agudo severo es un rasgo sobresaliente, pero no está limitado al dolor de esguinces/torceduras, dolor posoperatorio (el dolor que sigue a cualquier tipo de procedimiento quirúrgico), dolor postraumático, quemaduras, infarto del miocardio, pancreatitis aguda, y cólicos renales. Además los síndromes de dolor agudo relacionado con el cáncer que normalmente se deben a las interacciones terapéuticas tales como la toxicidad por quimioterapia, inmunoterapia, terapia hormonal o radioterapia. El dolor nociceptivo moderado a agudo severo es un rasgo sobresaliente, pero no se limita al dolor por cáncer que puede ser un dolor relacionado con el tumor (por ej., dolor óseo, dolor de cabeza o dolor facial, dolor visceral) o asociado con la terapia del cáncer (por ej., síndrome posquimioterapia, síndromes del dolor posquirúrgico crónico, síndrome posradiación), dolor de espalada que puede deberse a hernia de disco o discos intervertebrales desgarrados o anormalidades de las articulaciones fóveas lumbares, articulaciones sacroilíacas, músculos paraespinales o el ligamento longitudinal posterior.

Dolor neuropático

De acuerdo con la invención un compuesto de la presente invención se puede usar potencialmente para tratar el dolor neuropático y los síntomas del dolor neuropático incluyendo hiperalgesia, alodinia y dolor creciente. El dolor neuropático se define como dolor que se inicia o se origina por una lesión primaria o disfunción en el sistema nervioso (definición IASP). El daño nervioso puede originarse por traumatismo y enfermedad y de este modo el término "dolor neuropático" abarca muchos trastornos con diversas etiologías. Estos incluyen pero sin limitación neuropatía diabética, neuralgia posherpética, dolor de espalda, neuropatía por cáncer, neuropatía por VIH, dolor por síndrome del miembro fantasma, síndrome del túnel carpiano, alcoholismo crónico, hipotiroidismo, neuralgia trigémina, uremia, o deficiencias de vitaminas. El dolor neuropáticos es patológico ya que no tiene un rol protector. Además se hace presente después de que la causa original se ha disipado, normalmente dura por años, disminuyendo significativamente la calidad de vida de los pacientes (Woolf and Mannion 1999 Lancet 353: 1959-1964). Los síntomas del dolor neuropáticos son difíciles de tratar, ya que a menudo son heterogéneos incluso entre los pacientes con la misma enfermedad (Woolf & Decosterd 1999 Pain Supp. 6: S141-S147; Woolf and Mannion 1999 Lancet 353: 1959-1964). Incluyen el dolor espontáneo, que puede ser continuo, o dolor paroxismal y anormal, tal como la hiperalgesia (sensibilidad aumentada a un estímulo nocivo) y alodinia (sensibilidad a un estímulo normalmente inocuo).

Dolor agudo intenso y dolor crónico

El dolor agudo intenso y el dolor crónico pueden invocar las mismas vías accionadas por los procesos patofisiológicos y como tal cesan de proporcionar un mecanismo protector y en su lugar contribuyen a debilitar los síntomas asociados con un amplio rango de estados de enfermedad. El dolor es un rasgo de muchos traumatismos y estados de enfermedad. Cuando se produce una lesión sustancial, a través de la enfermedad o traumatismo, al tejido corporal las características de la actividad nociceptora se alteran. Hay una sensibilización en la periferia, localmente alrededor de la lesión y centralmente donde terminan los nociceptores. Esto conduce a la hipersensibilidad en el sitio de la lesión y en el tejido normal cercano. En el dolor agudo estos mecanismos pueden ser útiles y permitir que los procesos de reparación tengan lugar y la hipersensibilidad vuelva a la normalidad una vez que la lesión ha cicatrizado. Sin embargo, en muchos estados de dolor crónico, la hipersensibilidad

supera al proceso de cicatrización y normalmente se debe a la lesión del sistema nervioso. Esta lesión a menudo conduce a la mala adaptación de las fibras aferentes Woolf & Salter 2000 Science 288: 1765-1768). El dolor clínico está presente cuando el rasgo de molestia y sensibilidad anormal aparece entre los síntomas del paciente. Los pacientes tienden a ser más heterogéneos y pueden presentar varios síntomas de dolor. Hay un número de subtipos de dolor típicos: 1) dolor espontáneo que puede ser apagado, ardiente, o punzante; 2) las respuestas de dolor al estímulo nocivo son exageradas (hiperalgesia); 3) el dolor se produce por el estímulo normalmente inocuo (alodinia) (Meyer et al., 1994 Textbook of Pain 13-44). Si bien los pacientes con dolor de espalda, dolor artrítico, traumatismos del SNC, o dolor neuropático pueden tener síntomas similares, los mecanismos subyacentes son diferentes y, por lo tanto, pueden requerir diferentes estrategias de tratamiento.

Dolor crónico

El dolor crónico comprende uno o más del dolor nociceptivo crónico, dolor neuropático crónico, dolor inflamatorio crónico, dolor intermenstrual, hiperalgesia por dolor persistente, alodinia, sensibilización central, sensibilización periférica, desinhibición y facilitación aumentada.

El dolor crónico incluye dolor por cáncer, por ej., dolor por cáncer que surge de malignidad, adenocarcinoma en el tejido glandular, blastoma en el tejido embriónico de los órganos, carcinoma en el tejido epitelial, leucemia en tejidos que forman células sanguíneas, linfoma en el tejido linfático, mieloma en la médula ósea, sarcoma en el tejido conectivo o de apoyo, cáncer adrenal, linfoma relacionado con SIDA, anemia, cáncer de vesícula, cáncer de huesos, cáncer de cerebro, cáncer de pecho, tumores carcinoides, cáncer cervical, quimioterapia, cáncer de colon, citopenia, cáncer endometrial, cáncer esofágico, cáncer gástrico, cáncer de cabeza, cáncer de cuello, cáncer hepatobiliar, cáncer de riñón, leucemia, cáncer de hígado, cáncer de pulmón, linfoma, enfermedad de Hodgkin, linfoma, tumor de no-Hodgkin, tumores del sistema nervioso, cáncer oral, cáncer ovárico, cáncer pancreático, cáncer de próstata, cáncer rectal, cáncer cutáneo, cáncer de estómago, cáncer testicular, cáncer de tiroides, cáncer uretral, cáncer de huesos, cáncer sarcomas del tejido conectivo, cáncer de hueso primario o secundario, tumores que hacen metástasis al hueso, tumores que infiltran el nervio y víscera hueca, tumores cerca de las estructuras neurales. El dolor por cáncer además comprende dolor visceral, por ej., dolor visceral que surge del cáncer pancreático y/o metástasis en el abdomen, dolor somático, por ej., dolor

somático a uno o más del cáncer de hueso, metástasis en el hueso, dolor posquirúrgico, cáncer sarcomas del tejido conectivo, cáncer del tejido óseo, cáncer de las células formadoras de sangre de la médula ósea, mieloma múltiple, leucemia, cáncer de huesos primario o secundario.

Dolor inflamatorio

Las condiciones inflamatorias incluyen inflamación aguda, inflamación aguda persistente, inflamación crónica, e inflamación aguda y crónica combinada.

El dolor inflamatorio incluye dolor inflamatorio agudo y/o dolor inflamatorio crónico donde el dolor inflamatorio crónico puede ser dolor que involucra tanto la sensibilización periférica y central y/o el dolor de etiología mezclada que involucra tanto los componentes del dolor inflamatorio como del dolor neuropático o nociceptivo. El dolor inflamatorio además comprende hiperalgesia, por ej., hiperalgesia primaria y/o secundaria. Además, o en forma alternativa el dolor inflamatorio puede incluir alodinia. El dolor inflamatorio además comprende dolor que persiste más allá de la resolución de un trastorno subyacente o la afección inflamatoria o cicatrización de una lesión.

El dolor inflamatorio es dolor que surge de una afección inflamatoria, por ej., en respuesta a la lesión del tejido agudo debido a traumatismos, enfermedad, por ej., una enfermedad inflamatoria, reacción inmune, la presencia de sustancias extrañas, productos químicos o partículas infecciosas por ejemplo microorganismos. Las afecciones inflamatorias pueden ser o bien inflamación aguda o crónica o ambas.

El dolor inflamatorio puede surgir de una afección inflamatoria debido a una enfermedad inflamatoria tal como las enfermedades de las articulaciones inflamatorias, enfermedades del tejido conectivo inflamatorias, enfermedades autoinmunes inflamatorias, miopatías inflamatorias, enfermedades del sistema digestivo inflamatorias, enfermedades de las vías respiratorias inflamatorias, enfermedades de la inflamación inmune celular, hipersensibilizaciones y alergias, enfermedades de inflamación vascular, enfermedad inflamatoria no inmune, sinovitis, sinovitis vilonodular, atralgias, espondilitis anquilosante, espondiloartritis, espondiloartropatía, gota, enfermedad de Paget, trastornos periarticulares tales como bursitis, enfermedad reumatoide, artritis reumatoide y osteoartritis. La artritis reumatoide en particular, representa inflamación creciente asociada con dolor severo. El dolor artrítico es una forma de dolor inflamatorio y surge de la inflamación en una articulación que origina tanto sensibilización periférica como sensibilización central. En condiciones inflamatorias el sistema nociceptivo se activa por el estímulo mecánico normalmente

inocuo o no doloroso. Además cuando la articulación está en descanso se presenta el dolor y aparece un dolor espontáneo y la hiperalgesia (respuesta aumentada del dolor sobre la estimulación nociva y el dolor sobre la estimulación normalmente no dolorosa). Los procesos inflamatorios en los tejidos periféricos conducen a la sensibilización central en la médula espinal, que contribuye a hiperalgesia y alodinia típicamente asociada con el dolor inflamatorio. Otros tipos de dolor inflamatorio incluyen enfermedades del intestino inflamatorias (IBD).

Otros tipos de dolor

Otros tipos de dolor incluyen pero sin limitación:

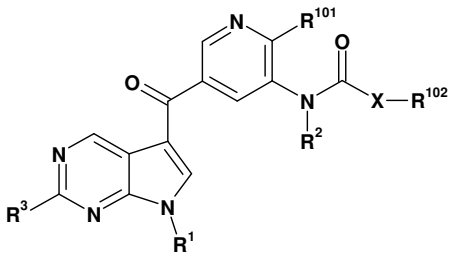
- Trastornos músculo esqueletales que incluyen pero sin limitación mialgia, fibromialgia, espondilitis, artropatías sero-negativas (no reumatoides), reumatismo no articular, distrofinopatía, glicogenólisis, polimiositis, piomiositis;
- Dolor central o “dolor talámico” como se define por el dolor originado por la lesión o disfunción del sistema nervioso que incluye pero sin limitación dolor central posapoplejía, esclerosis múltiple, lesión de la médula espinal, enfermedad de Parkinson, y epilepsia,
- Dolor cardiaco y vascular que incluye pero sin limitación angina, infarto del miocardio, estenosis mitral, pericarditis, fenómeno de Raynaud, escleredoma, isquemia del músculo esqueletal;
- Dolor visceral, y trastornos gastrointestinales. La víscera abarca los órganos de la cavidad abdominal. Estos órganos incluyen los órganos sexuales, el bazo y la parte del sistema digestivo. El dolor asociado con la víscera puede dividirse en dolor visceral digestivo y dolor visceral no digestivo. Los trastornos gastrointestinales normalmente encontrados (GI) incluyen los trastornos del intestino funcionales (FBD) y las enfermedades del intestino inflamatorias (IBD). Estos trastornos del GI incluyen una amplia variedad de estados de la enfermedad que son normalmente solo moderadamente controlados, que incluyen para FBD, reflujo gastroesofágico, dispepsia, el síndrome del intestino irritable (IBS) y el síndrome del dolor abdominal funcional (FAPS), y para IBD, la enfermedad de Crohn, ileitis, y colitis ulcerativa, que producen regularmente el dolor visceral. Otros tipos de dolor visceral incluyen el dolor asociado con dismenorrea, dolor pélvico, cistitis y pancreatitis;

El dolor de cabeza incluye pero sin limitación migraña, migraña con aura, migraña sin aura, cefalea histamínica, migraña del tipo tensión, dolor orofacial que incluye pero sin limitación dolor dental, dolor miofacial temporomandibular, tinnitus,

ardores, síndrome de las piernas inquietas y desarrollo bloqueador de potencial abusivo. Otras afecciones del dolor pueden incluir, dolor de espalda (por ej., dolor de espalda inferior crónico), dolor por cáncer, síndrome regional complejo, dolor neurótico relacionado con el VIH, dolor neuropático inducido por el posoperatorio, dolor posapoplejía, dolor por lesión de la médula espinal, dolor por lesión del nervio traumático, neuropatía periférica diabética, dolor por cistitis intersticial moderada/ severa, dolor por síndrome del intestino irritable, dolor por endometriosis moderada/ severa, dolor pélvico moderado / severo, dolor prostático moderado / severo, dolor por osteoartritis moderado / severo, neuralgia posherpética, dolor por artritis reumatoide, dolor por dismenorrea, dolor posoperatorio preventivo, neuralgia trigémina, bursitis, dolor dental, fibromialgia o dolor miofacial, dolor menstrual, migraña, dolor neuropático (que incluye neuropatía diabética dolorosa), dolor asociado con neuralgia posherpética, dolor posoperatorio, dolor referido, neuralgia trigémina, dolor visceral (que incluye cistitis intersticial e IBS) y dolor asociado con SIDA, alodinia, quemaduras, cáncer, hiperalgesia, hipersensibilización, traumatismo espinal y/o degeneración y apoplejía.

DESCRIPCIÓN DETALLADA

La realización 1 de la invención es un compuesto de Fórmula I:



(I)

o su sal aceptable para uso farmacéutico, donde

R^1 es

H, o

alquilo C_{1-5} opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de OH, $CON(R^5R^6)$, SO_2R^7, SR^7, OR^7, CH_2OH, CO_2R^5, $SONR^7R^7$, $NR^7SO_2R^5$, CN, NO_2 y R^8, o

un sistema anular seleccionado de cicloalquilo C_{3-5}, propelanilo, o un anillo heterociclilo saturado de 4 a 6 miembros, dicho sistema anular tiene hasta 3 heteroátomos del anillo seleccionados de N, O y S, y dicho sistema anular esta

$_5$ opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de metilo, OH, CON(R^5R^6), SO_2R^7, OR^7, CH_2OH, CO_2R^5, $SONR^7R^7$, $NR^7SO_2R^5$, CN, NO_2 y R^8;

R^2 es H o metilo;

R^3 es H, NH_2 o NH(C_{1-3} alquilo $_5$ opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de OH y O(C_{1-3} alquilo));

R^{101} es H, OH, metilo, ciclopropilo, metoxi, etilo, etoxi o CN,

X es un enlace, O, $(CH\text{-}R^4)_n$, NR^{104}, OCH_2 o CH_2O;

R^4 es independientemente H, CH_3, CH_2OH, CH_2OCH_3, OH, NH_2, $NHCH_3$, $N(CH_3)_2$, CH_2NH_2, CH_2NHCH_3,o $CH_2N(CH_3)_2$;

R^{104} es H, alquilos C_{1-3} o un carbociclo C_{4-6} saturado, cada uno de los cuales está $_5$ opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de alquilo C_{1-3} , CH_2OH y NH_2;

n es 1 o 2;

R^{102} es un sistema anular que es un sistema monocíclico, carbocíclico o heterocíclico de 3 a 7 miembros, o un sistema bicíclico de 8 a 14 miembros, dicho sistema anular puede ser saturado o parcial o completamente insaturado, donde el sistema anular heterocíclico puede tener hasta 5 heteroátomos del anillo seleccionados de N, S y O,

donde el sistema anular bicíclico puede ser 2 anillos (carbocíclico-carbocíclico, carbocíclico-heterocíclico, heterocíclico-carbocíclico o heterocíclico-heterocíclico fusionados o enlazados mediante un enlace simple;

dicho sistema anular está $_5$ opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de, donde sea posible,

halo, CN, NR^5R^6, SO_2R^7, SR^7, alquilos C_{1-4} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3} ,

cicloalquilo C_{3-6} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos halógeno, OH, O(alquilo C_{1-3}), O(cicloalquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos halógeno), O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}), $NR^5SO_2R^7$, =O, R^8, $C(O)R^8$, NO_2, $NR^5CO_2R^7$, NR^5COR^7,OR^8, $S(O)R^7$, y CH_2R^8;

R^5 y R^6 son cada uno de ellos independientemente

H, o

alquilo C_{1-5} opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de OH, $CONR^7R^7$, SO_2R^7, OR^7, CH_2OH,

CO_2R^7, $SONR^7R^7$, $NR^7SO_2R^7$, CN, NO_2 y R^9 ,

o

un sistema anular seleccionado de cicloalquilo C_{3-5} , propelanilo, o un anillo heterociclilo saturado de 4 a 6 miembros, dicho sistema anular está $_5$ opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de OH $CON(R^7R^7)$, SO_2R^7, CO_2R^7, $SONR^7R^7$, $NR^7SO_2R^7$, CN, NO_2, halo, NR^7R^7,SR^7, alquilo C_{1-4} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, cicloalquilo C_{3-6} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos halógeno, O(alquilo C_{1-3} sustituido con hasta 3 OH y/o alcoxi C_{1-3}, $NR^7SO_2R^7$,=O, NO_2, $NR^7CO_2R^7$, y $S(O)R^7$

o R^5 y R^6 junto con el N al cual están unidos pueden ser un anillo de 4 a 7 miembros que incluye opcionalmente hasta 2 de otros heteroátomos del anillo independientemente seleccionados de N, O, S, dicho anillos está opcionalmente sustituido con alcoxi C_{1-3} y/o alquilo C_{1-3};

R^7 es H, alquilo C_{1-5} o alcoxi C_{1-5},

dicho alquilo C_{1-5} o alcoxi C_{1-5} está $_5$ opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de halógeno;

R^8 es un sistema anular que es un sistema monocíclico, carbocíclico o heterocíclico de 3 a 7 miembros, o un sistema bicíclico de 8 a 14 miembros, dicho sistema anular puede ser saturado o parcial o completamente insaturado, donde el sistema anular heterocíclico puede tener hasta 5 heteroátomos del anillo seleccionados de N, S y O,

donde el sistema anular bicíclico puede ser 2 anillos (carbocíclico-carbocíclico, carbocíclico-heterocíclico, heterocíclico-carbocíclico o heterocíclico-heterocíclico fusionados o enlazados mediante un enlace simple;

dicho sistema anular está $_5$ opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de, donde sea posible,

halo, CN, NR^5R^6, SO_2R^7, SR^7, alquilos C_{1-4} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3} ,

cicloalquilo C_{3-6} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, alquilo C_{1-3} opcionalmente sustituido con 1 hasta 3 grupos halógeno, OH, O(alquilo C_{1-3}), O(cicloalquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos halógeno), O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}), $NR^5SO_2R^7$, =O, NO_2, NR^7COR^7,$NR^5CO_2R^7$, y $S(O)R^7$;

R^9 es un sistema anular que es un sistema monocíclico, carbocíclico o heterocíclico de

3 a 7 miembros, o un sistema bicíclico de 8 a 14 miembros, dicho sistema anular puede ser saturado o parcial o completamente insaturado, donde el sistema anular heterocíclico puede tener hasta 5 heteroátomos del anillo seleccionados de N, S y O,
donde el sistema anular bicíclico puede ser 2 anillos (carbocíclico-carbocíclico, carbocíclico-heterocíclico, heterocíclico-carbocíclico o heterocíclico-heterocíclico fusionados o enlazados mediante un enlace simple;
dicho sistema anular está $_5$ opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de, donde sea posible,
halo, NR^7R^7, SO_2R^7, SR^7, alquilo C_{1-4} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3} ,
cicloalquilo C_{3-6} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, alquilo C_{1-3} opcionalmente sustituido con 1 hasta 3 grupos halógeno, OH, O(alquilo C_{1-3}), O(cicloalquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos halógeno), O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}), $NR^7SO_2R^7$, =O, NO_2, $NR^7CO_2R^7$, NR^7COR^7, y $S(O)R^7$;
donde cada resto CH puede ser reemplazado por un resto CF.

La realización 2 de la invención es un compuesto o sal de acuerdo con la realización 1 donde R^1 es H, alquilo C_{1-5} $_5$ opcionalmente sustituido con hasta OH,
o R^1 es alquilo C_{1-5} sustituido con $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2H, CO_2CH_3, OCH_3, SCH_3, SO_2CH_3,
o R^1 es un sistema anular seleccionado de cicloalquilo C_{3-5}, propelanilo, u oxetanilo, dicho sistema anular está opcionalmente sustituido con metilo, OH o CH_2OH.

La realización 3 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 o 2 donde R^1 es t-butilo, hidroxi-t-butilo, dihidroxi-t-butilo, 1-hidroxiprop-2-ilo o 1,3-dihidroxiprop-2-ilo.

La realización 4 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 3 donde R^2 es H.

La realización 5 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 4 donde R^3 es H o NH_2.

La realización 6 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 5 donde R^3 es NH_2.

La realización 7 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 5 donde R^3 es H.

La realización 8 de la invención es un compuesto o sal de acuerdo con

cualquiera de las realizaciones 1 a 7 donde R^{101} es H.

La realización 9 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 7 donde R^{101} es OH.

La realización 10 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 9 donde X es un enlace, O, CH_2, C_2H_4, $CH(CH_3)CH_2$, $CH(CH_3)$, $CH(CH_2OH)$, CH_2O, $CH(NH_2)$, CH(OH) o NH.

La realización 11 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 10 donde X es CH_2.

La realización 12 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 11 donde R^{102} es un sistema anular que contiene nitrógeno opcionalmente sustituido que está enlazado al resto X mediante un átomo del anillo de nitrógeno.

La realización 13 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 11 donde R^{102} es un sistema anular opcionalmente sustituido donde el sistema anular se selecciona de

bencimidazolilo, bencisoxazolilo, benzofuranilo, benzoxazolilo, benzotriazolilo, bifenilo, bipirazolilo,

cinnolinilo, ciclobutilimidazolilo, ciclobutilpirazolilo, ciclobutiltiazolilo, ciclopentiltriazolilo, ciclopropilisoxazolilo, ciclopropiloxazolilo, ciclopropilpirazolilo, ciclopropiltriazolilo, diazirenifenilo,

dihidronaftiridinilo, dihidropirrolopirazolilo, dioxinopiridinilo, furazanilo, furopiridinilo, furopirrolilo,

imidazolilo, imidazopirazinilo, imidazopiridazinilo, imidazopiridinilo, imidazopirimidinilo, imidazotiadiazolilo,

imidazotiazolilo, indanilo, indazolilo, indolilo, isoindolilo, isoxazolopiridinilo, isoxazolilo, isoquinolinilo, naftiridinilo, oxazolilo, fenilo, fenilciclopropilo, fenilimidazolilo, fenilpirazolilo, fenilpirrolilo,

feniltetrazolilo, ftalazinilo, purinilo, pirazinilo, pirazolilo, pirazolopiridinilo, pirazolopirimidinilo, pirazolotriazinilo, piridinilo, piridazinilo, piridiniltriazolilo, pirimidinilo, pirroloimidazolilo, pirrolopirazinilo,

pirrolopirimidinilo, pirrolopiridinilo, pirrolilo, quinolinilo, quinazolilo, quinoxalinilo, tetrahidrobencisoxazolilo,

tetrahidrociclopentapirazolilo, tetrahidrotriazolopiridinilo, tetrazolopiridazinilo, tetrazolopiridinilo, tiazolilo, tiazolopiridinilo, tiazolopirimidinilo, tienilopirazolilo, tienopiridinilo, triazolopiridinilo y triazolilo,

La realización 14 de la invención es un compuesto o sal de acuerdo con la realización 13 donde los sustituyentes opcionales se seleccionan independientemente de, siempre que sea posible

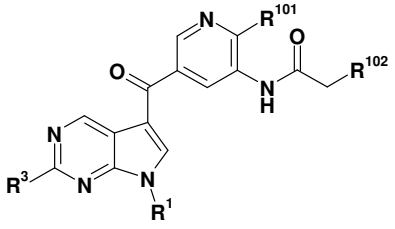
halo, metilo, etilo, propilo, isopropilo, ciclopropilo, CF_3, CHF_2, CH_2F, CH_2OCH_3, CN, CH_2OH, OCH_3, =O, NH_2, SCH_3, SO_2CH_3, fenoxi, fluorofenoxi, bencilo, SCF_3, OCF_3, SO_2CF_3, $NHSO_2CH_3$, $NHSO_2CF_3$, $C(O)CF_3$, $C(O)CH_3$, benzoílo, azetidinilmetilo, fluoroazetidinilmetilo y morfolinometilo.

La realización 15 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 11, 13 o 14 donde R_{102} se selecciona de fenilo, pirazol-1-ilo, 1,2,3-triazol-1-ilo, benzotriazol-2-ilo, piridin-2-ilo, piridin-3-ilo y piridin-4-ilo, cada uno de los cuales está opcionalmente sustituido con halo, metilo, etilo, propilo, isopropilo, ciclopropilo, CF_3, CHF_2, CH_2F, CH_2OCH_3, CN, CH_2OH, OCH_3, =O, NH_2, SCH_3, SO_2CH_3, fenoxi, fluorofenoxi, bencilo, SCF_3, OCF_3, SO_2CF_3, $NHSO_2CH_3$, $NHSO_2CF_3$, $C(O)CF_3$, $C(O)CH_3$, benzoílo, azetidinilmetilo, fluoroazetidinilmetilo y/o morfolinometilo.

La realización 16 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 15 con grupos R^5 y R^6 presentes, donde R^5 y R^6 son cada uno de ellos independientemente H, alquilo C_{1-3} opcionalmente sustituido con alcoxi C_{1-3}, cicloalquilo $C_{3-5,}$ propelanilo, oxetanilo, tetrahidrofuranilo o piranilo,

o R^5 y R^6 junto con el N a cual están unidos pueden ser un anillo de azetidina, pirrolidina, piperidina, piperazina, o morfolina, dicho anillo está opcionalmente sustituido con alcoxi C_{1-3} y/o alquilo C_{1-3}.

La realización 17 de la invención es un compuesto de acuerdo con la realización 1 de la fórmula IA:



(IA)

o su sal aceptable para uso farmacéutico, donde

R3 es H o NH_2 ;

R^1 es alquilo C_{2-4} opcionalmente sustituido con 1 o 2 grupos OH;

R^{101} es H o OH ;

y R^{102} es fenilo o un heterociclo de 5 o 6 miembros aromático o parcialmente insaturado, dicho heterociclo está opcionalmente fusionado a otro fenilo o anillo heterocíclico de 5 a 7 miembros, aromático o parcialmente insaturado, donde cada heterociclo tiene desde 1 a 3 heteroátomos del anillo seleccionado de N, O y S,
y dicho sistema anular está $_5$ opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de
halo, CF_3, alquilos C_{1-4} y cicloalquilo C_{3-5}.

La realización 18 de la invención es un compuesto de acuerdo con la realización 17 donde R^{101} es H.

La realización 19 de la invención es un compuesto de acuerdo con la realización 18 donde
R^1 es butilo, hidroxi-t-butilo o 1-hidroxiprop-2-ilo;
y R^{102} es 4-triflurometilfenilo, 4-clorofenilo, 2,4-difluorofenilo, 5-cloropiridin-2-ilo, 5-fluoropiridin-2-ilo, 3-triflurometilpirazolil-1-ilo, 4-triflurometilpirazol-1-ilo, 3-triflurometil-5-metilpirazol-1-ilo,
3-ciclopropilpirazol-1-ilo, 4-ciclopropilpirazol-1-ilo, 4-triflurometil (1,2,3-triazol-1-ilo), 4-ciclopropil-(1,2,3-triazol-1-ilo), o benzotriazol-2-ilo.

La realización 20 de la invención es un compuesto de acuerdo con la realización 1, seleccionado de: N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)fenil]acetamida;

N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-clorofenil)acetamida;

N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(5-fluoropiridin-2-il)acetamida;

N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida;

N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(3-ciclopropil-1H-pirazol-1-il]acetamida;

N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-ciclopropil-1H-1,2,3-triazol-1-il)acetamida;

N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-pirazol-1-il]acetamida;

N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida;

N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-

cloropiridin-2-il)acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(5-cloropiridin-2-il)acetamida;
N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida;
2-(4-clorofenil)-N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida
N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-pirazol-1-il]acetamida;
N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[4-(trifluorometil)fenil]acetamida;
N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[4-(trifluorometil)fenil]acetamida;
2-(4-clorofenil)-N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida
N-(5-{[2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[5-metil)-3-(trifluorometil-1H-pirazol-1-il]acetamida;
2-(5-cloropiridin-2-il)-N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-clorofenil)acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)fenil]acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-clorofenil)acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)fenil]acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[5-metil-3-(trifluorometil)-1H-pirazol-1-il]acetamida;
y
N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-(ciclopropil-1H-1,2,3-triazol-1-il)acetamida;
o su sal aceptable para uso farmacéutico.

La realización 21 de la invención es una composición farmacéutica que comprende un compuesto de la fórmula (I) o su sal aceptable para uso farmacéutico,

como se define en cualquiera de las realizaciones precedentes 1 a 20, y un vehiculo aceptable desde el punto de vista farmacéutico.

La realización 22 de la invención es un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las realizaciones 1 a 20, para uso como medicamento.

La realización 23 de la invención es un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las realizaciones 1 a 20, para uso en el tratamiento de una enfermedad para la cual se indica un antagonista del receptor Trk.

La realización 24 de la invención es un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las realizaciones 1 a 20, para uso en el tratamiento del dolor.

La realización 25 de la invención es el uso de un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las realizaciones 1 a 20, para la producción de un medicamento para tratar una enfermedad para la cual se indica un antagonista del receptor Trk.

La realización 26 de la invención es el uso de un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las realizaciones 1 a 20, para la producción de un medicamento para tratar el dolor.

La realización 27 de la invención es un método para el tratamiento de un mamífero, para tratar una enfermedad para la cual se indica un antagonista del receptor de Trk, que comprende tratar dicho mamífero con una cantidad eficaz de un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las realizaciones 1 a 20.

La realización 28 de la invención es un método para el tratamiento del dolor en un mamífero, que comprende tratar dicho mamífero con una cantidad eficaz de un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las realizaciones 1 a 20.

La realización 29 de la invención es un compuesto o sal de acuerdo con cualquiera de las realizaciones 1 a 20 para uso en un tratamiento médico en combinación con otra sustancia farmacéutica.

Otras realizaciones de la invención incluyen:

Compuestos o sales de fórmula (I) donde R^1 tiene un valor según se ejemplifica en los ejemplos a continuación;

Compuestos o sales de fórmula (I) donde X tiene un valor según se ejemplifica

en los ejemplos a continuación;

Compuestos o sales de fórmula (I) donde R^{102} tiene un valor según se ejemplifica en los ejemplos a continuación;

Compuestos o sales de fórmula (I) donde R^1, R^2, R^3, R^{101}, X y R^{102} tiene un valor según se ejemplifica en los ejemplos a continuación;

Un compuesto seleccionado de cualquiera de los ejemplos a continuación o su sal aceptable para uso farmacéutico; y

cualquier compuesto intermediario novedoso que se divulga en la presente.

Otras realizaciones se pueden prever basadas en la descripción a continuación.

"Halógeno" significa un grupo flúor, cloro, bromo o yodo.

Los grupos "alquilos", que contiene el número necesario de átomos de carbono, pueden ser sin ramificar o ramificados. Ejemplos de alquilos incluyen metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, sec-butilo y t-butilo.

Las "sales aceptables para uso farmacéutico" de los compuestos de fórmula I incluyen las sales de adición de ácido y de base (que incluyen disales, hemisales, etc.) de los mismos.

Las sales de adición de ácido se forman a partir de ácidos que forman sales no tóxicas. Los ejemplos incluyen las sales de acetato, aspartato, benzoato, besilato, bicarbonato/carbonato, bisulfato/sulfato, borato, camsilato, citrato, edisilato, esilato, formato, fumarato, gluceptato, gluconato, glucuronato, hexafluorofosfato, hibenzato, clorhidrato/cloruro, bromhidrato/bromuro, yohidrato/yoduro, isetionato, lactato, malato, maleato, malonato, mesilato, metilsulfato, naftilato, 2-napsilato, nicotinato, nitrato, orotato, oxalato, palmitato, pamoato, fosfato/ hidrógeno fosfato/dihidrógeno fosfato, sacarato, estearato, succinato, tartrato, tosilato y trifluoroacetato.

Las sales de adición de base se forman a partir de bases que forman sales no tóxicas. Los ejemplos incluyen las sales de aluminio, arginina, benzatina, calico, colina, dietilamina, diolamina, glicina, lisina, magnesio, meglumina, olamina, potasio, sodio, trometamina y zinc.

Para una revisión de las sales adecuadas, véase "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" de Stahl and Wermuth (Wiley-VCH, Weinheim, Alemania, 2002).

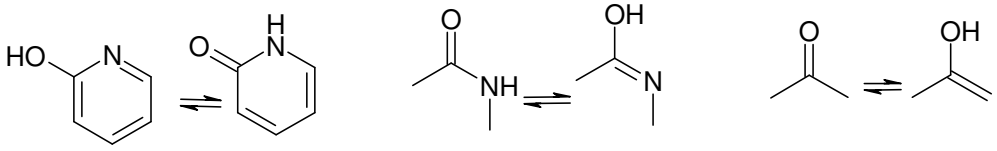
Los compuestos de la invención incluyen compuestos de fórmula I y sus sales como se definió en la presente anteriormente, los polimorfos, e isómeros de los mismos (que incluyen isómeros ópticos, geométricos y tautoméricos) como se

definieron en la presente anteriormente y compuestos isotópicamente marcados de fórmula I.

A menos que se especifique lo contrario, los compuestos de fórmula (I) que contienen uno o más átomos de carbono asimétricos pueden existir como dos o más esteroisómeros. Donde un compuesto de fórmula (I) contiene por ejemplo, un grupo ceto o guanidina o un resto aromático, puede ocurrir isomerismo tautomérico ("tautomerismo"). Sigue que un compuesto simple puede exhibir más de un tipo de isomerismo.

Se incluye dentro del alcance de los compuestos reivindicados de la presente invención todos los estereoisómeros, isómeros geométricos y formas tautoméricas de los compuestos de fórmula (I), que incluyen los compuestos que exhiben más de un tipo de isomerismo, y mezclas de uno o más de los mismos. Se incluyen además sales de adición de ácido o adición de base donde el contraión es ópticamente activo, por ejemplo, D-lactato, o L-lisina, o racémica, por ejemplo, DL-tartrato o DL-arginina.

Ejemplos de tipos de potenciales tautomerismos que se muestran mediante los compuestos de la invención incluyen tautomerismos de hidroxipiridina ⇔ piridona; amida ⇔ hidroxil-imina y ceto ⇔ enol:



Los isómeros cis/trans se pueden separar por técnicas convencionales bien conocidas por los expertos en la técnica, por ejemplo, cromatografía y cristalización fraccional.

Las técnicas convencionales para la preparación /aislamiento de enantiómeros individuales incluyen síntesis quiral de un precursor ópticamente puro adecuado o la resolución del racemato (o el racemato de una sal u otro derivado) utilizando, por ejemplo, cromatografía líquida de alta resolución quiral (HPLC).

En forma alternativa, el racemato (o un precursor racémico) se puede hacer reaccionar con un compuesto ópticamente activo adecuado, por ejemplo, un alcohol, o, en el caso donde el compuesto de fórmula (I) contiene un resto ácido o básico, un ácido o base tal como ácido tartárico o 1-feniletilamina. La mezcla diastereomérica resultante puede separarse por cromatografía y/o cristalización fraccional y uno o ambos de los estereoisómeros ser convertidos a los correspondientes enantiómeros puros por medios bien conocidos por un experto en la técnica.

Los compuestos quirales de la invención (y sus precursores quirales) se pueden obtener en forma enantioméricamente enriquecida utilizando cromatografía, típicamente HPLC, sobre una resina con una fase estacionaria asimétrica y con una fase móvil que consiste de un hidrocarburo, típicamente heptano o hexano, que contiene desde 0 hasta 50% de isopropanol, típicamente desde 2 hasta 20%, desde 0 hasta 5% de una alquilamina, típicamente 0,1% de dietilamina. La concentración del eluato da la mezcla enriquecida.

Las mezclas de estereoisómeros se pueden separar mediante técnicas convencionales conocidas por los expertos en la técnica [véase, por ejemplo, "Stereochemistry of Organic Compounds" de E L Eliel (Wiley, New York, 1994).]

La presente invención incluye todos los compuestos isotópicamente marcados aceptables para uso farmacéutico de fórmula (I) donde uno o más átomos se reemplazan por átomos que tienen el mismo número atómico, pero una masa atómica o número de masa diferente de la masa atómica o número de masa usualmente hallado en la naturaleza.

Ejemplos de isótopos adecuados para inclusión en los compuestos de la invención incluyen los isótopos de hidrógeno, tales como ^{2}H y ^{3}H, carbono, tales como ^{11}C, ^{13}C y ^{14}C, cloro, tales como ^{36}Cl, flúor, tales como ^{18}F, yodo tales como ^{123}I y ^{125}I, nitrógeno, tales como ^{13}N y ^{15}N, oxígeno, tales como ^{15}O, ^{17}O y ^{18}O, fósforo, tales como ^{32}P, y azufre, tales como ^{35}S.

Ciertos compuestos marcados isotópicamente de fórmula (I), por ejemplo, los que incorporan un isótopo radiactivo, son útiles en los estudios de distribución del tejido del sustrato y/o fármaco. Los isótopos radioactivos tritio, es decir ^{3}H, y carbono-14, *i.e.* ^{14}C, son útiles en particular para este fin en vista de su facilidad de incorporación y el medio listo de detección.

La sustitución con isótopos más pesados tal como deuterio (es decir, ^{2}H) puede dar ciertas ventajas terapéuticas que surgen de una mayor estabilidad metabólica (por ej., tiempo de vida útil en vivo aumentado o reducidos requerimientos de dosificación) y de este modo pueden ser preferidos en ciertas circunstancias.

La sustitución con isótopos de emisión de positrones, tales como ^{11}C, ^{18}F, ^{15}O y ^{13}N, puede ser útil en los estudios de Topografía de Emisión de Positrones (PET) para examinar la ocupancia del receptor del sustrato.

Los compuestos marcados isotópicamente de fórmula (I) se pueden preparar en general mediante técnicas convencionales conocidas por los expertos en la técnica o mediante procesos análogos a los que se describen en los ejemplos y preparaciones

adjuntas utilizando un reactivo marcado isotópicamente apropiado en lugar del reactivo no marcado previamente empleado.

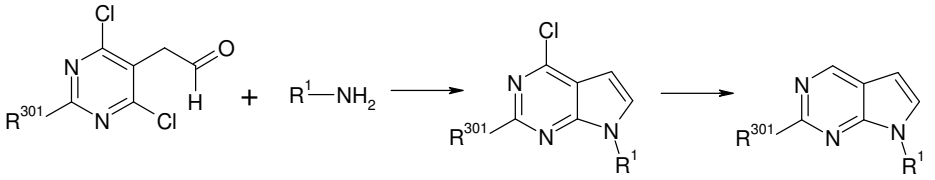
Las vías a continuación, que incluyen las que se mencionan en los ejemplos y preparaciones, ilustran métodos para sintetizar los compuestos de fórmula (I). El experto en la técnica apreciará que los compuestos de la invención, y los intermediarios, podrían producirse mediante métodos diferentes a los que se describen específicamente en la presente, por ejemplo, por la adaptación de los métodos que se describen en la presente, por ejemplo mediante métodos conocido en la técnica. Las guías adecuadas de síntesis, las interconversiones de grupo funcional, el uso de grupos protectores, etc., son por ejemplo: :"Comprehensive Organic Transformations" de RC Larock, VCH Publishers Inc. (1989); Advanced Organic Chemistry" de J. March, Wiley Interscience (1985); "Designing Organic Synthesis" by S Warren, Wiley Interscience (1978); "Organic Synthesis – The Disconnection Approach" de S Warren, Wiley Interscience (1982); "Guidebook to Organic Synthesis" by RK Mackie and DM Smith, Longman (1982); "Protective Groups in Organic Synthesis" by TW Greene and PGM Wuts, John Wiley and Sons, Inc. (1999); and "Protecting Groups" de PJ, Kocienski, Georg Thieme Verlag (1994); y cualquier versión actualizada de dichos trabajos estándares.

En los métodos de síntesis general, a menos que se especifique lo contrario, los sustituyentes son como se definieron anteriormente con referencia a los compuestos de fórmula (I) anterior. R^{1011} es igual que R^{101} o una versión adecuadamente protegida del mismo.

El esquema 1 ilustra la preparación de los intermediarios de fórmula general (Int 1), donde se pueden producir a partir de amina (Int3) donde, en esos casos donde R^1 contiene un alcohol, un forma protegida de R^1 donde se utiliza un grupo protector hidroxilo (PG) adecuado. Se puede usar cualquier grupo protector de oxígeno adecuado (como se describe en "Protecting Groups in Organic Synthesis" 3º edición T.W. Greene and P.G. Wuts, Wiley-Interscience, 1999). Los grupos protectores de oxígeno comunes adecuados para uso en la presente incluyen ter-butildimetilsililo (TBDMS), tetrahidropiranilo (THP) y terbutilsililo (TBS).

Los compuestos de formula (Int 1) se pueden preparar a partir de los compuestos de fórmula (Int 2) como se ilustra en el esquema 1.

Esquema 1



Int 4 **Int 3** **Int 2** **Int 1**

donde R^{301} puede ser H o halógeno, típicamente cloro.

Los compuestos de formula (Int 1) se pueden preparar a partir de amina (int 3) y (Int 4) en un paso de ciclización seguido de un paso de de clorinación. Las condiciones típicas empleadas involucran la agitación de la amina de fórmula general (Int 3) y el aldehído (Int 4) juntos, preferentemente en etanol a una temperatura desde temperatura ambiente hasta 80ºC.

Por ej., según se ejemplifica en las Preps. 1-5

El intermediario cloruro (Int 2) se reduce utilizando condiciones de literatura estándar, por ejemplo hidrogenación utilizando un catalizador adecuado tal como paladio sobre carbono y un aditivo tal como amoníaco en un solvente adecuado tal como etanol. En forma alternativa el cloruro puede ser eliminado desplazando el cloro con metano tiol seguido de la eliminación de níquel Raney del intermediario SMe.

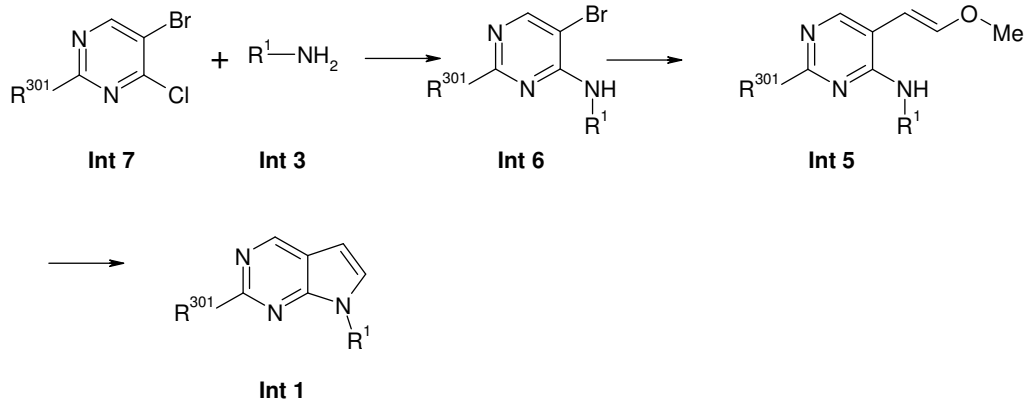
Por ej., según se ejemplifica en las Preps. 8-13

En esos casos donde R^1 contiene uno o más alcoholes, se puede utilizar una forma protegida de R^1 con un grupo protector hidroxilo adecuado (PG). Se puede usar cualquier sistema de protección/desprotección del grupo protector de oxígeno adecuado (como se describe en “Protecting Groups in Organic Synthesis” 3º edición T.W. Greene and P.G. Wuts, Wiley-Interscience, 1999). Los grupos protectores de oxígeno comunes adecuados para uso en la presente incluyen ter-butildimetilsililo (TBDMS), y tetrahidropiranilo (THP).

Los intermediarios de fórmula general (**Int 3**) y (**Int 4**) están o bien disponibles en el comercio o serán conocidos por los expertos en la técnica con referencia a los precedentes de la literatura y/o las preparaciones en la presente.

Los compuestos de formula (**Int 1**) se pueden preparar a partir de los compuestos de fórmula (**Int 7**) como se ilustra en el esquema 2.

Esquema 2



Int 7 **Int 3** **Int 6** **Int 5**

Int 1

Los compuestos de formula (Int 1) donde R^3 puede ser H o halógeno, típicamente cloro, se pueden preparar además a partir de compuestos de fórmula (Int 7) a través del desplazamiento de un halógeno, típicamente cloro, con aminas de fórmula (Int 3), en una reacción Suzuki catalizada con paladio seguido de una ciclización ácida.

Las condiciones típicas comprenden agitación de la amina de fórmula general (Int 3) y el intermediario de fórmula general (Int 7) junto con una base adecuada, tal como trietilamina, en un solvente tal como acetonitrilo o diclorometano, para dar los compuestos de fórmula general (Int 6).

El éter vinílico se puede introducir hacienda reaccionar el intermediario (Int 6) con un éster borónico adecuado y una base adecuada, tal como hidróxido de sodio y un catalizador adecuado tal como tetrakis(trifenilfosfina)paladio (0) en un solvente tal como THF a una temperatura desde temperatura ambiente hasta 70ºC.

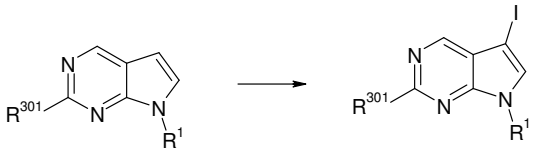
Los intermediarios de fórmula (Int 1) se pueden producir mediante el tratamiento del intermediario (Int 5) con un ácido tal como cloruro de hidrógeno en un solvente orgánico tal como isopropanol a una temperatura desde temperatura ambiente hasta 70ºC.

Por ej., según se ejemplifica en las Preps. 60-62

Los intermediarios de fórmula general (Int 3) y (Int 7) están o bien disponibles en el comercio o serán conocidos por los expertos en la técnica con referencia a los precedentes de la literatura y/o las preparaciones en la presente.

Los compuestos de formula (Int 8) se pueden preparar a partir de los compuestos de fórmula (Int 1) como se ilustra en el esquema 3.

Esquema 3



(Int 1) **(Int 8)**

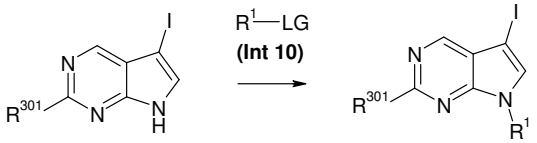
donde R^{301} es H o halógeno, típicamente cloro;

Los compuestos de formula (Int 8) se preparan típicamente por yodinación de los intermediarios de pirrolopirimidina (Int 1). Las condiciones típicas empleadas involucran la agitación del intermediario de fórmula general (XI) con un reactivo de yodinación tal como N-yodosuccinimida en un solvente adecuado, tal como DMF o acetonitrilo.

Por ej., según se ejemplifica en las Preps. 14-19, 40, 63.

Los compuestos de formula (Int 8) se pueden preparar además a partir de los compuestos de fórmula (Int 9) como se ilustra en el esquema 4.

Esquema 4



(Int 9) **(Int 8)**

donde R^{301} es H o halógeno, típicamente cloro; LG es halógeno o tosilato, triflato o mesilato;

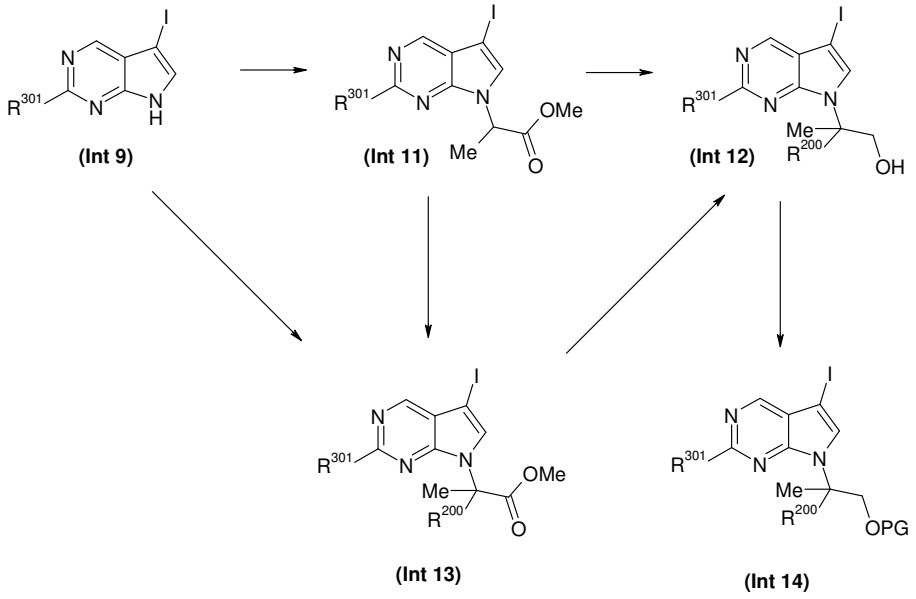
En forma alternativa, los intermediarios de fórmula general (Int 8) se pueden preparar por alquilación de los intermediarios de pirrolopirimidina (Int 9), con los compuestos de fórmula (Int 10) utilizando una base adecuada tal como carbonato de cesio o carbonato de potasio en un solvente orgánico. Una alternativa adecuada es utilizar un aditivo (tal como yoduro de potasio) como también una base. Las condiciones preferidas comprenden carbonato de cesio en DMF a temperatura ambiente.

En esos casos donde R^1 contiene uno o más alcoholes, una forma protegida de R^1 se puede usar como se describe en el esquema 1.

por ej., según se ejemplifica en la preparación 20.

Los compuestos de formula (Int 12) se pueden preparar a partir de los compuestos de fórmula (Int 11) como se ilustra en el esquema 5.

Esquema 5



donde R^{301} es H o halógeno, típicamente cloro;

Los intermediarios de formula general (Int 9) se hacen reaccionar en una reacción de alquilación para dar un intermediario éster (Int 11) o (Int 13), a partir del cual el grupo éster se puede reducir y proteger para suministrar un compuesto de fórmula general (Int 14), donde R^{200} es un H o grupo metilo. Como se mencionó previamente en el esquema 1 el grupo hidroxi se puede proteger con un grupo protector de oxígeno adecuado (PG), donde los grupos protectores preferidos son TBDMS, TBS y THP.

Las condiciones típicas empleadas para la alquilación involucran la agitación del compuesto de fórmula general (Int 9) con el haluro apropiado junto con una base adecuada, como se describe en el esquema 4. Los compuestos de la fórmula general (Int 11) donde R^{200} es H se pueden convertir a intermediarios (Int 13) donde R^{200} es metilo mediante otra alquilación, típicamente involucrando un agente de alquilación adecuado tal como yoduro de metilo y una base adecuada tal como t-butóxido de potasio en un solvente orgánico tal como THF.

Por ej., según se ejemplifica en las Preps. 20, 21, 41, 53

La reducción de los intermediarios de éster (Int 11) y (Int 13) se puede realizar

utilizando un reactivo reductor adecuado tal como borohidruro de litio, hidruro de litio aluminio o hidruro de diisobutilaluminio en un solvente adecuado tal como etanol o THF. En forma alternativa los intermediarios de fórmula general (Int 12) se pueden producir en una reacción de dos pasos por hidrolización del éster de fórmula (Int 11) o (Int 13) al ácido apropiado utilizando una base adecuada tal como hidróxido de litio acuoso en un solvente orgánico adecuado tal como THF, activando posteriormente el ácido utilizando un reactivo adecuado tal como cloroformiato de isobutilo y utilizando un agente reductor adecuado tal como borohidruro de sodio.

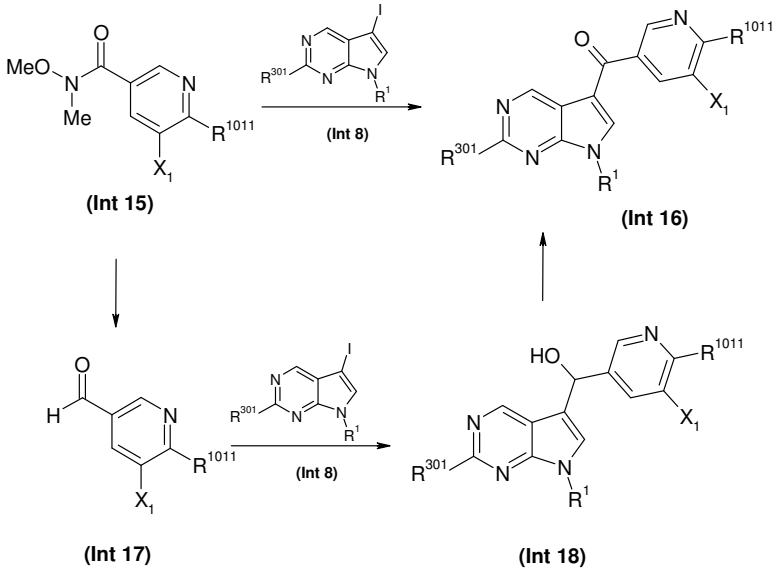
por ej., según se ejemplifica en las Preps. 22, 42, 43, 54

Los compuestos de formula general (Int 14) se pueden producir mediante la protección del grupo hidroxi de los intermediarios (Int 12) con un grupo protector de oxígeno (PG) adecuado, donde los grupos protectores preferidos son TBDMS y THP, como se describe en el esquema 1.

por ej., según se ejemplifica en las Preps. 44, 45, 55.

Los compuestos de formula (Int 16) se pueden preparar a partir de los compuestos de fórmula (Int 8) como se ilustra en el esquema 6.

Esquema 6



Donde R^{301} es H o halógeno, típicamente cloro, y X_1 es un halógeno adecuado, típicamente bromo o yodo;

Los compuestos de fórmula (Int 16) se pueden preparar a partir de los compuestos de fórmula (Int 8) y (int 15) a través de una metalación del intermediario (Int 8) (utilizando un reactivo organometálico adecuado tal como butillitio o cloruro de

isopropilmagnesio) y haciendo reaccionar con el intermediario Weinreb amina (Int 15) a una temperatura desde -78ºC hasta temperatura ambiente.

Por ej., según se ejemplifica en las Preps. 26, 27, 46, 47, 56, 58, 64

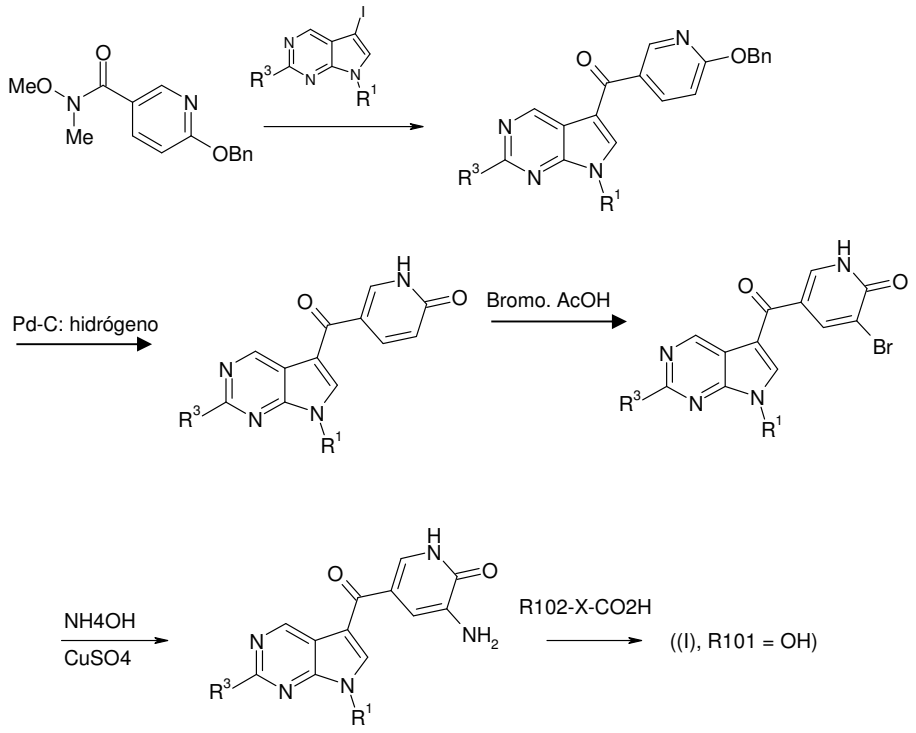
En forma alternativa, los compuestos de fórmula (Int 15) se pueden convertir en aldehídos de fórmula (Int 17) por la reducción del intermediario Weinreb amida utilizando un agente reductor adecuado. Las condiciones preferidas comprenden hidruro de diisopropilaluminio en THF a -78ºC, según se ejemplifica en la preparación 106.

Los compuestos de formula (Int 17) se pueden hacer reaccionar posteriormente con los compuestos de fórmula (Int 8) de acuerdo con el mismo procedimiento de metalación descripto anteriormente. El alcohol intermediario (Int 18) se puede oxidar posteriormente a la cetona (Int 16). Las condiciones de oxidación típicas involucran el uso de un reactivo de oxidación tal como el reactivo Dess-Martin en DCM o el ácido 2-yodoxibenzoico en un solvente adecuado tal como acetato de etilo a una temperatura desde temperatura ambiente hasta temperatura de reflujo.

por ej., según se ejemplifica en las Preps. 29, 30

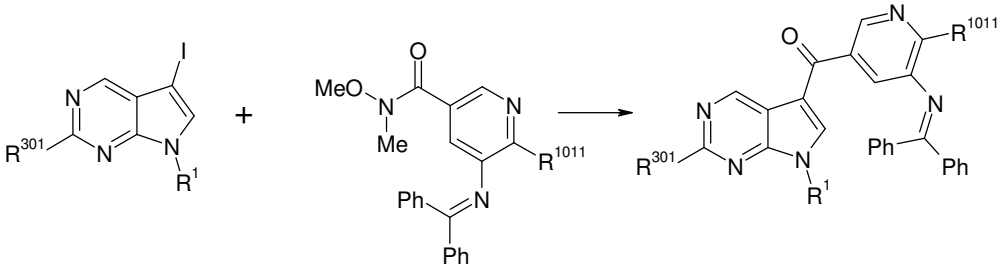
Los intermediarios de fórmula general (Int 15) y (Int 17) están o bien disponibles en el comercio o serán conocidos por los expertos en la técnica con referencia a los precedentes de la literatura y/o las preparaciones en la presente.

Los intermediarios correspondientes y los compuestos de fórmula (I) donde R^{101} es OH se consideran como tautómeros de piridonas y se pueden producir utilizando una metodología análoga usando un grupo protector de bencilo para el paso de Weinreb amida, viz R^{1011} es benciloxi (OBn), por ej., como se ilustra a continuación.



Los compuestos de formula (Int 20) se pueden preparar a partir de los compuestos de fórmula (Int 8) como se ilustra en el esquema 7.

Esquema 7



(Int 8) **(Int 19)** **(Int 20)**

Donde R^{301} es H o halógeno, típicamente cloro;

Los compuestos de formula (Int 20) se pueden preparar a partir de los compuestos de fórmula (Int 8) y (int 19) de acuerdo con un procedimiento de metalación como se describe en el esquema 6 anterior.

Las condiciones típicas empleadas involucran la metalación del intermediario haluro (Int 8) (utilizando un reactivo organometálico adecuado tal como butillitio o cloruro de isopropil magnesio) y haciendo reaccionar con el intermediario Weinreb

amida (Int 19) a una temperatura desde -78ºC hasta temperatura ambiente en un solvente adecuado tal como THF.

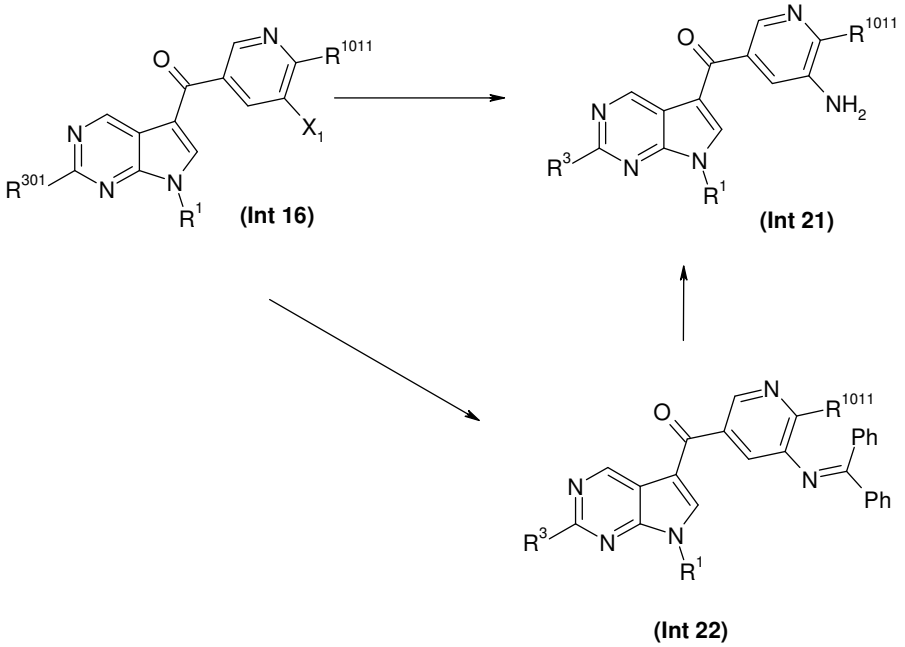
Por ej., según se ejemplifica en las Preps. 24, 25, 28, 50

Los intermediarios (Int 19) serán bien conocidos por los expertos en la técnica con referencia a los precedentes de la literatura y/o a las preparaciones en la presente.

Por ej., según se ejemplifica en la Prep. 23

Los compuestos de formula (Int 21) se pueden preparar a partir de los compuestos de fórmula (Int 16) como se ilustra en el esquema 8.

Esquema 8



donde X_1 es bromo o yodo;

Los compuestos de formula (Int 21) se pueden preparar a partir de los compuestos de fórmula (Int 16) a través de la aminación directa del haluro utilizando las condiciones de literatura estándares. Por ejemplo, la amina (Int 21) se prepara típicamente utilizando amoníaco con un catalizador de cobre adecuado tal como sulfato de cobre (II) u óxido de cobre (I) en un solvente adecuado tal como NMP en un recipiente cerrado a una temperatura entre temperatura ambiente y 140ºC. Donde R^{301} es Cl, esto también se desplaza por amoníaco en las mismas condiciones para proporcionar aminas de fórmula general (Int 21) donde R^3 es NH_2.

Por ej., según se ejemplifica en las Preps. 31, 32, 36, 48, 49, 57, 59, 65

La desprotección de un grupo protector de hidroxilo sobre R^1 (si está presente)

también se produce en estas condiciones. En estos casos, o bien el grupo protector se puede reaplicar como se describió previamente en el esquema 5 o la amina de fórmula general (Int 21) se puede utilizar directamente.

En forma alternativa, los compuestos de fórmula general (Int 21) donde R^3 es H, se pueden producir convirtiendo los intermediarios de fórmula general (Int 16) donde R^{301} es H, mediante los compuestos (Int 22). Las condiciones típicas empleadas involucran la agitación del haluro de fórmula general (Int 16), donde R^{301} es H, con benzofenona imina, una base adecuada tal como fosfato de potasio, un ligando adecuado tal como 2-di-ter-butilfosfino-2′,4′,6′-triisopropilfenil y un catalizador adecuado tal como tris(diobencilidenoacetona)dipaladio o un solvente orgánico tal como 1,2-dimetoxietano a una temperatura desde temperatura ambiente hasta el punto de ebullición del solvente.

El intermediario (Int 22) se puede desproteger para suministrar las aminas de fórmula general (Int 21). Las condiciones típicas emplean el tratamiento con un ácido acuoso tal como cloruro de hidrógeno o ácido cítrico en un solvente orgánico tal como THF.

Por ej., según se ejemplifica en las Preps. 33, 37-39

Los compuestos de formula (Int 20) se pueden preparar a partir de la fórmula (Int 22 donde R^{301} es Cl) como se ilustra en el esquema 9.

Esquema 9



(Int 22)
Donde R^{301} es Cl)

(Int 20)

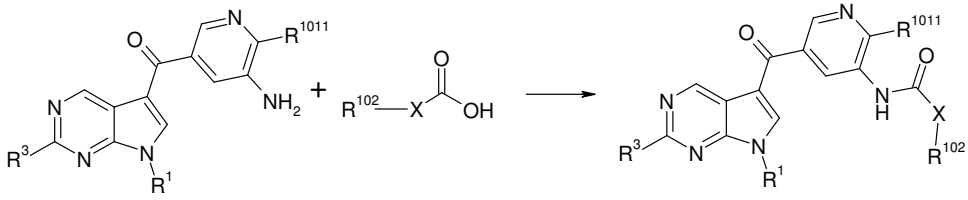
Los compuestos de formula (Int 20) se pueden preparar a partir de los compuestos de fórmula (Int 22) donde R^{301} es cloro a través de una reacción de aminación como se describió anteriormente. Donde el cloro se hace reaccionar con 2,4-dimetoxibencilamina y la amina se puede desproteger como se indicó previamente.

Las condiciones típicas empleadas involucran la agitación del cloro-pirimidina de fórmula general (Int 22), donde R^{301} es Cl, con 2,4-dimetoxibencilamina y un aditivo adecuado tal como 4-dimetilamino piridina en un solvente orgánico tal como 1,4-

dioxano a una temperatura desde temperatura ambiente hasta temperatura de reflujo. por ej., según se ejemplifica en la Prep. 51

Los compuestos de formula (I) se pueden preparar a partir de los compuestos de fórmula (Int 21) y (Int 23) como se ilustra en el esquema 10.

Esquema 10



(Int 21) **(Int 23)** **(I)**

Los compuestos de fórmula (I) se pueden preparar a partir de los compuestos de fórmula (Int 21 y (Int 23) mediante la formación de amida, si fuera necesario agregando una base adecuada (tal como DIPEA) y/o aditivo (tal como DMAP), y un solvente orgánico (tal como piridina).

Las condiciones típicas empleadas involucran la agitación de la fórmula general (Int 21) y el ácido de fórmula general (Int 23) junto con un reactivo de acoplamiento adecuado tal como HATU o anhídrido cíclico del ácido 1-propilfosfónico, si fuera necesario agregando una base adecuada tal como NMM, DIPEA, o TEA en un solvente orgánico tal como piridina, THF, DMF, o DMA a una temperatura desde temperatura ambiente hasta 50ºC. Una alternativa adecuada es utilizar un aditivo (tal como 4-dimetilaminopiridina) como también una base. Se puede utilizar cualquier solvente adecuado de los que se mencionaron anteriormente. Al menos un equivalente del ácido (Int 23) y al menos un equivalente del reactivo de acoplamiento se deben utilizar y si se desea se puede utilizar un exceso de uno o ambos.

Por ej., como se ejemplifica en los ejemplos 1-8, 34-45,48-53, 57-64, las preps. 34, 35, 52, 66-78.

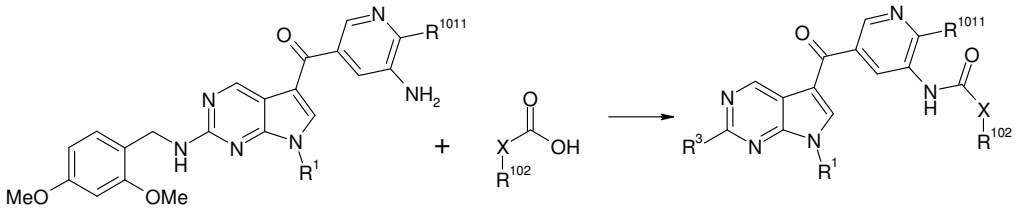
Donde R^1 contiene un grupo protector hidroxilo en el intermediario (Int 21), la eliminación del grupo protector (PG) se puede realizar in situ o como un paso adicional, agregando un ácido adecuado y un solvente orgánico al residuo bruto después de que se ha realizado la formación de amida. Los grupos protectores comunes a utilizar incluyen TBDMS, el cual se elimina fácilmente mediante el tratamiento con un ácido tal como cloruro de hidrógeno acuoso o ácido cítrico acuoso en un solvente orgánico tal como THF o mediante el tratamiento con una fuente de fluoruro tal como fluoruro de tetrabutilamonio en un solvente orgánico tal como THF, y

THP, el cual además se elimina fácilmente mediante el tratamiento con un ácido tal como cloruro de hidrógeno acuoso en un solvente orgánico tal como THF.
por ej., como se ejemplifica en los ejemplos 9-33, 54-56.

Los intermediarios de fórmula general (Int 23) están o bien disponibles en el comercio o serán conocidos por los expertos en la técnica con referencia a los precedentes de la literatura y/o las preparaciones en la presente.

Los compuestos de formula (I) donde R^3 es NH_2 se pueden preparar a partir de los compuestos de fórmula (Int 20) como se ilustra en el esquema 11.

Esquema 11

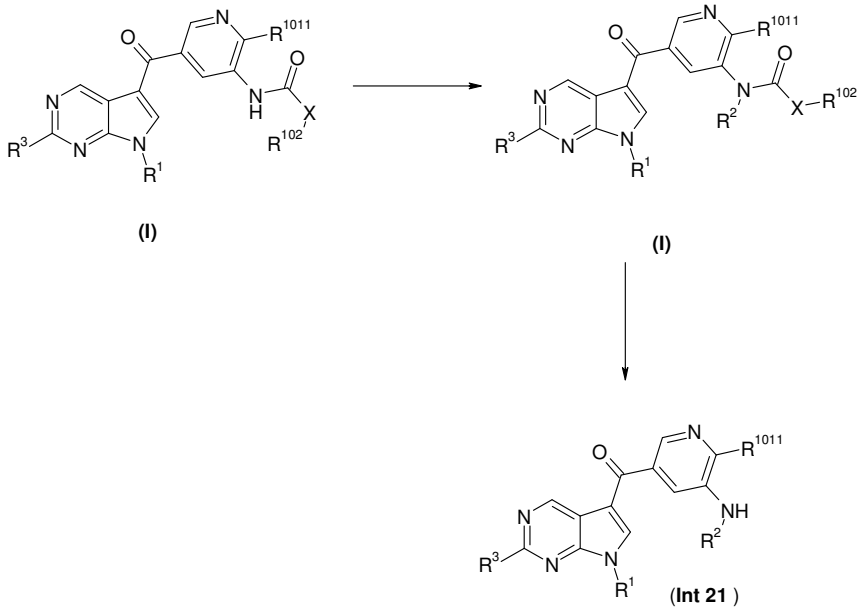


(Int 24) **(Int 23)** **(I)**

Los compuestos de fórmula (I) se pueden preparar a partir de los compuestos de fórmula (Int 24) a través de la formación del enlace amida como se describió previamente en el esquema 10 seguido de la eliminación del grupo dimetoxibencilamina in situ, agregando un ácido adecuado y solvente orgánico al residuo bruto después de haberse realización la formación de amida. Los ácidos adecuados para esta desprotección incluyen cloruro de hidrógeno o ácido trifluoroacético en un solvente orgánico tal como THF.
por ej., como se ejemplifica en los Ejemplos 46-47

Los compuestos de formula (I) donde R^2 es metilo se pueden preparar a partir de los compuestos de fórmula (I) donde R^2 es H como se ilustra en el esquema 12.

Esquema 12



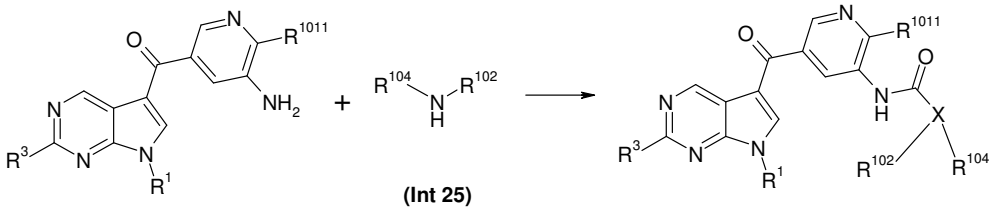
(I) **(I)** (**Int 21**)

Los compuestos de formula (I) donde R^2 es metilo se pueden preparar a partir de los compuestos de fórmula (I) donde R^2 es H de acuerdo con una reacción de alquilación con yoduro de metilo como se ilustra en el esquema 4.

Cuando XR^{102} es boc, esto se puede desproteger utilizando condiciones del grupo protector estándares para proporcionar el intermediario (Int 21).

Los compuestos de formula (I) donde X es NR^{104} se pueden preparar a partir de los compuestos de fórmula (Int 21) como se ilustra en el esquema 13.

Esquema 13



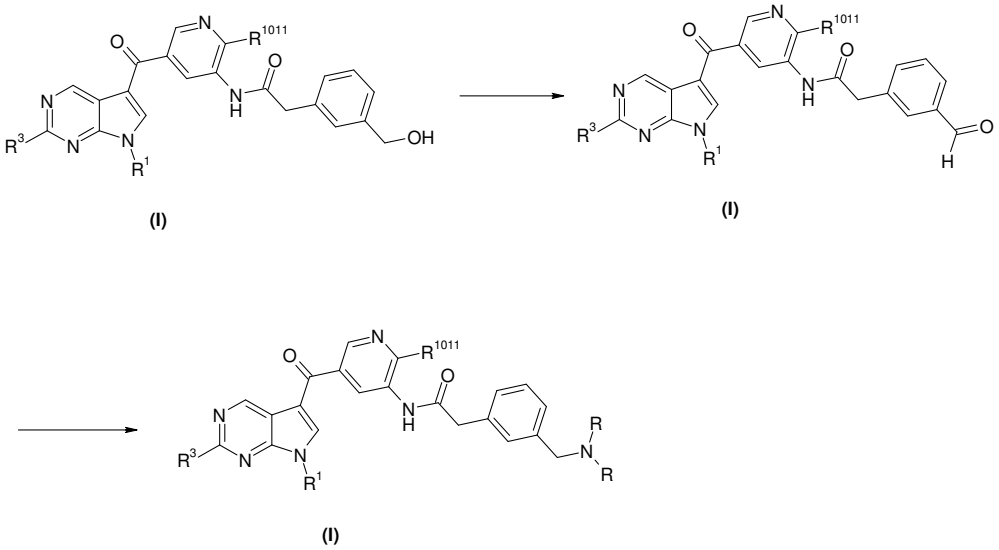
(Int 21) **(Int 25)** **(I)**

Los compuestos de formula (I) donde X es NR^{104} se pueden preparar a partir de los compuestos de fórmula (Int 21), (Int 25) y fenilcloroformiato. Las condiciones típicas comprenden cloroformiato de fenilo y los compuestos de fórmula (Int 24) con piridina en THF desde 0 hasta 100ºC, como se ejemplifica en el ejemplo 526.

Los compuestos de formula (I) donde un sustituyente en el anillo o anillos de R^{102} es un grupo aminometilo CH_2NR_2 se puede preparar a partir de los compuestos

de fórmula (1) como se ilustra en el esquema 14.

Esquema 14



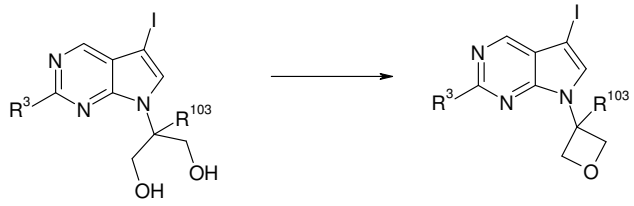
(I) (I)

(I)

Los compuestos de formula (I) donde existe un alcohol primario se pueden oxidar al aldehído utilizando periodinano Dess Martin en DCM a temperatura ambiente seguido de aminación reductora con una amina HNR_2 adecuada utilizando triacetoxiborohidruro de sodio y ácido acético en DCM.

Los compuestos de formula (Int 26) se pueden preparar a partir de los compuestos de fórmula (Int 27) como se ilustra en el esquema 15.

Esquema 15



Int 27 Int 26

donde R^{103} es Me o CH_2OH;

Los compuestos de formula (Int 26) se pueden preparar a partir de los compuestos de fórmula (Int 27) a través de la conversión de un alcohol en un grupo saliente adecuado seguido de la ciclización en condiciones básicas. Las condiciones preferidas comprenden cloruro de tosilo con n-butil litio en THF.

De acuerdo con otra realización la presente invención proporciona compuestos intermediarios novedosos.

Las sales aceptables para uso farmacéutico de un compuesto de fórmula (I) se

pueden preparar fácilmente mezclando las soluciones del compuesto de fórmula (I) y el ácido o base deseada, según sea apropiado. La sal puede precipitar a partir de la solución y recolectarse por filtración o se puede recubrir por evaporación del solvente. El grado de ionización en la sal puede variar desde completamente ionizado hasta casi no-ionizado.

Los compuestos de la invención destinados a uso farmacéutico se pueden administrar solos o en combinación con uno o más de otros compuestos de la invención o en combinación con uno o más de otros agentes farmacéuticos (o como cualquier combinación de los mismos). En general, se administrarán como una formulación en asociación con uno o más excipiente aceptables para uso farmacéutico. El término "excipiente" se usa en la presente para describir cualquier principio biológicamente inactivo diferente de los compuestos y sales de la invención. La elección del excipiente dependerá en gran medida de factores tales como el modo particular de administración, el efecto del excipiente en la solubilidad y estabilidad, y la naturaleza de la forma de dosificación. Por ejemplo, un compuesto de fórmula I, o su sal, o solvato aceptable para uso farmacéutico, como se definió anteriormente, se puede administrar en forma simultánea (por ej., como una combinación de dosis fija), en forma secuencial o en forma separada en combinación con uno o más de otros agentes farmacéuticos.

Ejemplos de agentes adicionales se podrían seleccionar a partir de uno o más de:

- Un modulador del canal Nav 1,7, tal como un compuesto que se divulga en el documento WO 2009/012242 o el documento WO2010/079443;
- Un modulador del canal de sodio alternativo, tal como un modulador Nav 1,3 (por ej., como se divulga en el documento WO2008/118758); o un modulador Nav 1,8 (por ej., como se divulga en el documento WO 2008/135826, en forma más particular N-[6-amino-5-(2-cloro-5-metoxifenil)piridin-2-il]-1-metil-1H-pirazol-5-carboxamida);
- Un inhibidor de la señalización del factor de crecimiento nervioso, tales como: Un agente que se une a NGF e inhibe la actividad biológica de NGF y/o las vías corriente abajo mediadas por la señalización de NGF (por ej., tanezumab), un antagonista TrkA o un antagonista p75;
- Un compuesto que aumenta los niveles de endocanabinoide, tal como un compuesto con actividad inhibidora de amid hidrolasa de ácido graso (FAAH), en particular los que se divulgan en el documento WO 2008/047229 (por ej., N-

piridazin-3-il-4-(3-{[5-(trifluorometil)piridin-2-il]oxi}bencilideno)piperideno-1-carboxamida);

- Un analgésico opioides, por ej., morfina, heroína, hidromorfona, oximorfona, levorfanol, levalorfan, metadona, meperidina, fentanilo, cocaína, codeína, dihidrocodeína, oxicodona, hidrocodona, propoxifeno, nalmefeno, nalorfina, naloxone, naltrexona, buprenorfina, butorfanol, nalbufina, o pentazocina;
- Un fármaco antiinflamatorio no esteroidal (NSAID), por ej., aspirina, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofeno, indometacin, vetoprofen, vetorolac, ácido meclofenámico, ácido mefenámico, meloxicam, nabumetona, naproxeno, nimesulide, nitroflurbiprofen, olsalazina, oxaprozin, fenilbutazona, piroxicam, sulfasalazina, sulindac, tolmetin o zomepirac
- Un sedante barbiturato, por ej. amobarbital, aprobarbital, butabarbital, butabital, mefobarbital, metarbital, metohexital, pentobarbital, fenobartital, secobarbital, talbutal, teamilal o tiopental;
- Una benzodiazepina que tiene una acción sedante, por ej., clordiazepóxido, clorazepato, diazepam, flurazepam, lorazepam, oxazepam, temazepam o triazolam;
- Un antagonista H_1 que tiene una acción sedante, por ej., difenidramina, pirilamina, prometazina, clorfeniramina o clorciclizina;
- Un sedante tal como glutehimida, meprobamato, metaqualona, o dicloralfenazona;
- Un relajante muscular esqueletal, por ej., baclofen, carisoprodol, clorzoxazona, ciclobenzaprina, metocarbamol u orfrenadina;
- Un antagonista del receptor NMDA, por ej.. dextrometorfan ((+)-3-hidroxi-N-metilmorfinan) o su metabolito dextrorfan ((+)-3-hidroxi-N-metilmorfinan), cetamina, memantina, pirroloquinolina quinina, ácido cis-4-(fosfonometil)-2-piperidincarboxílico, budipine, EN-3231 (MorphiDex®, una formulación combinada de morfina y dextrometorfan), topiramato, neramexano o perzinfotel que incluye un antagonista de NR2B, por ej., ifenprodil, traxoprodil o (–)-(R)-6-{2-[4-(3-fluorofenil)-4-hidroxi-1-piperidinil]-1-hidroxietil-3,4-dihidro-2(1H)-quinolinona;
- Un alfa-adrenérgico, por ej., doxazosin, tamsulosin, clonidina, guanfacina, dexmetatomidina, modafinil, o 4-amino-6,7-dimetoxi-2-(5-metano-sulfonamido-1,2,3,4-tetrahidroisoquinol-2-il)-5-(2-piridil) quinazolina;

- Un antidepresivo tricíclico, por ej., desipramina, imipramina, amitriptilina o nortriptilina;
- Un anticonvulsivo, por ej., carbamazepina, lamotrigina, topiratmato o valproato;
- Un antagonista de taquiquinina (NK), en particular un antagonista NK-3, NK-2 o NK-1, por ej., (αR,9R)-7-[3,5-bis(trifluorometil)bencil]-8,9,10,11-tetrahidro-9-metil-5-(4-metilfenil)-7H-[1,4]diazocino[2,1-g][1,7]-naftiridina-6-13-diona (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluorometil)fenil]etoxi-3-(4-fluorofenil)-4-morfolinil]-metil]-1,2-dihidro-3H-1,2,4-triazol-3-ona (MK-869), aprepitant, lanepitant, dapitant o 3-[[2-metoxi-5-(trifluorometoxi)fenil]-metilamino]-2-fenilpiperidina (2S,3S);
- Un antagonista muscarínico, por ej., oxibutinin, tolterodine, propiverine, cloruro de tropsio, darifenacin, solifenacin, temiverine e ipratropio;
- Un inhibidor selectivo COX-2, por ej., celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, o lumiracoxib;
- Un analgésico de alquitrán de hulla, en particular paracetamol;
- Un neuroléptico tales como droperidol, chlorpromazina, haloperidol, perfenazina, tioridazina, mesoridazina, trifluoperazina, flufenazina, clozapina, olanzapina, risperidona, ziprasidona, quetiapina, sertindol, aripiprazol, sonepiprazol, blonanserin, iloperidona, perospirona, raclopride, zotepina, bifeprunox, asenapina, lurasidona, amisulpride, balaperidona, palindore, eplivanserin, osanetant, rimonabant, meclinartant, Miraxion® o sarizotan;
- Un agonista del receptor vaniloide (por ej., resinferatoxina) o antagonista (por ej., capsazepina);
- Un beta-adrenérgico tal como propranolol;
- Un anestésico local tal como mexiletina;
- Un corticosteroide tal como dexametasona;
- Un agonista o antagonista del receptor 5-HT, en particular un agonista 5-$HT_{1B/1D}$ tal como eletriptan, sumatriptan, naratriptan, zolmitriptan o rizatriptan;
- Un antagonista del receptor 5-HT_{2A} tal como R(+)-alfa-(2,3-dimetoxi-fenil)-1-[2-(4-fluorofeniletil)]-4-piperidinmetanol (MDL-100907);
- Un antagonista 5-HT_3, tal como ondasetron
- Un analgésico colinérgico (nicotínico) tal como ispronicline (TC-1734), (E)-N-metil-4-(3-piridinil)-3-buten-1-amina (RJR-2403), (R)-5-(2-azetidinilmetoxi)-2-cloropiridina (ABT-594) o nicotina;
- Tramadol®;

- Un inhibidor PDEV, tales como 5-[2-etoxi-5-(4-metil-1-piperazinil-sulfonil)fenil]-1-metil-3-n-propil-1,6-dihidro-7H-pirazolo[4,3-d]pirimidin-7-ona (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahidro-2-metil-6-(3,4-metilenodioxifenil)-pirazino[2',1':6,1]-pirido[3,4-b]indol-1,4-diona (IC-351 o tadalafil), 2-[2-etoxi-5-(4-etil-piperazin-1-il-1-sulfonil)-fenil]-5-metil-7-propil-3H-imidazo[5,1-f][1,2,4]triazin-4-ona (vardenafil), 5-(5-acetil-2-butoxi-3-piridinil)-3-etil-2-(1-etil-3-azetidinil)-2,6-dihidro-7*H*-pirazolo[4,3-*d*]pirimidin-7-ona, 5-(5-acetil-2-propoxi-3-piridinil)-3-etil-2-(1-isopropil-3-azetidinil)-2,6-dihidro-7*H*-pirazolo[4,3-*d*]pirimidin-7-ona, 5-[2-etoxi-5-(4-etilpiperazin-1-ilsulfonil)piridin-3-il]-3-etil-2-[2-metoxietil]-2,6-dihidro-7H-pirazolo[4,3-d]pirimidin-7-ona, 4-[(3-cloro-4-metoxibencil)amino]-2-[(2S)-2-(hidroximetil)pirrolidin-1-il]-N-(pirimidin-2-ilmetil)pirimidin-5-carboxamida, 3-(1-metil-7-oxo-3-propil-6,7-dihidro-1H-pirazolo[4,3-d]pirimidin-5-il)-N-[2-(1-metilpirrolidin-2-il)etil]-4-propoxibencenosulfonamida;
- un ligando alfa-2-delta tales como gabapentin, pregabalin, 3-metilgabapentin, ácido (1α,3α,5α)(3-amino-metil-biciclo[3,2,0]hept-3-il)-acético, ácido (3S,5R)-3-aminometil-5-metil-heptanoico, ácido (3S,5R)-3-amino-5-metil-heptanoico, ácido (3S,5R)-3-amino-5-metil-octanoico, (2S,4S)-4-(3-clorofenoxi)prolina, (2S,4S)-4-(3-fluorobencil)-prolina, ácido [(1R,5R,6S)-6-(aminometil)biciclo[3,2,0]hept-6-il]acético, 3-(1-aminometil-ciclohexilmetil)-4H-[1,2,4]oxadiazol-5-ona, C-[1-(1H-tetrazol-5-ilmetil)-cicloheptil]-metilamina, ácido (3S,4S)-(1-aminometil-3,4-dimetil-ciclopentil)-acético, ácido (3S,5R)-3-aminometil-5-metil-octanoico, ácido (3S,5R)-3-amino-5-metil-nonanoico, (3S,5R)-3-amino-5-metil-octanoico, ácido (3R,4R,5R)-3-amino-4,5-dimetil-heptanoico y ácido (3R,4R,5R)-3-amino-4,5-dimetil-octanoico;
- Antagonista del receptor metabotrópico glutamato subtipo 1 (mGluR1);
- Un inhibidor de recaptación de serotonina tales como sertralina, metabolito sertralina demetilsertralina, fluoxetina, norfluoxetina (fluoxetina desmetil metabolito), fluvoxamina, paroxetina, citalopram, citalopram metabolito desmetilcitalopram, escitalopram, d,l-fenfluramina, femoxetina, ifoxetina, cianodotiepin, litoxetina, dapoxetina, nefazodona, ericlamina y trazodona;
- un inhibidor de recaptación de noradrenalina (norepinefrina), tales como maprotilina, lofepramina, mirtazepina, oxaprotilina, fezolamina, tomoxetina, mianserin, buproprion, buproprion metabolito hidroxibuproprion, nomifensina y viloxazina (Vivalan®), especialmente inhibidor de recaptación de noradrenalina tal como reboxetina, en particular (S,S)-reboxetina;

- Un inhibidor de recaptación de serotonina-noradrenalina dual, tales como venlafaxina, venlafaxina metabolito O-desmetilvenlafaxina, clomipramina, clomipramina metabolito desmetilclomipramina, duloxetina, milnacipran e imipramina;
- Un inhibidor de óxido nítrico sintasa inducible (iNOS) tales como S-[2-[(1-iminoetil)amino]etil]-L-homocisteína, S-[2-[(1-iminoetil)-amino]etil]-4,4-dioxo-L-cisteína, S-[2-[(1-iminoetil)amino]etil]-2-metil-L-cisteína, ácido (2S,5Z)-2-amino-2-metil-7-[(1-iminoetil)amino]-5-heptenoico, 2-[[(1R,3S)-3-amino-4- hidroxi-1-(5-tiazolil)-butil]tio]-5-cloro-3-piridincarbonitrilo; 2-[[(1R,3S)-3-amino-4-hidroxi-1-(5-tiazolil)butil]tio]-4-clorobenzonitrilo, (2S,4R)-2-amino-4-[[2-cloro-5-(trifluorometil)fenil]tio]-5-tiazolebutanol, 2-[[(1R,3S)-3-amino-4-hidroxi-1-(5-tiazolil) butil]tio]-6-(trifluorometil)-3 piridincarbonitrilo, 2-[[(1R,3S)-3-amino-4-hidroxi-1-(5-tiazolil)butil]tio]-5-clorobenzonitrilo, N-[4-[2-(3-clorobencilamino)etil]fenil]tiofeno-2-carboxamidina, o guanidinoetildisulfuro;
- Un inhibidor de acetilcolinesterasa tal como donepezilo;
- Un antagonista de prostaglandina E_2 subtipo 4 (EP4) tales como *N*-[({2-[4-(2-etil-4,6-dimetil-1H-imidazo[4,5-c]piridin-1-il)fenil]etil}amino)-carbonil]-4-metilbencenosulfonamida o ácido 4-[(1*S*)-1-({[5-cloro-2-(3-fluorofenoxi)piridin-3-il]carbonil}amino)etil]benzoico;
- Un inhibidor microsomal de prostaglandina E sintasa tipo 1 (mPGES-1);
- Un antagonista de leucotrieno B4; tales como ácido 1-(3-bifenil-4-ilmetil-4-hidroxi-croman-7-il)-ciclopentanocarboxílico (CP-105696), ácido 5-[2-(2-carboxietil)-3-[6-(4-metoxifenil)-5E-hexenil]oxifenoxi]-valérico (ONO-4057) o DPC-11870,

Un inhibidor de 5-lipoxigenasa, tales como zileuton, 6-[(3-fluoro-5-[4-metoxi-3,4,5,6-tetrahidro-2H-piran-4-il])fenoxi-metil]-1-metil-2-quinolona (ZD-2138), o 2,3,5-trimetil-6-(3-piridilmetil),1,4-benzoquinona (CV-6504).

Las composiciones farmacéuticas adecuadas para el suministro de compuestos y sales de la presente invención y los métodos para su preparación serán fácilmente evidentes para los expertos en la técnica. Estas composiciones y métodos para su preparación pueden hallarse, por ejemplo, en 'Remington's Pharmaceutical Sciences', 19º Edición (Mack Publishing Company, 1995).

Los compuestos y sales de la invención destinados al uso farmacéutico se pueden preparar y administrar como productos cristalinos o amorfos. Se pueden

obtener, por ejemplo, como tapones sólidos, polvos, o películas mediante métodos tales como precipitación, cristalización, liofilización, secado por aspersión, o secado por evaporación. El secado por microondas o radio frecuencia se puede utilizar para este fin.

Administración oral

Los compuestos de la invención se pueden administrar por vía oral. La administración oral puede involucrar la ingestión, de modo que el compuesto ingresa al tracto gastrointestinal, o se puede emplear la administración bucal o sublingual mediante la cual el compuesto ingresa al torrente sanguíneo directamente desde la boca.

Las formulaciones adecuadas para administración oral incluyen formulaciones sólidas, tales como comprimidos, cápsulas que contienen particulados, o polvos; pastillas (que incluyen las rellenas con líquido), gomas de mascar; multi o nano partículas; geles, solución sólida, liposoma, películas (que incluyen muco-adhesivas), óvulos, pulverizaciones y formulaciones líquidas.

Las formulaciones líquidas incluyen suspensiones, soluciones, jarabes y elixires. Estas formulaciones se pueden emplear como rellenos en cápsulas blandas o duras y típicamente comprenden un vehículo, por ejemplo, agua, etanol, polietilenglicol, propilenglicol, metilcelulosa, o un aceite adecuado, y uno o más agentes emulsionantes y/o agentes de suspensión. Las formulaciones líquidas además se pueden preparar por la reconstitución de un sólido, por ejemplo, de un sache.

Los compuestos de la invención se pueden utilizar en disolución rápida, formas de dosificación de desintegración rápida tales como las que se describen en Expert Opinion in Therapeutic Patents, 11 (6), 981-986 de Liang and Chen (2001).

Para las formas de dosificación de comprimidos, dependiendo de la dosis, el fármaco puede elaborarse desde 1% en peso hasta 80% en peso de la forma de dosificación, más típicamente desde 5% en peso hasta 60% en peso de la forma de dosificación. Además del fármaco, los comprimidos en general contienen un desintegrante. Ejemplos de desintegrantes incluyen glicolato de almidón y sodio, carboximetil celulosa sódica, carboximetil celulosa cálcica, croscarmelosa sódica, crospovidona, polivinilpirrolidona, metil celulosa, celulosa microcristalina, hidroxipropil celulosa sustituida con alquilo inferior, almidón pregelatinizado y alginato de sodio. En general, el desintegrante comprenderá desde 1% en peso hasta 25% en peso, con

preferencia desde 5% en peso hasta 20% en peso de la forma de dosificación.

Los aglutinantes se utilizan en general para impartir cualidades cohesivas a una formulación de comprimido. Los aglutinantes adecuados incluyen celulosa microcristalina, gelatina, azúcares, polietilenglicol, gomas naturales y sintéticas, polivinilpirrolidona, almidón pregelatinizado, hidroxipropil celulosa e hidroxipropil metilcelulosa. Los comprimidos además pueden contener diluyentes, tales como lactosa (monohidrato, monohidrato seco por aspersión, anhidro y similares), manitol, xilitol, dextrosa, sacarosa, sorbitol, celulosa microcristalina, almidón y dihidrato fosfato de calcio dibásico.

Los comprimidos además pueden comprender opcionalmente agentes tensioactivos, tales como lauril sulfato sódico y polisorbato 80, y deslizantes tales como dióxido de silicio y talco. Cuando están presentes, los tensioactivos pueden comprender desde 0,2% en peso hasta 5% en peso del comprimido, y los deslizantes pueden comprender desde 0,2% en peso hasta 1% en peso del comprimido.

En general además los comprimidos contienen lubricantes tales como estearato de magnesio, estearato de calico, estearato de zinc, estearil fumarato de sodio, y mezclas de estearato de magnesio con lauril sulfato de sodio. En general los lubricantes comprenden desde 0,25% en peso hasta 10% en peso, con preferencia desde 0,5% en peso hasta 3% en peso del comprimido.

Otros principios posibles incluyen antioxidantes, colorantes, agentes saborizantes, conservantes y agentes enmascaradores del sabor.

Ejemplos de comprimidos contienen hasta aproximadamente 80% del fármaco, desde aproximadamente 10% en peso, hasta aproximadamente 90% en peso de aglutinante, desde aproximadamente 0% en peso hasta aproximadamente 85% en peso de diluyente, desde aproximadamente 2% en peso hasta aproximadamente 10% en peso de desintegrante, y desde aproximadamente 0,25% en peso hasta aproximadamente 10% en peso de lubricante. [Asegúrese que estos rangos específicos sean relevantes]

Las mezclas de comprimidos se pueden comprimir directamente o por rodillo para formar comprimidos. Las mezclas de comprimidos o porciones de las mezclas pueden ser alternativamente granuladas húmedas, secas, o fundidas, solidificadas por fundición, o extrudidas antes de la compresión. La formulación final puede comprender una o más capas y puede ser recubierta o sin recubrir; incluso puede encapsularse.

La formulación de comprimidos se discute en “Pharmaceutical Dosage Forms: Tablets, Vol. 1”, by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980

(ISBN 0-8247-6918-X).

Las formulaciones anteriores para los diversos tipos de administración que se discutieron anteriormente se pueden formular para una inmediata y/o modificada liberación. Las formulaciones de liberación modificadas incluyen liberación retardada, sostenida, pulsada, controlada, focalizada y programada.

Las formulaciones de liberación modificada adecuadas a los fines de la invención se describen en la Patente Estadounidense No. 6,106,864. Los detalles de otras tecnologías de liberación adecuadas tales como las dispersiones de alta energía y las partículas osmóticas y recubiertas se encuentran en Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). El uso de goma de mascar para obtener liberación controlada se describe en WO 00/35298.

Administración Parenteral

Los compuestos y las sales de la invención se pueden administrar directamente en el flujo sanguíneo, dentro del músculo, o dentro de un órgano interno. Los medios adecuados para administración parenteral incluyen intravenosa, intraarterial, intraperitoneal, intratecal, intraventricular, intrauretral, intrastérmico, intracranial, intramuscular, y subcutáneo. Los dispositivos adecuados para administración parenteral incluyen inyectores de aguja (que incluyen micro agujas), inyectores libres de agujas y técnicas de infusión.

Las formulaciones parenterales son típicamente soluciones acuosas que pueden contener excipientes tales como sales, carbohidratos, y agentes amortiguadores (preferentemente hasta un pH desde 3 hasta 9), pero, para algunas aplicaciones, pueden formularse en forma más adecuada como una solución no acuosa estéril o como una forma seca que se va a utilizar junto con un vehículo adecuado tal como agua estéril, libre de pirógeno.

La preparación de formulaciones parenterales en condiciones estériles, por ejemplo, por liofilización, se puede obtener fácilmente utilizando técnicas farmacéuticas estándares bien conocidas por los expertos en la técnica.

La solubilidad de los compuestos de fórmula (I) y las sales que se utilizan en la preparación de soluciones parenterales se pueden incrementar mediante el uso de técnicas de formulación apropiadas, tales como la incorporación de agentes de solubilidad-mejoradores.

Las formulaciones para administración parenteral se pueden formular para liberación inmediata y/o modificada. De este modo, los compuestos y sales de la

invención se pueden formular como líquido sólido, semisólido o tixotrópico para administración como una acumulación implantada que proporciona liberación modificada del compuesto activo. Un ejemplo de estas formulaciones incluyen los stents recubiertos con fármacos.

Administración tópica

Los compuestos y sales de la invención además se pueden administrar por vía tópica a la piel o la mucosa, que es, por vía dérmica o transdérmica. Las formulaciones típicas a este fin incluyen geles, hidrogeles, lociones, soluciones, cremas, ungüentos, polvos para espolvorear, apósitos, espumas, películas, parches cutáneos, obleas, implantes, esponjas, fibras, vendajes, y microemulsiones. Se pueden utilizar además liposomas. Los vehículos típicos incluyen alcohol, agua, aceite mineral, petrolato líquido, petrolato blanco, glicerina, polietilenglicol, y propilenglicol. Se pueden incorporar mejoradoras de penetración [véase, por ejemplo, Finnin and Morgan, J Pharm Sci, 88 (10), 955-958 (Octubre 1999).] Otro medio de administración tópica incluyen administración por electroporación, iontoforesis, fonoforesis, sonoforesis e inyección con micro agujas o libres de agujas (por ej., Powderject™, Bioject™, *etc.*).

Administración por inhalación/ intranasal

Los compuestos y sales de la invención además se pueden administrar por vía intranasal o por inhalación, típicamente en la forma de un polvo seco (ya sea solo, como mezcla, por ejemplo, en una mezcla seca con lactosa, o como una partícula de componente mezclado, por ejemplo, mezclado con fosfolípidos, tales como fosfatidilcolina) desde un inhalador de polvo seco o en forma de un spray en aerosol desde un envase presurizado, bomba, pulverizador, a atomizador (preferentemente un atomizador que usa electrohidrodinámica para producir una niebla fina), o nebulizador, con o sin el uso de un propelente adecuado, tal como 1,1,12-tetrafluoroetano o 1,1,1,2,3,3,3-heptafluoropropano. Para uso intranasal, el polvo puede comprender un agente bioadhesivo, por ejemplo, quitosán o ciclodextrina.

Un recipiente presurizado, bomba, pulverizador, atomizador o nebulizador puede contener una solución o suspensión del o de los compuestos o sales de la invención que comprende, por ejemplo, etanol, etanol acuoso, o un agente alternativo adecuado para dispersar, solubilizar, o extender la liberación del principio activo, un propelente como solvente y un tensioactivo opcional, tal como sorbitán trioleato, ácido oleico, o un ácido oligoláctico.

Antes del uso en una formulación de polvo seco o suspensión, el producto farmacéutico se micronizа hasta un tamaño adecuado para su administración por inhalación (típicamente menos de 5 micrones). Esto puede obtenerse mediante cualquier método de desmenuzado, tales como molienda a chorro espiral, molienda a chorro de lecho fluido, procesamiento de fluido supercrítico para formar nanopartículas, homogenización de alta presión, o secado por aspersión.

Las cápsulas (que se producen, por ejemplo, de gelatina o HPMC), blister, y cartuchos para uso en un inhalador o insuflador se pueden formular para contener una mezcla en polvo del compuesto o sal de la invención, una base de polvo adecuada tal como lactosa o almidón y un modificador del rendimiento tal como leucina, manitol o estearato de magnesio. La lactosa puede ser anhidra o en la forma del monohidrato, preferentemente éste último. Otros excipientes adecuados incluyen dextrano, glucosa, maltosa, sorbitol, xilitol, fructosa, sacarosa y trehalosa.

Una formulación de solución adecuada para uso en un atomizador que utiliza electrohidrodinámica para producir una niebla fina puede contener desde 1μg hasta 20mg del compuesto o sal de la invención por accionamiento y el volumen de accionamiento puede variar desde 1μl hasta 100 μl.. Una formulación típica puede comprender un compuesto de fórmula (I) o su sal, propilenglicol, agua estéril, etanol y cloruro de sodio. Los solventes alternativos que se pueden utilizar en lugar de propilenglicol incluyen glicerol y polietilenglicol.

Los saborizantes adecuados, tales como mentol y levomentol, o los endulzantes tales como sacarina o sacarina sódica, se pueden agregar a esas formulaciones de la invención destinadas a la administración por inhalación/intranasal.

Las formulaciones para administración por inhalación/intranasal se pueden formular para liberación inmediata y/o modificada utilizando, por ejemplo, ácido poli(DL)-láctico-coglicólico (PGLA). Las formulaciones de liberación modificadas incluyen liberación retardada, sostenida, pulsada, controlada, focalizada y programada.

En el caso de inhaladores de polvo seco y aerosoles, la unidad de dosificación se determina por una cápsula prerrellena, blister o bolsa o por un sistema que utiliza una cámara de dosificación alimentada gravimétricamente. Las unidades de acuerdo con la invención están dispuestas típicamente para administra una dosis medida o “puff” que contiene desde 1 hasta 5000 ug del compuesto o sal. La dosis diaria general estará típicamente en el rango de 1 ug hasta 20 mg que se pueden administrar en una sola dosis o, en forma usual, en dosis divididas a lo largo del día.

Administración rectal/intravaginal

Los compuestos y sales de la invención se pueden administrar por vía rectal o vaginal, por ejemplo, en la forma de un supositorio, óvulo, o enema. La manteca cacao es una base de supositorio tradicional, pero se pueden usar varias alternativas bien conocidas según sea apropiado.

Administración oral y auricular

Los compuestos y sales de la invención se pueden administrar además directamente al ojo o al oído, típicamente en la forma de gotas de una suspensión micronizada o una solución en solución salina isotónica, ajustada al pH, estéril. Otras formulaciones adecuadas para administración ocular o auricular incluyen ungüentos, implantes biodegradables (por ej., esponjas de gel que pueden absorber, colágeno) e implantes no biodegradables (por ej., silicona), obleas, lentes y sistemas particulados o vesiculares, tales como niosomas o liposomas. Se pueden incorporar un polímero tal como el ácido poliacrílico entrecruzado, ácido hialurónico polivinilalcohólico; un polímero celulósico, por ejemplo, hidroxipropilmetilcelulosa, hidroxietilcelulosa, o metil celulosa; o un polímero heteropolisacárido, por ejemplo, goma gelan, junto con un conservante, tal como cloruro de benzalconio. Estas formulaciones además se pueden suministrar por iontoforesis.

Otras tecnologías

Los compuestos de la invención se pueden combinar con entidades macromoleculares solubles, tales como ciclodextrina y sus derivados adecuados o polímeros que contienen polietilenglicol, a fin de mejorar su solubilidad, velocidad de disolución, enmascaramiento del gusto, biodisponibilidad y/o estabilidad para el uso en cualquiera de los modos de administración antes mencionados.

Los complejos de fármaco-ciclodextrina, por ejemplo, en general son útiles para la mayoría de las formas de dosificación y las vías de administración. Ambos complejos de inclusión y no inclusión se pueden utilizar. Como alternativa a la complejación directa con el fármaco, la ciclodextrina se puede usar como aditivo auxiliar, es decir como vehículo, diluyente o solubilizante. Las que se usan más comúnmente para estos fines son alfa-, beta- y gamma-ciclodextrinas, ejemplos de las cuales se pueden hallar en las Solicitudes de Patentes Internacionales Nos. WO 91/11172, WO 94/02518 y WO 98/55148.

Para administración a pacientes humanos, la dosis diaria total de los compuestos y sales de la invención está típicamente en el rango de 0,1 mg hasta 200 mg dependiendo, por supuesto, del modo de administración, se prefiere en el rango de 1 mg hasta 100 mg y el más preferido el rango de 1 mg hasta 50 mg. La dosis diaria total se puede administrar en dosis simples o divididas.

Estas dosificaciones se basan en un sujeto humano promedio que tiene un peso de aproximadamente 65 kg hasta 70 kg. El profesional podrá determinar las dosis para los sujetos cuyo peso esté fuera del rango, tal como niños o adultos mayores.

Para los usos terapéuticos antes mencionados, la dosificación administrada, por supuesto, variará con el compuesto o sal empleada, el modo de administración, el tratamiento deseado y el trastorno indicado. La dosificación diaria total del compuesto de fórmula (I)/ sal / solvato (principio activo), en general, estará en el rango desde 1 mg hasta 1 gramo, preferentemente 1 mg hasta 250 mg, con mayor preferencia 10 mg hasta 100 mg. La dosis diaria total puede ser administrada en dosis únicas o divididas. La presente invención además abarca las composiciones de liberación sostenida.

La composición farmacéutica puede, por ejemplo, estar en una forma adecuada para inyección parenteral en forma de solución estéril, suspensión o emulsión, para administración tópica en forma de ungüento o crema o para administración rectal en forma de supositorio. La composición farmacéutica puede estar en formas de dosificación unitaria adecuadas para administración simple de dosificaciones precisas. La composición farmacéutica incluirá un vehículo o excipiente farmacéutico convencional y un compuesto de acuerdo con la invención en forma de un principio activo. Además, puede incluir otros agentes, vehículos, adyuvantes, etc. medicinales o farmacéuticos.

Ejemplos de formas de administración parenteral incluyen soluciones o suspensiones de compuestos activos en soluciones acuosas estériles, por ejemplo, soluciones de propilenglicol o dextrosa acuosas. Estas formas de dosificación se pueden amortiguar en forma adecuada, si se desea.

Los vehículos farmacéuticos adecuados incluyen diluyentes o rellenos inertes, agua y varios solventes orgánicos. Si se desea, las composiciones farmacéuticas pueden contener principios adicionales tales como saborizantes, aglutinantes, excipientes y similares. De este modo para la administración oral, se pueden emplear los comprimidos que contienen varios excipientes, tal como ácido cítrico junto con varios

desintegrantes tales como almidón, ácido algínico y ciertos silicatos complejos y con agentes aglutinantes tales como sacarosa, gelatina, y acacia. Además, los agentes lubricantes tales como estearato de magnesio, lauril sulfato sódico y talco a menudo son útiles a los fines de la compresión. Las composiciones sólidas de tipo similar además se pueden emplear en cápsulas de gelatina blanda o dura. Los materiales preferidos para ello, incluyen lactosa o azúcar de leche y polietilenglicoles de peso molecular alto. Cuando las suspensiones acuosas o elixires son las deseadas para administración oral el compuesto activo en la misma se puede combinar con varios agentes endulzantes o saborizantes, sustancias colorantes o tintes, y, si se desea, agentes emulsiones o de suspensión, junto con diluyentes tales como agua, etanol, propilenglicol, glicerina, o combinaciones de los mismos.

Los regímenes de dosificación se pueden ajustar para dar la respuesta óptima deseada. Por ejemplo, se puede administrar un único bolo, se pueden administrar varias dosis divididas en el tiempo o la dosis puede ser reducida en forma proporcional o aumentarse según lo indican las exigencias de la situación terapéutica. Es especialmente ventajoso formular composiciones parenterales en la forma unitaria de dosificación para facilitar la administración y la uniformidad de la dosificación. La forma unitaria de dosificación, tal como se usa en la presente, se refiere a las unidades físicamente discretas en forma de dosificaciones unitarias para los sujetos mamíferos a ser tratados, cada unidad contiene una cantidad predeterminada del compuesto activo calculada para producir el efecto terapéutico deseado en asociación con el vehículo farmacéutico requerido. La especificación par alas formas unitarias de dosificación de la invención se dictan y dependen directamente de (a) las características únicas del agente quimioterapéutico y el efecto terapéutico o profiláctico particular que se va a obtener, y (b) las limitaciones inherentes en la técnica de la composición tal como un compuesto activo para el tratamiento de la sensibilidad en individuos.

De este modo el técnico apreciaría, basado en la descripción que se proporciona en la presente, que la dosis y el régimen de dosificación se ajusta de acuerdo con los métodos bien conocidos en la técnica terapéutica. Es decir, la dosis máxima tolerable se puede establecer fácilmente, y la cantidad efectiva que proporciona un beneficio terapéutico detectable a un paciente además puede determinarse, como pueden los requerimientos temporales para administrar cada agente proporcionar un beneficio terapéutico al paciente. En consecuencia, mientras que cierta dosis y regímenes de administración se ejemplifican en la presente, estos ejemplos de ninguna manera limitan la dosificación y el régimen de administración que

puede ser proporcionado a un paciente en la práctica de la presente invención.

Debe observarse que los valores de dosificación pueden variar con el tipo y severidad de la afección a ser aliviada, y pueden incluir dosis simples o múltiples. Además debe entenderse que para cualquier sujeto particular, los regímenes de dosificación específicos deben ajustarse en el tiempo de acuerdo con la necesidad individual y el criterio profesional del persona que administra o supervisa la administración de las composiciones, y que los rangos de dosificación establecidos en la presente son a modo de ejemplo únicamente y no limitan el alcance o la práctica de la composición reivindicada. Por ejemplo, se pueden ajustar las dosis basado en los parámetros farmacocinéticas o farmacodinámicos que pueden incluir efectos clínicos tales como efectos tóxicos y/o valores de laboratorio. De este modo, la presente invención abarca la escala de dosificación intra paciente como lo determina un experto. La determinación de las dosificaciones y regímenes apropiados para la administración del agente quimioterapéutico son bien conocidas en la técnica relevante y entendidas por los expertos una vez que se proporcionan las enseñanzas divulgadas en la presente.

Una composición farmacéutica de la invención se puede preparar, envasar, o comercializarse por volumen, en forma de una dosis unitaria simple, o en forma de una pluralidad de dosis unitaria única. Tal como se usa en la presente, una “dosis unitaria” es una cantidad discreta de la composición farmacéutica que comprende una cantidad predeterminada del principio activo. La cantidad del principio activo es igual en general a la dosificación del principio activo que se administraría a un sujeto o una fracción conveniente de esta dosificación tal como, por ejemplo, la mitad o un tercio de esta dosificación.

Para dosificaciones parenterales, esto puede prepararse en forma conveniente como una solución o en forma de un polvo seco que requiere disolución por parte de un farmacéutico, profesional médico o el paciente. Puede proporcionarse en un botella o jeringa estéril. Por ejemplo puede proporcionarse como un polvo en una jeringa de múltiples compartimentos que permite que se mezclen el polvo seco y el solvente antes de su administración (para ayudar a la estabilidad y el almacenamiento a largo plazo). Se podrían utilizar jeringas que permiten múltiples dosificaciones para ser administradas desde un único dispositivo.

Las cantidades relativas del principio activo, el vehículo aceptable para uso farmacéutico, y cualquier principio adicional en una composición farmacéutica de la invención variará, dependiendo de la identidad, el tamaño, y la condición del sujeto

tratado y además dependen de la vía por la cual la composición debe administrarse. A modo de ejemplo, la composición puede comprender entre 0,1% y 100% (p/p) de principio activo.

Además del principio activo, una composición farmacéutica de la invención puede comprender además uno o más agentes activos para uso farmacéutico adicionales.

Las formulaciones de liberación controlada o sostenida de una composición farmacéutica de la invención pueden producirse utilizando tecnología convencional.

Tal como se usa en la presente, la "administración parenteral" de una composición farmacéutica incluye cualquier vía de administración caracterizada por la ruptura física de un tejido de un sujeto y la administración de la composición farmacéutica a través de la ruptura en el tejido. De es te modo la administración parenteral incluye, pero sin limitación, la administración de una composición farmacéutica por la inyección de la composición, mediante la aplicación de la composición a través de una incisión quirúrgica, mediante la aplicación de la composición a través de una herida no quirúrgica que penetra el tejido, y similares. En particular, la administración parenteral incluye, pero sin limitación, la administración subcutánea, intraperitoneal, intramuscular, de inyección intrasternal, y las técnicas de infusión dialítica del riñón.

Las formulaciones de composición farmacéutica adecuadas para administración parenteral comprenden el principio activo combinado con un vehículo aceptable para uso farmacéutico, tal como agua estéril o solución salina isotónica estéril. Estas formulaciones se pueden preparar, envasar, o comercializar en una forma adecuada para la administración del bolo o para administración continua. Las formulaciones inyectables se pueden preparar, envasar, o comercializar en una forma de dosificación unitaria, tales como en ampollas o en envases de múltiples dosis que contiene un conservante. Las formulaciones para administración parenteral incluyen, pero sin limitación, suspensiones, soluciones, emulsiones en vehículos oleosos o acuosos, pastas, y formulaciones de liberación sostenida implantables o biodegradables como se menciona a continuación. Estas formulaciones además pueden comprender uno o más principios adicionales que incluyen, pero sin limitación, agentes de suspensión, estabilizantes o dispersantes. En una realización de una formulación para administración parenteral, el principio activo se proporciona en forma seca (es decir en polvo o granular) para la reconstitución con un vehículo adecuado (por ej., agua libre de pirógeno estéril) antes de la administración parenteral de la

composición reconstituida.

Una composición de la presente invención se puede administrar mediante una variedad de métodos conocidos en la técnica. La vía y/o el modo de administración varían dependiendo de los resultados deseados. Los compuestos activos se pueden preparar con vehículos que protegen el compuesto contra la liberación rápida, tal como una formulación de liberación controlada, que incluye implantes, parches transdérmicos, y sistemas de administración microencapsulados. Se pueden utilizar polímeros biodegradables, biocompatibles, tales como acetato de etilenvinilo, polianhídridos, ácido poliglicólico, colágeno, poliortoésteres, y ácido poliláctico. Muchos métodos para la preparación de estas formulaciones se describen en, por ej., Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, (1978). Las composiciones farmacéuticas se producen preferentemente en condiciones de GMP.

Las composiciones farmacéuticas se pueden preparar, envasar, o comercializar en la forma de una suspensión o solución inyectable acuosa u oleosa. Esta suspensión o solución se puede formular de acuerdo con la técnica conocida, y puede comprender, además del principio activo, otros principios tales como los agentes dispersantes, agentes humectantes, o agentes de suspensión que se describen en la presente. Las formulaciones inyectables estériles se pueden preparar utilizan un diluyente o solvente aceptable para uso parenteral no tóxico, tal como agua o 1,3-butano diol, por ejemplo. Otros diluyentes y solventes aceptables incluyen, pero sin limitación, solución de Ringer, solución de cloruro de sodio isotónico, y aceites fijos tales como mono o di-glicéridos sintéticos. Otras formulaciones que se pueden administrar por vía parenteral que son útiles incluyen las que comprenden el principio activo en forma microcristalina, en una preparación liposomal, o en forma de un componente de un sistema polimérico biodegradable. Las composiciones para liberación sostenida o implantación pueden comprender materiales hidrófobos o poliméricos aceptables para uso farmacéutico tales como una emulsión, una resina de intercambio iónico, un polímero escasamente soluble, o una sal escasamente soluble.

La dosificación precisa administrada de cada principio activo variará dependiendo del número de factores, que incluye pero sin limitación, el tipo de animal y el tipo de estado de enfermedad que se trata, la edad del animal, y la vía o vías de administración.

Las siguientes preparaciones y ejemplos no limitantes ilustran la preparación de compuestos y sales de la presente invención.

EXPERIMENTAL GENERAL

Las preparaciones y ejemplos que siguen ilustran la invención pero no limitan la misma de manera alguna. Todos los materiales de partida están disponibles en el comercio o se describen en la literatura. Todas las temperaturas están en ºC. La cromatografió de columna flash se llevó a cabo utilizando gel de sílice Merck 60 (9385). La cromatografió de capa delgada (TLC) se llevó a cabo sobre gel de sílice Merck 60 placas (5729). "R_f" representa la distancia realizada por un compuesto dividida la distancia realizada por el solvente sobre una placa de TLC. Los puntos de fusión se determinaron utilizando un aparato Gallenkamp MPD350 y son precisos. La RMN se llevó a cabo utilizando un espectrómetro de RMN Varian-Unity Inova 400MHz o un espectrómetro de RMN Varian Mercury 400MHz . La espectroscopía de masa se llevó a cabo utilizando un espectrómetro de masa por electroaspersión de cuatro polos simple Finnigan Navigator o un espectrómetro de masa Finnigan aQa APCI.

Donde se establece los compuestos se prepararon de la manera que se describe para una preparación o ejemplo anterior, el experto apreciará que los tiempos de reacción, el número de equivalentes de los reactivos y las temperaturas de reacción se pueden modificar para cada reacción específica, y que, sin embargo puede ser necesario o deseable emplear diferentes condiciones de elaboración o purificación.

La invención se ilustra mediante los siguientes ejemplos no limitantes en los cuales se utilizan las siguientes abreviaturas y definiciones:

Las preparaciones y ejemplos que siguen ilustran la invención pero no limitan la misma de manera alguna. Todos los materiales de partida están disponibles en el comercio o se describen en la literatura. Todas las temperaturas están en ºC. La cromatografió de columna flash se llevó a cabo utilizando gel de sílice Merck 60 (9385) o sílice Redisep. La RMN se llevó a cabo utilizando un espectrómetro de RMN Varian-Mercury 400MHz o un espectrómetro de RMN Jeol ECX 400MHz.

Los espectros de masa se obtuvieron utilizando:

Waters ZQ ESCI

Applied Biosystem's API-2000 5 min LC-MS

Waters Alliance 2795 con ZQ2000 (ESI)

Aglient 110 HPLC 5 min (System 5)

Waters ZQ ESCI 8min LC-MS

Waters Alliance 2695 con ZQ2000 (ESI) 25 min

HP 1100 HPLC con detector de masa Waters Micromass ZQ 12,5 min LC-MS

Los espectros de masa UPLC se obtuvieron utilizando Waters Acquity ZQD (ESI) 1,5 min LC-MS

WATERS ACQUITY UPLC/WATERS 3100 MSD/PL-ELS 2100 ICE ELSD

Donde se han analizado los compuestos simples por LCMS, se utilizaron seis métodos. Estos se ilustran a continuación.

Sistema 1

Condiciones instrumentales y gradiente LC-MS 6 minutos

A: 0,1 % de ácido fórmico en agua

B: 0,1 % de ácido fórmico en acetonitrilo

Columna: C18 fase Waters Sunfire 50 x 4,6 mm con un tamaño de partícula de 5 micrones

Gradiente: 95-5% A en 3 min, 1 min de espera, 2 min de re-equilibrio, 1,5 ml/min de velocidad de flujo

UV: 210nm - 450nm DAD

Temperatura: 50℃

Sistema 2

Condiciones instrumentales y gradiente LC-MS 2 minutos

A: 0,1 % de ácido fórmico en agua

B: 0,1 % de ácido fórmico en acetonitrilo

Columna: C18 fase Phenomenex 20 x 4,0 mm con un tamaño de partícula de 3 micrones

Gradiente: 70-2% A en 1,5min, 0,3 min de espera, 0,2 de re-equilibrio, 1,8 ml/min de velocidad de flujo

UV: 210nm - 450nm DAD

Temperatura: 75℃

Sistema 3

Condiciones instrumentales y gradiente LC-MS 5 minutos

A: 0,1 % de ácido fórmico en agua

B: 0,1 % de ácido fórmico en acetonitrilo

Columna: C18 fase Waters Sunfire 50 x 4,6 mm con un tamaño de partícula de 5 micrones

Gradiente: 95-5% A en 3 min, 1 min de espera, 1 min de re-equilibrio, 1,5 ml/min de velocidad de flujo

UV: 225nm – ELSD - MS

Temperatura: ambiente

Sistema 4

Condiciones instrumentales y gradiente LC-MS 5 minutos

A: 0,1 % de hidróxido de amonio en agua

B: 0,1 % de hidróxido de amonio en acetonitrilo

Columna: C18 fase XTerra 50 x 4,6 mm con un tamaño de partícula de 5 micrones

Gradiente: 95-5% A en 3 min, 1 min de espera, 1 min de re-equilibrio, 1,5 ml/min de velocidad de flujo

UV: 225nm – ELSD - MS

Temperatura: ambiente

Sistema 5

Condiciones instrumentales y gradiente LC-MS 5 minutos

A: 0,0375 % de TFA en agua

B: 0,01875 % de TFA en acetonitrilo

Columna: C18 fase Welch XB 50 x 2,1 mm con un tamaño de partícula de 5 micrones

Gradiente: 99-0% A en 4 min., 0,70 min de re-equilibrio, 0,8 ml /min de velocidad de flujo

UV: 225nm – ELSD - MS

Temperatura: 50℃

Sistema 6

Condiciones instrumentales y gradiente LC-MS 5 minutos

A: 0,0375 % de TFA en agua

B: 0,01875 % de TFA en acetonitrilo

Columna: C18 fase Welch XB 50 x 2,1 mm con un tamaño de partícula de 5 micrones

Gradiente: 90-0% A en 4 min., 0,70 min de re-equilibrio, 0,8 ml /min de velocidad de flujo

UV: 225nm – ELSD - MS

Temperatura: 50℃

Sistema 7

Condiciones instrumentales y gradiente LC-MS 25 minutos

A: 10 mmoles de bicarbonato de amonio en agua

B: acetonitrilo

Columna: C18 fase XBridge 150 x 3,0 mm con un tamaño de partícula de 5 micrones

Gradiente: 95-5% A en 15 min, 10 min de espera, 2 min de re-equilibrio, 0,5 ml/min de velocidad de flujo

UV: 200nm - 350nm DAD

Temperatura: 30℃

Sistema 8

Condiciones instrumentales y gradiente LC-MS 3 minutos

A: 0,05% de ácido fórmico en agua

B: acetonitrilo

Columna: C18 fase Restek 30 x 2,1 mm con un tamaño de partícula de 3 micrones

Gradiente: 98-2% A en 2 min, 0,25 min de espera, 0,25 min de re-equilibrio, 1,5 ml/min de velocidad de flujo

UV: 200nm - 350nm DAD

Temperatura: 50℃

Sistema 9

Condiciones instrumentales y gradiente LC-MS 5 minutos

A: 0,05% de ácido fórmico en agua

B: acetonitrilo

Columna: C18 fase XBridge 50 x 4,6 mm con un tamaño de partícula de 5 micrones

Gradiente: 90-10% A en 3 min, 1 min de espera, 1min de re-equilibrio, 1,2 ml/min de velocidad de flujo

UV: 200nm - 260nm DAD

Temperatura: 25℃

Sistema 10

Condiciones instrumentales y gradiente LC-MS 5 minutos

A: 10 mM de acetato de amonio en agua

B: acetonitrilo

Columna: C18 fase Gemini NX 50 x 4,6 mm con un tamaño de partícula de 5 micrones

Gradiente: 90-10% A en 3 min, 1 min de espera, 1min de re-equilibrio, 1,2 ml/min de velocidad de flujo

UV: 200nm - 260nm DAD

Temperatura: 25℃

Donde se han purificado los compuestos simples por cromatografía líquida de alta resolución, a menos que se establezca lo contrario, se utilizó uno de cuatro métodos, y estos se muestran a continuación.

Waters Purification Systems con espec de masa o detección UV

Sistema de prep 1

Condiciones instrumentales y gradiente LC-MS 10 minutos prep
A: 0,1% de ácido fórmico en agua
B: 0,1% de ácido fórmico en acetonitrilo
Columna: C18 fase Sunfire 100 x 19,0 mm
Gradiente: 95-2% A en 7 min, 2 min de espera, 1 min de re-equilibrio, 18 ml/min de velocidad de flujo
Temperatura: ambiente

Sistema de prep 2

Condiciones instrumentales y gradiente LC-MS 10 minutos prep
A: 0,1% de DEA en agua
B: 0,1% de DEA en acetonitrilo
Columna: C18 fase Xterra 100 x 19,0 mm
Gradiente: 95-2% A en 7 min, 2 min de espera, 1 min de re-equilibrio, 18 ml/min de velocidad de flujo
Temperatura: ambiente

Sistema de prep 3

Condiciones instrumentales y gradiente LC-MS 7 minutos prep
A: 0,05% de amoníaco en agua
B: acetonitrilo
Columna: C18 fase Xbridge 50 x 19,0 mm
Gradiente: 90-20% A en 7 min, 20 ml/ min de velocidad de flujo
Temperatura: ambiente

Sistema de prep 4

Condiciones instrumentales y gradiente LC-MS 8 minutos prep
A: 0,1% de TFA en agua
B: acetonitrilo
Columna: C18 fase Sepax BR 100 x 21,2 mm
Gradiente: 96-33% A en 8 min, 30 ml/ min de velocidad de flujo
Temperatura: ambiente

Donde se establece los compuestos se prepararon de la manera que se describe para una preparación o ejemplo anterior, el experto apreciará que los tiempos de reacción, el número de equivalentes de los reactivos y las temperaturas de reacción han sido modificados para cada reacción específica, y que, sin embargo puede ser necesario o deseable emplear diferentes condiciones de elaboración o purificación. La

invención se ilustra mediante los siguientes ejemplos no limitantes en los cuales se utilizan las siguientes abreviaturas y definiciones:

AcOH – ácido acético; APCI – ionización química de presión atmosférica; Arbocel es un agente filtro; br s – ancho singulete; BINAP – 2,2'-bis(difenilfosfino)-1,1'-binaftil; nBuLi – n-butilitio; $CDCl_3$ – cloroformo deuterado; Cs_2CO_3 es carbonato de cesio; CuI es yoduro de cobre (I); $Cu(OAc)_2$ es acetato de cobre (II); δ – cambio químico; d – doblete; DAD – detector de matriz de diodo; DCE – 1,2-dicloroetano

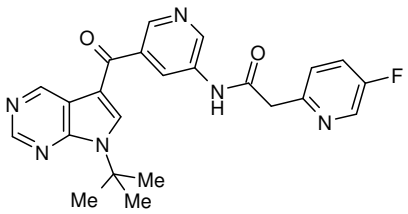
DCM – diclorometano; DEA – dietilamina; DIBAL – Diisobutilaluminio hidruro; DIPEA – diisopropiletilamina; DMAP – 4-dimetilaminopiridina; DME – dimetoxietano; DMF – N,N-dimetilformamida; DMF-DMA - N,N-dimetilformamida-dimetilacetal; DMSO – dimetilsulfóxido

DPPF – 1,1'-bis(difenilfosfino)ferroceno; ELSD – detector de dispersión de luz evaporativo; ESI – ionización por electroaspersión; Et_2O – éter dietílico; EtOAc/EA – acetato de etilo; EtOH – etanol; g – gramo; HATU - 2-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio hexafluorofosfato; HBTU es O-benzotriazol-1-il-N,N,N',N'-tetrametiluronio hexafluorofosfato; HCl es ácido clorhídrico;HOBT es N-hidroxibenzotriazol hidrato; HPLC – cromatografía líquida de alta resolución; IPA – alcohol isopropílico; K_2CO_3 es carbonato de potasio; $KHSO_4$ es sulfato hidrógeno de potasio; KOAc es acetato de potasio; KOH es hidróxido de potasio; K_3PO_4 es tribásico fosfato de potasio; KF - fluoruro de potasio; L es litro; LCMS – espectrometría de masa cromatografía líquida; LiHMDS – hexametildisilazida de litio; m – multiplete; mg – miligramo; ml – mililitro; M/Z – pico de espectro de masa; MeCN – acetonitrilo; MeOH – metanol; 2-MeTHF – 2-metiltetrahidrofurano; $MgSO_4$ es sulfato de magnesio; MnO_2 – dióxido de manganeso; $NaClO_2$ – clorito de sodio; NaH – hidruro de sodio; $NaHCO_3$ – hidrógeno carbonato de sodio; Na_2CO_3 – carbonato de sodio; NaH_2PO_4- fosfato de sodio; $NaHSO_3$ – bisulfito de sodio; $NaHSO_4$ - hidrógeno sulfato de sodio; NaOH – hidróxido de sodio; Na_2SO_4 – sulfato de sodio; NH_3 – amoníaco; NH_4Cl – cloruro de amonio; NMM – N-Metilmorfolina; NMR – resonancia magnética nuclear; Pd/C – paladio sobre carbono; $PdCl_2$ – dicloruro de paladio; $Pd_2(dba)_3$ es tris(dibencilidenoacetona)dipaladio(0); $Pd(PPh_3)_4$ - tetrakis(trifenfosfina paladio); $Pd(OAc)_2$ – acetato de paladio; PTSA – ácido para-toluenosulfónico; Prep – preparación; Tr – tiempo de retención; q – cuarteto; s – singulete; TBDMS – tertbutildimetilsililo; TBME – tertbutildimetiléter; anhídrido cíclico del ácido TCP – 1-propilfosfónico; TEA – trietilamina; TFA – ácido trifluoroacético; THF – tetrahidrofurano; TLC – cromatografía de capa delgada; (R, S) – mezcla racémica; WSCDI - 1-(3-

dimetilaminopropil)-3-etilcarbodiimida clorhidrato.

Para evitar dudas, los compuestos nombrados que se utilizan en la presente han sido designados utilizando IUAPC, Chemdraw y/o Name Pro ACD Labs Name Software v7,11™ o utilizando otra nomenclatura estándar. Los espectros de RMN se midieron en solventes deuterados y fueron consistentes con los nombres y las estructuras que se dan a continuación.

Ejemplo 1 N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-fluoropiridin-2-il)acetamida



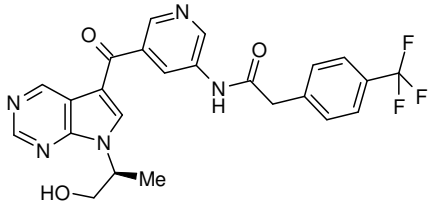
Se agregó ácido 2-(5-fluoropiridin-2-il)acético (23,1 mg, 0,149 mmoles) (véase Preparación 92) a ((5-aminopiridin-3-il)(7-*ter*-butil-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona (40 mg, 0,135 mmoles) (véase preparación 31), anhídrido cíclico del ácido 1-propilfosfónico (0,2 ml, 0,338 mmoles, 50% en EtOAc) y trietilamina (0,65 ml, 0,474 mmoles) en THF (3 ml). La mezcla se agitó a 25ºC durante 18 horas, se evaporó al vacío y se dividió entre bicarbonato de sodio acuoso saturado (5 ml) y acetato de etil o (5 ml). La fase orgánica se secó sobre sulfato de sodio, se evaporó al vacío y el residuo se trituró con pentano:éter dietílico (3:1, 1 ml) para dar el compuesto del título en forma de un sólido blancuzco en 65% de rendimiento, 38 mg.
^{1}H RMN (400 MHz, DMSO) δ*:* 1,79 (s, 9H), 3,95 (s, 2H), 7,50 (m, 1H), 7,72 (m, 1H), 8,21 (s, 1H), 8,50 (d, 1H), 8,76 (d, 1H), 8,95 (d, 1H), 9,00 (s, 1H), 9,48 (s, 1H), 10,72 (s, 1H); LCMS (Sistema 4): T_r = 2,86 min; m/z 433 $[M+H]^+$.

Los ejemplos 2 a 8 se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 1, partiendo de (5-aminopiridin-3-il)(7-*ter*-butil-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 31) y los ácidos apropiados.

Ejemplo	Nombre	Datos
2	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida	LCMS (sistema 4): T_r = 3,26 min; m/z 473 $[M+H]^+$

Ejemplo	Nombre	Datos
3	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(3-ciclopropil-1H-pirazol-1-il)acetamida	LCMS (sistema 4): T_r = 3,04 min; m/z 444 $[M+H]^+$
4	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-(ciclopropil-1H-1,2,3-triazol-1-il)acetamida	LCMS (sistema 4): T_r = 2,75 min; m/z 445 $[M+H]^+$
5	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 4): T_r = 3,04 min; m/z 472 $[M+H]^+$
6	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-cloropiridin-2-il)acetamida	LCMS (sistema 4): T_r = 2,92 min; m/z 449 $[M+H]^+$
7	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-ciclopropil-1H-pirazol-1-il)acetamida	LCMS (sistema 4): T_r = 2,96 min; m/z 443 $[M+H]^+$
8	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 4): : T_r = 3,00 min; m/z 472 $[M+H]^+$

Ejemplo 9 N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[4-(trifluorometil)fenil]acetamida;



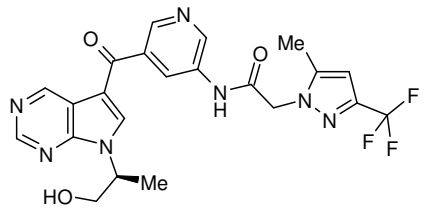
Se agregó ácido 4-(trifluorometil)fenilacético (33,6 g, 165 mmoles) a (5-aminopiridin-3-il){7-[(1S)-2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (45,2 g, 110 mmoles) (véase preparación 37), anhídrido cíclico del ácido 1-propilfosfónico (194 ml, 329 mmoles, 50% en EtOAc) y trietilamina (53,6 ml, 384 mmoles) en THF (400ml). La mezcla se agitó a 25ºC durante 2 horas, posteriormente se agregó bicarbonato de sodio acuoso saturado (250 ml) y la capa orgánica se separó. La fase acuosa se extrajo con EtOAc (2 x 200 ml) y todas las fases orgánicas se combinaron y se secaron sobre sulfato de sodio, posteriormente se evaporó al vacío.

El sólido de color marrón residuo se disolvió en THF (400 ml) y se agregó HCl acuoso (200 ml, 2M). La mezcla se agitó a temperatura ambiente durante 2 horas, posteriormente se enfrió hasta 0ºC y se agregó hidróxido de sodio (28 g). La mezcla se agitó durante 3 horas, posteriormente se agregó agua (100 ml). La capa orgánica se

separó y la fase acuosa se extrajo con EtOAc (2 x 300 ml) y todas las fases orgánicas se combinaron y se secaron sobre sulfato de sodio, posteriormente se evaporaron al vacío. El sólido bruto se recristalizó utilizando acetato de etilo (150 ml) para dar el compuesto del título en forma de un sólido de color blanco en 63% de rendimiento, 33,4 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,51 (d, 3H), 3,68-3,79 (m, 1H), 3,81-3,93 (m, 3H), 4,93-5,06 (m, 2H), 7,55-7,63 (m, 2H), 7,67-7,75 (m, 2H), 8,41-8,49 (m, 2H), 8,73 (d, 1H), 8,98 (s, 1H), 9,00 (d, 1H), 9,44 (s, 1H), 10,72 (s, 1H); LCMS (Sistema 1): T_r = 4,53 min; m/z 484 $[M+H]^+$.

Ejemplo 10: N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[5-metil-3-(trifluorometil)-1H-pirazol-1-il]acetamida



Se agregó 10% de ácido clorhídrico en 1,4-dioxano (0,2 ml) a la preparación 66 (59 mg, 0,098 mmoles) en THF (2 ml) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se evaporó al vacío y se trituró con pentano:éter dietílico (3:1, 1 ml) para dar el compuesto del título en forma de un sólido blancuzco en 86% de rendimiento, 41 mg.

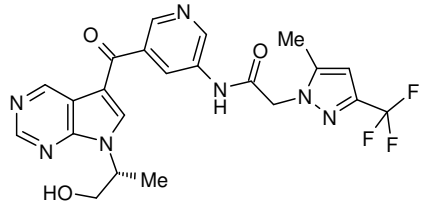
LCMS (sistema 4): T_r = 2,85 min; m/z 488,2 $[M+H]^+$.

Los ejemplos 11 a 16 se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 10, partiendo del alcohol protegido apropiado.

Ejemplo	Nombre	Datos
11	2-(4-clorofenil)-N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS (sistema 4): T_r = 2,89 min; m/z 450 $[M+H]^+$
12	N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 4): T_r = 2,88 min; m/z 474 $[M+H]^+$
13	N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[4-(trifluorometil)-1H-1,2,3-triazol-il]acetamida	LCMS (sistema 4): T_r = 2,68 min; m/z 475 $[M+H]^+$
14	2-(5-cloropiridin-2-il)-N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS (sistema 4): T_r = 2,72 min; m/z 451 $[M+H]^+$
15	2-(2H-benzotriazol-2-il)-N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS (sistema 4): T_r = 2,64 min; m/z 457 $[M+H]^+$

Ejemplo	Nombre	Datos
16	2-(2,4-difluorofenil)-N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS (sistema 4) Tr = 2,74 min; m/z 452 $[M+H]^+$

Ejemplo 17: N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[5-metil-3-(trifluorometil)-1H-pirazol-1-il]acetamida



Se agregó ácido (5-metil-3-trifluorometil-pirazol-1-il)acético (46,8 mg, 0,225 mmoles) a (R,S) (5-aminopiridin-3-il){7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (66 mg, 0,173 mmoles (véase la preparación 36), anhídrido cíclico del ácido 1-propilfosfónico (0,31 ml, 0,519 mmoles) y DIPEA (0,09 ml, 0,606 mmoles) en THF (5 ml). La mezcla se calentó a reflujo durante 48 horas, se evaporó al vacío y se dividió entre bicarbonato de sodio acuoso saturado (5 ml) y acetato de etil o (5 ml). La fase orgánica se secó sobre sulfato de sodio, se evaporó al vacío y el residuo se purificó por cromatografía de columna sobre gel de sílice (gradiente de EtoAc: Hexano 85: 15) para dar el intermediario en forma de un sólido blancuzco en 53% de rendimiento, 52 mg.

Se agregó 10% de ácido clorhídrico en 1,4-dioxano (0,4 ml) al intermediario (52 mg, 0,091 mmoles) en THF (2 ml) y la mezcla se agitó a temperatura ambiente durante 1,5 horas. La mezcla se evaporó al vacío y se trituró con pentano:éter dietílico (3:1, 1 ml) para dar el compuesto del título en forma de un sólido blancuzco en 94% de rendimiento, 42 mg.

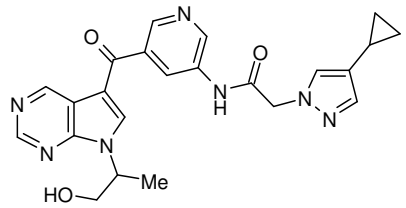
^{1}H RMN (400 MHz, DMSO) δ*:* 1,49 (d, 3H), 2,32 (d, 3H), 3,56 (m, 1H), 5,00 (m, 1H), 5,20 (s, 2H), 6,56 (s, 1H), 8,45 (s, 1H), 8,54 (s, 1H), 8,79 (s, 1H), 9,02 (s, 2H), 9,48 (s, 1H), 11,05 (s, 1H);

LCMS (sistema 4): T_r = 2,86 min; m/z 488 $[M+H]^+$.

Los ejemplos 18 a 24 se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 17, partiendo de 5-aminopiridin-3-il){7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (véase preparación 36).

Ejemplo	Nombre	Datos
18	2-(4-ciclopropil-1H-1,2,3-triazol-1-il)-N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS (sistema 4): T_r = 2,21 min; m/z 474 $[M+H]^+$
19	2-(5-fluoropiridin-2-il)-N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS (sistema 4): T_r = 2,24 min; m/z 435 $[M+H]^+$
20	N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[4-(trifluorometil)fenil]acetamida	LCMS (sistema 4): T_r = 2,98 min; m/z 484 $[M+H]^+$
21	N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[4-(trifluorometil)-1H-1,2,3-triazol-il]acetamida	LCMS (sistema 4): T_r = 2,70 min; m/z 475 $[M+H]^+$
22	N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 4): T_r = 2,80 min; m/z 474 $[M+H]^+$
23	2-(5-cloropiridin-2-il)-N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS (sistema 4): T_r = 2,49 min; m/z 451 $[M+H]^+$
24	2-(4-clorofenil)-N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS (sistema 2): T_r = 1,01 min; m/z 450 $[M+H]^+$

Ejemplo 25: (R,S) 2-(4-ciclopropil-1H-pirazol-1-il)-N-(5-{[7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 9 utilizando (R,S) (5-aminopiridin-3-il){7-[2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (véase preparación 39) y ácido (4-ciclopropil-1H-pirazol-1-il)acético (véase preparación 88) para dar el compuesto del título en forma de un sólido de color blanco en 14% de rendimiento, 20 mg.

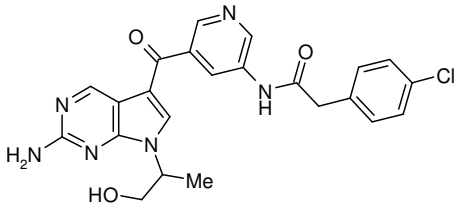
^{1}H RMN (400 MHz, DMSO) δ*:* 0,46 (d, 2H), 0,79 (d, 2H), 1,49 (d, 3H), 1,70 (m, 1H), 3,73 (m, 1H), 3,87 (m, 1H), 5,00 (s, 4H), 7,26 (s, 1H), 7,54 (s, 1H), 8,40 (s, 1H), 8,47 (s, 1H), 8,75 (d, 1H), 8,98 (s, 1H), 9,00 (d, 1H), 9,44 (s, 1H), 10,75 (s, 1H); LCMS (system 4): T_r = 2,53 min; m/z 445 $[M+H]^+$.

Los ejemplos 26 a 33 se prepararon de acuerdo con el método que se describió

anteriormente para el ejemplo 10, partiendo del alcohol protegido apropiado éter TBDMS.

Ejemplo	Nombre	Datos
26	N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[5-metil)-3-(trifluorometil-1H-pirazol-1-il]acetamida	LCMS (sistema 4): T_r = 2,89 min; m/z 502 $[M+H]^+$
27	N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)fenil]acetamida	LCMS (sistema 4): T_r = 3,03 min; m/z 498 $[M+H]^+$
28	2-(4-clorofenil)-N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida	^{1}H RMN (400 MHz, DMSO) δ*:* 1,73 (s, 6H), 3,75 (s, 2H), 3,96 (s, 2H), 7,39 (s, 4H), 8,22 (s, 1H), 8,51 (s, LCMS (sistema 4): T_r = 3,02 min; m/z 464,1 $[M+H]^+$
29	2-(5-cloropiridin-2-il)-N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida	LCMS (sistema 4): T_r = 2,72 min; m/z 465 $[M+H]^+$
30	N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(trifluorometil-1H-pirazol-1-il]acetamida	LCMS (sistema 4): T_r = 2,80 min; m/z 488 $[M+H]^+$
31	2-(4-ciclopropil-1H-1,2,3-triazol-1-il)-N-[5-({7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida	LCMS (sistema 4): T_r = 2,47 min; m/z 461 $[M+H]^+$
32	N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil-1H-1,2,3-triazol-1-il]acetamida	LCMS (sistema 4): T_r = 2,78 min; m/z 489 $[M+H]^+$
33	(R,S) 2-(4-ciclopropil-1H-pirazol-1-il)-N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida	LCMS (sistema 4): T_r = 2,68 min; m/z 460 $[M+H]^+$

Ejemplo 34 N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-clorofenil)acetamida (enantiómero 1)



Se agregó ácido 4-clorofenilacético (25 mg, 0,14 mmoles) a [2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il](5-aminopiridin-3-il)metanona (50 mg, 0,16 mmoles) (véase preparación 57) y HATU (91 mg, 0,24 mmoles) en piridina (2 ml).

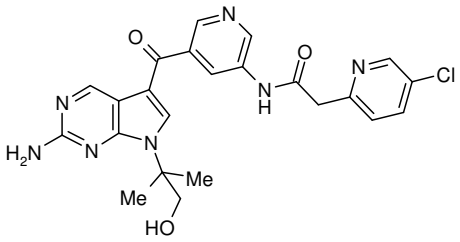
La mezcla se agitó a temperatura ambiente durante 16 horas. Se agregó bicarbonato de sodio acuoso saturado (5 ml), posteriormente se extrajo con acetato de etilo (3 x 5ml). Las fases orgánicas combinadas se lavaron con salmuera (5 ml), posteriormente se secaron sobre sulfato de sodio y se evaporaron al vacío. El residuo se purificó por TLC preparativa (95:5 DMC:MeOH) para dar el compuesto del título en forma de un sólido de color amarillo en 48% de rendimiento, 32 mg.

LCMS (sistema 5): T_r = 2,90 min; m/z 465 $[M+H]^+$.

Los ejemplos 35 a 45 se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 34, partiendo de [2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il](5-aminopiridin-3-il)metanona (véase preparación 57, enantiómero 1 o preparación 59, enantiómero 2) y los ácidos apropiados.

Ejemplo	**Nombre**	**Datos**
35	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(5-cloropiridin-2-il)acetamida;	Enantiómero 1 LCMS (sistema 5): T_r = 2,63 min; m/z 466 $[M+H]^+$
36	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)fenil]acetamida	Enantiómero 1 LCMS (sistema 5): T_r = 2,88 min; m/z 499 $[M+H]^+$
37	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(5-fluoropiridin-2-il)acetamida	Enantiómero 1 LCMS (sistema 5): T_r = 2,25 min; m/z 450 $[M+H]^+$
38	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	Enantiómero 1 LCMS (sistema 4): T_r = 2,39 min; m/z 489 $[M+H]^+$
39	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida	Enantiómero 1 LCMS (sistema 5): T_r = 2,61 min; m/z 490 $[M+H]^+$
40	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(5-fluoropiridin-2-il)acetamida	Enantiómero 2 LCMS (sistema 4): T_r = 1,89 min; m/z 450 $[M+H]^+$
41	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(5-cloropiridin-2-il)acetamida;	Enantiómero 2 LCMS (sistema 4): T_r = 2,16 min; m/z 466 $[M+H]^+$
42	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-clorofenil)acetamida	Enantiómero 2 LCMS (sistema 4): T_r = 2,63 min; m/z 465 $[M+H]^+$
43	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)fenil]acetamida	Enantiómero 2 LCMS (sistema 4): T_r = 2,73 min; m/z 499 $[M+H]^+$
44	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	Enantiómero 2 LCMS (sistema 4): T_r = 2,38 min; m/z 489 $[M+H]^+$
45	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida	Enantiómero 2 LCMS (sistema 5): T_r = 2,60 min; m/z 490 $[M+H]^+$

Ejemplo 46 N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(5-cloropiridin-2-il)acetamida



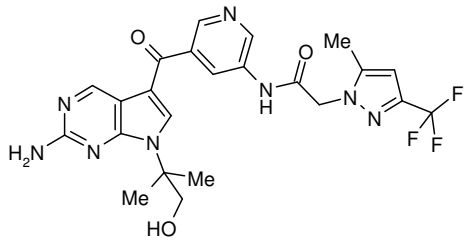
Se agregó ácido 2-(5-cloropiridin-2-il)acético (26,1 g, 152 mmoles) (véase Preparación 90) a (5-aminopiridin-3-il)(7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetil)-2-[(2,4-dimetobencil)amino]-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona (75,0 g, 130 mmoles) (véase preparación 51), anhídrido cíclico del ácido 1-propilfosfónico (187 ml, 317 mmoles, 50% de solución en EtOAc) y trietilamina (61,9 ml, 444 mmoles) en THF (423 ml). La mezcla se agitó a 25ºC durante 2 horas, posteriormente se agregó bicarbonato de sodio acuoso saturado (400 ml) y la capa orgánica se separó. La fase acuosa se extrajo con EtOAc (400 ml) y todas las fases orgánicas se combinaron y se secaron sobre sulfato de sodio, posteriormente se evaporó al vacío.

El sólido de color marrón residuo se disolvió en ácido trifluoroacético (300 ml) y la solución se agitó a 50ºC durante 3 horas, posteriormente se evaporó al vacío. Se agregó metanol (1800 ml) al residuo y la mezcla se filtró. El filtrado se evaporó al vacío y se azeotropeó con etanol (3 x 200 ml).

Se agregó carbonato de potasio (87,7 g, mmoles) a la trifluoroacetamida bruta en metanol (300 ml) y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla se vertió en agua (2000 ml) y se filtró. El sólido se lavó con agua (200 ml), posteriormente se trituró con etanol (2 x 200 ml a temperatura ambiente, más tarde 380 ml a 50ºC) para dar el compuesto del título en forma de un sólido de color amarillo en 48% de rendimiento, 29,9 g.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,64 (s, 6H), 3,90 (d, 2H), 3,95 (s, 2H), 5,05 (t, 1H), 6,54 (br s, 2H), 7,49 (d, 1H), 7,69 (s, 1H), 7,92 (dd, 1H), 8,40 (m, 1H), 8,56 (m, 1H), 8,64 (d, 1H), 8,94 (d, 1H), 8,96 (s, 1H), 10,71 (s, 1H); LCMS (Sistema 3): T_r = 9,92 min; m/z 480 $[M+H]^+$.

Ejemplo 47 N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[5-metil-3-(trifluorometil)-1H-pirazol-1-il]acetamida



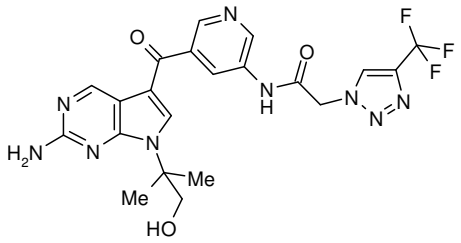
El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 46 utilizando (5-aminopiridin-3-il)(7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetil)-2-[(2,4-dimetobencil)amino]-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 51) y ácido (5-metil-3-trifluorometil-pirazol-1-il)acético (46,8 mg, 0,225 mmoles) para dar el compuesto del título en forma de un sólido de color marrón en 79% de rendimiento, 82 mg.

LCMS (sistema 1): T_r = 2,83 min; m/z 517 $[M+H]^+$.

Los ejemplos 48 a 53 se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 34, partiendo de [2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il](5-aminopiridin-3-il)metanona (véase preparación 48) y los ácidos apropiados.

Ejemplo	Nombre	Datos
48	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)fenil]acetamida	LCMS (sistema 5): T_r = 3,12 min; m/z 513 $[M+H]^+$
49	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-clorofenil)acetamida	LCMS (sistema 5): T_r = 2,89 min; m/z 479 $[M+H]^+$
50	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(2,4-difluorofenil)acetamida	MS (ESCI): m/z 481 $[M+H]^+$
51	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(5-fluoropiridin-2-il)acetamida	LCMS (sistema 5): T_r = 2,42 min; m/z 464 $[M+H]^+$
52	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 4): T_r = 2,54 min; m/z 503 $[M+H]^+$
53	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(3-ciclopropil-1H-pirazol-1-il]acetamida	LCMS (sistema 4) Tr = 2,23 min; m/z 475 $[M+H]^+$

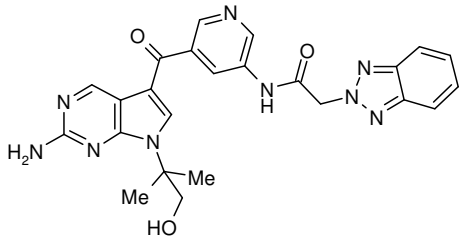
Ejemplo 54 N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 9 utilizando [7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetil)-2-amino-7*H*-pirrolo[2,3-*d*]pirimidin-5-il]{5-aminopiridin-3-il}metanona (véase preparación 48a) y ácido [4-(trifluorometil)-1H-1,2,3-triazol-1-il)acético (véase preparación 81) para dar el compuesto del título en forma de un sólido de color marrón en 85% de rendimiento, 62 mg.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,63 (s, 6H), 3,89 (d, 2H), 5,01 (br, 1H), 5,56 (s, 2H), 6,67 (br s, 2H), 7,72 (s, 1H), 8,36 (s, 1H), 8,70 (s, 1H), 8,94-8,96 (m, 3H), 11,05 (s, 1H); LCMS (sistema 5): Tr = 2,71 min; m/z 502 $[M-H]^+$.

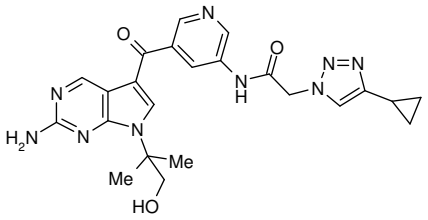
Ejemplo 55 N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(2H-benzotriazol-2-il)acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 9 utilizando {2-amino-7-[1,1-dimetil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}(5-aminopiridin-3-il)metanona (véase preparación 49) para dar el compuesto del título en forma de un sólido de color marrón en 46% de rendimiento, 20 mg.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,63 (s, 6H), 3,88 (d, 2H), 5,04 (t, 1H), 5,80 (s, 2H), 6,54 (s, 2H), 7,46-7,49 (m, 2H), 7,69 (s, 1H), 7,95-7,97 (m, 2H), 8,35 (s, 1H), 8,69 (s, 1H), 8,96 (s, 1H), 8,98 (s, 1H), 11,06 (s, 1H); MS (ESCI): m/z 486 $[M+H]^+$

Ejemplo 56 N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-(ciclopropil-1H-1,2,3-triazol-1-il)acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 10 utilizando N-[5-({2-amino-7-[1,1-dimetil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-(4-ciclopropil-1H-1,2,3-triazol-1-il)acetamida (véase preparación 52) para dar el compuesto del título en forma de un sólido de color amarillo en 24% de rendimiento, 14 mg.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 0,71-0,72 (m, 2H), 0,89-0,91 (m, 2H), 1,64 (s, 6H), 1,94-1,99 (m, 1H), 3,89 (d, 2H), 5,07 (t, 1H), 5,31 (s, 2H), 6,53 (s, 2H), 7,69 (s, 1H), 7,86 (s, 1H), 8,35 (s, 1H), 8,65 (s, 1H), 8,95 (m, 2H), 11,04 (s, 1H); LCMS (sistema 5): T_r = 2,42 min; m/z 476 $[M+H]^+$.

Los ejemplos 57 a 64 se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 1, partiendo de (2-amino-7-*ter*-butil-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)(5-aminopiridin-3-il)metanona (véase preparación 65) y los ácidos apropiados.

Ejemplo	**Nombre**	**Datos**
57	N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(3-ciclopropil-1H-pirazol-1-il)acetamida	LCMS (sistema 5): T_r = 2,90 min; m/z 459 $[M+H]^+$
58	N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-ciclopropil-1H-1,2,3-triazol-1-il)acetamida	LCMS (sistema 5) 12 min corrida): T_r = 6,13 min; m/z 460 $[M+H]^+$
59		LCMS (sistema 4): T_r = 2,60 min; m/z 448 $[M+H]^+$
60	N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 5): T_r = 2,99 min; m/z 487 $[M+H]^+$
61	N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida	LCMS (sistema 5): T_r = 3,04 min; m/z 488 $[M+H]^+$
62	N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 5): T_r = 3,09 min; m/z 487 $[M+H]^+$
63	N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-cloropiridin-2-il)acetamida;	LCMS (sistema 5): T_r = 2,95 min; m/z 464 $[M+H]^+$
64	N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[5-metil-3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 5): T_r = 3,09 min; m/z 501 $[M+H]^+$

Los siguientes ejemplos se prepararon de acuerdo con el método a (ejemplo 34 a 50ºC) o el método b (ejemplo 1 utilizando DIPEA) como se describió anteriormente a partir de (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (preparación 95) y el ácido apropiado.

Ejemplo	Nombre	Datos
65	2-(4-fluorofenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 1): T_r = 2,73 min; m/z 418 $[M+H]^+$.
66	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(trifluorometil)fenil]acetamida	LCMS (sistema 9): T_r = 3,22 min; m/z 468 $[M+H]^+$.
67	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)fenil]acetamida	LCMS (sistema 9): T_r = 3,22 min; m/z 468 $[M+H]^+$.
68	2-(3,4-diclorofenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 7): T_r = 11,34 min; m/z 468 $[M+H]^+$
69	2-(4-clorofenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	m/z 434 $[M+H]^+$
70	2-[2-(ciclopropiloxi)fenil])-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 4): T_r = 3,13 min; m/z 456 $[M+H]^+$ HPLC Prep (método 2) Utilizando ácido [2-(ciclopropiloxi)fenil]acético (Preparación 160).
71	2-(4-cianofenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,16 min; m/z 425 $[M+H]^+$
72	2-[4-ciano-3-(trifluorometil)fenil]-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 1): T_r = 2,82 min; m/z 493 $[M+H]^+$ Utilizando ácido [4-ciano-3-(trifluorometil)fenil]acético (Preparación 164).
73	2-[4-(ciclopropiloxi)fenil])-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 3) Tr = 3,05 min; m/z 456 $[M+H]^+$ Utilizando ácido [4-(ciclopropiloxi)fenil]acético (Preparación 161). Método de prep 2
74	2-[3-(ciclopropiloxi)fenil])-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 1) Tr = 2,52 min; m/z 456 $[M+H]^+$ Utilizando ácido [3-

Ejemplo	Nombre	Datos
		(ciclopropiloxi)fenil]acético (Preparación 162).
75	2-[3-(hidroximetil)fenil])-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,3 min; m/z 430 $[M+H]^+$
76	2-(4-ciano-3-fluorofenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,5 min; m/z 443 $[M+H]^+$
77	2-(4-ciano-3-metoxifenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,3 min; m/z 455 $[M+H]^+$
78	2-(6-fluoro-1-oxo-1,3-dihidro-2H-isoindol-2-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,5 min; m/z 473 $[M+H]^+$
79	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(3-piridin-2-il-1H-pirazol-1-il)acetamida	LCMS (sistema 2): T_r = 1,2 min; m/z 467 $[M+H]^+$.
80	2-(1H-bencimidazol-5-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,0 min; m/z 440 $[M+H]^+$
81	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-quinoxalin-6-ilacetamida	LCMS (sistema 2): T_r = 1,1 min; m/z 452 $[M+H]^+$
82	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(1,5-naftiridin-3-il)acetamida	LCMS (sistema 9): T_r = 2,63 min; m/z 452 $[M+H]^+$ Utilizando ácido 1,5-naftiridin-3-ilacético (preparación 188).
83	2-(3-amino-1,2-bencisoxazol-5-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 9): T_r = 2,76 min; mz 456 $[M+H]^+$ etil éster del ácido (3-amino-benzo[d]isoxazol-5-il)-acético (preparación 129)
84	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[2-(trifluorometil)-1H-bencimidazol-5-il]acetamida	LCMS (sistema 9): T_r = 2,90 min; m/z 508 $[M+H]^+$
85	2-imidazo[1,2-a]piridin-7-il-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 10): T_r = 2,57 min; m/z 440 $[M+H]^+$ utilizando ácido imidazo[1,2-a]piridin-7-il-acético (preparación 132).
86	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(1H-pirazol[4,3-d]piridin-1-il)acetamida	LCMS (sistema 9): T_r = 2,54 min; m/z 441 $[M+H]^+$ Utilizando ácido 1H-pirazolo[4,3-b]piridin-1-

Ejemplo	Nombre	Datos
		il)acético (preparación 190).
87	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(metilsulfonil)fenil]acetamida	LCMS (sistema 9): T_r = 2,74 min; m/z 478 $[M+H]^+$
88	2-(4-ciclopropil-1H-1,2,3-triazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 9): T_r = 2,68 min; m/z 431 $[M+H]^+$. Utilizando ácido 4-ciclopropil-1H-1,2,3-triazol-1-ilacético (preparación 83).
89	2-(1,3-benzoxazol-5-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 9): T_r = 2,79 min; m/z 441,1 $[M+H]^+$
90	2-(3-ciclopropil-1H-pirazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 9): T_r = 2,75 min; m/z 430 $[M+H]^+$ Ácido (3-ciclopropil-1H-pirazol-1-il)acético (preparación 80).
91	2-[5-(ciclopropiloxi)piridin-3-il]-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 3) Tr = 2,36 min; m/z 457 $[M+H]^+$ Método de prep 2 Utilizando ácido [5-(ciclopropiloxi)piridin-3-il]acético (Preparación 163).
92	2-(2,3-dihidro-1-benzofuran-5-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 3): T_r = 2,91 min; m/z 442 $[M+H]^+$ HPLC Prep (método 1)
93	2-(2H-indazol-2-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 3): T_r = 2,74 min; m/z 440 $[M+H]^+$ HPLC Prep (método 1)
94	2-(5-fluoro-2H-indazol-2-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 9): T_r = 2,96 min; m/z 458 $[M+H]^+$ Utilizando ácido (5-fluoro-2H-indazol-2-il)acético (preparación 174).
95	2-(5-fluoro-1H-indazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 9): T_r = 2,97 min; m/z 458 $[M+H]^+$ Utilizando ácido (5-fluoro-2H-indazol-1-il)acético (preparación 172).
96	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[5-metil-3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 8): T_r = 1,62 min; m/z 472 $[M+H]^+$

Ejemplo	Nombre	Datos
97	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 3): T_r = 2,97 min; m/z 458 $[M+H]^+$ HPLC Prep (método 1)
98	2-(5-cloropiridin-2-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 9): T_r = 2,86 min; m/z 435 $[M+H]^+$ Utilizando ácido (5-cloropiridin-2-il)acético (preparación 90).
99	2-(1H-indazol-6-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	m/z 440 $[M+H]^+$ Utilizando ácido 1H-indazol-6-ilacético (preparación 182).
100	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-quinolin-7-ilacetamida	LCMS (sistema 7): T_r = 8,73 min; m/z 451 $[M+H]^+$
101	2-(7-fluoro-2H-indazol-2-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 9): T_r = 2,95 min; m/z 458 $[M+H]^+$ Utilizando ácido (7-fluoro-2H-indazol-2-il)acético (preparación 178).
102	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(1H-pirazol[3,4-d]piridin-1-il)acetamida	LCMS (sistema 9): T_r = 2,72 min; m/z 441 $[M+H]^+$ Utilizando ácido 1H-pirazolo[3,4-b]piridin-1-il)acético (preparación 180).
103	2-(1H-indazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 3): T_r = 2,82 min; m/z 440 $[M+H]^+$ HPLC Prep (método 1)
104	2-(3-isopropil-5-metil-1H-pirazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,65 min; m/z 446 $[M+H]^+$ Utilizando ácido (3-ciclopropil-5-metil-1H-pirazol-1-il)acético (preparación 167).
105	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-isopropil-1H-1,2,3-triazol-1-il)acetamida	LCMS (sistema 8): T_r = 1,52 min; m/z 433 $[M+H]^+$
106	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida	LCMS (sistema 9): T_r = 2,98 min; m/z 459 $[M+H]^+$ Utilizando ácido [4-(trifluorometil)-1H-1,2,3-triazol-1-il]acético (preparación 81).
107	2-(7-fluoro-1H-indazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 9): T_r = 2,96 min; m/z 458 $[M+H]^+$ Utilizando ácido (7-fluoro-2H-indazol-1-il)acético (preparación 176).

Ejemplo	Nombre	Datos
108	2-(2H-benzotriazol-2-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,57 min; m/z 441 $[M+H]^+$
109	2-(7-fluoro-2-metil-1H-indol-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,64 min; m/z 471 $[M+H]^+$
110	2-(5-fluoro-2-metil-1H-indol-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,69 min; m/z 487 $[M+H]^+$
111	2-(1H-indol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,66 min; m/z 439 $[M+H]^+$
112	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[1-isopropil-5-(trifluorometil)-1H-pirazol-4-il]acetamida	LCMS (sistema 9): T_r = 3,13 min; m/z 500 $[M+H]^+$ Utilizando ácido 1-isopropil--5-(trifluorometil)-1H-pirazol-4-il)acético (preparación 185).
113	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(3-metil-1H-pirazol-1-il)acetamida	LCMS (sistema 8): T_r = 1,50 min; m/z 404 $[M+H]^+$
114	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(1H-pirazol-1-il)acetamida	LCMS (sistema 8): T_r = 1,45 min; m/z 390 $[M+H]^+$
115	2-(3,5-dimetil-1H-pirazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,55 min; m/z 418 $[M+H]^+$
116	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(2-metil-1H-indol-3-il)acetamida	LCMS (sistema 8): T_r = 1,62 min; m/z 453 $[M+H]^+$
117	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-metoxi-1H-indol-3-il)acetamida	LCMS (sistema 8): T_r = 1,57 min; m/z 469 $[M+H]^+$
118	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-piridin-3-ilacetamida	LCMS (sistema 8): T_r = 1,35 min; m/z 401 $[M+H]^+$
119	2-(5-cloro-1H-benzotriazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,61 min; m/z 475 $[M+H]^+$
120	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(2-tienil)-1H-pirazol-1-il]acetamida	LCMS (sistema 8): T_r = 1,61 min; m/z 472 $[M+H]^+$

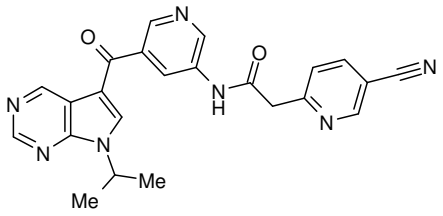
Ejemplo	Nombre	Datos
121	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(7-metilimidazo[1,2-a]pirimidin-2-il)acetamida	LCMS (sistema 8): T_r = 1,37 min; m/z 455 $[M+H]^+$
122	2-(2,6-dimetil-9H-purin-9-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,43 min; m/z 470 $[M+H]^+$
123	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(6-nitro-1H-indazol-1-il)acetamida	LCMS (sistema 8): T_r = 1,60 min; m/z 485 $[M+H]^+$
124	2-(5-fluoro-1-metil-1H-indazol-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,73 min; m/z 488 $[M+H]^+$. J. Med.Chem. 1992, 35, 2155-2165
125	2-(5-fluoro-2-metil-1H-indol-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,63 min; m/z 471 $[M+H]^+$
126	2-(6-cloroimidazo[1,2-a]piridin-2-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,45 min; m/z 474 $[M+H]^+$
127	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(2-metil-1H-bencimidazol-1-il)acetamida	LCMS (sistema 8): T_r = 1,36 min; m/z 454 $[M+H]^+$
128	2-imidazo[1,2-a]piridin-2-il-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,31 min; m/z 440 $[M+H]^+$
129	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-metoxi-1H-pirrolo[3,2-b]piridin-1-il)acetamida	LCMS (sistema 8): T_r = 1,49 min; m/z 470 $[M+H]^+$
130	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-metil-1H-pirazol-1-il)acetamida	LCMS (sistema 8): T_r = 1,49 min; m/z 404 $[M+H]^+$
131	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(7-metil-1H-bencimidazol-1-il)acetamida	LCMS (sistema 8): T_r = 1,43 min; m/z 454 $[M+H]^+$
132	2-(1H-indol-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,59 min; m/z 439 $[M+H]^+$
133	2-(1H-bencimidazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,40 min; m/z 440 $[M+H]^+$
134	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(3-metil-1H-pirazol-5-il)acetamida	LCMS (sistema 8): T_r = 1,45 min; m/z 404 $[M+H]^+$

Ejemplo	Nombre	Datos
135	2-(1H-benzotriazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,52 min; m/z 441 $[M+H]^+$
136	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(1-metil-1H-indol-3-il)acetamida	LCMS (sistema 8): T_r = 1,68 min; m/z 453 $[M+H]^+$
137	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-fenil-1H-pirrol-2-il)acetamida	LCMS (sistema 8): T_r = 1,66 min; m/z 465 $[M+H]^+$
138	2-(2-etil-3H-imidazo[4,5-b]piridinil-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,49 min; m/z 469 $[M+H]^+$
139	2-(5-cloro-1H-indol-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,67 min; m/z 473 $[M+H]^+$
140	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(1-fenil-1H-pirrol-3-il)acetamida	LCMS (sistema 8): T_r = 1,71 min, m/z 465 $[M+H]^+$. Se puede preparar mediante un método similar a Harrak, Y. et al. Bioorganic & Medicinal Chemistry (2007), 15(14), 4876-4890.
141	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-metil-1H-indol-3-il)acetamida	LCMS (sistema 8): T_r = 1,63 min; m/z 453 $[M+H]^+$
142	2-(2-etil-1H-bencimidazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,37 min; m/z 468 $[M+H]^+$
	2-imidazo[1,2-a]pirimidin-2-il-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,38 min; m/z 441 $[M+H]^+$
144	2-(1H-indazol-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,55 min; m/z 440 $[M+H]^+$
145	2-(5-fluoro-7-metoxi-1H-indol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,67 min; m/z 487 $[M+H]^+$
146	2-(1-bencil-1H-1,2,3-triazol-4-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,57 min; m/z 481 $[M+H]^+$
147	2-(6-fluoro-1-metil-1H-indazol-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,72 min; m/z 488 $[M+H]^+$ Utilizando ácido (6-cloro-1-metil-1H-indazol-3-il)acético (preparación 170).

Ejemplo	Nombre	Datos
148	2-(7-cloro-1H-indol-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,67 min; m/z 473 $[M+H]^+$
149	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-metil-4-fenil-1H-pirazol-1-il)acetamida	LCMS (sistema 8): T_r = 1,68 min; m/z 480 $[M+H]^+$
150	2-(5-bromopiridin-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,60 min; m/z 479 $[M+H]^+$
151	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-piridin-2-ilacetamida	LCMS (sistema 8): T_r = 1,41 min; m/z 401 $[M+H]^+$
152	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(6-metoxipiridin-3-il)acetamida	LCMS (sistema 8): T_r = 1,55 min; m/z 431 $[M+H]^+$
153	2-(2,5-dimetil-1H-indol-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,67 min; m/z 467 $[M+H]^+$
154	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(6-metilpiridin-3-il)acetamida	LCMS (sistema 8): T_r = 1,33 min; m/z 415 $[M+H]^+$
155	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(2-metilquinolin-7-il)acetamida	LCMS (sistema 8): T_r = 1,40 min; m/z 465 $[M+H]^+$ Utilizando ácido (2-metilquinolin-7-il)acético (preparación 165).
156	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-metoxi-2-metil-1H-indol-3-il)acetamida	LCMS (sistema 8): T_r = 1,60 min; m/z 483 $[M+H]^+$
157	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-tetrazolo[1,5-b]piridin-6--ilacetamida	LCMS (sistema 8): T_r = 1,46 min; m/z 443 $[M+H]^+$. (se puede preparar mediante un método similar al documento WO2010/129379, 11 Nov 2010)
158	2-(5-hidroxi-1H-indol-3-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,45 min; m/z 455 $[M+H]^+$
159	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5H-pirrolo[2,3-d]pirazin-7-il)acetamida	LCMS (sistema 8): T_r = 1,47 min; m/z 441 $[M+H]^+$
160	2-(5,6-dimetil-1H-bencimidazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,43 min; m/z 468 $[M+H]^+$

Ejemplo	Nombre	Datos
161	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-piridin-2-il-1H-1,2,3-triazol-1-il)acetamida	LCMS (sistema 8): T_r = 1,48 min; m/z 468 $[M+H]^+$
162	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-metil-1H-1,2,3-triazol-1-il)acetamida	LCMS (sistema 8): T_r = 1,43 min; m/z 405 $[M+H]^+$
163	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-metil-3-fenil-1H-pirazol-4-il)acetamida	LCMS (sistema 8): T_r = 1,55 min; m/z 480 $[M+H]^+$
164	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[2-(metiltio)pirimidin-5-il]acetamida	LCMS (sistema 8): T_r = 1,55 min, m/z 448 $[M+H]^+$. Se puede preparar mediante un método similar a Smrz, R. et al. Collection of Czechoslovak Chemical Communications (1976), 41(9), 2771-87
165	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-pirimidin-2-ilacetamida	LCMS (sistema 8): T_r = 1,44 min; m/z 402 $[M+H]^+$

Ejemplo 166: 2-(5-cianopiridin-2-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida



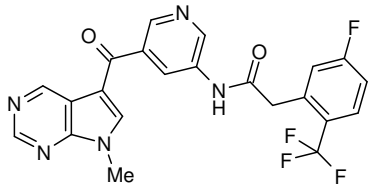
Se agregó cianuro de zinc (28 mg, 0,23 mmoles) a 2-(5-bromo-piridin-2-il)-N-[5-(7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-acetamida (ejemplo 317, 75 mg, 0,16 mmoles) en DMF (2 ml) y la mezcla se desgasifiqué con argón durante 10 minutos. A continuación se agregaron tris(dibencilidenoacetona)dipaladio (3 mg, 0,003 mmoles) y 1,1'-bis(difenilfosfino)ferroceno (7 mg, 0,012 mmoles) y la mezcla se calentó a 100ºC durante 40 min en irradiación por microondas. La mezcla se diluyó con EtOAc (5 ml) y se lavó con agua (2 ml), salmuera (2 ml) y se secó sobre sulfato de sodio. El filtrado se evaporó al vacío y se purificó por TLC preparativa (3% de MeOH en DCM) para dar el compuesto del título en forma de un sólido de color marrón claro en 18% de rendimiento, 12 mg.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,55 (d, 6H), 4,07 (s, 2H), 5,09 (m, 1H), 7,67 (d, 1H), 8,30 (m, 1H), 8,44 (s, 1H), 8,52 (s, 1H), 8,74 (d, 1H), 8,98-8,99 (m, 3H), 9,44 (s, 1H),

10,79 (s, 1H);

LCMS (sistema 9): T_r = 2,75 min; m/z 426 $[M+H]^+$.

Ejemplo 167 2-[-2-fluoro-3-(trifluorometil)fenil]-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida



Se agregó 1-(3-dimetilaminopropil)-3-etilcarbodiimida HCl (150 µL, 0,5M in DMF) al ácido 5-fluoro-2-(trifluorometil)fenilacético (90 µmol), N-metilmorfolina (25 µL, 150 µmoles), 1-hidroxibenzotriazol (15 µmol, 0,05M en DMF) y (5-aminopiridin-3-il)(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (preparación 110, 75 µmol, 0,25 M en DMF). La mezcla se agitó a 50ºC durante 2 horas y posteriormente se evaporó al vacío y se purificó por HPLC prep (método 4) para dar el compuesto del título.

LCMS (sistema 5): T_r = 2,66 min; m/z 458 $[M+H]^+$

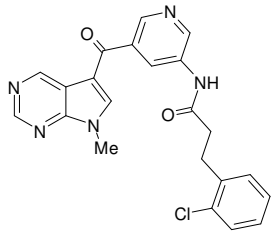
Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 167, partiendo de (5-aminopiridin-3-il)(7-metil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 110) y el ácido apropiado.

Ejemplo	**Nombre**	**Datos**
168	2-(3-metilfenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 5): T_r = 2,53 min; m/z 386 $[M+H]^+$
169	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[2-(trifluorometil)fenil]acetamida	LCMS (sistema 5): T_r = 2,61 min; m/z 440 $[M+H]^+$
170	2-(3,5-difluorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 5): T_r = 2,52 min; m/z 408 $[M+H]^+$
171	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(2,4,6-trifluorofenil)acetamida	LCMS (sistema 5): T_r = 2,50 min; m/z 426 $[M+H]^+$
172	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(2,3,6-trifluorofenil)acetamida	LCMS (sistema 5): T_r = 2,49 min; m/z 426 $[M+H]^+$
173	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(metilsulfonil)fenil]acetamida	LCMS (sistema 5): T_r = 2,13 min; m/z 450 $[M+H]^+$

174	2-[-3-fluoro-3-(trifluorometil)fenil]-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 5): T_r = 2,77 min; m/z 458 $[M+H]^+$
175	2-(3-metoxifenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS: T_r = 2,34 min; m/z 402 $[M+H]^+$
176	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(trifluorometoxi)fenil]acetamida	LCMS (sistema 5): T_r = 2,76 min; m/z 456 $[M+H]^+$
177	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(2,3,5-trifluorofenil)acetamida	LCMS (sistema 5): T_r = 2,54 min; m/z 426 $[M+H]^+$
178	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(2-metilquinolin-7-il)acetamida	LCMS (sistema 5): T_r = 1,95 min; m/z 437 $[M+H]^+$ Utilizando ácido (2-metilquinolin-7-il)acético (preparación 165).
179	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2fenilacetamida	LCMS (sistema 5): T_r = 2,37 min; m/z 372 $[M+H]^+$
180	2-(2-cloro-6-fluorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 5): T_r = 2,51 min; m/z 424 $[M+H]^+$
181	2-(4-metoxifenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS: T_r = 2,22 min; m/z 402 $[M+H]^+$
182	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-{4-[(trifluorometil)tio]fenil}acetamida	LCMS (sistema 5): T_r = 2,90 min; m/z 472 $[M+H]^+$
183	2-bifenil-4-il-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 6): T_r = 2,67 min; m/z 448 $[M+H]^+$
184	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(2,4,5-trifluorofenil)acetamida	LCMS (sistema 5): T_r = 2,54 min; m/z 426 $[M+H]^+$
185	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-{3-[(trifluorometil)tio]fenil}acetamida	LCMS (sistema 5): T_r = 2,86 min; m/z 472 $[M+H]^+$
186	2-(4-metilfenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 5): T_r = 2,53 min; m/z 386 $[M+H]^+$
187	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(3,4,5-trifluorofenil)acetamida	LCMS (sistema 5): T_r = 2,62 min; m/z 426 $[M+H]^+$

188	2-(2,4-dimetilfenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 5): T_r = 2,64 min; m/z 400 $[M+H]^+$
189	2-(2,3-dihidro-1-benzofuran-5-il)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 5): T_r = 2,37 min; m/z 414 $[M+H]^+$
190	2-(2,5-difluorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 5): T_r = 2,44 min; m/z 408 $[M+H]^+$
191	2-(2,4-difluorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 5): T_r = 2,46 min; m/z 408 $[M+H]^+$
192	2-[2-fluoro-3-(trifluorometil)fenil]-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 5): T_r = 2,72 min; m/z 458 $[M+H]^+$
193	2-(2,6-difluorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 5): T_r = 2,41 min; m/z 408 $[M+H]^+$
194	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(trifluorometil)fenil]acetamida	LCMS (sistema 2): T_r = 1,6 min; m/z 440 $[M+H]^+$
195	2-(3,4-difluorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,5 min; m/z 408 $[M+H]^+$
196	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometoxi)fenil]acetamida	LCMS (sistema 2): T_r = 1,6 min; m/z 456 $[M+H]^+$
197	2-(3-clorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,5 min; m/z 406 $[M+H]^+$

Ejemplo 198 3-(2-clorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}propanamida



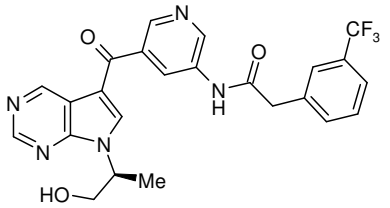
El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 167, partiendo de (5-aminopiridin-3-il)(7-metil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 110) y el ácido 3-(2-clorofenil)propanoico.

LCMS (sistema 5): T_r = 2,66 min; m/z 420 $[M+H]^+$

Los siguientes ejemplos se prepararon de acuerdo con el método b (ejemplo 1 utilizando DIPEA) como se describió partiendo de (5-aminopiridin-3-il)(7-ter-butil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 31) y los ácidos apropiados.

Ejemplo	Nombre	Datos
199	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(2-ciclopropil-1H-pirazol-1,3-oxazol-4-il)acetamida	LCMS (sistema 9): T_r = 3,16 min; m/z 445 $[M+H]^+$ Utilizando ácido (2-ciclopropil)-1,3-oxazol-4-il)acético (preparación 155).
200	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(metilsulfonil)fenil]acetamida	LCMS (sistema 9): T_r = 2,87 min; m/z 492 $[M+H]^+$
201	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(1,3-dimetil-1H-pirazol-4-il)acetamida	LCMS (sistema 9): T_r = 2,76 min; m/z 432 $[M+H]^+$
202	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(1-metil-1H-pirazol-4-il)acetamida	LCMS (sistema 9): T_r = 2,73 min; m/z 418 $[M+H]^+$
203	N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(3-ciclopropil-1-metil-1H-pirazol-4-il)acetamida	LCMS (sistema 9): T_r = 2,80 min; mz 458 $[M+H]^+$ ácido (3-ciclopropil-1-metil-1H-pirazol-4-il)-acético (preparación 125)

Ejemplo 204: N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)fenil]acetamida;



Se agregó 10% de ácido clorhídrico en 1,4-dioxano (0,2 ml) a N-(5-{7-[(S)-2-(ter-butil-dimetil-silaniloxi)-1-metil-etil]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-piridin-3-il)-2-(3-trifluorometil-fenil)-acetamida
(preparación **105,** 59 mg, 0,098 mmoles) en THF (2 ml) y la mezcla se agitó a

temperatura ambiente durante 18 horas. La mezcla se evaporó al vacío y se trituró con éter-pentano para dar el compuesto del título en forma de un sólido blancuzco en 86% de rendimiento, 41 mg.
LCMS (sistema 9): T_r = 2,97 min; m/z 484 $[M+H]^+$.

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 204 utilizando las preparaciones apropiadas como se describió.

Ejemplo	Nombre	Datos
205	N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)fenil]acetamida	LCMS (sistema 9): T_r = 2,89 min; m/z 484 $[M+H]^+$ Utilizando (preparación 142).
206	N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-(4-isopropil-1H-1,2,3-triazol-il)acetamida	LCMS (sistema 9): T_r = 2,52 min; m/z 449 $[M+H]^+$ Utilizando (preparación 144).
207	N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[1-isopropil-5-(trifluorometil)-1H-pirazol-4-il]acetamida	LCMS (sistema 9): T_r = 2,87 min; m/z 516 $[M+H]^+$ Utilizando (preparación 150).
208	2-(4-cianofenil)-N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS (sistema 9): T_r = 2,68 min; m/z 441 $[M+H]^+$ Utilizando (preparación 151).
209	N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(metilsulfonil)fenil]acetamida;	LCMS (sistema 9): T_r = 2,57 min; m/z 494 $[M+H]^+$ Utilizando (preparación 152).
210	N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-quinolin-7-ilacetamida	LCMS (sistema 9): T_r = 1,96 min; m/z 467 $[M+H]^+$ Utilizando (preparación 153).

Los siguientes ejemplos se prepararon de acuerdo con el método que se

describió anteriormente para el ejemplo 34, a 50ºC, partiendo de [2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il](5-aminopiridin-3-il)metanona (enantiómero 1, preparación 57) y los ácidos apropiados.

Ejemplo	Nombre	Datos
211	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-quinolin-7-ilacetamida	LCMS (sistema 10): T_r = 2,48 min; m/z 482 $[M+H]^+$
212	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-cianofenil)acetamida	LCMS (sistema 10): T_r = 2,57 min; m/z 456 $[M+H]^+$
213	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(trifluorometil)fenil]acetamida	LCMS (sistema 10): T_r = 2,87 min; m/z 499 $[M+H]^+$

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 34, a 50ºC, partiendo de [2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il](5-aminopiridin-3-il)metanona (enantiómero 2, preparación 59) y los ácidos apropiados.

Ejemplo	Nombre	Datos
214	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-cianofenil)acetamida	LCMS (sistema 9): T_r = 2,26 min; m/z 456 $[M+H]^+$
215	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(trifluorometil)fenil]acetamida	LCMS (sistema 9): T_r = 2,72 min; m/z 499 $[M+H]^+$
216	N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-quinolin-7-ilacetamida	LCMS (sistema 9): T_r = 1,62 min; m/z 482 $[M+H]^+$

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 34 a 50ºC, partiendo de (5-aminopiridin-3-il)(7-oxetan-3-il-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación 100) y el ácido apropiado.

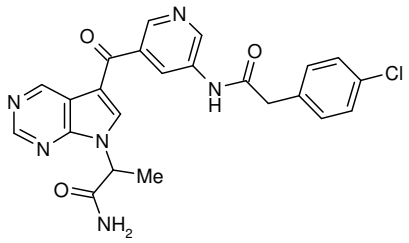
Ejemplo	Nombre	Datos
217	2-(3,4-diclorofenil)-N-{5-[(7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 3): T_r = 3,04 min; m/z 482 $[M+H]^+$
218	2-(4-cianofenil)-N-{5-[(7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,3 min; m/z 439 $[M+H]^+$

Ejemplo	Nombre	Datos
219	2-(4-clorofenil)-N-{5-[(7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,5 min; m/z 448 $[M+H]^+$
220	2-(3-clorofenil)-N-{5-[(7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,5 min; m/z 448 $[M+H]^+$
221	2-(3-cianofenil)-N-{5-[(7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,3 min; m/z 439 $[M+H]^+$
222	N-{5-[(7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-quinolin-7-ilacetamida	LCMS (sistema 2): T_r = 1,0 min; m/z 465 $[M+H]^+$
223	2-(6-cloroimidazo[1,2-a]piridin-2-il)-N-{5-[(7-oxetan-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS (sistema 2): T_r = 1,0 min; m/z 488 $[M+H]^+$
224	N-{5-[(7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(1-oxo-1,3-dihidro-2H-isoindol-2-ilacetamida	LCMS (sistema 2): T_r = 1,3 min; m/z 469 $[M+H]^+$

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 204 utilizando las preparaciones como se describió.

Ejemplo	Nombre	Datos
225	2-(5-cianofenil)-N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida	LCMS (sistema 9): T_r = 2,74 min; m/z 455,4 $[M+H]^+$ Utilizando preparación 131
226	N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(trifluorometil)fenil]acetamida	LCMS (sistema 9): T_r = 2,99 min; m/z 498 $[M+H]^+$ Utilizando preparación 136
227	N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-isopropil-1H-1,2,3-triazol-1-il)acetamida	^{1}H RMN (400 MHz, DMSO) δ: 1,22 (d, 6H), 1,71 (s, 6H), 2,96 (m, 2H), 3,94 (s, 2H), 5,35 (s, 2H), 7,87 (s, 1H), 8,20 (s, 1H), 8,44 (s, 1H), 8,75 (s, 1H), 8,98 (m, 2H), 9,46 (s, 1H), 11 (s, 1H) Utilizando preparación 144
228	N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-quinolin-7-ilacetamida	LCMS (sistema 9): T_r = 2,61 min; m/z 481 $[M+H]^+$ Utilizando preparación 140

Ejemplo 229 2-{5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}propanamida racémico



Se agregó 2-bromopropionamida (46,5 mg, 0,31 mmoles) a una mezcla de 2-(4-clorofenil)-N-[5-(7H-pirrolo[2,3-d]pirimidin-5-ilcarbonil)piridin-3-il]acetamida (ejemplo 308, 100 mg, 0,26 mmoles) y carbonato de cesio (150 mg, 0,46 mmoles) en DMF (1,3 ml). La mezcla se agitó a 60ºC durante 3 horas. La mezcla de reacción se enfrió y se agregó agua (10 ml). La mezcla se extrajo con EtOAc (3 x 10 ml), y las fases orgánicas combinadas se pasaron a través de un separador de fase y se evaporaron al vacío. La purificación por HPLC preparativa dio el compuesto del título en forma de un sólido de color blanco en 34% de rendimiento, 15 mg.

LCMS (sistema 3): T_r = 2,13 min; m/z 463 $[M+H]^+$.

Ejemplo 230: 2-{5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}-N,N-dimetilpropanamida racémico

El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 34 a 50ºC utilizando el ácido 2-{5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}propanoico racémico (ejemplo 354) y dimetilamina. La purificación se realizó por HPLC preparativa (método 1) para dar el compuesto del título.

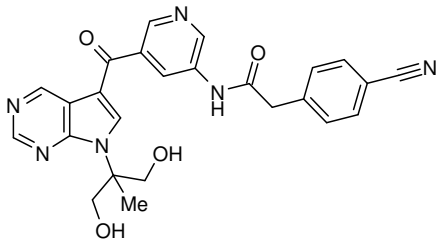
LCMS (sistema 3): T_r = 2,39 min; m/z 491 $[M+H]^+$.

Ejemplo 231: 2-{5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}-N,N-metilpropanamida racémico

El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 34 a 50ºC utilizando el ácido 2-{5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}propanoico (ejemplo 354) y metilamina. La purificación se realizó por HPLC preparativa (método 1) para dar el compuesto del título.

LCMS (sistema 3): T_r = 2,31 min; m/z 477 $[M+H]^+$.

Ejemplo 232 2-(4-cianofenil)-N-[5-({7-[2-hidroxi-1-(hidroximetiletil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida



Se agregó ácido 4-cianofenilacético (19 mg, 0,10 mmoles) a (5-aminopiridin-3-il){7-[2-{[*ter*-butil(dimetil)silil]oxi}-1--({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (preparación 116, 54 mg, 0,97 mmoles) anhídrido cíclico del ácido 1-propilfosfónico (0,17 ml, 0,291 mmoles) y trietilamina (0,047 ml, 0,291 mmoles) en tetrahidrofurano (3 ml). La mezcla se agitó a 50ºC durante 16 horas. Se agregó bicarbonato de sodio acuoso saturado (5 ml), posteriormente se extrajo con diclorometano (3 x 7 ml). Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron al vacío.

El residuo se disolvió en tetrahidrofurano (3 ml) y se agregó una solución de fluoruro de tetrabutilamonio en THF (1 ml de una solución 1M, 1mmol) y la solución se agitó durante 1 hora. Se agregó bicarbonato de sodio acuoso saturado (5 ml), posteriormente se extrajo con diclorometano (3 x 5 ml). Las fases orgánicas combinadas se secaron sobre sulfato de sodio, se evaporaron al vacío y se purificaron por HPLC preparativa (método 2).

LCMS (sistema 4): T_r = 2,52 min; m/z 471 $[M+H]^+$

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 232, partiendo de (5-aminopiridin-3-il){7-[2-{[*ter*-butil(dimetil)silil]oxi}-1--({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (preparación 116) y los ácidos apropiados.

Ejemplo	**Nombre**	**Datos**
233	N-[5-({7-[2-hidroxi-1-(hidroximetil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-quinolin-7-ilacetamida	LCMS (sistema 4) Tr = 2,52 min; m/z 497 $[M+H]^+$ Método de prep 1
234	N-[5-({7-[2-hidroxi-1-(hidroximetil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[5-metil-3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 4) Tr = 2,69 min; m/z 518 $[M+H]^+$ Método de prep 1
235	2-(4-clorofenil)-N-[5-({7-[2-hidroxi-1-(hidroximetiletil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS (sistema 4) Tr = 2,83 min; m/z 480 $[M+H]^+$ Método de prep 1
236	N-[5-({7-[2-hidroxi-1-(hidroximetil)-1-	LCMS (sistema 4) Tr = 2,81

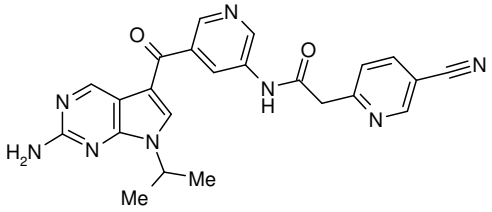
Ejemplo	Nombre	Datos
	metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[4-(trifluorometil)fenil]acetamida;	min; m/z 514 $[M+H]^+$ Método de prep 1
237	2-(5-cloropiridin-2-il)-N-[5-({7-[2-hidroxi-1-(hidroximetiletil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS (sistema 3) Tr = 2,37 min; m/z 481 $[M+H]^+$ Método de prep 1 Utilizando ácido (5-cloropiridin-2-il)acético (preparación 90).
238	N-[5-({7-[2-hidroxi-1-(hidroximetil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)fenil]acetamida;	LCMS (sistema 4) Tr = 2,84 min; m/z 514 $[M+H]^+$ Método de prep 1
239	N-[5-({7-[2-hidroxi-1-(hidroximetil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 3) Tr = 2,59 min; m/z 504 $[M+H]^+$ Método de prep 2

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 1, utilizando DIPEA y purificación por HPLC preparativa, partiendo de (2-amino-7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)(5-aminopiridin-3-il)metanona (preparación 122) y los ácidos apropiados.

Ejemplo	Nombre	Datos
240	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida	LCMS (sistema 9): T_r = 2,57 min; m/z 474 $[M+H]^+$ Utilizando ácido 4-(trifluorometil)-1H-1,2,3-triazol-1-il]acético (preparación 81).
241	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-cianofenil)acetamida	LCMS (sistema 9): T_r = 2,56 min; m/z 440 $[M+H]^+$
242	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-cloropiridin-2-il)acetamida;	LCMS (sistema 9): T_r = 2,46 min; m/z 450 $[M+H]^+$ Utilizando ácido (5-cloropiridin-2-il)acético (preparación 90).
243	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-fluoropiridin-2-il)acetamida;	LCMS (sistema 9): T_r = 2,20 min; m/z 434 $[M+H]^+$ Utilizando ácido (5-fluoropiridin-2-il)acético (preparación 92).
244	N-{5-[(2amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)fenil]acetamida	LCMS (sistema 10): T_r = 3,22 min; m/z 483 $[M+H]^+$
245	N-{5-[(2amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-	LCMS (sistema 10): T_r = 3,22 min; m/z 483 $[M+H]^+$

Ejemplo	Nombre	Datos
	(trifluorometil)fenil]acetamida	
246	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(1,3-benzoxazol-5-il)acetamida;	LCMS (sistema 9): T_r = 2,22 min; m/z 456 $[M+H]^+$
247	N-{5-[(2amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(metilsulfonil)fenil]acetamida	LCMS (sistema 9): T_r = 2,15 min; m/z 493 $[M+H]^+$
248	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-isopropil-1H-1,2,3-triazol-1-il]acetamida	LCMS (sistema 9): T_r = 2,16 min; m/z 448 $[M+H]^+$
249	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-ciclopropil-1H-1,2,3-triazol-1-il]acetamida	LCMS (sistema 9): T_r = 2,01 min; m/z 446 $[M+H]^+$ Utilizando preparación 83
250	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-clorofenil)acetamida	LCMS (sistema 10): T_r = 3,03 min; m/z 449 $[M+H]^+$
251	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[1-isopropil-5-(trifluorometil)-1H-pirazol-4-il]acetamida	LCMS (sistema 10): T_r = 3,03 min; m/z 515 $[M+H]^+$ Utilizando Prep 185
252	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 10): T_r = 2,92 min; m/z 473 $[M+H]^+$
253	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(3-ciclopropil-1H-pirazol-1-il)acetamida	LCMS (sistema 9) Tr 2,46 min; m/z 445 $[M+H]^+$
254	N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[1-isopropil-3-(trifluorometil)-1H-pirazol-4-il]acetamida	LCMS (sistema 9): T_r = 2,77 min; m/z 515 $[M+H]^+$

Ejemplo 255: N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-cianopiridin-2-il)acetamida;



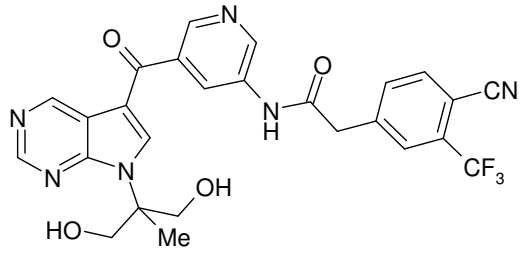
El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 166 utilizando N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-bromopiridin-2-il)acetamida (ejemplo 318) para dar el compuesto del título en 45% de rendimiento, 30 mg. ^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,45 (d, 6H), 4,06 (s, 2H), 4,84 (m, 1H), 6,62 (s, 2H), 7,66 (d, 1H), 7,97 (s, 1H), 8,29 (dd, 1H), 8,37 (t, 1H), 8,66 (d, 1H), 8,92 (s, 1H), 8,95-8,98 (m, 2H), 10,75 (s, 1H);LCMS

(System 10): T_r = 2,49 min; m/z 441 $[M+H]^+$.

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 34, a 50ºC, partiendo de [2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il](5-aminopiridin-3-il)metanona (preparación 48) y los ácidos apropiados.

Ejemplo	Nombre	Datos
256	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(trifluorometil)fenil]acetamida	LCMS (sistema 10): T_r = 2,91 min; m/z 513 $[M+H]^+$
257	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(1,3-benzoxazol-5-il)acetamida	LCMS (sistema 10): T_r = 2,48 min; m/z 486 $[M+H]^+$
258	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(metilsulfonil)fenil]acetamida;	LCMS (sistema 10): T_r = 2,50 min; m/z 523 $[M+H]^+$
259	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-cianofenil)acetamida	LCMS (sistema 10): T_r = 2,62 min; m/z 470 $[M+H]^+$
260	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[1-isopropil-5-(trifluorometil)-1H-pirazol-4-il]acetamida	LCMS (sistema 10): T_r = 2,89 min; m/z 545 $[M+H]^+$ Utilizando Prep 185

Ejemplo 261 4-ciano-3-(trifluorometil)fenil)-N-(5-(7-(1,3-dihidroxi-2-metilpropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)acetamida



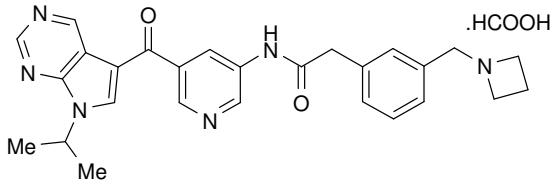
Se agregó ácido 2-(4-ciano-3-(trifluorometil)fenil acético (preparación 164, 29,8 mg, 0,13 mmoles) a una solución agitada de (5-aminopiridin-3-il){7-[2-{[*ter*-butil(dimetil)silil]oxi}-1--({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (preparación 116, 55,6 mg, 0,10 mmoles) y 2-(7-aza-1*H*-benzotriazol-1-il)-1,1,3,3-tetrametiluronio hexafluorofosfato 57 mg, 0,15 mmoles) en piridina (0,5 ml). La mezcla se agitó a 50ºC durante 16 horas, posteriormente se enfrió hasta temperatura ambiente y se dividió entre bicarbonato de sodio acuoso saturado (5 ml) y DCM (5 ml). La fase orgánica se separó y se concentró al vacío para dar un

residuo que se disolvió en 3 ml de THF y posteriormente se trató con 3 ml de una solución acuosa 1N de HCl. La mezcla se agitó rápidamente durante 4 horas a temperatura ambiente y posteriormente se basificó mediante la adición de 4 ml de una solución de NaOH acuosa 1N. La mezcla se extrajo con tres porciones de 5 ml separadas de una mezcla 95/5 DCM/MeOH. Los extractos orgánicos combinados se secaron por el pasaje a través de un separador de fase y posteriormente se concentraron para obtener un residuo bruto. Este residuo se disolvió en 1 ml de DMSO y se purificó por HPLC preparativa para dar el compuesto del título en forma de un sólido blancuzco en 56% de rendimiento, 30 mg. ^{1}H RMN (400 MHz, DMSO) δ*:* 1,68 (s, 3H), 3,83 (m, 2H), 4,01 (s, 2H), 4,19 (m, 2H), 5,00 (m, 2H), 7,82 (m, 1H), 8,01 (d, 1H), 8,18 (m, 1H), 8,21 (s, 1H), 8,66 (s, 1H), 8,97 (m, 2H), 9,40 (s, 1H), 10,78 (s, 1H).
LCMS (sistema 2): T_r = 0,90 min; m/z 539 $[M+H]^+$.

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 261, partiendo de (5-aminopiridin-3-il){7-[2-{[*ter*-butil(dimetil)silil]oxi}-1--({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (preparación 116) y los ácidos apropiados seguido de la desprotección del grupo sililo.

Ejemplo	**Nombre**	**Datos**
262	N-(5-(7-(1,3-dihidroxi-2-metilpropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)-2-(3-trifluorometoxi)fenil)acetamida	LCMS (sistema 2): T_r = 0,96 min; m/z 516 $[M+H]^+$
263	N-(5-(7-(1,3-dihidroxi-2-metilpropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)-2-(4-fluoro-3-(trifluorometoxi)fenil)acetamida	LCMS (sistema 2): T_r = 1,05 min; m/z 532 $[M+H]^+$
264	N-(5-(7-(1,3-dihidroxi-2-metilpropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)-3-(3-(trifluorometil)benzamida	LCMS (sistema 2): T_r = 1,04 min; m/z 500 $[M+H]^+$
265	N-(5-(7-(1,3-dihidroxi-2-metilpropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)-3-(3-fluoro-4-(trifluorometil)benzamida	LCMS (sistema 2): T_r = 1,09 min; m/z 532 $[M+H]^+$

Ejemplo 266 Sal formiato de 2-[3-(azetidin-1-ilmetil)fenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida



Se agregó clorhidrato azetidin (10 mg, 0,11 mmoles) a una solución agitada de 2-(3-formilfenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida (preparación 192, 23 mg, 0,05 mmoles) en DCM (1 ml) y ácido acético (0,04 ml, 0,60 mmoles). La mezcla de reacción se agitó durante 30 min a temperatura ambiente antes de la adición de triacetoxiborohidruro de sodio (29 mg, 0,14 mmoles) y se continuó con la agitación durante 3 horas. Se agregó agua (1 ml) y la mezcla se concentró al vacío (con azeotropamiento de tolueno). El residuo se purificó por HPLC preparativa para dar el compuesto del título en forma de una sal formiato en 12% de rendimiento, 3,4 mg.

LCMS: T_r = 2,95 min; m/z 469 $[M+H]^+$.

Ejemplo 267 2-{3-[(3-fluoroazetidin-1-il)metil]fenil}-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida

El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 266 utilizando 2-(3-formilfenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida (preparación 192, 60 mg, 0,14 mmoles) y 3-fluoroazetidina para dar el compuesto del título en 16% de rendimiento, 11 mg.

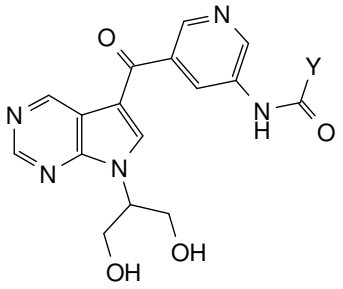
LCMS: T_r = 2,75 min; m/z 487 $[M+H]^+$.

Ejemplo 268 Sal formiato de N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[3-(morfolin-4-ilmetil)fenil]acetamida

El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 266 utilizando 2-(3-formilfenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida (preparación 192, 60 mg, 0,14 mmoles) y morfolina para dar el compuesto del título en forma de una sal formiato 30% de rendimiento, 21 mg.

LCMS: T_r = 2,70 min; m/z 499 $[M+H]^+$

Ejemplos 269-283 Método general:



La mezcla de (5-aminopiridin-3-il)(7-(2,2,3,3,9,9,10,10-octametil-4,8-dioxa-3,9-disilaundecan-6-il)-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (preparación 196, 54,2 mg, 0,10 mmoles), HATU (57 mg, 0,15 mmoles) y el ácido carboxílico necesario (0,13 mmoles) en piridina (0,5 ml) se agitaron a 50ºC durante 16 horas. Después del enfriamiento a temperatura ambiente, se agregó solución de bicarbonato de sodio saturado (5 ml) y la mezcla se extrajo con DCM (5 ml). La capa orgánica se pasó a través de un separador de fase y se evaporó al vacío El residuo resultante se disolvió en THF (2 ml) y se agregó HCl acuoso 1N (2 ml) a la solución. La mezcla de reacción se agitó durante 2 horas a temperatura ambiente y se templo con NaOH acuoso 1N (3 ml). A continuación la mezcla se trató de acuerdo con uno de los siguientes métodos:

Método A

La mezcla se extrajo con una mezcla de DCM/MeOH (95/5, 5 ml x 3), las capas orgánicas combinadas se pasaron a través de un separador de fase y se concentraron al vacío para obtener un residuo bruto. Este residuo se disolvió en DMSO (1 ml) y se purificó vía HPLC para dar el compuesto deseado.

Método B

La mezcla se suspendió en DCM/MeOH (95/5, 5 ml), el sólido se filtró y se lavó con agua (5 ml) y DCM (5 ml) y se secó al vacío para dar el compuesto deseado.

Método C

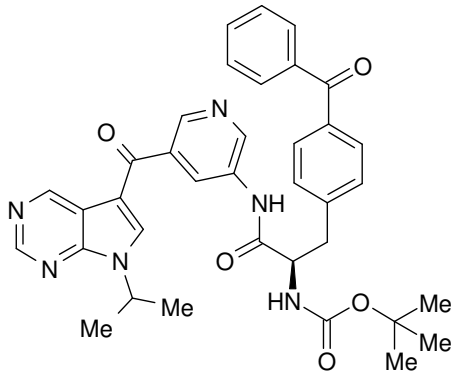
La mezcla se extrajo con una mezcla de EtOAc/MeOH (95/5, 5 ml x 3), las capas orgánicas combinadas se pasaron a través de un separador de fase y se concentraron al vacío para obtener un residuo bruto. Este residuo se disolvió en DMSO (1 ml) y se purificó vía HPLC preparativa para dar el compuesto deseado.

Ejemplo	**Nombre**	**Datos**
269	N-(5-(7-(1,3-dihidroxipropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)-3-(3-(trifluorometil)benzamida	LCMS: T_r = 2,69 min; m/z 486

		$[M+H]^+$
270	2-(4-clorofenil)-N-(5-(7-(1,3-dihidroxipropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)acetamida	LCMS: T_r = 2,63 min; m/z 466 $[M+H]^+$
271	N-(5-(7-(1,3-dihidroxipropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)-3-(3-(trifluorometoxi)benzamida	LCMS: T_r = 2,68 min; m/z 502 $[M+H]^+$
272	N-(5-(7-(1,3-dihidroxipropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)-2-(quinolin-7-il)acetamida	LCMS: T_r = 1,27 min; m/z 483 $[M+H]^+$
273	N-(5-(7-(1,3-dihidroxipropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)-2-(4-(trifluorometil)fenil)acetamida	LCMS: T_r = 2,69 min; m/z 500 $[M+H]^+$
274	N-(5-(7-(1,3-dihidroxipropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)-2-(3-(trifluorometil)fenil)acetamida	m/z 500 $[M+H]^+$
275	N-[5-({7-[2-hidroxi-1-(hidroximetil)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[2-metilquinolin-7-il)acetamida	m/z 497 $[M+H]^+$ Preparación 165
276	2-(3,4-diclorofenil)-N-[5-({7-[2-hidroxi-1-(hidroximetil)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	m/z 500 $[M+H]^+$
277	2-[3-fluoro-4-(trifluorometil)fenil]-N-[5-({7-[2-hidroxi-1-(hidroximetil)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	m/z 518 $[M+H]^+$
278	2-(2,4-diclorofenil)-N-[5-({7-[2-hidroxi-1-(hidroximetil)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	m/z 500 $[M+H]^+$
279	N-[5-({7-[2-hidroxi-1-(hidroximetil)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometoxi)fenil]acetamida;	m/z 516 $[M+H]^+$
280	N-[5-({7-[2-hidroxi-1-(hidroximetil)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[4-(trifluorometoxi)fenil]acetamida;	m/z 516 $[M+H]^+$
281	3-fluoro-N-[5-({7-[2-hidroxi-1-(hidroximetil)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-5-(trifluorometil)benzamida	m/z 504 $[M+H]^+$
282	2-(5-cloropiridin-2-il)-N-[5-({7-[2-hidroxi-1-(hidroximetiletil)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida	LCMS: T_r = 0,90 min; m/z 467 $[M+H]^+$.

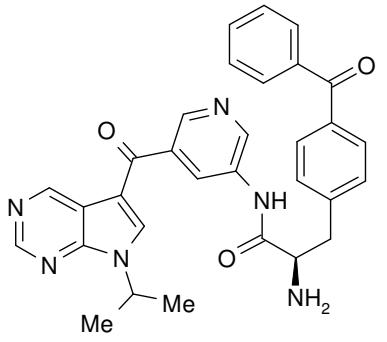
283	N-[5-({7-[2-hidroxi-1-(hidroximetil)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS: T_r = 1,81 min; m/z 490 $[M+H]^+$.

Ejemplo 284 4-benzoil-N-*afa*-(ter-butoxicarbonil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-L-fenilalaninamida



Se disolvió (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (20 mg, 0,07 mmoles) véase preparación 95) en piridina (1 ml) y se agregó 4-benzoíl-N-(ter-butoxicarbonil)-D-fenilalanina (26 mg, 0,07 mmoles) seguido de HATU (27 mg, 0,07 mmoles). La mezcla se agitó a 50ºC durante 5 horas y a continuación se enfrió, se evaporó al vacío y el material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de DCM:metanol 100:0 a 95:5) para dar el compuesto del título en forma de un sólido de color amarillo en 52% de rendimiento, 23 mg.

Ejemplo 285 4-benzoíl-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-D-fenilalaninamida



Se agitó 4-benzoil-N-*afa*-(ter-butoxicarbonil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-L-fenilalaninamida (ejemplo 284, 20 mg, 0,03 mmoles) con 10% de ácido clorhídrico en 1,4-dioxano (5 ml) a temperatura ambiente

durante 1 hora. La mezcla se evaporó al vacío y se purificó por HPLC preparativa para dar el compuesto del título en forma de una goma en 56% de rendimiento, 9 mg.
LCMS (sistema 5): T_r = 2,89 min; m/z 533 $[M+H]^+$.

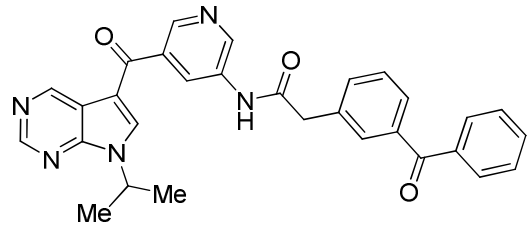
Ejemplo 286: 4-benzoil-N-*afa*-(ter-butoxicarbonil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-L-fenilalaninamida

El compuesto del título se preparó de acuerdo con el ejemplo 284 utilizando (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (preparación 95) y and 4-benzoíl-N-(ter-butoxicarbonil)-L-fenilalanina.

Ejemplo 287 4-benzoíl-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-L-fenilalaninamida

El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 285 utilizando 4-benzoil-N-*afa*-(ter-butoxicarbonil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-L-fenilalaninamida (preparación 286) para dar el compuesto del título en 36% de rendimiento, 5 mg.
LCMS (sistema 4): T_r = 2,30 min; m/z 533 $[M+H]^+$.

Ejemplo 288 2-(3-benzoílfenil)-N-(5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)acetamida



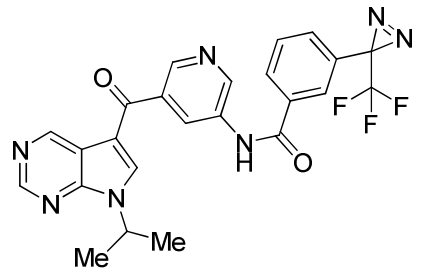
El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 34, partiendo de (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 95) y el ácido 2-(3-benzoílfenil)acético para dar el compuesto del título en 86% de rendimiento, 31 mg.
LCMS (sistema 3): T_r = 3,05 min; m/z 504 $[M+H]^+$.

Ejemplo 289: 2-(4-benzoílfenil)-N-(5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)acetamida

El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 34, partiendo de (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 95) y el ácido 2-(4-benzoílfenil)acético (JOC, 1961, 1635) para dar el compuesto del título en 94% de rendimiento, 34 mg. LCMS (sistema 3): T_r = 3,12 min; m/z 504 $[M+H]^+$.

Ejemplo 290 N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-3-[3-

(trifluorometil)-3H-diaziren-3-il]benzamida



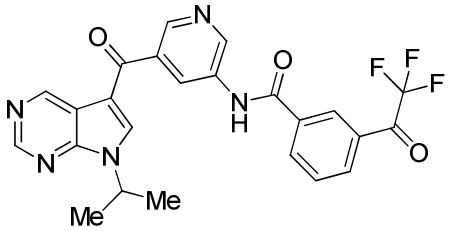
El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 34, partiendo de (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación 95) y el ácido 3-[3-(trifluorometil)-3H-diaziren-3-il]benzoico (preparación 197) para dar el compuesto del título en forma de un sólido de color blanco en 36% de rendimiento, 23 mg.

^{1}H RMN (400 MHz, d4-MeOH) δ:1,65 (s, 6H), 5,20 (m, 1H), 7,52-7,61 (m, 4H), 7,79 (s, 1H), 8,07 (m, 1H), 8,29 (s, 1H), 8,94 (s, 1H), 8,81 (m, 1H), 9,55 (s, 1H).

Ejemplo 291 N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-4-[3-(trifluorometil)-3H-diaziren-3-il]benzamida

El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 34, partiendo de (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación 95) y el ácido 4-[3-(trifluorometil)-3H-diaziren-3-il]benzoico para dar el compuesto del título en forma de un sólido de color blanco en 4% de rendimiento, 2 mg. LCMS (sistema 3): T_r = 3,64 min; m/z 494 $[M+H]^+$.

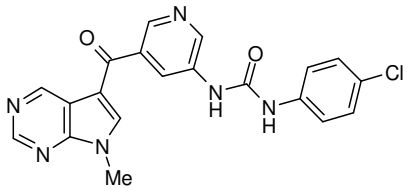
Ejemplo 292 N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-3-(trifluoroacetil)benzamida



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 34, partiendo de (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación 95) y el ácido 3-(trifluoroacetil)benzoico (preparación 200) para dar el compuesto del título en forma de un sólido de color blanco en 80% de rendimiento, 41 mg. LCMS (sistema 3): T_r = 2,52

min; m/z 482 $[M+H]^+$.

Ejemplo 293 1-(4-clorofenil)-3-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}urea



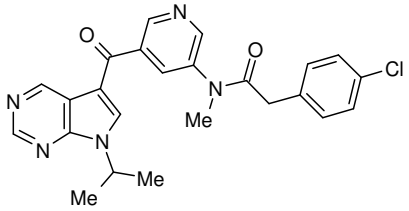
Se agregó 1-cloro-4-isocianatobenceno (24 mg, 0,15 mmoles) a (5-aminopiridin-3-il)(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (30 mg, 0,12 mmoles) (preparación 232) en piridina (1,0 ml). La mezcla se agitó a temperatura ambiente durante toda la noche y a continuación se evaporó al vacío para dar el producto en forma de un residuo bruto. El residuo bruto se purificó por HPLC preparativa para dar el compuesto del título en 49% de rendimiento, 24 mg.

LCMS: T_r = 1,58 min; m/z 407 $[M+H]^+$

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 293, partiendo de (5-aminopiridin-3-il)(7-metil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 232) y los isocianatos apropiados.

Ejemplo	Nombre	Datos
294	1-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-3-[4-(trifluorometil)fenil]urea	LCMS: T_r = 1,64 min; m/z 441 $[M+H]^+$
295	1-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-3-[3-(trifluorometil)fenil]urea	LCMS: T_r = 1,64 min; m/z 441 $[M+H]^+$
296	1-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-3-[4-(trifluorometoxi)fenil]urea	LCMS: T_r = 1,67 min; m/z 457 $[M+H]^+$

Ejemplo 297 2-(4-clorofenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-N-metilacetamida



Se agregó ácido (4-clorofenil)acético ((22 mg, 0,13 mmoles) a una mezcla en

agitación de ((7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)[5-(metilamino)piridin-3-il]metanona (30 mg, 0,10 mmoles) (preparación 149) y N-[(dimetilamino)(3H-[1,2,3]triazolo[4,5-b]piridin-3-iloxi)metileno]-N-metilmetanaminio hexafluorofosfato (57 mg, 0,15 mmoles) en piridina (1,0 ml). La mezcla se calentó hasta 50ºC durante 16 horas, se evaporó al vacío y se dividió entre bicarbonato de sodio acuoso saturado (10 ml) y EtOAc (10 ml). La capa acuosa se lavó con más EtOAc (2 x 10 ml). Los orgánicos combinados se secaron sobre Na_2SO_4, y se concentraron al vacío y se purificaron por HPLC preparativa para dar el compuesto del título en 43% de rendimiento, 19 mg,

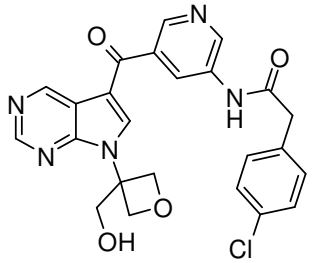
^{1}H RMN (400 MHz, DMSO) δ*:* 1,52 (d, 6H), 3,40 (br. s, 3H), 3,59 (s, 2H), 5,00-5,18 (m, 1H), 7,00-7,42 (m, 4H), 8,21 (s, 1H), 8,50 (s, 1H), 8,86 (s, 1H), 8,90-9,12 (m, 2H), 9,48 (s, 1H);

LCMS: T_r = 2,99 min; m/z 448 $[M+H]^+$

El siguiente ejemplo se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 297, partiendo de (7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)[5-(metilamino)piridin-3-il]metanona (preparación 149) y el ácido apropiado.

Ejemplo	**Nombre**	**Datos**
298	2-(4-cianofenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-N-metilacetamida	LCMS: $+T_r$ = 2,86 min; m/z 439 $[M+H]^+$

Ejemplo 299: 2-(4-clorofenil)-N-{5-[(7-(3-hidroximetil-oxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}acetamida



Se disolvió N-(5-{7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-piridin-3-il)-2-(4-cloro-fenil)-acetamida (preparación 203, 35 mg, 0,059 mmoles) en THF seco (0,5 ml) y se agregó tetrabutilamonio fluoruro (0,065 ml de una solución 1M en THF, 0,065 mmoles)**.** La reacción se agitó durante 30 min a

temperatura ambiente. La mezcla se dividió entre agua y EtOAc. Las capas se separaron y la capa acuosa se extrajo dos veces con EtOAc. Las capas orgánicas combinadas se concentraron y se purificaron por HPLC preparativa para dar el compuesto del título en rendimiento cuantitativo 28 mg.

LCMS (sistema 4): T_r = 3,03 min; m/z 478 $[M+H]^+$

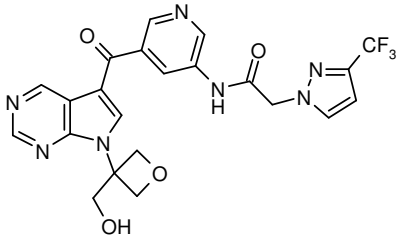
Ejemplo 300: N-{5-[7-(3-hidroximetil-oxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-trifluorometil-fenil)-acetamida:

El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 299 partiendo de N-(5-{7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-piridin-3-il)-2-(4-cloro-fenil)-acetamida (preparación 204) para dar el compuesto del título en forma de un sólido de color blanco en rendimiento cuantitativo, 30 mg. LCMS. T_r = 2,74 min; m/z 512 $[M+H]^+$.

Ejemplo 301: 2-(5-cloropiridin-2-il)-N-[5-({7-[3-hidroximetiletil)oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida

El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 299 partiendo de N-[5-({7-[3-({[ter-butil(dimetil)silil]oxi}metil)oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-(5-cloropiridin-2-il)acetamida (preparación 223) para dar el compuesto del título en forma de un líquido de color amarillo pálido en 87% de rendimiento, 23%. LCMS (sistema 4): T_r = 1,57 min; m/z 479 $[M+H]^+$.

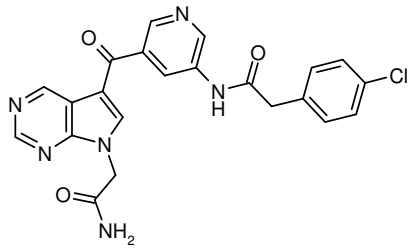
Ejemplo 302: N-[5-({7-[3-hidroximetil)oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 299 partiendo de N-[5-({7-[3-({[ter-butil(dimetil)silil]oxi}metil)oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida (34 mg, 0,055 mmoles) (preparación 224) para dar el compuesto del título en 63% de rendimiento, 17,7 mg.

LCMS (sistema 5) Tr = 1,57 min; m/z 502 $[M+H]^+$

Ejemplo 303: N-(5-{[7-(2-amino-2-oxoetil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-clorofenil)acetamida



A una solución agitada de 2-(4-clorofenil)-N-[5-(7H-pirrolo[2,3-d]pirimidin-5-ilcarbonil)piridin-3-il]acetamida (ejemplo 308, 50 mg, 0,13 mmoles) en DMF (1 ml) se agregó Cs_2CO_3 (75mg, 0,23 mmoles) seguido de 2-bromoacetamida (21,3mg, 0,154 mmoles). A continuación la reacción se agitó a temperatura ambiente durante toda la noche. La reacción se templó con agua (5 ml) y se extrajo con EtOAc (3 x 5 ml). Los orgánicos se combinaron, se lavaron con agua (5 ml) a continuación salmuera (5 ml), se secaron sobre sulfato de magnesio anhidro y se concentraron al vacío. La purificación por HPLC preparativa dio el compuesto del título en 59% de rendimiento, 34 mg.

LCMS (sistema 4): T_r = 1,56 min; m/z 449 $[M+H]^+$.

Ejemplo 304: 2-{5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}-N,N-dimetilacetamida

Se agregó sal de potasio del ácido {5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}acético (ejemplo 307, 50 mg, 0,102 mmoles) a una solución agitada de dimetil amina HCl (12,5 mg, 0,153 mmoles) y HATU (58,2mg, 0,153 mmoles) en piridina (2 ml) y la solución resultante se agitó a 50ºC (reactivado) durante14 horas. La reacción se enfrió hasta 25ºC, se diluyó con DCM (5 ml) a continuación se templó con $NaHCO_3$ (ac) saturado (5 ml) y se extrajo con más DCM (3 x 5 ml). Los orgánicos se combinaron, se lavaron con salmuera saturada (5 ml), se secaron sobre sulfato de magnesio anhidro y se concentraron al vacío. La purificación por HPLC preparativa dio el compuesto del título en 55% de rendimiento, 26,6mg.

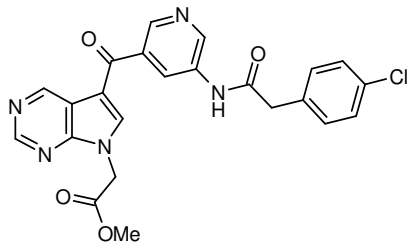
LCMS: T_r = 1,86 min; m/z 477 $[M+H]^+$.

Ejemplo 305: 2-(4-clorofenil)-N-[5-({7-[2-(metilamino)-2-oxoetil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida

Se agregó sal de potasio del ácido {5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}acético (ejemplo 307, 50 mg, 0,102 mmoles) a una solución agitada de metil amina HCl (10,3 mg, 0,153 mmoles) y HATU (58,2mg, 0,153 mmoles) en piridina (2 ml). La solución resultante se agitó a 50ºC (reactivado) durante 14 horas. La reacción se enfrió hasta 25ºC, se diluyó con DCM (5 ml) a continuación se templó con $NaHCO_3$ (ac) saturado (5 ml) y se extrajo con más DCM (3

x 5 ml). Los orgánicos se combinaron, se lavaron con salmuera saturada (5 ml), se secaron sobre sulfato de magnesio anhidro y se concentraron al vacío. La purificación por HPLC preparativa dio el compuesto del título en 65% de rendimiento, 30,5mg.
LCMS: T_r = 2,63 min; m/z 463 $[M+H]^+$.

Ejemplo 306: {5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}acetato de metilo



A una solución agitada de 2-(4-clorofenil)-N-[5-(7H-pirrolo[2,3-d]pirimidin-5-ilcarbonil)piridin-3-il]acetamida (ejemplo 308, 250mg, 0,638 mmoles) en DMF (4 ml) se agregó Cs_2CO_3 (374mg, 1,15 mmoles) seguido de bromoacetato de metilo (73uL, 0,766 mmoles). La reacción se agitó a 25ºC durante 3 horas y a continuación se templó con agua (10 ml) y se extrajo con EtOAc (3 x 10ml). Los orgánicos se combinaron, se lavaron con agua (10 ml) y salmuera saturada (10 ml), se secaron sobre sulfato de magnesio anhidro y se concentraron al vacío para dar un aceite de color amarillo pálido (356 mg) el cual se solidificó al asentarse. La purificación por cromatografía de columna sobre gel de sílice (gradiente de 0-100% 90:10:1 DCM/MeOH/NH3 en DCM (dio el compuesto del título en forma de un sólido de color amarillo pálido en 70% de rendimiento, ^{1}H RMN (400MHz, $CDCl_3$) δ 3,78 (s, 2H), 3,81 (s, 3H), 5,15 (s, 2H), 7,29-7,41 (m, 4H), 7,51 (s, 1H), 7,88 (s, 1H), 8,46 (m, 1H), 8,78-8,82 (m, 2H), 9,04 (s, 1H), 9,65 (s, 1H). LCMS (sistema 4): T_r = 2,07 min; m/z 464 $[M+H]^+$.

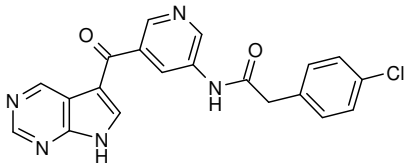
Ejemplo 307: sal potasio del ácido {5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}acético

A una suspensión de {5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}acetato de metilo (ejemplo 306, 197 mg, 0,425 mmoles) en MeOH (4 ml) se agregó una solución acuosa de KOH (0,425 ml de una solución 1M, 0,425 mmoles) y a continuación se agregó más MeOH (4 ml). La reacción se agitó durante 2 horas a temperatura ambiente. La reacción se concentró al vacío para dar el compuesto del título en forma de un sólido de color marrón claro en 99% de rendimiento, 205 mg.

LCMS (sistema 4): T_r = 1,76 min; m/z 450 $[M+H]^+$.

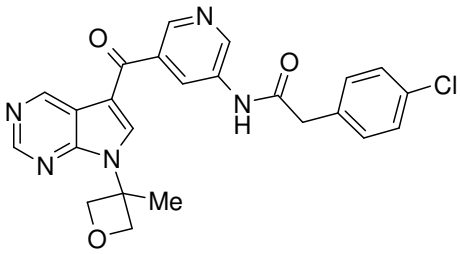
Ejemplo 308: 2-(4-clorofenil)-N-[5-(7-pirrolo[2,3-d]pirimidin-5-ilcarbonil)piridin-3-il]acetamida

El compuesto del título se preparó de acuerdo con el método que se describió para el ejemplo 46 para dar el compuesto del título en forma de un sólido de color blanco en 87% de rendimiento, 930 mg.



^{1}H RMN (400 MHz, DMSO) δ*:* 3,74 (s, 2H), 7,38 (m, 4H), 8,34 (s, 1H), 8,46 (s, 1H), 8,71 (s, 1H), 8,94 (s, 1H), 8,97 (s, 1H), 9,45 (s, 1H), 10,66 (s, 1H), 13,14 (s, 1H);LCMS (sistema 9): T_r = 2,87 min; m/z 392 $[M+H]^+$.

Ejemplo 309: 2-(4-clorofenil)-N-(5-{[7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida



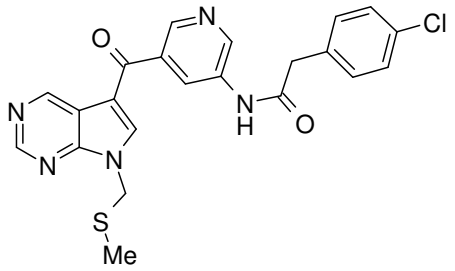
Se agregó (5-aminopiridin-3-il)[7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il]metanona (preparación 222, 15,5 mg, 0,05 mmoles) a una mezcla en agitación de ácido 4-clorofenilacético (11,1mg, 0,065 mmoles) y HATU (28,5 mg, 0,075 mmoles) en piridina (0,25 ml). La mezcla se calentó a 50ºC y se agitó durante 16 horas. La mezcla se dejó enfriar hasta temperatura ambiente y se agregó solución de bicarbonato de sodio saturado (5 ml). La mezcla se extrajo con acetato de etilo (3 x 5 ml) y las fracciones orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$) y el solvente se eliminó a presión reducida para obtener el producto bruto el cual se autopurificó.

LCMS (sistema 4): T_r = 3,08 min; m/z 462 $[M+H]^+$.

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 309 partiendo de (5-aminopiridin-3-il)(7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación 222) y los ácidos apropiados.

Ejemplo	Nombre	Datos
310	2-(5-cloropiridin-2-il)-N-(5-{[7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida	LCMS (sistema 2): T_r = 0,88 min; m/z 463 $[M+H]^+$ Utilizando preparación 90
311	N-(5-{[7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida	LCMS (sistema 2): T_r = 0,97 min; m/z 486 $[M+H]^+$
312	N-(5-{[7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida	LCMS (sistema 2): T_r = 0,92 min; m/z 487 $[M+H]^+$ Utilizando preparación 85

Ejemplo 313: 2-(4-clorofenil)-N-[5-({7-[(metiltio)metil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida



Se agregó carbonato de potasio (38 mg, 0,275 mmoles) a una solución en agitación de 2-(4-clorofenil)-N-[5-(7H-pirrolo[2,3-d]pirimidin-5-ilcarbonil)piridin-3-il]acetamida (ejemplo 308, 60,0 mg, 0,153 mmoles) en DMF (1,0 ml) a temperatura ambiente. Después de 10 min, se agregó clorometil metil sulfuro (19 µL, 0,23 mmoles) a la mezcla y la reacción se agitó durante 24 horas a temperatura ambiente. Se agregó agua (3 ml) a la mezcla y se extrajo con EtOAc (3 x 5 ml). Las fracciones orgánicas combinadas se lavaron con agua (5 ml), salmuera (5 ml), se secaron sobre sulfato de magnesio y se concentraron a presión reducida para dar un aceite de color amarillo pálido. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de 100% de DCM hasta 90:10:1 DCM/MeOH/NH_3) para dar el compuesto del título en forma de un sólido de color amarillo pálido en 36% de rendimiento, 25 mg.

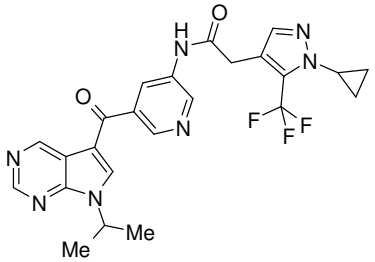
^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 2,13 (s, 3H), 3,79 (s, 2H), 5,39 (s, 2H), 7,30-7,34 (m, 3H), 7,40-7,43 (m, 2H), 8,02 (s, 1H), 8,52 (m, 1H), 8,74-8,75 (d, 1H), 8,82-8,83 (d, 1H), 9,05 (s,1H), 9,65 (s, 1H); LCMS (sistema 4): T_r = 1,97 min; m/z 452; 454 $[M+H]^+$.

Ejemplo 314: 2-(4-clorofenil)-N-[5-({7-[(metilsulfonil)metil]-7H-pirrolo[2,3-d]pirimidin-5-

il}carbonil)piridin-3-il]acetamida

Se agregó peroxomonosulfato de potasio (oxona, 67,2 mg, 0,110 mmoles) a una solución en agitación de 2-(4-clorofenil)-N-[5-({7-[(metiltio)metil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida (ejemplo 313, 25,0 mg, 0,055 mmoles) en metanol (1,0 ml) y agua (0,25 ml) a 0ºC. Después de 1 hora, la reacción se dejó entibiar hasta temperatura ambiente y se agitó durante 24 horas. La mezcla de reacción se enfrió hasta 0ºC y se agregó metabisulfito de sodio (0,5M, 1 ml). La mezcla de reacción se evaporó a presión reducida para eliminar el metanol. Se agregó agua (3 ml) a la mezcla y se extrajo con EtOAc (3 x 5 ml). Las fracciones orgánicas combinadas se lavaron con agua (5 ml), salmuera (5 ml), se secaron sobre sulfato de magnesio, el solvente se eliminó a presión reducida para dar el producto bruto en forma de un sólido blancuzco. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de 100% de DCM hasta 90:10:1 DCM/MeOH/NH_3) para dar el compuesto del título en forma de un sólido de color amarillo pálido en 17% de rendimiento, 27 mg. LCMS (sistema 4): T_r = 1,91 min; m/z 484; 486 $[M+H]^+$.

Ejemplo 315: 2-(1-ciclopropil-5-trifluorometil-1H-pirazol-4-il)-N-[5-(7-isopropil-7H-pirrolo [2, 3-d] pirimidin-5-carbonil)-piridin-3-il]-acetamida



A una solución de (5-amino-piridin-3-il)-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 95, 50 mg, 0,17 mmoles), ácido (1-ciclopropil-5-trifluorometil-1H-pirazol-4-il)-acético (preparación 141, 47,1 mg, 0,21 mmoles) y TEA (0,08 ml, 0,62 mmoles) en THF (1 ml), se agregó anhídrido cíclico del ácido 1-propilfosfónico (50% de solución en EtOAc, 0,26 ml, 0,44 mmoles) y la mezcla se agitó a temperatura ambiente durante 14 horas. La mezcla de reacción se evaporó a presión reducida el residuo se dividió entre acetato de etilo y agua. La capa orgánica se lavó con bicarbonato de sodio saturado y se secó (Na_2SO_4) y se evaporó al vacío. La purificación por cromatografía de columna sobre gel de sílice (gradiente de EtOAc:Hexano 0:100 a 80:20) dio el compuesto del título en forma de un sólido de color blanco en 76% de rendimiento, 67 mg. ^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,05-

1,07 (m, 2H), 1,08-1,15 (m, 2H), 1,54 (d, 6H), 3,73-3,76 (m, 3H), 5,06-5,13 (m, 1H), 7,55 (s, 1H), 8,44 (s, 1H), 8,51 (s, 1H), 8,73 (s, 1H), 8,94 (d, 1H), 8,99 (s, 1H), 9,44 (s, 1H), 10,61 (s, 1H).LCMS (Sistema 10): T_r = 3,03 min; m/z 498 $[M+H]^+$

Ejemplo 316: N-(5-{[2-amino-7-(1-hidroxi-1-metilpropan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(5-bromopiridin-2-il)acetamida

El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 34, a 50ºC utilizando [2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il](5-aminopiridin-3-il)metanona (preparación 48) y el ácido (5-bromopiridin-2-il)acético para (dar el compuesto del título en forma de un sólido de color amarillo en 60% de rendimiento, 75 mg. LCMS (sistema 10): T_r = 2,69 min; m/z 524 $[M+H]^+$

Ejemplo 317: 2-(5-bromopiridin-2-il)-N-{5-{(7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida

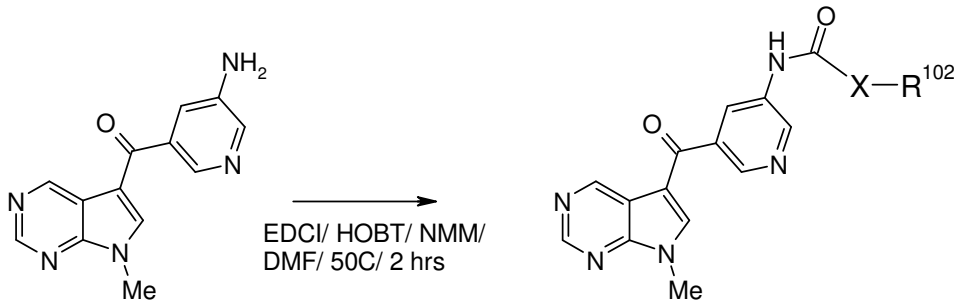
El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 1 con DIPEA utilizando (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación 95) y el ácido (5-bromopiridin-2-il)acético para dar el compuesto del título en forma de un sólido de color amarillo en 45% de rendimiento, 75 mg. LCMS (sistema 9): T_r = 2,97 min; m/z 479 $[M+H]^+$.

Ejemplo 318: N-{5-[(2-amino-7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-bromopiridin-2-il)acetamida;

El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 1 con DIPEA utilizando (2-amino-7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)(5-aminopiridin-3-il)metanona
(preparación 122) y ácido (5-bromopiridin-2-il)acético para dar el compuesto del título en forma de un aceite incoloro en 57% de rendimiento, 75 mg.
LCMS (sistema 10): T_r = 2,81 min; m/z 494 $[M+H]^+$.

Protocolo de biblioteca 1

Los compuestos a continuación se prepararon en paralelo de la siguiente manera.

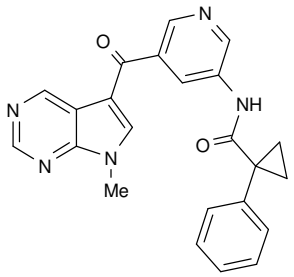


Se preparó una solución de reserva de 0,25 M de (5-amino-piridin-3-il)-(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 110) en DMF anhidro Las soluciones de reserva (0,30M) de cada monómero ácido se prepararon en DMF anhidro. Se preparó una solución de reserve de EDCI (0,5 M) y HOBT (0,05 M) en DMF anhidro. 300µl (90 µmol) de cada solución de monómero ácido se dispersó hacia los recipientes de 8 ml, seguido de 300 µl (75 umol) de solución de (5-amino-piridin-3-il)-(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona. Se agregaron N-metil morfolina (150 µmol, 2,0 eq), 300 µl de solución de EDCI (150 µmol) y HOBT (15µmol) a cada recipiente. Los recipientes se taparon y se agitaron a 50ºC durante 2 horas. El solvente se eliminó utilizando un Speedvac, y el producto final se purificó por HPLC en las condiciones mencionadas para dar los compuestos finales

Ejemplo	Nombre	Datos
319	2-(4-clorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS: T_r = 2,59 min; m/z 406 $[M+H]^+$
320	3-(4-clorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}propanamida	LCMS: T_r = 2,70 min; m/z 420 $[M+H]^+$
321	3-(3-metilfenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}propanamida	LCMS: T_r = 2,69 min; m/z 400 $[M+H]^+$
322	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-3-(piridin-3-il)propanamida	LCMS: T_r = 1,80 min; m/z 387 $[M+H]^+$
323	3-(3-clorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}propanamida	LCMS: T_r = 2,69 min; m/z 420 $[M+H]^+$
324	3-(3-fluorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}propanamida	LCMS: T_r = 2,56 min; m/z 404 $[M+H]^+$
325	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[2-(trifluorometoxi)fenoxi]acetamida	LCMS: T_r = 2,80 min; m/z 472 $[M+H]^+$

Ejemplo	Nombre	Datos
326	3-(2-metilfenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}propanamida	LCMS:Tr = 2,63 min; m/z 400 $[M+H]^+$
327	3-(2-fluorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}propanamida	LCMS: T_r = 2,53 min; m/z 404 $[M+H]^+$
328	3-(4-fluorofenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}propanamida	LCMS: T_r = 2,55 min; m/z 404 $[M+H]^+$
329	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-3-fenilpropanamida	LCMS:Tr = 2,50 min; m/z 386 $[M+H]^+$
330	3-(4-metilfenil)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}propanamida	LCMS:Tr = 2,65 min; m/z 400 $[M+H]^+$
331	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-{[(trifluorometil)sulfonil]amino}fenil)acetamida	LCMS: T_r = 2,60 min; m/z 519 $[M+H]^+$
332	N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-fenoxiacetamida	LCMS: T_r = 2,53 min; m/z 388 $[M+H]^+$
333	2-[4-(metoximetil)fenil]-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS: T_r = 2,31 min; m/z 416 $[M+H]^+$
334	2-(4-fluorofenoxi)-N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida	LCMS: T_r = 2,44 min; m/z 406 $[M+H]^+$

Ejemplo 336: N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-1-fenilciclopropanocarboxamida



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el protocolo de biblioteca 1, partiendo de (5-amino-piridin-3-il)-(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 110) y el ácido 1-fenilciclopropanocarboxílico para dar el compuesto del título. LCMS: T_r = 2,61 min; m/z 398 $[M+H]^+$.

Ejemplo 337: N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}indano-2-carboxamida

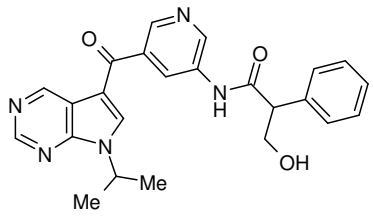
El compuesto del título se preparó de acuerdo con el método que se describió

anteriormente para el protocolo de biblioteca 1, partiendo de (5-amino-piridin-3-il)-(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 110) y el ácido indano-2-carboxílico para dar el compuesto del título. LCMS: T_r = 2,58 min; m/z 398 $[M+H]^+$.

Ejemplo 338: N-{5-[(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-fenilpropanamida

El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el protocolo de biblioteca 1, partiendo de (5-amino-piridin-3-il)-(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 110) y el ácido (2R)-2-fenilpropanoico para dar el compuesto del título. LCMS: T_r = 2,52 min; m/z 386 $[M+H]^+$.

Ejemplo 339: 3-hidroxi-2-fenil-N-(5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)propanamida



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 167, partiendo de (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 95) y el ácido trópico para dar el compuesto del título en forma de un sólido de color amarillo en 7% de rendimiento, 15 mg.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,57 (d, 6H), 3,16-3,22 (m, 1H), 3,37-3,41 (m, 1H), 3,60-3,64 (m, 1H), 5,10 (m, 1H), 6,30 (t, 1H), 7,10 (t, 1H), 7,20 (t, 2H), 7,30-7,32 (m, 3H), 8,12 (s, 1H), 8,15 (d, 1H), 8,61 (s, 1H), 8,96 (s, 1H), 9,44 (s, 1H).

LCMS (sistema 10): T_r = 2,36 min; m/z 430 $[M+H]^+$.

El siguiente ejemplo se preparó de acuerdo con los ejemplos 1 y 34 para los métodos a y b según se describió anteriormente.

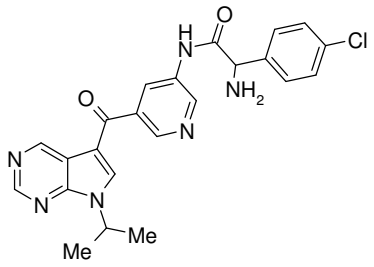
Ejemplo	Nombre	Datos
340	N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]-piridin-3-il}-2-(5-metoxi-1H-indol-1-il)acetamida	LCMS (sistema 8): T_r = 1,63 min; m/z 469 $[M+H]^+$

Los siguientes ejemplos se prepararon de acuerdo con el ejemplo 356, utilizando (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona

(preparación 95) y el ácido apropiado.

Ejemplo	Nombre	Datos
343	3-cloro-N-(5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)benzamida	LCMS Tr = 2,95 min; m/z 420 $[M+H]^+$.
344	4-cloro-N-(5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)benzamida	LCMS Tr = 2,93 min; m/z 420 $[M+H]^+$.
345	N-(5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-4-(trifluorometil)benzamida	LCMS Tr = 2,99 min; m/z 454 $[M+H]^+$.
346	N-(5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-4-(trifluorometoxi)benzamida	LCMS Tr = 3,05 min; m/z 470 $[M+H]^+$.
347	2-(2-cianofenoxi)-N-(5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida	LCMS Tr = 0,67 min; m/z 441 $[M+H]^+$.
348	N-(5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometoxi)fenoxi]acetamida	LCMS Tr = 3,01 min; m/z 500 $[M+H]^+$.

Ejemplo 350: 2-amino-2-(4-clorofenil)-N-5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)acetamida

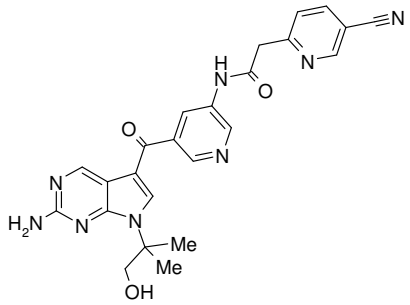


A (1-(4-clorofenil)-2-((5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)amino)-2-oxoetil)carbamato de ter-butilo (preparación 299, 64 mg, 0,11 mmoles) se agregó 4M de HCl/dioxano (5 ml) y la reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se evaporó al vacío y se purificó por HPLC de fase inversa preparativa para dar el compuesto del título en forma de un sólido de color beige en 8% de rendimiento, 4 mg.

^{1}H RMN (400 MHz, MeOD) δ*:* 1,59 (d, 6H), 4,63 (s, 1H), 5,16 (m, 1H), 7,35 (d, 2H), 7,47 (d, 2H), 8,33 (s, 1H), 8,62 (s, 1H), 8,69 (s, 1H), 8,88 (s, 1H), 8,92 (s, 1H), 9,47 (s, 1H).

LCMS Tr = 2,81 min; EM m/z 449 $[M+H]^+$.

Ejemplo 351: N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(5-ciano-piridin-2-il)-acetamida

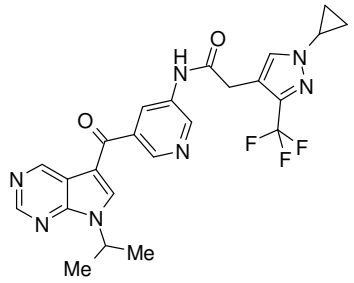


A una solución de N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(5-bromo-piridin-2-il)-acetamida (ejemplo 316, 75 mg, 0,143 mmoles) en DMF (2 ml) se agregó $Zn(CN)_2$ (25 mg, 0,215 mmoles) y la mezcla se desgasifiqué con argón durante 10 minutos. Posteriormente se agregaron $Pd_2(dba)_3$ (3 mg, 0,002 mmoles) y 1,1'-bis(difenilfosfino)ferroceno (6 mg, 0,011 mmoles) y la mezcla de reacción resultante se calentó a 100ºC durante 40 min en irradiación por microondas. La mezcla de reacción se diluyó con EtOAc (20 ml) y se lavó con agua (2 x 10 ml) y salmuera (10 ml). La capa orgánica se secó (Na_2SO_4) y se evaporó al vacío. El material bruto se purificó por TLC preparativa (7% MeOH en DCM) para dar el compuesto del título en forma de un sólido de color amarillo en 31% de rendimiento, 21 mg.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,63 (s, 6H), 3,89 (d, 2H), 4,06 (s, 2H), 5,04 (t, 1H), 6,53 (s, 2H), 7,65-7,68 (m, 2H), 8,29 (dd, 1H), 8,40 (s, 1H), 8,64 (d, 1H), 8,93-8,97 (m, 3H), 10,75 (s, 1H).

LCMS (sistema 10): T_r = 2,50 min; EM m/z 471 $[M+H]^+$

Ejemplo 352: 2-(1-ciclopropil-3-trifluorometil-1H-pirazol-4-il)-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-acetamida



A una solución de (5-amino-piridin-3-il)-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 95, 50 mg, 0,17 mmoles), ácido (1-ciclopropil-3-

trifluorometil-1H-pirazol-4-il)-acético (preparación 148, 47,1 mg, 0,21 mmoles) y TEA (0,08 ml, 0,62 mmoles) en THF (1 ml), se agregó anhídrido cíclico del ácido 1-propifosfónico (50% de solución en EtOAc, 0,26 ml, 0,44 mmoles) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se evaporó a presión reducida el residuo se dividió entre EtOAc y agua. La capa orgánica se lavó con bicarbonato de sodio saturado y se secó (Na_2SO_4), se evaporó al vacío. La purificación por cromatografía de columna sobre gel de sílice (EtOAc) dio el compuesto del título en forma de un sólido de color blanco en 77% de rendimiento, 68 mg.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 1,00-1,01 (m, 2H), 1,06-1,14 (m, 2H), 1,54 (d, 6H), 3,70 (s, 2H), 3,84 (m, 1H), 5,08-5,12 (m, 1H), 7,98 (s, 1H), 8,45 (s, 1H), 8,51 (s, 1H), 8,74 (s, 1H), 8,96 (d, 1H), 8,99 (s, 1H), 9,44 (s, 1H), 10,60 (s, 1H).

LCMS (sistema 10): T_r = 3,02 min; EM m/z 498 $[M+H]^+$

Ejemplo 353: 2-{5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}propananoato de metilo racémico

El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 229 utilizando 2-(4-clorofenil)-N-[5-(7H-pirrolo[2,3-d]pirimidin-5-ilcarbonil)piridin-3-il]acetamida (ejemplo 308), 2-bromopropionato de metilo y carbonato de cesio. Se purificó utilizando HPLC preparativa (método 1) para dar el compuesto del título.

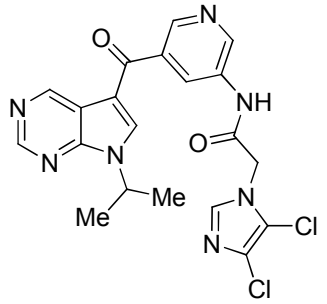
LCMS (sistema 2): T_r = 1,42 min; EM m/z 478 $[M+H]^+$

Ejemplo 354: Ácido 2-{5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}propanoico racémico

El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 155 utilizando 2-{5-[(5-{[(4-clorofenil)acetil]amino}piridin-3-il)carbonil]-7H-pirrolo[2,3-d]pirimidin-7-il}propananoato de metilo (ejemplo 353) para dar el compuesto del título en forma de un sólido de color blanco en 100% de rendimiento, 97 mg.

LCMS (sistema 2): T_r = 1,40 min; m/z 464 $[M+H]^+$.

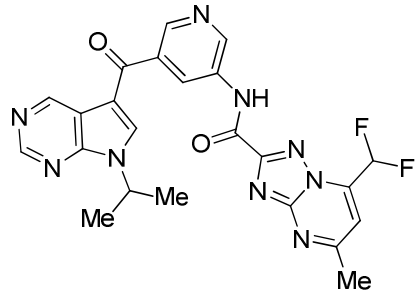
Ejemplo 355: 2-(4,5-dicloro-imidazol-1-il)-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-acetamida (método d)



Se agregó ácido (4,5-dicloro-imidazol-1-il)-acético (25,2 mg, 0,130 mmoles) a (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (28,1 mg, 0,1 mmoles), HATU (49,4 mg, 0,130 mmoles) y DIPEA (51,7 uL, 0,300 mmoles) en DMF anhidro (1 ml). La mezcla se agitó a 50ºC durante 16 horas y posteriormente se evaporó al vacío y se purificó por HPLC prep (método 5) para dar el compuesto del título en 46% de rendimiento, 21,2 mg.

LCMS (sistema 8): T_r = 1,55 min; m/z 458 $[M+H]^+$

Ejemplo 356: [5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 7-difluorometil-5-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-carboxílico (método e)



Se agregó ácido 7-difluorometil-5-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-carboxílico (29,64 mg, 0,130 mmoles) a (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (28,1 mg, 0,1 mmoles), HATU (49,42 mg, 0,130 mmoles) y DIPEA (22,4 uL, 0,13 mmoles) en DMF anhidro (1 ml). La mezcla se agitó a 50ºC durante 16 horas y posteriormente se evaporó al vacío y se purificó por HPLC prep (método 5) para dar el compuesto del título en 12 % de rendimiento, 6,1 mg.

LCMS (sistema 8): T_r = 1,56 min; m/z 492 $[M+H]^+$

Los siguientes ejemplos se prepararon de acuerdo con uno de los métodos para el ejemplo 355, (método d) y 356 (método e) utilizando (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación 95).

Ejemplo	**Nombre**	**Datos**
357	2-(4,5-dicloro-imidazol-1-il)-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-acetamida	LCMS (sistema 8): T_r = 1,55 min; m/z 458 $[M+H]^+$. HPLC Prep (método 5)
358	2-(3,5-dimetil-1,2,4-triazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]acetamida	LCMS (sistema 8): T_r = 1,43 min; m/z 419 $[M+H]^+$. HPLC Prep (método 5)
359	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(2-metil-imidazol-1-il)-acetamida	LCMS (sistema 8): T_r = 1,27 min; m/z 404 $[M+H]^+$. HPLC Prep (método 5)
360	2-imidazo[2,1-a]tiazol-6-il-N-{5-[(7-	LCMS (sistema 8): T_r = 1,42

Ejemplo	Nombre	Datos
	isopropil-7H-pirrolo[2,3-d]pirimidin-5-ilcarbonil)piridin-3-il]acetamida	min; m/z 446 $[M+H]^+$. HPLC Prep (método 5)
361	2-(4-hidroxi-ftalazin-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il}acetamida	LCMS (sistema 8): T_r = 1,46 min; m/z 468 $[M+H]^+$. HPLC Prep (método 5)
362	2-(2,3-dimetil-imidazo[2,1-a]tiazol-6-il-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]acetamida	LCMS (sistema 8): T_r = 1,48 min; m/z 474 $[M+H]^+$. HPLC Prep (método 5)
363	2-[4-(1-hidroxi-ciclopentil)-1,2,3-triazol-1-il]-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]acetamida	LCMS (sistema 8): T_r = 1,44 min; m/z 475 $[M+H]^+$. HPLC Prep (método 5) (a partir de Prep 294)
364	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(5-m-tolil-tetrazol-1-il)-acetamida	LCMS (sistema 8): T_r = 1,57 min; m/z 482 $[M+H]^+$. HPLC Prep (método 5)
365	2-[4-(4-fluoro-fenil)-imidazol-1-il]-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-acetamida	LCMS (sistema 8): T_r = 1,45 min; m/z 484 $[M+H]^+$. HPLC Prep (método 5)
366	2-(5-isopropil-pirazol-1-il)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-ilcarbonil)-piridin-3-il]-acetamida	LCMS (sistema 8): T_r = 1,60 min; m/z 432 $[M+H]^+$. HPLC Prep (método 5) (el ácido se puede preparar en un análogo al método que se da en el documento WO03/072572)
367	2-(2-etil-imidazo[2,1-b]-1,3,4-tiadiazol-6-il)-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]acetamida	LCMS (sistema 8): T_r = 1,60 min; m/z 475 $[M+H]^+$. HPLC Prep (método 5)
368	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(2-metil-imidazo[2,1-b]tiazol-6-il)-acetamida	LCMS (sistema 8): T_r = 1,45 min; m/z 460 $[M+H]^+$. HPLC Prep (método 5) (a partir de Prep 289)
369	2-(3-cloro-5-metil-1,2,4-triazol-1-il)-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-acetamida	LCMS (sistema 8): T_r = 1,48 min; m/z 439 $[M+H]^+$. HPLC Prep (método 5)
370	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(2-fenil-imidazol-1-il)-acetamida	LCMS (sistema 8): T_r = 1,34 min; m/z 466 $[M+H]^+$. HPLC Prep (método 5)
371	2-(2-cloro-imidazo[2,1-a]tiazol-6-il-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]acetamida	LCMS (sistema 8): T_r = 1,59 min; m/z 480 $[M+H]^+$. HPLC Prep (método 5)
372	2-imidazol-1-il-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-acetamida	LCMS (sistema 8): T_r = 1,26 min; m/z 390 $[M+H]^+$. HPLC Prep (método 5)

Ejemplo	Nombre	Datos
373	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(3-metil-imidazo[2,1-b]tiazol-6-il)-acetamida	LCMS (sistema 8): T_r = 1,46 min; m/z 460 $[M+H]^+$. HPLC Prep (método 5)
374	2-[1-(4-hidroxi-fenil)-1H-pirrol-3-il]-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-acetamida	LCMS (sistema 8): T_r = 1,57 min; m/z 481 $[M+H]^+$. HPLC Prep (método 5)
375	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-[1,2,4]triazolo[1,5-a]pirimidin-6-il-acetamida	LCMS (sistema 8): T_r = 1,41 min; m/z 442 $[M+H]^+$. HPLC Prep (método 5)
376	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-pirazin-2-il-acetamida	LCMS (sistema 8): T_r = 1,44 min; m/z 402 $[M+H]^+$. HPLC Prep (método 5)
377	2-[4-(3-hidroxi-fenil)-1,2,3-triazol-1-il]-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]acetamida	LCMS (sistema 8): T_r = 1,48 min; m/z 483 $[M+H]^+$. HPLC Prep (método 5) (a partir de Prep 292)
378	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(5-fenil-imidazol-1-il)-acetamida	LCMS (sistema 8): T_r = 1,63 min; m/z 468 $[M+H]^+$. HPLC Prep (método 5)
379	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 7-difluorometil-5-metil-[1,2,4]triazolo[1,5-a]pirimidin-2-carboxílico	LCMS (sistema 8): T_r = 1,56 min; m/z 492 $[M+H]^+$. HPLC Prep (método 5)
380	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido furo[3,2-c]piridin-4-carboxílico	LCMS (sistema 8): T_r = 1,73 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5)
381	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4-metil-furazan-3-carboxílico	LCMS (sistema 8): T_r = 1,61 min; m/z 392 $[M+H]^+$. HPLC Prep (método 5)
382	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1-metil-1H-indazol-3-carboxílico	LCMS (sistema 8): T_r = 1,75 min; m/z 440 $[M+H]^+$. HPLC Prep (método 5)
383	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1H-indol-2-carboxílico	LCMS (sistema 8): T_r = 1,67 min; m/z 425 $[M+H]^+$. HPLC Prep (método 5)
384	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2-metil-4-trifluorometil-tiazol-5-carboxílico	LCMS (sistema 8): T_r = 1,62 min; m/z 475 $[M+H]^+$. HPLC Prep (método 5)

Ejemplo	Nombre	Datos
385	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-ciclopropil-oxazol-4-carboxílico	LCMS (sistema 8): T_r = 1,67 min; m/z 417 $[M+H]^+$. HPLC Prep (método 5)
386	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido piridazin-3-carboxílico	LCMS (sistema 8): T_r = 1,52 min; m/z 388 $[M+H]^+$. HPLC Prep (método 5)
387	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 3-metil-5-trifluorometil-1H-pirazol-4-carboxílico	LCMS (sistema 8): T_r = 1,53 min; m/z 458 $[M+H]^+$. HPLC Prep (método 5) (ácido a partir de Prep 290)
388	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4-metil-piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,70 min; m/z 401 $[M+H]^+$. HPLC Prep (método 5)
389	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 3-ciclobutil-1H-pirazol-4-carboxílico	LCMS (sistema 8): T_r = 1,59 min; m/z 430 $[M+H]^+$. HPLC Prep (método 5)
390	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido oxazol-5-carboxílico	LCMS (sistema 8): T_r = 1,46 min; m/z 377 $[M+H]^+$. HPLC Prep (método 5)
391	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4-metil-1H-imidazol-2-carboxílico	LCMS (sistema 8): T_r = 1,52 min; m/z 390 $[M+H]^+$. HPLC Prep (método 5)
392	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1H-pirrolo[2,3-c]piridin-5-carboxílico	LCMS (sistema 8): T_r = 1,56 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5) (ácido: Synthesis, 1993, 295-297)
393	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metil-pirazin-2-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 402 $[M+H]^+$. HPLC Prep (método 5)
394	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1,3-dimetil-1H-pirazol-4-carboxílico	LCMS (sistema 8): T_r = 1,53 min; m/z 404 $[M+H]^+$. HPLC Prep (método 6)
395	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1H-pirazolo[4,3-b]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,46 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5) (ácido: véase US 20110111046)
396	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-etil-isoxazol-3-carboxílico	LCMS (sistema 8): T_r = 1,63 min; m/z 405 $[M+H]^+$. HPLC Prep (método 5)
397	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2-metil-2H-pirazol-3-carboxílico	LCMS (sistema 8): T_r = 1,54 min; m/z 390 $[M+H]^+$. HPLC Prep (método 5)

Ejemplo	Nombre	Datos
398	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido quinolin-3-carboxílico	LCMS (sistema 8): T_r = 1,66 min; m/z 437 $[M+H]^+$. HPLC Prep (método 5)
399	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-fluoro-1H-pirrolo[2,3-b]piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,61 min; m/z 444 $[M+H]^+$. HPLC Prep (método 5) (ácido: WO2008/107543)
400	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1,5-dimetil-1H-pirazol-3-carboxílico	LCMS (sistema 8): T_r = 1,57 min; m/z 404 $[M+H]^+$. HPLC Prep (método 5)
401	[2-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-ciclopropil-oxazol-4-carboxílico	LCMS (sistema 8): T_r = 1,64 min; m/z 417 $[M+H]^+$. HPLC Prep (método 5)
402	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4-trifluorometil-tiazol-5-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 461 $[M+H]^+$. HPLC Prep (método 5)
403	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 6,7-dihidro-5H-pirrolo[1,2c]imidazol-1-carboxílico	LCMS (sistema 8): T_r = 1,51 min; m/z 416 $[M+H]^+$. HPLC Prep (método 5) El ácido se puede preparar por oxidación del aldehído que se describe en Tetrahedron, 1999, 8111)
404	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido tieno[3,2-c]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,77 min; m/z 443 $[M+H]^+$. HPLC Prep (método 5)
405	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1-metil-3-trifluorometil-1H-pirazol-4-carboxílico	LCMS (sistema 8): T_r = 1,60 min; m/z 458 $[M+H]^+$. HPLC Prep (método 5)
406	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido imidazo[1,5-a]piridin-7-carboxílico	LCMS (sistema 8): T_r = 1,47 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)
407	[5-(7-isopropil-7H-pirrolo[2,3-b]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1H-pirrolo[2,3-b]piridin-4-carboxílico	LCMS (sistema 8): T_r = 1,54 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)
408	[3-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 3-etil-isoxazol-5-carboxílico	LCMS (sistema 8): T_r = 1,60 min; m/z 405 $[M+H]^+$. HPLC Prep (método 5)
409	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4-metoxi-piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,67 min; m/z 417 $[M+H]^+$. HPLC Prep (método 5)
410	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido pirimidin-5-carboxílico	LCMS (sistema 8): T_r = 1,46 min; m/z 388 $[M+H]^+$. HPLC Prep (método 5)
411	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-	

Ejemplo	Nombre	Datos
	5-carbonil)-piridin-3-il]-amida del ácido 3-metil-1H-pirazol-4-carboxílico	LCMS (sistema 8): T_r = 1,46 min; m/z 390 $[M+H]^+$. HPLC Prep (método 5)
412	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metil-1H-pirrolo[2,3-b]piridin-3-carboxílico	LCMS (sistema 8): T_r = 1,54 min; m/z 440 $[M+H]^+$. HPLC Prep (método 5)
413	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metil-pirimidin-4-carboxílico	LCMS (sistema 8): T_r = 1,60 min; m/z 402 $[M+H]^+$. HPLC Prep (método 5)
414	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido tieno[3,2-b]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,64 min; m/z 443 $[M+H]^+$. HPLC Prep (método 5)
415	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido pirazolo[1,5-a]pirimidin-6-carboxílico	LCMS (sistema 8): T_r = 1,54 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5)
416	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4,5,6,7-tetrahidro-1,2-bencisoxazol-3-carboxílico	LCMS (sistema 8): T_r = 1,75 min; m/z 431 $[M+H]^+$. HPLC Prep (método 5)
417	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido imidazo[1,5-a]piridin-3-carboxílico	LCMS (sistema 8): T_r = 1,75 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)
418	[5-(7-isopropil-7H-pirrolo[2,3-b]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido furo[3,2-c]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,65 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)
419	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1,4,5,6-tetrahidro-ciclopentapirazol-3-carboxílico	LCMS (sistema 8): T_r = 1,59 min; m/z 416 $[M+H]^+$. HPLC Prep (método 5)
420	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4-amino-pirimidin-5-carboxílico	LCMS (sistema 8): T_r = 1,41 min; m/z 403 $[M+H]^+$. HPLC Prep (método 5)
421	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1H-pirrolo[2,3-c]piridin-3-carboxílico	LCMS (sistema 8): T_r = 1,32 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)
422	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-metil-isonicotinamida	LCMS (sistema 8): T_r = 1,51 min; m/z 401 $[M+H]^+$. HPLC Prep (método 5)
423	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido imidazo[1,2-a]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,33 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)
424	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1H-1,2,4-triazol-3-carboxílico	LCMS (sistema 8): T_r = 1,38 min; m/z 377 $[M+H]^+$. HPLC Prep (método 7)

Ejemplo	Nombre	Datos
425	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metoxi-piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,66 min; m/z 417 $[M+H]^+$. HPLC Prep (método 5)
426	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido cinolin-4-carboxílico	LCMS (sistema 8): T_r = 1,57 min; m/z 438 $[M+H]^+$. HPLC Prep (método 5)
427	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido [1,2,4]triazolo[1,5-a]piridin-7-carboxílico	LCMS (sistema 8): T_r = 1,51 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5)
428	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido pirazolo[1,5-a]pirimidin-2-carboxílico	LCMS (sistema 8): T_r = 1,54 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5)
429	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,62 min; m/z 387 $[M+H]^+$. HPLC Prep (método 5)
430	5-cloro-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-nicotinamida	LCMS (sistema 8): T_r = 1,62 min; m/z 421 $[M+H]^+$. HPLC Prep (método 5)
431	[5-(7-isopropil-7H-pirrolo[2,3-b]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4H-furo[3,2-b]pirrol-5-carboxílico	LCMS (sistema 8): T_r = 1,59 min; m/z 415 $[M+H]^+$. HPLC Prep (método 5)
432	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido imidazo[1,2-a]piridin-7-carboxílico	LCMS (sistema 8): T_r = 1,34 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)
433	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1-etil-1H-pirazol-4-carboxílico	LCMS (sistema 8): T_r = 1,52 min; m/z 404 $[M+H]^+$. HPLC Prep (método 5)
434	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1-isopropil-1H-imidazol-4-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 418 $[M+H]^+$. HPLC Prep (método 5) (Ácido :WO2010/009062
435	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 8-metoxi-imidazo[1,2,-a]pirazin-6-carboxílico	LCMS (sistema 8): T_r = 1,62 min; m/z 457 $[M+H]^+$. HPLC Prep (método 5) El ácido se puede preparar por carbonilación del bromuro por ej., WO2010/078408)
436	[5-(7-isopropil-7H-pirrolo[2,3-b]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1H-pirrolo[2,3-b]piridin-5-carboxílico	LCMS (sistema 8): T_r = 1,55 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)

Ejemplo	Nombre	Datos
437	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2-metil-5-propil-2H-pirazol-3-carboxílico	LCMS (sistema 8): T_r = 1,69 min; m/z 432 $[M+H]^+$. HPLC Prep (método 5)
438	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4-isopropil-tiazol-2-carboxílico	LCMS (sistema 8): T_r = 1,79 min; m/z 435 $[M+H]^+$. HPLC Prep (método 5) (ácido: WO2007/017144
439	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 3-metil-furo[2,3-c]piridin-5-carboxílico	LCMS (sistema 8): T_r = 1,77 min; m/z 441 $[M+H]^+$. HPLC Prep (método 5) (ácido: WO04052348)
440	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 6-metil-piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,69 min; m/z 401 $[M+H]^+$. HPLC Prep (método 5)
441	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-cloro-1-metil-3-trifluorometil-1H-pirazol-4-carboxílico	LCMS (sistema 8): T_r = 1,63 min; m/z 492 $[M+H]^+$. HPLC Prep (método 5)
442	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metoxi-1H-bencimidazol-2-carboxílico	LCMS (sistema 8): T_r = 1,63 min; m/z 456 $[M+H]^+$. HPLC Prep (método 5) (ácido: US2007/017144)
443	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4-cloro-1,5-dimetil-1H-pirazol-3-carboxílico	LCMS (sistema 8): T_r = 1,65 min; m/z 438 $[M+H]^+$. HPLC Prep (método 5)
444	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1H-pirrolo[3,2-c]piridin-4-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)
445	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4-etil-piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,76 min; m/z 415 $[M+H]^+$. HPLC Prep (método 5) (ácido: JOC, 1990, 55, 738-741)
446	[5-(7-isopropil-7H-pirrolo[2,3-b]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2,3-dihidro-1,4-dioxino[2,3-b]piridin-7-carboxílico	LCMS (sistema 8): T_r = 1,54 min; m/z 445 $[M+H]^+$. HPLC Prep (método 5)
447	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido pirrolo[3,2-b]piridin-5-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)

Ejemplo	Nombre	Datos
448	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido pirazolo[1,5-a]piridin-5-carboxílico	LCMS (sistema 8): T_r = 1,59 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5) (ácido: J. Med. Chem. (2007), 45(21), 4594-4597)
449	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 6-metoxi-quinolin-3-carboxílico	LCMS (sistema 8): T_r = 1,68 min; m/z 467 $[M+H]^+$. HPLC Prep (método 5)
450	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metil-2-(2,2,2-trifluoro-etil-2H-pirazol-3-carboxílico	LCMS (sistema 8): T_r = 1,66 min; m/z 472 $[M+H]^+$. HPLC Prep (método 5) (ácido: WO 2008/016192)
451	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-4-trifluorometil-nicotinamida	LCMS (sistema 8): T_r = 1,58 min; m/z 455 $[M+H]^+$. HPLC Prep (método 5)
452	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1-(2-ciano-etil)-1H-pirazol-4-carboxílico	LCMS (sistema 8): T_r = 1,46 min; m/z 429 $[M+H]^+$. HPLC Prep (método 5)
453	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido furo[3,2-c]piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,45 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5) (ácido: J.Het.Chem. (1987),24(2), 373-6)
454	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1H-pirrolo[3,2-c]piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,32 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)
455	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido furo[3,2-c]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,70 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5)
456	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2,4-dimetil-oxazol-5-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 405 $[M+H]^+$. HPLC Prep (método 5)
457	[1-(7-isopropil-7H-pirrolo[2,3-c]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metil-1H-pirrolo[2,3-b]piridin-3-carboxílico	LCMS (sistema 8): T_r = 1,32 min; m/z 440 $[M+H]^+$. HPLC Prep (método 5) (ácido: WO07017144)
458	[5-(7-isopropil-7H-pirrolo[1,2-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5,6-dihidro-4H-pirrolo[1,2-b]pirazol-2-carboxílico	LCMS (sistema 8): T_r = 1,59 min; m/z 416 $[M+H]^+$. HPLC Prep (método 5)

Ejemplo	Nombre	Datos
459	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2-ciclobutil-tiazol-4-carboxílico	LCMS (sistema 8): T_r = 1,79 min; m/z 447 $[M+H]^+$. HPLC Prep (método 5) (ácido: WO2009098448)
460	3-fluoro-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-isonicotinamida	LCMS (sistema 8): T_r = 1,53 min; m/z 405 $[M+H]^+$. HPLC Prep (método 5)
461	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2-metil-imidazo[1,2,-a]pirimidin-3-carboxílico	LCMS (sistema 8): T_r = 1,52 min; m/z 441 $[M+H]^+$. HPLC Prep (método 5)
462	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metil-isoxazol-3-carboxílico	LCMS (sistema 8): T_r = 1,57 min; m/z 391 $[M+H]^+$. HPLC Prep (método 5)
463	[4,6-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 54,6-dimetoxi-pirimidin-2-carboxílico	LCMS (sistema 8): T_r = 1,62 min; m/z 448 $[M+H]^+$. HPLC Prep (método 5)
464	[6-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metil-pirazin-2-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 402 $[M+H]^+$. HPLC Prep (método 5)
465	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1-metil-1H-imidazol-4-carboxílico	LCMS (sistema 8): T_r = 1,49 min; m/z 390 $[M+H]^+$. HPLC Prep (método 5)
466	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-cloro-piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,71 min; m/z 421 $[M+H]^+$. HPLC Prep (método 5)
467	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1,8-naftiridin-2-carboxílico	LCMS (sistema 8): T_r = 1,68 min; m/z 438 $[M+H]^+$. HPLC Prep (método 5)
468	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1-metil-1H-imidazol-2-carboxílico	LCMS (sistema 8): T_r = 1,59 min; m/z 390 $[M+H]^+$. HPLC Prep (método 5)
469	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metoximetil-isoxazol-3-carboxílico	LCMS (sistema 8): T_r = 1,56 min; m/z 421 $[M+H]^+$. HPLC Prep (método 5)
470	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido ftalazin-1-carboxílico	LCMS (sistema 8): T_r = 1,67 min; m/z 438 $[M+H]^+$. HPLC Prep (método 5)

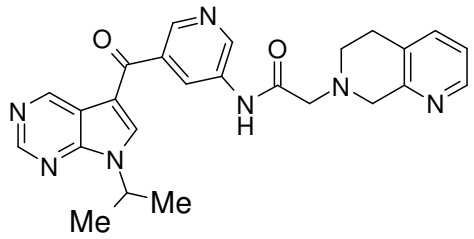
Ejemplo	Nombre	Datos
471	[5-(7-isopropil-7H-pirrolo[1,2-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5,6-dihidro-4H-pirrolo[1,2-b]pirazol-3-carboxílico	LCMS (sistema 8): T_r = 1,55 min; m/z 416 $[M+H]^+$. HPLC Prep (método 5)
472	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-bromo-pirimidin-4-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 467 $[M+H]^+$. HPLC Prep (método 5)
473	6-ciano-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-nicotinamida	LCMS (sistema 8): T_r = 1,55 min; m/z 412 $[M+H]^+$. HPLC Prep (método 5)
474	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido pirazolo[1,5-a]pirimidin-3-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5)
475	[3-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 3-metil-1H-pirazolo[3,4-b]piridin-5-carboxílico	LCMS (sistema 8): T_r = 1,53 min; m/z 441 $[M+H]^+$. HPLC Prep (método 5)
476	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 7-metil-pirazolo[1,5-b]piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,73 min; m/z 440 $[M+H]^+$. HPLC Prep (método 5)
477	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metil-oxazol-4-carboxílico	LCMS (sistema 8): T_r = 1,59 min; m/z 391 $[M+H]^+$. HPLC Prep (método 5)
478	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido tieno[3,4-c]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,74 min; m/z 443 $[M+H]^+$. HPLC Prep (método 5) (ácido: WO 2002100857)
479	[2,6-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-dimetil-pirimidin-4-carboxílico	LCMS (sistema 8): T_r = 1,65 min; m/z 416 $[M+H]^+$. HPLC Prep (método 5)
480	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4-ciano-piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,62 min; m/z 412 $[M+H]^+$. HPLC Prep (método 5)
481	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-metoximetil-1-metil-1H-pirazol-3-carboxílico	LCMS (sistema 8): T_r = 1,56 min; m/z 434 $[M+H]^+$. HPLC Prep (método 5) (ácido: Prep 299)
482	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4,5-dicloro-1H-imidazol-2-carboxílico	LCMS (sistema 8): T_r = 1,68 min; m/z 444 $[M+H]^+$. HPLC Prep (método 5) (ácido: Angewandte Chemie, 1988, 1417-1418)

Ejemplo	Nombre	Datos
483	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4-metoxi-8-metil-1,7-naftiridin-2-carboxílico	LCMS (sistema 8): T_r = 1,78 min; m/z 482 $[M+H]^+$. HPLC Prep (método 5) (ácido: se puede preparar usando la química delineada en WO07011811)
484	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2-etil-4-metil-oxazol-5-carboxílico	LCMS (sistema 8): T_r = 1,63 min; m/z 419 $[M+H]^+$. HPLC Prep (método 5)
485	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-5-metoxi-nicotinamida	LCMS (sistema 8): T_r = 1,57 min; m/z 417 $[M+H]^+$. HPLC Prep (método 5)
486	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1H-pirazolo[3,4-b]piridin-5-carboxílico	LCMS (sistema 8): T_r = 1,49 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5)
487	[5-(7-isopropil-7H-pirrolo[2,3-b]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 3H-imidazo[4,5-b]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,44 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5)
488	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 8-metoxi-imidazo[1,2,-a]pirazin-2-carboxílico	LCMS (sistema 8): T_r = 1,61 min; m/z 457 $[M+H]^+$. HPLC Prep (método 5) (ácido: se puede preparar a partir del derivado halo apropiado por ej., WO07028051)
489	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-isonicotinamida	LCMS (sistema 8): T_r = 1,51 min; m/z 387 $[M+H]^+$. HPLC Prep (método 5)
490	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 3-metil-piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,70 min; m/z 401 $[M+H]^+$. HPLC Prep (método 5)
491	[5-(7-isopropil-7H-pirrolo[2,3-b]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido furo[2,3-b]piridin-5-carboxílico	LCMS (sistema 8): T_r = 1,59 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5) (ácido: WO 9516688)
492	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 3-isopropil-1,2,4-triazolo[4,3-a]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,57 min; m/z 469 $[M+H]^+$. HPLC Prep (método 5)

Ejemplo	Nombre	Datos
493	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido oxazol-4-carboxílico	LCMS (sistema 8): T_r = 1,50 min; m/z 377 $[M+H]^+$. HPLC Prep (método 5)
494	[3-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-cloro-piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,62 min; m/z 421 $[M+H]^+$. HPLC Prep (método 5)
495	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido imidazo[1,2-a]pirimidin-6-carboxílico	LCMS (sistema 8): T_r = 1,44 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5) (ácido a partir de Prep 300)
496	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-ciclopropil-isoxazol-3-carboxílico	LCMS (sistema 8): T_r = 1,67 min; m/z 417 $[M+H]^+$. HPLC Prep (método 5)
497	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2-ciclopropil-2H-pirazol-3-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 416 $[M+H]^+$. HPLC Prep (método 5)
498	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 4,7-dimetil-pirazol5,1-c][1,2,4]triazina-3-carboxílico	LCMS (sistema 8): T_r = 1,69 min; m/z 456 $[M+H]^+$. HPLC Prep (método 5)
499	N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-4-metil-nicotinamida	LCMS (sistema 8): T_r = 1,51 min; m/z 401 $[M+H]^+$. HPLC Prep (método 5)
500	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1-ciclobutil-1H-imidazol-4-carboxílico	LCMS (sistema 8): T_r = 1,64 min; m/z 430 $[M+H]^+$. HPLC Prep (método 5) (ácido a partir de Prep 288)
501	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido pirazolo[1,5-a]piridin-2-carboxílico	LCMS (sistema 8): T_r = 1,65 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)
502	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido tetrazolo[1,5-1]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,51 min; m/z 428 $[M+H]^+$. HPLC Prep (método 5) comercial
503	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5,6,7,8-tetrahidro-1,2,4-triazolo[4,3-a]piridin-3-carboxílico	LCMS (sistema 8): T_r = 1,60 min; m/z 431 $[M+H]^+$. HPLC Prep (método 5) comercial
504	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2-metil-5-trifluorometil-oxazol-4-carboxílico	LCMS (sistema 8): T_r = 1,69 min; m/z 459 $[M+H]^+$. HPLC Prep (método 5)
505	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido furo[3,2-b]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,36 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)

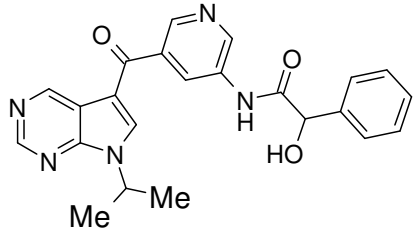
Ejemplo	Nombre	Datos
506	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido pirazolo[3,4-a]piridin-6-carboxílico	LCMS (sistema 8): T_r = 1,57 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5)
507	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2H-indazol-3-carboxílico	LCMS (sistema 8): T_r = 1,65 min; m/z 426 $[M+H]^+$. HPLC Prep (método 5)
508	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 3-metil-isoxazol[5,4-b]b]piridin-5-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 442 $[M+H]^+$. HPLC Prep (método 5) (Ácido - Synthesis, 2009, 1858-1864)
509	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido piridazin-4-carboxílico	LCMS (sistema 8): T_r = 1,45 min; m/z 388 $[M+H]^+$. HPLC Prep (método 5)
510	[5-(7-isopropil-7H-pirrolo[2,3-b]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2,3-dihidro-1,4-dioxino[2,3-c]piridin-7-carboxílico	LCMS (sistema 8): T_r = 1,66 min; m/z 445 $[M+H]^+$. HPLC Prep (método 5) (ácido: WO 2010/067332)
511	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 1H-pirazolo[3,4-b]piridin-3-carboxílico	LCMS (sistema 8): T_r = 1,58 min; m/z 427 $[M+H]^+$. HPLC Prep (método 5) (ácido: WO 2011/084486)
512	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 5-fluoro-1H-indazol-3-carboxílico	LCMS (sistema 8): T_r = 1,68 min; m/z 444 $[M+H]^+$. HPLC Prep (método 5)
513	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 2,5-dimetil-2H-pirazol-3-carboxílico	LCMS (sistema 8): T_r = 1,59 min; m/z 404 $[M+H]^+$. HPLC Prep (método 5)
514	[5-(7-isopropil-7H-pirrolo[2,3-b]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido tiazolo[4,5-b]piridin-7-carboxílico	LCMS (sistema 8): T_r = 1,56 min; m/z 444 $[M+H]^+$. HPLC Prep (método 5)
515	[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-amida del ácido 6-cloro-imidazo[1,2,-b]piridazin-2-carboxílico	LCMS (sistema 8): T_r = 1,68 min; m/z 461 $[M+H]^+$. HPLC Prep (método 5)

Ejemplo 517: 2-(5,8-dihidro-6H-[1,7]naftiridin-7-il)-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-acetamida



A una solución en DMF clorhidrato del ácido (5,8-dihidro-6H-[1,7]naftiridin-7-il)-acético (preparación 235) (34,2 mg, 0,18 mmoles) se agregaron (5-amino-piridin-3-il)-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 95, 50 mg, 0,18mmoles), HATU (136,4 mg, 0,36 mmoles) y base de Hunig (0,092 ml, 0,54 mmoles). La mezcla se calentó a 50ºC durante 20 horas y a continuación se diluyó con acetato de etilo, se lavó con agua, salmuera, se secó sobre sulfato de sodio y se evaporó hasta sequedad al vacío. El sólido bruto se purificó sobre TLC preparativa eluyendo con 5% de MeOH/EtOAc para dar el compuesto del título en forma de un sólido blancuzco en 26% de rendimiento, 21 mg. ^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,55 (d, 6H), 2,85-2,92 (m, 4H), 3,45 (s, 2H), 3,80 (s, 2H), 5,10 (m, 1H), 7,19 (dd, 1H), 7,56 (d, 1H), 8,32 (d, 1H), 8,53 (s, 1H), 8,56 (t, 1H), 8,73 (d, 1H), 8,99 (s, 1H), 9,07 (d, 1H), 9,45 (s, 1H), 10,31 (s, 1H); LCMS (sistema 9): T_r = 1,77 min; m/z 456 $[M+H]^+$.

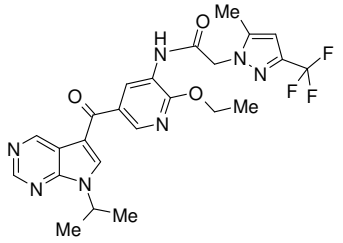
Ejemplo 518: 2-hidroxi-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-fenil-acetamida



A una solución agitada de N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-fenil-2-(tetrahidro-piran-2-iloxi)-acetamida (60 mg, 0,12 mmoles) (preparación 237) en dioxano (1 ml) se agregó dioxano-HCl (1 ml de una solución 4N) a 0ºC. La mezcla se agitó a temperatura ambiente durante 2 horas. Todos los volátiles se eliminaron al vacío y el sólido obtenido se trituró con éter dietílico para dar el compuesto del título en forma de un sólido amarillento en 78% de rendimiento, 42 mg. ^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,55 (d, 6H), 5,08-5,12 (m, 1H), 5,19 (s, 1H), 7,30 (t, 1H), 7,37 (t, 2H), 7,53 (d, 2H), 8,56 (s, 1H), 8,63 (s, 1H), 8,76 (br s, 1H), 9,05 (s, 1H), 9,17 (br s, 1H), 9,48 (br s, 1H), 10,56 (s, 1H); LCMS (sistema 10): T_r = 2,81 min; m/z

416 $[M+H]^+$.

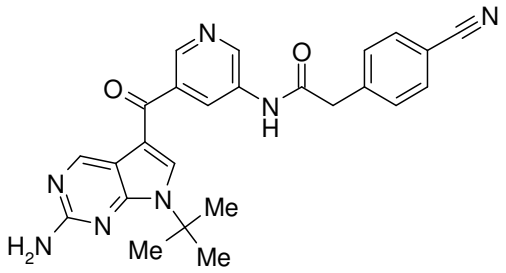
Ejemplo 519: N-[2-etoxi-5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(5-metil-3-trifluorometil-pirazol-1-il)-acetamida



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 1, partiendo de (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación 242) y el ácido (5-metil-3-trifluorometil-pirazol-1-il)acético para dar el compuesto del título en forma de un sólido blancuzco en 50% de rendimiento, 40 mg.

^{1}H RMN (400 MHz, CDCl3) δ*:* 1,38 (t, 3H), 1,60 (d, 6H), 2,38 (s, 3H), 4,50 (q, 2H), 4,95 (s, 2H), 5,14-5,22 (m, 1H), 6,44 (s, 1H), 7,93 (s, 1H), 8,41 (s, 1H), 8,44 (s, 1H), 8,99 (s, 1H), 9,04 (s, 1H), 9,57 (s, 1H); LCMS (sistema 10): T_r = 3,48 min; m/z 516 $[M+H]^+$.

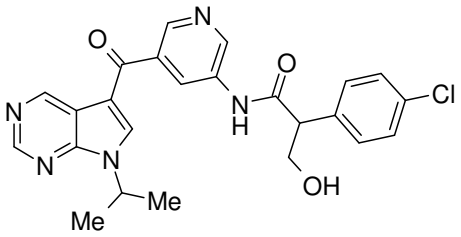
Ejemplo 520: N-[5-(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(4-ciano-fenil)-acetamida



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 1, utilizando ((2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)-(5-amino-piridin-3-il)-metanona (preparación 65) y el ácido 4-ciano fenil acético para dar el compuesto del título en forma de un sólido blancuzco en 58% de rendimiento, 23 mg.

LCMS (sistema 10): T_r = 2,78 min; m/z 454 $[M+H]^+$.

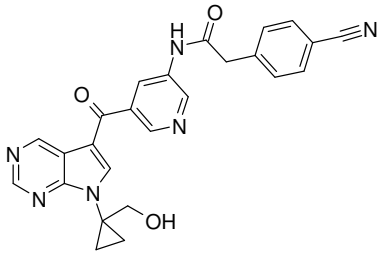
Ejemplo 521: 2-(4-cloro-fenil)-3-hidroxi-N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-propionamida



Se agregó ácido 2-(4-cloro-fenil)-3-hidroxi-propiónico (570 mg, 2,84 mmoles) (preparación 244) a una solución de (5-amino-piridin-3-il)-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (200 mg, 0,71 mmoles) (preparación 95) en THF (5 ml). Se agregaron Di-isopropil etilamina (0,64 ml, 3,56 mmoles), EDCI.HCl (273 mg, 1,42 mmoles) y HOBT (193 mg, 1,42 mmoles) y la mezcla se agitó a 25ºC durante 48 horas. La mezcla de reacción se templó con solución de bicarbonato de sodio acuoso saturado (2 ml) y se extrajo con acetato de etilo (3 x 15 ml). La capa orgánica combinada se lavó con agua (5 ml), salmuera (5 ml), se secó sobre sulfato de sodio y se evaporó al vacío. El material bruto se purificó por TLC preparativa (diclorometano: Metanol 93:7) para dar el compuesto del título en forma de un sólido de color amarillo en 3% de rendimiento, 10 mg.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,55 (d, 6H), 3,58-3,61 (m, 1H), 3,88-3,91 (m, 1H), 4,04 (t, 1H), 5,07-5,13 (m, 2H), 7,41 (s, 4H), 8,47 (s, 1H), 8,50 (s, 1H), 8,72 (s, 1H), 8,99 (s, 2H), 9,43 (s, 1H), 10,65 (s, 1H); LCMS (sistema 10): T_r = 2,99 min; m/z 464 $[M+H]^+$.

Ejemplo 522: 2-(4-cianofenil)-N-{5-[(7-(1-hidroximetil-ciclopropil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}acetamida



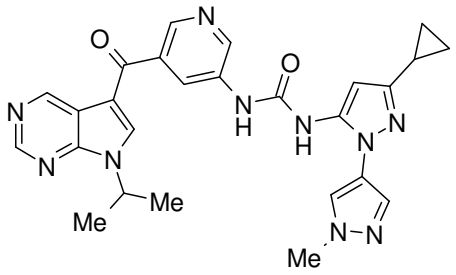
Se agregó ácido (4-ciano-fenil)-acético (6,1 mg, 0,04 mmoles) a una solución de (5-amino-piridin-3-il)-{7-[1-(tetrahidro-piran-2-iloximetil)-ciclopropil]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona (15 mg, 0,04 mmoles) (preparación 251) en THF (1 ml). A continuación se agregaron anhídrido cíclico del ácido 1-propilfosfónico (0,07 ml, 0,11 mmoles) y trietilamina (0,02 ml, 0,13 mmoles) y la mezcla se agitó a 25ºC durante 4 horas. La mezcla de reacción se templó con solución de bicarbonato de sodio acuoso saturado (2 ml) y se extrajo con acetato de etilo (3 x 5 ml). La capa orgánica

combinada se lavó con agua (5 ml), salmuera (5 ml), se secó sobre sulfato de sodio y se evaporó al vacío. El bruto se disolvió en metanol (1 ml), se agregó PTSA (5 mg) y se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se templó con solución de bicarbonato de sodio acuoso saturado (2 ml) y se extrajo con diclorometano (5 x 5 ml). La capa orgánica combinada se lavó con salmuera (5 ml), se secó sobre sulfato de sodio y se evaporó al vacío. El material bruto se purificó por TLC preparativa (diclorometano: Metanol 95:5) para dar el compuesto del título en forma de un sólido de color blanco en 58% de rendimiento, 10 mg.
$^{+1}$H RMN (400 MHz, DMSO-*d6*) δ: 1,13-1,15 (m, 2H), 1,27-1,29 (m, 2H), 3,66 (d, 2H), 3,87 (s, 2H), 5,00 (t, 1H), 7,56 (d, 2H), 7,82 (d, 2H), 8,22 (s, 1H), 8,45 (s, 1H), 8,74 (s, 1H), 8,96 (s, 1H), 9,00 (s, 1H), 9,44 (s, 1H), 10,73 (s, 1H); LCMS (sistema 10): T_r = 2,57 min; m/z 453 $[M+H]^+$.

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 522 partiendo de (5-amino-piridin-3-il)-(7-(3-metil-oxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 251) y los ácidos apropiados.

Ejemplo	Nombre	Datos
523	2-(5-cloro-piridin-2-il)-N-{5-[7-(1-hidroximetil-ciclopropil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-acetamida	LCMS (sistema 10): T_r = 2,53 min; m/z 463 $[M+H]^+$
524	N-{5-[7-(1-hidroximetil-ciclopropil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-trifluorometil-fenil)-acetamida:	LCMS (sistema 10): T_r = 2,89 min; m/z 496 $[M+H]^+$.
525	N-{5-[7-(1-hidroximetil-ciclopropil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(3-trifluorometil-pirazol-1-il)-acetamida	LCMS (sistema 9): T_r = 2,71 min; m/z 486 $[M+H]^+$.

Ejemplo 526: 1-(3-ciclopropil-1'-metil-1'H-[1,4']bipirazolil-5-il)-3-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-urea



Se agregó cloroformiato de fenilo (0,03 ml, 0,24 mmoles) lentamente a una solución de 3-ciclopropil-1'-metil-1'H-[1,4']bipirazolil-5-ilamina (preparación 297, 40 mg, 0,19 mmoles) y piridina (0,03 ml) en THF (2 ml) a 0ºC y la mezcla se agitó a temperatura ambiente durante 4 horas. Una solución de (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación **95,** 55,4 mg, 0,19 mmoles) en DMF (1 ml) a continuación se agregó y la mezcla de reacción se calentó a 100ºC durante 16 horas. La mezcla se enfrió y se diluyó con acetato de etilo (15 ml), y se lavó con solución de $NaHCO_3$ acuoso saturado (2 x 10 ml), agua (10 ml), salmuera (10 ml), se secó sobre sulfato de sodio y se evaporó hasta sequedad al vacío. El material bruto se purificó sobre placa de TLC preparativa (eluyendo con 5% de metanol en DCM) para dar el compuesto del título en forma de un sólido blancuzco en 15% de rendimiento, 15 mg. ^{1}H RMN (400 MHz, DMSO-d6) δ: 0,64-0,65 (m, 2H), 0,85-0,88 (m, 2H), 1,56 (d, 6H), 1,82-1,85 (m, 1H), 3,89 (s, 3H), 5,09-5,12 (m, 1H), 6,10 (s, 1H), 7,66 (s, 1H), 8,05 (s, 1H), 8,36 (s, 1H), 8,52 (s, 1H), 8,61 (br s, 1H), 8,65 (s, 1H), 8,78 (s, 1H), 8,99 (s, 1H), 9,45 (s, 2H); LCMS (sistema 10): T_r = 2,75 min; m/z 511 $[M+H]^+$.

Ejemplo 527: 1-(3-ter-butil-1'-metil-1'H-[1,4']bipirazolil-5-il)-3-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-urea

El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 526, utilizando (5-amino-piridin-3-il)(7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación 95) y 3-ter-butil-1'-metil-1'H-[1,4']bipirazolil-5-ilamina (preparación 296) para dar el compuesto del título en forma de un sólido de color amarillo en 35% de rendimiento, 17 mg. LCMS (sistema 10): T_r = 3,01 min; m/z 527 $[M+H]^+$.

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 1, partiendo de (2-amino-7-*ter*-butil-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)(5-aminopiridin-3-il)metanona (preparación 65) y los ácidos apropiados.

Ejemplo	Nombre	Datos
528	N-[5-(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(1H-benzoimidazol-2-il)-acetamida	LCMS (sistema 10): T_r = 2,79 min; m/z 469 $[M+H]^+$.
529	N-[5-(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(5-bromo-piridin-2-il)-acetamida	LCMS (sistema 10): T_r = 2,94 min; m/z 508 $[M+H]^+$
530	N-[5-(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(5-ciano-piridin-2-il)-acetamida	LCMS (sistema 10): T_r = 2,78 min; m/z 455 $[M+H]^+$ (el ácido se puede preparar por cianación de un derivado de bromo apropiado).

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 522 utilizando (5-amino-piridin-3-il)-{7-[(S)-1-metil-2-(tetrahidro-piran-2-iloxi)-etil]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona (preparación 33) y el ácido apropiado.

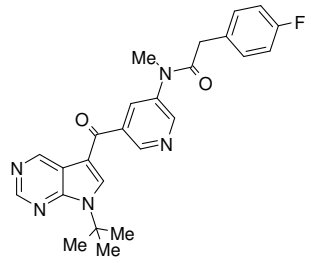
Ejemplo	Nombre	Datos
531	2-(4-difluorometoxi-fenil)-N-{5-[7-((S)-2-hidroxi-1-metil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-acetamida	LCMS (sistema 9): T_r = 2,80 min; m/z 482 $[M+H]^+$
532	N-{5-[7-((S)-2-hidroxi-1-metil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-indazol-2-il-acetamida	LCMS (sistema 9): T_r = 2,58 min; m/z 456 $[M+H]^+$
533	2-(1H-benzoimidazol-2-il)-N-{5-[7-((S)-2-hidroxi-1-metil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-acetamida	LCMS (sistema 10): T_r = 2,42 min; m/z 456 $[M+H]^+$.
534	N-{5-[7-((S)-2-hidroxi-1-metil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-trifluorometoxi-fenil)-acetamida	LCMS (sistema 9): T_r = 2,99 min; m/z 500 $[M+H]^+$
535	2-(3,4-difluoro-fenil)-N-{5-[7-((S)-2-hidroxi-1-metil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-acetamida	LCMS (sistema 9): T_r = 2,75 min; m/z 452 $[M+H]^+$

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para d]pirimidin-5-il]metanona (preparación 186) y el ácido apropiado.

Ejemplo	Nombre	Datos
536	2-(5-cloro-piridin-2-il)-N-{5-[7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-acetamida	LCMS (sistema 10): T_r = 2,92 min; m/z 479

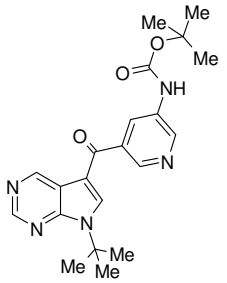
Ejemplo	Nombre	Datos
		$[M+H]^+$
537	2-(5-fluoro-piridin-2-il)-N-{5-[7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-acetamida	LCMS (sistema 10): T_r = 2,79 min; m/z 463 $[M+H]^+$.
538	2-(3-ciclopropil-pirazol-1-il)-N-{5-[7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-acetamida	LCMS (sistema 10): T_r = 2,89 min; m/z 474 $[M+H]^+$.
539	2-(4-fluoro-fenil)-N-{5-[7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-acetamida	LCMS (sistema 10): T_r = 3,03 min; m/z 462 $[M+H]^+$.

Ejemplo 540: N-[5-(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(4-fluoro-fenil)-N-metil-acetamida



A una solución agitada de N-[5-(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(4-fluoro-fenil)-acetamida (ejemplo **546,** 115 mg, 0,27 mmoles) en THF anhidro (4,5 ml), se agregó NaH (60% en aceite de parafina, 10,7 mg, 0,27 mmoles) a 0ºC en nitrógeno y la mezcla resultante se agitó durante 10 min. A continuación se agregó MeI (0,017 ml, 0,27 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 1 hora. Se agregó cloruro de amonio acuoso saturado (5 ml), y la mezcla se extrajo con acetato de etilo (2 x 10 ml). La fase orgánica se lavó con agua (10 ml), salmuera (10 ml), se secó sobre sulfato de sodio y se evaporó hasta sequedad al vacío. El material bruto se purificó por TLC preparativa (eluyendo con 5% de metanol en DCM) para dar el compuesto del título en forma de un sólido blancuzco en 46% de rendimiento, 55 mg. ^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,79 (s, 9H), 3,28 (s, 3H), 3,58 (br, 2H), 7,08-7,20 (m, 4H), 8,20 (s, 1H), 8,32 (s, 1H), 8,83 (s, 1H), 8,97 (br, 1H), 9,01 (s, 1H), 9,50 (s, 1H); LCMS (sistema 10): T_r = 3,08 min; m/z 446 $[M+H]^+$.

Ejemplo 541: Ter-butil éster del ácido [5-(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-carbámico

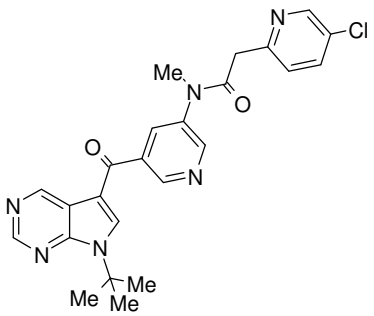


A una solución agitada de (5-amino-piridin-3-il)-(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 31) (200 mg, 0,68 mmoles) en DCM (4 ml) se agregó boc-anhídrido (0,155 ml, 0,68 mmoles) y base de Hunig (0,24 ml, 1,36 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. Se diluyó con DCM (15 ml) y se lavó con agua (2 x 10 ml), salmuera (10 ml), se secó sobre sulfato de sodio y se evaporó hasta sequedad al vacío El material bruto se purificó por cromatografía de columna sobre gel de sílice (metanol:DCM 2,98) para dar el compuesto del título en forma de una goma de color marrón claro en 41% de rendimiento. LCMS (sistema 10): T_r = 3,16 min; m/z 396 $[M+H]^+$.

Ejemplo 542: Ter-butil éster del ácido [5-(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-metil-carbámico

El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 540 utilizando ter-butil éster del ácido [5-(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-carbámico (ejemplo 541) para dar el compuesto del título en forma de un sólido de color amarillo en 79% de rendimiento, 90 mg. LCMS (sistema 10): T_r = 3,83 min; m/z 410 $[M+H]^+$.

Ejemplo 543: N-[5-(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(5-cloro-piridin-2-il)-N-metil-acetamida



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 1, utilizando (7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)-(5-metilamino-piridin-3-il)-metanona (preparación 187) y ácido (5-cloro-piridin-2-il)-acético (véase preparación 90) para dar el compuesto del título en forma de un sólido

blancuzco en 21% de rendimiento, 25 mg. ^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,78 (s, 9H), 3,32 (s, 3H), 3,77 (brs, 2H), 7,26 (br, 1H), 7,83 (br, 1H), 8,21 (s, 1H), 8,32 (s, 1H), 8,48 (s, 1H), 8,85 (s, 1H), 8,97 (s, 1H), 9,02 (s, 1H), 9,51 (s, 1H); LCMS (sistema 10): T_r = 3,29 min; m/z 463,2 $[M+H]^+$.

Ejemplo 544: N-[5-(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(4-cloro-fenil)-N-metil-acetamida

El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 1, utilizando (7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)-(5-metilamino-piridin-3-il)-metanona (preparación 187) y ácido 4-cloro fenil acético para dar el compuesto del título en forma de un sólido blancuzco en 45% de rendimiento, 21 mg.

LCMS (sistema 10): T_r = 3,28 min; m/z 462 $[M+H]^+$.

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 1, partiendo de (5-aminopiridin-3-il)(7-ter-butil-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 31) y los ácidos apropiados.

Ejemplo	Nombre	Datos
545	N-[5-(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(4-cloro-fenil)-acetamida	LCMS (sistema 10): T_r = 3,18 min; m/z 448 $[M+H]^+$.
546	N-[5-(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(4-fluoro-fenil)-acetamida	LCMS (sistema 10): T_r = 3,08 min; m/z 432 $[M+H]^+$.

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 1, a 50ºC, partiendo de [2-amino-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-il]-(5-amino-piridin-3-il)-metanona (preparación 261) y el ácido apropiado.

Ejemplo	Nombre	Datos
547	N-{5-[2-amino-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(5-cloro-piridin-2-il)-acetamida	LCMS (sistema 10): T_r = 2,85 min; m/z 494 $[M+H]^+$. (ácido: Prep 90)
548	N-{5-[2-amino-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(5-fluoro-piridin-2-il)-acetamida	LCMS (sistema 10): T_r = 2,77 min; m/z 478 $[M+H]^+$. (ácido a partir de Prep 92)
549	N-{5-[2-amino-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-	LCMS (sistema 10): T_r = 3,02 min; m/z 517

Ejemplo	Nombre	Datos
	(3-trifluorometil-pirazol-1-il)-acetamida	$[M+H]^+$. (ácido a partir de Prep 85)
550	N-{5-[2-amino-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-trifluorometil-[1,2,3]triazol-1-il)-acetamida	LCMS (sistema 10): T_r = 2,93 min; m/z 518 $[M+H]^+$. (ácido a partir de Prep 81)
551	N-{5-[2-amino-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-trifluorometil-pirazol-1-il)-acetamida	LCMS (sistema 10): T_r = 3,01 min; m/z 517 $[M+H]^+$. (ácido a partir de Prep 85)
552	N-{5-[2-amino-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-ciclopropil-[1,2,3]triazol-1-il)-acetamida	LCMS (sistema 10): T_r = 2,69 min; m/z 490 $[M+H]^+$. (ácido a partir de Prep 83)

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 522 utilizando (5-amino-piridin-3-il)-{7-[(S)-1-metil-2-(tetrahidro-piran-2-iloxi)-etil]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona (preparación 49) y el ácido apropiado.

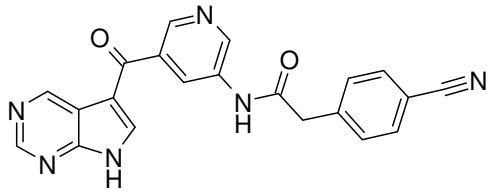
Ejemplo	Nombre	Datos
553	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-indazol-2-il-acetamida	LCMS (sistema 10): T_r = 2,67 min; m/z 485 $[M+H]^+$.
554	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-oxo-4H-quinazolin-3-il)-acetamida	LCMS (sistema 10): T_r = 2,52 min; m/z 513 $[M+H]^+$.
555	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(3,5-difluoro-piridin-2-il)-acetamida	LCMS (sistema 9): T_r = 2,07 min; m/z 482 $[M+H]^+$. (ácido a partir de Prep 265)
556	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(5-metil-piridin-2-il)-acetamida	LCMS (sistema 9): T_r = 1,36 min; m/z 460 $[M+H]^+$. (ácido a partir de Prep 274)
557	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-{4-[metil(metilsulfonil)amino]fenil}acetamida;	LCMS (sistema 9): T_r = 2,19 min; m/z 552 $[M+H]^+$. (ácido a partir de Prep 271)
558	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(1H-benzoimidazol-2-il)-acetamida	LCMS (sistema 9): T_r = 1,42 min; m/z 485 $[M+H]^+$.
559	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(2-oxo-5-trifluorometil-2H-piridin-1-il)-acetamida	LCMS (sistema 9): T_r = 2,18 min; m/z 530 $[M+H]^+$.

Ejemplo	Nombre	Datos
560	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(5-cloro-3-fluoro-piridin-2-il)-acetamida	LCMS (sistema 9): T_r = 2,23 min; m/z 498 $[M+H]^+$.
561	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(5-etoxi-piridin-2-il)-acetamida	LCMS (sistema 10): Tr = 2,64 min; m/z 490 $[M+H]^+$ (el ácido se puede preparar a partir del bromuro apropiado utilizando el método del documento WO2011/114271)
562	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(5-trifluorometil-piridin-2-il)-acetamida	LCMS (sistema 9): T_r = 2,40 min; m/z 514 $[M+H]^+$.
563	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-trifluorometil-pirazol-1-il)-acetamida	LCMS (sistema 9): T_r = 2,39 min; m/z 503 $[M+H]^+$. (ácido a partir de Prep 85)
564	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-metanosulfonilamino-fenil)-acetamida	LCMS (sistema 9) Tr = 4,47 min; (12 min. corrida); m/z 538 $[M+H]^+$

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para los ejemplos 73-87 utilizando (5-amino-piridin-3-il)-{7-[(S)-1-metil-2-(tetrahidro-piran-2-iloxi)-etil]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona (preparación 49) y el ácido apropiado.

Ejemplo	Nombre	Datos
565	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-difluorometoxi-fenil)-acetamida	LCMS (sistema 9): T_r = 2,56 min; m/z 511 $[M+H]^+$.
567	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-trifluorometoxi-fenil)-acetamida	LCMS (sistema 9): T_r = 2,74 min; m/z 529 $[M+H]^+$.
568	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(3,4-difluoro-fenil)-acetamida	LCMS (sistema 9): T_r = 2,50 min; m/z 481 $[M+H]^+$.
569	N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(5-cloro-pirimidin-2-il)-acetamida	LCMS (sistema 10): T_r = 2,35 min; m/z 481 $[M+H]^+$ (el ácido se puede preparar por oxidación del aldehído apropiado WO04110453).

Ejemplo 570: 2-(4-cianofenil)-N-[5-(7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il]-acetamida

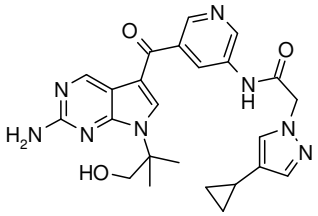


El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 343 utilizando 2-(4-ciano-fenil)-N-{5-[7-(2-trimetilsilanil-etoximetil)-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]-piridin-3-il}-acetamida (preparación 277) para dar el compuesto del título en forma de un sólido de color blanco 99% de rendimiento, ^{1}H NMR (400 MHz, DMSO-d_6) δ:. 3,87 (s, 2H), 7,55 (d, 2H), 7,81 (d, 2H), 8,36 (s, 1H), 8,47 (s, 1H), 8,72 (s, 1H), 8,97 (m, 2H), 9,47 (s, 1H), 10,66 (s, 1H), 13,14 (s, 1H); LCMS (sistema 10): T_r = 2,48 min; m/z 383 $[M+H]^+$.

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 1 partiendo de (5-amino-piridin-3-il)-(7-(3-metil-oxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 222) y el ácido apropiado.

Ejemplo	Nombre	Datos
571	N-{5-[7-(3-metil-oxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-trifluorometil-fenil)-acetamida:	LCMS (sistema 10): T_r = 3,02 min; m/z 496 $[M+H]^+$
572	N-{5-[7-(3-metil-oxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(3-trifluorometil-fenil)-acetamida:	LCMS (sistema 10): T_r = 2,98 min; m/z 496 $[M+H]^+$.
573	2-(3-fluoro-4-trifluorometil-fenil)-N-{5-[7-(3-metil-oxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-acetamida	LCMS (sistema 10): T_r = 3,01 min; m/z 514 $[M+H]^+$.
574	N-{5-[7-(3-metil-oxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-3-trifluorometil-acetamida:	LCMS (sistema 10): T_r = 3,00 min; m/z 482 $[M+H]^+$.
575	N-{5-[7-(3-metil-oxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-3-trifluorometoxi-benzamida:	LCMS (sistema 10): T_r = 3,05 min; m/z 498 $[M+H]^+$

Ejemplo 576: N-{5-[2-amino-7-(2-hidroxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}-2-(4-ciclopropil-pirazol-1-il)-acetamida



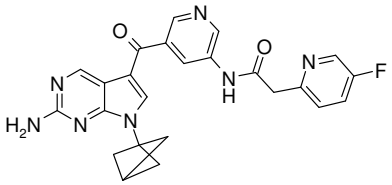
El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 1 utilizando {2-amino-7-[1,1-dimetil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}(5-amino-piridin-3-il)metanona (preparación 49) y ácido (4-ciclopropil-pirazol-1-il)-acético para dar el compuesto del título en forma de un sólido de color blanco en 72 % de rendimiento, 16,5 mg.

LCMS (sistema 10): T_r = 2,62 min; m/z 475 $[M+H]^+$.

Ejemplo 577: N-[5-(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(4-ciclopropil-pirazol-1-il)-acetamida

El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 1, utilizando ((2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)-(5-amino-piridin-3-il)-metanona (véase preparación 65) y el ácido 4-ciclopropil-pirazol-1-il)-acético para dar el compuesto del título en forma de un sólido color amarillo pálido en 16 % de rendimiento, 12 mg. LCMS (sistema 10): T_r = 2,80 min; m/z 459 $[M+H]^+$.

Ejemplo 578: N-[5-(2-amino-7-biciclo[1,1,1]pent-1-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(5-fluoro-piridin-2-il)-acetamida



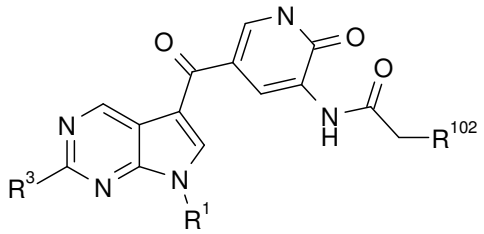
A una solución de (5-amino-piridin-3-il)-[7-biciclo[1,1,1]pent-1-il-2-(4-metoxi-bencilamino)-7H-pirrolo[2,3-d]pirimidin-5-il]-metanona (preparación 287) (50 mg **,** 0,11 mmoles) en THF (5 ml) a temperatura ambiente se agregó ácido 5-fluoro piridin-2-il acético (27 mg, 0,17 mmoles), TEA (0,08 ml, 0,56 mmoles) y anhídrido cíclico del ácido 1-propilfosfónico (50% de solución en EtOAc, 0,20 ml, 0,34 mmoles). La mezcla resultante se agitó antes durante 18 horas. La mezcla se concentró bajo presión reducida y el residuo se dividió entre bicarbonato de sodio acuoso saturado (10 ml) y acetato de etilo (25 ml). La fase orgánica se secó sobre sulfato de sodio, y se

concentró a presión reducida. Se agregó TFA (1,5 ml) y la mezcla resultante se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró bajo presión reducida y el residuo se dividió entre bicarbonato de sodio acuoso saturado (10 ml) y acetato de etilo (30 ml). La fase orgánica se secó sobre sulfato de sodio, se concentró a presión reducida, se purificó por TLC preparativa (MeOH:DCM 5: 95) para dar el compuesto del título en forma de un sólido blancuzco en 31% de rendimiento, 16 mg. ^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 2,32 (s, 6H), 2,66 (s, 1H), 3,94 (s, 2H), 6,57 (s, 2H), 7,49 (m, 1H), 7,69-7,73 (m, 2H), 8,38 (s, 1H), 8,50 (d, 1H), 8,65 (d, 1H), 8,92 (s, 1H), 8,96 (d, 1H), 10,67 (s, 1H); LCMS (sistema 10): T_r = 2,85 min; m/z 458 $[M+H]^+$.

Los siguientes ejemplos se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 578 partiendo de (5-amino-piridin-3-il)-[7-biciclo[1,1,1]pent-1-il-2-(4-metoxi-bencilamino)-7H-pirrolo[2,3-d]pirimidin-5-il]-metanona (preparación 287) y el ácido apropiado.

Ejemplo	Nombre	Datos
579	N-[5-(2-amino-7-biciclo[1,1,1]pent-1-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(3-metanosulfonil-fenil)-acetamida	LCMS (sistema 10): T_r = 2,87 min; m/z 517 $[M+H]^+$.
580	N-[5-(2-amino-7-biciclo[1,1,1]pent-1-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(3-trifluorometil-pirazol-1-il)-acetamida	LCMS (sistema 10): T_r = 2,92 min; m/z 497 $[M+H]^+$.
581	N-[5-(2-amino-7-biciclo[1,1,1]pent-1-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(4-trifluorometil-[1,2,3]triazol-1-il)-acetamida	LCMS (sistema 10): T_r = 2,89 min; m/z 498 $[M+H]^+$. (ácido: Prep 81)
582	N-[5-(2-amino-7-biciclo[1,1,1]pent-1-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(4-ciano-fenil)-acetamida	LCMS (sistema 10): T_r = 2,94 min; m/z 464 $[M+H]^+$.
583	N-[5-(2-amino-7-biciclo[1,1,1]pent-1-il-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-(5-cloro-piridin-2-il)-acetamida	LCMS (sistema 9): T_r = 6,28 min; m/z 474 $[M+H]^+$. (ácido a partir de Prep 90)

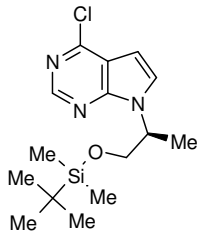
Los ejemplos 584-5923 ilustran los compuestos de la fórmula general:



que están dentro de la fórmula general (I) en virtud del tautomerismo de piridona.

Ejemplo	Nombre	Datos
584	2-(4-cianofenoxi)-N-(2-oxo-5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}-1,2-dihidropiridin-3-il)acetamida	LCMS Tr = 5,25 min; m/z 441 $[M+H]^+$.
585	N-(2-oxo-5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}-1,2-dihidropiridin-3-il)-2-[2-(trifluorometoxi)fenoxi]acetamida	LCMS Tr = 4,04 min; m/z 516 $[M+H]^+$.
586	2-(2-ciclopropil-1,3-oxazol-4-il)-N-(2-oxo-5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}-1,2-dihidropiridin-3-il)acetamida	LCMS Tr = 3,39 min; m/z 447 $[M+H]^+$.
587	2-[5-metil-3-(trifluorometil)-1H-pirazol-1-il]-N-(2-oxo-5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}-1,2-dihidropiridin-3-il)acetamida	LCMS Tr = 3,51 min; m/z 488 $[M+H]^+$.
588	N-(2-oxo-5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}-1,2-dihidropiridin-3-il)-2-[quinolin-7-il)acetamida	LCMS Tr = 3,51 min; m/z 485 $[M+H]^+$.
589	2-(4-clorofenoxi)-N-(2-oxo-5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}-1,2-dihidropiridin-3-il)acetamida	LCMS Tr = 3,82 min; m/z 450 $[M+H]^+$.
590	2-(5-cloropiridin-2-il)-N-(2-oxo-5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}-1,2-dihidropiridin-3-il)acetamida	LCMS Tr = 3,22 min; m/z 451 $[M+H]^+$.
591	N-(2-oxo-5-{[7-(propan-2-il)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}-1,2-dihidropiridin-3-il)-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida	LCMS Tr = 3,31 min; m/z 475 $[M+H]^+$.
592	N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}-2-oxo-piridin-3-il)-2-(5-cloropiridin-2-il))acetamida	
593	N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)-2-oxo-piridin-3-il]-2-[4-(trifluorometil)fenil]acetamida;	m/z 500, RT 4,94

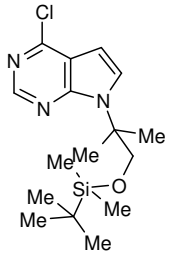
Preparación 1: 7-[(1S)-2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-4-cloro-7H-pirrolo[2,3-d]pirimidina



Se agregó (S)-2-*ter*-butildimetilsililoxi-1-metiletilamina (120 g, 636 mmoles) a (4,6-dicloropirimidin-5-il)acetaldehído (52,8 g, 276 mmoles) in etanol (500 ml). La mezcla se calentó a reflujó durante 45 minutos. La mezcla de reacción se evaporó al vacío, a continuación el residuo se diluyó con agua (400 ml) y se extrajo con acetato de etilo (600 ml). El extracto orgánico se evaporó al vacío y el material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de pentano:EtOAc 90:10 a 80:20) para dar el compuesto del título en forma de un líquido de color amarillo en 67% de rendimiento, 60,4 g.

^{1}H RMN (400 MHz, CDCl3) δ*:* -0,92 (s, 6H), 0,80 (s, 9H), 1,58 (d, 3H), 3,86 (m, 2H), 5,04 (m, 1H), 6,59 (d, 1H), 7,40 (d, 1H), 8,60 (s, 1H).

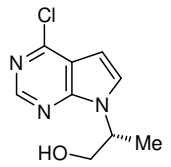
Preparación 2: 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil]-4-cloro-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 1 utilizando (4,6-dicloropirimidin-5-il)acetaldehído y 1-{[*ter*-butil(dimetil)silil]oxi}-2-metilpropan-2-amina para dar el compuesto del título en forma de un aceite de color amarillo en 38% de rendimiento, 377 mg.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 0,00 (s, 6H), 0,94 (s, 9H), 1,97 (s, 6H), 4,28 (s, 2H), 6,78 (d, 1H), 7,66 (d, 1H), 8,83 (s, 1H).

Preparación 3: (2R)-2-(4-cloro-7H-pirrolo[2,3-d]pirimidin-7-il)propan-1-ol

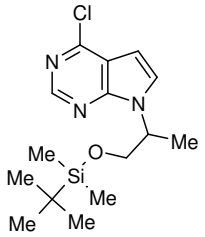


El compuesto del título se preparó de acuerdo con el método que se describió

anteriormente para la preparación 1 utilizando (4,6-dicloropirimidin-5-il)acetaldehído y (R)-2-amino-1-propanol para dar el compuesto del título en forma de un aceite de color amarillo en 100% de rendimiento, 11,12 g.

LCMS (sistema 2): T_r = 0,89 min; m/z 212 $[M+H]^+$.

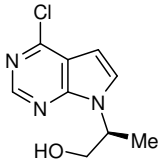
Preparación DL3: (R,S)-7-[2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-4-cloro-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 1 utilizando (4,6-dicloropirimidin-5-il)acetaldehído y 2-*ter*-butildimetilsililoxi-1-metiletilamina para dar el compuesto del título en forma de un aceite de color naranja en 77% de rendimiento, 4,08 g.

^{1}H RMN (400 MHz, CDCl3) δ*: -0,90* (s, 6H), 0,82 (s, 9H), 1,58 (d, 3H), 3,84 (m, 2H), 5,05 (m, 1H), 6,59 (d, 1H), 7,42 (d, 1H), 8,60 (s, 1H).

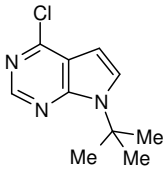
Preparación 4: (2S)-2-(4-cloro-7H-pirrolo[2,3-d]pirimidin-7-il)propan-1-ol



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 1 utilizando (4,6-dicloropirimidin-5-il)acetaldehído y (S)-2-amino-1-propanol para dar el compuesto del título en forma de un aceite de color crema en 98% de rendimiento, 10,9 g.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,42 (d, 3H), 3,72 (m, 2H), 4,89 (m, 1H), 6,63 (d, 1H), 7,83 (d, 1H), 8,59 (s, 1H).

Preparación 5: 7-*ter*-butil-4-cloro-7H-pirrolo[2,3-d]pirimidina

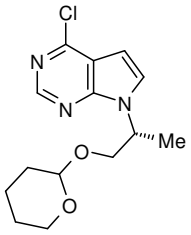


El compuesto del título se preparó de acuerdo con el método que se describió

anteriormente para la preparación 1 utilizando (4,6-dicloropirimidin-5-il)acetaldehído y *ter*-butilamina para dar el compuesto del título en forma de un líquido de color amarillo en 77% de rendimiento, 1,61 g.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,75 (s, 9H), 6,60 (d, 1H), 7,79 (d, 1H), 8,63 (s, 1H).

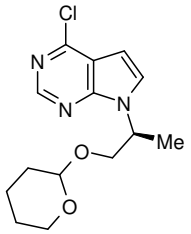
Preparación 6: 4-cloro-7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina



Se agregó 2,3-dihidropiran (25,0 ml, 270 mmoles) a (2R)-2-(4-cloro-7H-pirrolo[2,3-d]pirimidin-7-il)propan-1-ol (11,00 g, 51,97 mmoles) (véase preparación 3) y tolueno-4-sulfonato de piridinio (3,92 g, 15,6 mmoles) en DCM (150 ml). La mezcla de reacción se lavó con agua (200 ml) y la fase acuosa se extrajo con DCM (2 x 150 ml). Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de heptano:EtOAc 100:0 a 70:30) para dar el compuesto del título en forma de un aceite color amarillo en 100% de rendimiento, 15,65 g.

LCMS (sistema 2): T_r = 1,30 min; m/z 296 $[M+H]^+$.

Preparación 7: 4-cloro-7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina

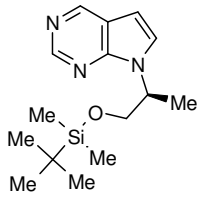


El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 6, utilizando (2S)-2-(4-cloro--7H-pirrolo[2,3-*d*]pirimidin-7-il)propan-1-ol (véase preparación 4) para dar el compuesto del título en forma de un aceite de color amarillo en 87% de rendimiento, 11,5 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,43-1,71 (m, 9H), 3,42 (m, 1H), 3,57 (m, 1H), 3,69 (m, 1H), 4,00 (m, 1H), 4,52 (m, 1H), 5,19 (m, 1H), 6,60 (d, 1H), 7,44 (d, 1H), 8,61 (s, 1H).

Preparación 8: 7-[(1S)-2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]--7H-pirrolo[2,3-

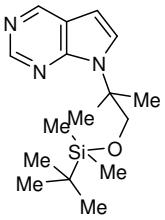
d]pirimidina



Se agregó paladio (10% sobre carbono, 18 g) a 7-[(1S)-2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-4-cloro-7H-pirrolo[2,3-d]pirimidina (182 g, 558 mmoles) (véase preparación 1) en etanol (900 ml) y solución de amoníaco concentrado (100 ml) y se hidrogenó (60 psi, 20ºC) durante 18 horas. La mezcla de reacción se filtró a través de Arbocel™ y el filtrado se evaporó al vacío. Se agregó éter dietílico (300 ml) al residuo y la mezcla se filtró. El filtrado se evaporó al vacío para dar el compuesto del título en forma de un aceite de color naranja en 94% de rendimiento, 162,7 g.

^{1}H RMN (400 MHz, CDCl3) δ*:* -0,90 (s, 3H), 0,80 (s, 9H), 1,58 (d, 3H), 3,86 (m, 2H), 5,06 (m, 1H), 6,53 (d, 1H), 7,40 (d, 1H), 8,83 (s, 1H), 8,96 (s, 1H).

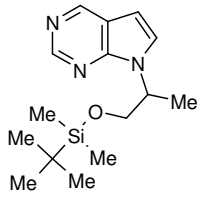
Preparación 9: 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil]-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 8 utilizando 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil]-4-cloro-7H-pirrolo[2,3-d]pirimidina (véase preparación 2) para dar el compuesto del título en forma de un sólido de color blanco en 97% de rendimiento, 327 mg.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 0,01 (s, 6H), 0,94 (s, 9H), 2,02 (s, 6H), 4,30 (s, 2H), 6,92 (d, 1H), 7,84 (d, 1H), 9,13 (s, 1H), 9,21 (s, 1H).

Preparación 10: (R,S)-7-[2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7H-pirrolo[2,3-d]pirimidina

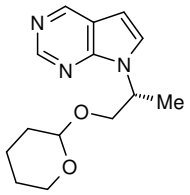


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 8 utilizando (R,S)-7-[2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-4-cloro-

7H-pirrolo[2,3-d]pirimidina (véase preparación DL3) para dar el compuesto del título en forma de un líquido de color marrón en 78% de rendimiento, 1,12 g.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 0,01 (s, 6H), 0,88 (s, 9H), 1,69 (d, 3H), 4,09 (m, 2H), 5,20 (m, 1H), 6,84 (d, 1H), 7,92 (d, 1H), 8,96 (s, 1H), 9,18 (s, 1H).

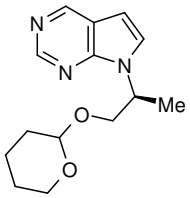
Preparación 11: 7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 8 utilizando 4-cloro-7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina (véase preparación 6) para dar el compuesto del título en forma de un aceite de color amarillo en 100% de rendimiento, 13,78 g.

LCMS (sistema 2): T_r = 0,73 min; m/z 262 $[M+H]^+$.

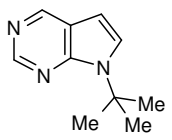
Preparación 12: 7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 8 utilizando 4-cloro-7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina (véase preparación 7) para dar el compuesto del título en forma de un aceite incoloro en 90% de rendimiento, 9,18 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,44-1,69 (m, 9H), 3,42 (m, 1H), 3,57 (m, 1H), 3,69 (m, 1H), 4,02 (m, 1H), 4,54 (m, 1H), 5,27 (m, 1H), 6,69 (d, 1H), 7,57 (d, 1H), 8,91 (s, 1H), 8,99 (s, 1H).

Preparación 13: 7-*ter*-butil-7H-pirrolo[2,3-d]pirimidina

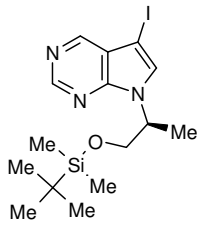


El compuesto del título se preparó de acuerdo con el método que se describe

para la preparación 8 utilizando 7-*ter*-butil-4-cloro-7H-pirrolo[2,3-d]pirimidina (véase preparación 5) para dar el compuesto del título en forma de un líquido de color amarillo en 94% de rendimiento, 1,27 g.

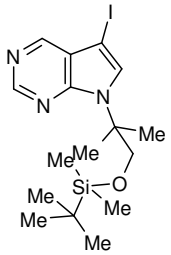
^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,75 (s, 9H), 6,57 (d, 1H), 7,66 (d, 1H), 8,78 (s, 1H), 8,98 (s, 1H).

Preparación 14: 7-[(1S)-2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-5-yodo-7H-pirrolo[2,3-d]pirimidina



Se agregó N-yodosuccinimida (124 g, 553 mmoles) a 7-[(1S)-2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7H-pirrolo[2,3-d]pirimidina (153,4 g, 526 mmoles) (véase preparación 8) en acetonitrilo (700 ml). La mezcla se agitó a temperatura ambiente durante 16 horas, a continuación se agregó tiosulfato de sodio acuoso saturado (700 ml). a mezcla se extrajo con EtOAc (800 ml) a continuación el extracto orgánico se secó sobre sulfato de magnesio y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de pentano:EtOAc 90:10 a 80:20) para dar el compuesto del título en forma de un sólido de color amarillo en 66% de rendimiento, 145 g. ^{1}H RMN (400 MHz, $CDCl_3$) δ*:* -0,90 (d, 6H) 0,80 (s, 9H) 1,58 (d, 3H) 3,84 (m, 2H) 5,07 (m, 1H) 7,48 (s, 1H) 8,73 (s, 1H) 8,86 (s, 1H).

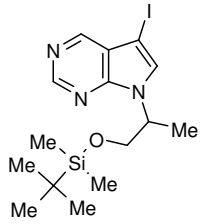
Preparación 15: 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil]-5-yodo-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 14 utilizando 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil]-7H-pirrolo[2,3-d]pirimidina (véase preparación 9) para dar el compuesto del título en forma de un aceite de color marrón en 59% de rendimiento, 270 mg.

^{1}H RMN(400 MHz, $CDCl_3$) δ*:* 0,01 (s, 6H), 0,92 (s, 9H), 2,00 (s, 6H), 4,20 (s, 2H), 7,95 (s, 1H), 9,02 (s, 1H), 9,16 (s, 1H).

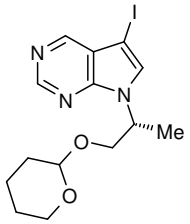
Preparación 16: (R,S)-7-(2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil)-5-yodo-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 14 utilizando (R,S)-7-[2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7H-pirrolo[2,3-d]pirimidina (véase preparación 10) para dar el compuesto del título en forma de un líquido de color amarillo en 74% de rendimiento, 1,18 g.

LCMS (sistema 1): T_r = 4,03 min; m/z 418 $[M+H]^+$.

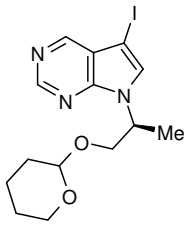
Preparación 17: 5-yodo-7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 14 utilizando 7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina (véase preparación 11) para dar el compuesto del título en forma de un aceite de color marrón en 34% de rendimiento, 7,50 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,43-1,74 (m, 9H), 3,42 (m, 1H), 3,54 (m, 1H), 3,67 (m, 1H), 3,99 (m, 1H), 4,54 (m, 1H), 5,23 (m, 1H), 7,51 (s, 1H), 8,74 (s, 1H), 8,88 (s, 1H).

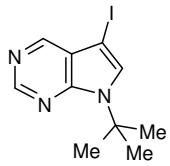
Preparación 18: 5-yodo-7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 14 utilizando 7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina (véase preparación 12) para dar el compuesto del título en forma de un aceite de color marrón en 71% de rendimiento, 9,68 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,44-1,65 (m, 9H), 3,45 (m, 1H), 3,56 (m, 1H), 3,67 (m, 1H), 3,99 (m, 1H), 4,54 (m, 1H), 5,24 (m, 1H), 7,51 (s, 1H), 8,76 (s, 1H), 8,89 (s, 1H).

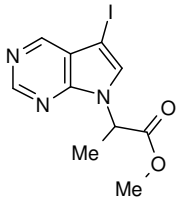
Preparación 19: 7-*ter*-butil-5-yodo-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 14 utilizando 7-*ter*-butil-7H-pirrolo[2,3-d]pirimidina (véase preparación 13) para dar el compuesto del título en forma de un sólido de color amarillo en 71% de rendimiento, 1,55 g.

LCMS (sistema 1): T_r = 3,12 min; m/z 302 $[M+H]^+$.

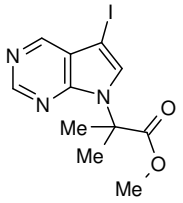
Preparación 20: (R,S) 2-(5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)propanoato de metilo



Se agregó metil-2-bromopropionato (6,83 ml, 61,2 mmoles) a una mezcla de 5-yodo-7H-pirrolo[2,3-d]pirimidina (15,0 g, 61,0 mmoles) y carbonato de cesio (35,9 g, 110,0 mmoles) en DMF (75 ml). La mezcla se agitó a temperatura ambiente durante 4 horas. La reacción se diluyó con agua (250 ml) y se extrajo con éter dietílico (100 ml). La capa orgánica se lavó con salmuera (70 ml), se secó sobre sulfato de sodio y se evaporó al vacío para dar el compuesto del título en forma de un sólido blancuzco en 83% de rendimiento, 16,87 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,82 (d, 3H), 3,76 (s, 3H), 5,72 (q, 1H), 7,48 (s, 1H), 8,76 (s, 1H), 8,89 (s, 1H).

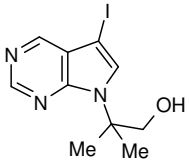
Preparación 21: 2-(5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropanoato de metilo



Se agregó t-butóxido de potasio (71,3 ml, 71,3 mmoles, 1,0 M en THF) a (R,S) 2-(5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)propanoato de metilo (16,9 g, 50,9 mmoles) (véase preparación 20) y yodometano (4,44 ml, 71,3 mmoles) en THF (100 ml). La mezcla se agitó a temperatura ambiente durante 15 minutos a continuación se agregaron agua (20 ml) y HCl acuoso (0,3 ml, 2M). Se eliminó THF por evaporación al vacío, a continuación el residuo acuoso se extrajo con EtOAc (250 ml). La fase orgánica se secó sobre sulfato de magnesio y se evaporó al vacío. El sólido bruto se purificó por cromatografía de columna sobre gel de sílice (80:20 pentano:EtOAc) para dar el compuesto del título en forma de sólido de color blanco en 51% de rendimiento, 8,92 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,93 (s, 6H), 3,68 (s, 3H), 7,43 (s, 1H), 8,75 (s, 1H), 8,85 (s, 1H).

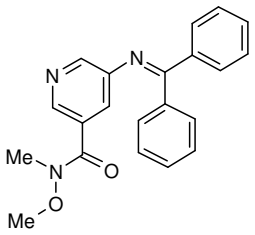
Preparación 22: 2-(5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropano-1-ol



Se agregó borohidruro de litio (32,3 ml, 64,6 mmoles, 2,0 M en THF) a 2-(5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropanoato de metilo (8,92 g, 25,9 mmoles (véase preparación 21) en etanol (70 ml). La mezcla se agitó a temperatura ambiente durante 17 horas, posteriormente se agregó agua (70 ml). La mezcla se evaporó al vacío posteriormente el residuo se separó entre DCM (250 ml) y agua (50 ml). La fase acuosa se extrajo con DCM:MeOH (90:10, 2 x 250 ml) y las fases orgánicas combinadas se secaron sobre sulfato de magnesio y se evaporaron al vacío para dar el compuesto del título en forma de un sólido blancuzco en 100% de rendimiento, 8,20 g.

^{1}H RMN (400 MHz, DMSO-d6) δ*:* 1,65 (s, 6H), 3,16 (d, 2H), 7,77 (s, 1H), 8,67 (s, 1H), 8,80 (s, 1H).

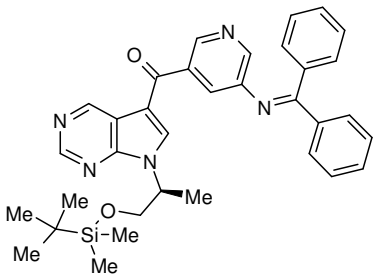
Preparación 23: 5-[(difenilmetileno)amino]-N-metoxi-N-metilnicotinamida



Se agregó benzofenona imina (205 ml, 1,22 moles) a 5-bromo-N-metoxi-N-metilisonicotinamida (250 g, 1,02 moles), tris(dibencilidenoacetona)dipaladio (28,0 g, 31,0 mmoles), 2-di-ter-butilfosfino-2′,4′,6′-triisopropilbifenilo (34,7 g, 82,0 mmoles) y tribásico fosfato de potasio recién molido (541 g, 2,55 moles) en 1,2-dimetoxietano (2500 ml). La mezcla se agitó a 50ºC durante 17 horas. La mezcla de reacción se filtró a través de Arbocel™ y e taco se lavó con EtOAc (500 ml). El filtrado se evaporó al vacío y el material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de heptano:EtOAc 70:30 a 0:100) para dar el compuesto del título en forma de una goma de color naranja en 51% de rendimiento, 180,0 g.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 3,19 (s, 3H), 3,37 (s, 3H), 7,18-7,23 (m, 2H), 7,29 (m, 1H), 7,32-7,39 (m, 3H), 7,46-7,53 (m, 2H), 7,57 (m, 1H), 7,67-7,73 (m, 2H), 8,09 (d, 1H), 8,27 (d, 1H).

Preparación 24: {7-[(1S)-2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}{5-[(difenilmetileno)amino]piridin-3-il}metanona

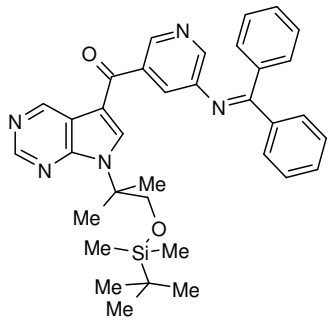


Se agregó cloruro de isopropil magnesio (68,8 ml, 138 mmoles, 2,0 M en THF) a 7-[(1S)-2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-5-yodo-7H-pirrolo[2,3-d]pirimidina (52,2 g, 125 mmoles) (véase preparación 14) en THF (400 ml) a 0ºC, en nitrógeno. La mezcla se agitó a 0ºC durante 1 hora, posteriormente se agregó gota a gota una solución de 5-[(difenilmetileno)amino]-N-metoxi-N-metilnicotinamida (47,5 g , 138 mmoles) (véase preparación 23) en THF (100 ml) a 0ºC. La mezcla se entibió hasta temperatura ambiente y se agitó a esta temperatura durante 16 horas. La mezcla de reacción se templó con 10% de cloruro de amonio acuoso (250 ml) y se extrajo con acetato de etilo (2 x 250 ml). Los extractos orgánicos combinados se lavaron con

salmuera (250 ml), se secaron sobre sulfato de sodio, se evaporaron al vacío y el material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de EtOAc:pentano 10:90 a 60:40) para dar el compuesto del título en forma de una goma incolora en 88% de rendimiento, 63,2 g.

T_r = 7,94 min; m/z 576 $[M+H]^+$.

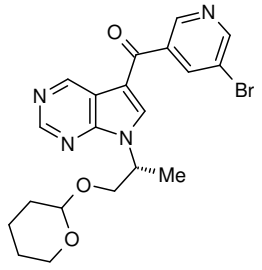
Preparación 25: [7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]{5-[(difenilmetileno)amino]piridin-3-il}metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 24 utilizando 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil]-5-cloro-7H-pirrolo[2,3-d]pirimidina (véase preparación 15) y 5-[(difenilmetileno)amino]-N-metoxi-N-metilnicotinamida (véase preparación 23) para dar el compuesto del título en forma de una goma incolora en 56% de rendimiento, 1,49 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 0,21 (s, 6H), 0,67 (s, 9H), 1,80 (s, 6H), 4,10 (s, 2H), 7,14 (d, 2H), 7,33 (m, 3H), 7,45 (m, 2H), 7,54 (m, 1H), 7,58 (t, 1H), 7,79 (d, 2H), 7,89 (s, 1H), 8,18 (d, 1H), 8,58 (d, 1H), 9,01 (s, 1H), 9,60 (s, 1H).

Preparación 26: (5-bromopiridin-3-il){7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona

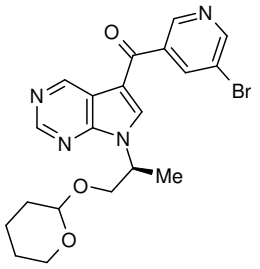


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 24 utilizando 5-cloro-7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina (véase preparación 17) y 5-bromo-N-metoxi-N-metilnicotinamida para dar el compuesto del título en forma de un aceite de color

marrón en 66% de rendimiento, 215 mg.

LCMS (sistema 2): T_r = 1,27 min; m/z 447 $[M+H]^+$.

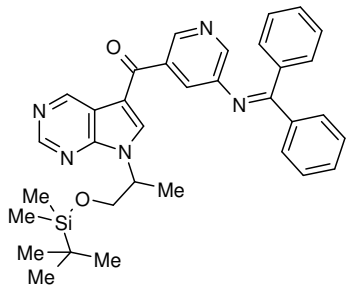
Preparación 27: (5-bromopiridin-3-il){7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 24 utilizando 5-cloro-7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidina (véase preparación 18) y 5-bromo-N-metoxi-N-metilnicotinamida para dar el compuesto del título en forma de un aceite incoloro en 32% de rendimiento, 181 mg.

LCMS (sistema 2): T_r = 1,27 min; m/z 447 $[M+H]^+$.

Preparación 28: (R,S) {7-[2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}{5-[(difenilmetileno)amino]piridin-3-il}metanona

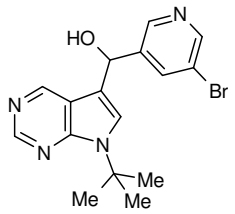


Se agregó n-butillitio (0,57 ml, 1,31 mmoles, 2,3 M en THF) a (R,S) 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil)-5-yodo-7H-pirrolo[2,3-d]pirimidina (500 mg, 1,19 mmoles) (véase preparación 16) en éter seco (20 ml) a 78ºC, y la mezcla de reacción se agitó durante 30 minutos. A continuación se agregó gota a gota a la misma temperatura 5-[(difenilmetileno)amino]-N-metoxi-N-metilnicotinamida (372 mg, 1,07 mmoles) (véase preparación 23) en éter seco (25 ml). Después de 15 minutos, la mezcla se templó con cloruro de amonio acuoso saturado (50 ml) y se extrajo con acetato de etilo (70 ml). El extracto orgánico se secó sobre sulfato de sodio, se evaporó al vacío y se purificó por cromatografía de columna sobre gel de sílice (gradiente de EtoAc 70: 30) para dar el compuesto en forma de un sólido blancuzco en

19% de rendimiento, 134 mg.

LCMS (sistema 4): T_r = 4,53 min; m/z 576 $[M+H]^+$.

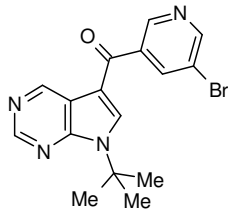
Preparación 29: (R,S) (5-bromopiridin-3-il)(7-*ter*-butil-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanol



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 28 utilizando 7-*ter*-butil-5-cloro-7H-pirrolo[2,3-d]pirimidina (véase preparación 19) y 5-bromo-piridin-3-carbaldehído para dar el compuesto del título en forma de un aceite incoloro en 37% de rendimiento, 486 mg.

LCMS (sistema 4): T_r = 2,94 min; m/z 362 $[M+H]^+$.

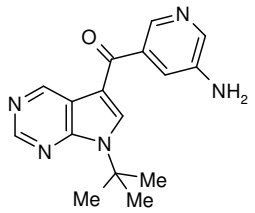
Preparación 30: (5-bromopiridin-3-il)(7-*ter*-butil-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona



Se agregó ácido 2-yodoxibenzoico (909 mg, 3,25 mmoles) a (R,S) (5-bromopiridin-3-il)(7-*ter*-butil-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanol (405 mg, 1,34 mmoles) (véase preparación 29) en acetato de etilo (30 ml) y la mezcla se reflujó durante 4 horas. La mezcla se filtró y el filtrado se evaporó al vacío para dar el compuesto del título en forma de un sólido de color blanco en 95% de rendimiento, 554 mg.

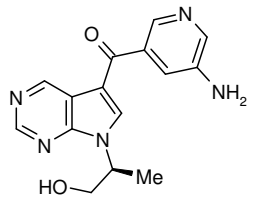
LCMS (sistema 4): T_r = 3,28 min; m/z 360 $[M+H]^+$.

Preparación 31: (5-aminopiridin-3-il)(7-*ter*-butil-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona



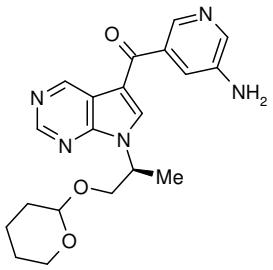
Se agregó pentahidrato sulfato de cobre (55 mg, 0,24 mmoles) a (5-bromopiridin-3-il)(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (292 mg, 0,81 mmoles) (véase preparación 30) y solución de amoníaco concentrado (20 ml). La mezcla se calentó en un recipiente cerrado a 140ºC durante 17 horas. La mezcla de reacción se evaporó al vacío y el residuo se agitó en ácido clorhídrico acuoso (10 ml, 2M) a temperatura ambiente durante 17 horas. La mezcla de reacción se basificó hasta pH 9 utilizando carbonato de sodio acuoso saturado a continuación se extrajo con DCM (3 x 20 ml). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio y se evaporaron al vacío para dar el compuesto del título en forma de un sólido de color blanco en 49% de rendimiento, 240 mg.
LCMS (sistema 4): T_r = 2,68 min; m/z 296 $[M+H]^+$.

Preparación 32: (5-aminopiridin-3-il)(7-[(1S)-2-hidroxi-1-metiletil]-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 31 utilizando (5-bromopiridin-3-il){7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (véase preparación 27) para dar el compuesto del título en forma de un sólido de color blanco en 10% de rendimiento, 134 mg.
LCMS (sistema 2): T_r = 0,59 min; m/z 298 $[M+H]^+$.

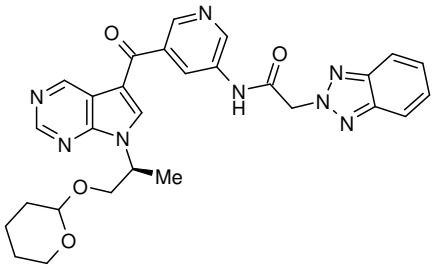
Preparación 33: (5-aminopiridin-3-il){7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona



Se agregó benzofenona imina (0,40 ml, 2,4 mmoles) a (5-bromopiridin-3-il){7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (891 mg, 2,0 mmoles) (véase preparación 27), tris(dibencilidenoacetona)dipaladio (55 mg, 0,06 mmoles), 2-di-ter-butilfosfino-2′,4′,6′-triisopropilfenilo (68 mg, 0,16 mmoles) y tribásico fosfato de potasio recién molido (1,06 g, 5,0 mmoles) en 1,2-dimetoxietano (4 ml). La mezcla se agitó a 50ºC durante 17 horas. La mezcla de reacción se diluyó con DCM (10 ml), se filtró a través de Arbocel™ y el taco se lavó con DCM (5 ml). l filtrado se evaporó al vacío y el material bruto se disolvió en THF (10 ml). Se agregó ácido cítrico acuoso (5 ml, 2M) y la mezcla se agitó a temperatura ambiente durante 16 horas. Se agregó agua (40 ml) posteriormente se agregó hidróxido de sodio para basificar la mezcla. La mezcla se extrajo con EtOAc (3 x 40 ml), y las fases orgánicas combinadas se secaron sobre sulfato de magnesio y se evaporaron al vacío. El residuo se purificó por cromatografía de columna sobre gel de sílice (gradiente de EtOAc:MeOH 100:0 a 80:20) para dar el compuesto del título en forma de un aceite color blanco en 70% de rendimiento, 506 mg.

LCMS (sistema 1): T_r = 3,27 min; m/z 382 $[M+H]^+$.

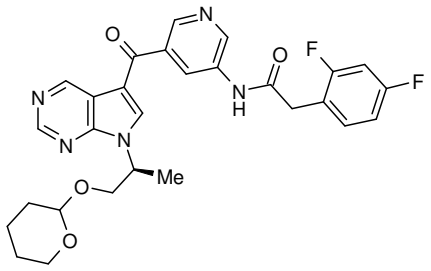
Preparación 34: 2-(2H-benzotriazol-2-il)-N-[5-({7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 1 utilizando (5-aminopiridin-3-il){7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (véase preparación 33) y ácido benzotriazol-2-il-acético para dar el compuesto del título en forma de un sólido de color amarillo en 72% de rendimiento, 70 mg.

LCMS (sistema 5): T_r = 2,98min; m/z 541 $[M+H]^+$.

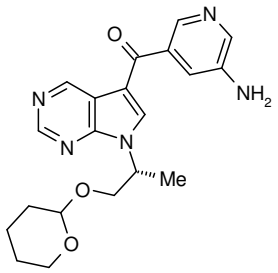
Preparación 35: 2-(2,4-difluorofenil)-N-[5-({7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 1 utilizando (5-aminopiridin-3-il){7-[(1S)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (véase preparación 33) y ácido 1,5-difluorofenilacético para dar el compuesto del título en forma de un sólido de color amarillo en 75% de rendimiento, 75 mg.

LCMS (sistema 5): T_r = 3,08min; m/z 536 $[M+H]^+$.

Preparación 36: (5-aminopiridin-3-il){7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona

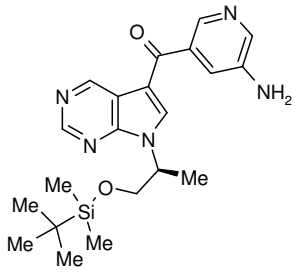


Se agregó óxido de cobre (I) (9,2 mg, 0,06 mmoles) a (5-bromopiridin-3-il){7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (285 mg, 0,64 mmoles) (véase preparación 26) y solución de amoníaco concentrado (2 ml) en 1-metil-2-pirrolidinona (0,5 ml). La mezcla se calentó en un recipiente cerrado a 80ºC durante 17 horas. Se agregaron acetato de etilo (5 ml) y agua (5 ml) a la mezcla de reacción y a continuación se filtró a través de un filtro de fibra de vidrio. La fase orgánica se secó sobre sulfato de magnesio y se evaporó al vacío. El sólido bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de EtOAc:MeOH :cNH3 100:0 a 95_5_0,5) para dar el compuesto del título en forma de un aceite incoloro en 70% de rendimiento, 171 mg.

LCMS (sistema 2): T_r = 0,78 min; m/z 382 $[M+H]^+$.

Preparación 37: (5-aminopiridin-3-il){7-[(1S)-2--{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-

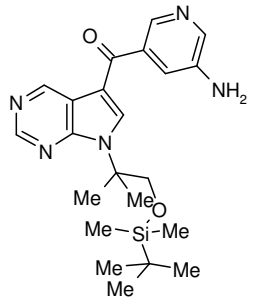
7*H*-pirrolo[2,3-*d*]pirimidin-5-il}metanona



Se agregó ácido cítrico acuoso (120 ml, 2,0 M) a {7-[(1S)-2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}{5-[(difenilmetileno)amino]piridin-3-il}metanona (63,2 g, 110 mmoles) (véase preparación 24) en THF (274 ml) y la mezcla se agitó a temperatura ambiente durante 17 horas. La mezcla se enfrió hasta 0ºC, se agregó agua (200 ml) y la mezcla se basificó utilizando hidróxido de sodio (28 g). La mezcla se extrajo con acetato de etilo (150 ml) posteriormente la fase acuosa se extrajo con acetato de etilo (2 x 200 ml). Las fases orgánicas se lavaron con salmuera (600 ml), se secaron sobre sulfato de sodio y se evaporaron al vacío para dar el compuesto del título en forma de un semisólido en rendimiento cuantitativo, 45,2 g.

LCMS (sistema 2): T_r = 1,16 min; m/z 412 $[M+H]^+$.

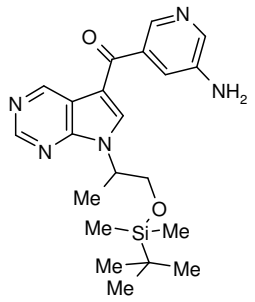
Preparación 38: (5-aminopiridin-3-il)[7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil)-7*H*-pirrolo[2,3-*d*]pirimidin-5-il]metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 37 utilizando [7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}{5-[(difenilmetileno)amino]piridin-3-il}metanona (véase preparación 25) para dar el compuesto del título en forma de un sólido de color blanco en 81% de rendimiento, 872 mg.

^{1}H RMN (400 MHz, DMSO-d6) δ*:* 0,22 (s, 6H), 0,63 (s, 9H), 1,66 (s, 6H), 4,12 (s, 2H), 5,65 (s, 2H), 7,27 (dd, 1H), 8,08 (s, 1H), 8,14-8,17 (m, 2H), 8,97 (s, 1H), 9,45 (s, 1H).

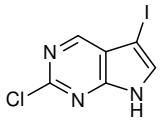
Preparación 39: (R,S) (5-aminopiridin-3-il){7-[2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7*H*-pirrolo[2,3-*d*]pirimidin-5-il}metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 37 utilizando (R,S) {7-[2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}{5-[(difenilmetileno)amino]piridin-3-il}metanona (véase preparación 28) para dar el compuesto del título en forma de un sólido de color blanco en 89% de rendimiento, 86 mg.

LCMS (sistema 4): T_r = 1,37 min; m/z 412 $[M+H]^+$.

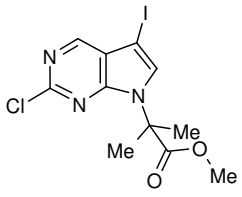
Preparación 40: 2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina



Se agregó N-yodosuccinimida (742 g, 3,30 moles) a 2-cloro-7H-pirrolo[2,3-d]pirimidina (482,5 g, 3,14 moles) en acetonitrilo (2500 ml) a 12ºC. La mezcla se agitó a temperatura ambiente durante1 hora a continuación se agregó metabisulfito de sodio (650 g en 4500 ml de agua). La mezcla se agitó durante 1 hora a continuación se filtró para dar el compuesto del título en forma de un sólido de color naranja en 82% de rendimiento, 716,2 g.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 7,83 (s, 1H), 8,63 (s, 1H), 12,73 (s, 1H).

Preparación 41: 2-(2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropanoato de metilo

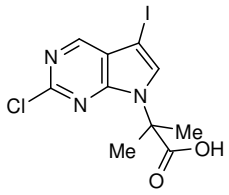


Se agregó 2-bromo-2-metilpropanoato de metilo (663 ml, 5,13 mmoles) a 2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina (358,1 g, 1,28 moles) (véase preparación 40),

yoduro de potasio (21,3 g, 128 mmoles) y carbonato de cesio (1,670 g, 5,13 moles) en DMF (7162 ml). La mezcla se calentó a 60ºC durante 19 horas. La mezcla de reacción se diluyó con agua (7000 ml) y se agitó a temperatura ambiente durante 42 horas. La mezcla se filtró y el sólido se lavó con agua (500 ml) para dar el compuesto del título en forma de un sólido de color beige en 92% de rendimiento, 445,8 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,89 (s, 6H), 3,65 (s, 3H), 7,39 (s, 1H), 8,56 (s, 1H).

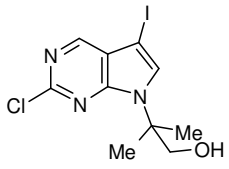
Preparación 42: Ácido 2-(2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropanoico



Se agregó monohidrato hidróxido de litio (4,08 g, 97,5 mmoles) a 2-(2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropanoato de metilo (18,5 g, 48,7 mmoles (véase preparación 41) en THF (185 ml) y agua (45 ml). La mezcla se agitó a 60ºC durante 3 horas a continuación el volumen de la mezcla de reacción se redujo a un tercio por evaporación al vacío. El residuo acuoso se acidificó utilizando HCl acuoso (2,0 M) a continuación se extrajo con EtOAc (4 x 200 ml). La fase orgánica se evaporó al vacío y el material bruto se trituró con hexano (100 ml) para dar el compuesto del título en forma de un sólido de color blanco en 90% de rendimiento, 16,0 g.

LCMS (sistema 5) Tr = 2,24 min; m/z 366 $[M+H]^+$

Preparación 43: 2-(2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropan-1-ol



Vía a

Se agregó cloroformiato de isobutilo (6,6 mmoles, 50,02 mmoles) al ácido 2-(2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropanoico (16,6 g, 45,48 mmoles (véase preparación 42) y trietilamina (12,64 ml) en THF (300 ml) a 0ºC en nitrógeno. La mezcla se agitó a temperatura ambiente durante 3 horas a continuación se filtró a través de un tapón corto de celite™. El filtrado se enfrió hasta 0ºC y se agregó borohidruro de sodio (8,6 g, 227,6 mmoles) en agua (300 ml). La mezcla se agitó durante 10 minutos a 0ºC, se extrajo con acetato de etilo (3 x 150 ml) a continuación el

extracto orgánico se lavó con salmuera (150 ml) y se secó sobre sulfato de sodio. La solución se evaporó al vacío y el residuo se trituró con hexano para dar el compuesto del título en forma de un sólido de color blanco en 63% de rendimiento, 10,0 g.

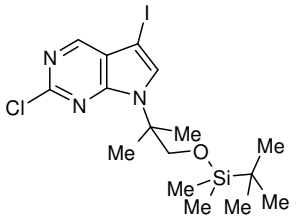
^{1}H RMN (400 MHz, DMSO-D_6) δ: 1,64 (s, 6H), 3,85 (d, 2H), 4,99 (t, 1H), 7,82 (s, 1H), 8,63 (s, 1H).

Vía b

Se agregó gota a gota diisobutilaluminio hidruro (300 ml, 300 mmoles, 1M en THF) a 2-(2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropanoato de metilo (51,8 g, 136 mmoles) (véase preparación 41) en THF (150 ml) a 0ºC. La mezcla se agitó durante 90 minutos posteriormente se agregaron metanol (27,9 ml) y HCl acuoso (20 ml, 2M). Se agregaron agua (100 ml), HCl acuoso (280 ml, 2M) y EtOAc (150 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. La mezcla se filtró y el sólido se lavó con agua (150 ml) y ter-butilmetil éter (150 ml) para dar el compuesto del título en forma de un sólido de color blanco en 56% de rendimiento, 26,8 g.

LCMS (sistema 1) Tr = 4,88 min; m/z 352 $[M+H]^+$

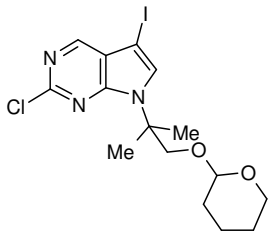
Preparación 44: 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil]-2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina



Se agregó cloruro de t-butildimetilsililo (78,8 g, 518 mmoles) a 2-(2-cloro-5-iodo-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropan-1-ol (140 g, 398 mmoles) (véase preparación 43) e imidazol (67,8 g, 996 mmoles) en DMF (996 ml) a 0ºC. La mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla se vertió en bicarbonato de sodio acuoso saturado (1500 ml) y se extrajo con heptano:EtOAc (1:1, 1500 ml). El extracto orgánico se lavó con salmuera (2 x 900 ml), a continuación se secó sobre sulfato de magnesio y se evaporó al vacío para dar el compuesto del título en forma de una goma de color marrón en 96% de rendimiento, 178,2 g.

LCMS (sistema 1) Tr = 8,32 min; m/z 466 $[M+H]^+$

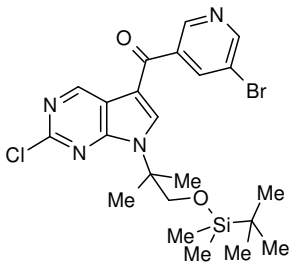
Preparación 45: 2-cloro-7-[1,1-dimetil-2-(tetrahidro-2H-piran-2-iloxi)etil]-5-yodo-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 6, utilizando 2-(2-cloro--7H-pirrolo[2,3-*d*]pirimidin-7-il)metilpropan-1-ol (véase preparación 43) para dar el compuesto del título en forma de un aceite de color amarillo en 74% de rendimiento, 7,3 g.

LCMS (sistema 5) Tr = 4,01 min; m/z 436 $[M+H]^+$

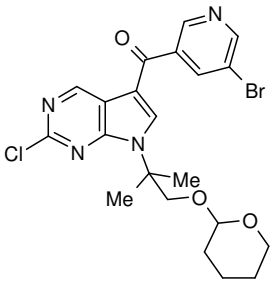
Preparación 46: (5-bromopiridin-3-il)[7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil)—2-cloro-7*H*-pirrolo[2,3-*d*]pirimidin-5-il]metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 28 utilizando 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil]-2-cloro—5-yodo-7H-pirrolo[2,3-d]pirimidina (véase preparación 44) y 5-bromo-N-metoxi-N-metilnicotinamida para dar el compuesto del título en forma de un sólido de color amarillo en 42% de rendimiento, 1,40 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: -0,18 (s, 6 H), 0,63 (s, 9 H), 1,72 (s, 6H), 4,09 (s, 2H), 8,24 (s, 1H), 8,39 (s, 1H), 8,95 (s, 1H), 8,99 (d, 1H), 9,36 (s, 1H).

Preparación 47 (5-bromopiridin-3-il){2-cloro-7-[1,1-dimetil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona

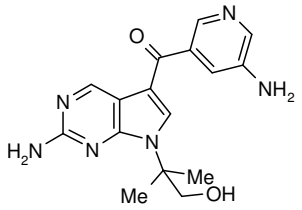


El compuesto del título se preparó de acuerdo con el método que se describe

para la preparación 28 utilizando 2-cloro-7-[1,1-dimetil-2-(tetrahidro-2H-piran-2-iloxi)etil]-5-yodo-7H-pirrolo[2,3-d]pirimidina (véase preparación 45) y 5-bromo-N-metoxi-N-metilnicotinamida para dar el compuesto del título en forma de un sólido de color amarillo en 41% de rendimiento, 3,0 g.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1,42-1,62 (m, 6H), 1,83 (s, 6H), 3,35-3,39 (m, 1H), 3,53-3,56 (m, 1H), 3,85 (d, 1H), 4,22 (d, 1H), 4,47 (m, 1H), 7,98 (s, 1H), 8,25 (s, 1H), 8,87 (s, 1H), 8,94 (s, 1H), 9,45 (s, 1H).

Preparación 48: [2-amino-7-(2-hidroxi-1,1-dimetiletil)-7*H*-pirrolo[2,3-*d*]pirimidin-5-il](5-aminopiridin-3-il)metanona



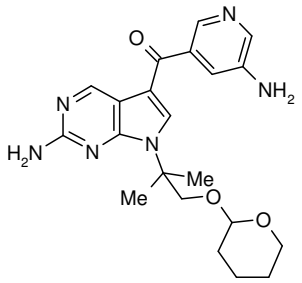
El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 36 utilizando (5-bromopiridin-3-il)[7-(2-{[ter-butil(dimetil)silil]oxi}-1,1-dimetiletil)—2-cloro-7H-pirrolo[2,3-d]pirimidin-5-il]metanona (véase preparación 46) para dar el compuesto del título en forma de un sólido de color amarillo en 48% de rendimiento, 300 mg.

1H RMN (400 MHz, DMSO-D6) δ: 1,64 (s, 6H), 3,90 (d, 2H), 5,07 (t, 1H), 5,60 (s, 2H), 6,50 (s, 2H), 7,23 (s, 1H), 7,61 (s, 1H), 8,11 (m, 2H), 8,93 (s, 1H).

Además se aisló de la mezcla de reacción [7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}{5-[(difenilmetileno)amino]piridin-3-il}metanona (preparación 48a).

^{1}H RMN (400 MHz, DMSO) δ*:* -0,18 (s, 6H), 0,66 (s, 9H), 1,67 (s, 6H), 4,05 (s, 2H), 5,59 (s, 2H), 6,51 (s, 2H), 7,19 (s, 1H), 7,57 (s, 1H), 8,07 (s, 1H), 8,10 (s, 1H), 8,93 (s, 1H).

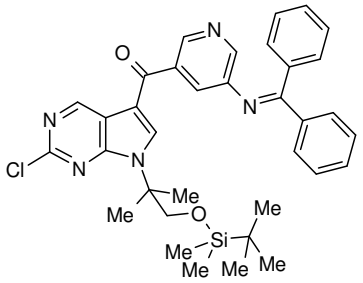
Preparación 49: {2-amino-7-[1,1-dimetil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}(5-aminopiridin-3-il)metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 36 utilizando (5-bromopiridin-3-il){2-cloro-7-[1,1-dimetil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (véase preparación 47) para dar el compuesto del título en forma de un sólido de color amarillo en 52% de rendimiento, 1,3 g.

LCMS (sistema 5) Tr = 2,72 min; m/z 411 $[M+H]^+$

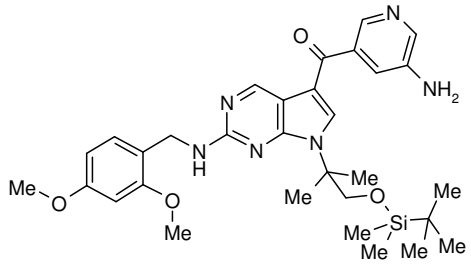
Preparación 50: [7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil)-2-cloro-7H-pirrolo[2,3-d]pirimidin-5-il}{5-[(difenilmetileno)amino]piridin-3-il}metanona



Se agregó cloruro de isopropil magnesio (105 ml, 210 mmoles, 2,0 M en THF) a 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-metiletil]-2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina (89,0 g, 190 mmoles) (véase preparación 44) en THF (450 ml) a 0ºC, en nitrógeno. La mezcla se agitó a 0ºC durante 1 hora, posteriormente se agregó gota a gota una solución de 5-[(difenilmetileno)amino]-N-metoxi-N-metilnicotinamida (72,6 g , 210 mmoles) (véase preparación 23) en THF (200 ml) a 0ºC. La mezcla se entibió hasta temperatura ambiente y se agitó a esta temperatura durante 16 horas. La mezcla de reacción se templó con 10% de cloruro de amonio acuoso (500 ml) y la fase orgánica se separó. La fase acuosa se extrajo con acetato de etilo (2 x 300 ml). Los extractos orgánicos combinados se lavaron con salmuera (400 ml), se secaron sobre sulfato de sodio, se evaporaron al vacío y el material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de heptano:EtOAc 100:90 a 60:40) para dar el compuesto del título en forma de una goma incolora en 66% de rendimiento, 78,9 g.

LCMS (sistema 1) Tr = 8,60 min; m/z 624 $[M+H]^+$

Preparación 51: (5-aminopiridin-3-il){7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil)-2-[(2,4-dimetoxibencil)amino-7*H*-pirrolo[2,3-*d*]pirimidin-5-il}metanona

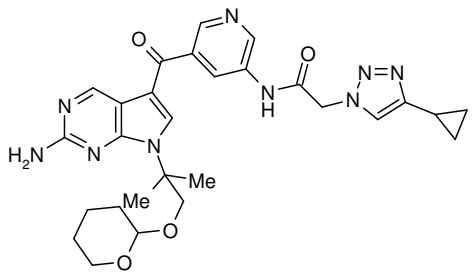


Se agregó 2,4-dimetoxibencilamina (99,4 g, 594 mmoles) a [7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil)-2-cloro-7H-pirrolo[2,3-d]pirimidin-5-il}{5-[(difenilmetileno)amino]piridin-3-il}metanona (53,0 g, 85 mmoles) (véase preparación 50) y 4-dimetilaminopiridina (2,07 g, 17,0 mmoles) en 1,4-dioxano (170 ml). La mezcla se calentó hasta reflujó durante 2 días a continuación se enfrió hasta temperatura ambiente y se filtró. El filtrado se evaporó al vacío, el residuo se disolvió en EtOAc (300 ml) y se lavó con cloruro de amonio acuoso saturado (500 ml). La fase orgánica se secó sobre sulfato de magnesio y se evaporó al vacío.

El residuo bruto se disolvió en THF (200 ml) y se agregó ácido cítrico acuoso (200 ml, 2M) La mezcla se agitó a temperatura ambiente durante 5 horas, posteriormente se diluyó con agua (200 ml). La mezcla se extrajo con EtOAc (300 ml) y el extracto orgánico se lavó con carbonato de potasio acuoso (300 ml, 2M). La fase orgánica se secó sobre sulfato de magnesio, se evaporó al vacío y el residuo se purificó por cromatografía de columna sobre gel de sílice (gradiente de pentano: EtOAc 100:0 a 0:100, seguido de EtOAc:MeOH 95:5) para dar el compuesto del título en forma de un aceite incoloro en 78% de rendimiento, 39,0 g.

LCMS (sistema 1) Tr = 5,97 min; m/z 591 $[M+H]^+$

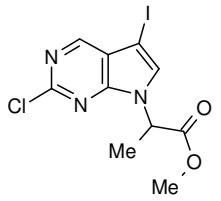
Preparación 52: N-[5-({2-amino-7-[1,1-dimetil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-(4-ciclopropil-1H-1,2,3-triazol-1il)acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 1 utilizando {2-amino-7-[1,1-dimetil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}(5-aminopiridin-3-il)metanona (véase preparación 49) y ácido (4-ciclopropil-1H-1,2,3-triazol-1-il)acético (véase preparación 83) para dar el compuesto del título en forma de un sólido de color amarillo en 86% de rendimiento, 70 mg.

LCMS (sistema 5): T_r = 2,87 min; m/z 560 $[M+H]^+$.

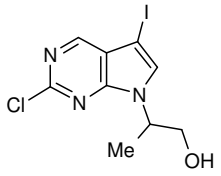
Preparación 53: (R,S) 2-(2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)propanoato de metilo



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 20 utilizando 2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina (véase preparación 40) para dar el compuesto del título en forma de un sólido de color marrón en 62% de rendimiento, 18,0 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,77 (d, 3H), 3,75 (s, 3H), 5,67 (q, 1H), 7,46 (s, 1H), 8,58 (s, 1H).

Preparación 54: (R,S)2-(2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidin-7-il)propan-1-ol

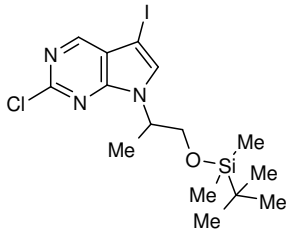


El compuesto del título se preparó de acuerdo con el método que se describió para la preparación 22, utilizando (R,S) 2-(2-cloro--7H-pirrolo[2,3-*d*]pirimidin-7-il)metilpropanoato de metilo (véase preparación 53) para dar el compuesto del título en forma de un aceite de color amarillo en 75% de rendimiento, 11,0 g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 1,40 (d, 3H), 3,62-3,74 (m, 2H), 4,83 (m, 1H), 4,98 (t, 1H), 8,03 (s, 1H), 8,64 (s, 1H).

Preparación 55: 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-2-cloro-5-yodo-7H-

pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 44, utilizando 2-(2-cloro-5-yodo-7H-pirrolo[2,3-*d*]pirimidin-7-il)propan-1-ol (véase preparación 54) para dar el compuesto del título en forma de un sólido de color amarillo en 89% de rendimiento, 12,50 g.

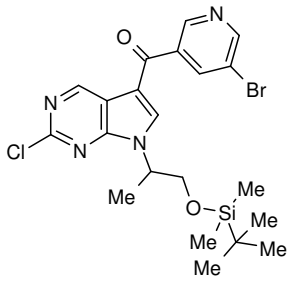
^{1}H RMN (400 MHz, DMSO) δ*:* -0,09 (s, 6H), 0,80 (s, 9H), 1,53 (d, 3H), 3,80 (d, 2H), 5,04 (m, 1H), 7,46 (s, 1H), 8,55 (s, 1H).

Los enantiómeros se separaron utilizando una Chiralpak IC 20 x 250 mm, 98:2:0,1 heptano:IPA:dietilamina (caudal – 18,0 ml/minuto).

Enantiómero 1 rendimiento 5,2 g, 99% e.e (primer pico eluyendo a 7,10 mins)

Enantiómero 2 rendimiento 5,0 g, 99% e.e (primer pico eluyendo a 7,64 mins)

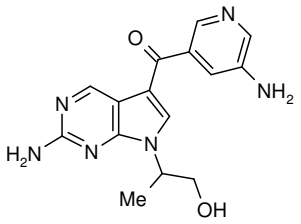
Preparación 56: (5-bromopiridin-3-il)[7-(2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil)—2-cloro-7*H*-pirrolo[2,3-*d*]pirimidin-5-il]metanona (enantiómero 1)



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 28 utilizando 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina (véase preparación 55, enantiómero 1) y 5-bromo-N-metoxi-N-metilnicotinamida para dar el compuesto del título en forma de un sólido de color amarillo en 30% de rendimiento, 1,0 g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: -0,14 (s, 6H), 0,61 (s, 9H), 1,52 (d, 3H), 3,91-3,96 (m, 2H), 5,00 (m, 1H), 8,37 (s, 1H), 8,58 (s, 1H), 8,95 (s, 1H), 9,00 (s, 1H), 9,33 (s, 1H).

Preparación 57: [2-amino-7-(2-hidroxi-1-metiletil)-7*H*-pirrolo[2,3-*d*]pirimidin-5-il](5-aminopiridin-3-il)metanona (enantiómero 1)

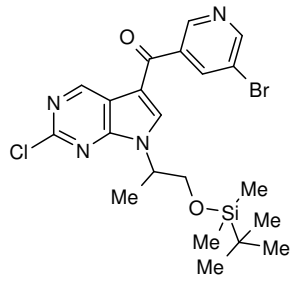


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 36

utilizando (5-bromopiridin-3-il)[7-(2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil)-2-cloro-7*H*-pirrolo[2,3-*d*]pirimidin-5-il]metanona (véase preparación 56) para dar el compuesto del título en forma de un sólido de color amarillo en 51% de rendimiento, 450 mg.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 1,41 (d, 3H), 3,66 (m, 2H), 4,74 (m, 1H), 5,01 (t, 1H), 5,59 (s, 2H), 6,55 (s, 2H), 7,22 (s, 1H), 7,83 (s, 1H), 8,11-8,13 (m, 2H), 8,91 (s, 1H); LCMS (system 5) Tr = 1,72 min; m/z 313 $[M+H]^+$.

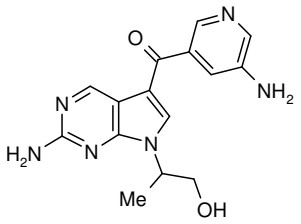
Preparación 58: (5-bromopiridin-3-il)[7-(2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil)—2-cloro-7*H*-pirrolo[2,3-*d*]pirimidin-5-il]metanona (enantiómero 2)



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 28 utilizando 7-(2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina (véase preparación 55, enantiómero 2) y 5-bromo-N-metoxi-N-metilnicotinamida para dar el compuesto del título en forma de un sólido de color amarillo en 30% de rendimiento, 1,4 g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: -0,14 (s, 6H), 0,61 (s, 9H), 1,52 (d, 3H), 3,91-3,96 (m, 2H), 5,00 (m, 1H), 8,37 (s, 1H), 8,58 (s, 1H), 8,95 (s, 1H), 9,00 (s, 1H), 9,33 (s, 1H).

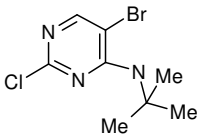
Preparación 59 [2-amino-7-(2-hidroxi-1-metiletil)-7*H*-pirrolo[2,3-*d*]pirimidin-5-il](5-aminopiridin-3-il)metanona (enantiómero 2)



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 36 utilizando (5-bromopiridin-3-il)[7-(2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil)-2-cloro-7*H*-pirrolo[2,3-*d*]pirimidin-5-il]metanona (véase preparación 58) para dar el compuesto del título en forma de un sólido de color amarillo en 51% de rendimiento, 450 mg.

LCMS (sistema 5) Tr = 1,70 min; m/z 313 $[M+H]^+$

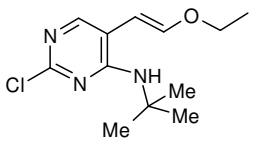
Preparación 60: 5-bromo-*N*-*ter*-butil-2-cloropirimidin-4-amina



Se agregó ter-butilamina (5,28 g, 72 mmoles) a 5-bromo-2,4-dicloropirimidina (15 g, 66 mmoles) y trietilamina (19,9 g, 197 mmoles) en acetonitrilo (450 ml) a temperatura ambiente y la mezcla se agitó a temperatura ambiente durante 16 horas. A continuación la mezcla se evaporó al vacío y el residuo bruto se separó entre EtOAc (450 ml) y agua (400 ml). La capa orgánica se separó, se lavó con salmuera (400 ml), posteriormente se secó sobre sulfato de sodio y se evaporó al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (hexano:EtOAc 88:12) para dar el compuesto del título en forma de un aceite de color amarillo en 52% de rendimiento, 8,8 g.

LCMS (sistema 5): T_r = 3,46 min; m/z 265 $[M+H]^+$.

Preparación 61: *N*-*ter*-butil-2-cloro-5-[(*E*)-2-etoxivinil]pirimidin-4-amina

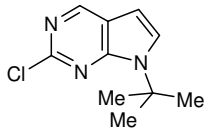


Se agregó gota a gota catecolborano (7,8 g, 65,4 mmoles) en THF (50 ml) a una solución del 40% de etoxiacetileno en hexano (12,8 ml, 72,5 mmoles) en nitrógeno a 0-5ºC. La mezcla se agitó a temperatura ambiente durante 2 horas, posteriormente

se calentó a 70ºC durante 2 horas. A continuación la mezcla se enfrió hasta temperatura ambiente y se agregó una solución de 5-bromo-*N*-*ter*-butil-2-cloropirimidin-4-amina (10 g., 37,8 mmoles) (véase preparación 60) en THF (50 ml). La solución se desgasificó con argón durante aproximadamente 25 minutos seguido de la adición de $Pd(PPh_3)_4$ (1,3 g, 1,13 mmoles) e hidróxido de sodio en polvo (4,53 g, 113 mmoles). La mezcla se calentó a 70° C durante 16 horas y a continuación se enfrió hasta temperatura ambiente. Se agregó EtOAc (200 ml) y la mezcla se filtró a través de un taco de Celite™. El filtrado se evaporó al vacío y el residuo se purificó por cromatografía de columna sobre gel de sílice (gradiente de hexano:EtOAc 93:7 a 90:10) para dar el compuesto del título en forma de un aceite de color amarillo en 55% de rendimiento, 5,3 g.

LCMS (sistema 5): T_r = 3,65 min; m/z 256 $[M+H]^+$.

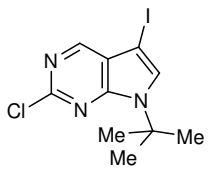
Preparación 62: 7-*ter*-butil-2-cloro-7H-pirrolo[2,3-d]pirimidina



Se agregó HCl concentrado (25 ml) a *N*-*ter*-butil-2-cloro-5-[(*E*)-2-etoxivinil]pirimidin-4-amina (5,3 g, 20,72 mmoles) (véase preparación 61) en isopropanol (210 ml) y la mezcla se calentó a reflujo durante 4 horas. A continuación la mezcla de reacción se evaporó al vacío y el residuo se basificó con $NaHCO_3$ acuoso saturado y se extrajo con EtOAc (200 ml). El extracto orgánico se secó sobre sulfato de sodio y se evaporó al vacío. El residuo se purificó por cromatografía de columna sobre gel de sílice (gradiente de hexano:EtOAc 93:7 a 90:10) para dar el compuesto del título en forma de un aceite color amarillo en 85% de rendimiento, 3,7 g.

LCMS (sistema 5): T_r = 3,42 min; m/z 210 $[M+H]^+$.

Preparación 63: 7-*ter*-butil-2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina

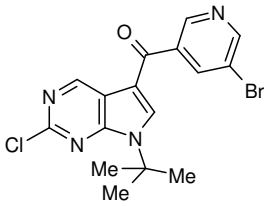


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 14 utilizando 7-*ter*-butil-2-cloro-7H-pirrolo[2,3-d]pirimidina (véase preparación 62) para dar el compuesto del título en forma de un líquido de color

marrón en 87% de rendimiento, 4,7 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,55 (s, 9H), 7,39 (s, 1H), 8,54 (s, 1H).

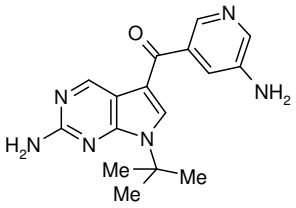
Preparación 64: (5-bromopiridin-3-il)(7-*ter*-butil-2-cloro-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 28 utilizando 7-*ter*-butil-2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina (véase preparación 63) y 5-bromo-N-metoxi-metilnicotinamida para dar el compuesto del título en forma de un aceite de color marrón en 36% de rendimiento, 2,1 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,82 (s, 9H), 7,78 (s, 1H), 8,25 (s, 1H), 8,88 (s, 1H), 8,92 (s, 1H), 9,44 (s, 1H).

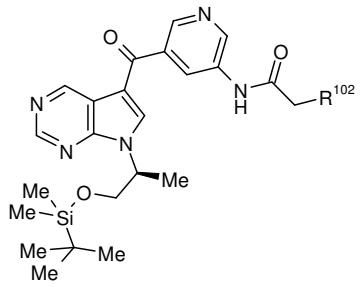
Preparación 65: (2-amino-7-*ter*-butil-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)(5-aminopiridin-3-il)metanona

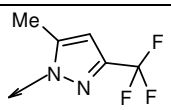
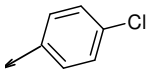
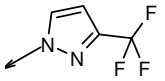
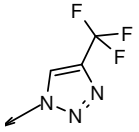
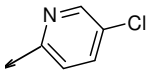


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 36 utilizando (5-bromopiridin-3-il)(7-*ter*-butil-2-cloro-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 64) para dar el compuesto del título en forma de un sólido de color blanco en 55% de rendimiento, 870 mg.

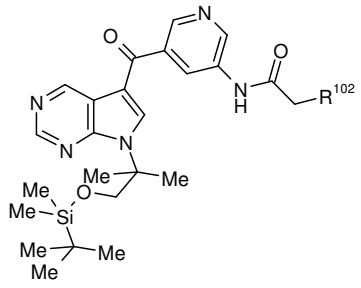
LCMS (sistema 5): T_r = 2,42 min; m/z 311 $[M+H]^+$.

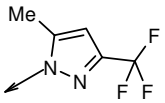
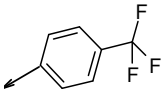
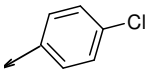
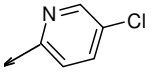
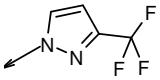
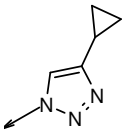
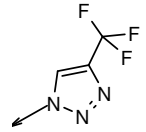
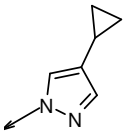
Las preparaciones 66 a 70 se prepararon de acuerdo con el ejemplo 1, partiendo de (5-aminopiridin-3-il){7-[(1S)-2--{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7*H*-pirrolo[2,3-*d*]pirimidin-5-il}metanona (véase preparación 37) y los ácidos apropiados de fórmula:



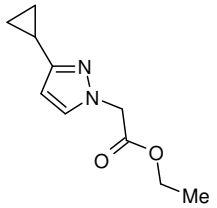
Preparación	**R^{102}**	**Datos**
66		LCMS (sistema 4): T_r = 3,73min; m/z 602 $[M+H]^+$.
67		LCMS (sistema 4): T_r = 3,87min; m/z 563 $[M+H]^+$.
68		LCMS (sistema 4): T_r = 1,71min; m/z 588 $[M+H]^+$.
69		LCMS (sistema 4): T_r = 3,51min; m/z 589 $[M+H]^+$.
70		LCMS (sistema 4): T_r = 3,55min; m/z 565 $[M+H]^+$.

Las preparaciones 71 a 78 se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 1, partiendo de (5-aminopiridin-3-il)[7-(2-{[*ter*-butil(dimetil)silil]oxi}-1,1-dimetiletil)-7*H*-pirrolo[2,3-*d*]pirimidin-5-il]metanona (véase preparación 38) y los ácidos apropiados de fórmula:



Preparación	R^{102}	Datos
71		LCMS (sistema 4): T_r = 3,88 min; m/z 616 $[M+H]^+$
72		LCMS (sistema 4): T_r = 4,09 min; m/z 612 $[M+H]^+$
73		LCMS (sistema 4): T_r = 4,07 min; m/z 578 $[M+H]^+$
74		LCMS (sistema 4): T_r = 3,81 min; m/z 579 $[M+H]^+$
75		LCMS (sistema 4): T_r = 3,79 min; m/z 602 $[M+H]^+$
76		LCMS (sistema 4): T_r = 3,58 min; m/z 575 $[M+H]^+$
77		LCMS (sistema 4): T_r = 3,74 min; m/z 603 $[M+H]^+$
78		LCMS (sistema 4): T_r = 3,78 min; m/z 573 $[M+H]^+$

Preparación 79: (3-ciclopropil-1H-pirazol-1-il)acetato de etilo

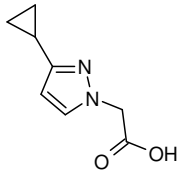


Se agregó carbonato de potasio (7,67 g, 55,56 mmoles) a 3-ciclopropil-1H-pirazol (2,0 g, 18,52 mmoles) en DMF seco (20 ml) a 25ºC y la mezcla se agitó durante 20 minutos. Se agregó bromoacetato de etilo (2,06 ml, 18,52 mmoles) a continuación la mezcla se agitó durante 2 días a temperatura ambiente. La mezcla de reacción se neutralizó con HCl acuoso (1,0 M), se extrajo con éter (40 ml) y el extracto orgánico se

lavó con salmuera (30 ml), se secó sobre sulfato de sodio, a continuación se evaporó al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (hexano:EtOAc 88:12) para dar el compuesto del título en forma de un aceite de color amarillo en 42% de rendimiento, 1,50 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 0,59 (d, 2H), 0,83 (d, 2H), 1,19 (t, 3H), 1,83 (m, 1H), 4,13 (q, 2H), 4,91 (s, 2H), 5,94 (d, 1H), 7,54 (d, 1H).

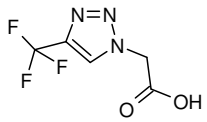
Preparación 80: Ácido (3-ciclopropil-1H-pirazol-1-il)acético.



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 42 utilizando (3-ciclopropil-1H-pirazol-1-il)acetato de etilo (véase preparación 79) para dar el compuesto del título en forma de un sólido de color blanco en 83% de rendimiento, 4,06 g.

LCMS (sistema 4): T_r = 1,16 min; m/z 167 $[M+H]^+$.

Preparación 81: Ácido 4-(trifluorometil)-1H-1,2,3-triazol-1-il]acético.

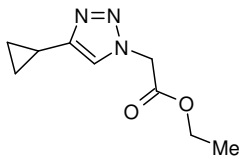


Se agregó trifluorometil acetileno (22,0 g, 0,234 moles) en THF (210 ml) a asacorbato de sodio (2,77 g, 14,0 mmoles), azidoacetato de etilo (27,1 g, 0,210 moles) y sulfato de cobre (4,76 ml, 0,3 M en agua) en agua (105 ml). La mezcla se agitó a temperatura ambiente durante 240 horas a continuación se evaporó al vacío. El residuo se extrajo con EtOAc (500 ml) y la fase orgánica se secó sobre sulfato de magnesio y a continuación se evaporó al vacío.

Se agregó hidróxido de sodio (7,32 g, 0,183 moles) en agua (30 ml) al residuo (32,7 g, 0,146 moles en metanol (50 ml) y la mezcla se agitó a temperatura ambiente durante 17 horas. El metanol se evaporó al vacío y el residuo se diluyó con agua (10 ml). Se agregó sulfato hidrógeno de potasio (26,6 g, 0,195 moles) en agua (70 ml). La solución se evaporó al vacío y el sólido bruto se purificó por cristalización utilizando agua para dar el compuesto del título en forma de un sólido de color blanco en 75% de rendimiento, 25,8 g.

^{1}H RMN (400 MHz, DMSO-d6) δ*:* 5,40 (s, 2H), 8,85 (s, 1H), 13,50 (br s, 1H).

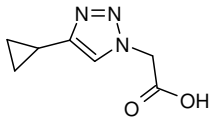
Preparación 82: (4-ciclopropil-1H-1,2,3-triazol-1-il)acetato de etilo



Se agitaron ciclopropilacetileno (15 g, 0,116 moles), azidoacetato de etilo (11,5 g, 0,174 moles), trietilamina (0,32 ml, 2,33 mmoles) y yoduro de cobre (442 mg, 2,33 mmoles) en acetonitrilo (100 ml) y se agitaron a 25ºC durante 18 horas. La mezcla se evaporó al vacío y el residuo se separó entre agua (100 ml) y acetato de etilo (100 ml). La fase orgánica se secó sobre sulfato de sodio, se evaporó al vacío y se purificó por cromatografía de columna sobre gel de sílice (EtoAc: Hexano 40: 60) para dar el compuesto del título en forma de un líquido incoloro en 95% de rendimiento, 21,6 g

^{1}H RMN (400 MHz, DMSO) δ*:* 0,68 (m, 2H), 0,90 (m, 2H), 1,21 (t, 3H), 1,95 (m, 1H), 4,17 (q, 2H), 5,29 (s, 2H), 7,81 (s, 1H).

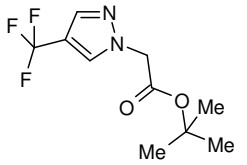
Preparación 83: Ácido (4-ciclopropil)-1H-1,2,3-triazol-1-il)acético.



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 42 utilizando (4-ciclopropil-1H-1,2,3-triazol-1-il)acetato de etilo (véase preparación 82) para dar el compuesto del título en forma de un sólido de color amarillo en 63% de rendimiento, 13,0 g.

LCMS (sistema 4): T_r = 1,86 min; m/z 186 $[M+H]^+$.

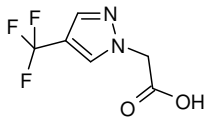
Preparación 84: [4-(trifluorometil)-1H-pirazol-1-il]acetato de ter-butilo



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 79 utilizando 4-(trifluorometil-1H-pirazol y bromoacetato de ter-butilo para dar el compuesto del título en forma de un sólido de color amarillo en 24% de rendimiento, 1,32 g.

LCMS (sistema 4): T_r = 3,64min; m/z 251 $[M+H]^+$.

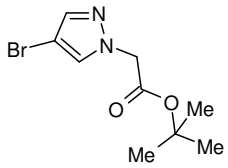
Preparación 85: Ácido [4-(trifluorometil)-1H-pirazol-1-il)acético.



Se agregó ácido trifluoroacético (10 ml) a [4-(trifluorometil)-1H-pirazol-1-il]acetato de ter-butilo (1,3 g, 5,2 mmoles) (véase preparación 84) en DCM seco (10 ml) y la mezcla se agitó durante 18 horas a 25ºC. A continuación la mezcla se evaporó al vacío y el residuo se purificó por trituración con éter dietílico:pentano (1:9, 2ml) para dar el compuesto del título en forma de un sólido de color blanco en 79% de rendimiento, 800 mg.

LCMS (sistema 4): T_r = 1,39min; m/z 193 $[M+H]^+$.

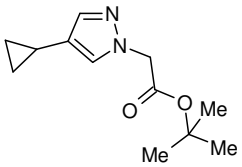
Preparación 86: [4-bromo-1H-pirazol-1-il]acetato de ter-butilo



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 79 utilizando 4-bromo-1H-pirazol y bromoacetato de ter-butilo para dar el compuesto del título en forma de un sólido de color amarillo en 34% de rendimiento, 48,0 g.

^{1}H RMN (400 MHz, CDCl3) δ*:* 1,42 (s, 9H), 4,70 (s, 2H), 7,40 (s, 2H).

Preparación 87: [4-(4-ciclopropil-1H-pirazol-1-il)acetato de ter-butilo

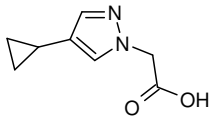


Se agregó acetato de paladio (215 mg, 0,957 mmoles) a [4-bromo-1H-pirazol-1-il]acetato de ter-butilo (5 g, 19,14 mmoles) (véase preparación 86), ácido ciclopropil borónico (8,22 g, 95,74 mmoles), fosfato de potasio (8,12 g, 38,29 mmoles) y triciclohexilfosfina (537 mg, 1,91 mmoles) en tolueno. agua (60 ml: 15 ml). La mezcla se desgasificó durante 20 minutos a continuación se reflujó durante 18 horas. La mezcla de reacción se filtró a través de Celite™, el filtrado se evaporó al vacío y el residuo se purificó por cromatografía de columna sobre gel de sílice (gradiente de EtOAc: Hexano 15: 85) para dar el compuesto en forma de un sólido blancuzco en

21% de rendimiento, 1,3 g.

LCMS (sistema 4): T_r = 3,17min; m/z 223 $[M+H]^+$.

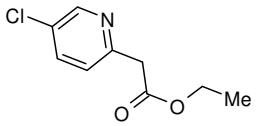
Preparación 88: Ácido (4-ciclopropil-1H-pirazol-1-il)acético.



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 85 utilizando (4-ciclopropil-1H-pirazol-1-il)acetato de ter-butilo (véase preparación 87) para dar el compuesto del título en forma de un sólido de color amarillo en 75% de rendimiento, 1,0 g.

LCMS (sistema 4): R_t=1,13min; m/z 165$[M+H]^+$.

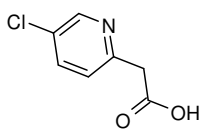
Preparación 89: (5-cloropiridin-2-il)acetato de etilo



Se agregó carbonato de cesio (71 g, 218 mmoles) a 2-bromo-5-cloropiridina (14 g, 73 mmoles) y malonato de dietilo (22 ml, 145 mmoles) en 1,4-dioxano seco (280 ml) y la solución se desgasificó con argón durante 30 minutos. A continuación se agregaron óxido de cobre (I) (2,8 g, 14,55 mmoles) y ácido picolínico (3,6 g, 29 mmoles) y la mezcla se agitó en un recipiente cerrado a 130ºC durante 24 horas. La mezcla se enfrió hasta temperatura ambiente, se templó con agua (100 ml) y se extrajo con EtOAc (3 x 100 ml) Los extractos orgánicos se lavaron con agua (200 ml), salmuera (200 ml), se secaron sobre sulfato de sodio y se evaporaron al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (EtOAc: Hexano 92: 8) para dar el compuesto del título en forma de un aceite de color amarillo en 54% de rendimiento, 8,0 g

^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 1,17 (t, 3H), 3,85 (s, 2H), 4,08 (q, 2H), 7,42 (d, 1H), 7,90 (dd, 1H), 8,54 (d, 1H).

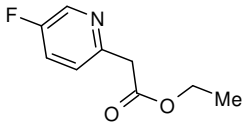
Preparación 90: Ácido (5-cloropiridin-2-il)acético



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 42 utilizando (5-cloropiridin-2-il)acetato de etilo (véase preparación 89) para dar el compuesto del título en forma de un sólido de color marrón en 51% de rendimiento, 3,5 g.

LCMS (sistema 4): T_r = 1,00 min; m/z 172 $[M+H]^+$.

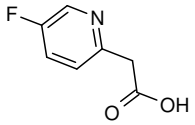
Preparación 91: (5-fluoropiridin-2-il)acetato de etilo



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 89 utilizando 2-bromo-5-fluoropiridina para dar el compuesto del título en forma de un sólido de color amarillo en 20% de rendimiento, 5 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 1,17 (t, 3H), 3,84 (s, 2H), 4,08 (q, 2H), 7,42-7,45 (m, 1H), 7,67-7,72 (m, 1H), 8,48 (d, 1H).

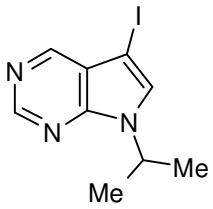
Preparación 92: Ácido (5-fluoropiridin-2-il)acético



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 42 utilizando (5-fluoropiridin-2-il)acetato de etilo (véase preparación 91) para dar el compuesto del título en forma de un sólido de color marrón en 57% de rendimiento, 2,4 g.

^{1}H NMR (400 MHz, DMSO-d_6) δ*:* 3,75 (s, 2H), 7,41-7,44 (m, 1H), 7,65-7,70 (m, 1H), 8,47 (d, 1H), 12,50 (br s, 1H).

Preparación 93 5-yodo-7-isopropil-7H-pirrolo[2,3-d]pirimidina

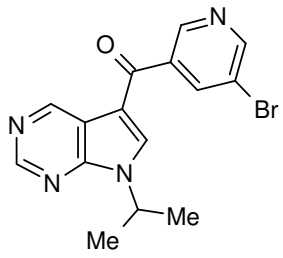


A una mezcla de 5-yodo-7H-pirrolo[2,3-d]pirimidina (preparación 201, 2,90 g, 12,0 mmoles) y carbonato de cesio (5,78 g, 17,8 mmoles) en DMF (45 ml) se agregó 2-yodopropano (1,78 ml, 17,8 mmoles). La mezcla se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se vertió posteriormente sobre cloruro de

amonio acuoso saturado (500 ml) y un precipitado sólido. El sólido se recolectó por filtración, se enjuagó con agua (200 ml) y se secó a presión reducida durante 17 horas para dar el compuesto del título en forma de un sólido de color marrón en 77% de rendimiento, 2,61 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,53 (d, 6H), 5,15 (m, 1H), 7,40 (s, 1H), 8,73 (s, 1H), 8,88 (s, 1H); LCMS (sistema 2): T_r = 1,02 min; m/z 288 $[M+H]^+$.

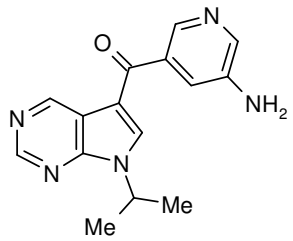
Preparación 94: (5-bromopiridin-3-il)(7-isopropil--7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona



A una solución agitada de 5-yodo-7-isopropil-7H-pirrolo[2,3-d]pirimidina (preparación 93, 4,85 g, 16,9 mmoles) en THF (90 ml) a 0ºC, en nitrógeno se agregó cloruro de isopropil magnesio (9,28 ml, 18,6 mmoles, 2,0 M en éter dietílico). La mezcla se agitó a 0ºC durante 1 hora, posteriormente se agregó gota a gota una solución de 5-bromo-N-metoxi-N-metilnicotinamida (preparación 227, 4,55 g, 18,6 mmoles) en THF (10 ml) a 0ºC. La mezcla se entibió hasta temperatura ambiente y se agitó durante 16 horas. La mezcla de reacción se templó con cloruro de amonio acuoso (200 ml) y se extrajo con acetato de etilo (3 x 200 ml). Los orgánicos combinados se concentraron a presión reducida y se purificaron por cromatografía de columna de gel de sílice eluyendo con gradiente de EtOAc:DCM 95:5 a 50:50 para dar un aceite de color marrón claro. El material bruto se recristalizó utilizando EtOAc:heptano (15::200 ml) para dar el compuesto del título en forma de un sólido de color blanco en 33% de rendimiento, 2,16 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,60 (d, 6H), 5,20 (m, 1H), 7,79 (s, 1H), 8,28 (dd, 1H), 8,90 (d, 1H), 8,95 (d, 1H), 9,03 (s, 1H), 9,59 (s, 1H); LCMS (sistema 2): T_r = 1,36 min; m/z 346 $[M+H]^+$.

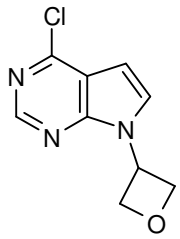
Preparación 95: (5-aminopiridin-3-il)(7-isopropil--7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 31 utilizando (5-bromopiridin-3-il)(7-isopropil-2-cloro-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona (véase preparación 94) para dar el compuesto del título en forma de un sólido de color blanco en 69% de rendimiento, 1,20 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,58 (d, 6H), 3,98 (br s, 2H), 5,18 (m, 1H), 7,39 (dd, 1H), 7,89 (s, 1H), 8,29 (br s, 1H), 8,43 (br s, 1H), 9,01 (s, 1H), 9,59 (s, 1H); LCMS (sistema 2): T_r = 0,50 min; m/z 282 $[M+H]^+$.

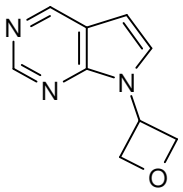
Preparación 96: 4-cloro-7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 1 utilizando (4,6-dicloropirimidin-5-il)acetaldehído y (preparación 208) y oxetan3-amina para dar el compuesto del título en forma de un aceite de color amarillo en 67% de rendimiento, 2,81 g.

LCMS (sistema 1): Tr = 1,92 min; m/z 210, 212 $[M+H]^+$.

Preparación 97: 7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidina

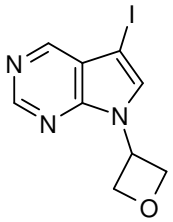


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 8 utilizando 4-cloro-7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidina (preparación 96) para dar el compuesto del título en forma de un sólido de color blanco en 90% de rendimiento, 1,20 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 4,97-5,06 (m, 4H), 5,96 (m, 1H), 6,74 (d, 1H), 8,04 (d,

1H), 8,80 (s, 1H), 9,03 (s, 1H).

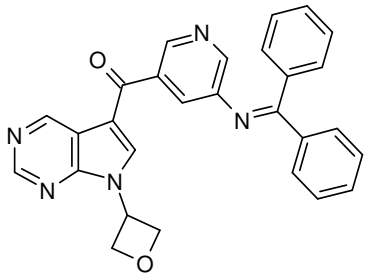
Preparación 98: 5-yodo-7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 14 utilizando 7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidina (preparación 97) para dar el compuesto del título en forma de un sólido de color blanco en 49% de rendimiento, 999 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 4,92-5,08 (m, 4H), 5,94 (m, 1H), 8,28 (s, 1H), 8,75 (s, 1H), 8,85 (s, 1H).

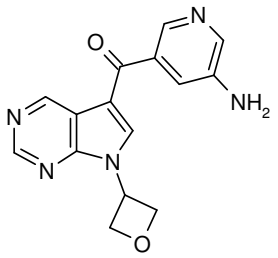
Preparación 99: {5-[(difenilmetileno)amino]piridin-3-il}(7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidin-5-il)metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 94 utilizando 5-cloro-7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidina (preparación 98) y 5-[(difenilmetileno)amino]-N-metoxi-N-metilnicotinamida (preparación 23) para dar el compuesto del título en forma de un sólido de color amarillo en 55% de rendimiento, 253 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 4,95-5,06 (m, 2H), 5,15-5,24 (m, 2H), 5,96 (m, 1H), 7,21-7,80 (m, 11H), 8,22 (d, 1H), 8,52 (s, 1H), 8,62 (m, 1H), 9,01 (s, 1H), 9,44 (s, 1H).

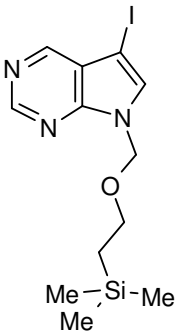
Preparación 100: (5-aminopiridin-3-il)(7-oxetan-3-il-7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 37 utilizando {5-[(difenilmetileno)amino]piridin-3-il}(7-oxetan-3-il-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (preparación 99) para dar el compuesto del título en forma de un sólido de color amarillo en 96% de rendimiento, 128 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 4,95-5,04 (m, 2H), 5,14-5,22 (m, 2H), 5,66 (br s, 2H), 5,97 (m, 1H), 7,33 (m, 1H), 8,19 (d, 1H), 8,25 (d, 1H), 8,62 (s, 1H), 9,00 (s, 1H), 9,46 (s, 1H).

Preparación 101: 5-yodo-7--{[2-(trimeilsilil)etoxi]metil}-7H-pirrolo[2,3-d]pirimidina

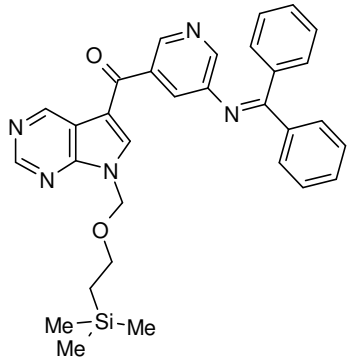


A una solución agitada de 5-yodo-7H-pirrolo[2,3-d]pirimidina (preparación 201, 735 mg, 3,00 mmoles) en DMF (5 ml) a 0ºC se agregó hidruro de sodio (132 mg, 3,30 mmoles, 60% en aceite). La mezcla se agitó a temperatura ambiente durante 30 minutos, se enfrió hasta -20ºC y se agregó 2-(trimetilsilil)etoximetil cloruro (0,58 ml, 3,30 mmoles). La mezcla de reacción se agitó a -20ºC durante 3 horas, posteriormente se agregó agua (30 ml). La mezcla se extrajo con EtOAc (2 x 50 ml), y las fases orgánicas combinadas se secaron sobre sulfato de magnesio y se evaporaron a presión reducida. El material bruto se purificó por cromatografía de columna sobre gel de sílice eluyendo con un gradiente de heptano:EtOAc 100:0 a 50:50) para dar el compuesto del título en forma de un sólido de color blanco en 61% de rendimiento, 691 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ: -0,11 (s, 9H), 0,81 (t, 2H), 3,51 (t, 2H), 5,61 (s, 2H), 8,01 (s, 1H), 8,77 (s, 1H), 8,89 (s, 1H).

Preparación 102 {5-[(difenilmetileno)amino]piridin-3-il}(7-{[2-(trimetilsilil)etoxi]metil}-

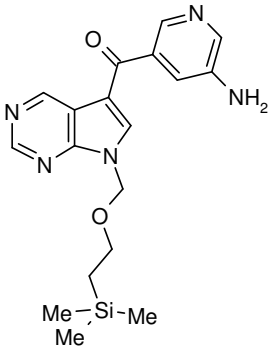
7H-pirrolo[2,3-d]pirimidin-5-il)metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 28 utilizando 5-yodo-7--{[2-(trimeilsilil)etoxi]metil}-7H-pirrolo[2,3-d]pirimidina (preparación 101) y 5-[(difenilmetileno)amino]-N-metoxi-N-metilnicotinamida (preparación 23) para dar el compuesto del título en forma de un aceite de color amarillo en 32% de rendimiento, 460 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ: -0,11 (s, 9H), 0,84 (m, 2H), 3,59 (m, 2H), 5,71 (s, 2H), 7,27 (m, 2H), 7,37 (m, 3H), 7,51 (m, 2H), 7,59 (m, 2H), 7,73 (d, 2H), 8,22 (d, 1H), 8,38 (s, 1H), 8,56 (d, 1H), 9,00 (s, 1H), 9,45 (s, 1H); LCMS (sistema 9): T_r = 2,36 min; m/z 534 $[M+H]^+$.

Preparación 103: (5-aminopiridin-3-il)(7-{[2-(trimetilsilil)etoxi]metil}-7H-pirrolo[2,3-d]pirimidin-5-il)metanona

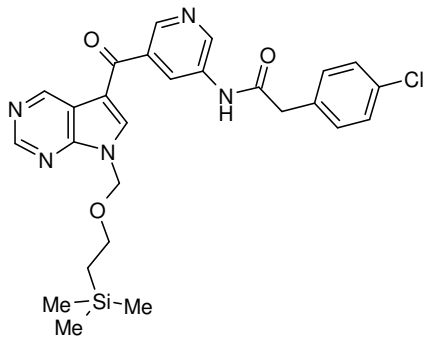


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 37 utilizando {5-[(difenilmetileno)amino]piridin-3-il}(7-{[2-(trimetilsilil)etoxi]metil}-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (preparación 102) para dar el compuesto del título en forma de un aceite incoloro en 73% de rendimiento, 2,10 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 0,09 (s, 9H), 0,84 (t, 2H), 3,60 (t, 2H), 5,66 (m, 4H), 7,30 (s, 1H), 8,18 (s, 2H), 8,55 (s, 1H), 9,02 (s, 1H), 9,47 (s, 1H); LCMS (sistema 9): T_r

= 3,25 min; m/z 370 $[M+H]^+$.

Preparación 104: 2-(4-clorofenil)-N-5-(7-((2-(trimetilsilil)etoxi)metil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)acetamida

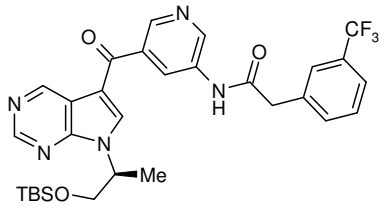


El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para los ejemplo 73-87, utilizando (5-aminopiridin-3-il)(7-{[2-(trimetilsilil)etoxi]metil}-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (preparación 103) y ácido 4-clorofenilacético para dar el compuesto del título en forma de un sólido de color blanco en 66% de rendimiento, 223 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* -0,11 (s, 9H), 0,82 (t, 3H), 3,60 (t, 2H), 3,74 (s, 2H), 5,70 (s, 2H), 7,37 (t, 4H), 8,47 (s, 1H), 8,60 (s, 2H), 8,72 (s, 1H), 8,98 (s, 1H), 9,03 (s, 1H), 9,48 (s, 1H);

LCMS (sistema 9): T_r = 3,50 min; m/z 522 $[M+H]^+$.

Preparación 105: N-[5-({7-[(1S)-2-{[ter-butil(dimetil)silil]oxi}-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)fenil]acetamida

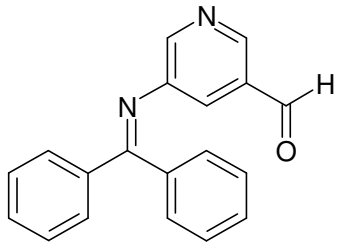


Se preparó de acuerdo con el ejemplo 1, utilizando (S) (5-aminopiridin-3-il){2-{[*ter*-butil(dimetil)silil]oxi}-1-metiletil]-7*H*-pirrolo[2,3-*d*]pirimidin-5-il}metanona (véase preparación 37) y ácido 3-trifluorometilfenilacético con DIPEA como base.

^{1}H RMN (400 MHz, DMSO) δ*:* -0,24 (s, 3H), -0,18 (s, 3H), 0,56 (s, 9H), 1,52 (d, 3H), 3,86 (m,3H), 3,94 (m, 1H), 5,06 (m, 1H), 7,58 (t, 1H), 7,63 (t,2H), 7,72 (s, 1H), 8,45 (s, 1H), 8,50 (s, 1H), 8,67 (d, 1H), 8,93 (d, 1H), 8,98 (s,1H), 9,45 (s,1H), 10,73 (s,1H).

LCMS (sistema 9): T_r = 3,89min; m/z 598 $[M+H]^+$.

Preparación 106: 5-[(difenilmetileno)amino]nicotinaldehído



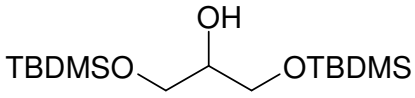
A una solución agitada de 5-[(difenilmetileno)amino]-N-metoxi-N-metilnicotinamida (preparación 23, 7,50 g, 0,021 moles) en THF (150 ml) a -70ºC se agregó hidruro de diisopropilaluminio (42 ml, 0,042 moles, 1,0 M en THF) y la mezcla resultante se agitó a -70ºC durante 2 horas. Se agregaron agua (20 ml) y acetato de etil o(100 ml). La fase orgánica se separó, se concentró a presión reducida, se purificó por cromatografía de columna de gel de sílice eluyendo con EtOAc: éter de petróleo 1:10 para dar el compuesto del título en forma de un sólido de color marrón en 65% de rendimiento, 4 g.

El compuesto del título además se preparó de acuerdo con el siguiente proceso:

Una mezcla de 5-bromonicotinaldehído (2,790 mg, 15,0 mmoles), difenilmetanimina (3,01 ml, 18 mmoles), $Pd_2(dba)_3$ (412 mg, 0,45 mmoles), di-ter-butil(2',4',6'-triisopropil-[1,1'-bifenil]-2-il)fosfina (510 mg , 1,2 mmoles) y K_3PO_4 (7,960 mg, 37,5 mmoles) en DME (30,0 ml) se agitó a 50ºC durante 16 horas. Después de enfriar hasta temperatura ambiente, la reacción se diluyó con DCM (50 ml) y la mezcla se filtró a través de un taco de arbocel. La torta de filtro se lavó con DCM (50 ml) y el filtrado se concentró a presión reducida. El material bruto se recristalizó a partir de acetato de etilo/heptano para dar el compuesto deseado en forma de un sólido en 78% de rendimiento, 3,341 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 7,18-7,26 (m, 2H), 7,30-7,39 (m, 3H), 7,47-7,54 (m, 2H), 7,55-7,62 (m, 2H), 7,68-7,75 (m, 2H), 8,25 (d, 1H), 8,63 (d, 1H), 10,00 (s, 1H).

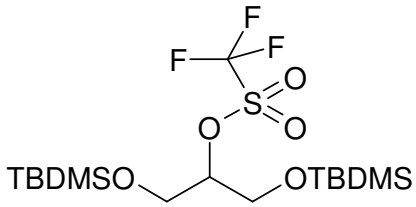
Preparación 107: 2,2,3,3,9,9,10,10-octametil-4,8-dioxa-3,9-disilaundecan-6-ol



A una solución agitada de glicerol (4,01 ml, 55 mmoles) e imidazol (18,7 g, 275 mmoles) en DMF (150 ml) a 0ºC se agregó cloruro de ter-butildimetilsililo (17,2 g, 113 mmoles) en DMF (33 ml). La mezcla de reacción se dejó entibiar hasta temperatura

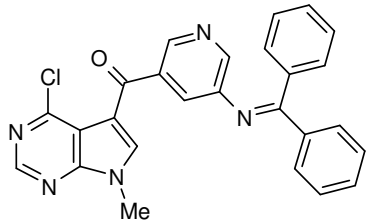
ambiente y se agitó durante 16 horas. Se agregó agua (500 ml) a la mezcla y la mezcla resultante se extrajo con heptano (500 ml x 3). Las capas orgánicas combinadas se lavaron con agua (300 ml), se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. El material bruto se purificó por cromatografía de columna sobre gel de sílice con un eluado gradiente de heptano:EtOAc 100:0 a 80:20) para dar el compuesto del título en forma de un aceite incoloro en 68% de rendimiento, 11,9 g.
^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,03 (s, 12H), 0,86 (s, 18H), 3,40-3,59 (m, 5H), 4,58 (d, 1H).

Preparación 108: 2,2,3,3,9,9,10,10-octametil-4,8-dioxa-3,9-disilaundecan-6-il trifluorometanosulfonato



A una solución agitada de 2,2,3,3,9,9,10,10-octametil-4,8-dioxa-3,9-disilaundecan-6-ol (preparación 107, 6,410 mg, 20 mmoles) y piridina (2,42 ml, 30 mmoles) en DCM (40 ml) a -50ºC se agregó anhídrido trifluorometanosulfónico (5,05 ml, 30 mmoles) y la reacción se agitó a -30ºC durante 2 horas. Se agregó HCl 1N acuoso (40 ml) a la reacción y la mezcla se extrajo con DCM (40 ml x 3). Las capas orgánicas combinadas se concentraron a presión reducida para obtener un aceite incoloro el cual se utilizó en el próximo paso (preparación 196) sin purificación posterior.

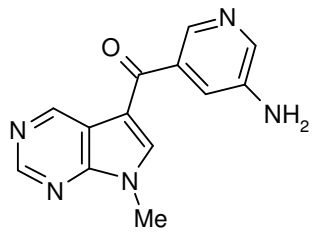
Preparación 109: 4-cloro-[7-metil-7H-pirrolo[2,3-d]pirimidin-5-il]{5-[(difenilmetileno)amino]piridin-3-il}metanona



El compuesto del título se preparó de acuerdo con el método que se describió para la preparación 28, seguido de la preparación 30 utilizando 4-cloro-5-yodo-7-metil-7H-pirrolo[2,3-*d*]pirimidina (preparación 226) y 5-[(difenilmetileno)amino]nicotinaldehído (preparación 106) para dar el compuesto del título en forma de un aceite de color amarillo (11,0 g, 48%).

^{1}H RMN (400 MHz, DMSO) δ*:* 3,87 (s, 3H), 7,06 (m, 2H), 7,28 (m, 2H), 7,37 (m, 2H), 7,45 (m, 3H), 7,70 (m, 3H), 8,15 (d, 1H), 8,49 (d, 1H), 8,69 (s, 1H).

Preparación 110 (5-aminopiridin-3-il)(7-metil--7H-pirrolo[2,3-*d*]pirimidin-5-il)metanona



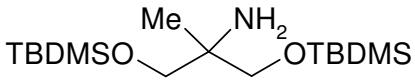
Se agregó ácido cítrico (200 ml, 2,0 M) a 4-cloro-[7-metil-7H-pirrolo[2,3-d]pirimidin-5-il]{5-[(difenilmetileno)amino]piridin-3-il}metanona (preparación 109, 30 g, 0,066 mmoles) en THF (200 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Se agregó éter (200 ml) y las fases se separaron. La capa acuosa se neutralizó con carbonato de sodio acuoso a continuación el sólido se recolectó por filtración y se secó al vacío para dar (5-aminopiridin-3-il)(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)metanona en forma de un sólido de color marrón, 18 g, 95%.

Se agregó sal de sodio metanotiol (15,5 g, 0,22 moles) a (5-aminopiridin-3-il)(7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (21 g, 0,073 moles) en metanol (300 ml) y la mezcla se agitó a temperatura ambiente durante 7 horas. La mezcla de reacción se vertió en agua helada (200 ml) y el precipitado se filtró. La torta de filtro se lavó con agua (100 ml) a continuación acetona (20 ml) para dar el (5-aminopiridin-3-il)[7-metil-4-(metiltio)-7H-pirrolo[2,3-d]pirimidin-5-il]metanona en forma de un sólido de color marrón, 15 g, 69%.

Se agregó níquel Raney (10 g) a (5-aminopiridin-3-il)[7-metil-4-(metiltio)-7H-pirrolo[2,3-d]pirimidin-5-il]metanona (1,5 g, 5,0 mmoles) y amoníaco concentrado (150 ml) en 1,4-dioxano (150 ml). La mezcla se reflujó durante 6 horas a continuación se filtró. El filtrado se evaporó al vacío y se purificó por HPLC preparativa (método 4) para dar el compuesto del título en forma de un sólido de color marrón claro en 100% de rendimiento, 1,9 g.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 3,88 (s, 3H), 5,63 (s, 2H), 7,27 (m, 1H), 8,14-8,18 (m, 2H), 8,40 (s, 1H), 8,97 (s, 1H), 9,42 (s, 1H).

Preparación 111: 2,2,3,3,6,9,9,10,10-Nonametil-4,8-dioxa-3,9-disilaundecan-6-amina

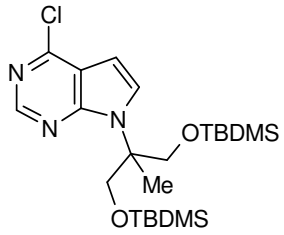


El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 44 utilizando 2-amino-2-metil-1,3-propanodiol para

dar el compuesto del título en forma de un aceite incoloro en 100% de rendimiento, 23,0 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 0,05 (s, 12H), 0,87-0,99 (m, 21H), 3,36-3,42 (m, 4H).

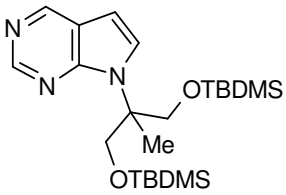
Preparación 112: 7-[2-{[*ter*-butil(dimetil)silil]oxi}--({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-4-cloro-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 1 utilizando 2,2,3,3,6,9,9,10,10-nonametil-4,8-dioxa-3,9-disilaundecan-6-amina para dar el compuesto del título en forma de una goma incolora en 75% de rendimiento, 8,91 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 0,09-0,11 (m, 12H), 0,78-0,79 (m, 18H), 1,74 (s, 3H), 4,06-4,09 (m, 2H), 4,29-4,31 (m, 2H), 6,52 (m, 1H), 7,44-7,45 (m, 1H), 8,56 (m, 1H).

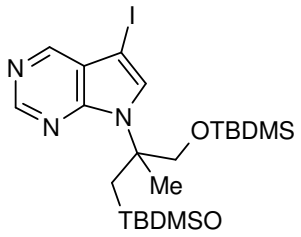
Preparación 113: 7-[2-{[*ter*-butil(dimetil)silil]oxi}--({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 8 utilizando 7-[2-{[*ter*-butil(dimetil)silil]oxi}--({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-4-cloro-7H-pirrolo[2,3-d]pirimidina (preparación 112) para dar el compuesto del título en forma de un aceite de color amarillo en 99% de rendimiento, 8,14 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* -0,13 (s,6H), -0,10 (s,6H), 0,78 (s,18H), 1,75 (s, 3H), 4,11 (d, 2H), 4,33 (d, 2H), 6,45 (d, 1H), 7,41 (d, 1H), 8,78 (s,1H), 8,90 (s, 1H).

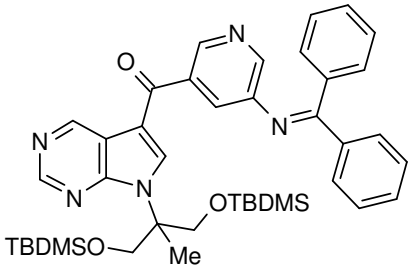
Preparación 114: 7-[2-{[*ter*-butil(dimetil)silil]oxi}--({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-5-yodo-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 14 utilizando 7-[2-{[*ter*-butil(dimetil)silil]oxi}--({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidina (preparación 113) para dar el compuesto del título en forma de un aceite de color amarillo en 88% de rendimiento, 7,98 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* -0,10 (s, 12H), 0,79 (s, 18H), 1,75 (s, 3H), 4,07 (d, 2H), 4,27 (d, 2H), 7,49 (s, 1H), 8,70 (s, 1H), 8,82 (s, 1H).

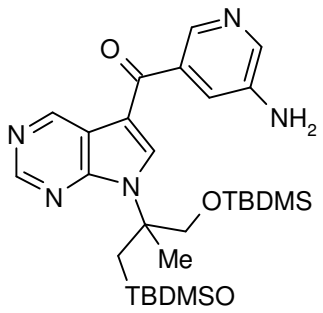
Preparación 115: {7-[2-{[*ter*-butil(dimetil)silil]oxi}-1-({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}{5-[(difenilmetileno)amino]piridin-3-il}metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 28 utilizando 7-[2-{[*ter*-butil(dimetil)silil]oxi}--({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-5-yodo-7H-pirrolo[2,3-d]pirimidina (preparación 114) y 5-[(difenilmetileno)amino]-N-metoxi-N-metilnicotinamida (preparación 23) para dar el compuesto del título en forma de una espuma de color amarillo en 69% de rendimiento, 1,76 g.

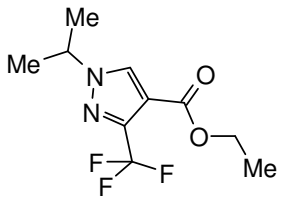
^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 0,10-0,12 (m, 12H), 0,73-0,76 (m, 18H), 1,77 (s, 3H), 4,06-4,09 (m, 2H), 4,34-4,36 (m, 2H), 7,11-7,16 (m, 2H), 7,28-7,33 (m, 3H), 7,42-7,47 (m, 2H), 7,50-7,54 (m, 2H), 7,78-7,80 (m, 2H), 7,93 (s, 1H), 8,15-8,16 (m, 1H), 8,56 (m, 1H), 8,94 (s, 1H), 9,58 (s, 1H).

Preparación 116: (5-aminopiridin-3-il){7-[2-{[*ter*-butil(dimetil)silil]oxi}-({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-7*H*-pirrolo[2,3-*d*]pirimidin-5-il}metanona



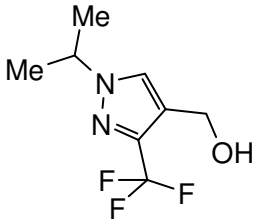
El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 37 utilizando {7-[2-{[*ter*-butil(dimetil)silil]oxi}-1-({[ter-butil(dimetil)silil]oxi}metil)-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}{5-[(difenilmetileno)amino]piridin-3-il}metanona (preparación 115) para dar el compuesto del título en forma de un aceite de color amarillo en 85% de rendimiento, 1,15 g.
LCMS (sistema 1): T_r = 4,01 min; m/z 556 $[M+H]^+$.

Preparación 117: Etil éster del ácido 1-isopropil-3-trifluorometil-1H-pirazol-4-carboxílico



A una suspensión de etil éster del ácido 5-trifluorometil-1H-pirazol-4-carboxílico (13 g, 62,5 mmoles) y carbonato de cesio (61,1 g, 187,5 mmoles) en DMF (70 ml) se agregó 2-yodo-propano (6,86 ml, 68,75 mmoles) y la mezcla resultante se dejó asentar a temperatura ambiente durante 16 horas. La mezcla de reacción bruta se vertió en agua (100 ml) y se extrajo con EtOAc (100 ml x 3). Los orgánicos combinados se lavaron con agua (50 ml x 2), salmuera (50 ml), se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida para dar el compuesto del título en forma de un sólido blancuzco en 65% de rendimiento, 10,2 g.
^{1}H RMN (400 MHz, DMSO) δ*:* 1,33 (t, 3H), 1,53 (d, 6H), 4,30 (q, 2H), 4,50-4,57 (m, 1H), 8,00 (s, 1H); LCMS (sistema 9): T_r = 3,55 min; m/z 251 $[M+H]^+$.

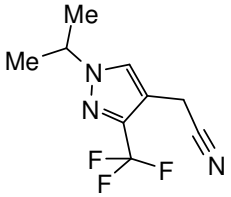
Preparación 118: (1-isopropil-3-trifluorometil-1H-pirazol-4-il)-metanol



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 183 utilizando etil éster del ácido 1-isopropil-3-trifluorometil-1H-pirazol-4-carboxílico (preparación 117) para dar el compuesto del título en forma de un sólido blancuzco en 97% de rendimiento, 8,3 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,50 (d, 6H), 1,72 (t, 1H), 4,47-4,54 (m, 1H), 4,65 (d, 2H), 7,50 (s, 1H); LCMS (sistema 9): T_r = 2,77 min; m/z 209 $[M+H]^+$.

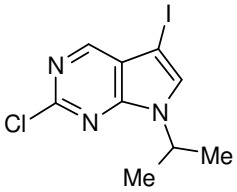
Preparación 119: (1-isopropil-3-trifluorometil-1H-pirazol-4-il)-acetonitrilo



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 184 utilizando (1-isopropil-3-trifluorometil-1H-pirazol-4-il)-metanol (preparación 118) para dar el compuesto del título en forma de un sólido blancuzco en 58% de rendimiento, 5 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,42 (d, 6H), 3,92 (s, 2H), 4,56-4,63 (m, 1H), 8,06 (s, 1H).

Preparación 120 2-cloro-5-yodo-7-isopropil-7H-pirrolo[2,3-d]pirimidina

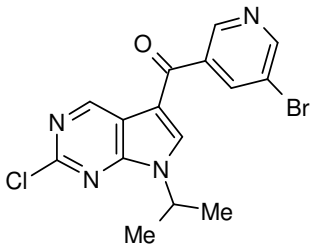


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 93 utilizando 2-cloro-5-yodo-7-isopropil--7H-pirrolo[2,3-d]pirimidina (preparación 40) para dar el compuesto del título en forma de un sólido de color blanco en 87% de rendimiento, 5,5 g.

^{1}H RMN (400 MHz, DMSO) δ: 1,50 (d, 6H), 5,10 (m, 1H), 7,36 (s, 1H), 8,55 (s, 1H); LCMS (Sistema 10) Tr = 3,6 min; m/z 322 $[M+H]^+$.

Preparación 121: (5-bromopiridin-3-il)(2-cloro-7-isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-

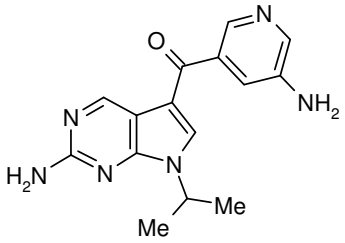
il)metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 28 utilizando 2-cloro-5-yodo-7-isopropil--7H-pirrolo[2,3-d]pirimidina (preparación 120) y 5-bromo-N-metoxi-N-metilnicotinamida para dar el compuesto del título en forma de un sólido de color amarillo en 41% de rendimiento, 1,2 g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 1,54 (d, 6H), 5,02 (m, 1H), 8,41 (d, 1H), 8,63 (s, 1H), 9,0 (m, 2H), 9,33 (s, 1H).

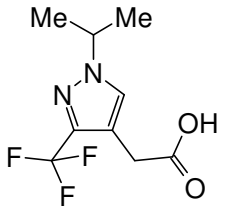
Preparación 122: (2-amino-7-isopropil-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)(5-aminopiridin-3-il)metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 31 utilizando (5-bromopiridin-3-il)(2-cloro-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación 121) para dar el compuesto del título en forma de un sólido de amarillo en 58% de rendimiento, 500 mg.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 1,47 (d, 6H), 4,82-4,86 (m, 1H), 5,60 (s, 2H), 6,58 (s, 2H), 7,23 (s, 1H), 7,88 (s, 1H), 8,12 (m, 2H), 8,91 (s, 1H); LCMS (Sistema 9) Tr = 0,99 min; m/z 297 $[M+H]^+$.

Preparación 123: Ácido (1-isopropil-3-trifluorometil-1H-pirazol-4-il)-acético

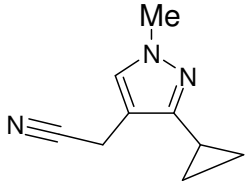


El compuesto del título se preparó de acuerdo con el método que se describe

para la preparación 185 utilizando (1-isopropil-3-trifluorometil-1H-pirazol-4-il)-acetonitrilo (preparación 119) para dar el compuesto del título en forma de un sólido blancuzco en 82% de rendimiento, 4,5 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,41 (d, 6H), 3,50 (s, 2H), 4,52-4,58 (m, 1H), 7,89 (s, 1H), 12,35 (br, 1H); LCMS (sistema 10): Tr = 1,56 min; m/z 235 $[M-H]^-$

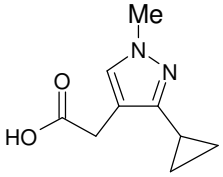
Preparación 124: (3-ciclopropil-1-metil-1H-pirazol-4-il)-acetonitrilo



A una suspensión de ter-butóxido de potasio (8,95 g, 79,9 mmoles) en DME (250 ml) -78ºC en nitrógeno se agregó una solución de 1-(isocianometil sulfonil)-4-metil benceno (9,36 g, 47,94 mmoles) en DME (50 ml). Después de agitar durante 10 minutos, se agregó una solución de 3-ciclopropil-1-metil-1H-pirazol-4-carbaldehído (6 g, 39,95 mmoles) en DME (100 ml). La mezcla resultante se dejó agitar a -78ºC durante 1 hora y a continuación a temperatura ambiente durante 1 hora. Se agregó metanol (50 ml) y la mezcla resultante se reflujó durante 1 hora. La mezcla de reacción se templó con cloruro de amonio acuoso saturado (200 ml) y se extrajo con EtOAc (2 x 200 ml). Las capas orgánicas combinadas se lavaron con salmuera (2 x 50 ml), se secaron sobre sulfato de sodio, se filtraron y se concentraron bajo presión reducida. El material bruto se purificó por cromatografía de columna sobre gel de sílice con EtOAc 90:10 para dar el compuesto del título en forma de sólido blancuzco en 67% de rendimiento, 4,3 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,67-0,7 (m, 2H), 0,79-0,83 (m, 2H), 1,75-1,80 (m, 1H), 3,68 (s, 3H), 3,79 (s, 2H), 7,54 (s, 1H); LCMS (sistema 9): T_r = 2,53 min; m/z 162 $[M+H]^+$.

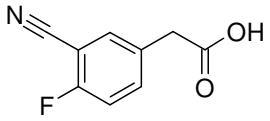
Preparación 125: Ácido (3-ciclopropil-1-metil-1H-pirazol-4-il)-acético



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 141 utilizando (3-ciclopropil-1-metil-1H-pirazol-4-il)-acetonitrilo (preparación 124) para dar el compuesto del título en forma de un sólido blancuzco en 83% de rendimiento, 4 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 0,62-0,66 (m, 2H), 0,73-0,77 (m, 2H), 1,67-1,74 (m, 1H), 3,38 (s, 2H), 3,66 (s, 3H), 7,40 (s, 1H), 12,22 (br, 1H); LCMS (sistema 9): T_r = 1,97 min; m/z 181 $[M+H]^+$.

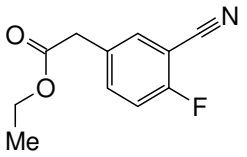
Preparación 126: Ácido (3-ciano-4-fluoro-fenil)-acético



A una solución de ácido (3-bromo-4-fluoro-fenil)-acético (10 g, 42,9 mmoles) en DMF (65 ml) se agregó cianuro de cobre (I) (7,7 g, 85,8 mmoles) y se calentó a 130ºC durante 24 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con acetato de etilo (250 ml). La capa orgánica se lavó con agua (5 x 50 ml), salmuera (50 ml), se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. El material bruto se recristalizó a partir de éter dietílico y hexano para dar el compuesto del título en forma de un sólido de color amarillo en 65% de rendimiento, 5 g.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 3,68 (s, 2H), 7,48 (t, 1H), 7,66-7,71 (m, 1H), 7,82 (dd, 1H), 12,53 (br s, 1H); LCMS (sistema 10): T_r = 1,39 min; m/z 178 $[M-H]^-$

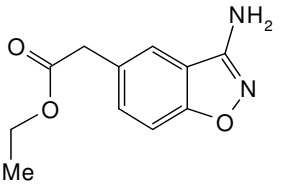
Preparación 127: Etil éster del ácido (3-ciano-4-fluoro-fenil)-acético



A una suspensión del ácido (3-ciano-4-fluoro-fenil)-acético (500 mg, 2,79 mmoles) (preparación 126) y carbonato de potasio (770 mg, 5,58 mmoles) en DMF (5 ml) se agregó yoduro de etilo (0,89 ml, 11,16 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción bruta se vertió en agua (10 ml) y se extrajo con acetato de etilo (3 x 15 ml). Las capas orgánicas combinadas se lavaron con agua (5l x 10 ml), salmuera (10 ml), se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida para dar el compuesto del título en forma de un sólido blancuzco en 87% de rendimiento, 500 mg.

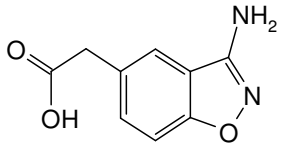
^{1}H RMN (400 MHz, DMSO) δ: 1,26 (t, 3H), 3,61 (s, 2H), 4,16 (q, 2H), 7,17 (t, 1H), 7,49-7,55 (m, 2H).

Preparación 128: Etil éster del ácido (3-aminobenzo[d]isoxazol-5-il)-acético



A una solución del ácido (3-ciano-4-fluoro-fenil)-acético (preparación 127, 400 mg, 1,93 mmoles) y ácido acetohidroxámico (362 mg, 4,83 mmoles) en DMF (40 ml) y agua (15 ml) se agregó carbonato de potasio (1,6 g, 11,58 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 12 horas. La mezcla de reacción se diluyó con agua (100 ml) y el precipitado de color blanco resultante se recolectó por filtración. El material bruto se purificó por cromatografía de columna sobre gel de sílice eluyendo con un gradiente de diclorometano: metanol 100:0 a 97:3) para dar el compuesto del título en forma de un sólido blancuzco en 59% de rendimiento, 250 mg. LCMS (sistema 9): T_r = 2,87 min; m/z 221 $[M+H]^+$.

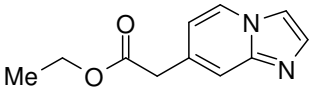
Preparación 129: Ácido (3-aminobenzo[d]isoxazol-5-il)-acético



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 141 utilizando etil éster del ácido (3-amino-benzo[d]isoxazol-5-il)-acético (preparación 128) para dar el compuesto del título en forma de un sólido blancuzco en 69% de rendimiento, 30 mg.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 3,65 (s, 2H), 6,36 (br s, 2H), 7,36-7,42 (m, 2H), 7,69 (s, 1H), 12,37 (br s, 1 H); LCMS (sistema 10): T_r = 1,65 min; m/z 193 $[M+H]^+$.

Preparación 130: Etil éster del ácido imidazo[1,2-a]piridin-7-il-acético

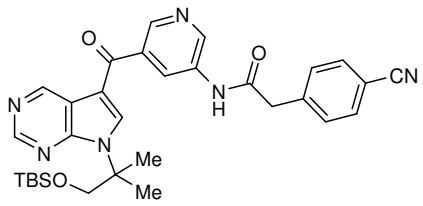


A una solución agitada de 7-bromo-imidazo[1,2-a]piridina (600 mg, 3,0 mmoles) y dietil malonato (0,93 ml, 6,1 mmoles) en dioxano seco (15 ml) se agregó carbonato de cesio (3 g, 9,1 mmoles). Se burbujeó argón a través de la mezcla durante 10 minutos y a continuación se agregaron yoduro de cobre (I) (116 mg, 0,61 mmoles) y ácido picolínico (150 mg, 1,22 mmoles). La mezcla resultante se calentó en un tubo cerrado a 130ºC durante 24 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se templó con agua (10 ml) y se extrajo con EtOAc (3 x 20 ml) Las capas orgánicas combinadas se lavaron con agua (2 x 10 ml), salmuera (10 ml), se secaron

sobre sulfato de sodio, se filtraron y se concentraron bajo presión reducida. El material bruto se purificó por cromatografía de columna sobre gel de sílice eluyendo con un gradiente de diclorometano: metanol 100:0 a 98:2) para dar el compuesto del título en forma de una goma blancuzca en 29% de rendimiento, 180 mg.

LCMS (sistema 10): T_r = 2,61 min; m/z 205 $[M+H]^+$.

Preparación 131: N-(5-{[7-(2-{[ter-butil(dimetil)silil]oxi}-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-cianofenil)acetamida

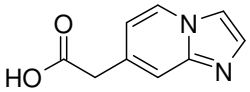


Se preparó de acuerdo con el método que se describió para el ejemplo 1 utilizando (5-aminopiridin-3-il)[7-(2-{[ter-butil(dimetil)silil]oxi}-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]metanona (preparación 38) y ácido 4-cianofenacético con DIPEA.

^{1}H RMN (400 MHz, DMSO) δ*:* -0,26 (s, 6H), 0,58 (s, 9H), 1,75 (s, 6H), 3,86 (s, 2H), 4,10 (s, 2H), 7,54 (d, 2H), 7,82 (d, 2H), 8,16 (s, 1H), 8,51 (s, 1H), 8,68 (s, 1H), 8,88 (s, 1H), 8,98 (s, 1H), 9,47 (s, 1H), 10,73 (s, 1H);

LCMS (sistema 9): T_r = 3,80 min; m/z 569 $[M+H]^+$.

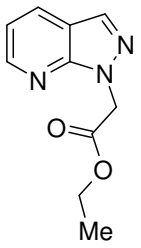
Preparación 132: Ácido imidazo[1,2-a]piridin-7-il-acético



A una solución de etil éster del ácido imidazo[1,2-a]piridin-7-il-acético (180 mg, 0,65 mmoles) (preparación 130) en dioxano (4 ml) a 0ºC se agregó solución de hidróxido de sodio acuoso 2N (4 ml). A continuación la mezcla de reacción se calentó a 90ºC durante 6 horas. Después de enfriar hasta 0ºC, la mezcla se acidificó hasta pH 4 con ácido clorhídrico acuoso 2N y se extrajo con 20% de isopropanol en diclorometano (8 x 10 ml). Los orgánicos combinados se secaron sobre sulfato de sodio y se concentraron a presión reducida para dar el compuesto del título en forma de un sólido blancuzco en 70% de rendimiento, 80 mg.

LCMS (sistema 10): T_r = 1,40 min; m/z 177 $[M+H]^+$.

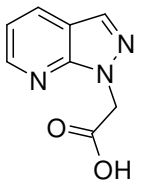
Preparación 133: Etil éster del ácido pirazolo[3,4-a]piridin-1-il-acético



A una solución de 7-aza-indazol (250 mg, 2,1 mmoles) y bromoacetato de etilo (0,47 ml, 4,2 mmoles) en DMF (8 ml) se agregó K_2CO_3 (1,16 g, 8,4 mmoles) y la mezcla resultante se agitó a 70ºC durante 16 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con acetato de etilo (20 ml). La capa orgánica se lavó con agua (2 x 5 ml), salmuera (5 ml), se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. El material bruto se purificó utilizando cromatografía de columna sobre gel de sílice con EtOAc:hexano 10:90 para dar el compuesto del título en forma de sólido blancuzco en 49% de rendimiento, 210 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 1,19 (t, 3H), 4,14 (q, 2H), 5,35 (s, 2H), 7,25-7,28 (m, 1H), 8,22 (s, 1H), 8,29 (d, 1H), 8,55 (d, 1H).

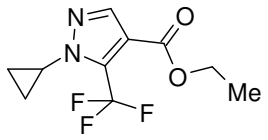
Preparación 134: Ácido pirazolo[3,4-a]piridin-1-il-acético



A una solución agitada de etil éster del ácido pirazolo[3,4-a]piridin-1-il-acético (210 mg, 1,02 mmoles) (preparación 133) en THF (4 ml) y agua (1 ml) a 0ºC se agregó LiOH.H_2O (129 mg, 3,06 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. El pH de la mezcla se ajustó hasta pH 4 con ácido clorhídrico acuoso 2N y se extrajo con 20% de isopropanol en diclorometano (8 x 5 ml). Los orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron a presión reducida para dar el compuesto del título en forma de un sólido blancuzco en 40% de rendimiento, 70 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 5,22 (s, 2H), 7,25 (dd, 1H), 8,19 (s, 1H), 8,27 (dd, 1H), 8,55 (dd, 1H), 13,15 (brs, 1H); LCMS (sistema 9): T_r = 1,93 min; m/z 178 $[M+H]^+$.

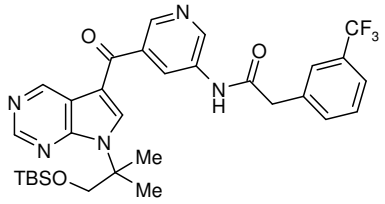
Preparación 135: Etil éster del ácido 1-ciclopropil-5-trifluorometil-1H-pirazol-4-carboxílico



Se disolvió etil éster del ácido 4,4,4-trifluoro-3-oxo-butírico (16 g, 86,4 mmoles) en anhídrido acético (33,6 g, 329,6 mmoles) y se agregó a la mezcla ortoformiato de trietilo (38,4 g, 260 mmoles). La mezcla resultante se reflujó durante 18 horas. La mezcla se concentró bajo presión reducida para obtener 20 g de etil éster del ácido 2-[1-etoxi-met-(E)-ilideno]-4,4,4-trifluoro-3-oxo-butírico en forma bruta. Esto se colocó en EtOH (50 ml) y se agregó a una suspensión de clorhidrato ciclopropil hidrazina (9,95 g, 91,7 mmoles) y DIPEA (28,3 ml, 166,7 mmoles) en EtOH (150 ml) a -20ºC. la mezcla resultante se entibió lentamente hasta temperatura ambiente y se agitó durante 16 horas. La mezcla se concentró bajo presión reducida y el residuo se dividió entre EtOAc (50 ml) y agua (50 ml). La capa orgánica se lavó con HCl 2N (25 ml), agua (25 ml), salmuera (25 ml), se secó (Na_2SO_4) y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (EtOAc:hexano 5:95) para dar el compuesto del título en forma de sólido de color blanco en 7% de rendimiento, 1,4 g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 1,10-1,21 (m, 4H), 1,26 (t, 3H), 3,90 (m, 1H), 4,26 (q, 2H), 7,98 (s, 1H).

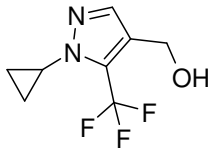
Preparación 136: N-(5-{[7-(2-{[ter-butil(dimetil)silil]oxi}-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(3-(trifluorometil)fenil]acetamida



Se preparó de acuerdo con el método que se describió para el ejemplo 1 utilizando (5-aminopiridin-3-il)[7-(2-{[ter-butil(dimetil)silil]oxi}-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]metanona (preparación 38) y ácido 3-trifluorometilfenilacético con DIPEA.

^{1}H RMN (400 MHz, DMSO) δ*:* -0,27 (s, 6H), 0,56 (s, 9H), 1,75 (s, 6H), 3,87 (s, 2H), 4,09 (s, 2H), 7,57-7,64

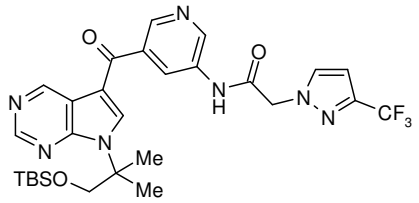
Preparación 137: (1-ciclopropil-5-trifluorometil-1H-pirazol-4-il)-metanol



Una solución de etil éster del ácido 1-ciclopropil-5-trifluorometil-1H-pirazol-4-carboxílico (preparación 135, 1,4 g, 5,64 mmoles) en tolueno seco (25 ml) se enfrió hasta -78ºC y se agregó gota a gota a la misma DIBAL-H (11,8 ml de solución 1,2 M en tolueno, 14,1 mmoles) . La mezcla de reacción se agitó a -78ºC durante 2 horas y se vertió en HCl 2N (10 ml). Esto se agitó durante otras 4 horas a temperatura ambiente seguido de extracción con EtOAc (2 x 25 ml) y las capas orgánicas combinadas se lavaron con agua (2 x 10 ml), salmuera (10 ml) se secaron (Na_2SO_4) y se evaporaron al vacío para dar el compuesto del título en forma de un sólido blancuzco en 100% de rendimiento, 1,2 g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 1,03-1,17 (m, 4H), 3,68-3,73 (m, 1H), 4,42 (d, 2H), 5,15 (t, 1H), 7,51 (s, 1H); LCMS (sistema 10): T_r = 2,68 min; m/z 207 $[M+H]^+$

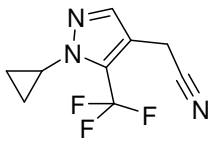
Preparación 138: N-(5-{[7-(2-{[ter-butil(dimetil)silil]oxi}-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-isopropil-1H-1,2,3-triazol-1-il)acetamida



Se preparó de acuerdo con el método que se describió para el ejemplo 1 utilizando (5-aminopiridin-3-il)[7-(2-{[ter-butil(dimetil)silil]oxi}-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]metanona (preparación 38) y ácido [4-trifluorometil)-1H-pirazol-1-il]acético (preparación 85) con DIPEA como base.

LCMS (sistema 9): T_r = 3,67 min; m/z 577 $[M+H]^+$.

Preparación 139: (1-ciclopropil-5-trifluorometil-1H-pirazol-4-il)-acetonitrilo

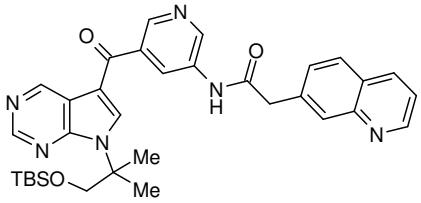


Una solución de (1-ciclopropil-5-trifluorometil-1H-pirazol-4-il)-metanol (preparación 137, 1,2 g, 5,82 mmoles) en DCM (15 ml) se enfrió hasta 0ºC y se agregó cloruro de tionilo (0,85 ml, 11,7 mmoles). La mezcla de reacción se agitó a 0ºC

durante 2 horas y se diluyó con DCM. La capa orgánica se lavó con agua, salmuera y se secó (Na_2SO_4) y se evaporó al vacío. El residuo bruto obtenido se disolvió en dioxano (25 ml) y agua (25 ml) y se agregó bromuro de tetrabutil amonio (1,38 g, 4,28 mmoles) La mezcla de reacción se agitó durante 10 min seguido de la adición de KCN (1,28 g, 19,82 mmoles) y la mezcla resultante se agitó durante otras 16 horas a temperatura ambiente. La mezcla se diluyó con EtOAc (50 ml) y se lavó con agua (1 x 10 ml), salmuera (1 x 10 ml), se secó sobre (Na_2SO_4) y se evaporó al vacío El material bruto se purificó por cromatografía de columna sobre gel de sílice (hexano:EtOAc 10:90) para dar el compuesto del título en forma de sólido de color amarillo claro en 56% de rendimiento, 700 mg.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,06-1,13 (m, 2H), 1,24-1,29 (m, 2H), 3,61-3,62 (m, 1H), 3,66 (s, 2H), 7,49 (s, 1H).

Preparación 140: N-(5-{[7-(2-{[ter-butil(dimetil)silil]oxi}-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-quinolin-7-ilacetamida

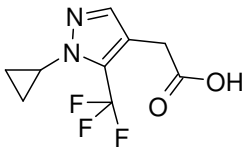


Se preparó de acuerdo con el método que se describió para el ejemplo 1 utilizando (5-aminopiridin-3-il)[7-(2-{[ter-butil(dimetil)silil]oxi}-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]metanona (preparación 38) y ácido 2-quinolin-7-ilacético con DIPEA como base.

^{1}H RMN (400 MHz, DMSO) δ*:* -0,28 (s, 6H), 0,55 (s, 9H), 1,74 (s, 6H), 3,98 (s, 2H), 4,09 (s, 2H), 7,51 (m, 1H), 7,60 (m, 1H), 7,94 (m, 1H), 8,00 (s, 1H), 8,16 (s, 1H), 8,33 (m, 1H), 8,54 (m, 1H), 8,67 (s, 1H), 8,84 (m, 1H), 8,91 (s, 1H), 8,98 (s, 1H), 9,47 (s, 1H), 10,77 (s, 1H);

LCMS (sistema 9): T_r = 3,72 min; m/z 595 $[M+H]^+$.

Preparación 141: Ácido (1-ciclopropil-5-trifluorometil-1H-pirazol-4-il)-acético

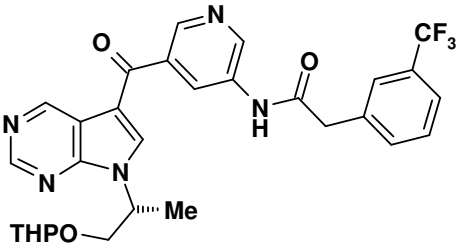


A una solución de (1-ciclopropil-5-trifluorometil-1H-pirazol-4-il)-acetonitrilo (preparación 139, 700 mg, 3,25 mmoles) en EtOH (15 ml) se agregó NaOH 1N acuoso

(15 ml). La solución resultante se calentó a 60ºC durante 16 horas. La mezcla se concentró y el residuo se disolvió en agua (10 ml) y se lavó con EtOAc. El pH de la capa acuosa se ajustó hasta 5 utilizando HCl 1N y se extrajo con 10% de IPA en DCM (4 x 30 ml). La capa orgánica se secó (Na_2SO_4) y se evaporó al vacío para dar el compuesto del título en forma de un sólido en 85% de rendimiento, 650 mg.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 1,04-1,07 (m, 2H), 1,11-1,16 (m, 2H), 3,55 (s, 2H), 3,69-3,73 (m, 1H), 7,47 (s, 1H), 12,45 (br, 1H); LCMS (sistema 10): T_r = 1,50 min; m/z 233 $[M-H]^+$.

Preparación 142: N-[5-({7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)fenil]acetamida

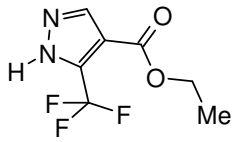


Se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 1 utilizando (5-aminopiridin-3-il){7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (preparación 36) y ácido 3-trifluorometilfenilacético con DIPEA como base.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 1,29-1,42 (m, 5H), 1,54 (d, 3H), 3,50 (m, 1H), 3,71 (m, 1H), 3,86 (s, 2H), 3,93 (m, 1H), 4,05 (m, 1H), 4,44 (s, 1H), 4,58 (s, 1H), 5,17 (m, 1H), 7,56 (m, 1H), 7,63 (m, 2H), 7,72 (s, 1H), 8,47 (m, 2H), 8,70 (s, 1H), 8,96 (m, 2H), 9,45 (s, 1H), 10,72 (s, 1H);

LCMS (sistema 9): T_r = 3,56 min; m/z 568 $[M+H]^+$.

Preparación 143: Etil éster del ácido 5-trifluorometil-1H-pirazol-4-carboxílico

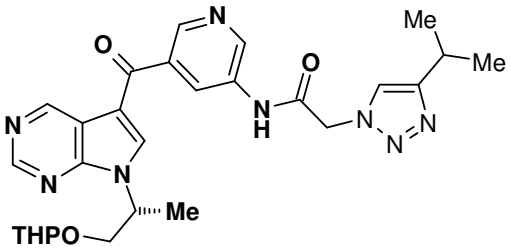


A una suspensión de clorhidrato hidrazina (10 g, 147 mmoles) en EtOH (500 ml), se agregó lentamente DIPEA (45,3 ml, 267 mmoles) a -20ºC y se agitó durante 10 min. A continuación se agregó etil éster del ácido 2-[1-etoxi-met-(E)-ilideno]-4,4,4-trifluoro-3-oxo-butírico (preparación **135,** 32 g, 133,33 mmoles) a la solución anterior y la mezcla resultante se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se concentró bajo presión reducida y el residuo se dividió entre EtOAc (200

ml) y agua (50 ml). La capa orgánica se lavó con agua (25 ml), se secó (Na_2SO_4) y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (hexano:EtOAc 90:10) para dar el compuesto del título en forma de sólido de blancuzco en 43% de rendimiento, 13 g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 1,26 (t, 3H), 4,25 (q, 2H), 8,57 (s, 1H), 14,10 (br s, 1H).

Preparación 144: N-[5-({7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-(4-isopropil-1H-1,2,3-triazol-1-il)acetamida

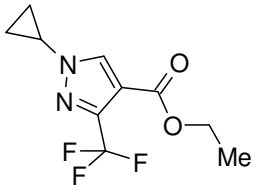


Se preparó de acuerdo con el método que se describió anteriormente para el ejemplo 1 utilizando (5-aminopiridin-3-il){7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (preparación 36) y ácido 4-(trifluorometil)-1H-1,2,3-triazol-1-il]acético con DIPEA como base.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 1,22 (6H, d), 1,23-1,30 (m, 5H), 1,54(d, 3H), 3,4 (1H, m), 3,72 (m, 1H), 3,88 (m, 1H), 3,95 (m, 1H), 4,10 (m, 1H), 4,45 (s, 1H), 4,59 (s, 1H), 5,20 (1H, m), 5,36 (s, 2H), 7,88 (s, 1H), 8,43 (m, 1H), 8,53 (d, 1H), 8,75 (s, 1H), 8,97 (m, 2H), 9,45 (s, 1H), 10,96 (s, 1H);

LCMS (sistema 9): T_r = 2,86 min; m/z 533 $[M+H]^+$.

Preparación 145: Etil éster del ácido 1-ciclopropil-3-trifluorometil-1H-pirazol-4-carboxílico

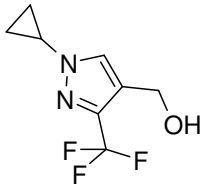


Se agregaron sucesivamente ácido ciclopropil borónico (11 g, 127 mmoles), acetato de cobre (17,4 g, 95,7 mmoles), piridina (17,7 g, 223 mmoles) y trietilamina (22,4 ml, 160 mmoles) a una solución de etil éster del ácido 5-trifluorometil-1H-pirazol-4-carboxílico (preparación 143, 6,63 g, 31,9 mmoles) en THF (70 ml) y la mezcla resultante se dejó agitar a 60ºC durante 36 horas. La mezcla de reacción se filtró sobre

un lecho de celite y el filtrado se concentró al vacío y se diluyó con EtOAc (200 ml). La capa orgánica se lavó con HCl 1N (1 x 25 ml), salmuera (1 x 25 ml), y se secó (Na_2SO_4) y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (hexano:EtOAc 85:15) para dar el compuesto del título en forma de sólido de color marrón en 29% de rendimiento, 2,3 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,08-1,14 (m, 2H), 1,17-1,21 (m, 2H), 1,33 (t, 3H), 3,62-3,67 (m, 1H), 4,30 (q, 2H), 8,01 (s, 1H); LCMS (sistema 10): T_r = 3,39 min; m/z 249 $[M+H]^+$.

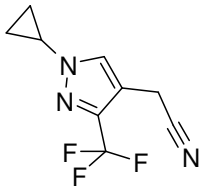
Preparación 146: (1-ciclopropil-3-trifluorometil-1H-pirazol-4-il)-metanol



Una solución de etil éster del ácido 1-ciclopropil-3-trifluorometil-1H-pirazol-4-carboxílico (preparación 145, 3,5 g, 14,11 mmoles) en tolueno seco (70 ml) se enfrió hasta -78ºC y se agregó gota a gota a la misma DIBAL-H (29,4 ml de solución 1,2 M en tolueno, 25,3 mmoles) . La mezcla de reacción se agitó a -78ºC durante 2 horas y a continuación se vertió en HCl 2N (25 ml) seguido de otra agitación durante 2 horas a temperatura ambiente. La mezcla se extrajo con EtOAc (2 x 50 ml) y las capas orgánicas combinadas se lavaron con agua (2 x 15 ml), salmuera (15 ml) se secaron (Na_2SO_4) y se evaporaron al vacío para dar el compuesto del título en forma de un sólido blancuzco en 100% de rendimiento, 3 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,02-1,07 (m, 2H), 1,11-1,16 (m, 2H), 1,68 (t, 1H), 3,57-3,63 (m, 1H), 4,64 (d, 2H), 7,53 (s, 1H); LCMS (sistema 10): T_r = 2,57 min; m/z 207 $[M+H]^+$.

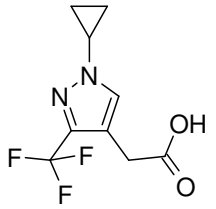
Preparación 147: (1-ciclopropil-3-trifluorometil-1H-pirazol-4-il)-acetonitrilo



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 139 utilizando (1-ciclopropil-3-trifluorometil-1H-pirazol-4-il)-metanol (preparación 146) para dar el compuesto del título en forma de un sólido de color amarillo en 70% de rendimiento, 2,2 g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 0,98-1,03 (m, 2H), 1,06-1,11 (m, 2H), 3,83-3,88 (m, 1H), 3,91 (s, 2H), 8,08 (s, 1H); LCMS (sistema 10): T_r = 3,10 min; m/z 216 $[M+H]^+$.

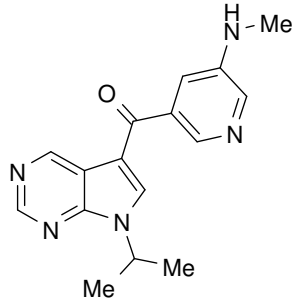
Preparación 148: Ácido (1-ciclopropil-3-trifluorometil-1H-pirazol-4-il)-acético



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 141 utilizando (1-ciclopropil-3-trifluorometil-1H-pirazol-4-il)-acetonitrilo (preparación 147) para dar el compuesto del título en forma de un sólido en 79% de rendimiento, 1,9 g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 0,96-1,07 (m, 4H), 3,49 (s, 2H), 3,76-3,84 (m, 1H), 7,91 (s, 1H), 12,27 (br, 1H); LCMS (sistema 10): T_r = 1,41 min; m/z 233 $[M-H]^+$.

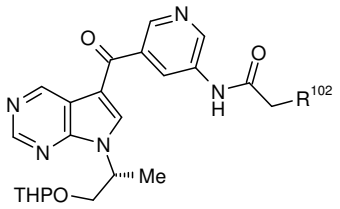
Preparación 149: (7-isopropil-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)[5-(metilamino)piridin-3-il]metanona

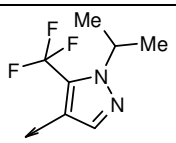
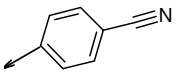
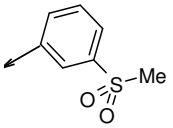
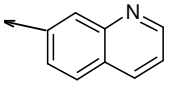


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 31 utilizando (5-bromopiridin-3-il)(7-isopropil-2-cloro-7*H*-pirrolo[2,3-*d*]pirimidin-5-il)metanona (preparación 94) y metilamina (20 ml) en 13% de rendimiento, 78 mg.

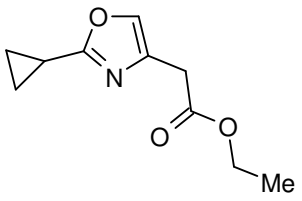
LCMS (sistema 2): T_r = 0,91 min; m/z 296 $[M+H]^+$

Las siguientes preparación se prepararon de acuerdo con el método que se describió anteriormente para el ejemplo 1 utilizando (5-aminopiridin-3-il){7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}metanona (preparación 36) y el correspondiente ácido carboxílico con DIPEA. Todos los ácidos carboxílicos están disponibles en el comercio a menos que se mencione lo contrario.



Preparación	Nombre	R^{102}	Datos
150	N-[5-({7-[(1R)-1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[1-isopropil-(trifluorometil)-1H-pirazol-4-il]acetamida		LCMS (sistema 9): T_r = 3,24 min; m/z 600 $[M+H]^+$ Utilizando (Prep 185).
151	2-(4-cianofenil)-N-[5-({7-[(1R)1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida		LCMS (sistema 9): T_r = 2,94 min; m/z 525 $[M+H]^+$.
152	N-[5-({7-[(1R)- 1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(metilsulfonil)fenil]acetamida		LCMS (System 9): T_r = 2,82 min; m/z 578 $[M+H]^+$
153	N-[5-({7-[(1R)1-metil-2-(tetrahidro-2H-piran-2-iloxi)etil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-quinolin[-7-ilacetamida		LCMS (sistema 9): T_r = 2,97 min; m/z 551 $[M+H]^+$.

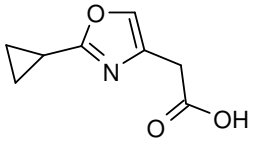
Preparación 154: (2-ciclopropil-1,3-oxazol-4-il)acetato de etilo



Se agregó 4-cloroacetoacetato de etilo (20,0 g, 122,0 mmoles) a ciclopropanocarboxamida (3,52 g, 41,5 mmoles) en tolueno (100 ml) y 1,4-dioxano (100 ml). La mezcla se reflujó a 120ºC durante 17 horas a continuación se evaporó al vacío. El sólido bruto se purificó por cromatografía de columna sobre gel de sílice (80:20 éter de petróleo: EtOAc) para dar el compuesto en forma de un sólido blancuzco en 50% de rendimiento, 4,00 g.

^{1}H RMN (300 MHz, DMSO-d_6) δ*:* 0,80-1,00 (m, 4H), 1,20 (t, 3H), 2,10 (m, 1H), 3,50 (s, 2H), 4,10 (q, 2H), 7,80 (s, 1H).

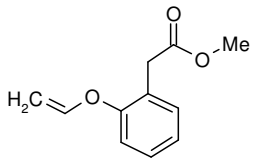
Preparación 155: Ácido (2-ciclopropil-1,3-oxazol-4-il)acético**.**



Se agregó monohidrato de hidróxido litio (7,83 g, 186,7 mmoles) a (2-ciclopropil-1,3-oxazol-4-il)acetato de etilo (preparación 154, 7,00 g, 35,9 mmoles) en THF (200 ml) y agua (100 ml). La mezcla se agitó a temperatura ambiente durante 2 horas a continuación el volumen de la mezcla de reacción se redujo a un tercio por evaporación al vacío. El residuo acuoso se acidificó utilizando HCl acuoso (1,0 M) a continuación se extrajo con EtOAc (200 ml). La fase orgánica se evaporó al vacío y el material bruto se trituró con éter dietílico (100 ml) para dar el compuesto del título en forma de un sólido de color blanco en 66% de rendimiento, 4,00 g.

^{1}H RMN (300 MHz, $CDCl_3$) δ*:* 1,05 (m, 4H), 2,10 (m, 1H), 3,60 (s, 2H), 7,40 (s, 1H), 10,00 (br s, 1H).

Preparación 156: [2-(viniloxi)fenil]acetato de metilo

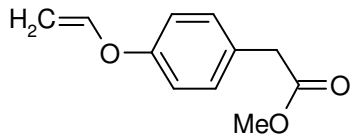


Se agregó acetato de cobre (1,42 g, 7,82 mmoles) a DCM (6 ml) y se agitó durante 20 minutos, con un tubo de secado unido. Se agregaron trivinilcicloboroxano (1,24 g, 5,16 mmoles), carbonato de cesio (2,55 g, 7,82 mmoles) y 2-hidroxifenil acetato de metilo (1,30 g, 7,82 mmoles) y la mezcla se agitó a temperatura ambiente durante 17 horas. Se agregó bicarbonato de sodio acuoso saturado (25 ml) y la mezcla se extrajo con DCM (20 ml). La fase orgánica se filtró, se secó sobre sulfato de magnesio y se evaporó al vacío para dar el compuesto del título en forma de un aceite de color negro en 52% de rendimiento, 784 mg. Este material se utilizó bruto en pasos

posteriores.

^{1}H RMN (400 MHz, $CDCl_3$) δ: 3,67 (s, 2H), 3,39 (s, 3H), 4,40 (dd, 1H), 4,69 (dd, 1H), 6,59 (dd, 1H), 6,97-7,08 (m, 2H), 7,23-7,28 (m, 2H).

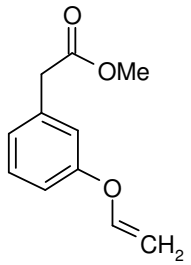
Preparación 157: [4-(viniloxi)fenil]acetato de metilo



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 156 utilizando 4-hidroxifenil acetato de metilo para dar el compuesto del título en forma de un aceite incoloro en 70% de rendimiento, 914 mg.

^{1}H RMN (400 MHz, $CDCl_3$) δ: 3,58 (s, 2H), 3,39 (s, 3H), 4,42 (m, 1H), 4,75 (m, 1H), 6,62 (m, 1H), 6,94-6,97 (m, 2H), 7,21-7,24 (m, 2H).

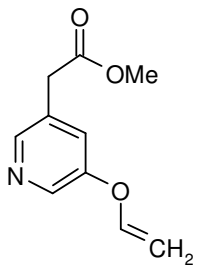
Preparación 158: [3-(viniloxi)fenil]acetato de metilo



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 156 utilizando 3-hidroxifenil acetato de metilo para dar el compuesto del título en forma de un aceite incoloro en 56% de rendimiento, 835 mg.

^{1}H RMN (400 MHz, $CDCl_3$) δ: 3,61 (s, 2H), 3,70 (s, 3H), 4,44 (m, 1H), 4,78 (m, 1H), 6,63 (m, 1H), 6,89-6,94 (m, 2H), 7,00 (m, 1H), 7,27 (m, 1H).

Preparación 159: [5-(viniloxi)piridin-3-IL]acetato de metilo

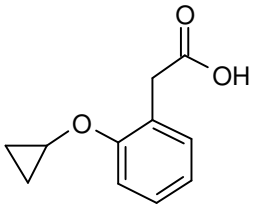


El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 156 utilizando 5-(5-hidroxipiridin-3-il)acetato de

metilo para dar el compuesto del título en forma de un sólido de color amarillo en 25% de rendimiento, 76 mg.

LCMS (sistema 2): T_r = 0,85 min; m/z 194 $[M+H]^+$.

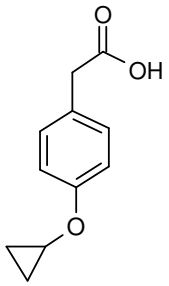
Preparación 160: Ácido [2-(ciclopropiloxi)fenil]acético



Se enfrió dietil zinc (2,34 ml, 2,34 mmoles, 1M en heptano) hasta 0ºC en nitrógeno a continuación se agregó gota a gota cloroyodometano (0,35 ml, 4,68 mmoles) en DCE (1 ml). La mezcla se agitó en nitrógeno a 0ºC durante 20 minutos a continuación se agregó [2-(viniloxi)fenil]acetato de metilo (Preparación 156, 150 mg, 0,78 mmoles) en DCE (1 ml). La mezcla de reacción se agitó a 0ºC durante 30 minutos a continuación se agitó a temperatura ambiente durante 17 horas. Se agregó cloruro de amonio acuoso saturado (10 ml) y la mezcla se extrajo con DCM (4 x 8 ml). Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron al vacío. Se agregó hidróxido de sodio (3,28 ml, 3,28 mmoles, 1M) al residuo en THF (3 ml). La mezcla se calentó a 80ºC durante 17 horas a continuación se evaporó al vacío. Se agregó ácido clorhídrico (10 ml, 1M) al residuo a continuación se extrajo con EtOAc (10 ml). La fase orgánica se evaporó al vacío para dar el compuesto del título en forma de un aceite de color amarillo en 53% de rendimiento, 83 mg.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 0,65-0,71 (m, 4H), 3,54 (s, 2H), 3,71 (m, 1H), 6,82-6,87 (m, 2H), 7,05-7,23 (m, 2H).

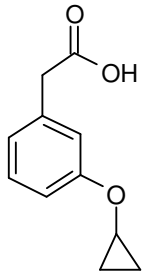
Preparación 161: Ácido [4-(ciclopropiloxi)fenil]acético



Se preparó de acuerdo con el método que se describe para la preparación 160 utilizando [4-(viniloxi)fenil]acetato de metilo (preparación 157) para dar el compuesto del título en forma de un aceite incoloro en 44% de rendimiento, 360 mg.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 0,65-0,71 (m, 4H), 3,59 (s, 2H), 3,71 (m, 1H), 6,99-7,02 (m, 2H), 7,16-7,20 (m, 2H).

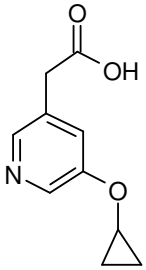
Preparación 162: Ácido [3-(ciclopropiloxi)fenil]acético



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 160 utilizando [3-(viniloxi)fenil]acetato de metilo (preparación 158) para dar el compuesto del título en forma de un aceite incoloro en 33% de rendimiento, 50 mg.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 0,74–0,81 (m, 4H), 3,57–3,67 (m, 2H), 3,72 (m, 1H), 6,74-7,03 (m, 3H), 7,22 (m, 1H).

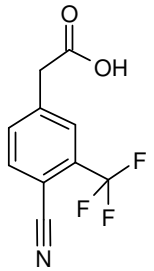
Preparación 163: Ácido [5-(ciclopropiloxi)piridin-3-il]acético



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 160 utilizando [5-(viniloxi)piridin-3-il]acetato de metilo (preparación 159) para dar el compuesto del título en forma de un aceite de color amarillo en 38% de rendimiento, 28 mg.

LCMS (sistema 2): T_r = 0,55 min; m/z 194 $[M+H]^+$.

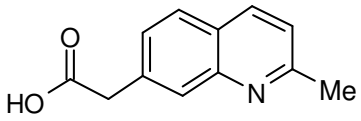
Preparación 164: Ácido [4-ciano-3-(trifluorometil)fenil]-acético



Se agregó diisopropilamida de litio (13,8 ml, 24,8 mmoles, 1,8 M en THF) a 4-metil-2-(trifluorometil)benzonitrilo (2,30 g, 12,4 mmoles) en THF (20 ml) a -78ºC y se agitó durante 5 minutos a -78ºC. Se agregó exceso de dióxido de carbono sólido a continuación la mezcla se agitó a temperatura ambiente durante 17 horas. Se agregaron cloruro de amonio acuoso saturado (10,5 ml) y EtOAc (20 ml) a continuación la capa acuosa se acidificó con solución ácida de HCl (1 M). Esto se extrajo con EtOAc (3 x 15 ml) y las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron al vacío para dar el compuesto del título en forma de un aceite de color marrón en 88% de rendimiento, 2,52 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 3,81 (s, 2H), 7,62 (d, 1H), 7,73 (s, 1H), 7,83 (d, 1H).

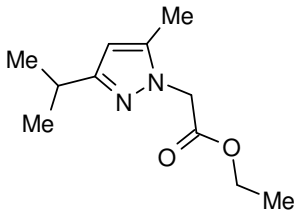
Preparación 165: Ácido (2-metilquinolin-7-il)acético



Se agregó aldehído crotónico (33,0 ml, 0,40 moles) al ácido 3-aminofenilacético (30,0 g, 0,20 mmoles) en ácido clorhídrico concentrado (400 ml) y tolueno (100 ml) a 110ºC. La mezcla se calentó a 110ºC durante 90 minutos. La capa se separó, se lavó con éter dietílico (350 ml) a continuación se neutralizó con amoníaco acuoso. La solución acuosa se lavó con cloroformo (3 x 500 ml) y la fase orgánica se evaporó al vacío. El residuo sólido se reflujó con cloroformo (900 ml) y metanol (100 ml) a continuación la solución se decantó y se purificó por cromatografía de columna sobre gel de sílice (gradiente de cloroformo:MeOH 9:1 para dar una mezcla de ácidos isoméricos. Esto se purificó por cristalización fraccional utilizando isopropanol para dar el compuesto del título en forma de un sólido de color blanco en 12% de rendimiento, 4,90 g.

^{1}H RMN (400 MHz, DMSO-d6) δ*:* 2,64 (s, 3H), 3,78 (s, 2H), 7,37 (d, 1H), 7,44 (dd, 1H), 7,80 (s, 1H), 7,84 (d, 1H), 8,19 (d, 1H), 12,40 (br s, 1H).

Preparación 166: (3-isopropil-5-metil-1H-pirazol-1-il)acetato de etilo

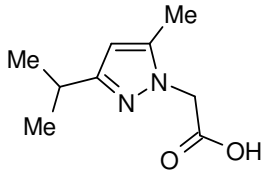


Se agregó bromoacetato de etilo (1,00 ml, 9,03 mmoles) a 5-isopropil-3-metil-1H-pirazol (1,07 g, 8,60 mmoles) y carbonato de potasio (3,57 g, 25,9 moles) en DMF

(10 ml). La mezcla se agitó a temperatura ambiente durante 17 horas a continuación se agregaron EtOAc (20 ml) y HCl acuoso (20 ml, 1M). La fase orgánica se secó sobre sulfato de magnesio a continuación se evaporó al vacío. El residuo se purificó por cromatografía de columna de gel de sílice (hexano:EtOAc 4:1) para dar el compuesto del título en forma de un aceite de color amarillo en 34% de rendimiento, 607 mg.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,26 (m, 9H), 2,03 (s, 3H), 2,96 (m, 1H), 4,21 (q, 2H), 4,78 (s, 2H), 7,13 (s, 1H).

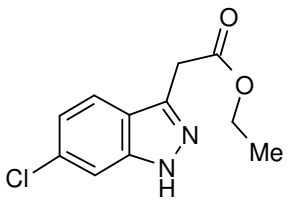
Preparación 167: Ácido (3-isopropil-5-metil-1H-pirazol-1-il)acético



Se agregó hidróxido de litio (342 mg, 8,15 mmoles) en agua (4 ml) a (3-isopropil-5-metil-1H-pirazol-1-il)acetato de etilo (preparación 166, 571 mg, 2,72 mmoles) en metanol (4 ml) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Se agregó ácido clorhídrico acuoso (2 m) para acidificar la mezcla a continuación la solución se extrajo con EtOAc (10 ml). La fase orgánica se secó sobre sulfato de magnesio y se evaporó al vacío para dar el compuesto del título en forma de un sólido de color crema en 66% de rendimiento, 328 mg.

m/z 183 $[M+H]^+$

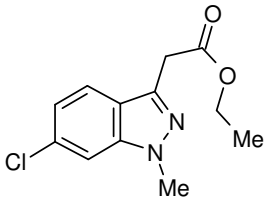
Preparación 168: (6-cloro-1H-indazol-3-il)acetato de etilo



Se agregó ácido sulfúrico concentrado (0,25 ml) a una solución de ácido (6-cloro-1H-indazol-3-il)acético (2,024 g, 9,60 mmoles) en EtOH (10 ml). La mezcla se calentó a 80ºC durante 4 horas a continuación se evaporó al vacío. El residuo se separó entre EtOAc (30 ml) y 5% de bicarbonato de sodio acuoso (30 ml). La fase orgánica se secó sobre sulfato de sodio, se evaporó al vacío y se purificó por cromatografía de columna sobre gel de sílice (DCM:MeOH 99:1) para dar el compuesto 3 en forma de un sólido de color blanco e n83% de rendimiento, 1,90 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 1,17 (t, 3H), 4,00 (s, 2H), 4,10 (q, 2H), 7,11 (d, 1H), 7,56 (s, 1H), 7,74 (d, 1H), 13,00 (s, 1H).

Preparación 169: (6-cloro-1-metil-1H-indazol-3-il)acetato de etilo

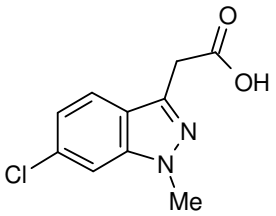


Se agregó hidruro de sodio (24 mg, 0,602 mmoles, 60% en aceite) a (6-cloro-1H-indazol-3-il)acetato de etilo (preparación 168, 120 mg, 0,502 mmoles) en THF (4 ml), a 0ºC y la mezcla se agitó durante 30 minutos. A continuación se agregó yodometano (0,09 ml, 1,508 mmoles). La mezcla se agitó a temperatura ambiente durante 30 min, posteriormente se agregó agua (4 ml). La mezcla se evaporó al vacío y el residuo acuoso se acidificó con HCl acuoso (6 M). Esto se extrajo con acetato de etilo (10) y la fase orgánica se secó sobre sulfato de sodio y se evaporó al vacío para dar el compuesto del título en forma de un sólido de color blanco en 100% de rendimiento, 150 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 1,18 (t, 3H), 3,89 (s, 3H), 4,07 (s, 2H), 4,13 (q, 2H), 7,15 (d, 1H), 7,56 (s, 1H), 7,74 (d, 1H);

LCMS (sistema 9): T_r = 3,48 min; m/z 253 $[M+H]^+$.

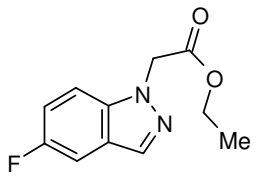
Preparación 170: Ácido (6-cloro-1-metil-1H-indazol-3-il)-acético



Se agregó hidróxido de potasio (5,93 ml, 10%) a (6-cloro-1-metil-1H-indazol-3-il)acetato de etilo (preparación 169, 1,78 g, 0,704 mol) en MeOH (30 ml). La mezcla se agitó durante 1 hora a 25ºC a continuación el metanol se evaporó al vacío. El residuo acuoso se lavó con éter dietílico (30 ml) a continuación se acidificó con HCl acuoso(6 M). La mezcla se extrajo con acetato de etilo (30 ml) y la fase orgánica se secó sobre sulfato de sodio, se evaporó al vacío y se purificó por cromatografía de columna sobre gel de sílice (DCM:MeOH 95: 5) para dar el compuesto en forma de un sólido blancuzco en 56% de rendimiento, 865 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 3,79 (s, 2H), 4,14 (s, 3H), 7,12 (d, 1H), 7,73 (d, 1H), 7,83 (s, 1H). 12,51 (s, 1H).

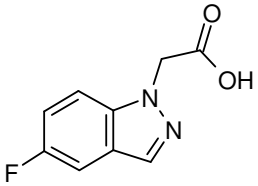
Preparación 171: (5-fluoro-1H-indazol-1-il)acetato de etilo



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 93 utilizando 5-fluoro-1H-indazol y bromoacetato de etilo para dar el compuesto del título en forma de un sólido blancuzco en 53% de rendimiento, 260 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 1,24 (t, 3H), 4,22 (q, 2H), 5,13 (s, 2H), 7,17 (m, 1H), 7,28 (m, 1H), 7,37 (d, 1H), 7,99 (s, 1H); LCMS (Sistema 9): T_r = 3,14 min; m/z 223 $[M+H]^+$.

Preparación 172: Ácido (5-fluoro-1H-indazol-1-il)acético

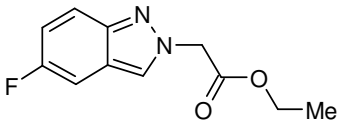


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 155 utilizando (5-fluoro-1H-pirazol-1-il)acetato de etilo (preparación 171) para dar el compuesto del título en forma de un sólido de color amarillo en 62% de rendimiento, 140 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 5,26 (s, 2H), 7,28 (m, 1H), 7,54 (dd, 1H), 7,68 (dd, 1H), 8,06 (s, 1H), 13,11 (br s, 1H).

LCMS (sistema 9): T_r = 1,49 min; m/z 193 $[M-H]^-$

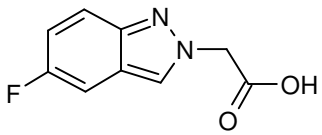
Preparación 173: (5-fluoro-2H-indazol-2-il)acetato de etilo



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 93 utilizando 5-fluoro-1H-indazol y bromoacetato de etilo para dar el compuesto del título en forma de un sólido blancuzco en 27% de rendimiento, 130 mg.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,26 (t, 3H), 4,25 (q, 2H), 5,17 (s, 2H), 7,06-7,11 (m, 1H), 7,21-7,24 (m, 1H), 7,64-7,68 (m, 1H), 7,96 (s, 1H); LCMS (System 9): T_r = 3,04 min; m/z 223 $[M+H]^+$

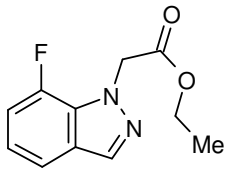
Preparación 174: Ácido (5-fluoro-2H-indazol-2-il)acético



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 155 utilizando (5-fluoro-2H-pirazol-2-il)acetato de etilo (preparación 173) para dar el compuesto del título en forma de un sólido de color amarillo en 100% de rendimiento, 160 mg.

LCMS (sistema 9): T_r = 1,49 min; m/z 193 $[M-H]^-$

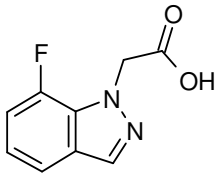
Preparación 175: (7-fluoro-1H-indazol-1-il)acetato de etilo



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 93 utilizando 7-fluoro-1H-indazol y bromoacetato de etilo para dar el compuesto del título en forma de un sólido blancuzco en 41% de rendimiento, 200 mg.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,29 (t, 3H), 4,22 (q, 2H), 5,28 (s, 2H), 6,98-7,07 (m, 2H), 7,49 (m, 1H), 8,02 (d, 1H).

Preparación 176: Ácido (7-fluoro-1H-indazol-1-il)acético

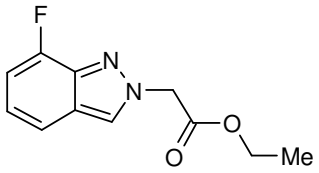


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 155 utilizando (7-fluoro-1H-pirazol-1-il)acetato de etilo (preparación 175) para dar el compuesto del título en forma de un sólido de color amarillo en 68% de rendimiento, 120 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 5,27 (s, 2H), 7,12 (m, 1H), 7,23 (m, 1H), 7,60 (d, 1H), 8,17 (d, 1H), 13,18 (br s, 1H); LCMS (System 9):

T_r = 1,38 min; m/z 195 $[M+H]^+$

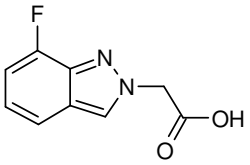
Preparación 177: (7-fluoro-2H-indazol-2-il)acetato de etilo



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 93 utilizando 7-fluoro-1H-indazol y bromoacetato de etilo para dar el compuesto del título en forma de un sólido blancuzco en 35% de rendimiento, 175 mg.

^{1}H NMR (400 MHz, $CDCl_3$) δ*:* 1,28 (t, 3H), 4,25 (q, 2H), 5,28 (s, 2H), 6,93 (m, 1H), 6,99 (m, 1H), 7,43 (d, 1H), 8,06 (d, 1H).

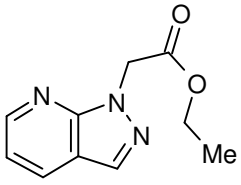
Preparación 178: Ácido (7-fluoro-2H-indazol-2-il)acético



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 155 utilizando (7-fluoro-2H-pirazol-2-il)acetato de etilo (preparación 177) para dar el compuesto del título en forma de un sólido de color amarillo en 75% de rendimiento, 110 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 5,34 (s, 2H), 6,97-7,05 (m, 2H), 7,56 (d, 1H), 8,50 (d, 1H), 13,30 (br s, 1H); LCMS (System 9): T_r = 1,40 min; m/z 195 $[M+H]^+$

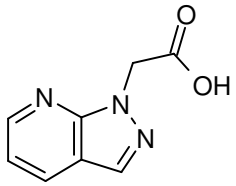
Preparación 179: 1H-pirazol[3,4-b]piridin-1-ilacetato de etilo



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 93 utilizando 1*H*-pirazolo[3,4-*b*]piridina y bromoacetato de etilo para dar el compuesto del título en forma de un sólido blancuzco en 49% de rendimiento, 210 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 1,19 (t, 3H), 4,14 (q, 2H), 5,35 (s, 2H), 7,27 (m, 1H), 8,22 (s, 1H), 8,27 (d, 1H), 8,55 (d, 1H).

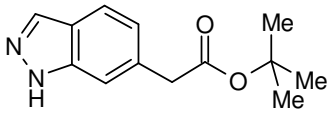
Preparación 180: Ácido 1H-pirazolo[3,4-b]piridin-1-ilacético



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 155 utilizando 1H-pirazol[3,4-b]piridin-1-ilacetato de etilo (véase preparación 179) para dar el compuesto del título en forma de un sólido de color amarillo en 40% de rendimiento, 70 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 5,22 (s, 2H), 7,25 (dd, 1H), 8,19 (dd, 1H), 8,27 (dd, 1H), 8,55 (s, 1H), 13,15 (br s, 1H).

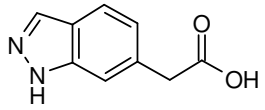
Preparación 181: 1H-indazol-6-ilacetato de ter-butilo



Se desgasificaron 6-bromo-1H-indazol (1,3 g, 6,6 mmoles) y t-butilacetato (1,33 ml, 9,9 mmoles) en tolueno (20 ml) con argón durante 15 minutos. A continuación la mezcla se enfrió hasta 0ºC y se agregó gota a gota LiHMDS (16,5 ml, 16,5 mmoles, 1M en hexano). Se agregaron bis(dibencilidenoacetona)paladio (380 mg, 0,66 mmoles) y tri-t-butil fosfina tetrafluoroborato (383 mg, 1,32 mmoles) y la mezcla se agitó a 10ºC durante 2 horas. La mezcla se templó con agua (10 ml) y se extrajo con EtOAc (3 x 25 ml). Las fases orgánicas combinadas se lavaron con agua (2 x 10 ml), salmuera (10 ml), y se secaron sobre sulfato de sodio (Na_2SO_4). El filtrado se evaporó al vacío y se purificó por cromatografía de columna de gel de sílice (hexano:EtOAc 80:20) para dar el compuesto del título en forma de un aceite de color blanco 65%, 1,00 g).

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,43 (s, 9H), 3,64 (s, 2H), 7,08 (dd, 1H), 7,39 (s, 1H), 7,69 (d, 1H), 8,03 (s, 1H), 10,05 (br s, 1H).

Preparación 182: Ácido 1H-indazol-6-ilacético

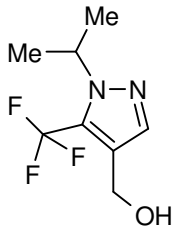


Se agregó ácido clorhídrico (10 ml, 4M en 1,4-dioxano) a 1H-indazol-6-ilacetato de ter-butilo (preparación 181, 1,00 g, 4,3 mmoles) en 1,4-dioxano (5 ml) a 0ºC y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla se evaporó al

vacío y el residuo se trituró con éter seco ara dar el compuesto del título en forma de un sólido de color blanco en 100% de rendimiento, 800 mg.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 3,69 (s, 2H), 7,00 (d, 1H), 7,41 (s, 1H), 7,67 (d, 1H), 8,02 (s, 1H), 12,81 (br s, 1H).

Preparación 183: [1-isopropil-5-(trifluorometil)-1H-pirazol-4-il]metanol

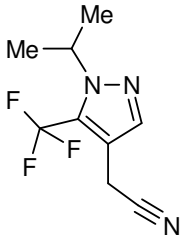


Se agregó hidruro de diisobutilaluminio (99 ml, 120 mmoles, solución 1,2 M en tolueno) a 1-isopropil-5-(trifluorometil)-1H-pirazol-4-carboxílato de etilo ((WO 2007071900, 12 g, 48 mmoles) en tolueno (220 ml) a -78ºC. La mezcla de reacción se agitó a -78ºC durante 2 horas a continuación se vertió en HCl acuoso (100 ml, 2M). La mezcla se agitó durante 4 horas a temperatura ambiente a continuación se extrajo con EtOAc (400 ml). La fase orgánica se lavó con agua (200 ml), salmuera (200 ml), y se secó sobre sulfato de sodio. El filtrado se evaporó al vacío para dar el compuesto del título en forma de un aceite incoloro en 100% de rendimiento, 10,5 g.

^{1}H RMN (400 MHz, $CDCl_3$) δ*:* 1,51 (d, 6H), 4,57-4,66 (m, 3H), 7,58 (s, 1H).

^{1}H RMN (400 MHz, DMSO) δ: 1,26 (s, 4H), 3,83 (s, 2H), 6,47 (d, 1H), 7,26 (d, 1H), 8,83 (s, 1H), 8,88 (s, 1H); LCMS (sistema 10): T_r = 1,67 min; m/z 189,9 $[M+H]^+$.

Preparación 184: [1-isopropil-5-(trifluorometil)-1H-pirazol-4-il]acetonitrilo



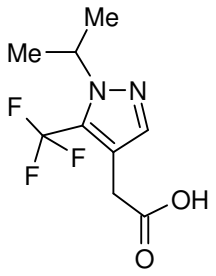
Se agregó cloruro de tionilo (5,26 ml, 72 mmoles) a [1-isopropil-5-(trifluorometil)-1H-pirazol-4-il]metanol (preparación 183, 7,5 g, 36 mmoles) en DCM (75 ml) a 0ºC y la mezcla se agitó durante 2 horas. La mezcla se diluyó con DCM (30 ml) y la fase orgánica se lavó con agua (75 ml), salmuera (75 ml) y se secó sobre sulfato de sodio. El filtrado se evaporó al vacío para dar 4-(clorometil)-1-isopropil-5-(trifluorometil)-1*H*-pirazol en 86% de rendimiento, 7 g.

Se agregó bromuro de tetrabutil amonio (7,95 g, 24,7 mmoles) a 4-(clorometil)-

1-isopropil-5-(trifluorometil)-1*H*-pirazol (7 g, 31 mmoles) en dioxano (75 ml) y agua (75 ml) y la mezcla se agitó durante 10 min. Se agregó cianuro de potasio (7,42 g, 114 mmoles) y la mezcla se agitó durante 16 horas a temperatura ambiente. La mezcla se diluyó con EtOAc (100 ml) y la fase orgánica se lavó con agua (100 ml), salmuera (100 ml) y se secó sobre sulfato de sodio. El filtrado se evaporó al vacío y se purificó por cromatografía de columna de gel de sílice (hexano:EtOAc 90:10) para dar el compuesto del título en forma de un aceite de color blanco 100%, 7,00 g).

^{1}H RMN (400 MHz, DMSO-d6) δ*:* 1,43 (s, 6H), 3,99 (d, 2H), 4,61 (s, 1H), 7,71 (s, 1H).

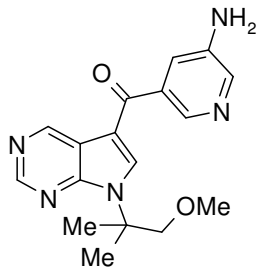
Preparación 185: Ácido [1-isopropil-5-(trifluorometil)-1H-pirazol-4-il]acético



Se agregó hidróxido de sodio acuoso (150 ml de una solución 1M) a [1-isopropil-5-(trifluorometil)-1H-pirazol-4-il]acetonitrilo (preparación 184, 6,2 g, 28,6 mmoles) en EtOH (150 ml) y la mezcla se calentó a 60ºC durante 16 horas. La mezcla se evaporó al vacío y el residuo se disolvió en agua (50 ml) a continuación se lavó con EtOAc (100 ml). La fase acuosa se acidificó hasta 5 utilizando HCl 1N y se extrajo con 10% de IPA en DCM (4 x 100 ml). Las fases orgánicas combinadas se secaron sobre sulfato de sodio y se evaporaron al vacío para dar el compuesto del título en forma de un sólido de color blanco en 75% de rendimiento, 5,0 g.

^{1}H RMN (400 MHz, DMSO-d6) δ*:* 1,42 (s, 6H), 3,56 (d, 2H), 4,58 (m, 1H), 7,57 (s, 1H), 12,28 (br s, 1H).

Preparación 186: (5-amino-piridin-3-il)-[7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-il]-metanona

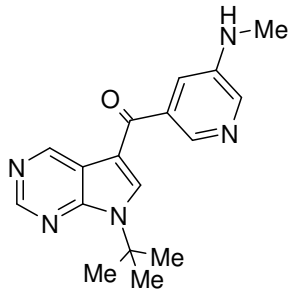


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 65 utilizando (5-bromo-piridin-3-il)-[7-(2-metoxi-1,1-dimetil-etil)-7H-

pirrolo[2,3-d]pirimidin-5-il]-metanona (preparación 263) para dar el compuesto del título en forma de un sólido blancuzco en 41% de rendimiento, 650 mg.

^{1}H RMN (400 MHz, DMSO-D6) δ 1,76 (s, 6H), 3,19 (s, 3H), 3,96 (s, 2H), 5,65 (s, 2H), 7,30 (s, 1H), 8,05 (s, 1H), 8,16 (s, 2H), 8,97 (s, 1H), 9,44 (s, 1H); LCMS (sistema 10): T_r = 2,56 min; m/z 327 $[M+H]^+$.

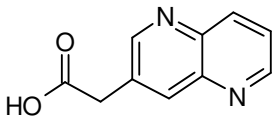
Preparación 187: (7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)-(5-metilamino-piridin-3-il)-metanona



Se trató ter-butil éster del ácido [5-(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-metil-carbámico (ejemplo 542) con HCl 4N en dioxano a temperatura ambiente durante 2 horas. La solvente se eliminó al vacío y el sólido obtenido se trituró con éter dietílico para dar el compuesto del título en forma de un sólido de color blanco en 100% de rendimiento, 76 mg.

$^{+1}$H RMN (400 MHz, DMSO-*d6*) δ: 1,80 (s, 9H), 2,84 (s, 3H), 7,27 (br s, 1 H), 8,21 (d, 1H), 8,29 (s, 1H), 8,41 (s, 1H), 9,03 (s, 1H), 9,49 (s, 1H); LCMS (sistema 10): T_r = 2,74 min; m/z 310 $[M+H]^+$.

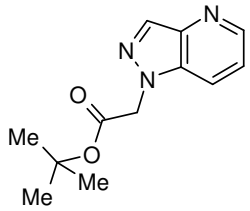
Preparación 188: Ácido 1,5-naftiridin-3-ilacético



Una mezcla de 3-bromo-1,5-naftiridina (540 mg, 2,58 mmoles), dietilmalonato (0,8 ml, 5,17 mmoles) y carbonato de cesio (2,53 g, 7,75 mmoles) en 1,4-dioxano (6 ml) se desgasificó con argón durante 15 minutos a continuación se agregó ácido picolínico (64 mg, 0,517 mmoles) y CuI (50 mg, 0,258 mmoles). La mezcla se calentó en un tubo cerrado a 110ºC durante 24 horas a continuación se enfrió hasta temperatura ambiente , se diluyó con acetato de etilo (10 ml), se lavó con agua (10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de sodio a continuación se evaporó al vacío y se purificó por cromatografía de columna sobre gel de sílice (hexano:EtOAc 70:30) para dar 450 mg de 1,5-naftiridin-3-ilacetato de etilo.

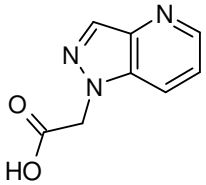
Se agregó hidróxido de sodio (10 ml, 2,0 m) a 1,5-naftifiridin-3-ilacetato de etilo en 1,4-dioxano (10 ml) y la mezcla se calentó a 100ºC durante 6 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se acidificó hasta pH 4 utilizando HCl 2M acuoso y a continuación se evaporó al vacío. El residuo se azeotropeó con tolueno (2 x 15 ml) a continuación se disolvió en THF (50 ml) y se agitó a 40ºC durante 30 min. La mezcla se filtró, el filtrado se evaporó al vacío y el residuo se trituró con éter dietílico para dar el compuesto del título en forma de un sólido blancuzco, 200 mg.
^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 3,94 (s, 2H), 7,76 (m, 1H), 8,31 (s, 1H), 8,42 (d, 1H), 8,91 (d, 1H), 8,99 (dd, 1H), 12,65 (br s, 1H); LCMS (System 10): T_r = 1,49 min; m/z 187 $[M-H]^+$

Preparación 189: 1H-pirazol[4,3-b]piridin-1-ilacetato de ter-butilo



Se agregó bromoacetato de ter-butilo (0,55 ml, 3,69 mmoles) a 1H-pirazolo[4,3-b]piridina (220 m, 1,85 mmoles) y Cs_2CO_3 (723mg, 2,22 mmoles) en DMF anhidro (7 ml). La mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó con acetato de etilo (50 ml), se lavó con agua (3 x 30 ml), salmuera (30 ml), se secó sobre sulfato de sodio, se evaporó al vacío y se purificó por cromatografía de columna sobre gel de sílice (hexano:EtOAc 80:20) para dar una goma incolora en 51% de rendimiento, 220 mg.
^{1}H RMN (400 MHz, DMSO-D_6) δ: 1,39 (s, 9H), 5,32 (s, 2H), 7,42 (dd, 1H), 8,14 (d, 1H), 8,32 (s, 1H), 8,55 (d, 1H).

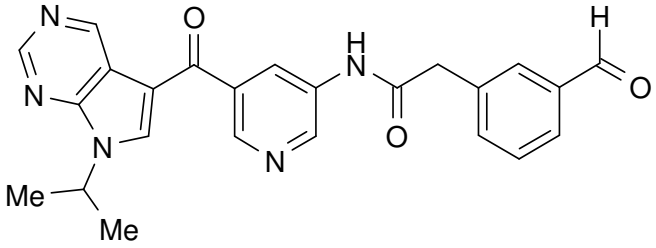
Preparación 190: Ácido 1H-pirazolo[4,3-b]piridin-1-ilacético



Se disolvió 1H-pirazolo[4,3-b]piridin-1-ilacetato de ter-butilo (preparación 189, 220 mg, 0,944 mmoles) en HCl (4 ml, 4,0 M en 1,4-dioxano) y se agitó en nitrógeno a temperatura ambiente durante 4 horas. La mezcla se evaporó al vacío y el residuo se trituró con éter dietílico anhidro ara dar el compuesto del título en forma de un sólido de color blancuzco en 60% de rendimiento, 120 mg.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 5,36 (s, 2H), 7,51 (dd, 1H), 8,30 (d, 1H), 8,36 (s, 1H), 8,62 (d, 1H); LCMS (Sistema 10): Tr = 1,39 min; m/z 176 $[M-H]^+$.

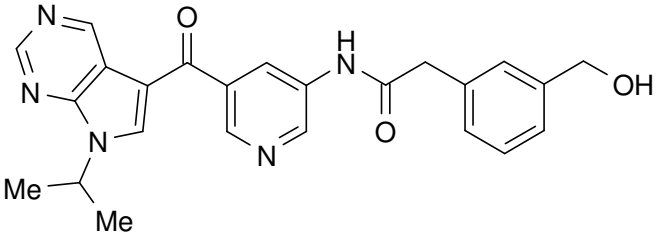
Preparación 192: 2-(3-formilfenil)-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida



Se agregó Dess Martin periodinano (392 mg, 0,93 mmoles) a una solución de 2-[3-(hidroximetil)fenil])-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida (preparación 193, 265 mg, 0,62 mmoles) en diclorometano (15 ml) y la mezcla se agitó a temperatura ambiente durante 18 horas. Se agregó agua (10 ml) y la capa acuosa se extrajo con una mezcla 95:5 de diclorometano /metanol (3 x 10 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron al vacío. El residuo se purificó por cromatografía de columna utilizando gel de sílice (gradiente de diclorometano a diclorometano/metanol 10:0 a 9:1) para dar el compuesto del título en forma de un sólido de color marrón en 80% de rendimiento, 211 mg.

LCMS (sistema 4): T_r = 2,11 min; m/z 428 $[M+H]^+$.

Preparación 193: 2-[3-(hidroximetil)fenil])-N-{5-[(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}acetamida

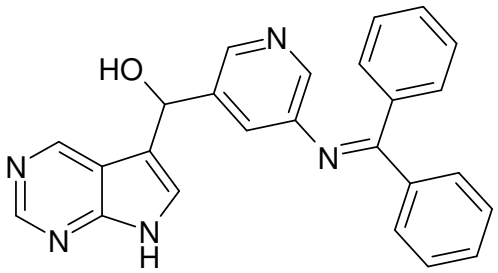


Una mezcla de (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (preparación 95, 250 mg, 0,89 mmoles), ácido [4-(hidroximetil)fenil]acético (177 mg, 1,06 mmoles) y HATU (505 mg, 1,33 mmoles) en piridina (7 ml) se agitó a 50ºC durante 3 horas, a continuación a temperatura ambiente durante 18 horas. La mezcla se concentró al vacío y se azeotropeó con tolueno. El residuo se purificó por

cromatografía de columna utilizando gel de sílice (gradiente de diclorometano a diclorometano/metanol 10:0 a 9:1) para dar el compuesto del título en forma de una goma. Este material se disolvió en una mezcla 9:1 de diclorometano/metano (1,5 ml) y se agregó gota a gota a éter dietílico (100 ml), el precipitado resultante se filtró y se secó al vacío para dar el compuesto del título en forma de un sólido de color blanco, 412 mg, el cual se utilizó bruto en reacciones posteriores.

LCMS (sistema 2): T_r = 1,33 min; m/z 430 $[M+H]^+$.

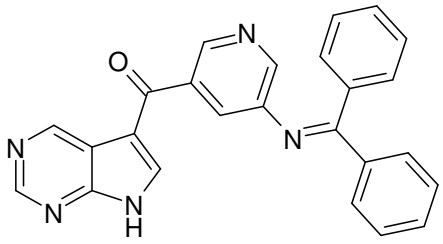
Preparación 194: {5-[(difenilmetileno)amino]piridin-3-il}(7H-pirrolo[2,3-d]pirimidin-5-il)metanol



Una mezcla de 7H-pirrolo[2,3-d]pirimidina (preparación 202, 953 mg, 8,0 mmoles), 5-[(difenilmetileno)amino]nicotinaldehído (preparación 106, 3,340 mg, 11,7 mmoles) y KOH (1,350 mg, 24 mmoles) en MeOH (16 ml) se agitó durante 16 horas a temperatura ambiente. La reacción se neutralizó con solución de cloruro de amonio acuoso saturado y la mezcla se extrajo con EtOAc (3 x 200 ml). Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron al vacío para obtener un residuo bruto. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de EtOAc:MeOH 100:0 a 80:20) para dar el compuesto del título en forma de un sólido en 62% de rendimiento, 2,003 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 5,88-5,99 (m, 2H), 6,96-6,99 (m, 1H), 7,04-7,14 (m, 3H), 7,16-7,27 (m, 3H), 7,43-7,51 (m, 2H), 7,51-7,58 (m, 1H), 7,64-7,69 (m,2H), 7,89 (d, 1H), 8,21 (d, 1H), 8,72 (s, 1H), 8,73 (s, 1H), 11,92 (br s, 1H)

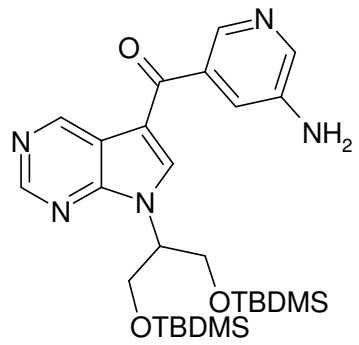
Preparación 195: {5-[(difenilmetileno)amino]piridin-3-il}(7H-pirrolo[2,3-d]pirimidin-5-il)metanona



A una solución agitada de {5-[(difenilmetileno)amino]piridin-3-il}(7H-pirrolo[2,3-d]pirimidin-5-il)metanol (preparación 194, 1,820 mg, 4,5 mmoles) en MeCN (45 ml) se agregó MnO_2 (1960 mg, 22,5 mmoles) en porciones y la mezcla resultante se agitó a 50ºC durante toda la noche. Se agregó otra porción de MnO_2 (1960 mg, 22,5 mmoles) a la reacción y la mezcla se calentó a reflujo durante 5 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se filtró a través de un taco de arbocel, la torta de filtro se enjuagó con DCM (100 ml) y el filtrado resultado se concentró al vacío. El material resultante se purificó por cromatografía de columna sobre gel de sílice (gradiente de EtOAc:MeOH 100:0 a 90:10) para dar el compuesto del título en forma de un sólido en 61% de rendimiento, 1,120 mg.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 7,24-7,33 (m, 2H), 7,37-7,64 (m, 7H), 7,64-7,78 (m, 3H), 8,28 (d, 1H), 8,53 (d, 1H), 8,94 (s, 1H), 9,41 (s, 1H), 13,09 (br s, 1H)

Preparación 196: (5-aminopiridin-3-il){7-[2-{[*ter*-butil(dimetil)silil]oxi}-({[ter-butil(dimetil)silil]oxi}metil)etil]-7*H*-pirrolo[2,3-*d*]pirimidin-5-il}metanona



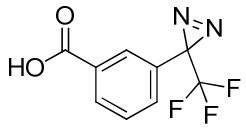
Una mezcla de {5-[(difenilmetileno)amino]piridin-3-il}(7H-pirrolo[2,3-d]pirimidin-5-il)metanona (preparación 195, 1,120 mg, 2,77 mmoles) y Cs_2CO_3 (2,710 mg, 8,31 mmoles) en DMF (10 ml) se agitó a temperatura ambiente durante 30 minutos. Una solución de 2,2,3,3,9,9,10,10-octametil-4,8-dioxa-3,9-disilaundecan-6-il trifluorometanosulfonato bruto (preparación 108) en DMF (3,8 ml) se agregó a continuación a la reacción y la mezcla resultante se agitó a temperatura ambiente durante 16 horas. La reacción se templó con cloruro de amonio acuoso saturado (100 ml) y la mezcla se extrajo con EtOAc (100 ml x 3). Las capas orgánicas combinadas se lavaron con agua (5 ml), se secaron sobre sulfato de sodio y se concentraron al vacío. El material resultante se purificó por cromatografía de columna sobre gel de sílice (gradiente de heptano:EtOAc 100:0 a 50:50) para dar (5-((difenilmetileno)amino)piridin-3-il)(7-(2,2,3,3,9,9,10,10-octametil-4,8-dioxa-3,9-

disilaundecan-6-il)-7H-pirrolo[2,3-d]pirimidin-5-il)metanona.

El material anterior se disolvió en THF (20 ml) y se agregó ácido nítrico acuoso 1N (20 ml) a la solución. La mezcla de reacción se agitó durante 4 horas a temperatura ambiente, se diluyó con agua (100 ml) y se basificó con NaOH hasta pH 7. La mezcla resultante se extrajo con EtOAc (3 x 150 ml), las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron al vacío. El material resultante se purificó por cromatografía de columna sobre gel de sílice (hetano:EtOAc = 40:60 a 0:100) para dar el compuesto deseado en forma de un sólido de color blanco en 49% de rendimiento, 739 mg.

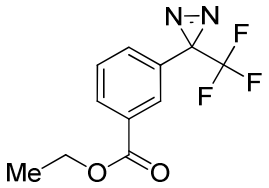
^{1}H RMN (400 MHz, DMSO-d_6) δ: -0,11 (s, 6H), -0,07 (s, 6H), 0,68 (s, 18H), 3,99-4,16 (m, 4H), 5,01-5,11 (m, 1H), 5,65 (br s, 2H), 7,21-7,26 (m, 1H), 8,13 (d, 1H), 8,17 (d, 1H), 8,38 (s, 1H), 8,98 (s, 1H), 9,44 (s, 1H).

Preparación 197: Ácido 3-(3-(trifluorometil)-3H-diazirin-3-il)benzoico



Se agitó 3-(3-(trifluorometil)-3H-diazirin-3-il)benzoato de etilo (preparación 198, 60 mg, 0,23 mmoles) en una mezcla 2:1 de THF:agua (2 ml). Se agregó hidróxido de litio (5 mg, 0,23 mmoles) y la mezcla se agitó a 25ºC durante 18 horas. La mezcla de reacción se acidificó hasta pH 1 utilizando ácido clorhídrico acuoso 6M y a continuación se extrajo con acetato de etilo (3 x 20 ml). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio y se evaporaron al vacío para dar el compuesto del título en forma de un sólido en 75%, 40 mg. Este material se utilizó en el próximo paso sin purificación posterior.

Preparación 198: 3-(3-(trifluorometil)-3H-diazirin-3-il)benzoato de metilo

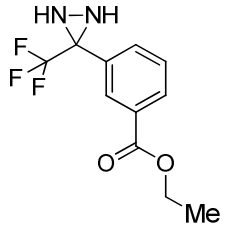


Se agitó 3-(3-(trifluorometil)diazirin-3-il)benzoato de etilo (preparación 199, 226 mg, 0,87 mmoles) en metanol (10 ml) con trietilamina (0,36 ml, 2m61 mmoles). Se disolvió yodo (662 mg, 2,61 mmoles) en 2 ml de metanol y se agregó en porciones hasta que persistió el color naranja-marrón. La mezcla de reacción se evaporó al vacío, y el residuo se diluyó con NaOH ac. 1M (30 ml) y a continuación se extrajo con EtOAc (3 x 30 ml). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se

evaporaron al vacío para dar el compuesto del título en forma de un goma en 27%, 60 mg. Este material se utilizó en el próximo paso sin purificación posterior.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,40 (t, 3H), 4,38 (q, 2H), 7,46-7,51 (m, 2H), 7,83 (s, 1H), 8,08 (d, 1H).

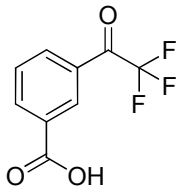
Preparación 199: 3-(3-(trifluorometil)diazirin-3-il)benzoato de etilo



A una solución de 3-(2,2,2-trifluoroacetil)benzoato de etilo (500 mg, 2,15 mmoles) en etanol se agregó piridina (5 ml) y clorhidrato de hidroxilamina (500 mg, 7,2 mmoles) y la mezcla resultante se agitó a 57ºC durante 3 horas. La mezcla de reacción se enfrió y se pasó a través de una columna de intercambio iónico eluyendo con metanol (30 ml). La solución de metanol se evaporó al vacío para dar 3-(2,2,2-trifluoro-1-(hidroxiimino)etil)benzoato de (E)-etilo en forma de un aceite en 71% de rendimiento, 401 mg el cual se utilizó en el próximo paso sin purificación posterior. A una solución agitada de 3-(2,2,2-trifluoro-1-(hidroxiimino)etil)benzoato de (E)-etilo (401 mg, 1,54 mmoles) en diclorometano (10 ml) se agregó DMAP (17 mg, 0,14 mmoles) y la mezcla se enfrió hasta 0ºC. Se agregó cloruro de 4-metilbenceno-1-sulfonilo (331 mg, 1,74 mmoles) en porciones en forma de una solución en diclorometano (5 ml). La mezcla de reacción se dejó asentar posteriormente a temperatura ambiente durante 18 horas. La mezcla se diluyó con agua (10 ml) y la capa orgánica se separó, se secó sobre sulfato de magnesio y se evaporó al vacío para dar 3-(2,2,2-trifluoro-1-(tosiloxi)imino)etil)benzoato de (E)-etilo en forma de un aceite en 78% de rendimiento 500 mg. Este material se utilizó en el próximo paso sin purificación posterior. Una mezcla de 3-(2,2,2-trifluoro-1-(tosiloxi)imino)etil)benzoato de (E)-etilo (500 mg, 1,2 mmoles) en éter dietílico (5 ml) en un matraz de 3 cuellos equipado con un termómetro interno y un condensador se enfrió hasta -78ºC. Se introdujo gas amoníaco durante 5 min y a continuación se continuó la agitación durante 45 min. La mezcla de reacción se entibió hasta -33ºC y se agitó durante 2 horas después de lo cual se dejó entibiar hasta temperatura ambiente durante toda la noche con agitación. La mezcla se evaporó al vacío y el material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de diclorometano:acetato de etilo 100:0 a 90:10) para dar el compuesto del título en forma de una goma en 76% de rendimiento, 240mg.

^{1}H RMN (400 MHz, DMSO) δ*:* 1,31 (t, 3H), 4,31 (q, 2H), 7,40-7,44 (m, 1H), 7,74 (d, 1H), 8,02 (d, 1H), 8,20 (s, 1H).

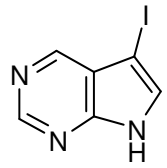
Preparación 200: Ácido 3-(2,2,2-trifluoroacetil)benzoico



El compuesto del título se preparó de acuerdo con el método que se describió para la preparación 42 partiendo de 3-(2,2,2-trifluoroacetil)benzoato de etilo para dar el compuesto del título en forma de un sólido de color blanco en 26% de rendimiento, 23 mg.

^{1}H RMN (400 MHz, DMSO) δ*:* 7,71 (t, 1H), 8,32 (d, 1H), 8,45 (d, 1H), 8,80 (s, 1H).

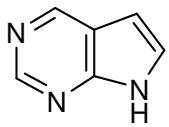
Preparación 201: 5-yodo-7H-pirrolo[2,3-d]pirimidina



Una mezcla de 7H-pirrolo[2,3-d]pirimidina (preparación 202, 28,0 g, 235 mmoles) y N-yodosuccinimida (55,4 g, 246 mmoles) en acetonitrilo (470 ml) se agitó a temperatura ambiente durante 16 horas. Los sólidos se filtraron, se enjuagaron con acetonitrilo (150 ml) y se secaron al vacío. El sólido se disolvió en 1,5 litros de solución de hidróxido de sodio acuoso 1N y se agregó solución de cloruro hidrógeno acuoso 2N hasta aprox. pH 9. El precipitado resultante se filtró, se enjuagó con agua (300 ml), y se secó al vacío durante 16 horas a 70ºC, aprox. 10 mbar, para dar el compuesto del título en 81% de rendimiento, 46,84 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 7,82 (s, 1H), 8,73 (s, 1H), 8,80 (s, 1H), 12,56 (br s, 1H); LCMS (sistema 1): T_r = 0,87 min; m/z 246 $[M+H]^+$.

Preparación 202: 7H-pirrolo[2,3-d]pirimidina

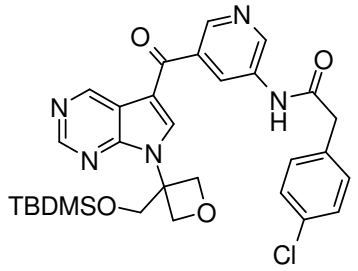


En cada uno de los cuatro recipientes de reacción separados, se suspendió 4-cloro-7H-pirrolo[2,3-d]pirimidina (50,0 g, 260 mmoles) en etanol (1,4 l) y solución de hidróxido de amonio concentrado (140 ml). Se agregó 10% de paladio sobre carbono

(2,5 g) a cada recipiente y la mezcla se presurizó hasta 20 psi hidrógeno y se agitó a temperatura ambiente durante toda la noche. Esas reacciones que todavía contienen el material de partida se cargaron con otro 1 g de 10% de paladio sobre carbono, se presurizó hasta 20 psi hidrógeno y se agitó hasta que el material de partida se había consumido. La mezcla de reacción se filtró sobre arbocel, se lavó con etanol, y el filtrado se evaporó para obtener un sólido de color blanco. Los cuatro productos de reacción brutos se combinaron, se suspendieron en 500 ml de agua y se extrajeron con acetato de etilo (3 x 500 ml). Las capas orgánicas se combinaron, se secaron sobre sulfato de magnesio, se filtraron y el filtrado se concentró al vacío para obtener 122 g de un sólido de color blanco. La capa acuosa se extrajo posteriormente con 5% de metanol en acetato de etilo (3 x 500 ml), las capas orgánicas se combinaron, se secaron sobre sulfato de magnesio, se filtraron y el filtrado se concentró al vacío para obtener otros 30 g del sólido de color blanco. Los sólidos se combinaron para obtener el compuesto del título en 98% de rendimiento, 152 g

^{1}H RMN (400 MHz, DMSO) δ*:* 6,63 (dd, 1H), 7,43 (dd, 1H), 8,96 (s, 1H), 9,07 (s, 1H), 11,65 (br. s., 1 H).

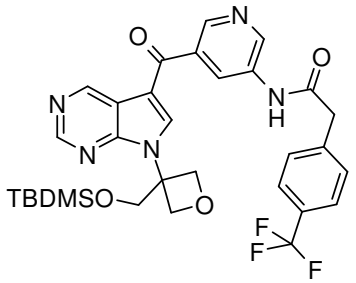
Preparación 203: N-(5-{7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-piridin-3-il)-2-(4-cloro-fenil) acetamida:



Se disolvió (5-amino-piridin-3-il)-{7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona (preparación 216, 30 mg, 0,068 mmoles) en piridina seco (2 ml) en nitrógeno y a esto se agregó ácido (4-cloro-fenil)-acético (17 mg, 0,102 mmoles) seguido de HATU (39 mg, 0,102 mmoles). La reacción se calentó hasta 50ºC y se agitó durante toda la noche. La reacción se enfrió hasta temperatura ambiente, se diluyó con diclorometano y se agregó bicarbonato de sodio acuoso saturado. Las fases se separaron y la capa acuosa se extrajo con diclorometano (3 x 5 ml). Los orgánicos combinados se concentraron hasta sequedad para dar N-(5-{7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-piridin-3-il)-2-(4-cloro-fenil)-acetamida en forma de un sólido de color amarillo pálido, 35 mg, 87% de rendimiento.

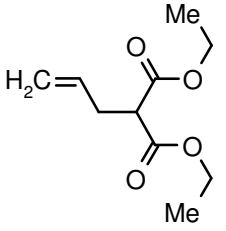
^{1}H RMN (400 MHz, $CDCl_3$) δ -0,23 (s, 6 H) 0,65 (s, 9 H) 3,77 (s, 2 H) 4,26 (s, 2 H) 4,89 (d, *J*=7,6 Hz, 2 H) 5,27 (d, *J*=7,8 Hz, 2 H) 7,30 (d, *J*=8,6 Hz, 2 H) 7,37 - 7,44 (m, 2 H) 7,72 (s, 1 H) 8,49 (s, 1 H) 8,70 (d, *J*=2,3 Hz, 1 H) 8,78 (s, 1 H) 8,94 (s, 1 H) 9,64 (s, 1 H).

Preparación 204: N-(5-{7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-piridin-3-il)-2-(4-trifluorometil-fenil)-acetamida:



Se disolvió (5-amino-piridin-3-il)-{7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona (preparación 216, 30 mg, 0,068 mmoles) en piridina seco (2 ml) en nitrógeno y a esto se agregó ácido (4-trifluorometil-fenil)-acético (21 mg, 0,102 mmoles) seguido de HATU (39 mg, 0,102 mmoles). La mezcla de reacción se calentó hasta 50ºC y se agitó durante toda la noche. La reacción se enfrió a continuación hasta temperatura ambiente, se diluyó con diclorometano (5 ml) y se agregó bicarbonato de sodio acuoso saturado (5 ml). Las fases se separaron y la capa acuosa se extrajo con diclorometano (3 x 5 ml). Los orgánicos combinados se concentraron hasta sequedad para dar N-(5-{7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-piridin-3-il)-2-(4-trifluorometil-fenil)-acetamida en forma de un sólido de color amarillo pálido, 39 mg, 92% de rendimiento.
^{1}H RMN (400 MHz, DMSO-d_6) δ -0,29 (s, 6 H) 0,58 (s, 9 H) 3,84 (s, 2 H) 4,16 (s, 2 H) 4,77 (d, *J*=7,4 Hz, 2 H) 5,21 (d, *J*=7,4 Hz, 2 H) 7,56 (d, *J*=7,8 Hz, 2 H) 7,68 (d, *J*=7,8 Hz, 2 H) 8,28 (s, 1 H) 8,46 (t, *J*=2,1 Hz, 1 H) 8,69 (d, *J*=2,0 Hz, 1 H) 8,91 - 8,95 (m, 2 H) 9,46 (s, 1 H) 10,71 (s, 1 H).

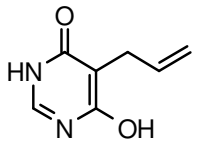
Preparación 205: Dietil éster del ácido 2-alil-malónico



Se agregó dietil éster del ácido malónico (100 g, 0,625 moles) gota a gota a 0ºC a una mezcla de etóxido de sodio (46,8 g, 0,688 moles) en etanol (1 litro). La

mezcla de reacción se agitó durante 4 horas. Se agregó gota a gota 3-bromo-propeno (83,2 g, 0,688 moles) a la mezcla a 0ºC. Después de la adición, la mezcla se entibió hasta reflujo y se agitó durante toda la noche. La mezcla se enfrió hasta temperatura ambiente, se filtró y el solvente se eliminó al vacío para dar el compuesto del título en 86% de rendimiento, 100 g el cual se utilizó para el próximo paso sin purificación posterior.

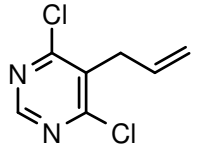
Preparación 206: 5-alil-6-hidroxi-3H-pirimidin-4-ona



Se agregó gota a gota dietil éster del ácido 2-alil-malónico (preparación 205, 100 g, 0,5 mol) a una mezcla de metóxido de sodio (27 g, 0,5 mol) en etanol (1 litro) a 0-5ºC y la mezcla se agitó a esta temperatura durante 10 min. Se agregó formamidina acetato (51,9 g, 0,5 moles) y la mezcla se agitó a temperatura ambiente durante toda la noche. El solvente se eliminó al vacío, y se agregaron ácido clorhídrico acuoso (36,5%) y agua para ajustar el pH hasta aproximadamente 3 a 0-20ºC. La mezcla resultante se filtró para dar el compuesto del título en forma de un sólido incoloro en 57% de rendimiento, 87,12 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ: 2,96 (d, 1H), 4,89 (m, 2H), 5,76 (m, 1H), 7,89 (s, 1H).

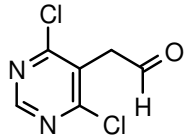
Preparación 207: 5-alil-4,6-dicloro-pirimidina



Se agregó 5-alil-6-hidroxi-3H-pirimidin-4-ona (preparación 206, 40 g, 0,263 moles) a $POCl_3$ (100 ml) a temperatura ambiente. La solución se agitó y se entibió hasta reflujo durante 8 horas. La mezcla se evaporó al vacío para eliminar la mayoría del $POCl_3$. El residuo se vertió lentamente sobre agua helada, el cual se extrajo con acetato de etilo (500 ml x 4), se lavó con salmuera (300 ml), se secó sobre sulfato de sodio y se evaporó al vacío para dar el compuesto del título en forma de un aceite de color amarillo en 59% de rendimiento, 31 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 3,59 (m, 2H), 5,09 (m, 2H), 5,79 (m, 1H), 8,59 (s, 1H).

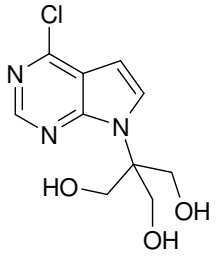
Preparación 208: (4,6-dicloro-pirimidin-5-il)-acetaldehído



A una solución agitada de 5-alil-4,6-dicloro-pirimidina (preparación 207, 30 g, 0,159 moles) en diclorometano seco (400 ml) se burbujeó ozono a -70ºC durante 30 min. Después que el exceso de ozono se purgó por gas nitrógeno, se agregó dimetil sulfuro (10 ml) a -5ºC, y la reacción se agitó durante 2 horas. La mezcla se lavó con agua, salmuera, se secó sobre sulfato de sodio, y se evaporó al vacío. El material bruto se purificó por trituración a partir de éter dietílico-pentano para dar el compuesto del título en forma de un sólido incoloro en 84% de rendimiento, 10 g.

^{1}H RMN (400 MHz, DMSO) δ*:* 4,15 (s, 2H), 8,74 (s, 1H), 9,80 (s, 1H).

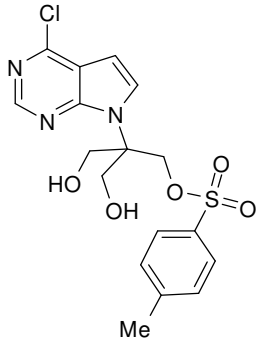
Preparación 209: 2-(4-cloro-pirrolo[2,3-d]pirimidin-7-il)-2-hidroximetil-propano-1,3-diol



Se agregó trisamina (1,27 g, 10,5 mmoles) a (4,6-dicloro-pirimidin-5-il)-acetaldehído (preparación 208, 1,0 g, 5,2 mmoles) en etanol (40 ml) y se agitó a temperatura de reflujo durante 16 horas. La mezcla de reacción se evaporó al vacío y se dividió entre diclorometano y bicarbonato de sodio acuoso saturado. La fase acuosa separada se extrajo con diclorometano dos veces más y los orgánicos combinados se lavaron con salmuera saturada y se evaporaron al vacío para dar el compuesto del título en forma de una espuma de color amarillo pálido en 74% de rendimiento, 1,0 g.

^{1}H RMN (400 MHz,$CDCl_3$) δ ppm 2,97 (br. s, 1H), 3,09 - 3,27 (m, 2H), 3,51 (d, *J*=9,18 Hz, 1H), 3,83 - 4,00 (m, 4H), 4,06 (d, *J*=11,13 Hz, 1H), 5,43 (dd, *J*=6,44, 1,76 Hz, 1H), 6,16 (dd, *J*=10,74, 4,69 Hz, 1H), 8,40 (s, 1H); LCMS (System 2): T_r = 1,04 min; m/z 258 $[M+H]^+$.

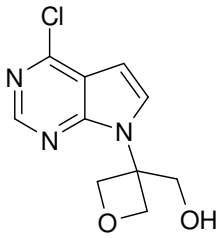
Preparación 210: 2-(4-cloro-pirrolo[2,3-d]pirimidin-7-il)-3-hidroxi-2-hidroximetil-propil éster del ácido tolueno-4-sulfónico



Se agregaron trietilamina (0,879 ml, 6,31 mmoles) y clorhidrato trimetilamina (253 mg, 2,65 mmoles) a una solución de 2-(4-cloro-pirrolo[2,3-d]pirimidin-7-il)-2-hidroximetil-propano-1,3-diol (preparación 209, 650 mg, 2,52 mmoles) en diclorometano (20 ml) a 0ºC. La mezcla se trató en porciones con cloruro de tosilo (505 mg, 2,65 mmoles) y se agitó a 0ºC durante 16 horas. La mezcla de reacción se trató con agua y se agitó durante 10 min. La mezcla resultante se lavó con ácido cítrico, bicarbonato de sodio acuoso saturado, y salmuera saturada, a continuación se evaporó al vacío. El producto bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de EtOAc:DCM 0:100 a 30:70) para dar el compuesto del título en forma de un sólido incoloro en 55% de rendimiento, 570 mg.

LCMS (sistema 2): T_r = 1,28 min; m/z 412 $[M+H]^+$.

Preparación 211: [3-(4-cloro-pirrolo[2,3-d]pirimidin-7-il)-oxetan-3-il]-metanol

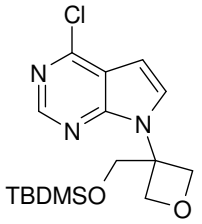


Se agregó n-butillitio (12,2 ml, 30,6 mmoles, 2,5 M en hexanos) al 2-(4-cloro-pirrolo[2,3-d]pirimidin-7-il)-3-hidroxi-2-hidroximetil-propil éster del ácido tolueno-4-sulfónico (preparación 210, 5,73 g, 13,9 mmoles) en THF (100 ml) a 0ºC y se agitó durante 5 min. La mezcla de reacción se entibió a continuación hasta temperatura ambiente y se agitó durante 16 horas, en cuyo momento se templó con cloruro de amonio acuoso saturado. La mezcla resultante se extrajo con acetato de etilo (100 ml x 3) y las fases orgánicas combinadas se secaron ($MgSO_4$) y se concentraron al vacío. El producto bruto se trituró con diclorometano y se filtró para dar el compuesto del título en 36% de rendimiento, 1,2 g,

^{1}H RMN (400 MHz, MeOH-d_4) δ: 4,15 (s, 2H), 4,92 (d, *J*=7,22 Hz, 2H), 5,22 (d, *J*=7,03

Hz, 2 H), 6,69 (d, *J*=3,51 Hz, 1H), 7,51 (d, *J*=3,71 Hz, 1H), 8,51 (s, 1H).

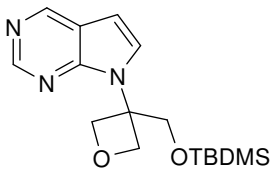
Preparación 212: 7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-4-cloro-7H-pirrolo[2,3-d]pirimidina



Se agregó imidazol (277 mg, 4,07 mmoles) a [3-(4-cloro-pirrolo[2,3-d]pirimidin-7-il)-oxetan-3-il]-metanol (preparación 211, 650 mg, 2,71 mmoles) en diclorometano (10 ml), y esta mezcla se trató con una solución de cloruro de t-butildimetilsililo (495 mg, 3,25 mmoles) en diclorometano (5 ml). La mezcla resultante se agitó a temperatura ambiente durante 16 horas, posteriormente se templó con agua (50 ml). La mezcla se extrajo con diclorometano (3 x 50 ml), y las fases orgánicas combinadas se lavaron con agua y salmuera saturada y se evaporaron al vacío para dar el compuesto del título en forma de un aceite de color marrón pálido en 91% de rendimiento, 875 mg.

^{1}H RMN (400 MHz, DMSO) δ*:* -0,21 (s, 6H), 0,77 (s, 9H), 4,22 (s, 2H), 4,88 (d, *J*=7,22 Hz, 2H), 5,19 (d, *J*=7,03 Hz, 2H), 6,61 (d, *J*=3,71 Hz, 1H), 7,11 (d, *J*=3,71 Hz, 1H), 8,55 (s, 1H); LCMS (sistema 2): T_r = 1,82 min; m/z 354 $[M+H]^+$.

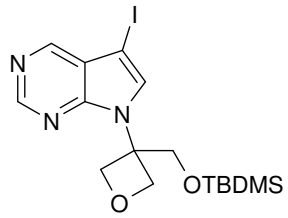
Preparación 213: 7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 8 utilizando 7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-4-cloro-7H-pirrolo[2,3-d]pirimidina (preparación 212) para dar el compuesto del título en forma de un aceite de color marrón en 82% de rendimiento, 650 mg.

^{1}H RMN (400 MHz, DMSO) δ*:* -0,24 (s, 6H), 0,76 (s, 9H), 4,24 (s, 2H), 4,91 (d, *J*=7,03 Hz, 2H), 5,22 (d, *J*=7,03 Hz, 2H), 6,55 (d, *J*=3,51 Hz, 1H), 7,08 (d, *J*=3,71 Hz, 1H), 8,78 (s, 1H), 8,97 (s, 1H); LCMS (sistema 2): T_r = 0,90 min; m/z 320 $[M+H]^+$.

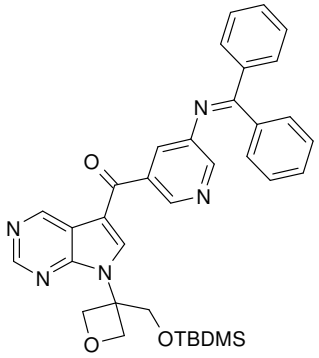
Preparación 214: 7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-5-yodo-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 14 utilizando 7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidina (preparación 213) y DMF para dar el compuesto del título en forma de un aceite de color marrón en 75% de rendimiento, 675 mg.

^{1}H RMN (400 MHz, DMSO) δ*:* -0,24 (s, 6H), 0,77 (s, 9H), 4,20 (s, 2H), 4,88 (d, *J*=7,22 Hz, 2H), 5,21 (d, *J*=7,03 Hz, 2H), 7,17 (s, 1H), 8,77 (s, 1H), 8,81 (s, 1H); LCMS (sistema 2): T_r = 1,55 min; m/z 446 $[M+H]^+$.

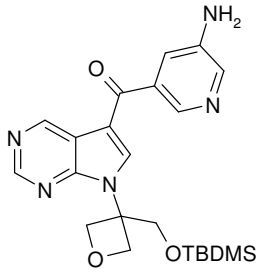
Preparación 215: (7-(3-(((ter-butildimetilsilil)oxi)metil)oxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il)(5-((difenilmetileno)amino)piridin-3-il)metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 24 utilizando 77-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-5-yodo-7H-pirrolo[2,3-d]pirimidina (preparación 214) y 5-[(difenilmetileno)amino]-N-metoxi-N-metilnicotinamida (preparación 23) para dar el compuesto del título en forma de un sólido de color púrpura en 51% de rendimiento, 240 mg.

^{1}H RMN (400 MHz, DMSO) δ*:* 0,20 (s, 6H), 0,70 (s, 9H), 4,28 (s, 2H), 4,89 (d, *J*=7,22 Hz, 2H), 5,20 (d, *J*=7,22 Hz, 2H), 7,11 - 7,18 (m, 2H), 7,33 (m, 3H), 7,40 - 7,48 (m, 2H), 7,49 - 7,57 (m, 3H), 7,79 (d, *J*=7,42 Hz, 2H), 8,18 (d, *J*=2,54 Hz, 1H), 8,60 (d, *J*=1,95 Hz, 1H), 8,93 (s, 1H), 9,60 (s, 1H).

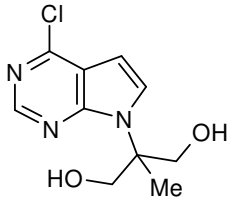
Preparación 216: (5-amino-piridin-3-il)-{7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 37 utilizando (7-(3-(((ter-butildimetilsilil)oxi)metil)oxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il)(5-((difenilmetileno)amino)piridin-3-il)metanona (preparación 215) para dar el compuesto del título en forma de un sólido incoloro en 76% de rendimiento, 132 mg.

^{1}H RMN (400 MHz, DMSO) δ*:* 0,01 (s, 6H), 0,88 (s, 9H), 4,11 (br. s, 2H), 4,45 (s, 2H), 5,17 (m, 2H), 5,40 (m, 2H), 7,58 (s, 1H), 7,80 (s, 1H), 8,45 (s, 1H), 8,61 (s, 1H), 9,15 (s, 1H), 9,83 (s, 1H).

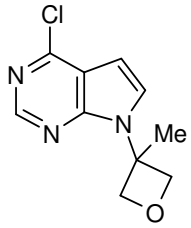
Preparación 217: 2-(4-cloro-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropan-1,3-diol



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 1 utilizando (4,6-dicloropirimidin-5-il)acetaldehído y (preparación 208) y 2-amino-2-metilpropano-1,3-diol para dar el compuesto del título en forma de un líquido de color amarillo en 79% de rendimiento, 3,88 g.

^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 1,66 (s, 3H), 3,86 (dd, 2H), 4,13 (dd, 2H), 4,92 (t, 2H), 6,58 (d, 1H), 7,73 (d, 1H), 8,59 (s, 1H).

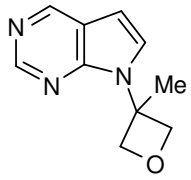
Preparación 218: 4-cloro-7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidina



Se agregó n-Buli (6,6 ml, de una solución 2,5 M en hexano, 16,5 mmoles) a una solución de 2-(4-cloro-7H-pirrolo[2,3-d]pirimidin-7-il)-2-metilpropan-1,3-diol (preparación 217, 3,63 g, 15,0 mmoles), en THF (80 ml) a -78ºC. La mezcla de

reacción se dejó entibiar hasta -50ºC en 2 horas y se agregó TsCl (3,15 mg, 16,5 mmoles) en THF (20 ml) a la reacción. La reacción se dejó entibiar hasta 0ºC en 3 horas y se agregó lentamente n-BuLi adicional (6,6 ml de una solución 2,5 M en solución de hexano, 16,5 mmoles) a la mezcla de reacción. La mezcla se agitó durante 1 hora a 0ºC y se agitó a 60ºC durante 16 horas. Después de enfriar hasta temperatura ambiente, la reacción se templó mediante 50 ml de solución de NH_4Cl acuoso saturado y 100 ml de agua, y la mezcla se extrajo con EtOAc (3 x 100 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron al vacío. El residuo bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de EtOAc:heptano 20:80 a 70:30) para dar un sólido en 55% de rendimiento, 1,87 mg.
^{1}H RMN (400 MHz, DMSO-d_6) δ: 1,79 (s, 3H) 4,72 (d, 2H) 5,15 (d, 2H) 6,69 (d, 1H) 7,78 (d, 1H) 8,59 (s, 1H).

Preparación 219: 7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidina

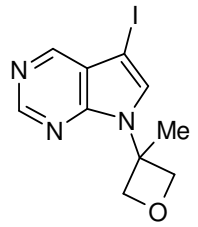


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 8 utilizando 4-cloro-7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidina (preparación 218) para dar el compuesto del título en forma de un líquido de color amarillo en 22% de rendimiento, 0,341 g.
^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 1,81 (s, 3H), 4,72-4,77 (m, 2H), 5,16-5,21 (m, 2H), 6,69 (d, 1H), 7,66 (d, 1H), 8,76 (s, 1H), 9,02 (s, 1H).

El compuesto del título además se preparó de acuerdo con el siguiente método: Se agregó lentamente LiHMDS (14,5 ml de una solución 1M en THF, 14,5 mmoles) a una solución de 2-metil-2-pirrolo[2,3-d]pirimidin-7-il-propano-1,3-diol (preparación 278, 3 g, 14,5 mmoles) en THF anhidro (200 ml) durante un período de 2 horas (utilizando una bomba de jeringa) en nitrógeno a 0ºC. Después de la terminación de la adición, la mezcla de reacción se agitó durante otros 40 min antes de agregar lentamente TsCl (2,76 g, 14,5 mmoles) en forma de una solución en THF (50 ml). La mezcla se agitó durante otra hora a 0ºC.. La TLC mostró el consume del material de partid y otro equivalente de LiHMDS (14,5 ml, 14,5 mmoles) se agregó a la mezcla y se calentó a 60º durante 16 horas. A continuación se agregó solución de NH_4Cl acuoso (200 ml) y la mezcla se extrajo con EtOAc (3 x 100 ml). Las capas orgánicas se secaron (Na_2SO_4) y se evaporaron al vacío. El material bruto se purificó por cromatografía de

columna sobre gel de sílice (gradiente de EtOAc:hecano 3:7 a 2:3) para dar el compuesto del título en forma de una goma incolora en 37% de rendimiento, 1 g.

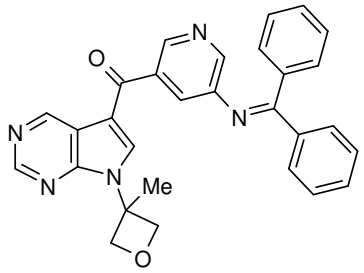
Preparación 220: 5-yodo-7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 14 utilizando 7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidina (preparación 219) para dar el compuesto del título en forma de un líquido de color amarillo en 78% de rendimiento, 0,44 g.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,80 (s, 3H), 4,71 (d, 2H), 5,18 (d, 2H), 7,94 (s, 1H), 8,76 (s, 1H), 8,82 (s, 1H).

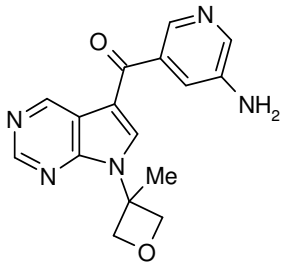
Preparación 221: {5-[(difenilmetileno)amino]piridin-3-il}(7-(3.metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il)metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 24 utilizando 5-cloro-7-(3-metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidina (preparación 220) para dar el compuesto del título.

LCMS (sistema 2): T_r = 1,24 min; m/z 474 $[M+H]^+$.

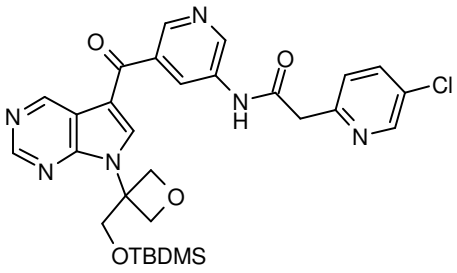
Preparación 222: {5-aminopiridin-3-il}[7-(3.metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il]metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 37 utilizando {5-[(difenilmetileno)amino]piridin-3-il}(7-(3.metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (preparación 221) para dar el compuesto del título en forma de un sólido de color blanco en 14% de rendimiento en dos pasos, 64 mg.

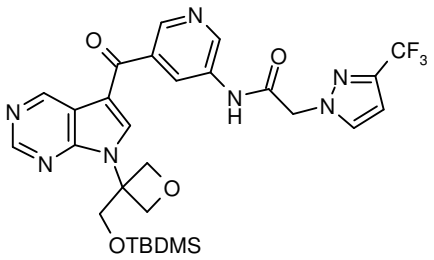
^{1}H RMN (400 MHz, DMSO-d_6) δ*:* 1,89 (s, 3H), 4,75 (d, 2H), 5,23 (d, 2H), 5,64 (br s, 2H), 7,29-7,36 (m, 1H), 8,17 (d, 1H), 8,24 (d, 1H), 8,41 (s, 1H), 8,95 (s, 1H), 9,46 (s, 1H); LCMS (Sistema 4): T_r = 2,30 min; m/z 310 $[M+H]^+$.

Preparación 223: N-[5-({7-[3-({[ter-butil(dimetil)silil]oxi}metil)oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-(5-cloropiridin-2-il)acetamida



Se agregó (5-amino-piridin-3-il)-{7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona (preparación 216, 30 mg, 0,068 mmoles) a una mezcla agitada del ácido (5-cloropiridin-2-il)acético (17,5 mg, 0,102 mmoles) y HATU (38,8 mg, 0,102 mmoles) en piridina (2 ml). La mezcla de reacción se entibió hasta 50ºC y se agitó a esta temperatura durante 14 horas. A continuación la reacción se enfrió y se agregó otra porción de HAT U(38,8 mg, 0,102 mmoles). La reacción se entibió hasta 50ºC y se agitó a esta temperatura durante 8 horas y a continuación se dejó enfriar hasta temperatura ambiente y se agitó durante otras 60 horas. La mezcla de reacción se diluyó posteriormente con DCM (20 ml) y la solución resultante se templó con $NaHCO_3$ saturado (20 ml). Las capas se separaron y la capa acuosa se extrajo con DCM (3 x 20 ml). Las capas orgánicas combinadas se lavaron con salmuera (20 ml) y a continuación se concentraron al vacío para dar el producto bruto en forma de un aceite de color amarillo pálido (35 mg) el cual se tomó para el uso en la preparación del ejemplo 238.

Preparación 224: N-[5-({7-[3-({[ter-butil(dimetil)silil]oxi}metil)oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[3-(trifluorometil)-1H-pirazol-1-il)acetamida



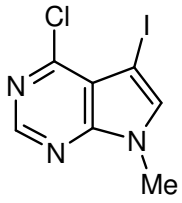
Se agregó (5-amino-piridin-3-il)-{7-[3-(ter-butil-dimetil-silaniloximetil)-oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona (preparación 216, 30 mg, 0,068 mmoles) a una mezcla agitada del ácido [3-(trifluorometil)-1H-pirazol-1-il]acético. (19,8 mg, 0,102 mmoles) y HATU (38,8 mg, 0,102 mmoles) en piridina (2 ml). La mezcla de reacción se entibió hasta 50ºC y se agitó a esta temperatura durante 14 horas. La mezcla de reacción enfrió hasta temperatura ambiente posteriormente y se diluyó con DCM (20 ml) y la solución resultante se templó con $NaHCO_3$ saturado (20 ml). Las capas se separaron y la capa acuosa se extrajo con DCM (3 x 20 ml). Las capas orgánicas combinadas se lavaron con salmuera saturada (20 ml) y a continuación se concentraron al vacío para dar el producto bruto en forma de un sólido de color amarillo pálido (44 mg) el cual se tomó para el uso en la preparación del ejemplo 239.

Preparación 225: 4-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina



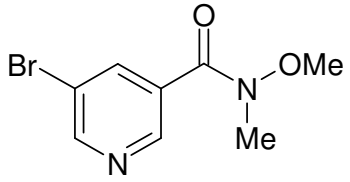
A una suspensión de 4-cloro-7H-pirrolo[2,3-d]pirimidina (70,5 g, 0,45 moles) en DCM (1,8 l) se agregó N-yodosuccinimida (120 g, 0,54 moles) en porciones. Después de la adicion, la mezcla se agitó a temperatura ambiente durante toda la noche. El sólido se filtró y se lavó con agua (250 ml), MeOH (280 ml) y CH_2Cl_2 (280 ml) en forma secuencial. El sólido se secó al vacío para dar 4-cloro-5-yodo-7H-pirrolo[2,3-*d*]pirimidina en forma de un sólido de color marrón e n79% de rendimiento, 107g.

Preparación 226: 4-cloro-5-yodo-7-metil-7H-pirrolo[2,3-d]pirimidina



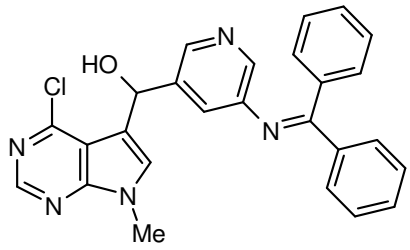
A una mezcla de 4-cloro-5-yodo-7H-pirrolo[2,3-*d*]pirimidina (preparación 225, 30 g, 0,1 mol), Cs_2CO_3 (50 g, 0,15 mol) en DMF (150 ml), MeI (28,4 g, 0,2 moles) se agregó gota a gota a 0ºC. Después de la adicion, la mezcla se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se enfrió hasta 0ºC y se templó por la adición de agua (500 ml). A continuación el sólido se recolectó por filtración y se lavó con Et_2O (100 ml) para dar 4-cloro-5-yodo-7-metil-7H-pirrolo[2,3-d]pirimidina en forma de un sólido de color marrón en 61% de rendimiento, 20g.

Preparación 227: 5-bromo-N-metoxi-N-metil-nicotinamida



A una solución de ácido 5-bromo-nicotínico (100 g, 0,5 moles) en THF (2 l) a 0ºC, se agregó $(COCl)_2$ (95 g, 0,74 mol). Después de agitar durante 0,5 horas, se agregaron Et_3N (152 g, 1,5 mol) y O,N-dimetil hidroxilamina HCl (140 g, 1,5 mol). La mezcla de reacción se agitó a temperatura ambiente durante 2,5 horas y a continuación se agregaron agua (200 ml) y EtOAc (500 ml). La capa orgánica se separó, se secó ($MgSO_4$) y se concentró al vacío para dar el compuesto del título en forma de un aceite de color marrón en 82% de rendimiento, 100%.

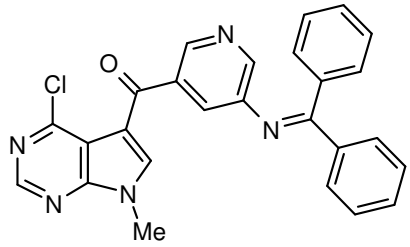
Preparación 228: (4-cloro-7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)(5-((difenilmetileno)amino)piridin-3-il)metanol



A una solución agitada de 4-cloro-5-yodo-7-metil-7H-pirrolo[2,3-d]pirimidina (preparación 226, 6,6 g, 22,7 mmoles) en THF (130 ml) se agregó n-BuLi (18,2 ml de una solución 2,5M en hexano, 45 mmoles) a -75ºC en N_2 y la mezcla se agitó durante 50 min. Una solución de 5-((difenilmetileno)nicotinaldehído (preparación 106, 6,5 g, 22,7 mmoles) en THF seco (50 ml) se agregó y la mezcla se agitó a -70ºC durante 80 min. La mezcla se templó con solución de NH_4Cl acuoso saturado y se extrajo con EtOAc (300 ml). La capa orgánica se secó (Na_2SO_4) y se concentró al vacío para dar el compuesto del título en forma de un sólido de color marrón en 48% de rendimiento,

5,2g.

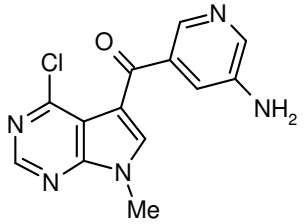
Preparación 229: (4-cloro-7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)(5-((difenilmetileno)amino)piridin-3-il)metanona



A una solución de (4-cloro-7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)(5-((difenilmetileno)amino)piridin-3-il)metanol (preparación 228, 11,4 g, 25 mmoles) en CH_2Cl_2 (150 ml), se agregó en porciones Dess-Martin periodinano (15,9 g , 37 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 10 horas, y posteriormente se agregó NaOH (30 ml). La mezcla se agitó a 50ºC otra 0,5 hora. A continuación la mezcla se separó y la capa acuosa se extrajo por CH_2Cl_2 (100 ml × 2). Las capas orgánicas combinadas se concentraron y se lavaron con éter para dar el compuesto del título en forma de un sólido de color marrón en 99% de rendimiento, 11g.

^{1}H RMN (400 MHz, $CDCl_3$) δ 3,87 (s, 3H), 7,06 (m, 2H), 7,27 (m, 3H), 7,37 (m, 2H), 7,45 (m, 3H), 7,71 (m, 2H), 8,15 (d, J=2,4,1H), 8,49 (d, J=1,2,1H), 8,68 (s, 1H).

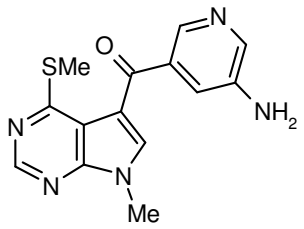
Preparación 230: (5-aminopiridin-3-il)(4-cloro-7-metil-7H-pirrolo[2,3-*d*]pirimidin-5-il)-metanona



Un solución de [5-(benzidrilideno-amino)piridin-3-il]-(4-cloro-7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 229, 30 g, 0,066 mmoles) en THF (200 ml) se agregó ácido cítrico acuoso (200 ml), la mezcla se agitó a temperatura ambiente durante 30 minutos. Se agregó éter y las capas se separaron. La capa acuosa se ajustó hasta pH 7 por Na_2CO_3 acuoso. A continuación la mezcla se filtró. La torta de filtro se evaporó con tolueno y el residuo se lavó con EtOAc (200 ml) para dar el compuesto del título en forma de un sólido de color marrón en 95% de rendimiento,

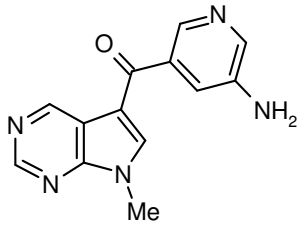
18g.

Preparación 231: (5-aminopiridin-3-il)(7-metil-4-metilsulfanil-7H-pirrolo[2,3-*d*]pirimidin-5-il)-metanona



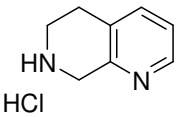
A una solución de (5-amino-piridin-3-il)-(4-cloro-7-metil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 230, 21 g, 0,073 moles) en MeOH (300 ml) se agregó CH_3SNa (15,5 g, 0,22 mol). La mezcla resultante se agitó durante 7 horas a temperatura ambiente. La mezcla se vertió en agua helada (200 ml), el precipitado se filtró, la torta de filtro se lavó con agua (100 ml) a continuación acetona (20 ml) para dar (5-aminopiridin-3-il)(7-metil-4-metilsulfanil-7H-pirrolo[2,3-*d*]pirimidin-5-il)-metanona en forma de un sólido de color marrón en 69% de rendimiento, 15 g.

Preparación 232: (5-aminopiridin-3-il)(7-metil-7H-pirrolo[2,3-*d*]pirimidin-5-il)-metanona



Una mezcla de (5-aminopiridin-3-il)(7-metil-4-metilsulfanil-7H-pirrolo[2,3-*d*]pirimidin-5-il)-metanona (preparación 231, 1,5 g, 5 mmoles) Ni Raney (10 g) y NH_3H_2O (150 ml) en dioxano (150 ml) se reflujó durante 6 horas. La mezcla se filtró a través de celite, y se concentró. El residuo se purificó mediante HPLC preparativa para dar (5-aminopiridin-3-il)(7-metil-7H-pirrolo[2,3-*d*]pirimidin-5-il)-metanona en forma de un sólido de color marrón en 15% de rendimiento, 0,19 g. ^{1}H RMN (400 MHz DMSO-d_6) 3,88 (s, 3H), 5,63 (s, 2H), 7,27-7,28 (m, 1H), 8,15-8,18 (m, 2H), 8,40 (s, 1H), 8,97 (s, 1H), 9,42 (s, 1H).

Preparación 233: Clorhidrato 5,6,7,8-tetrahidro-[1,7]naftiridina

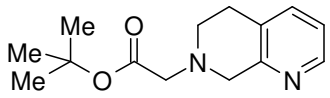


Una solución metanólica (25 ml) de 7-bencil-5,6,7,8-tetrahidro-[1,7]naftiridina (J. Het. Chem. 2001, 38, 535) (1,5g, 6,69 mmoles) se desgasificó con argón durante 20

min seguido de la adición de HCl 4N en dioxano (2 ml) y Pd/C (300 mg, 20% en peso) y se agitó en 50 psi de presión de hidrógeno a temperatura ambiente durante 24 horas. Después de la terminación de la reacción la mezcla se filtró sobre un taco corto de celite y se lavó con metanol (4 x 25 ml). El filtrado se evaporó hasta sequedad al vacío y se cristalizó a partir de metanol para dar el compuesto del título en forma de un sólido amarillento en 65% de rendimiento (calculado como sal 2HCl), 900 mg.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 3,10 (t, 2H), 3,40 (q, 2H), 4,36 (s, 2H), 7,50 (dd, 1H), 7,91 (d, 1H), 8,55 (d, 1H), 9,96 (brs, 2H); LCMS (sistema 10): T_r = 1,56 min; m/z 135,2 $[M+H]^+$.

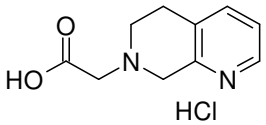
Preparación 234: Ter-butil éster del ácido (5,8-dihidro-6H[1,7]naftiridin-7-il)-acético



Una solución en DMF (8 ml) de Clorhidrato 5,6,7,8-tetrahidro-[1,7]naftiridina (preparación 233, 400 mg,1,93 mmoles), ter-butil éster del ácido bromo-acético (414,1 mg, 2,12 mmoles) y trietilamina (1,64 ml, 11,92 mmoles) se calentó a 80ºC durante 16 horas. La mezcla de reacción se diluyó con EtOAc (40 ml), se lavó con agua (3 x 25 ml), salmuera (20 ml), se secó sobre Na_2SO_4 y se evaporó hasta sequedad al vacío para dar el compuesto del título en forma de un sólido pegajoso incoloro en 100% de rendimiento, 480 mg.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,43 (s, 9H), 2,81 (s, 4H), 3,34 (s, 2H), 3,72 (s, 2H), 7,16 (dd, 1H), 7,51 (d, 1H), 8,29 (d, 1H); LCMS (system 10): T_r = 3,02 min; m/z 249,4 $[M+H]^+$.

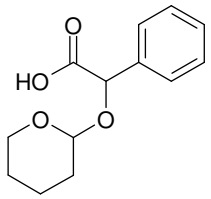
Preparación 235: Clorhidrato ácido (5,8-dihidro-6H[1,7]naftiridin-7-il)-acético



Se trató ter-butil éster del ácido (5,8-dihidro-6H[1,7]naftiridin-7-il)-acético (preparación 234, 1,25 g, 5,03 mmoles) con HCl 4N en dioxano (25 ml) a temperatura ambiente durante 2 horas. La mezcla se evaporó hasta sequedad al vacío y el residuo sólido se trituró con éter dietílico para dar el compuesto del título en forma de un sólido de color blanco en 78% de rendimiento (calculado como sal HCl), 900 mg.

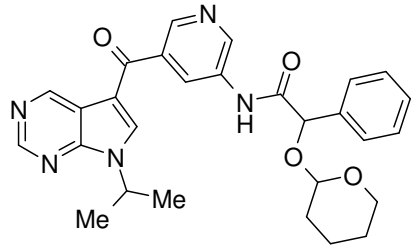
^{1}H RMN (400 MHz, MeOD) δ*:* 3,38 (t, 2H), 3,79 (t, 2H), 4,38 (s, 2H), 4,84 (s, 2H), 7,79 (dd, 1H), 8,25 (d, 1H), 8,70 (d, 1H).

Preparación 236: Ácido fenil-[(tetrahidro-piran-2-iloxi)]-acético



A una solución agitada del ácido hidroxi-fenil-acético (2 g, 13,4 mmoles) en DCM (30 ml) se agregó PTSA (51,2 mg, 0,27 mmoles) a 0ºC seguido de la adición de 3,4-dihidro-2H-piran (1,55 g, 18,4 mmoles). La mezcla se agitó a 0ºC durante otros 15 min y a continuación se entibió gradualmente hasta temperatura ambiente y se agitó durante otra 1,5 hora. La mezcla de reacción se diluyó con DCM (100 ml). La capa orgánica se lavó con Na_2CO_3 acuoso saturado (2 x 20 ml), agua (20 ml), salmuera (20 ml), se secó (Na_2SO_4) y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (EtOAc: éter de petróleo 2:5) para dar el compuesto del título en forma de un sólido pegajoso de color amarillo en 48% de rendimiento, 1,5 g. LCMS (sistema 10): T_r = 1,82 min; m/z 237 $[M+H]^+$.

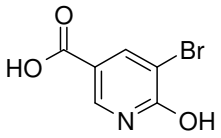
Preparación 237: N-[5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)-piridin-3-il]-2-fenil-2-(tetrahidro-piran-2-iloxi)-acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 1 utilizando el ácido fenil-[(tetrahidro-piran-2-iloxi)]-acético (preparación 246) y (5-amino-piridin-3-il)-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 95) para dar el compuesto del título en forma de un sólido de color amarillo en 68% de rendimiento, 60 mg.

LCMS (sistema 10): T_r = 3,56 min; m/z 500,2 $[M+H]^+$.

Preparación 238: Ácido 5-bromo-6-hidroxi-nicotínico

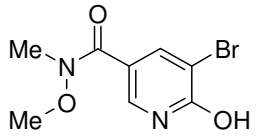


Se agregó gota a gota bromo (3,6 ml, 70,5 mmoles) a una suspensión del ácido 6-hidroxi-nicotínico (7 g, 50,32 mmoles) en agua (70 ml) a 0ºC y la mezcla se agitó a

temperatura ambiente durante 4 horas. El sólido precipitado se filtró, se lavó con agua fría y se secó para dar el compuesto del título en forma de un sólido blancuzco en 82% de rendimiento, 9 g.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 8,03 (d, 1H), 8,14 (d, 1H), 12,57 (br s, 1H).

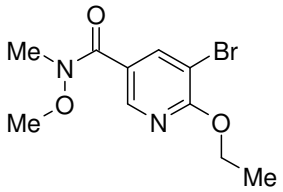
Preparación 239: 5-bromo-6-hidroxi-N-metoxi-N-metil-nicotinamida



Se tomaron el ácido 5-bromo-6-hidroxi-nicotínico (preparación 238, 4 g, 18,4 mmoles), HATU (13,95 g, 36,71 mmoles), O,N-dimetil-hidroxilamina clorhidrato (2,15 g, 22,02 mmoles) y DIPEA (15,82 ml, 91,75 mmoles) en DMF anhidro (30 ml). La mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se diluyó con EtOAc (150 ml), se lavó con Na_2CO_3 acuoso saturado (2 x 50 ml), agua (4 x 30 ml), salmuera (30 ml), se secó (Na_2SO_4) y se evaporó al vacío. La mezcla bruta se purificó por cromatografía de columna sobre gel de sílice (gradiente de EtOAc:Hex 4:6 a 6:4) para dar el compuesto del título en forma de un sólido pegajoso de color amarillo claro en 38% de rendimiento, 1,8 g.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 3,22 (s, 3H), 3,61 (s, 3H), 7,95 (d, 1H), 8,14 (d, 1H), 12,45 (br s, 1H); LCMS (system 10): Tr = 1,67 min; m/z 261, 263 $[M+H]^+$.

Preparación 240: 5-bromo-6-etoxi-N-metoxi-N-metil-nicotinamida

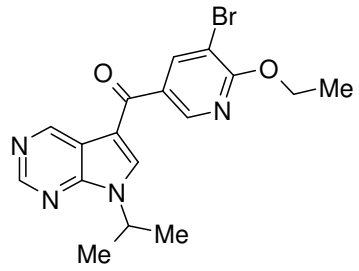


Una mezcla de 5-bromo-6-hidroxi-N-metoxi-N-metil-nicotinamida (preparación 239, 1,80 g, 6,90 mmoles), yoduro de etilo (2,8 ml, 34,5 mmoles) y carbonato de plata (3,8 g, 13,8 mmoles) en DCM (10 ml) se agitó a temperatura ambiente durante 40 horas. La mezcla de reacción se diluyó con DCM (50 ml) y se lavó con agua (2 x 30 ml), salmuera (20 ml), se secó sobre (Na_2SO_4) y se evaporó al vacío El material bruto se purificó por cromatografía de columna sobre gel de sílice (EtOAc: éter de petróleo 2:5) para dar el compuesto del título en forma de un sólido pegajoso de color amarillo en 30% de rendimiento, 600 mg.

^{1}H RMN (400 MHz, CDCl3) δ*:* 1,44 (t, 3H), 3,35 (s, 3H), 3,57 (s, 3H), 4,47 (q, 2H), 8,23 (d, 1H), 8,54 (d, 1H).

Preparación 241: (5-bromo-6-etoxi-piridin-3-il)(7isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-

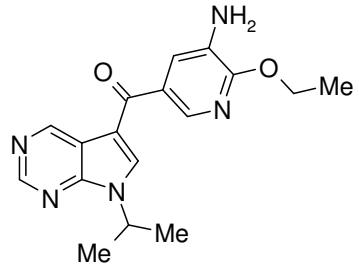
il)-metanona



Una solución de 5-yodo-7-isopropil--7H-pirrolo[2,3-d]pirimidina (preparación 93, 530 mg, 1,85 mmoles) en éter dietílico anhidro (8 ml) se enfrió hasta -78ºC en nitrógeno y se agregó n-BuLi (1 ml de una solución 2,03 M en hexano, 2,03 mmoles) gota a gota en un período de 10 min. Justo después de la terminación de la adición de n-BuLi, se agregó lentamente una solución de 5-bromo-6-etoxi-N-metoxi-N-metil-nicotinamida (preparación 240) en éter dietílico anhidro (7 ml) a la mezcla y se agitó a la misma temperatura durante otra hora. La mezcla de reacción se entibió hasta temperatura ambiente y se dejó agitar durante otra hora antes de templarse con NH_4Cl acuoso saturado (15 ml). La mezcla se extrajo con EtOAc (3 x 15 ml), se lavó con agua (20 ml), salmuera (15 ml), se secó (Na_2SO_4) y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (EtOAc: éter de petróleo 2:10) para dar el compuesto del título en forma de una goma de color amarillo en 49% de rendimiento, 350 mg.

^{1}H RMN (400 MHz, CDCl3) δ*:* 1,50 (t, 3H), 1,60 (d, 6H), 4,55 (q, 2H), 5,15-5,20 (m, 1H), 7,82 (s, 1H), 8,32 (d, 1H), 8,57 (d, 1H), 9,00 (s, 1H), 9,53 (s, 1H).

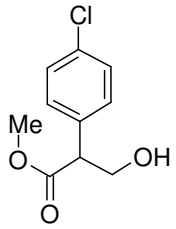
Preparación 242: (5-amino-6-etoxi-piridin-3-il)(7isopropil-7H-pirrolo[2,3-*d*]pirimidin-5-il)-metanona



Se agregó óxido de cobre (I) (38,6 mg, 0,27 mmoles) a (5-bromo-6-etoxi-piridin3-il)-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)-metanona (preparación 241, 350 mg , 0,89 mmoles) en solución de amoníaco concentrado (6 ml) y NMP (1 ml). La mezcla se calentó en un recipiente cerrado a 130ºC durante 17 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con agua (10 ml). Se extrajo

con 20% de i-PrOH en DCM (6 x 50 ml), se secó (Na_2SO_4) y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (MeOH:DCM 5:95) para dar el compuesto del título en forma de un sólido de color amarillo en 24% de rendimiento. LCMS (sistema 10): T_r = 2,99 min; m/z 326 $[M+H]^+$.

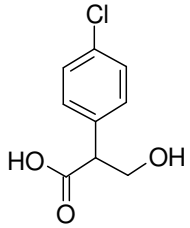
Preparación 243: Metil éster del ácido 2-(4-cloro-fenil)-3-hidroxi-propiónico



A una solución agitada de metil éster del ácido (4-cloro-fenil)-acético (2 g, 10,8 mmoles) en DMSO (22 ml) se agregó metóxido de sodio (29,2 mg, 0,54 mmoles) a 0ºC. A continuación se agregó paraformaldehído (342 mg, 11,4 mmoles) y la mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se diluyó con EtOAc (100 ml) y se lavó con agua (3 x 20 ml), salmuera (20 ml), se secó sobre (Na_2SO_4) y se evaporó al vacío El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de hexano:EtOAc 100:0 a 84:16) para dar el compuesto del título en forma de una goma incolora en 52% de rendimiento, 1,2 g.

^{1}H RMN (400 MHz, DMSO) δ: 2,23 (t, 1H), 3,70 (s, 3H), 3,79-3,83 (m, 2H), 4,05-4,12 (m, 1H), 7,20 (d, 2H), 7,30 (d, 2H); LCMS (system 10): T_r = 3,03 min; m/z 215 $[M+H]^+$.

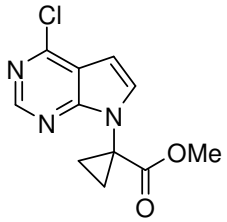
Preparación 244: Ácido 2-(4-cloro-fenil)-3-hidroxi-propiónico



A una solución agitada de metil éster del ácido 2-(4-cloro-fenil)-3-hidroxi-propiónico (preparación 243, 500 mg, 2,33 mmoles) en THF (7 ml) se agregó una solución de monohidrato hidróxido de litio (244 mg, 5,82 mmoles) en agua (2 ml) gota agota a 0ºC y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se acidificó (pH ~3) con ácido clorhídrico 2N y se extrajo con DCM (3 x 20 ml). Las capas orgánicas combinadas se lavaron con salmuera (10 ml), se secaron (Na_2SO_4) y se evaporaron al vacío para dar el compuesto del título en forma de un sólido de color blanco en 90% de rendimiento, 420 mg.

$^{+1}$H RMN (400 MHz, DMSO-*d6*) δ: 3,58 (dd, 1H), 3,66 (t, 1H), 3,87 (t, 1H), 7,32 (d, 2H), 7,38 (d, 2H), 12,36 (br, 1H).

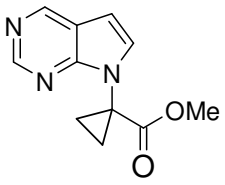
Preparación 245: Metil éster del ácido 1-(4-cloro-pirrolo[2,3-d]pirimidin-7-il)-ciclopropanocarboxílico



A una solución agitada de (4,6-dicloro-pirimidin-5-il)-acetaldehído (preparación 208, 2 g, 10,5 mmoles) y clorhidrato metil éster del ácido1-amino-ciclopropano-carboxílico (1,33 g, 11,6 mmoles) en etanol (30 ml) se agregó trietilamina (4,4 ml, 31,6 mmoles) y la mezcla se calentó en un tubo cerrado a 100ºC durante 10 horas. Se agregó a continuación ácido acético (1,21 ml, 21,1 mmoles) y la mezcla se calentó a 100ºC durante 16 horas adicionales. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con DCM (200 ml). La capa orgánica se lavó con agua (2 x 50 ml), salmuera (50 ml), se secó (Na_2SO_4) y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de hexano:EtOAc 100:0 a 90:10) para dar el compuesto del título en forma de un sólido en 35% de rendimiento, 900 mg.

^{1}H RMN (400 MHz, DMSO) δ: 1,63-1,66 (m, 2H), 1,96-1,99 (m, 2H), 3,63 (s, 3H), 6,60 (d, 1H), 7,23 (d, 1H), 8,65 (s, 1H); LCMS (sistema 10): T_r = 2,89 min; m/z 252,1 $[M+H]^+$.

Preparación 246: Metil éster del ácido 1-pirrolo[2,3-d]pirimidin-7-il)-ciclopropanocarboxílico

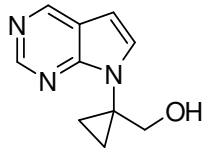


Una solución de metil éster del ácido 1-(4-cloro-pirrolo[2,3-d]pirimidin-7-il)-ciclopropanocarboxílico (preparación 245, 920 mg, 3,65 mmoles) en etanol (20 ml) se desgasificó con argón durante 15 min. Se agregaron hidróxido de amonio (4 ml) y 10% de paladio sobre carbono y la mezcla de reacción se agitó a temperatura ambiente en hidrógeno (presión de balún) durante 5 horas). La mezcla de reacción se filtró sobre un lecho de celite, se lavó con etanol (2 x 10 ml) y el filtrado se evaporó al vacío. El

material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de DCM:metanol 100:0 a 98:2) para dar el compuesto del título en forma de una goma en 59% de rendimiento, 470 mg.

^{1}H RMN (400 MHz, DMSO) δ: 1,63-1,66 (m, 2H), 1,95-1,99 (m, 2H), 3,63 (s, 3H), 6,55 (d, 1H), 7,20 (d, 1H), 8,90 (s, 1H), 8,94 (s, 1H); LCMS (sistema 10): T_r = 2,22 min; m/z 218,2 $[M+H]^+$.

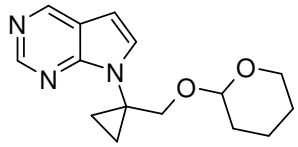
Preparación 247: (1-pirrolo[2,3-d]pirimidin-7-il-ciclopropil)-metanol



A una solución agitada de metil éster del ácido 1-pirrolo[2,3-d]pirimidin-7-il)-ciclopropanocarboxílico (preparación 246, 610 mg, 2,80 mmoles) en etanol (15 ml) se agregó borohidruro de sodio (318,7 mg, 8,42 mmoles) y la mezcla se calentó hasta reflujo durante 16 horas. La mezcla reacción se templó con agua (5 ml) y se extrajo con EtOAc (3 x 10 ml). Las capas orgánicas combinadas se lavaron con agua (5 ml), salmuera (5 ml), se secaron (Na_2SO_4) y se evaporaron al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de DCM:metanol 100:0 a 98:2) para dar el compuesto del título en forma de un sólido de color amarillo claro en 47% de rendimiento, 250 mg.

^{1}H RMN (400 MHz, DMSO) δ: 1,26 (s, 4H), 3,83 (s, 2H), 6,47 (d, 1H), 7,26 (d, 1H), 8,83 (s, 1H), 8,88 (s, 1H); LCMS (sistema 10): T_r = 1,67 min; m/z 189,9 $[M+H]^+$.

Preparación 248: 7-[1-(tetrahidro-piran-2-iloximetil)-ciclopropil]-7H-pirrolo[2,3-d]pirimidina

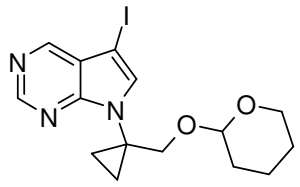


A una solución agitada de (1-pirrolo[2,3-d]pirimidin-7-il-ciclopropil)-metanol (preparación 247, 240 mg, 1,27 mmoles) en THF (12 ml) se agregó 3,4-dihidro-2H-piran (0,46 ml, 5,07 mmoles) seguido de la adición de PTSA (24 mg, 0,13 mmoles). La mezcla de reacción se agitó a 60ºC durante 4 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se templó con solución de bicarbonato de sodio acuoso saturado (15 ml) y se extrajo con diclorometano (3 x 25 ml). La capa orgánica combinada se lavó con salmuera (10 ml), se secó sobre sulfato de sodio y se evaporó

al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de diclorometano:metanol 100:0 a 98:2) para dar el compuesto del título en forma de una goma de color marrón claro en 90% de rendimiento, 320 mg.

^{1}H RMN (400 MHz, DMSO) δ: 1,18-1,26 (m, 4H), 1,31-1,55 (m, 5H), 1,67-1,69 (m, 1H), 3,28-3,31 (m, 1H), 3,44 (t, 1H), 3,68 (d, 1H), 3,88 (d, 1H), 4,46 (s, 1H), 6,45 (d, 1H), 7,33 (d, 1H), 8,88-8,90 (m, 2H); LCMS (sistema 10): T_r = 2,82 min; m/z 274,6 $[M+H]^+$.

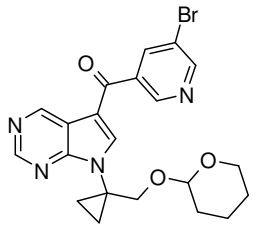
Preparación 249: 5-yodo-7-[1-(tetrahidro-piran-2-iloximetil)-ciclopropil]-7H-pirrolo[2,3-d]pirimidina



A una solución agitada de 7-[1-(tetrahidro-piran-2-iloximetil)-ciclopropil]-7H-pirrolo[2,3-d]pirimidina (preparación 248, 390 mg, 1,43 mmoles) en DMF (8 ml) se agregó N-yodosuccinimida (481,5 mg, 2,14 mmoles) y se agitó a temperatura ambiente durante 4 horas. La mezcla reacción se templó con agua (8 ml) y se extrajo con acetato de etilo (3 x 20 ml). La capa orgánica combinada se lavó con agua (5 x 15 ml), salmuera (10 ml), se secó sobre sulfato de sodio y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de diclorometano:metanol 100:0 a 99:1) para dar el compuesto del título en forma de un sólido en 79% de rendimiento, 450 mg.

^{1}H RMN (400 MHz, DMSO) δ: 1,18-1,70 (m, 10H), 3,28-3,32 (m, 1H), 3,42 (t, 1H), 3,65 (d, 1H), 3,87 (d, 1H), 4,47 (s, 1H), 7,44 (s, 1H), 8,70 (s, 1H), 8,90 (s, 1H); LCMS (sistema 10): T_r = 3,28 min; m/z 400,2 $[M+H]^+$.

Preparación 250: (5-bromo-piridin-3-il)-{7-[1-(tetrahidro-piran-2-iloximetil)-ciclopropil]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona

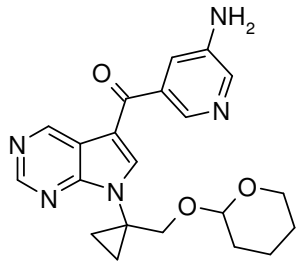


A una solución agitada de 5-yodo-7-[1-(tetrahidro-piran-2-iloximetil)-ciclopropil]-7H-pirrolo[2,3-d]pirimidina (preparación 249, 450 mg, 1,13 mmoles) en éter dietílico (6

ml) se agregó n-butil litio (2 M en hexano, 0,62 ml, 1,24 mmoles) gota a gota a -70ºC. A continuación se agregó gota a gota una solución de 5-bromo-N-metoxi-N-metil-nicotinamida (304 mg, 1,24 mmoles) en éter dietílico (2,5 ml) a -70ºC y se agitó a la misma temperatura durante otros 30 minutos. La reacción se dejó entibiar hasta temperatura ambiente lentamente. La reacción se templó con solución de cloruro de amonio acuoso (10 ml) y se extrajo con acetato de etilo (3 x 20 ml). La capa orgánica combinada se lavó con agua (20 ml), salmuera (20 ml), se secó sobre sulfato de sodio y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de diclorometano:metanol 100:0 a 98:2) para dar el compuesto del título en forma de sólido pegajoso color marrón claro en 35% de rendimiento, 250 mg.

$^{+1}$H RMN (400 MHz, DMSO-*d6*) δ: 1,25-1,57 (m, 10H), 3,17-3,28 (m, 2H), 3,64 (d, 1H), 3,95 (d, 1H), 4,57 (s, 1H), 8,36 (s, 1H), 8,40 (s, 1H), 8,96 (s, 1H), 8,99 (s, 1H), 9,02 (s, 1H), 9,45 (s, 1H); LCMS (sistema 10): Tr = 3,17 min; m/z 456,8, 459 $[M+H]^+$.

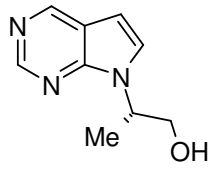
Preparación 251: (5-amino-piridin-3-il)-{7-[1-(tetrahidro-piran-2-iloximetil)-ciclopropil]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona



A una solución agitada de (5-bromo-piridin-3-il)-{7-[1-(tetrahidro-piran-2-iloximetil)-ciclopropil]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona (preparación 250, 200 mg, 0,45 mmoles) en 1-metil-pirrolidin-2-ona (1,5 ml) se agregó hidróxido de amonio (15 ml). A continuación se agregó óxido de cobre (I) (3 mg, 0,02 mmoles) y la mezcla de reacción se calentó en un tubo cerrado a 130ºC durante 16 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se extrajo con 10% de metanol en diclorometano (5 x 25 ml). La capa orgánica combinada se secó sobre sulfato de sodio y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de diclorometano:metanol 100:0 a 96:4) para dar el compuesto del título en forma de sólido pegajoso de color blanco en 45% de rendimiento, 80 mg.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,17-1,53 (m, 10H), 3,17-3,28 (m, 2H), 3,63 (d, 1H), 3,94 (d, 1H), 4,55 (s, 1H), 5,64 (s, 2H), 7,27 (s, 1H), 8,18-8,20 (m, 3H), 8,99 (s, 1H), 9,42 (s, 1H); LCMS (sistema 10): T_r = 2,59 min; m/z 394,1 $[M+H]^+$.

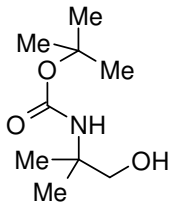
Preparación 252: (S)-2-pirrolo[2,3-d]pirimidin-7-il-propan-1-ol



El compuesto del título se preparó de acuerdo con el método que se describió anteriormente para la preparación 8, utilizando (2S)-2-(4-cloro-7H-pirrolo[2,3-*d*]pirimidin-7-il)propan-1-ol (preparación 4) para dar el compuesto del título en forma de un sólido de color blanco en 100% de rendimiento, 2,8 g.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,43 (d, 3H), 3,68-3,79 (m, 2H), 4,89-4,94 (m, 1H), 4,97 (t, 1H), 6,61 (d, 1H), 7,71 (d, 1H), 8,75 (s, 1H), 8,97 (s, 1H).

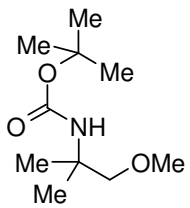
Preparación 253: Ter-butil éster del ácido (2-hidroxi-1,1-dimetil-etil)-carbámico



A una mezcla de 2-amino-2-metil-propan-1-ol (2 g, 22,43 mmoles) y trietilamina (3,12 ml, 22,43 mmoles) en THF se agregó boc-anhídrido (4,89 g, 22,43 mmoles) lentamente a 0ºC y se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua, salmuera, se secó sobre sulfato de sodio y se evaporó al vacío para dar el compuesto del título en forma de un aceite incoloro en 92% de rendimiento, 3,9 g.

^{1}H RMN (400 MHz, DMSO) δ: 1,23 (s, 6H), 1,42 (s, 9H), 3,56-3,58 (d, 2H), 4,00 (brs, 1H), 4,62 (brs, 1H).

Preparación 254: Ter-butil éster del ácido (2-metoxi-1,1-dimetil-etil)-carbámico

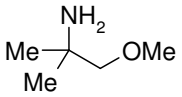


Se agregó KOH (3,47 g, 61,82 mmoles) a una solución de ter-butil éster del ácido (2-hidroxi-1,1-dimetil-etil)-carbámico (preparación 253, 3,9 g, 20,6 mmoles) en 1,4-dioxano (30 ml) seguido de la lenta adición de dimetil sulfato a temperatura ambiente. La mezcla se dejó agita posteriormente a temperatura ambiente durante 48 horas. La masa de reacción se filtró sobre un taco corto de celite, se lavó con DCM (3

x 50 ml). El filtrado combinado se lavó con agua (2 x 50 ml), salmuera (30 ml), se secó sobre sulfato de sodio y se evaporó al vacío para dar el compuesto del título en forma de un aceite de color amarillo 88% de rendimiento, 3,7 g.

^{1}H RMN (400 MHz, DMSO) δ: 1,27 (s, 6H), 1,41 (s, 9H), 3,29 (s, 2H), 3,35 (s, 3H), 4,73 (brs, 1H).

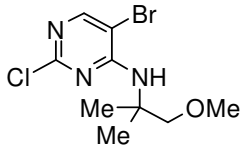
Preparación 255: 2-metoxi-1,1-dimetil-etilamina



Se agregó lentamente TFA (5,8 ml, 78,7 mmoles) a una solución de DCM (25 ml) de ter-butil éster del ácido (2-metoxi-1,1-dimetil-etil)-carbámico (preparación 254, 3,2 g, 15,74 mmoles) a 0ºC. La mezcla se dejó agitar a temperatura ambiente durante otras 3 horas y a continuación todos los volátiles se eliminaron a vacío. El residuo se trató con solución de $NaHCO_3$ acuoso saturado (50 ml) y se extrajo con una mezcla de IPA/DCM (1,4) (4 x 50 ml). Los orgánicos combinados se secaron sobre sulfato de sodio y se evaporaron hasta sequedad al vacío para dar el compuesto del título en forma de un aceite de color marrón en 100% de rendimiento, 1,6 g.

^{1}H RMN (400 MHz, DMSO) δ: 1,32 (s, 6H), 3,30 (s, 2H), 3,35 (s, 3H), 7,80 (brs, 2H).

Preparación 256: (5-bromo-2-cloro-pirimidin-4-il)-(2-metoxi-1,1-dimetil-etil)-amina

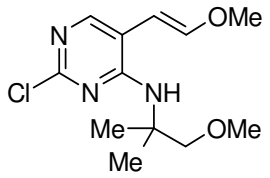


Se agregó lentamente trietilamina (73,1 ml, 526,6 mmoles) a una solución de 5-bromo-2,3-dicloro-pirimidina (40 g, 175,5 mmoles) en acetonitrilo (400 ml) a 0ºC y a continuación se agregó 2-metoxi-1,1-dimetil-etilamina (preparación 255, 23,4 g, 263,3 mmoles) a la mezcla en porciones. La mezcla de reacción se agitó durante otras 16 horas a temperatura ambiente. La TLC mostró la presencia de pirimidina de partida sin reaccionar, pero la reacción no continuó posteriormente. Todos los volátiles se eliminaron al vacío y el residuo se colocó en acetato de etilo, se lavó con agua, salmuera, se secó sobre sulfato de sodio y se evaporó hasta sequedad al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (malla 100-200, gradiente de acetato de etilo:hexano 1:9 a 2:4) para dar el compuesto del título en forma de un sólido de color blanco en 23% de rendimiento (10 g de pirimidina de partida se recuperó), 12 g.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,40 (s, 6H), 3,32 (s, 3H), 3,48 (s, 2H), 6,19 (s, 1H),

8,29 (s, 1H); LCMS (sistema 10): Tr = 3,56 min; m/z 294, 296 $[M+H]^+$.

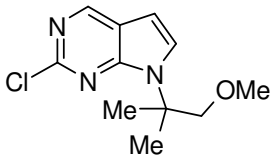
Preparación 257: [2-cloro-5-((E)-2-etoxi-vinil)-pirimidin-4-il]-(2-metoxi-1,1-dimetil-etil)-amina



El compuesto del título se preparó de acuerdo con el método que se describió para la preparación 61 utilizando (5-bromo-2-cloro-pirimidin-4-il)-(2-metoxi-1,1-dimetil-etil)-amina (preparación 256), catecol borano y etoxiacetileno (40% en hexano) para dar el compuesto del título en forma de una goma de color marrón claro en 44% de rendimiento, 2,6 g.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,25 (t, 3H), 1,37 (s, 6H), 3,26 (s, 3H), 3,56 (s, 2H), 3,92 (q, 2 H), 5,74 (d, 1H), 6,12 (s, 1H), 6,94 (d, 1H), 7,88 (s, 1H); LCMS (sistema 10): T_r = 3,65 min; m/z 286,3 $[M+H]^+$.

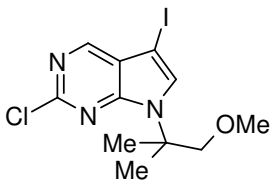
Preparación 258: 2-cloro-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 62 utilizando [2-cloro-5-((E)-2-etoxi-vinil)-pirimidin-4-il]-(2-metoxi-1,1-dimetil-etil)-amina (preparación 257) para dar el compuesto del título en forma de un sólido blancuzco en 91% de rendimiento, 2g.

^{1}H RMN (400 MHz, DMSO-D6) δ 1,68 (s, 6H), 3,17 (s, 3H), 3,85 (s, 2H), 6,62 (d, 1H), 7,63 (d, 1H), 8,90 (s, 1H); LCMS (sistema 10): T_r = 3,29 min; m/z 240 $[M+H]^+$.

Preparación 259: 2-cloro-5-yodo-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidina

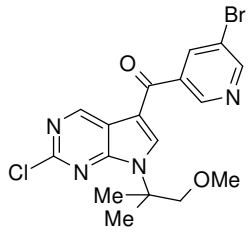


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 63 utilizando 2-cloro-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidina (preparación 258) para dar el compuesto del título en forma de un sólido

amarillento en 75% de rendimiento, 2,3 g.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,67 (s, 6H), 3,17 (s, 3H), 3,83 (s, 2H), 7,81 (s, 1H), 8,64 (s, 1H); LCMS (sistema 10): T_r = 3,65 min; m/z 365,8 $[M+H]^+$.

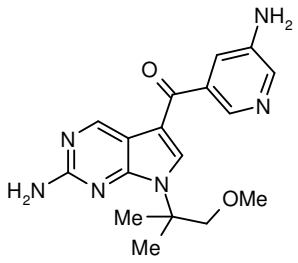
Preparación 260: (5-bromo-piridin-3-il)-[-2-cloro-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-il]-metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 64 utilizando 2-cloro-5-yodo-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidina (preparación 259) y 5-bromo-N-metoxi-N-metil-nicotinamida para dar el compuesto del título en forma de una goma de color amarillo en 34% de rendimiento, 900 mg.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,73 (s, 6H), 3,21 (s, 3H), 3,90 (s, 2H), 8,22 (s, 1H), 8,42 (t, 1H), 8,98 (t, 2H), 9,35 (s, 1H).

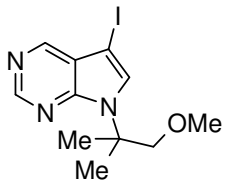
Preparación 261: [2-amino-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-il]-(5-amino-piridin-3-il)-metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 65 utilizando (5-bromo-piridin-3-il)-[2-cloro-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-il]-metanona (preparación 260) para dar el compuesto del título en forma de un sólido de color amarillo en 41% de rendimiento, 300 mg.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,68 (s, 6H), 3,19 (s, 3H), 3,89 (s, 2H), 5,61 (s, 2H), 6,54 (s, 2H), 7,23 (s, 1H), 7,55 (s, 1H), 8,11 (dd, 2H), 8,93 (s, 1H); LCMS (sistema 10): T_r = 2,40 min; m/z 341,2 $[M+H]^+$.

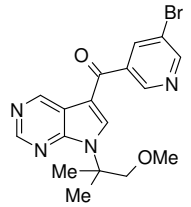
Preparación 262: 5-yodo-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidina



Una solución de THF anhidro (100 ml) de 2-(5-yodo-pirrolo[2,3-d]pirimidin-7-il)-2-metil-propan-1-ol (preparación 22) (32 g, 100,91 mmoles) se agregó lentamente a una suspensión de NaH (60% en aceite de parafina, 2,98 g, 121,13 mmoles) en THF anhidro (200 ml) a 0ºC en nitrógeno. La mezcla se entibió hasta temperatura ambiente y se agitó durante otros 30 minutos y nuevamente se enfrió hasta 0ºC y se agregó gota a gota yoduro de metilo (19 ml, 302,82 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas, se templó con cloruro de amonio acuoso saturado, y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera (5 ml), se secó sobre sulfato de sodio y se evaporó hasta sequedad al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (malla 100-200, gradiente de heptano:EtOAc 100:0 a 70:30) para dar el compuesto del título en forma de un sólido pegajoso de color amarillo en 22% de rendimiento, 7,5 g.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,70 (s, 6H), 3,15 (s, 3H), 3,89 (s, 2H), 7,77 (s, 1H), 8,70 (s, 1H), 8,82 (s, 1H); LCMS (sistema10): T_r = 3,42 min; m/z 331,6 $[M+H]^+$.

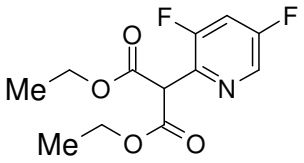
Preparación 263: (5-bromo-piridin-3-il)-[7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidin-5-il]-metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 64 utilizando 5-yodo-7-(2-metoxi-1,1-dimetil-etil)-7H-pirrolo[2,3-d]pirimidina (preparación 262) y 5-bromo-N-metoxi-N-metil-nicotinamida para dar el compuesto del título en forma de una goma de color marrón en 51% de rendimiento, 3g.

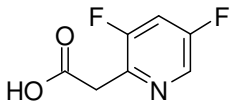
^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,76 (s, 6H), 3,19 (s, 3H), 3,96 (s, 2H), 8,17 (s, 1H), 8,42 (t, 1H), 8,98 (brs, 2H), 9,00 (s, 1H), 9,47 (s, 1H); LCMS (sistema 10): Tr = 3,13 min; m/z 388,6, 390,6 $[M+H]^+$.

Preparación 264: Dietil éster del ácido 2-(3,5-difluoro-piridin-2-il)-malónico



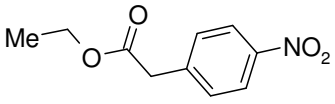
A una solución agitada de 2,3,5-trifluoro-piridina (2 g, 15,02 mmoles) en dimetil sulfóxido (20 ml) se agregó dietil malonato (4,60 g, 28,72 mmoles), A continuación se agregó carbonato de cesio (9,35 g, 28,72 mmoles) y la mezcla de reacción se calentó hasta 110ºC durante 16 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con acetato de etilo (100 ml). La capa orgánica se lavó con agua (2 x 25 ml), salmuera (25 ml), se secó sobre sulfato de sodio y se evaporó al vacío para dar el compuesto del título en forma de un aceite en 85% de rendimiento, 3,5 g.
^{1}H RMN (400 MHz, DMSO) δ: 1,25-1,30 (m, 6 H), 4,20-4,29 (m, 4 H), 4,88 (s, 1 H), 7,77-7,81 (m, 1 H), 8,01 (s, 1 H).

Preparación 265: Ácido (3,5-difluoro-piridin-2-il)acético



A una solución agitada de dietil éster del ácido 2-(3,5-difluoro-fenil)-2-il)-malónico (1 g, 3,56 mmoles) (preparación 264) en THF (15 ml) se agregó una solución de monohidrato hidróxido de litio (462 mg, 10,4 mmoles) en agua (4 ml) gota agota a 0ºC y la mezcla resultante se agitó hasta reflujo durante 2 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se acidificó (pH ~3) con ácido clorhídrico 2N y se extrajo con 20% de isopropanol-diclorometano (5 x 20 ml). Las capas orgánicas se secaron (Na_2SO_4) y se evaporaron al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice gradiente de DCM: MeOH 100:0 a 95:5) para dar el compuesto del título en 53% de rendimiento, 336 mg.
^{1}H RMN (400 MHz, DMSO-D6) δ 3,32 (s, 2H), 7,74-7,79 (m, 1H), 7,99 (t, 1H); LCMS (sistema 10): T_r = 0,65 min; m/z 174 $[M+H]^+$.

Preparación 266: Etil éster del ácido (4-nitro-fenil)-acético

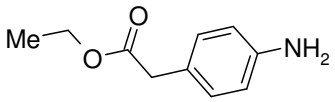


A una solución agitada del ácido (4-nitro-fenil)-acético (3 g, 16,4 mmoles) en etanol (30 ml) se agregó ácido sulfúrico (1 ml) y la mezcla de reacción se calentó hasta reflujo durante 16 horas. La mezcla reacción se neutralizó con solución de NaOH acuoso 2N y se extrajo con EtOAc (3 x 50 ml). Las capas orgánicas combinadas se

secaron (Na_2SO_4) y se evaporaron al vacío para dar el compuesto del título en forma de aceite de color amarillo claro en 98% de rendimiento, 3,4 g.

^{1}H RMN (400 MHz, DMSO) δ: 1,25 (t, 3H), 3,71 (s, 2H), 4,16 (q, 2H), 7,45 (d, 2H), 8,18 (d, 2H).

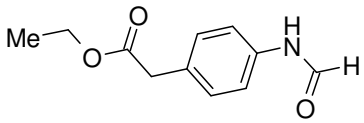
Preparación 267: Etil éster del ácido (4-amino-fenil)-acético



Una solución de etil éster del ácido (4-nitro-fenil)-acético (preparación 266, 3,4 g, 16,1 mmoles) en metanol (100 ml) se desgasificó con argón durante 15 min., se trató con 10% de paladio sobre carbón (700 mg), y a continuación se agitó a temperatura ambiente en hidrógeno (presión de balún) durante 16 horas. La mezcla de reacción se filtró a través de celite, se lavó con metanol (2 x 20 ml) y el filtrado se evaporó al vacío para dar el compuesto del título en forma de un aceite en 96% de rendimiento, 2,8 g.

^{1}H RMN (400 MHz, DMSO) δ: 1,23 (t, 3H), 3,47 (s, 2H), 3,60 (br s, 2H), 4,11 (q, 2 H), 6,63 (d, 2H), 7,05 (d, 2H).

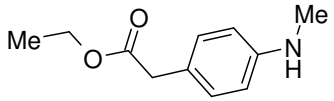
Preparación 268: Etil éster del ácido (4-formilamino-fenil)-acético



Una mezcla de anhídrido acético (0,33 ml, 3,57 mmoles) y ácido fórmico (0,17 ml, 4,46 mmoles) se calentó a 60ºC durante 2 horas. La mezcla de reacción se enfrió hasta 0ºC, una solución de etil éster del ácido (4-amino-fenil)-acético (preparación 267, 500 mg, 2,79 mmoles) en THF (10 ml) se agregó lentamente a la mezcla de reacción y la reacción se dejó agitar a temperatura ambiente durante 16 horas. La mezcla reacción se neutralizó con solución de Na_2CO_3 acuoso saturado y se extrajo con éter dietílico (2 x 25 ml). Las capas orgánicas se secaron (Na_2SO_4) y se evaporaron al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de DCM:MeOH 100:0 a 98:2) para dar el compuesto del título en forma de un aceite en 93% de rendimiento, 500 mg.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 1,17 (t, 3H), 3,59 (s, 2H), 4,05 (q, 2H), 7,20 (d, 2H), 7,52 (d, 2H), 8,25 (d, 1H), 10,15 (s, 1H).

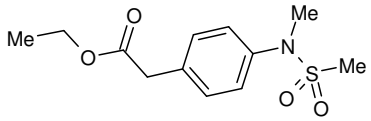
Preparación 269: Etil éster del ácido (4-metilamino-fenil)-acético



A una solución agitada de etil éster del ácido (4-formilamino-fenil)-acético (preparación 268, 500 mg, 2,41 mmoles) en THF (10 ml) se agregó complejo de borano-dimetil sulfuro (0,3 ml, 3,13 mmoles) a 0ºC y la mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se templó con MeOH (5 ml) y se evaporó al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de hexano:EtOAc 100:0 a 75:25) para dar el compuesto del título en forma de un aceite en 91% de rendimiento, 460 mg.

^{1}H RMN (400 MHz, DMSO) δ: 1,23 (t, 3H), 2,81 (s, 3H), 3,48 (s, 2H), 3,66 (br s, 1 H), 4,11 (q, 2H), 6,56 (d, 2H), 7,09 (d, 2 H).

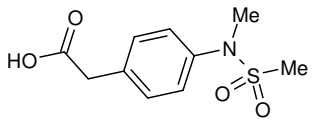
Preparación 270: Etil éster del ácido [4-(metanosulfonil-metil-amino)-fenil]-acético



A una solución agitada de etil éster del ácido (4-metilamino-fenil)-acético (preparación 269, 418 mg, 2,16 mmoles) en piridina (4 ml) se agregó cloruro de metanosulfonilo (0,25 ml, 3,24 mmoles) y la mezcla se agitó a temperatura ambiente durante 3 horas. La mezcla reacción se templó con agua (10 ml) y se extrajo con EtOAc (3 x 15 ml). Las capas orgánicas combinadas se lavaron con agua (10 ml), salmuera (10 ml), se secaron (Na_2SO_4) y se evaporaron al vacío para dar el compuesto del título en forma de una goma 78% de rendimiento, 460 mg.

^{1}H RMN (400 MHz, DMSO) δ: 1,25 (t, 3H), 2,82 (s, 3H), 3,30 (s, 3H), 3,59 (s, 2H), 4,14 (q, 2H), 7,28-7,33 (m, 4H).

Preparación 271: Ácido [4-(metanosulfonil-metil-amino)-fenil]-acético

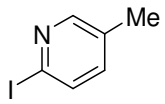


El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 265 utilizando etil éster del ácido [4-(metanosulfonil-metil-amino)-fenil]-acético (preparación 270) para dar el compuesto del título en forma de un sólido en 85% de rendimiento, 350 mg.

^{1}H RMN (400 MHz, DMSO-*d6*) δ: 2,92 (s, 3H), 3,21 (s, 3H), 3,55 (s, 2H), 7,28 (d,

2H), 7,33 (d, 2H); LCMS (sistema 10): T_r = 1,05 min; m/z 244 $[M+H]^+$.

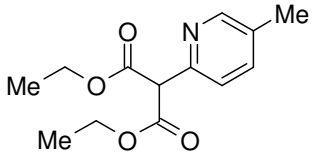
Preparación 272: 2-yodo-5-metil-piridina



A una solución agitada de 2-bromo-5-metil-piridina (2 g, 11,6 mmoles) en acetonitrilo (25 ml) se agregó yoduro de sodio (6,97 g, 46,5 mmoles) y la mezcla se calentó hasta reflujo. Se agregó gota a gota cloruro de acetil o (1,24 ml, 17,44 mmoles) en condiciones de reflujo y la mezcla de reacción se calentó hasta reflujo durante 16 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se templó con solución de Na_2CO_3 acuoso saturado (15 ml) y se extrajo con EtOAc (3 x 25 ml) Las capas orgánicas combinadas se lavaron con salmuera (10 ml), se secaron (Na_2SO_4) y se evaporaron al vacío para dar el compuesto del título en forma de un aceite en 55% de rendimiento, 1,4 g.

LCMS (sistema 10): T_r = 3,10 min; m/z 220 $[M+H]^+$.

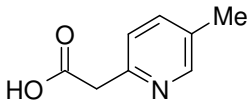
Preparación 273: Dietil éster del ácido 2-(5-metil-piridin-2-il)-malónico



A una solución agitada de 2-yodo-5-metil-piridina (preparación 272, 1 g, 4,57 mmoles) y malonato de dietilo (2,08 ml, 13,70 mmoles) en dioxano anhidro (12 ml) se agregó carbonato de cesio (4,46 g, 13,7 mmoles) y la solución se desgasificó con argón durante 30 min. Se agregaron CuI (174 mg, 0,91 mmoles) y ácido picolínico (225 mg, 1,83 mmoles) y la mezcla resultante se calentó en un tubo cerrado a 100ºC durante 16 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, se templó con agua (25 ml) y se extrajo con EtOAc (3 x 25 ml) Las capas orgánicas combinadas se lavaron con agua (2 x 10 ml), y salmuera (10 ml), se secaron (Na_2SO_4) y se evaporaron al vacío. El material bruto se purificó por cromatografía de columna sobre gel de sílice (gradiente de hexano:EtOAc 100:0 a 90:10) para dar el compuesto del título en forma de un aceite en 23% de rendimiento, 300 mg.

^{1}H RMN (400 MHz, DMSO-D6) δ: 1,15-1,18 (m, 6H), 2,29 (s, 3H), 4,12-4,17 (m, 4H), 5,01 (s, 1H), 7,30 (d, 1H), 7,62 (dd, 1H), 8,34 (s, 1H).

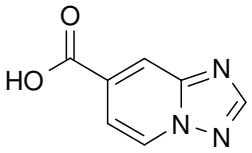
Preparación 274: Ácido (5-metil-piridin-2-il)acético



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 265 utilizando dietil éster del ácido 2-(5-metil-piridin-2-il)-malónico (preparación 273) para dar el compuesto del título en forma de un sólido en 83% de rendimiento, 100 mg.

^{1}H RMN (400 MHz, DMSO-D6) δ: 2,26 (s, 3H), 3,64 (s, 2H), 7,21 (d, 1H), 7,53 (d, 1H), 8,29 (s, 1H); LCMS (sistema 10): T_r = 0,73 min; m/z 152 $[M+H]^+$.

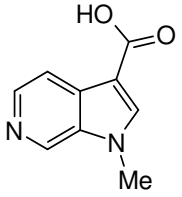
Preparación 275: Ácido [1,2,4]triazolo[1,5-a]piridin-7-carboxílico



A una solución de 2-aminoisonicotinato de metilo (28,8 g, 191 mmoles) en DMF (97,5 ml) se agregó DMF-DMA (70,6 ml, 496 mmoles) y la mezcla se calentó hasta 130ºC durante 12 horas. La mezcla se concentró a continuación para dar un residuo. Al residuo se agregó MeOH (381 ml), seguido de NH_2OHSO_4 (31,9 g, 248 mmoles) y la mezcla resultante se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se concentró para dar [1,2,4]triazolo[1,5-a]piridin-7-carboxilato de metilo en 18% de rendimiento, 6g. A una solución de [1,2,4]triazolo[1,5-a]piridin-7-carboxilato de metilo (3 g, 16 mmoles) en metanol se agregó LiOH acuoso 1M (70 ml) y la mezcla resultante se agitó durante 10 horas a temperatura ambiente. El pH se ajustó hasta 5-6 utilizando HCl acuoso y la mezcla completa se extrajo con EtOAc (30 ml x 3). Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron al vacío para dar el compuesto del título en forma de un sólido de color blanco en 38% de rendimiento, 1,05 g.

1H RMN (400 MHz, DMSO-d6) δ: 7,56-7,58 (m, 1H), 8,32 (m, 1H), 8,66 (m, 1H), 9,04-9,06 (m, 1H), 13,5-14,0 (s, 1H).

Preparación 276: Ácido 1-metil-1H-pirrolo[2,3-c]piridin-3-carboxílico

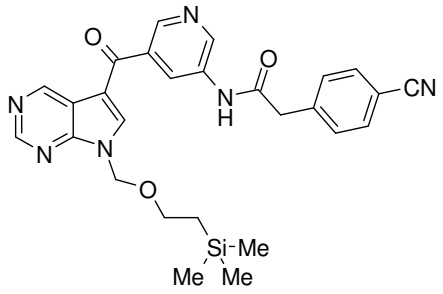


Se disolvió 1-metil-1H-pirrolo[2,3-c]piridin-3-carbaldehído (WO 05066132) (6,5

g, 40,6 mmoles) en una mezcla de THF (120 ml) y ter-butil alcohol (40 ml) en nitrógeno. Se agregó 2-metil-2-buteno (120 ml de una solución 2M en THF, 46 mmoles) seguido de una solución de $NaClO_2$ (11,0 g, 122 mmoles) y NaH_2PO_4 (21,9 g, 183 mmoles) en agua (30 ml). La mezcla de reacción se agitó a temperatura ambiente en nitrógeno durante toda la noche. La mezcla de reacción se concentró al vacío para eliminar solventes orgánicos, y el residuo se filtró. El precipitado contenía el compuesto del título en forma de un sólido de color blanco en 57% de rendimiento, 4,1 g.

1H RMN (400MHz, DMSO-d6) δ: 3,96 (S, 3H), 7,87-7,89 (d, 1H), 8,23 (s, 1H), 8,28 (d, 1H), 8,91 (s, 1H), 12,3 (s, 1H).

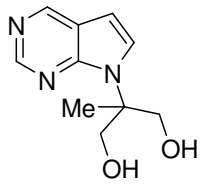
Preparación 277: 2-(4-cianofenil)-N-{5-[(7-(2-trimetilsilanil-etoximetil)-7H-pirrolo[2,3-d]pirimidin-5-carbonil]-piridin-3-il}acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 1 utilizando (5-amino-piridin-3-il)-[7-(2-trimetilsilanil-etoximetil)-7H-pirrolo[2,3-d]pirimidin-5-il]-metanona (preparación 103) y ácido 4-cianofenilacético para dar el compuesto del título en forma de un sólido blancuzco en 71% de rendimiento, 235 mg.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* -0,11 (s, 9H), 0,82 (t, 2H), 3,59 (t, 2H), 3,87 (s, 2H), 5,70 (s, 2H), 7,55 (d, 2H), 7,82 (d, 2H), 8,47 (s, 1H), 8,61 (s, 1H), 8,73 (s, 1H), 8,98 (s, 1H), 9,04 (s, 1H), 9,48 (s, 1H), 10,75 (s, 1H); LCMS (Sistema 10): T_r = 3,25 min; m/z 513 $[M+H]^+$.

Preparación 278: 2-metil-2-pirrolo[2,3-d]pirimidin-7-il)-propano-1,3-diol

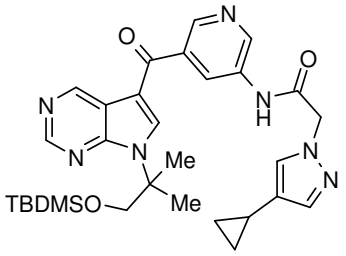


El compuesto del título se preparó de acuerdo con el método que se describió para la preparación 246, utilizando 2-(4-cloro-pirrolo[2,3-d]pirimidin-7-il)-2-metil-

propano-1,3-diol (preparación 217) para dar el compuesto del título en forma de un sólido blancuzco en 93% de rendimiento, 800 mg.

^{1}H RMN (400 MHz, DMSO-D6) δ: 1,65 (s, 3H), 3,87-3,91 (m, 2H), 4,10-4,14 (m, 2H), 4,94 (t, 2H), 6,55 (d, 1H), 7,63 (d, 1H), 8,72 (s, 1H), 8,95 (s, 1H).

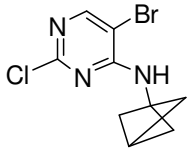
Preparación 279: N-(5-{7-[2-(ter-butil-dimetil-silaniloxi)-1,1-dimetil-etil]-7H-pirrolo[2,3-d]pirimidin-5-carbonil}-piridin-3-il)-2-(4-ciclopropil-pirazol-1-il)-acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para el ejemplo 1 utilizando **(**5-amino-piridin-3-il)-{7-[2-(ter-butil-dimetil-silaniloxi)-1,1-dimetil-etil]-7H-pirrolo[2,3-d]pirimidin-5-il}-metanona (preparación 38) y ácido (4-ciclopropil-1H-pirazol-1-il)acético (preparación 88) para dar el compuesto del título en forma de un sólido blancuzco en 41% de rendimiento, 55 mg.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* -0,24 (s, 6H), 0,46 (m, 2H), 0,60 (s, 9H), 0,79 (m, 2H), 1,67 (m, 1H), 1,75 (s, 6H), 4,11 (s, 2H), 4,98 (s, 2H), 7,26 (s, 1H), 7,52 (s, 1H), 8,16 (s, 1H), 8,46 (s, 1H), 8,71 (d, 1H), 8,91 (d, 1H), 8,99 (s, 1H), 9,47 (s, 1H), 10,75 (s, 1H); LCMS (System 10): T_r = 3,78 min; m/z 574 $[M+H]^+$.

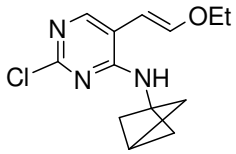
Preparación 280: Biciclo[1,1,1]pent-1-il-(5-bromo-2-cloro-pirimidin-4-il)-amina



A una solución de 5-bromo-2,4-dicloro-pirimidina (6 g, 26,3 mmoles) y biciclo[1,1,1]pent-1-ilamina (4,7 g**,** 39,5 mmoles) en acetonitrilo (60 ml), se agregó TEA (16,5 ml, 118 mmoles), y la mezcla se agitó a 25ºC durante 18 horas. Los volátiles se eliminaron al vacío y el residuo se dividió entre agua y EtOAc. La fase orgánica se secó (Na_2SO_4) y se evaporó al vacío. La purificación por cromatografía de columna sobre gel de sílice (EtOAc:hexano 1:99) dio el compuesto del título en forma de un sólido de color blanco en 82% de rendimiento, 4,8 g.

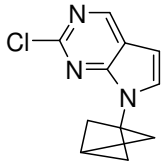
^{1}H RMN (400 MHz, DMSO-D6) δ*:* 2,10 (d, 6H), 2,48-2,50 (m, 1H), 8,26 (d, 2H); LCMS (Sistema 10) : T_r = 3,64 min; m/z 276 $[M+H]^+$.

Preparación 281: Biciclo[1,1,1]pent-1-il-[2-cloro-5-((Z)-2-etoxi-vinil)-pirimidin-4-il]-amina



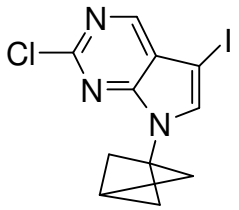
A una solución agitada de biciclo[1,1,1]pent-1-il-(5-bromo-2-cloro-pirimidin-4-il)-amina (preparación 280, 2 g, 7,29 mmoles) en tolueno seco (70 ml) se agregó (Z)-1-etoxi-2-(tributilestanil)eteno (2,7 ml, 8,03 mmoles). La mezcla de reacción se purgó con N_2 durante 20 min y a continuación se agregó $Pd(PPh_3)_4$ (421 mg, 0,36 mmoles), seguido de la desgasificación durante otros 20 min y calentamiento hasta 110ºC en N_2 durante toda la noche. La reacción se enfrió hasta temperatura ambiente, se templó con una solución 2M de KF y se filtró a través de un taco de celite. El filtrado se dividió entre agua (50 ml) y EtOAc (200 ml). La fase orgánica se lavó con salmuera (2 x 25 ml), se secó (Na_2SO_4) y se evaporó al vacío. El residuo bruto se purificó por cromatografía de columna sobre gel de sílice (EtOAc: Hexano 18: 82) para dar el compuesto en forma de un sólido de color verde pálido en 77% de rendimiento, 1,5 g.
^{1}H RMN (400 MHz, DMSO-D6) δ*:* 1,24 (t, 3H), 2,08 (d, 6H), 2,47 (m, 1H), 3,99 (q, 2H), 5,17 (d, 1H), 6,55 (d, 1H), 7,90 (s, 1H), 8,39 (s, 1H); LCMS (Sistema 10): T_r = 3,54 min; m/z 266 $[M+H]^+$.

Preparación 282: 7-biciclo[1,1,1]pent-1-il-2-cloro-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describió para la preparación 62, utilizando biciclo[1,1,1]pent-1-il-[2-cloro-5-((Z)-2-etoxi-vinil)-pirimidin-4-il]-amina (preparación 281) para dar el compuesto del título en forma de un sólido blancuzco en 89% de rendimiento, 1,4 g.
^{1}H RMN (400 MHz, DMSO-D6) δ*:* 2,41 (d, 6H), 2,69 (m, 1H), 6,67 (d, 1H), 7,61 (d, 1H), 8,92 (s, 1H); LCMS (Sistema 10): T_r = 3,45 min; m/z 220 $[M+H]^+$.

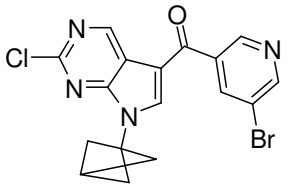
Preparación 283: 7-biciclo[1,1,1]pent-1-il-2-cloro-5-yodo-7H-pirrolo[2,3-d]pirimidina



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 63 utilizando 7-biciclo[1,1,1]pent-1-il-2-cloro-7H-pirrolo[2,3-d]pirimidina (preparación 282) para dar el compuesto del título en forma de un líquido de color marrón en 72% de rendimiento, 1,3g.

^{1}H RMN (400 MHz, DMSO-D6) δ*:* 2,40 (d, 6H), 2,68 (m, 1H), 7,90 (s, 1H), 8,67 (s, 1H); LCMS (Sistema 10): T_r = 3,89 min; m/z 346 $[M+H]^+$.

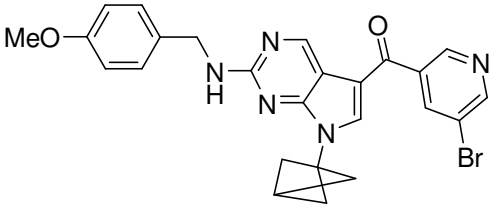
Preparación 284: (7-biciclo[1,1,1]pent-1-il-2-cloro-7H-pirrolo[2,3-d]pirimidin-5-il)-(5-bromo-piridin-3-il)-metanona



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 64 utilizando 7-biciclo[1,1,1]pent-1-il-2-cloro-7H-pirrolo[2,3-d]pirimidina (preparación 283) para dar el compuesto del título en forma de un sólido blancuzco en 58% de rendimiento, 1,1 g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 2,47 (d, 6H), 2,72 (m, 1H), 8,40-8,42 (m, 2H), 8,99-9,00 (m, 2H), 9,33 (s, 1H); LCMS (Sistema 10): T_r = 3,73 min; m/z 405 $[M+H]^+$.

Preparación 285: [7-biciclo[1,1,1]pent-1-il-2-(4-metoxi-bencilamino)-7H-pirrolo[2,3-d]pirimidin-5-il]-(5-bromo-piridin-3-il)-metanona

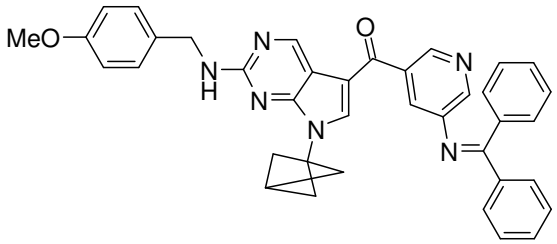


A una solución de (7-biciclo[1,1,1]pent-1-il-2-cloro-7H-pirrolo[2,3-d]pirimidin-5-il)-(5-bromo-piridin-3-il)-metanona (preparación 284, 1,1 g, 2,72 mmoles) y se agregó 4-metoxi bencilamina (1,06 ml, 8,16 mmoles) en dioxano (40 ml), DIPEA (1,7 ml, 10,8 mmoles) y la mezcla se calentó a 110ºC bajo irradiación de microondas durante 6

horas. Los volátiles se eliminaron al vacío y el residuo se dividió entre agua (50 ml) y acetato de etilo (150 ml). La fase orgánica se secó sobre sulfato de sodio, se evaporó al vacío y se purificó por cromatografía de columna sobre gel de sílice (gradiente de EA: Hexano 25: 75) para dar el compuesto en forma de un sólido de color blanco en 84 % de rendimiento, 1,15 g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 2,35 (d, 6H), 2,64 (m, 1H), 3,70 (s, 3H), 4,45 (d, 2H), 6,85 (d, 2H), 7,27 (d, 2H), 7,75 (s, 2H), 8,32 (m, 1H), 8,91-8,94 (m, 2H); LCMS (Sistema 10): T_r = 3,81 min; m/z 504,2 $[M+H]^+$.

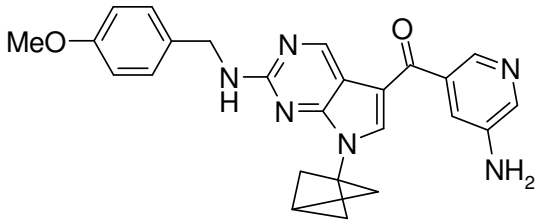
Preparación 286: [5-(benzidrilideno-amino)-piridin-3-il]-[7-biciclo[1,1,1]pent-1-il-2-(4-metoxi-bencilamino)-7H-pirrolo[2,3-d]pirimidin-5-il]-metanona



A una solución agitada de [7-biciclo[1,1,1]pent-1-il-2-(4-metoxi-bencilamino)-7H-pirrolo[2,3-d]pirimidin-5-il]-(5-bromo-piridin-3-il)-metanona (preparación 285, 1,18 g, 2 mmoles) y benzofenoneímina (0,50 ml, 3 mmoles) en tolueno seco (50 ml), se agregó carbonato de cesio (3,2 g, 10 mmoles) y la mezcla de reacción se purgó en N_2 durante 20 min y a continuación se agregaron $Pd(OAc)_2$ (45 mg, 0,2 mmoles) y BINAP (125 mg, 0,2 mmoles) seguido de desgasificación durante otros 10 min y a reflujo durante toda la noche. La masa de reacción se enfrió hasta temperatura ambiente y se filtró a través de un taco de celite. El filtrado se dividió entre agua (25 ml) y EtOAc (100 ml). La fase orgánica se lavó con salmuera (10 ml), se secó (Na_2SO_4) y se evaporó al vacío. La purificación por cromatografía de columna sobre gel de sílice (EtOAc:hexano 25:75) dio el compuesto del título en forma de un sólido de color amarillo en 85 % de rendimiento, 1,1g.

^{1}H RMN (400 MHz, DMSO-D_6) δ: 2,36 (d, 6H), 2,65 (m, 1H), 3,70 (s, 3H), 4,44 (d, 2H), 6,84 (d, 2H), 7,24-7,29 (m, 4H), 7,36-7,37 (m, 3H), 7,50-7,52 (m, 4H), 7,58 (m, 1H), 7,70-7,72 (m, 3H), 8,15 (d, 1H), 8,48 (d, 1H), 8,89 (s, 1H); LCMS (sistema 9): T_r = 4,02 min; m/z 605 $[M+H]^+$.

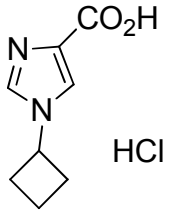
Preparación 287: [5-(amino-piridin-3-il]-[7-biciclo[1,1,1]pent-1-il-2-(4-metoxi-bencilamino)-7H-pirrolo[2,3-d]pirimidin-5-il]-metanona



A una solución de [5-(benzidrilideno-amino)-piridin-3-il]-[7-biciclo[1,1,1]pent-1-il-2-(4-metoxi-bencilamino)-7H-pirrolo[2,3-d]pirimidin-5-il]-metanona (preparación 286, 475 mg, 0,78 mmoles) en THF (15 ml), se agregó ácido cítrico (15 ml de una solución acuosa 1N) a temperatura ambiente y la mezcla de reacción se agitó durante 2 horas. La reacción se templó a continuación con solución de Na_2CO_3 acuoso saturado y se extrajo con EtOAc (2 x 25 ml). Las fases orgánicas se secaron (Na_2SO_4) y se evaporaron al vacío. La purificación por cromatografía de columna sobre alúmina neutra (metanol:DCM 3: 97) para dar el compuesto en forma de un sólido de color amarillo pálido en 92 % de rendimiento, 320 mg.

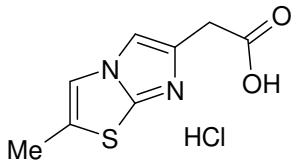
^{1}H RMN (400 MHz, DMSO-D_6) δ: 2,36 (d, 6H), 2,64 (m, 1H), 3,70 (s, 3H), 4,45 (d, 2H), 5,59 (s, 2H), 6,84 (d, 2H), 7,22 (m, 1H), 7,28 (d, 2H), 7,57 (s, 1H), 7,72 (br s, 1H), 8,10-8,12 (m, 2H), 8,92 (s, 1H); LCMS (Sistema 10): T_r = 3,10 min; m/z 441 $[M+H]^+$.

Preparación 288: Clorhidrato del ácido 1-ciclobutil-1H-imidazol-4-carboxílico



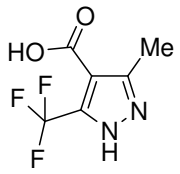
Se agregó 3-(dimetilamino)-2-isocianoacrilato de etilo (WO 2007042545) (45 g, 0,27 moles) a ciclobutilamina (50 g, 0,70 moles) y se calentó a reflujo durante 2 horas. A continuación la solución se enfrió y se concentró. El residuo se purificó por cromatografía de columna de gel de sílice (3:1 EtOAc:heptano). El residuo oleoso se trituró con TBME:heptano (1:1) y el sólido resultante se recolectó y se secó, dando etil éster del ácido 1-ciclobutil-1H-imidazol-4-carboxílico (35 g, 67%, segundo cultivo no cosechado). Se disolvió etil éster del ácido 1-ciclobutil-1H-imidazol-4-carboxílico (35 g, 0,21 moles) en HCl 6N (300 ml) y se reflujó durante 1 día. La solución se concentró hasta sequedad al vacío. El sólido se azeotropeó con tolueno, se trituró con tolueno y a continuación se secó al vacío, dando el compuesto del título 88% de rendimiento, 37,2 g, m/z 167 $[M+H]^+$.

Preparación 289: Clorhidrato de ácido (2-metilimidazo[2,1-b]tiazol-6-il)acético



Se agregó 4-bromo-3-oxobutanoato de etilo (92 g, 0,35 moles) a una solución de 5-metiltiazol-2-amina (40 g, 0,35 moles) en acetona (400 ml). La mezcla se dejó asentar durante toda la noche y a continuación se evaporó para dar bromuro de 2-amino-3-(4-etoxi-2,4-dioxobutil-5-metiltiazol-3-io en 82% de rendimiento, 101 g. A continuación se reflujó bromuro de 2-amino-3-(4-etoxi-2,4-dioxobutil)-5-metiltiazol-3-io (101 g, 0,28 moles) en etanol (250 ml) durante 2 horas. A continuación el solvente se evaporó para dar bromhidrato de 2-(2-metilimidazo[2,1-b]tiazol-6-il)acetato de etilo en forma de cristales de color amarillo en 97% de rendimiento, 85 g. Se agregó K_2CO_3 sólido a una solución de bromhidrato de 2-(2-metilimidazo[2,1-b]tiazol-6-il)acetato de etilo (85 g, 0,28 moles) en agua (300 ml) hasta pH ~8. El producto se extrajo con cloroformo (3 x 100 ml), y los extractos combinados se secaron sobre Na_2SO_4 y se evaporaron para dar 2-(2-metilimidazo[2,1-b]tiazol-6-il)acetato de etilo en 84% de rendimiento, 52 g. Se reflujó 2-(2-metilimidazo[2,1-b]tiazol-6-il)acetato de etilo (52 g, 0,23 moles) en 10% de HCl acuoso o(150 ml) durante 2 horas. La solución se evaporó hasta sequedad para dar el compuesto del título en forma de cristales de color marrón en 59% de rendimiento 32,3 g; m/z 197 $[M+H]^+$.

Preparación 290: Ácido 3-metil-5-(trifluorometil)-1H-pirazol-4-carboxílico



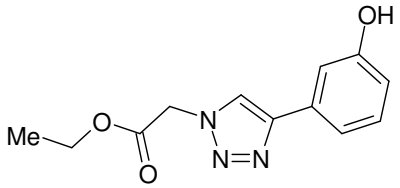
A una solución de acetoacetato de bencilo (57,6 g, 300 mmoles) en MeOH (50 ml) en un recipiente de presión de 350 ml se agregó H_2NMe (150 ml de una solución 2M en MeOH, 300 mmoles) y ácido acético (2 ml). El recipiente tapado se colocó en un baño oleoso a 70ºC y la mezcla de reacción se agitó durante 16 horas. Después de que la mezcla se había enfriado hasta temperatura ambiente, el solvente se evaporó al vacío dejando una emulsión de color amarillo, el cual se disolvió en EtOAc (500 ml) y se agregó $MgSO_4$ para eliminar el agua. El agente de secado se filtró, y el solvente se evaporó al vacío para dar 3-(metilamino)but-2-enoato de bencilo en forma de un aceite de color amarillo viscoso en rendimiento cuantitativo 60 g el cual se utilizó sin purificación posterior.

A una solución de 3-(metilamino)but-2-enoato de bencilo (60 g, 300 mmoles) y piridina (27 ml, 330 mmoles) en THF (500 ml), se enfrió hasta -20ºC, se agregó anhídrido triflico (45 ml, 315 mmoles) durante un período de 30 min. Durante la adicion, la temperatura se mantuvo por debajo de -10ºC. La mezcla de reacción se dejó entibiar hasta temperatura ambiente durante toda la noche dando por resultado una mezcla de reacción transparente de color amarillo. El solvente se evaporó al vacío y el residuo de color naranja se colocó en agua (1 litro) y Et_2O (1 litro). Al cabo de la agitación la mezcla se colocó en un embudo de separación de 3 litros, todo el material sólido se disolvió. La capa orgánica se separó y se lavó con agua (3 x 500 ml), salmuera (500 ml), y se secó sobre $MgSO_4$. La filtración y la evaporación del solvente al vacío dio 3-(metilamino)-2-(trifluoroacetil)but-2-enoato de bencilo en forma de un sólido blancuzco en 97% de rendimiento, 90 g que se utilizó sin purificación adicional.

A una solución de 3-(metilamino)-2-(trifluoroacetil)but-2-enoato de bencilo (90 g, 300 mmoles) en una mezcla de THF (900 ml) y ácido acético (100 ml) se agregó monohidrato de hidrazina (14,6 ml, 300 mmoles) durante un período de 5 min. La mezcla de reacción se calentó hasta reflujo durante 3 horas, se dejó enfriar hasta temperatura ambiente y los solventes se evaporaron al vacío para dar una masa de color amarillo brillante. La masa se disolvió en EtOAc (1 litro) y agua (1 litro) con calentamiento suave, se dejó enfriar hasta temperatura ambiente y la capa acuosa se neutralizó hasta pH 7-8 con $NaHCO_3$. La mezcla se transfirió a un embudo de separación de 3 litros, las capas se mezclaron vigorosamente, se separaron y la capa orgánica se lavó con agua (3 x 500 ml) se secó ($MgSO_4$), se filtró y se evaporó al vacío para dar 3-metil-5-(trifluorometil)-1*H*-pirazol-4-carboxilato de bencilo en forma de un sólido blancuzco en 89% de rendimiento 74 g que se utilizó sin purificación posterior.

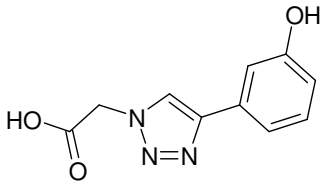
Una mezcla de 3-metil-5-(trifluorometil)-1*H*-pirazol-4-carboxilato de bencilo (74 g, 285 mmoles), Pd/C (45 g, 10% sobre C) y EtOAC (1 litro) se trató en un aparato Parr a temperatura ambiente con H_2 (15 psi) durante 5 horas. El catalizador se filtró sobre celite y el solvente se eliminó al vacío. Se agregaron Et_2O (1 litro) y agua (200 ml) y la capa acuosa se hizo levemente básica (pH 8-9) con Na_2CO_3. Las capas se separaron y la capa acuosa se extrajo con Et_2O (5 × 200 ml). A la capa acuosa se agregó gota a gota HCl conc. Hasta pH 4-5 y seguido de la extracción con Et_2O (3 × 500 ml). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se evaporaron al vacío para dar el compuesto del título en 74% de rendimiento, p.f. 308-310ºC (grados) m/z 195 $[M+H]^+$

Preparación 291: [4-(3-hidroxifenil)-1H-1,2,3-triazol-1-il]acetato de etilo



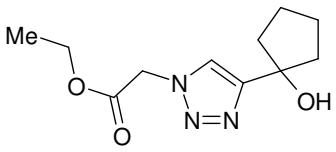
Se disolvió azidoacetato de etilo (14,9 g, 115 mmoles) en ter-butano (200 ml), y se agregó 95% de hidroxibenzonitrilo (13,7 g, 110 mmoles). Una solución de ascorbato de sodio (2,18 g, 11 mmoles) en agua (100 ml) se agregó, seguido de una solución 0,3 M de sulfato de cobre en argón. La mezcla se agitó a temperatura ambiente durante 12 horas. La solución se evaporó hasta sequedad al vacío, el residuo se disolvió en EtOAc (100 ml), se secó ($MgSO_4$), se filtró, se evaporó al vacío para dar el compuesto del título en forma de cristales de color marrón en ~100% (27,7 g) de rendimiento.
EM m/z 246 $[M-H]^-$

Preparación 292: Hidrato ácido [4-(3-hidroxifenil)-1H-1,2,3-triazol-1-il]acético.



Se disolvió [4-(3-hidroxifenil)-1H-1,2,3-triazol-1-il]acetato de etilo (preparación 291, 27,2 g , 0,110 moles) en metanol (200 ml), y se agregó una solución de NaOH (4,84 g, 121 mmoles) en agua (40 ml). La solución se mantuvo a temperatura ambiente durante 24 horas. Se evaporó metanol al vacío, se agregó agua (120 ml), y la solución se reflujó con carbón activado. La mezcla se filtró, y se agregó HCl 11 M al filtrado. La mezcla se disolvió por adición de agua (120 ml) y se enfrió para llevar a cabo la cristalización. Los cristales se filtraron, se lavaron con agua (2 x 15 ml), y se evaporaron hasta sequedad para dar el compuesto del título en forma de cristales de color marrón (pf 186,3--188,7ºC) en 99,0% de rendimiento 23,9 g. EM m/z 218 $[M-H]^-$

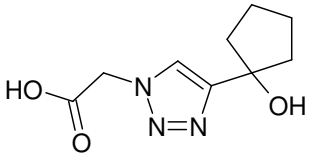
Preparación 293: [4-(1-hidroxiciclopentil)-1H-1,2,3-triazol-1-il]acetato de etilo



Se disolvió azidoacetato de etilo (2,58 g, 20 mmoles) en ter-butanol (15 ml), y se agregó 1-hidroxiciclopentanocarbonitrilo (2,20 g, 20 mmoles). Una solución de ascorbato de sodio (0,792 g, 4 mmoles) en agua (10 ml) seguido de una solución 0,3M de sulfato de cobre (0,67 ml) se agregó a la mezcla, y se continuó la agitación a

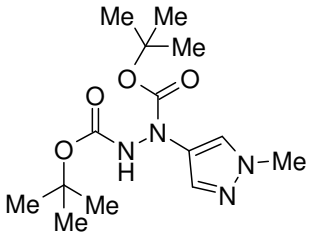
temperatura ambiente durante otras 48 horas. La solución se evaporó hasta sequedad al vacío, y el residuo se disolvió en EtOAc (50 ml), se secó ($MgSO_4$), se filtró y se evaporó al vacío para dar el compuesto del título en forma de cristales de color verde-amarillo en 98%, 4,69 g.
EM m/z 238 $[M-H]^-$

Preparación 294: Ácido 4-(hidroxiciclopentil)-1H-1,2,3-triazol-1-il]acético.



A una solución de [4-(1-hidroxiciclopentil)-1H-1,2,3-triazol-1-il]acetato de etilo (preparación 293, 36,4 g, 1,51 mmoles) en agua (50 ml), se agregó una solución de NaOH (7,60 g, 190 mmoles) en agua (25 ml). La solución se reflujó con carbón activado, se filtró a través de celite, y se agregó $NaHSO_4$ (25,8 g, 190 mmoles) Se agregó EtOAc (50 ml) al filtrado. El precipitado formado se separó por filtración, se disolvió en EtOAc (100 ml), y la solución se filtró. La capa acuosa se extrajo con EtOAc (10 x 50 ml), y los extractos combinados se evaporaron hasta un volumen de 100 ml. El precipitado se filtró, se lavó con acetato de etilo (2 x 50 ml), y se concentró a presión reducida para dar el compuesto del título en forma de una sustancia cristalina incolora en 87% de rendimiento, 27,8 g. P.f. 124,0-126,0ºC; EM m/z 212 $[M+H]^+$

Preparación 295: 1-(1-metil-1H-pirazol-4-il)hidrazina-1,2-dicarboxilato de di-ter-butilo

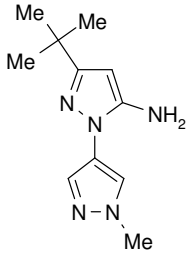


A una solución de 4-yodo-1-metil-1H-pirazol (21 g, 0,12 moles) en éter seco (200 ml) a -78ºC se agregó n-BuLi (84,5 ml de una solución 2,5 M en hexano, 0,18 moles) durante un período de 30 min y la mezcla se agitó durante otros 30 min. Una solución de (Z)-diaceno-1,2-dicarboxilato de di-ter-butilo (30,4 g, 0,12 moles) en éter (100 ml) se agregó a la mezcla de reacción durante un período de 10 min y la mezcla resultante se agitó a -78ºC durante 1 hora. La reacción se entibió hasta 0ºC y se templó con agua helada y se extrajo con éter (3 x 100 ml). La capa orgánica se

separó, se secó (Na_2SO_4) y se evaporó al vacío. El material bruto se lavó con hexano y a continuación se secó al vacío para dar el compuesto del título en 30% de rendimiento, 11,2 g.

^{1}H RMN (400 MHz, DMSO-d_6): d 9,60 (s, 1 H), 7,62 (s, 1 H), 7,25 (s, 1 H), 3,76 (s, 3 H), 1,44 (m, 18 H). LCMS: 313 (M+H) +

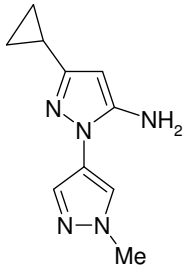
Preparación 296: 3-ter-butil-1'-metil-1'H-1,4'-bipirazol-5-amina



Una mezcla de 1-(1-metil-1H-pirazol-4-il)hidrazina-1,2-dicarboxilato de di-ter-butilo (preparación 295, 12,3 g, 0,039 moles) y 4,4-dimetil-3-oxopentanonitrilo (5,4 g, 0,043 moles) se disolvió en MeOH (36 ml) y HCl (12 ml) se agregó lentamente. La mezcla de reacción se agitó a 65ºC durante 16 horas. La reacción se destiló para eliminar MeOH y se basificó con solución de $NaHCO_3$ acuoso saturado hasta pH~8 seguido de extracción con DCM. La capa orgánica se separó, se secó (Na_2SO_4) seguido de concentración al vacío. La mezcla bruta se purificó por cromatografía de columna sobre gel de sílice (hexano:EtOAc 50:50) para dar el compuesto del título en 41% de rendimiento, 7,2 g.

^{1}H RMN (400 MHz, DMSO-d6) d 7,91 (s, 1 H), 7,58 (s, 1 H), 5,28 (s, 1 H), 5,04 (s, 2 H), 3,81 (s, 3 H), 1,21 (s, 9 H); LCMS: m/z 220 $[M+H]^+$

Preparación 297: 3-ciclopropil-1'-metil-1'H-1,4'-bipirazol-5-amina



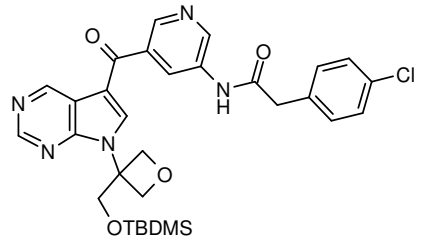
El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 296: utilizando 1-(1-metil-1H-pirazol-4-il)hidrazina-1,2-dicarboxilato de di-ter-butilo (preparación 295) y 3-ciclopropil-3-oxopropanonitrilo para dar el compuesto del título en 48% de rendimiento, 1,7g.

^{1}H RMN (400 MHz, DMSO-d_6): 0,55-0,57 (m, 2H), 0,75-0,80 (m, 2H), 1,68-1,72 (m,

1H), 3,83(s, 3H), 5,08-5,09 (m, 3H), 7,57(s, 1H), 7,90(s, 1H).

LCMS: $[M+H]^+$ 204

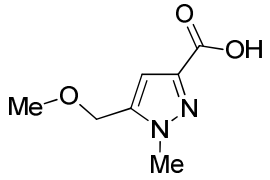
Preparación 298: N-[5-({7-[3-({[ter-butil(dimetil)silil]oxi}metil)oxetan-3-il]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-(4-clorofenil)acetamida



El compuesto del título se preparó de acuerdo con el método que se describe para la preparación 223 utilizando {5-aminopiridin-3-il}(7-(3.metiloxetan-3-il)-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (preparación 222) para dar el compuesto del título en forma de un sólido de color blanco en 87% de rendimiento, 35 mg.

LCMS (sistema 2): T_r = 1,49 min; m/z 592 $[M+H]^+$.

Preparación 299: Ácido 5-(metoximetil)-1-metil-1H-pirazol-3-carboxílico

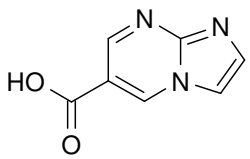


A una solución de 5-(metoximetil)-1-metil-1H-pirazol-3-carboxilato de etilo (WO9743277) (177 mg, 0,893 mmoles) en MeOH, se agregó una solución 0,5 M de LiOH (5,3 ml, 2,68 mmoles). La reacción se agitó a temperatura ambiente durante toda la noche. La solución se evaporó hasta sequedad y el residuo se ajustó hasta pH 5 con una solución de HCl 2N. La solución acuosa se extrajo con EtOAc y la capa orgánica se secó sobre Na_2SO_4 y se evaporó al vacío para dar el compuesto del título en forma de un sólido de color blanco 95%, 145mg.

^{1}H RMN (400MHz, metanol-d4) 6,68 (s, 1 H), 4,44 (s, 2 H), 3,84 (s, 3 H), 3,29 (s, 3 H).

EM m/z 171 $[M+H]^+$

Preparación 300: Ácido imidazo[1,2-a]pirimidin-6-carboxílico

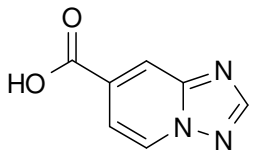


Una mezcla de 6-bromoimidazo[1,2-a]pirimidina (1,17 g, 6 mmoles), BINAP (18 mg, 0,06 mmoles), PdCl2 (6 mg) in MeOH (30 ml) y trietilamina (1,8 ml) se calentó

hasta 80ºC en CO (50 psi) durante 12 horas en DMF (97,5 ml). Se agregó DMF-DMA (70,6 ml, 495,8 mmoles) y la mezcla se calentó hasta 130ºC durante 12 horas. La mezcla se filtró y se concentró para dar imidazo[1,2-a]pirimidin-6-carboxilato de metilo (365 mg, 35%) en forma de un sólido de color amarillo el cual se utilizó en el próximo paso sin purificación posterior. A una solución de imidazo[1,2-a]pirimidin-6-carboxilato de metilo (365 mg, 2,1 mmoles) en metanol se agregó LiOH acuoso 1M (90 ml) y la mezcla resultante se agitó durante 10 horas a temperatura ambiente. El pH se ajustó hasta 5-6 utilizando HCl acuoso y la mezcla completa se extrajo con EtOAc (3 x 30 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron al vacío para dar el compuesto del título en forma de un sólido de color blanco en 39% de rendimiento, 133 mg.

^{1}H RMN (400 MHz, DMSO-d_6): δ 9,15 (m, 1H), 8,8 (m, 1H), 7,9 (m, 1H), 7,65 (m, 1H),

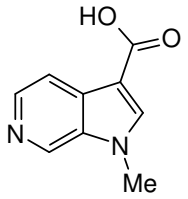
Preparación 301: Ácido [1,2,4]triazolo[1,5-a]piridin-7-carboxílico



A una solución de 2-aminoisonicotinato de metilo (28,8 g, 191 mmoles) en DMF (97,5 ml) se agregó DMF-DMA (70,6 ml, 496 mmoles) y la mezcla se calentó hasta 130ºC durante 12 horas. La mezcla se concentró a continuación para dar un residuo. Al residuo se agregó metanol (381 ml), seguido de NH_2OHSO_4 (31,9 g, 248 mmoles) y la mezcla resultante se agitó a temperatura ambiente durante toda la noche. La mezcla de reacción se concentró para dar [1,2,4]triazolo[1,5-a]piridin-7-carboxilato de metilo en 18% de rendimiento, 6g. A una solución de [1,2,4]triazolo[1,5-a]piridin-7-carboxilato de metilo (3 g, 16 mmoles) en metanol se agregó LiOH acuoso 1M (70 ml) y la mezcla resultante se agitó durante 10 horas a temperatura ambiente. El pH se ajustó hasta 5-6 utilizando HCl acuoso y la mezcla completa se extrajo con EtOAc (30 ml x 3). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron al vacío para dar el compuesto del título en forma de un sólido de color blanco en 38% de rendimiento, 1,05 g.

^{1}H RMN (400 MHz, DMSO-d_6): δ 13,5-14,0 (s, 1H), 9,04-9,06 (m, 1H), 8,66 (m, 1H), 8,32 (m, 1H), δ7,56-7,58 (m, 1H).

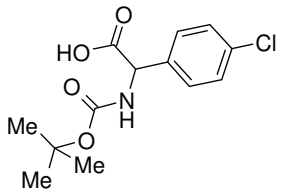
Preparación 302: Ácido 1-metil-1H-pirrolo[2,3-c]piridin-3-carboxílico



Se disolvió 1-metil-1H-pirrolo[2,3-c]piridin-3-carbaldehído (WO 05066132) (6,5 g, 40,6 mmoles) en un solvente mezcla de THF (120 ml) y ter-butil alcohol (40 ml) en nitrógeno. Se agregó solución 2M de 2-metil-2-buteno en THF (120 ml, 46 mmoles) seguido de una solución de $NaClO_2$ (11,02 g, 122 mmoles) y NaH_2PO_4 (21,9 g, 183 mmoles) en agua (30 ml). La mezcla de reacción se agitó a temperatura ambiente en nitrógeno durante toda la noche. La mezcla de reacción se concentró al vacío para eliminar solventes orgánicos, y el residuo se filtró. El precipitado contenía el compuesto del título en forma de un sólido de color blanco en 57% de rendimiento, 4,1 g.

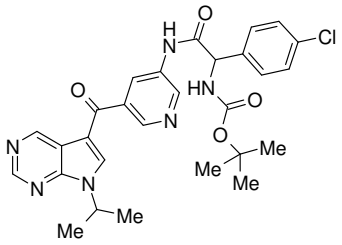
^{1}H RMN: DMSO-d6 400MHz: δ 3,96 (S, 3 H), 7,87-7,89 (d, 1 H), 8,23 (s, 1 H), 8,28 (d, 1 H), 8,91 (s, 1 H), 12,3 (s, 1 H).

Preparación 303: Ácido 2-((ter-butoxicarbonil)amino)-2-(4-clorofenil)acético



A 4-clorofenilglicina (1,50 g, 8,08 mmoles) e hidróxido de sodio (0,65 g, 16,2 mmoles) en agua (20 ml) se agregó bicarbonato de di-ter-butilo (1,76 g, 8,08 mmoles) en acetonitrilo (15 ml) y la mezcla se agitó a temperatura ambiente durante 18 horas. A continuación la mezcla se lavó con DCM (20 ml) y se acidificó utilizando HCl 2N. La capa acuosa resultante se extrajo con DCM (2 x 25 ml) y las capas orgánicas combinadas se lavaron con salmuera antes de ser secadas sobre $MgSO_4$, se filtraron y se evaporaron al vacío para dar el compuesto del título en forma de un aceite incoloro en 87% de rendimiento, 2,00 g.

Preparación 304: (1-(4-clorofenil)-2-((5-(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-carbonil)piridin-3-il)amino)-2-oxoetil)carbamato de ter-butilo



A piridina (4 ml) en un recipiente cerrado se agregó ácido 2-((ter-butoxicarbonil)amino)-2-(4-clorofenil)acético (67 mg, 0,24 mmoles) (véase preparación 303), (5-aminopiridin-3-il)(7-isopropil-7H-pirrolo[2,3-d]pirimidin-5-il)metanona (52 mg, 0,18 mmoles) (véase preparación 95) y *N*,*N*,*N*',*N*'-tetrametil-*O*-(7-azabenzotriazol-1-il)uronio hexafluorofosfato (105 mg, 0,28 mmoles). La reacción se calentó a 50ºC durante 18 horas y a continuación se evaporó al vacío y se purificó por cromatografía de columna (gradiente de 100:0 a 88:12 DCM:MeOH) para dar el compuesto del título en 49% de rendimiento, 64 mg. LCMS (básico): T_r = 0,81 min; m/z 549 $[M+H]^+$.

Actividad biológica

Los Ensayos de enzima TRK aislada utilizan el kit HTRF KinEASE-TK (Cisbio Cat# 62TK0PEJ) con dominios citoplasmáticos His-marcados recombinantes de cada receptor TRK de origen Invitrogen (véase la tabla a continuación). Esta actividad-ensayo mide la fosforilación de los residuos de tirosina dentro de un sustrato del kit HTRF el cual ha sido validado por Cisbio para una variedad de tirosina quinasas incluyendo los receptores de TRK.

Detalles del ensayo:

Blanco	Invitrogen Cat#	Aminoácidos	Enzima FAC	FAC ATP	Tiempo de reacción del ensayo
TRKA	PV3144 (NTRK1)	aa 441-796	4nM	40uM	35min
TRKB	PV3616 (NTRK2)	aa 526-838	1nM	1,4uM	40min
TRKC	PV3617 (NTRK3)	aa 510-825	10nM	15uM	30min

Las soluciones de reserva de 0,5 mM de los compuestos de ensayo se preparan y se diluyen en serie en 100% de DMSO. Una curva estándar que utiliza el compuesto del ejemplo 135 que se divulga en WO2005/116035 de 150uM también se prepara en cada placa de ensayo. El efecto del porcentaje alto (HPE) se define por 150uM PF-00593157-00 y 0% de efecto (ZPE) se define por 100% de DMSO. Las

placas negras de bajo volumen Greiner que contienen 0,2 ul del compuesto diluido en serie, estándares y HPE/ZPE se crean utilizando el dispenser de nanolitros Bravo.
El buffer 1X enzimático se prepara a partir de buffer 5X enzimático del kit Cisbio KinEASE TK utilizando agua MilliQ. A continuación el buffer se suplementa con MgCl 10 mM y DTT 2 mM (ambos de Sigma). En el caso de TRKB, el buffer además se suplementa con buffer enzimático suplementario 125 nM (SEB) del kit Cisbio.

2X FAC de enzima y 2X FAC de ATP diluidos en buffer enzimático completo 1X se incuba a temperatura ambiente durante 20 minutos para preactivar la enzima. A continuación de este paso de preactivación, se agregan 5 ul/pocillo de mezcla de enzima + ATP utilizando un Multidrop Micro para la placa de ensayo, manchado con 0,2 ul de 100% del compuesto de DMSO. Esto se deja durante 20 minutos a temperatura ambiente antes de agregar 5 ul de 2 uM de TK-sustrato-biotina (del kit Cisbio) diluido en buffer enzimático 1X (1 uM de FAC) utilizando el Multidrop Micro. La reacción se incuba a temperatura ambiente durante el tiempo de reacción de ensayo optimizado (véase la tabla). La reacción se detiene agregando 10 ul/pocillo de buffer de detección HTRF que contiene 0,25 uM de estreptavidina-XL665 (0,125 uM de FAC) y 1:200 TK anticuerpo-criptato utilizando un Multidrop.

Después de la adicion del reactivo de detección, las placas se cubren y se incuban a temperatura ambiente durante 60 minutos. Se lee la señal HTRF utilizando un lector Envision, medido como una relación de emisiones a dos longitud de onda diferentes, 620 nm y 665 nm. Cualquier compuesto que inhibe la acción de la TRK quinasa tendrá un valor de relación de fluorescencia inferior 665/620 nM que los compuestos que no inhiben la TRK quinasa. Los datos del compuesto de ensayo se expresan como porcentaje de la inhibición definida por los valores de HPE y ZPE para cada placa. El porcentaje de inhibición en presencia del compuesto de ensayo se grafica contra la concentración del compuesto sobre una escala log para determinar una IC_{50} a partir de la curva sigmoide resultante.

Los ensayos basados en células se llevaron a cabo utilizando líneas celulares de DiscoveRx que utilizan su tecnología PathHunter y los reactivos en un ensayo antagonista:

Blanco	Línea celular DiscoverRx Cat#	Neurotrofina cognado
TRKA	93-0462C3	NGF
TRKA coexpresada con p75	93-0529C3	NGF
TRKB	93-0463C3	BDNF
TRKB coexpresada con p75	93-0530C3	BDNF
TRKC	93-0464C3	NT3
TRKC coexpresada con p75	93-0531C3	NT3

Los ensayos se basan en la tecnología de Complementación de Fragmentos Enzimáticos privados de Discover Rx (EFC). En el caso de líneas celulares TRK, la proteína aceptora enzimática (EA) se fusiona a una proteína SH2 y el receptor de interés TRK ha sido marcado con una marca Prolink.

Al cabo de la unión de neurotrofina, el receptor TRK se torna fosforilado, y la proteína SH2 marcada se une Esto da por resultado la complementación funcional y la actividad de β-Galactosidasa recuperada lo cual se puede medir utilizando el sustrato Galacton Star luminiscente dentro de los kits de reactivos PathHunter.

En general, los inhibidores de pequeñas moléculas se unen al dominio quinasa de modo que no compiten con la neurotrofina (agonista) el cual se une a un sitio extracelular. Esto significa que la IC_{50} es una buena medición de afinidad y no debe estar afectada pro la concentración del estimulante de neurotrofina.

Las células PathHunter criopreservadas se usan ya sean de lotes producidos internos como lotes a granel adquiridos directamente de Discover Rx. Las células criopreservadas se revitalizan, se centrifugan a 1000 rpm durante 4 minutos para eliminar los medios de congelamiento, y se resuspenden en MEM + 0,5% de suero de caballo (ambos Invitrogen) hasta $5e^5$células/ml. A continuación las células se plaquean usando un Multidrop dentro de las placas tratadas con cultivo de tejido blanco Greiner a 20 ul/pocillo y se incuban durante 24 horas a 37ºC, 5% de CO_2, humedad alta. El día del ensayo, las placas celulares se dejan enfriar hasta temperatura ambiente durante 30 minutos antes del ensayo.

Las soluciones de reserva de 4 mM de los compuestos de ensayo se preparan y se diluyen en serie en 100% de DMSO. Una curva estándar que utiliza el compuesto del ejemplo 135, WO2005/116035 a una concentración superior de 150uM también se prepara en cada placa de ensayo. El efecto del porcentaje alto (HPE) se define por 150uMdel compuesto del ejemplo 135, WO2005/116035 y 0% de efecto (ZPE) se define por 100% de DMSO. Las placas que contienen 1 ul del compuesto diluido en serie, estándar y HPE/ZPE se diluyen 1/66 en buffer de ensayo (PBS menos Ca^{2+}, menos Mg^{2+} con 0,05% de F127 plurónico) utilizando un Wellmate. Utilizando un Platemate Plus, se transfieren posteriormente 5 ul de 1/66 de compuestos de ensayo diluidos a la placa celular y se dejan alcanzar el equilibrio incubando durante 30 min a temperatura ambiente antes de la adición del estímulo agonista: 10 ul/pocillo de 2 nM (0,571 nm de FAC) de la neurotrofina cognado (Peprotech) diluida en buffer agonista (HBSS con 0,25% de BSA). La concentración del ensayo final de los compuestos de ensayo es 8,66 μM, (el compuesto del ejemplo 135, WO2005/116035 FAC es 0,325

uM). Las placas se dejan a temperatura ambiente durante otras 2 horas antes de la adición de 10 ul del reactivo de detección PathHunter Discover Rx (producido agregando 1 parte de Galacton Star, 5 partes de Emeral II y 19 partes de buffer de ensayo celular según las instrucciones del fabricante).

Después de la adicion del reactivo, las placas se cubren y se incuban a temperatura ambiente durante 60 minutos. La señal de luminiscencia se lee usando un Envision. Los datos del compuesto de ensayo se expresan como porcentaje de la inhibición definida por los valores de HPE y ZPE para cada placa. El porcentaje de inhibición en presencia del compuesto de ensayo se grafica contra la concentración del compuesto sobre una escala log para determinar una IC_{50} a partir de la curva sigmoide resultante.

Ensayos de penetración del cerebro

In Vitro

Los datos de MDCK-BCRP: MDCK-BCRP se recolectaron de acuerdo con el método que se describe en "A 96-Well Efflux Assay To Identify ABCG2 Substrates Using a Stably Transfected MDCK II Cell Line" http://pubs.acs.org/doi/full/10,1021/mp050088t

Yongling Xiao, Ralph Davidson, Arthur Smith, Dennis Pereira, Sabrina Zhao, John Soglia, David Gebhard, Sonia de Morais, and David B. Duignan, *Mol. Pharm.* , **2006**, *3* (1), pp 45–54.

Los datos de MDCK-MDR1: MDCK-MDR1 se recolectaron de acuerdo con el método que se describe en "Are MDCK Cells Transfected with the Human *MDR1* Gene a Good Model of the Human Intestinal Mucosa?" http://www.springerlink.com/content/qfhqlqbr4fnp3khf/fulltext.pdf

Fuxing Tang, Kazutoshi Horie, and Ronald T. Borchardt, *Pharmaceutical Research,* Vol. 19, No. 6, Junio 2002.

In Vivo

La penetración del cerebro se midió de acuerdo con el método que se describe en "Assessing brain free fraction in early drug discovery". Read, K; Braggio, S., Expert Opinion Drug Metab Toxicol. (2010) 6 (3) 337- 344.

Número de ejemplo	Potencia de enzima TrkA (nM)	Potencia de enzima TrkB (nM)	Potencia de célula TrkA (nM)	Potencia de célula TrkB (nM)	Potencia de célula TrkC (nM)	MDCK MDR1 Papp AB (x10-6 cm/sec)	MDCK MDR1 Papp BA (x10-6 cm/sec)	RRCK BCRP Papp AB (x10-6 cm/sec)	RRCK BCRP Papp BA (x10-6 cm/sec)
1	3.7		9.5	1.5		5.5	14		
2	8.4	113	5.3	3.9	1.1	<1	15		
3	4.1		5.1	1.8		8.7	20		
4	3.9	162	5.7	6.5	4.4	<1	13	12	39
5	2.6	73	3.5	3.6	2.0	1.5	14		
6	2.5		2.0	1.3		6.9	16		
7	11	41	2.1	0.8		5.6	20		
8	2.4	15	1.9	2.0	2.3	1.8	15		
9	3.7	94	13	6.6	5.9	<1	20	9	43
10	5.7	78	30	18	18	<1	14		
11	3.3	197	17	11	6.6	<1	23		
12	9.2	547	68	22	<1		3.1		
13	20	449	1130	184	<1		1.0		
14	13	773	41	15	4.8	<1	21		
15	17	514	143	40	<1		15		
16	16	445	99	15					
17	23		103	45	<1		13		
18	128	>8660		5300	<1	<1			
19	249	5480	1840	206	<1		8.5		
20	14	635	22	19	<1		17		
21	71		5740	1770	<1		1.3		
22	25		596	190	<1		6.9		
23	26		93	52	<1		31		
24	125	427	37	27	8.9	<1	10		
25	24	433	65	19	<1		13		
26	3.5	30	14	5.9	8.6	<1	16	7.5	32
27	2.8	55	3.9	5.4	3.2	<1	17		
28	4.9	75	2.7	1.9	<1		20		
29	2.8	68	5.8	4.0		1.3	23		
30	4.0	98	11	7.5	<1		15		
31	18		401	198	<1		2.6		
32	9.0	423	87	59	18	<1	3.4		
33	5.7	96	2.0	1.6		1.0	24		
34	3.6	200	23	25	13	<1	11		
35	8.9	223	103	37	<1		5.3		
36	4.5	303	11	13	13	<1	12		
37	67		2250	571					
38	7.2		1060	589	<1		2.1		
39	24	>8660		4710	<1	<1			
40	67		2580	506	<1		2.4		
41	7.6		203	70	<1		6.3		
42	3.8	191	44	27	13	<1	9.5		
43	5.1	136	17	19	11	<1	13		
44	12		996	554	<1		1.6		
45	25	>8660		3790	<1	<1			
46	3.2	94	6.0	4.2	0.9	<1	18	7	31
47	25	27	35	13	<1		21		
48	1.7	40	2.9	3.6	2.5	<1	12		
49	2.1	37	3.1	2.1	2.1	<1	17		
50	6.6	143	10.0	2.1	<1		24		
51	7.8	198	35	7.5	9.9	<1	11		
52	3.1	103	22	16	8.1	<1	9.1		
53	4.0	163	16	5.0	8.6	<1	13		
54	6.7		368	174	<1		1.3		
55	7.0	179	12	4.5	<1		20		
56	9.5	962	451	517		1.1	1.0		
57	1.2	40	4.0	2.5		5.1	26		
58	2.1	315	11	11		1.2	54		
59	4.6	110	3.4	2.4		5.7	24		
60	1.8	13	1.6	0.9	<1		18		
61	4.5	100	13	8.4	1.4	<1	39		
62	1.8	41	1.9	2.7		5	99		
63	1.2	25	2.6	1.8	0.4	5.6	20		
64	1.5	19	2.0	1.4	<1		4.2		

Ejemplo	Enzima Trka (IC50)	Ejemplo	Enzima Trka (IC50)	Ejemplo	Enzima Trka (IC50)
65	55,6	109	65,1	153	71,5
66	3,55	110	36,5	154	94,1
67	4,15	111	46,2	155	49,1
68	12,1	112	57,8	156	133
69	10,9	113	300	157	174
70	22,8	114	976	158	230
71	135	115	102	159	234
72	63,3	116	103	160	1080
73	283	117	68,4	161	6270
74	1210	118	2550	162	324
75	567	119	233	163	1840
76	173	120	53	164	133
77	64,3	121	5200	165	3400
78	203	122	5840	166	110
79	1580	123	143	167	3470
80	392	124	244	168	702
81	197	125	148	169	3100
82	908	126	95,7	170	3100
83	355	127	1330	171	1280
84	2860	128	206	172	3840
85	70,8	129	3860	173	9810
86	95,5	130	284	174	210
87	63,2	131	831	175	2590
88	56,6	132	131	176	165
89	21,7	133	681	177	3100
90	8,81	134	330	178	3100
91	1030	135	312	179	3080
92	41,5	136	334	180	3100
93	12,4	137	496	181	3100
94	54,8	138	8310	182	543
95	3,95	139	65,7	183	1850
96	5,45	140	219	184	579
97	4,86	141	59,5	185	67,4
98	5,16	142	1380	186	719
99	19,5	143	4730	187	2630
100	25,6	144	71,5	188	277
101	204	145	37,4	189	836
102	42,9	146	573	190	820
103	41,7	147	76,4	191	873
104	20	148	93,4	192	173
105	25,6	149	3570	193	3570
106	14,8	150	51	194	101
107	12,3	151	232	195	835
108	7,63	152	82,5	196	791
197	430	242	8,71	287	4350
198	2350	243	38,4	288	43,1
199	22,1	244	4,69	289	1370
200	10,1	245	4,7	290	167
201	482	246	35,6	291	3230
202	412	247	71	292	37,7
203	316	248	23,7	293	20,2
204	4,24	249	35,8	294	61,4

Ejemplo	Enzima Trka (IC50)	Ejemplo	Enzima Trka (IC50)	Ejemplo	Enzima Trka (IC50)
205	12,2	250	3,48	295	31,9
206	123	251	33,1	296	47,7
207	110	252	5,18	297	299
208	129	253	3,92	298	1460
209	272	254	52,6	299	539
210	185	255	42,7	300	52,2
211	34,9	256	1,09	301	428
212	59	257	12,2	302	156
213	3,03	258	11,8	303	1220
214	65,9	259	8,62	304	3900
215	4,4	260	16,8	305	2640
216	31,6	261	128	306	S/D
217	83,3	262	32,3	307	S/D
218	1210	263	73,6	308	592
219	286	264	84,8	309	53,9
220	462	265	69	310	98,4
221	3100	266	2950	311	238
222	692	267	2120	312	166
223	1660	268	579	313	S/D
224	3100	269	557	314	835
225	27,7	270	343	315	39,1
226	3,61	271	39	316	S/D
227	12,5	272	697	317	S/D
228	14,9	273	342	318	S/D
229	138	274	38,6	319	188
230	63,7	275	5100	320	3100
231	S/D	276	295	321	3100
232	274	277	434	322	9800
233	96,5	278	54,3	323	3100
234	84,9	279	439	324	3100
235	70,5	280	498	325	111
236	25,2	281	161	326	2980
237	73,9	282	1010	327	3100
238	9,36	283	297	328	3100
239	22,6	284	2020	329	9810
240	19,2	285	7820	330	3100
241	45,3	286	19,5	331	9810
332	2180	381	2780	426	228
333	9800	382	45,7	427	93,4
334	1550	383	130	428	960
336	9800	384	4770	429	2740
337	4280	385	81,6	430	297
338	2730	386	9800	431	235
339	251	387	6880	432	2790
340	451	388	165	433	246
343	53,9	389	84,3	434	99,9
344	326	390	9800	435	5490
345	362	391	246	436	205
346	253	392	135	437	107
347	155	393	1360	438	31,2
348	36,6	394	7120	439	22,5
350	153	395	1350	440	676
351	21,1	396	177	441	8390

Ejemplo	Enzima Trka (IC50)	Ejemplo	Enzima Trka (IC50)	Ejemplo	Enzima Trka (IC50)
352	62,6	397	9800	442	36,6
353	S/D	398	138	443	47,7
354	S/D	399	153	444	496
355	302	400	593	445	5,51
356	56,3	401	132	446	812
357	302	402	9800	447	919
358	9800	403	1220	448	272
359	9800	404	118	449	155
360	956	405	1630	450	3150
361	7640	406	2640	451	7170
362	1910	407	2600	452	542
363	1030	408	654	453	634
364	5040	409	70,4	454	633
365	2040	410	9800	455	1070
366	354	411	9800	456	6960
367	5640	412	5,18	457	674
368	753	413	9800	458	213
369	3000	414	158	459	4,06
370	3540	415	2590	460	9800
371	97	416	52	461	9800
372	9800	417	71,2	462	1320
373	813	418	40,2	463	186
374	224	419	15,1	464	3010
375	9800	420	9800	465	2130
376	5100	421	1730	466	400
377	2630	422	451	467	538
378	716	423	1330	468	5100
379	56,3	424	4310	469	523
380	422	425	796	470	166
471	751	517	4390	562	3,75
472	1720	518	7,3	563	3,11
473	7280	519	47,9	564	1,57
474	4420	520	4,57	565	17,9
475	643	521	92,7	567	20,8
476	65	522	43,7	568	12,1
477	3030	523	11,4	569	34,4
478	587	524	4,53	570	6970
479	2160	525	9,48	571	2,92
480	531	526	1,51	572	9,5
481	313	527	4,64	573	17,9
482	6860	528	2,25	574	14,2
483	118	529	3,93	575	3,09
484	192	530	5,9	576	296
485	20	531	52,4	577	1,9
486	805	532	11,1	578	6,07
487	9800	533	31,3	579	8,11
488	64,6	534	20,3	580	0,825
489	9800	535	51,2	581	3,21
490	9800	536	1,57	582	9,79
491	1410	537	10,6	583	0,681
492	1690	538	1,51	584	581
493	848	539	4,08	585	36,7
494	2570	540	153	586	1000

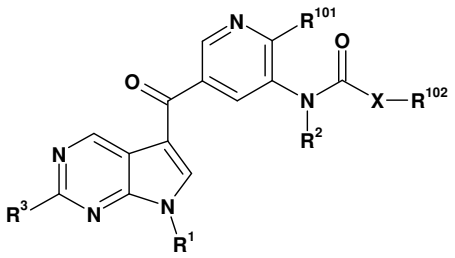
Ejemplo	Enzima Trka (IC50)	Ejemplo	Enzima Trka (IC50)	Ejemplo	Enzima Trka (IC50)
495	9,80E+03	541	S/D	587	20,5
496	199	542	S/D	588	334
497	43,5	543	50	589	31,3
498	2340	544	31,6	590	71,2
499	9,80E+09	545	2,95	591	142
500	25,8	546	5,34		
501	201	547	3,88		
502	6280	548	21,2		
503	963	549	3,22		
504	1020	550	16,1		
505	1630	551	2,78		
506	67	552	7,62		
507	5,45	553	4,4		
508	1630	554	270		
509	9800	555	150		
510	249	556	3,16		
511	144	557	9,47		
512	12,6	558	5,56		
513	1890	559	374		
514	9800	560	1610		
515	1140	561	112		

Todas las publicaciones mencionadas en la presente solicitud se incorporan a la presente como referencia en su totalidad.

Si bien la invención ha sido descripta anteriormente con referencia a las realizaciones divulgadas, los expertos en la técnica apreciarán fácilmente que los experimentos específicos detallados son sólo ilustrativos de la invención. Debe entenderse que se pueden realizar varias modificaciones sin apartarse del espíritu de la invención. En consecuencia, la invención está limitada sólo por las siguientes reivindicaciones

REIVINDICACIONES

1. Un compuesto de Fórmula I:



(I)

o su sal aceptable para uso farmacéutico, donde

R^1 es

H, o

alquilo C_{1-5} opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de OH, $CON(R^5R^6)$, SO_2R^7, SR^7, OR^7, CH_2OH, CO_2R^5, $SONR^7R^7$, $NR^7SO_2R^5$, CN, NO_2 y R^8, o

un sistema anular seleccionado de cicloalquilo C_{3-5}, propelanilo, o un anillo heterociclilo saturado de 4 a 6 miembros, dicho sistema anular tiene hasta 3 heteroátomos del anillo seleccionados de N, O y S, y dicho sisetema anular esta opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de metilo, OH, $CON(R^5R^6)$, SO_2R^7, OR^7, CH_2OH, CO_2R^5, $SONR^7R^7$, $NR^7SO_2R^5$, CN, NO_2 y R^8;

R^2 es H o metilo;

R^3 es H, NH_2 o $NH(C_{1-3}$ alquilo $_5$ opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de OH y $O(C_{1-3}$ alquilo));

R^{101} es H, OH, metilo, ciclopropilo, metoxi, etilo, etoxi o CN,

X es un enlace, O, $(CH\text{-}R^4)_n$, NR^{104}, OCH_2 o CH_2O;

R^4 es independientemente H, CH_3, CH_2OH, CH_2OCH_3, OH, NH_2, $NHCH_3$, $N(CH_3)_2$, CH_2NH_2, CH_2NHCH_3,o $CH_2N(CH_3)_2$;

R^{104} es H, alquilo C_{1-3} o un carbociclo C_{4-6} saturado, cada uno de los cuales está opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de alquilo C_{1-3}, CH_2OH y NH_2;

n es 1 o 2;

R^{102} es un sistema anular que es un sistema monocíclico, carbocíclico o heterocíclico

de 3 a 7 miembros, o un sistema bicíclico de 8 a 14 miembros, dicho sistema anular puede ser saturado o parcial o completamente insaturado, donde el sistema anular heterocíclico puede tener hasta 5 heteroátomos del anillo seleccionados de N, S y O,
donde el sistema anular bicíclico puede ser 2 anillos (carbocíclico-carbocíclico, carbocíclico-heterocíclico, heterocíclico-carbocíclico o heterocíclico-heterocíclico fusionados o enlazados mediante un enlace simple;
dicho sistema anular está opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de, donde sea posible,
halo, CN, NR^5R^6, SO_2R^7, SR^7, alquilos C_{1-4} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3} , cicloalquilo C_{3-6} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos halógeno, OH, O(alquilo C_{1-3}), O(cicloalquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos halógeno), O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}), $NR^5SO_2R^7$, =O, R^8, $C(O)R^8$, NO_2, $NR^5CO_2R^7$, NR^5COR^7,OR^8, $S(O)R^7$, y CH_2R^8;
R^5 y R^6 son cada uno de ellos independientemente

H, o

alquilo C_{1-5} opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de OH, $CONR^7R^7$, SO_2R^7, OR^7, CH_2OH, CO_2R^7, $SONR^7R^7$, $NR^7SO_2R^7$, CN, NO_2 y R^9 ,

o

un sistema anular seleccionado de cicloalquilo C_{3-5} , propelanilo, o un anillo heterociclilo saturado de 4 a 6 miembros, dicho sistema anular está opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de OH $CON(R^7R^7)$, SO_2R^7, CO_2R^7, $SONR^7R^7$, $NR^7SO_2R^7$, CN, NO_2, halo, NR^7R^7,SR^7, alquilo C_{1-4} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, cicloalquilo C_{3-6} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos halógeno, O(alquilo C_{1-3} sustituido con hasta 3 OH y/o alcoxi C_{1-3}, $NR^7SO_2R^7$,=O, NO_2, $NR^7CO_2R^7$, y $S(O)R^7$,
o R^5 y R^6 junto con el N al cual están unidos pueden ser un anillo de 4 a 7 miembros que incluye opcionalmente hasta 2 de otros heteroátomos del anillo independientemente seleccionados de N, O, S, dicho anillos está opcionalmente sustituido con alcoxi C_{1-3} y/o alquilo C_{1-3};
R^7 es H, alquilo C_{1-5} o alcoxi C_{1-5},
dicho alquilo C_{1-5} o alcoxi C_{1-5} está $_5$ opcionalmente sustituido con hasta 3

sustituyentes independientemente seleccionados de halógeno;

R^8 es un sistema anular que es un sistema monocíclico, carbocíclico o heterocíclico de 3 a 7 miembros, o un sistema bicíclico de 8 a 14 miembros, dicho sistema anular puede ser saturado o parcial o completamente insaturado, donde el sistema anular heterocíclico puede tener hasta 5 heteroátomos del anillo seleccionados de N, S y O,

donde el sistema anular bicíclico puede ser 2 anillos (carbocíclico-carbocíclico, carbocíclico-heterocíclico, heterocíclico-carbocíclico o heterocíclico-heterocíclico fusionados o enlazados mediante un enlace simple;

dicho sistema anular está opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de, donde sea posible,

halo, CN, NR^5R^6, SO_2R^7, SR^7, alquilo C_{1-4} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3} ,

cicloalquilo C_{3-6} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, alquilo C_{1-3} opcionalmente sustituido con 1 hasta 3 grupos halógeno, OH, O(alquilo C_{1-3}), O(cicloalquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos halógeno), O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}), $NR^5SO_2R^7$, =O, NO_2, NR^7COR^7,$NR^5CO_2R^7$, y $S(O)R^7$;

R^9 es un sistema anular que es un sistema monocíclico, carbocíclico o heterocíclico de 3 a 7 miembros, o un sistema bicíclico de 8 a 14 miembros, dicho sistema anular puede ser saturado o parcial o completamente insaturado, donde el sistema anular heterocíclico puede tener hasta 5 heteroátomos del anillo seleccionados de N, S y O,

donde el sistema anular bicíclico puede ser 2 anillos (carbocíclico-carbocíclico, carbocíclico-heterocíclico, heterocíclico-carbocíclico o heterocíclico-heterocíclico fusionados o enlazados mediante un enlace simple;

dicho sistema anular está $_5$ opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de, donde sea posible,

halo, NR^7R^7, SO_2R^7, SR^7, alquilo C_{1-4} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3} ,

cicloalquilo C_{3-6} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, alquilo C_{1-3} opcionalmente sustituido con 1 hasta 3 grupos halógeno, OH, O(alquilo C_{1-3}), O(cicloalquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}, O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos halógeno), O(alquilo C_{1-3} opcionalmente sustituido con hasta 3 grupos OH y/o alcoxi C_{1-3}), $NR^7SO_2R^7$, =O, NO_2, $NR^7CO_2R^7$, NR^7COR^7, y $S(O)R^7$;

donde cada resto CH puede ser reemplazado por un resto CF.

2. Un compuesto o sal de acuerdo con la reivindicación 1 donde R^1 es H, alquilo $C_{1\text{-}5}$ $_5$ opcionalmente sustituido con hasta 2 OH,

o R^1 es alquilo $C_{1\text{-}5}$ sustituido con $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CO_2H, CO_2CH_3, OCH_3, SCH_3, SO_2CH_3,

o R^1 es un sistema anular seleccionado de cicloalquilo $C_{3\text{-}5}$, propelanilo, u oxetanilo, dicho sistema anular está opcionalmente sustituido con metilo, OH o CH_2OH.

3. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 o 2 donde R^1 es t-butilo, hidroxi-t-butilo, dihidroxi-t-butilo, 1-hidroxiprop-2-ilo o 1,3-dihidroxiprop-2-ilo.

4. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 3 donde R^2 es H.

5. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 4 donde R^3 es H o NH_2.

6. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 5 donde R^3 es NH_2.

7. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 5 donde R^3 es H.

8. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 7 donde R^{101} es H.

9. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 7 donde R^{101} es OH.

10. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 9 donde X es un enlace, O, CH_2, C_2H_4, $CH(CH_3)CH_2$, $CH(CH_3)$, $CH(CH_2OH)$, CH_2O, $CH(NH_2)$, CH(OH) o NH.

11. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 10 donde X es CH_2.

12. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 11 donde R^{102} es un sistema anular que contiene nitrógeno opcionalmente sustituido que está enlazado al resto X mediante un átomo del anillo de nitrógeno.

13. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 11 donde R^{102} es un sistema anular opcionalmente sustituido donde el sistema anular se selecciona de

bencimidazolilo, bencisoxazolilo, benzofuranilo, benzoxazolilo, benzotriazolilo, bifenilo, bipirazolilo,

cinnolinilo, ciclobutilimidazolilo, ciclobutilpirazolilo, ciclobutiltiazolilo, ciclopentiltriazolilo, ciclopropilisoxazolilo, ciclopropiloxazolilo, ciclopropilpirazolilo, ciclopropiltriazolilo, diazirenifenilo,
dihidronaftiridinilo, dihidropirrolopirazolilo, dioxinopiridinilo, furazanilo, furopiridinilo, furopirrolilo,
imidazolilo, imidazopirazinilo, imidazopiridazinilo, imidazopiridinilo, imidazopirimidinilo, imidazotiadiazolilo,
imidazotiazolilo, indanilo, indazolilo, indolilo, isoindolilo, isoxazolopiridinilo, isoxazolilo, isoquinolinilo, naftiridinilo, oxazolilo, fenilo, fenilciclopropilo, fenilimidazolilo, fenilpirazolilo, fenilpirrolilo,
feniltetrazolilo, ftalazinilo, purinilo, pirazinilo, pirazolilo, pirazolopiridinilo, pirazolopirimidinilo, pirazolotriazinilo, piridinilo, piridazinilo, piridiniltriazolilo, pirimidinilo, pirroloimidazolilo, pirrolopirazinilo,
pirrolopirimidinilo, pirrolopiridinilo, pirrolilo, quinolinilo, quinazolilo, quinoxalinilo, tetrahidrobenzisoxazolilo,
tetrahidrociclopentapirazolilo, tetrahidrotriazolopiridinilo, tetrazolopiridazinilo, tetrazolopiridinilo, tiazolilo, tiazolopiridinilo, tiazolopirimidinilo, tienilopirazolilo, tienopiridinilo, triazolopiridinilo y triazolilo,

14. Un compuesto o sal de acuerdo con la reivindicación 13 donde los sustituyentes opcionales se seleccionan independientemente de, donde sea posible,
halo, metilo, etilo, propilo, isopropilo, ciclopropilo, CF_3, CHF_2, CH_2F, CH_2OCH_3, CN, CH_2OH, OCH_3, =O, NH_2, SCH_3, SO_2CH_3, fenoxi, fluorofenoxi, bencilo, SCF_3, OCF_3, SO_2CF_3, $NHSO_2CH_3$, $NHSO_2CF_3$, $C(O)CF_3$, $C(O)CH_3$, benzoílo, azetidinilmetilo, fluoroazetidinilmetilo y morfolinometilo.

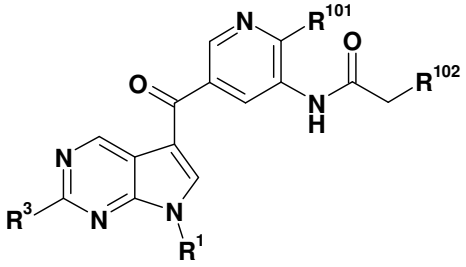
15. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 11, 13 o 14 donde R^{102} se selecciona de fenilo, pirazol-1-ilo, 1,2,3-triazol-1-ilo, benzotriazol-2-ilo, piridin-2-ilo, piridin-3-ilo y piridin-4-ilo,
cada uno de los cuales está opcionalmente sustituido con halo, metilo, etilo, propilo, isopropilo, ciclopropilo, CF_3, CHF_2, CH_2F, CH_2OCH_3, CN, CH_2OH, OCH_3, =O, NH_2, SCH_3, SO_2CH_3, fenoxi, fluorofenoxi, bencilo, SCF_3, OCF_3, SO_2CF_3, $NHSO_2CH_3$, $NHSO_2CF_3$, $C(O)CF_3$, $C(O)CH_3$, benzoílo, azetidinilmetilo, fluoroazetidinilmetilo y/o morfolinometilo.

16. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 15 con grupos R^5 y R^6 presentes, donde R^5 y R^6 son cada uno de ellos independientemente H, alquilo C_{1-3} opcionalmente sustituido con alcoxi C_{1-3},

cicloalquilo $C_{3-5,}$ propelanilo, oxetanilo, tetrahidrofuranilo o piranilo,

o R^5 y R^6 junto con el N a cual están unidos pueden ser un anillo de azetidina, pirrolidina, piperidina, piperazina, o morfolina, dicho anillo está opcionalmente sustituido con alcoxi C_{1-3} y/o alquilo C_{1-3}.

17. Un compuesto de acuerdo con la reivindicación 1 de la fórmula IA:



(IA)

o su sal aceptable para uso farmacéutico, donde

R^3 es H o NH_2 ;

R^1 es alquilo C_{2-4} opcionalmente sustituido con 1 o 2 grupos OH;

R^{101} es H o OH ;

y R^{102} es fenilo o un heterociclo de 5 o 6 miembros aromático o parcialmente insaturado, dicho heterociclo está opcionalmente fusionado a otro fenilo o anillo heterocíclico de 5 a 7 miembros, aromático o parcialmente insaturado, donde cada heterociclo tiene desde 1 a 3 heteroátomos del anillo seleccionado de N, O y S,

y dicho sistema anular está opcionalmente sustituido con hasta 3 sustituyentes independientemente seleccionados de

halo, CF_3, alquilos C_{1-4} y cicloalquilo C_{3-5}.

18. Un compuesto o sal de acuerdo con la reivindicación 17 donde R^{101} es H.

19. Un compuesto o sal de acuerdo con la reivindicación 18 donde

R^1 es butilo, hidroxi-t-butilo o 1-hidroxiprop-2-ilo;

y R^{102} es 4-trifluorometilfenilo, 4-clorofenilo, 2,4-difluorofenilo, 5-cloropiridin-2-ilo, 5-fluoropiridin-2-ilo, 3-trifluorometilpirazolil-1-ilo, 4-trifluorometilpirazol-1-ilo, 3-trifluorometil-5-metilpirazol-1-ilo,

3-ciclopropilpirazol-1-ilo, 4-ciclopropilpirazol-1-ilo, 4-trifluorometil (1,2,3-triazol-1-ilo), 4-ciclopropil-(1,2,3-triazol-1-ilo), o benzotriazol-2-ilo.

20. Un compuesto de acuerdo con la reivindicación 1, seleccionado de: N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)fenil]acetamida;

N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-

3-il)-2-(4-clorofenil)acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(5-fluoropiridin-2-il)acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(trifluorometil)-1H-pirazol-1-il]acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[3-(3-ciclopropil-1H-pirazol-1-il]acetamida;
N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-ciclopropil-1H-1,2,3-triazol-1-il)acetamida;
N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-pirazol-1-il]acetamida;
N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida;
N-{5-[(2-amino-7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(5-cloropiridin-2-il)acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(5-cloropiridin-2-il)acetamida;
N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-1,2,3-triazol-1-il]acetamida;
2-(4-clorofenil)-N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida
N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-[4-(trifluorometil)-1H-pirazol-1-il]acetamida;
N-[5-({7-[(1S)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[4-(trifluorometil)fenil]acetamida;
N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]-2-[4-(trifluorometil)fenil]acetamida;
2-(4-clorofenil)-N-[5-({7-[(1R)-2-hidroxi-1-metiletil]-7H-pirrolo[2,3-d]pirimidin-5-il}carbonil)piridin-3-il]acetamida
N-(5-{[2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[5-metil)-3-(trifluorometil-1H-pirazol-1-il]acetamida;
2-(5-cloropiridin-2-il)-N-(5-{[7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-clorofenil)acetamida;

N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)fenil]acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-(4-clorofenil)acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1-metiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[4-(trifluorometil)fenil]acetamida;
N-(5-{[2-amino-7-(2-hidroxi-1,1-dimetiletil)-7H-pirrolo[2,3-d]pirimidin-5-il]carbonil}piridin-3-il)-2-[5-metil-3-(trifluorometil)-1H-pirazol-1-il]acetamida;
y N-{5-[(7-ter-butil-7H-pirrolo[2,3-d]pirimidin-5-il)carbonil]piridin-3-il}-2-(4-(ciclopropil-1H-1,2,3-triazol-1-il)acetamida;
o su sal aceptable para uso farmacéutico.

21. Una composición farmacéutica que comprende un compuesto de la fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las reivindicaciones precedentes 1 a 20, y un vehiculo aceptable desde el punto de vista farmacéutico.

22. Un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las reivindicaciones 1 a 20, para uso como medicamento.

23. Un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las reivindicaciones 1 a 20, para uso en el tratamiento de una enfermedad para la cual se indica un antagonista del receptor Trk.

24. Un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las reivindicaciones 1 a 20, para uso en el tratamiento del dolor.

25. El uso de un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las reivindicaciones 1 a 20, para la producción de un medicamento para tratar una enfermedad para la cual se indica un antagonista del receptor Trk.

26. El uso de un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las reivindicaciones 1 a 20, para la producción de un medicamento para tratar el dolor.

27. Un método para el tratamiento de un mamífero, para tratar una enfermedad para la cual se indica un antagonista del receptor de Trk, que comprende tratar dicho mamífero con una cantidad eficaz de un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las reivindicaciones 1 a 20.

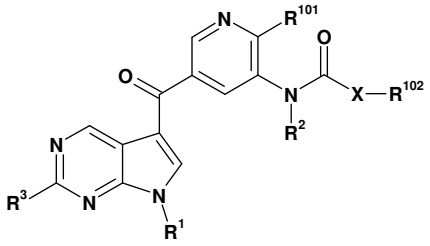
28. Un método para el tratamiento del dolor en un mamífero, que comprende tratar

dicho mamífero con una cantidad eficaz de un compuesto de fórmula (I) o su sal aceptable para uso farmacéutico, como se define en cualquiera de las reivindicaciones 1 a 20.

29. Un compuesto o sal de acuerdo con cualquiera de las reivindicaciones 1 a 20 para uso en un tratamiento médico en combinación con otra sustancia farmacéutica.

RESUMEN

La presente invención se refiere a compuestos de Fórmula (I)



(I)

y sus sales aceptables para uso farmacéutico donde los sustituyentes son como se describen en la presente, y su uso en medicina, en particular como antagonistas de Trk.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
PC71681A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2012/051363	22/03/2012	05/04/2011
Applicant		
PFIZER LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

   PYRROLO[2,3-D]PYRIMIDINE DERIVATIVES AS INHIBITORS OF TROPOMYOSIN-RELATED KINASES

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/051363

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 A61P35/00 A61P25/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/116035 A1 (PFIZER PROD INC [US]; MARX MATTHEW ARNOLD [US]; LA GRECA SUSAN DEBORAH) 8 December 2005 (2005-12-08) the whole document	1-29
A,P	WO 2011/093672 A2 (HANMI PHARM IND CO LTD [KR]; KOREA INST SCI & TECH [KR]; JUNG SEUNG HY) 4 August 2011 (2011-08-04) the whole document	1-29

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 April 2012	07/05/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fritz, Martin

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/051363

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005116035 A1	08-12-2005	BR PI0511512 A	26-12-2007
		CA 2566160 A1	08-12-2005
		EP 1773836 A1	18-04-2007
		JP 4842929 B2	21-12-2011
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		US 2006035912 A1	16-02-2006
		WO 2005116035 A1	08-12-2005
WO 2011093672 A2	04-08-2011	KR 20110088960 A	04-08-2011
		WO 2011093672 A2	04-08-2011