SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-198153- -00000-0000

Fecha: 2014-09-08 17:35:13 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 7

Industria y Comercio

SUPERINTENDENCIA

T=F=6

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCION DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS MACROCÍCLICOS PARA EL TRATAMIENTO DE ENFERMEDADES

SOLICITANTE: PFIZER INC.

DIRECCIÓN: 235 East 42nd Street, New York, New York 10017 (US).

APODERADO: CARLOS R. OLARTE

BOGOTÁ 8 de septiembre de 2014

P2014/000108

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA

Industria y Comercio
SUPERINTENDENCIA

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Act. 411 PRESENTACION Folios: 17

PETITORIO - FORMULARIO ÚI
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2014/000108**

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2)

SOLICITANTE (71)

Nombre: PFIZER INC.

Dirección: 235 East 42nd Street, New York, New York 10017 (US).
Nacionalidad o Domicilio: Estadounidense
Lugar de Constitución: Estados Unidos

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/IB2013/051391 Fecha Febrero 20, 2013

Publicación Internacional No. WO2013/132376 Fecha Septiembre 12, 2013

(6)

Título (54) **DERIVADOS MACROCÍCLICOS PARA EL TRATAMIENTO DE ENFERMEDADES**

Clasificación Internacional (51) C07D 491/08, C07D 491/18, C07D 498/08, C07D 498/18, C07D 498/22, C07D 513/18, A61K 31/4353, A61P 35/00

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Marzo 6,2012	61/607,485
US	Enero 31, 2013	61/759,307

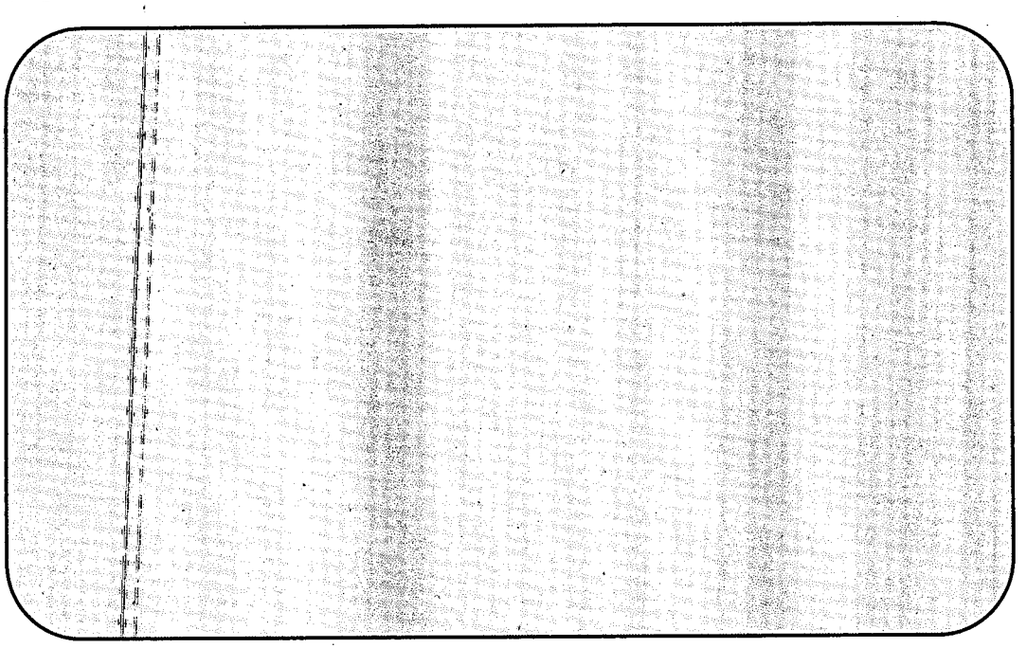
(9)

Comprobante de pago No. 14- **Fecha** _____

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] 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.
- [x] 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

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Estados Unidos de América
Nacionalidad: Gran Bretaña

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0095373

Bogotá D.C., Septiembre 08 de 2014 - 10:31:33

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	664107485	05/09/2014	12.212.250.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	515.000.00	515.000.00
				$515.000.00

SON: **QUINIENTOSQUINCE MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-*******-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-198153- -00000-0000
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Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACION - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia: 2020	Fecha: 14 / 9 / 8 (AAAA / MM / DD)	Recorrido:
Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	No. Radicación	Consecutivo	Item
1	11-198153	0	
2			
3			
4			
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9			
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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*
7	CD X
8	Disquete
9	DVD
10	Folleto
11	Rollo
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones:

el cd anexo contiene (10) archivos en formato PDF, los cuales son procesados y subidos al sistema

Claudia

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-198153- -00000-0000
Fecha: 2014-09-08 17:35:13 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
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7

PATENTE DE INVENCIÓN ☐ **MODELO DE U** ...

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

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 **P2014/000108**

SOLICITUD DE:

1

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

[X] Capítulo I. [ ] Capítulo II.

2

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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

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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/IB2013/051391 Fecha Febrero 20, 2013

Publicación Internacional No. WO2013/132376 Fecha Septiembre 12, 2013

6

Título (54) **DERIVADOS MACROCÍCLICOS PARA EL TRATAMIENTO DE ENFERMEDADES**

Clasificación Internacional (51) C07D 491/08, C07D 491/18, C07D 498/08, C07D 498/18, C07D 498/22, C07D 513/18, A61K 31/4353, A61P 35/00

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Marzo 6,2012	61/607,485
US	Enero 31, 2013	61/759,307

9

Comprobante de pago No. 14- **Fecha** _____

10 **ANEXOS**

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- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [x] Declaraciones. Declaración bajo la Regla 417(ii) del PCT.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
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- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
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- [ ] 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

WK 4682687

ESCRITURA PUBLICA NUMERO ----- TRESCIENTOS VEINTIUNO (321).- ----------

En la ciudad de Bogotá, Distrito Capital, República de Colombia, a los Veintitres - - - (23) días del mes de Marzo ----- 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: ----------

CARLOS REINALDO OLARTE GARCIA - ----------

C.C. No. 79.782.747.----------

Se Dio 3 Copias 29 MAR. 2007

NOTARIA VEINTISIETE María Eugenia Rojas de Urueta

Compareció **CARLOS REINALDO OLARTE GARCIA** mayor de edad, vecino de ésta ciudad, identificado con la cédula de ciudadanía número 79.782.747, obrando en su propio nombre 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 seis (6) folios autenticados, el poder y sus traducciones el cual del siguiente tenor: ----------

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

El suscrito, PFIZER INC, domiciliado en 235 East 42nd Street, New York, New York 10017, USA, nombramos por el presente otorga 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

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

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.-----

Firma (ilegible) Gregg C. Benson, Assistant General Counsel -----

Fecha: 20 February 2007.----------

Ciudad, Groton, Connecticut 06340 USA.----------

CERTIFICACION NOTARIAL ----------

En esta fecha,----------

el Notario Público suscrito certifica: ----------

Que GREGG C. BENSON mayor y domiciliado PFIZER INC., EASTERN POINT ROAD, GROTON, CONNECTICUT 06340 USA

NOTARIO PUBLICO
(HAY SELLO ADHERIDO)

APOSTILLE
(Convención de la Haya, Octubre 5, 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. PAIS: Reino Unido de Gran Bretaña e irlanda del Norte
ESTE DOCUMENTO PUBLICO
2. HA SIDO FIRMADO POR **STEPHEN DAVID FINN**
3. ACTUANDO EN SU CALIDAD DE **NOTARIO PUBLIC**
4. LLEVA EL SELLO/ESTAMPILLA DE DICHO NOTARIO PUBLICO

CERTIFICADO

5. EN **LONDRES**
6. EL DIA **FEBRERO 27, 2007**
7. POR EL SECRETARIO PRINCIPAL DE ESTADO DE SU MAJESTAD PARA ASUNTOS EXTERIORES Y DE LA COMUNIDAD.
8. NR. **H303068**
9. SELLO/ESTAMPILLA
10. FIRMADO

O. WILLIAM
(HAY FIRMA)

Si este documento va a ser usado en un país no miembro de la Convención de La Haya de Octubre 5, 1961,debe ser presentado ante la sección consular de la misión representante de ese país. Una apostilla o certificado de legalización solamente confirma que la firma, sello o estampilla en el documento es auténtica. No significa que el contenido del documento sea correcto o que la Oficina de Extranjería de la Comunidad apruebe el contenido.

CERTIFICADO DE AUTENTICIDAD: El suscrito Traductor e Interprete Oficial juramentado, y debidamente registrado en el Ministerio de Relaciones Exteriores, con el presente certifica que esta es una traducción auténtica, verdadera, y precisa al Idioma Castellano, del documento en Inglés, **anexo.**

FIDEL ANTONIO MURCIA MURCIA

Traductor e Interprete Oficial
Resolución No. 488/94 Ministerio de Justicia

NOTARIA VEINTISIETE
María Eugenia Rojas de Urueta

TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION 488/94
MINJUSTICIA
FIDEL ANTONIO MURCIA MURCIA

BOGOTA DC. MARZO 12, 2007

TRADUCCIÓN OFICIAL LEGALIZACIONES EN PODER

(VERIFIQUE ANTES DE PROCEDER)

NOTA DE TRADUCCIÓN: SE TRATA DE UN PODER CONFERIDO POR **PFIZER INC** A **OLARTE RAISBECK & FRIERI LTD,** DE FECHA **FEB-20-2007**, SUSCRITO EN GROTON, CONNECTICUT, USA, EN IDIOMA CASTELLANO E INGLES, CON CERTIFICACIÓN NOTARIAL TAMBIEN EN INGLES Y CASTELLANO; Y CERTIFICACIÓN NOTARIAL Y APOSTILLE IN IDIOMA INGLES, CUYA TRADUCCIÓN ES LA SIGUIENTE:

SE INFORMA QUE YO, STEPHEN DAVID FINN DE 31 AMERSHAM HILL DRIVE HIGH WYCOMBE BUCKINGHAMSHIRE, REINO UNIDO, NOTARIO DEBIDAMENTE AUTORIZADO,

CERTIFICO SOLAMENTE QUE EL DOCUMENTO ANEXO AL PRESENTE TITULADO,

PODER, firmado por Gregg C Benson

En este día ha sido presentado a mi por Servicios Consulares Blair en nombre de su cliente Pfizer, y que dichos Servicios Consulares Blair han manifestado ante mi mediante tal presentación que su mencionado cliente ha manifestado ante ellos que el documento anexo es un documento original auténtico.

FIRMADO, y sellado en 31 Amersham Hill Drive antes mencionado, el 23 de Febrero 2007.

(HAY FIRMA)
STEPHEN FINN

TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION 488/94
MINJUSTICIA
FIDEL ANTONIO MURCIA MURCIA

BE IT KNOWN that I, STEPHEN DAVID FINN of 31 Amersham Hill Drive High Wycombe Buckinghamshire United Kingdom a duly authorised Notary Public

CERTIFY only that the document annexed hereto, namely:

GENERAL POWER signed by Gregg C. Benson.

has this day been presented to me by Blair Consular Services on behalf of their client Pfizer, and that the said Blair Consular Services have represented to me by such presentation that their said client has represented to them that the annexed document is an authentic original document.

SIGNED and sealed at 31 Amersham Hill Drive aforesaid on 23rd February 2007.

Stephen Finn
Notary Public

NOTARIA VEINTISIETE
María Eugenia Rojas de Urrutia

6396

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: **Stephen David Finn**

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 **27 February 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: **H303068**

9. Stamp: / timbre:

10. Signature: **O Williams**

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 LTDA.

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

Zayde Chalhin
José Luis Londoño
Felipe Mendoza
Simón Salinas
Alexander Agudelo
Camilo A. Rodríguez

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

General Power

The undersigned,

PFIZER INC.

domiciled in

235 East 42nd Street, New York, New York 10017 USA

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 Rojas de Urueta

Signature/Firma: _____

Gregg C. Benson, Assistant General Counsel

Date/Fecha: 20 February 2007

City,Country: Groton, Connecticut 06340 USA

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification	**Certificación Notarial**
On this date, 20 February 2007 The undersigned Notary Public certifies:	En esta fecha, el Notario Público suscrito certifica:
1. That GREGG C. BENSON of legal age and domiciled in PFIZER INC., EASTERN POINT ROAD, GROTON, CONNECTICUT 06340 USA signed the foregoing document.	1. Que mayor de edad y domiciliado suscribió el documento que antecede.
2. That the grantor has executed the foregoing document as ASSISTANT GENERAL COUNSEL OF PFIZER INC.	2. Que el otorgante ha suscrito el referido documento en su carácter de de
3. That Pfizer Inc. having its principal place of business located in 235 East 42nd Street, New York, NY 10017 USA 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. Que con sede principal ubicada en está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.
4. That the grantor has the authority to execute the General Power and that his/her representation is legal.	4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima.
5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):	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):

NOTARY PUBLIC (Signature): Nancy M George

NANCY M. GEORGE
Notary Public
My Commission Expires 30 June 2011

WK 4682689

suscribió el documento que antecede. ---
2- Que el otorgante ha suscrito el referido documento en su carácter de ----
4. Que con sede principal ubicada en.-----
está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.
4.- Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima.- ----------
5. El fundamento de mis certificaciones contenidas en los puntos 2, 3, y 4 fue la exhibición de (los) (del) siguiente(s) documento(s) auténtico(s): NANCY M. GEORGE Notary Public My commissión Expires 30 June 2001.- ----------
BOGOTA, MARZO 12, 2007- ----------
TRADUCCION OFICIAL LEGALIZACIONES EN PODER ----------
NOTA DE TRADUCCION: SE TRATA DE UN PODER CONFERIDO POR PFIZER INC A OLARTE RAISBECK & FRIERI LTD DE FECHA FEB-20-2007, SUSCRITO EN GROTON CONNECTICUT, USA, EN IDIOMA CASTELLANO E INGLES, CON CERTIFICACION NOTARIAL TAMBIEN EN INGLES Y CASTELLANO; Y CERTIFICACION NOTARIAL Y APOSTILLE IN IDIOMA INGLES, CUYA TRADUCCIÓN ES LA SIGUIENTE: ------
SE INFORMA QUE YO, STEPHEN DAVID FINN DE 31 AMERSHAM HILL DRIVE HIGH WYCOMBE BUCKINGHAMSHIRE, REINO UNIDO NOTARIO DEBIDAMENTE AUTORIZADO ----------
CERTIFICO SOLAMENTE QUE EL DOCUMENTO ANEXO AL PRESENTE TITUADO, ----------
PODER, firmado por Gregg C Benson----------
En este día ha sido presentado a mi por Servicios Consulares Blair en nombre de su cliente Pfizer, y que dichos Servicios Consulares

NOTARIA VEINTISIETE
María Eugenia Rojas de Urueta

REPUBLICA 2. María Eugen de Urdl NOTARIa Veinticiete de Sant

Blair han manifestado ante mi mediante tal presentación que su mencionado cliente ha manifestado ante ellos que el documento anexo es un documento original auténtico.----------

FIRMADO, y sellado en 31 Amersham Hill Drive antes mencionado, el 23 de Febrero 2007.----------

(HAY FIRMA) STEPHEN FINN NOTARIO PUBLICO (HAY SELLO ADHERIDO).- ----------

APOSTILLE

(Convención de la Haya, Octubre 5, 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e irlanda del Norte --------

ESTE DOCUMENTO PUBLICO

2. HA SIDO FIRMADO POR: STEPHEN DAVID FINN----------

3. ACTUANDO EN CALIDAD DE NOTARIO PUBLIC----------

4 LLEVA EL SELLO/ESTAMPILLA DE DICHO NOTARIO PUBLICO ----------

CERTIFICADO

5. EN LONDRES----------

6) EL DÍA FEBRERO 27, 2007 ---------- ----------

7. POR EL SECRETARIO PRINCIPAL DE ESTADO DE SU MAJESTAD PARA ASUNTOS EXTERIORES Y LA COMUNIDAD.-

8 NR.H303068 ----------

9. SELLO/ ESTAMPILLA: == ---------- ----------

10. Firmado O. WILLIAM (HAY FIRMA)----------

CERTIFICADO DE AUTENTICIDAD: El suscrito Traductor e Interprete Oficial juramentado, y debidamente registrado en el Ministerio de Relaciones Exteriores, con el presente certifica que esta es una traducción auténtica, verdadera, y precisa al Idioma Castellano, del documento en Inglés, anexo.----------

FIDEL ANTONIO MURCIA MURCIA Traductor e Interprete Oficial Resolución No. 488/94 Ministerio de Justicia (fdo. Fidel Murcia)".- ----------

WK 4682690

SEGUNDO.- Que solicita a la señora Notaria la incorporación de dichos documentos al protocolo de ésta notaría para que de su tenor se expidan las copias que más adelante se soliciten ------

---

El(los) compareciente(s) hace(n) constar que han verificado cuidadosamente sus nombres completos, estado(s) civil(es), los número(s) de sus documentos de identidad; Declara(n) que todas las informaciones consignadas en el presente instrumento son correctas y, en consecuencia, asumen la responsabilidad que se derive de cualquier inexactitud en los mismos. Conocen la ley y saben que el Notario responde de la regularidad formal de los instrumentos que autoriza, pero no de la veracidad de las declaraciones de los interesados.

NOTARIA VEINTISIETE
María Eugenia Rojas de Uribe

ADVERTENCIA, OTORGAMIENTO Y AUTORIZACION.- Leído el presente instrumento por el (los) compareciente (s) y advertido (s) sobre las formalidades legales, lo aprueban y firman conmigo y ante mí la(el) Notaria(o) quién lo autoriza. A los otorgantes se les advirtió finalmente que una vez firmado el presente instrumento, La(el) Notaria(o) no aceptará correcciones o modificaciones sino en la forma y casos previstos por la Ley. ---Se utilizaron las hojas de papel Notarial Nos: WK 4682687, WK 4682689, WK 4682690.- ----------

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

DERECHOS LEGALES: $ 38.110.oo

RESOLUCION 7880 DE 2006

IVA $ 12.078.oo

CARLOS REINALDO OLARTE GARCIA

C.C.No. 79'782.747 Bta

TEL: 601-7700

MARIA EUGENIA ROJAS DE URUETA

NOTARIA(O) VENTISIETE (27) DE BOGOTA

REPUBLICA DE COLOMBIA
27
María Eugenia R3jas
de Urueta
NOTARIa
Notaría Veintisiete de Santafé

redb.

Es fiel y Sexta (6ª)
fotocopia de la Escritura Pública No. 321
de fecha 23 de Marzo de 2007
tomada de su original que expido en
Seis (6) hojas útiles de papel
común autorizado (Decreto1343 de 1970) con destino a
Interesado

Dado en Santafé de Bogotá D.C., a 22 MAYO 2007
El Notario Veintisiete de Santafé de Bogotá.

REPUBLICA DE COLOMBIA
María Eugenia R8jas
de Urueta
NOTARIa
Notaría Veintisiete de Santafé de Bogotá

LISTA DE INVENTORES

PCT/IB2013/051391

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Nacionalidad: Estadounidense

Robert Louis HOFFMAN
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Nacionalidad: Estadounidense

Paul Francis RICHARDSON
5365 Renaissance Avenue,
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Nacionalidad: Gran Bretaña

Neal William SACH
4291 Corte Favor,
San Diego, California, 92130,
Estados Unidos de América
Nacionalidad: Gran Bretaña

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VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application PFIZER INC., 61/607,485, Filed 06 March 2012 is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from BAILEY, Simon to PFIZER INC., dated 27 June 2012 (27.06.2012)
VIII-2-1(iv)		an assignment from BURKE, Benjamin Joseph to PFIZER INC., dated 27 June 2012 (27.06.2012)
VIII-2-1(iv)		an assignment from COLLINS, Michael Raymond to PFIZER INC., dated 27 June 2012 (27.06.2012)
VIII-2-1(iv)		an assignment from CUI, Jingrong Jean to PFIZER INC., dated 12 July 2012 (12.07.2012)
VIII-2-1(iv)		an assignment from DEAL, Judith Gail to PFIZER INC., dated 12 July 2012 (12.07.2012)
VIII-2-1(iv)		an assignment from HOFFMAN, Robert Louis to PFIZER INC., dated 28 June 2012 (28.06.2012)
VIII-2-1(iv)		an assignment from HUANG, Qinhua to PFIZER INC., dated 16 July 2012 (16.07.2012)
VIII-2-1(iv)		an assignment from JOHNSON, Ted William to PFIZER INC., dated 28 June 2012 (28.06.2012)
VIII-2-1(iv)		an assignment from KANIA, Robert Steven to PFIZER INC., dated 12 July 2012 (12.07.2012)
VIII-2-1(iv)		an assignment from KATH, John Charles to PFIZER INC., dated 16 July 2012 (16.07.2012)
VIII-2-1(iv)		an assignment from LE, Phuong Thi Quy to PFIZER INC., dated 18 July 2012 (18.07.2012)
VIII-2-1(iv)		an assignment from MCTIGUE, Michele Ann to PFIZER INC., dated 27 June 2012 (27.06.2012)
VIII-2-1(iv)		an assignment from PALMER, Cynthia Louise to PFIZER INC., dated 27 June 2012 (27.06.2012)
VIII-2-1(iv)		an assignment from RICHARDSON, Paul Francis to PFIZER INC., dated 27 June 2012 (27.06.2012)

VIII-2-1(iv)		an assignment from SACH, Neal William to PFIZER INC., dated 28 June 2012 (28.06.2012)

VIII-2-2	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, BAILEY, Simon
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, BURKE, Benjamin Joseph
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, COLLINS, Michael Raymond
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, CUI, Jingrong Jean
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, DEAL, Judith Gail
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, HOFFMAN, Robert Louis
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, HUANG, Qinhua
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, JOHNSON, Ted William
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, KANIA, Robert Steven
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, KATH, John Charles
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, LE, Phuong Thi Quy
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, MCTIGUE, Michele Ann
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, PALMER, Cynthia Louise
VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, RICHARDSON, Paul Francis

VIII-2-2(ii)		PFIZER INC., 61/759,307, Filed 31 January 2013 is entitled as employer of the inventor, SACH, Neal William

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VIII-1-1	**Declaration: Identity of the Inventor** Declaration as to the identity of the inventor (Rules 4.17(i) and 51bis.1(a)(i))	In relation to this international application
	Name (LAST, First) Address	BAILEY, Simon of 12144 Wooded Vista Lane San Diego, California 92128 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	BURKE, Benjamin Joseph of 5761 Campanile Way San Diego, California 92115 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	COLLINS, Michael Raymond of 17330 Campillo Drive San Diego, California 92128-2150 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	CUI, Jingrong Jean of 13718 Treviso Court San Diego, California 92130 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	DEAL, Judith Gail of 24136 Safiro Court Wildomar, California 92595 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	HOFFMAN, Robert Louis of 728 Foxhall Court San Marcos, California 92078 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	HUANG, Qinhua of 4219 Calle Mar De Ballenas San Diego, California 92130 United States of America is the inventor of the subject matter for which protection is sought by way of this international application

	Name (LAST, First) Address	JOHNSON, Ted William of 1740 Sorrel Court Carlsbad, California 92011 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	KANIA, Robert Steven of 10670 Haven Brook Place San Diego, California 92130 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	KATH, John Charles of 4168 Eastridge La Mesa, California 91941 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	LE, Phuong Thi Quy of 2657 Prato Lane San Diego, California 92108 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	MCTIGUE, Michele Ann of 515 Hermes Avenue Encinitas, California 92024 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	PALMER, Cynthia Louise of 9847 Ogram Drive La Mesa, California 91941 United States of America is the inventor of the subject matter for which protection is sought by way of this international application
	Name (LAST, First) Address	RICHARDSON, Paul Francis of 5365 Renaissance Avenue San Diego, California 92122 United States of America is the inventor of the subject matter for which protection is sought by way of this international application

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	Name (LAST, First) Address	SACH, Neal William of 4291 Corte Favor San Diego, California 92130 United States of America is the inventor of the subject matter for which protection is sought by way of this international application

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VIII-3-1	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	In relation to this international application PFIZER INC. is entitled to claim priority of earlier application No. 61/607,485 by virtue of the following:
VIII-3-1(iv)		an assignment from BAILEY, Simon to PFIZER INC., dated 27 June 2012 (27.06.2012)
VIII-3-1(iv)		an assignment from BURKE, Benjamin Joseph to PFIZER INC., dated 27 June 2012 (27.06.2012)
VIII-3-1(iv)		an assignment from COLLINS, Michael Raymond to PFIZER INC., dated 27 June 2012 (27.06.2012)
VIII-3-1(iv)		an assignment from CUI, Jingrong Jean to PFIZER INC., dated 12 July 2012 (12.07.2012)
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VIII-3-1(iv)		an assignment from MCTIGUE, Michele Ann to PFIZER INC., dated 27 June 2012 (27.06.2012)
VIII-3-1(iv)		an assignment from PALMER, Cynthia Louise to PFIZER INC., dated 27 June 2012 (27.06.2012)

VIII-3-1(iv)		an assignment from RICHARDSON, Paul Francis to PFIZER INC., dated 27 June 2012 (27.06.2012)
VIII-3-1(iv)		an assignment from SACH, Neal William to PFIZER INC., dated 28 June 2012 (28.06.2012)

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Print Out (Original in Electronic Form)

VIII-3-2	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	In relation to this international application PFIZER INC. is entitled to claim priority of earlier application No. 61/759,307 by virtue of the following:
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, BAILEY, Simon
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, BURKE, Benjamin Joseph
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, COLLINS, Michael Raymond
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, CUI, Jingrong Jean
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, DEAL, Judith Gail
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, HOFFMAN, Robert Louis
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, HUANG, Qinhua
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, JOHNSON, Ted William
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, KANIA, Robert Steven
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, KATH, John Charles
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, LE, Phuong Thi Quy
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, MCTIGUE, Michele Ann
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, PALMER, Cynthia Louise
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, RICHARDSON, Paul Francis
VIII-3-2(ii)		PFIZER INC. is entitled as employer of the inventor, SACH, Neal William

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

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12 September 2013 (12.09.2013)

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C07D 498/18 (2006.01) *A61P 35/00* (2006.01)

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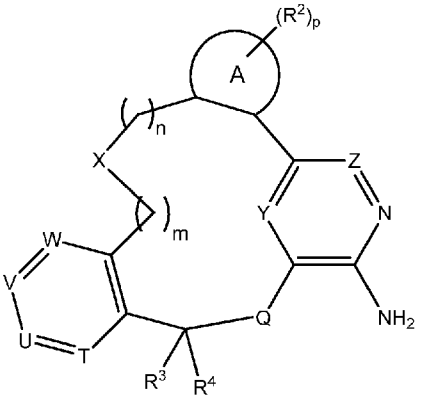
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[Continued on next page]

(54) Title: MACROCYCLIC DERIVATIVES FOR THE TREATMENT OF PROLIFERATIVE DISEASES



(Φ)

(57) Abstract: The invention relates to compounds of formula (Φ) as further defined herein and to the pharmaceutically acceptable salts thereof, to pharmaceutical compositions comprising such compounds and salts, and to the uses thereof. The compounds and salts of the present invention inhibit anaplastic lymphoma kinase (ALK) and/or EML4-ALK and are useful for treating or ameliorating abnormal cell proliferative disorders, such as cancer.

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MACROCYCLIC DERIVATIVES FOR THE TREATMENT OF PROLIFERATIVE DISEASES

Field of the Invention

The present invention relates to compounds of formulae (Φ) and (I)-(XXX) and their pharmaceutically acceptable salts, to pharmaceutical compositions comprising such compounds and salts, and to the uses thereof. The compounds and salts of the present invention inhibit anaplastic lymphoma kinase (ALK) and are useful for treating or ameliorating abnormal cell proliferative disorders, such as cancer.

Background of the Invention

Anaplastic lymphoma kinase (ALK) is a member of the receptor tyrosine kinase superfamily, and at an amino acid sequence level is most closely related to members such as Ros-1, leucocyte tyrosine kinase, the insulin receptor and cMet (hepatic growth factor receptor) (Kostich M et al, Genome Biology, 2002, 3 ,1-12). As with all members of this gene family, it possesses an extracellular ligand binding domain, a transmembrane spanning sequence, and an intracellular kinase catalytic region/signalling domain. The identity of the signalling ligand for ALK is not yet elucidated and different mechanisms have been proposed in the literature (Stoica G.E. et al., *J. Biol. Chem*., 2001, 276, 16772-16779; Stoica G.E. et al., *J. Biol. Chem*., 2002, 277, 35990-35999; Mewng K. et al., *PNAS*, 2000, 97, 2603-2608; Perez-Pinera P. et al., *J. Biol. Chem*., 2007, 282, 28683-28690). The stimulation of ALK leads to an intracellular signalling cascade via phopholipase-C, PI3Kinase and STAT3 (amongst other signalling proteins) (Turner S.D. et al., *Cell Signal*, 2007, 19, 740-747).

ALK is largely expressed in the developing nervous system (Iwahara T. et al., *Oncogene*, 1997, 14, 439-449). Its relative abundance does tend to decrease in the adult animal, though its expression is maintained in certain regions of the brain, spinal cord and the eye (Vernersson E. et al., *Gene Expression Patterns*, 2006, 6, 448-461).

ALK has an important role in oncology (Webb T.R. et al., *Expert Reviews in Anticancer Therapy*, 2009 9 331-355). Point mutations in the full length ALK enzyme that lead to activation of the enzyme, and also increase in expression of the full length enzyme, have both been shown to lead to neuroblastoma. In addition, the fusion of ALK with other proteins due to genetic translocation events has also been shown to lead to activated kinase domain associated with cancer. A number of such ALK translocations leading to gene fusions are seen in lymphomas, the most prevalent being the nucleophosmin NPM-ALK fusion seen in anaplastic large cell lymphomas. ALK fusion with EML4 leads to a chimeric protein (EML4-ALK) thought to be responsible for a 3-5% of non small cell lung adenocarcinomas (NSCLC) (Soda M. et al., *Nature*, 2007, 448, 561-567).

Crizotinib is a potent dual tyrosine kinase inhibitor (TKI) targeting c-Met and ALK that has recently found application in the treatment of NSCLC patients harbouring the EML4-ALK fusion event (Kwak et al., *New Eng. J. of Med.*, 2010, 363, 18, 1693-1703). Crizotinib is disclosed in PCT Publication No. WO 2006/021884 and United States Patent No. 7,858,643. Acquired resistance to crizotinib therapy has be reported and attributed to a L1196M and a C1156Y mutation in the EL4-ALK fusion protein (Choi Y.L. et al., *N. Engl. J. Med.*, 2010, 363, 18, 1734-1739). As crizotinib therapy becomes more widely available to patients harbouring the EML4-ALK gene fusion event, it is likely that the L1196M and C1156Y mutations and possibly other mutations will play a more prevalent role in acquired resistance to crizotinib therapy. See, e.g., Morris et al. United States Patent Publication Number 2011/0256546 describing other ALK inhibitor resistance mutations occurring in the ALK kinase domain of the related gene fusion NPM-ALK).

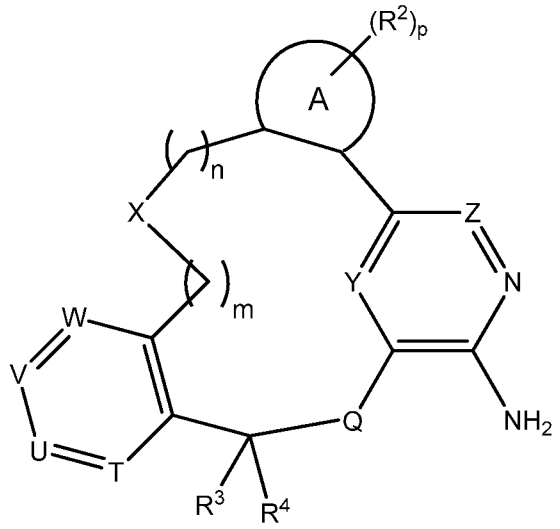
Accordingly, there is a need for ALK inhibitors and EML4-ALK inhibitors that have an appropriate pharmacological profile, for example in terms of potency, selectivity, pharmacokinetics, ability to cross the blood brain barrier and duration of action. More specifically, there is a need for ALK inhibitors that inhibit the EML4-ALK fusion protein having a L1196M and/or C1156Y mutation. In this context, the present invention relates to novel ALK inhibitors.

Summary of the Invention

The present invention provides, in part, novel compounds and pharmaceutically acceptable salts thereof that can modulate the activity of ALK and/or EML4-ALK, thereby effecting biological functions, including but not limited to inhibiting cell proliferation and cell invasiveness, inhibiting metastasis, inducing apoptosis or inhibiting angiogenesis. Also provided are pharmaceutical compositions and medicaments, comprising the compounds or salts of the invention, alone or in combination with other therapeutic agents or palliative agents. The present invention also provides, in part, methods for preparing the novel compounds, salts and compositions thereof, and methods of using the foregoing.

It will be understood that each embodiment describing the inventive compounds herein may be combined alone or in combination with any other embodiment describing the inventive compounds provided that such embodiments are not inconsistent with each other.

In one aspect, the invention provides a compound of the formula (Φ)



(Φ)

wherein:

X is selected from the group consisting of $-(CR^5R^6)_qO(CR^5R^6)_r-$, $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ and $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$; or

X is a C_6-C_{12} arylene or a 5-12 membered heteroarylene, each of which is optionally substituted by 0-4 R^{12} substituents;

Y and Z are each independently N or CH, with the proviso that when Y is N, Z is CH and when Z is N, Y is CH;

T is N or CR^{11a}; U is N or CR^{11b}; V is N or CR^{11c}; and W is N or CR^{11d}; provided no more than two of T, U. V and W are N;

Q is O or CH_2;

A is a ring selected from the group consisting of C_6-C_{12} aryl and 5-12 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 and R^{12} is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, -

$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qC_3$-C_6 cycloalkyl, $-(CR^5R^6)_qC_6$-C_{12} aryl, $-(CR^5R^6)_q$-3-12 membered heteroalicyclic, $-(CR^5R^6)_q$ 5-6 membered heteroaryl, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

each R^{11a}, R^{11b}, R^{11c} and R^{11d} is independently selected from the group consisting of hydrogen, halogen and C_1-C_6 alkyl;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment of this aspect, T is CR^{11a}; U is CR^{11b}; V is CR^{11c}; and W is CR^{11d}. In another embodiment of this aspect, T is N; U is CR^{11b}; V is CR^{11c}; and W is CR^{11d}. In another embodiment of this aspect, T is CR^{11a}; U is N; V is CR^{11c}; and W is CR^{11d}. In another embodiment of this aspect, T is CR^{11a}; U is CR^{11b}; V is N; and W is CR^{11d}. In a further embodiment of this aspect, T is CR^{11a}; U is CR^{11b}; V is CR^{11c}; and W is N. In another embodiment of this aspect, T and U are N; V is CR^{11c}; and W is CR^{11d}. In another embodiment of this aspect, T and V are N; U is CR^{11b}; and W is CR^{11d}. In another embodiment of this aspect, T and W are N; U is CR^{11b}; and V is CR^{11c}. In yet another embodiment of this aspect, U and V are N; T is CR^{11a}; and W is CR^{11d}. In another embodiment of this aspect, U and W are N; T is CR^{11a}; and V is CR^{11c}. In another embodiment of this aspect, V and W are N; T is CR^{11a}; and U is CR^{11b}.

In some embodiments, at least one of R^{11a}, R^{11b}, R^{11c}, and R^{11d} is halo, preferably fluoro or chloro. In other embodiments, at least two of R^{11a}, R^{11b}, R^{11c}, and R^{11d} are halo, preferably fluoro or chloro. In some such embodiments, R^{11b} is halo, preferably fluoro. In some embodiments, each of R^{11a}, R^{11c}, and R^{11d} is hydrogen. In specific embodiments, T is CR^{11a}; U is CR^{11b}; V is CR^{11c}; and W is CR^{11d}; R^{11b} is halo, in particular fluoro; and each of R^{11a}, R^{11c}, and R^{11d} is hydrogen.

In another aspect of this embodiment, Y is CH and Z is CH. In another embodiment, Y is CH and Z is N. In another embodiment, Y is N and Z is CH.

In one embodiment of this aspect, X is $-(CR^5R^6)_qO(CR^5R^6)_r-$. In some such embodiments, when X is $-(CR^5R^6)_qO(CR^5R^6)_r-$, m is 0 and n is 3. In other such embodiments, m is 1 and n is 2. In other such embodiments, m is 2 and n is 1. In still other embodiments, m is 3 and n is 0. In further such embodiments, m is 3 and n is 3. In other such embodiment s, m is 2 and n is 2. In another such embodiment, m is 1 and n is 1. In still another such embodiment, m is 0, n is 3, q is 0 and r is 0. In another such embodiment, m is 1, n is 2, q is 0 and r is 0. In another such embodiment, m is 2, n is 1, q is 0 and r is 0. In another such embodiment, m is 3, n is 0, q is 0 and r is 0.

In another embodiment of this aspect, X is selected from the group consisting of $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ and $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$. In some such embodiments, X is $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$. In other such embodiments, X is $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$. In other such embodiments of this aspect, X is $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$.

In another embodiment of this aspect, X is $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$. In some such embodiments, when X is $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, m is 0 and n is 3. In other such embodiments, m is 1 and n is 2. In other such embodiments, m is 2 and n is 1. In other such embodiments, m is 3 and n is 0. In still other such embodiments, m is 3 and n is 3. In further such embodiments, m is 2 and n is 2. In still other such embodiments, m is 1 and n is 1.

In another embodiment of this aspect, X is $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$. In some such embodiments, when X is $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$, m is 0 and n is 1. In other such embodiments, m is 0 and n is 2. In other such embodiments, m is 0 and n is 3. In other such embodiments, m is 2 and n is 0. In still other such embodiments, m is 2 and n is 2. In still another such embodiment, m is 0, n is 1, q is 0 and r is 0. In another such embodiment, m is 0, n is 2, q is 0 and r is 0. In still another such embodiment, m is 0, n is 3, q is 0 and r is 0. In another such embodiment, m is 0, n is 0, q is 0 and r is 1. In another such embodiment, m is 0, n is 0, q is 0 and r is 2. In still another such embodiment, m is 2, n is 0, q is 0 and r is 0.

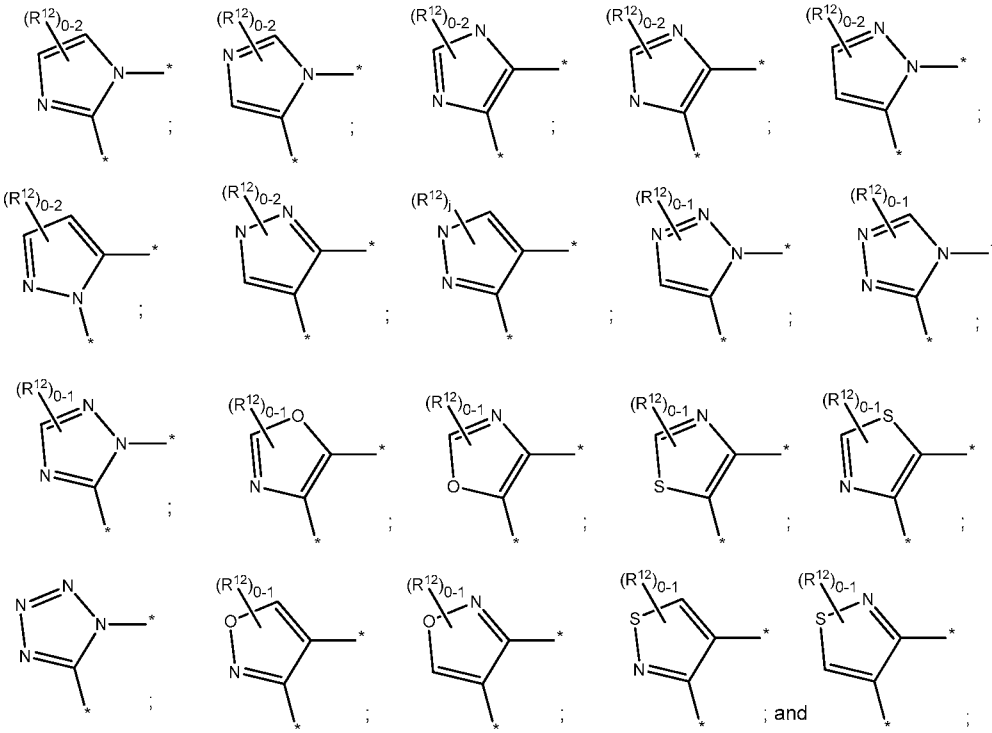
In another embodiment of this aspect, X is $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$. In some such embodiments, when X is $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$, m is 0 and n is 1. In other such embodiments, m is 0 and n is 2. In other such embodiments, m is 2 and n is 0. In other such embodiments, m is 0 and n is 3. In other such embodiments, m is 2 and n is 0. In still other such embodiments, m is 2 and n is 2. In still another such embodiment, m is 0, n is 1, q is 0 and r is 0. In another such embodiment, m is 0, n is 2, q is 0 and r is 0. In still another such embodiment, m is 0, n is 3, q is 0 and r is 0. In another such embodiment, m is 0, n is 0, q is 0 and r is 1. In another such embodiment, m is 0, n is 0, q is 0 and r is 2. In another such embodiment, m is 2, n is 0, q is 0 and r is 0. In another such embodiment, m is 1, n is 1, q is 0 and r is 0. In another such embodiment, m is 2, n is 1, q is 0 and r is 0.

In still another such embodiment, m is 3, n is 0, q is 0 and r is 0.

In another embodiment of this aspect, X is a C_6-C_{12} arylene or a 5-12 membered heteroarylene, each of which is optionally substituted by 0-4 R^{12} substituents. In some such embodiments, m is 0 and n is 1. In other such embodiments, m is 0 and n is 2. In some embodiment of this aspect , X is a a C_6-C_{12} arylene or a 5-12 membered heteroarylene selected from the group consisting of a 1,2-disubstituted phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and

isoxazole ring, each of which is optionally substituted by 0-4 R^{12} substituents. In some such embodiments, m is 0, and n is 1. In other such embodiments, m is 0, and n is 2.

In specific embodiments, X is selected from the group consisting of:



; and

where the asterisks (*) represent the points of attachment to the macrocyclic ring.

In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein each hydrogen on said C_1-C_6 alkyl, and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$.

In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl. In specific embodiments, R^1 is hydrogen, methyl, ethyl or cyclopropyl. In some embodiments, R^1 is hydrogen. In other embodiments, R^1 is methyl. In other embodiments, R^1 is ethyl. In other embodiments, R^1 is cyclopropyl.

In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$.

In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN.

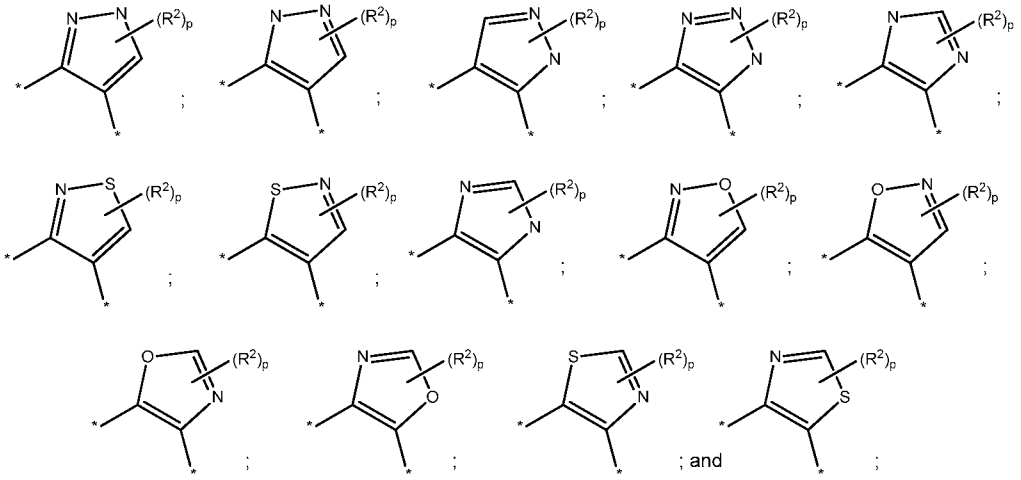
In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In frequent embodiments, R^3 and R^4 are each independently hydrogen or methyl. In some such embodiments, each of R^3 and R^4 is hydrogen. In other such embodiments, one of R^3 and R^4 is hydrogen and the other is methyl.

In some embodiments of this aspect, Q is O. In other embodiments of this aspect, Q is CH_2.

In one embodiment of this aspect, A is a ring selected from the group consisting of C_6-C_{12} aryl and 5-12 membered heteroaryl. In embodiments of this aspect, ring A is optionally substituted by 0 to 4 substituent groups labelled as $-(R^2)_p$, where p is 0, 1, 2, 3 or 4. It will be understood by those of skill in the art that the number of R^2 substituents on ring A is limited by the number of open valence positions on ring A, where two of the valence positions are used to incorporate the A-ring into the macrocyclic core.

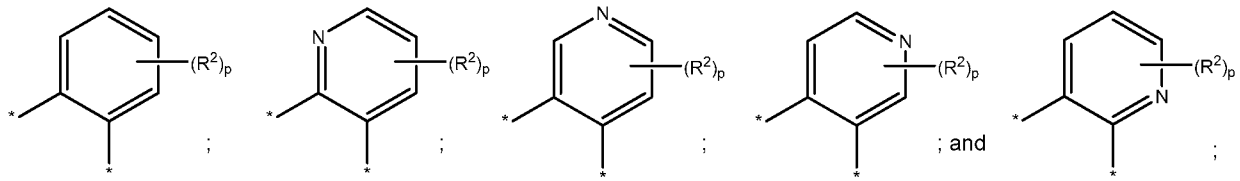
In another embodiment of this aspect, A is a C_6-C_{12} aryl or 5-12 membered heteroaryl ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine and triazine. In other such embodiments, A is a ring selected from the group consisting of pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In certain embodiments, A is a ring selected from the group consisting of pyrazole, triazole, thiazole, isothiazole, and isoxazole. In specific embodiments, A is a pyrazole ring. In other embodiments, A is triazole ring. In other embodiments, A is isothiazole ring. In still other embodiments, A is isoxazole ring. In further embodiments, A is a phenyl or pyridyl ring.

In some embodiments of this aspect, A is selected from the group consisting of:



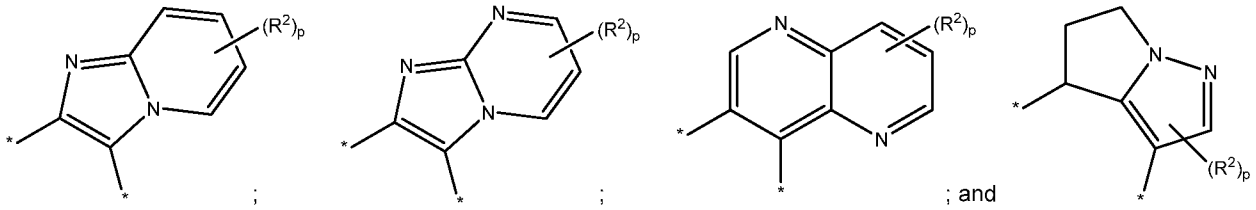
where the asterisks (*) represent the points of attachment to the macrocyclic ring. In some such embodiments, p is 0, 1 or 2, and each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN.

In other embodiments of this aspect, A is a ring selected from the group consisting of:



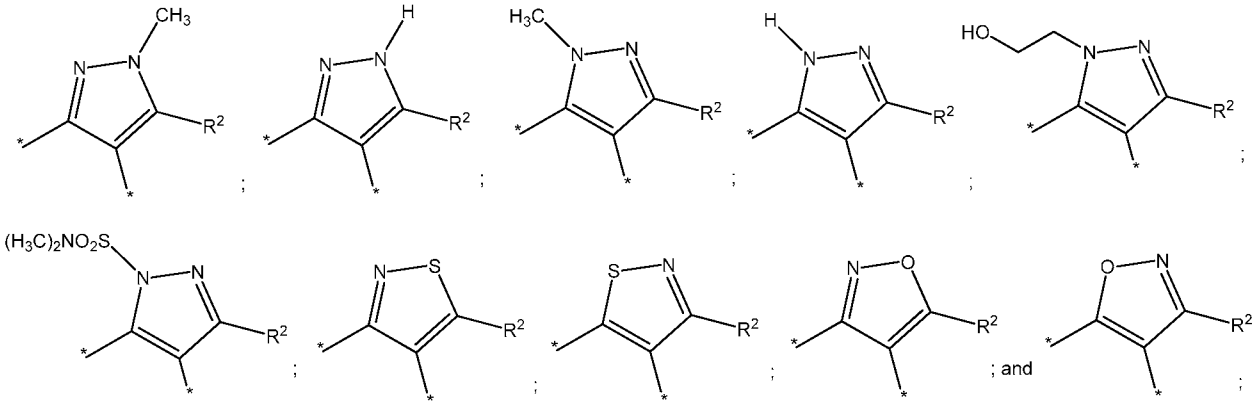
where the asterisks (*) represent the points of attachment to the macrocyclic ring. In some such embodiments, p is 0, 1 or 2, and each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN.

In other embodiments of this aspect, A is a ring selected from the group consisting of:



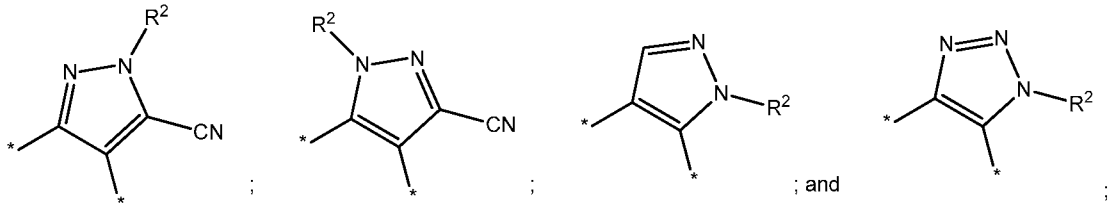
where the asterisks (*) represent the points of attachment to the macrocyclic ring. In some such embodiments, p is 0, 1 or 2, and each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN.

In specific embodiments, A is selected from the group consisting of:



where the asterisks (*) represent the points of attachment to the macrocyclic ring, and wherein R^2 is selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN. In some such embodiments, R^2 is selected from the group consisting of methyl, ethyl, cyclopropyl, methoxy, ethoxy and -CN.

In other specific embodiments, A is selected from the group consisting of:



where the asterisks (*) represent the points of attachment to the macrocyclic ring, and wherein R^2 is selected from the group consisting of C_1-C_6 alkyl, and C_3-C_6 cycloalkyl; and wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen or -OH. In some such embodiments, R^2 is selected from the group consisting of methyl, ethyl, -2-hydroxyethyl, propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, difluoroethyl, trifluoroethyl, cyclopropyl and cyclobutyl.

Certain preferred embodiments of formula (Φ), or a pharmaceutically acceptable salt thereof, have one, two or more of the following preferred features, which may occur in combination to the extent they are not inconsistent with each other:

T is CR^{11a}; U is CR^{11b}; V is CR^{11c}; and W is CR^{11d}; wherein at least one of R^{11a}, R^{11b}, R^{11c}, and R^{11d} is halo, preferably fluoro or chloro;

R^{11b} is halo, preferably fluoro, and each of R^{11a}, R^{11c}, and R^{11d} is hydrogen;

X is $-(CR^5R^6)_qO(CR^5R^6)_r-$, wherein each of R^5 and R^6 is H; m is 0; and n is 0;

X is $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, wherein each of R^5 and R^6 is H; m is 0; and n is 0;

X is $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$,wherein each of R^5 and R^6 is H, m is 0 and n is 0;

q is 1, and r is 1;

q is 0, and r is 1;

Y and Z are each CH;

Y is N and Z is CH;

Q is O;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

R^1 is hydrogen, methyl, ethyl or cyclopropyl;

R^1 is methyl;

A is a C_6-C_{12} aryl or 5-12 membered heteroaryl ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole;

A is a C_6-C_{12} aryl or 5-12 membered heteroaryl ring of phenyl, pyrazole, imidazole, triazole, thiazole, isothiazole, oxazole and isoxazole;

A is a C_6-C_{12} aryl or 5-12 membered heteroaryl ring of phenyl, pyrazole, triazole, isothiazole and isoxazole;

A is a pyrazole;

p is 0, 1 or 2;

R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and –CN;

R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^3 and R^4 are each independently hydrogen or methyl;

one of R^3 and R^4 is hydrogen and the other is methyl;

R^5 and R^6 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^5 and R^6 are each independently hydrogen or methyl;

each of R^5 and R^6 is hydrogen;

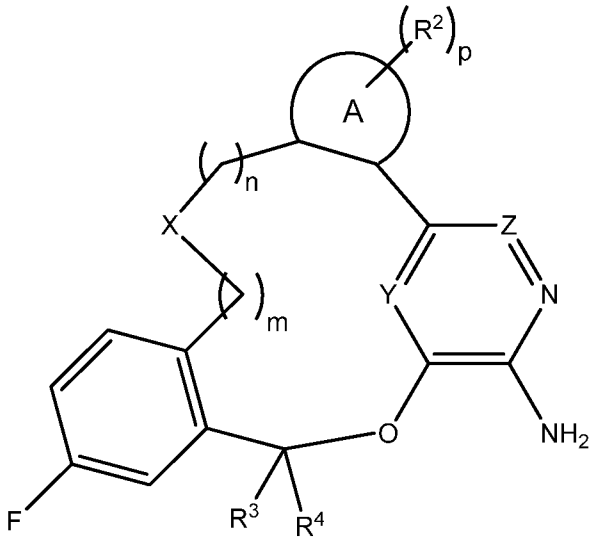
R^7 and R^8 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein each hydrogen on said C_1-C_6 alkyl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$; and

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

The embodiments described above as suitable for compounds of formula (Φ), including the cominations of preferred embodiments, are also suitable for compounds of formulae (I) to (XXX), to the extent they are not inconsistent with each other, as further described herein.

The specific aromatic and heteroaromatic groups described above as suitable for ring A in formula Φ are also suitable for ring A in the compounds of formulae (I) to (XXX), as further described herein.

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



(I)

wherein:

X is selected from the group consisting of $-(CR^5R^6)_qO(CR^5R^6)_r-$, $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ and $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$;

Y and Z are each independently N or CH, with the proviso that when Y is N, Z is CH and when Z is N, Y is CH;

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6

alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ or -$C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ or -$C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ and -$C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ or -$C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ or -$C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment of this aspect, Y is N. In another embodiment of this aspect, Z is N. In another aspect of this embodiment, Y is CH and Z is CH.

In another embodiment of this aspect, X is $-(CR^5R^6)_qO(CR^5R^6)_r-$. In some such embodiments, when X is $-(CR^5R^6)_qO(CR^5R^6)_r-$, m is 0 and n is 3. In other such embodiments, m is 1 and n is 2. In other such embodiments, m is 2 and n is 1. In other such embodiments, m is 3 and n is 0. In still other such embodiments, m is 3 and n is 3. In other such embodiments, m is 2 and n is 2. In further such embodiments, m is 1 and n is 1. In other such embodiments, m is 0, n is 3, q is 0 and r is 0. In still other such embodiments, m is 1, n is 2, q is 0 and r is 0. In other such embodiments, m is 2, n is 1, q is 0 and r is 0. In still other such embodiments, m is 3, n is 0, q is 0 and r is 0.

In another embodiment of this aspect, X is selected from the group consisting of $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ and $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$. In one such embodiment of this aspect, X is $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$. In another such embodiment of this aspect, X is $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$. In another such embodiment of this aspect, X is $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$.

In another embodiment of this aspect, X is $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$. In some such embodiments, when X is $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, m is 0 and n is 3. In other such embodiments, m is 1 and n is 2. In other such embodiments, m is 2 and n is 1. In other such embodiments, m is 3 and n is 0. In still other such embodiments, m is 3 and n is 3. In other such embodiments, m is 2 and n is 2. In further such embodiments, m is 1 and n is 1. In other such embodiments, m is 0, n is 3, q is 0 and r is 0. In still other such embodiments, m is 1, n is 2, q is 0 and r is 0. In other such embodiments, m is 2, n is 1, q is 0 and r is 0. In still other such embodiments, m is 3, n is 0, q is 0 and r is 0. In other such embodiments, m is 1, n is 1, q is 0 and r is 0.

In another embodiment of this aspect, X is $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$. In some such embodiments, when X is $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$, m is 0 and n is 2. In other such embodiments, m is 0 and n is 1. In still other such embodiments, m is 2 and n is 0. In further such embodiments, m is 2 and n is 2. In other such embodiments, m is 0, n is 2, q is 0 and r is 0. In still other such embodiments, m is 0, n is 1, q is 0 and r is 0. In other such embodiments, m is 2, n is 0, q is 0 and r is 0.

In another embodiment of this aspect, X is $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$. In some such embodiments, when X is $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$, m is 0 and n is 2. In other such embodiments, m is 0 and n is 1. In still other such embodiments, m is 2 and n is 0. In other such embodiments, m is 0, n is 2, q is 0 and r is 0. In still other such embodiments, m is 0, n is 1, q is 0 and r is 0. In other such embodiments, m is 2, n is 0, q is 0 and r is 0.

In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein each hydrogen on said C_1-C_6 alkyl, and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl. In specific embodiments, R^1 is hydrogen, methyl, ethyl or cyclopropyl. In some embodiments, R^1 is hydrogen. In other embodiments, R^1 is methyl. In other embodiments, R^1 is ethyl. In other embodiments, R^1 is cyclopropyl.

In another embodiment of this aspect, each R^2 is independently selected from the group consisting of, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$.

In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole.

In another embodiment of this aspect, A is a ring selected from the group consisting of a phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In specific embodiments of this aspect, A is a ring selected from the group consisting of the specific rings indicated as suitable for compounds of formula Φ, above.

In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In frequent embodiments, R^3 and R^4 are each independently hydrogen or methyl. In some such embodiments, each of R^3 and R^4 is hydrogen. In other such embodiments, one of R^3 and R^4 is hydrogen and the other is methyl.

Certain preferred embodiments of formula (I), or a pharmaceutically acceptable salt thereof, have one, two or more of the following preferred features, which may occur in combination to the extent they are not inconsistent with each other:

X is $-(CR^5R^6)_qO(CR^5R^6)_r-$, wherein each of R^5 and R^6 is H; m is 0; and n is 0;

X is $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, wherein each of R^5 and R^6 is H; m is 0; and n is 0;

X is $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$,wherein each of R^5 and R^6 is H, m is 0 and n is 0;

q is 1, and r is 1;

q is 0, and r is 1;

Y and Z are each CH;

Y is N and Z is CH;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

R^1 is hydrogen, methyl, ethyl or cyclopropyl;

R^1 is methyl;

A is a C_6-C_{12} aryl or 5-12 membered heteroaryl ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole;

A is a C_6-C_{12} aryl or 5-12 membered heteroaryl ring of phenyl, pyrazole, imidazole, triazole, thiazole, isothiazole, oxazole and isoxazole;

A is a C_6-C_{12} aryl or 5-12 membered heteroaryl ring of phenyl, pyrazole, triazole, isothiazole and isoxazole;

A is a pyrazole;

p is 0, 1 or 2;

R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and –CN;

R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^3 and R^4 are each independently hydrogen or methyl;

one of R^3 and R^4 is hydrogen and the other is methyl;

R^5 and R^6 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

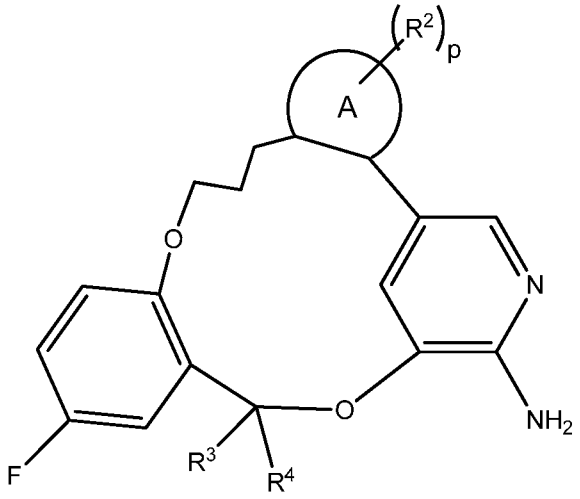
R^5 and R^6 are each independently hydrogen or methyl;

each of R^5 and R^6 is hydrogen;

R^7 and R^8 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein each hydrogen on said C_1-C_6 alkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

In another aspect, the invention provides a compound of the formula (II)



(II)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be

independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} are independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$.

In another aspect of this embodiment, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN.

In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In frequent embodiments, R^3 and R^4 are each independently hydrogen or methyl. In some such embodiments, each of R^3 and R^4 is hydrogen. In other such embodiments, one of R^3 and R^4 is hydrogen and the other is methyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In specific embodiments of this aspect, A

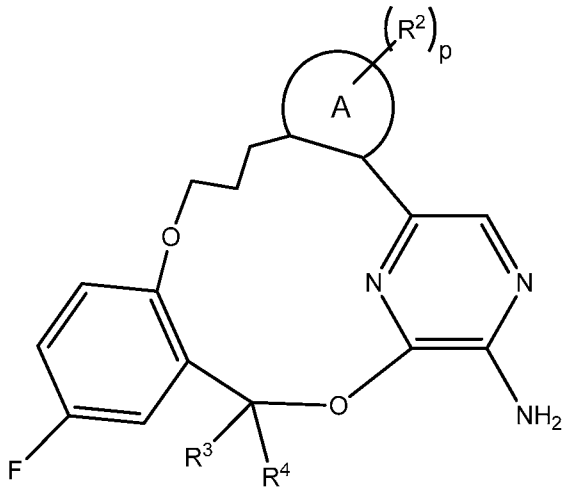
is a ring selected from the group consisting of the specific rings indicated as suitable for compounds of formula Φ, above.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole; each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In other such embodiments, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another aspect, the invention provides a compound of the formula (III)



(III)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$,

$-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} are independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In frequent embodiments, R^3 and R^4 are each independently hydrogen or methyl. In some such embodiments, each of R^3 and R^4 is hydrogen. In other such embodiments, one of R^3 and R^4 is hydrogen and the other is methyl.

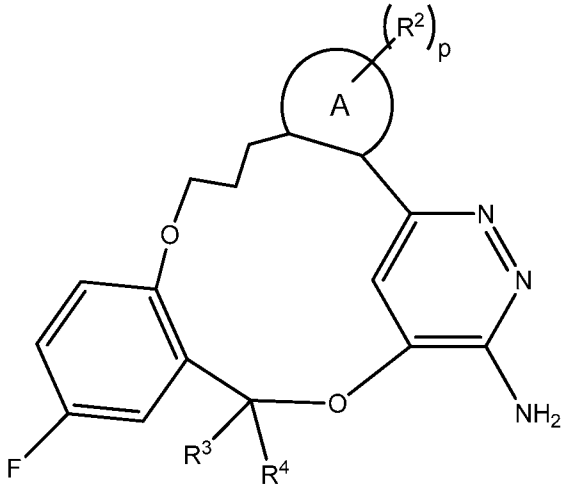
In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In specific embodiments of this aspect, A is a ring selected from the group consisting of the specific rings indicated as suitable for compounds of formula Φ, above.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole; each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another aspect, the inventions provides a compound of the formula (IV)



(IV)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$,

$-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} are independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In frequent embodiments, R^3 and R^4 are each independently hydrogen or methyl. In some such embodiments, each of R^3 and R^4 is hydrogen. In other such embodiments, one of R^3 and R^4 is hydrogen and the other is methyl.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole,

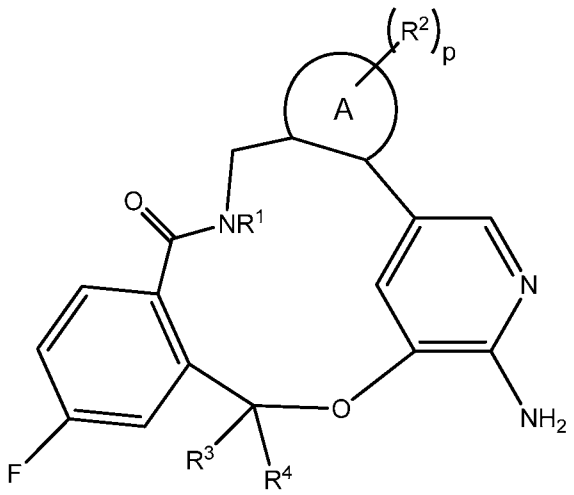
tetrazole, thiazole, isothiazole, oxazole and isoxazole. In specific embodiments of this aspect, A is a ring selected from the group consisting of the specific rings indicated as suitable for compounds of formula Φ, above.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole; each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole; each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another aspect, the invention provides a compound of the formula (V)



(V)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6

cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $--C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein each hydrogen on said C_1-C_6 alkyl, and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl. In specific embodiments, R^1 is hydrogen, methyl, ethyl or cyclopropyl. In some embodiments, R^1 is hydrogen. In other embodiments, R^1 is methyl. In other embodiments, R^1 is ethyl. In other embodiments, R^1 is cyclopropyl.

In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In frequent embodiments, R^3 and R^4 are each independently hydrogen or methyl. In some such embodiments, each of R^3 and R^4 is hydrogen. In other such embodiments, one of R^3 and R^4 is hydrogen and the other is methyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole,

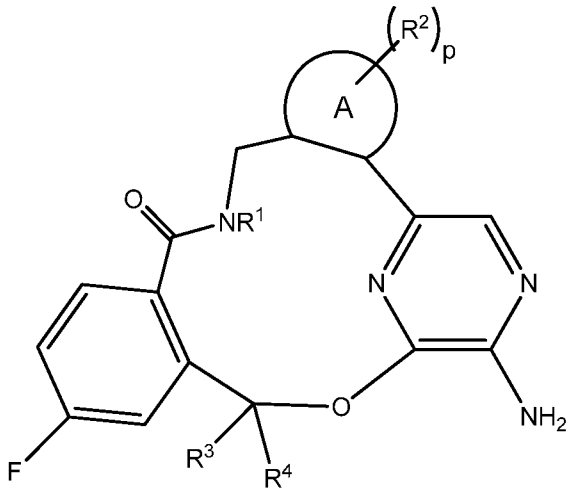
tetrazole, thiazole, isothiazole, oxazole and isoxazole. In specific embodiments of this aspect, A is a ring selected from the group consisting of the specific rings indicated as suitable for compounds of formula Φ, above.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole; each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another aspect, the invention provides a compound of the formula (VI)



(VI)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be

independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein each hydrogen on said C_1-C_6 alkyl, and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl. In specific embodiments, R^1 is hydrogen, methyl, ethyl or cyclopropyl. In some embodiments, R^1 is hydrogen. In other embodiments, R^1 is methyl. In other embodiments, R^1 is ethyl. In other embodiments, R^1 is cyclopropyl.

In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In frequent embodiments, R^3 and R^4 are each independently hydrogen or methyl. In some such embodiments, each of R^3 and R^4 is hydrogen. In other such embodiments, one of R^3 and R^4 is hydrogen and the other is methyl.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In another embodiment of this

aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

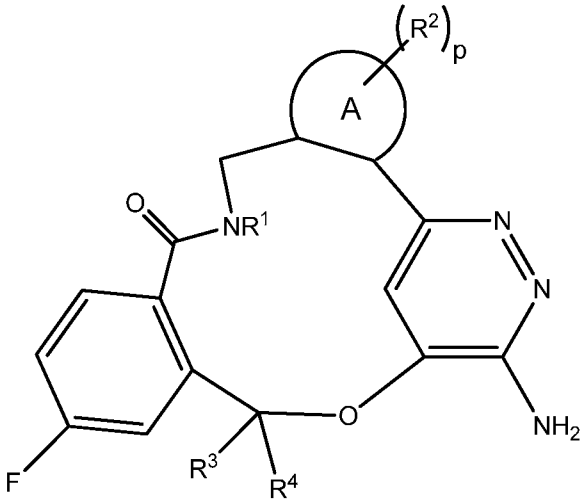
In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In specific embodiments of this aspect, A is a ring selected from the group consisting of the specific rings indicated as suitable for compounds of formula Φ, above.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole; each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another aspect, the invention provides a compound of the formula (VII)



(VII)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered

heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein each hydrogen on said C_1-C_6 alkyl, and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl. In specific embodiments, R^1 is hydrogen, methyl, ethyl or cyclopropyl. In some embodiments, R^1 is hydrogen. In other embodiments, R^1 is methyl. In other embodiments, R^1 is ethyl. In other embodiments, R^1 is cyclopropyl.

In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In frequent embodiments, R^3 and R^4 are each

independently hydrogen or methyl. In some such embodiments, each of R^3 and R^4 is hydrogen. In other such embodiments, one of R^3 and R^4 is hydrogen and the other is methyl.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In specific embodiments of this aspect, A is a ring selected from the group consisting of the specific rings indicated as suitable for compounds of formula Φ, above.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole; each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

Certain preferred embodiments of formulae (V), (V) and (VI), or a pharmaceutically acceptable salt thereof, have one, two or more of the following preferred features, which may occur in combination to the extent they are not inconsistent with each other:

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

R^1 is hydrogen, methyl, ethyl or cyclopropyl;

R^1 is methyl;

A is a C_6-C_{12} aryl or 5-12 membered heteroaryl ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole;

A is a C_6-C_{12} aryl or 5-12 membered heteroaryl ring of phenyl, pyrazole, imidazole, triazole, thiazole, isothiazole, oxazole and isoxazole;

A is a C_6-C_{12} aryl or 5-12 membered heteroaryl ring of phenyl, pyrazole, triazole, isothiazole and isoxazole;

A is a pyrazole;

p is 0, 1 or 2;

R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and –CN;

R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^3 and R^4 are each independently hydrogen or methyl;

one of R^3 and R^4 is hydrogen and the other is methyl;

R^5 and R^6 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

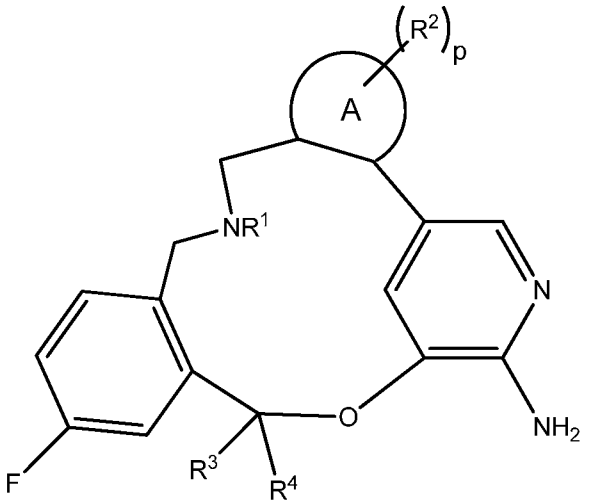
R^5 and R^6 are each independently hydrogen or methyl;

each of R^5 and R^6 is hydrogen;

R^7 and R^8 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl; wherein each hydrogen on said C_1-C_6 alkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

In another aspect, the invention provides a compound of the formula (VIII)



(VIII)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic,

and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein each hydrogen on said C_1-C_6 alkyl, and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl. In specific embodiments, R^1 is hydrogen, methyl, ethyl or cyclopropyl. In some embodiments, R^1 is hydrogen. In other embodiments, R^1 is methyl. In other embodiments, R^1 is ethyl. In other embodiments, R^1 is cyclopropyl.

In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In frequent embodiments, R^3 and R^4 are each independently hydrogen or methyl. In some such embodiments, each of R^3 and R^4 is hydrogen. In other such embodiments, one of R^3 and R^4 is hydrogen and the other is methyl.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

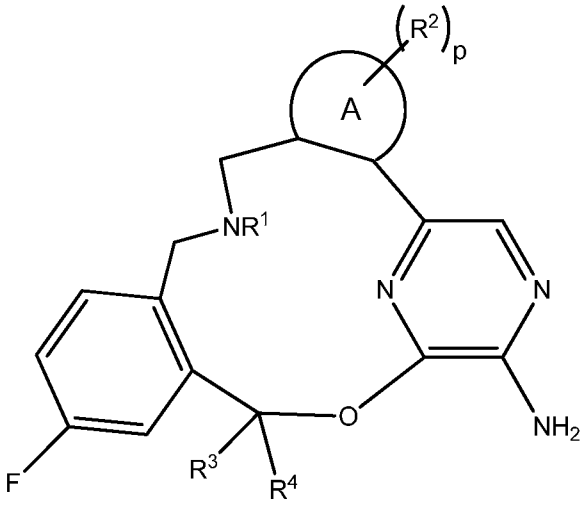
In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In specific embodiments of this aspect, A is a ring selected from the group consisting of the specific rings indicated as suitable for compounds of formula Φ, above.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole; each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another aspect, the invention provides a compound of the formula (IX)



(IX)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein each hydrogen on said C_1-C_6 alkyl, and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl. In specific embodiments, R^1 is hydrogen, methyl, ethyl or cyclopropyl. In some embodiments, R^1 is hydrogen. In other embodiments, R^1 is methyl. In other embodiments, R^1 is ethyl. In other embodiments, R^1 is cyclopropyl.

In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein meach hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In frequent embodiments, R^3 and R^4 are each independently hydrogen or methyl. In some such embodiments, each of R^3 and R^4 is hydrogen. In other such embodiments, one of R^3 and R^4 is hydrogen and the other is methyl.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In specific embodiments of this aspect, A is a ring selected from the group consisting of the specific rings indicated as suitable for compounds of formula Φ, above.

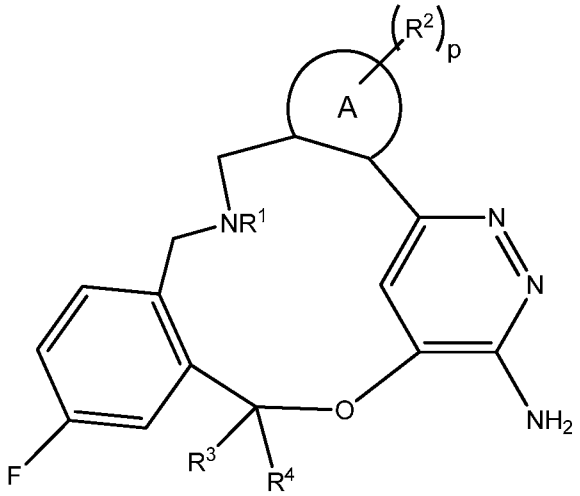
In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole; each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$,

$-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another aspect, the invention provides a compound of the formula (X)



(X)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently

optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In one embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, wherein each hydrogen on said C_1-C_6 alkyl, and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl.

In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$. In another embodiment of this aspect, each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl. In frequent embodiments, R^3 and R^4 are each independently hydrogen or methyl. In some such embodiments, each of R^3 and R^4 is hydrogen. In other such embodiments, one of R^3 and R^4 is hydrogen and the other is methyl.

In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In another embodiment of this aspect, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In specific embodiments of this aspect, A is a ring selected from the group consisting of the specific rings indicated as suitable for compounds of formula Φ, above.

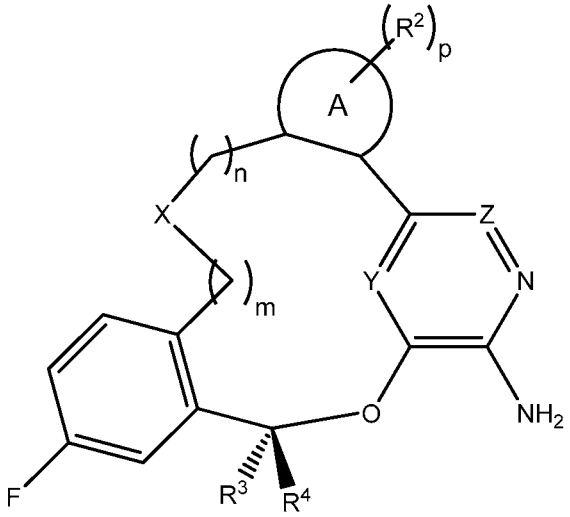
In another embodiment of this aspect, A is a ring selected from phenyl, pyridine, triazine, pyrazole, imidazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole. In some such embodiments, R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another embodiment of this aspect, A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole; each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$,

$-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; and R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl.

In another aspect, the invention provides a compound of the formula (XI)



(XI)

wherein:

X is selected from the group consisting of $-(CR^5R^6)_qO(CR^5R^6)_r-$, $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ and $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$;

Y and Z are each independently N or CH, with the proviso that when Y is N, Z is CH and when Z is N, Y is CH;

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -

NH_2, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or - $C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

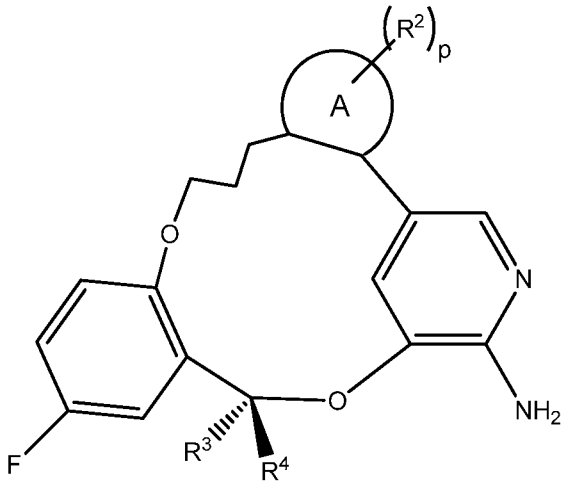
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The same embodiments described herein as relevant to compounds of formula (I) are also applicable to compounds of formula (XI).

In another aspect, the invention provides a compound of the formula (XII)



(XII)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$,

$-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} are independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

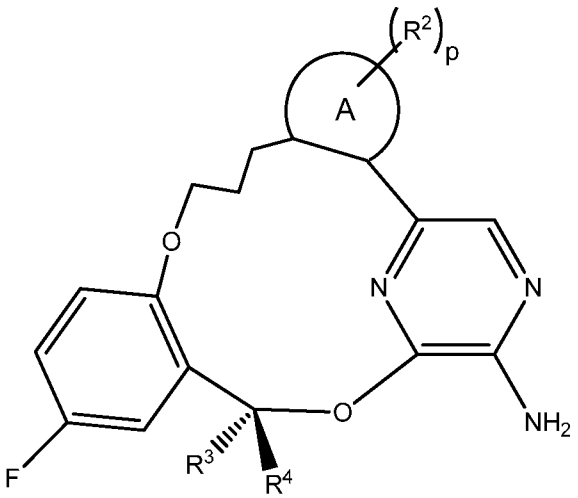
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The same embodiments described herein as relevant to compounds of formula (II) are also applicable to compounds of formula (XII).

In another aspect, the invention provides a compound of the formula (XIII)



(XIII)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6

membered heteroaryl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} are independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

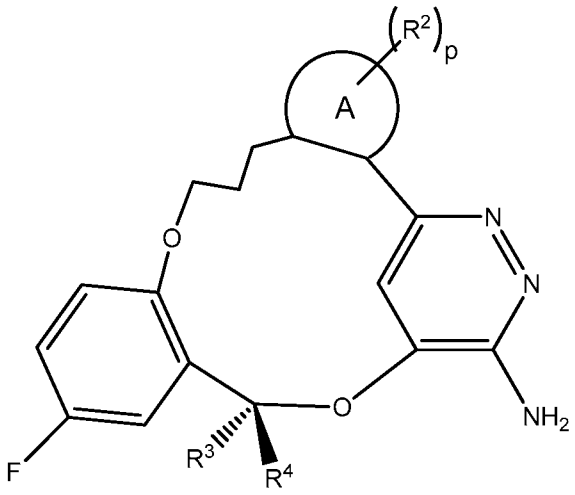
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The same embodiments described herein as relevant to compounds of formula (III) are also applicable to compounds of formula (XIII).

In another aspect, the inventions provides a compound of the formula (XIV)



(XIV)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$

and -C(O)NR^9R^{10}; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} are independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

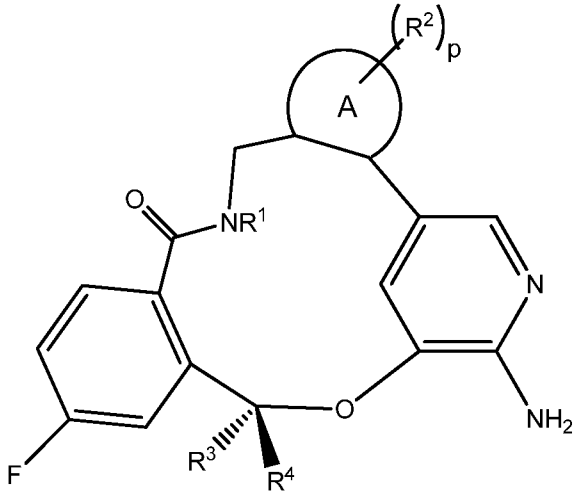
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The same embodiments described herein as relevant to compounds of formula (IV) are also applicable to compounds of formula (XIV).

In another aspect, the invention provides a compound of the formula (XV)



(XV)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered

heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

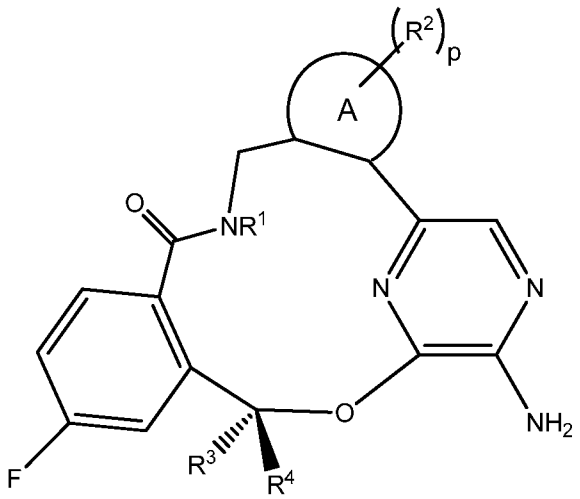
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The same embodiments described herein as relevant to compounds of formula (V) are also applicable to compounds of formula (XV).

In another aspect, the invention provides a compound of the formula (XVI)



(XVI)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

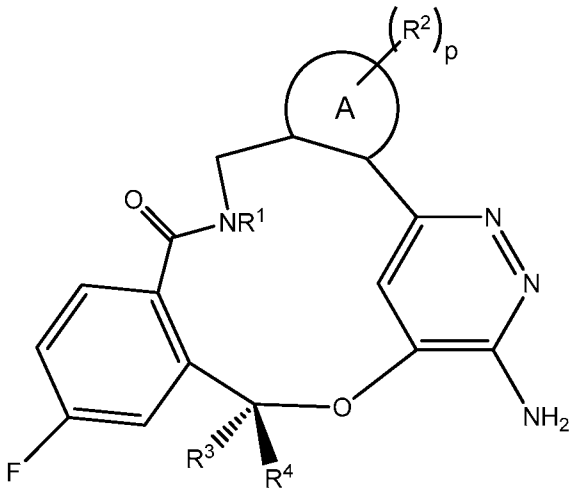
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The same embodiments described herein as relevant to compounds of formula (VI) are also applicable to compounds of formula (XVI).

In another aspect, the invention provides a compound of the formula (XVII)



(XVII)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -

NH_2, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

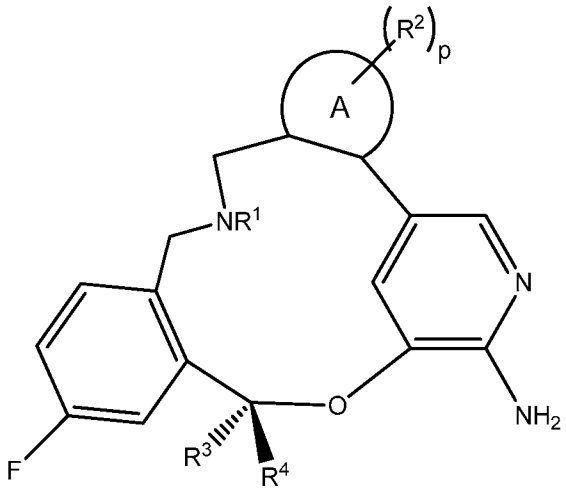
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The same embodiments described herein as relevant to compounds of formula (VII) are also applicable to compounds of formula (XVII).

In another aspect, the invention provides a compound of the formula (XVIII)



(XVIII)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

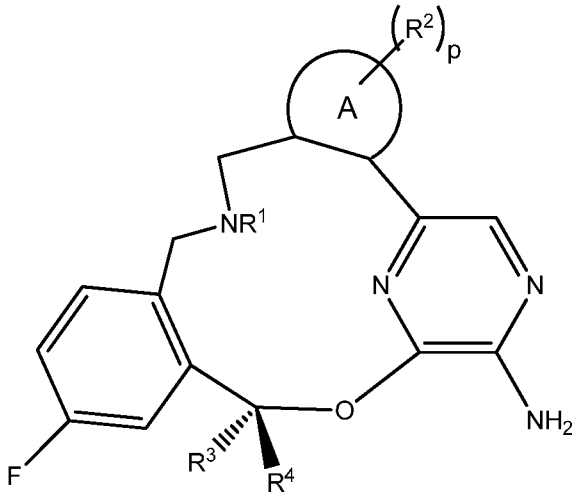
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The same embodiments described herein as relevant to compounds of formula (VIII) are also applicable to compounds of formula (XVIII).

In another aspect, the invention provides a compound of the formula (XIX)



(XIX)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

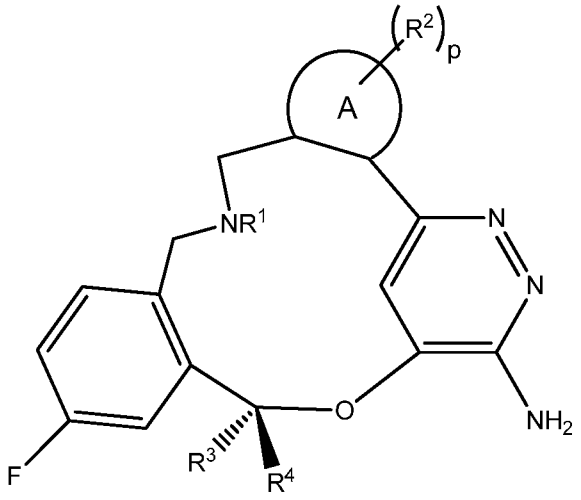
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The same embodiments described herein as relevant to compounds of formula (IX) are also applicable to compounds of formula (XIX).

In another aspect, the invention provides a compound of the formula (XX)



(XX)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

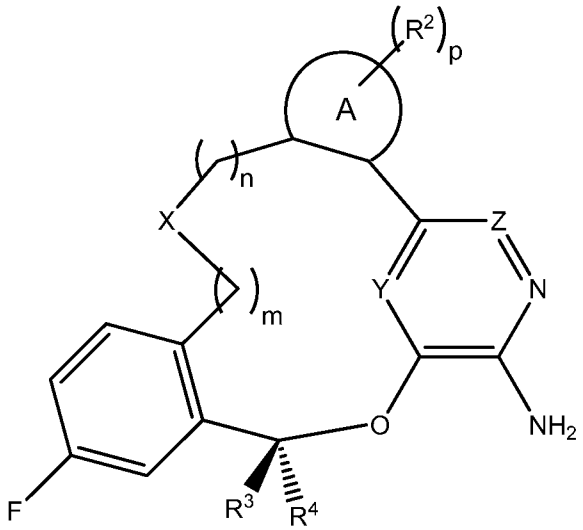
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The same embodiments described herein as relevant to compounds of formula (X) are also applicable to compounds of formula (XX).

In another aspect, the invention provides a compound of the formula (XXI)



(XXI)

wherein:

X is selected from the group consisting of -$(CR^5R^6)_qO(CR^5R^6)_r$-, -$(CR^5R^6)_qN(R^1)(CR^5R^6)_r$-, -$(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r$- and -$(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r$-;

Y and Z are each independently N or CH, with the proviso that when Y is N, Z is CH and when Z is N, Y is CH;

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ or -$C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ and -$(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ or -$C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

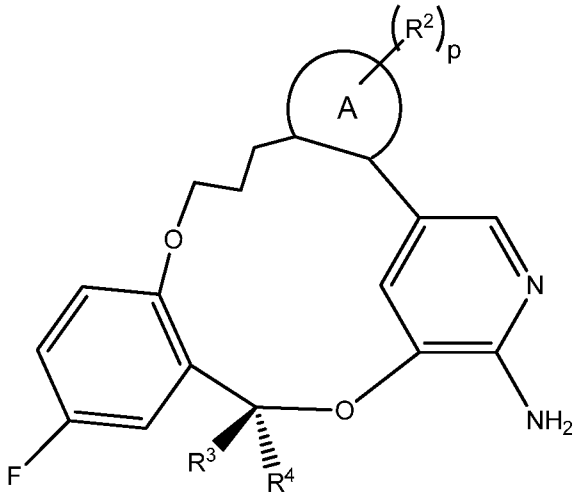
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The embodiments described herein as relevant to compounds of formula (I) and (XI) are also applicable to compounds of formula (XXI), to the extent they are compatible with the definition of R^3 and R^4 in formula (XXI).

In another aspect, the invention provides a compound of the formula (XXII)



(XXII)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$,

$-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} are independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

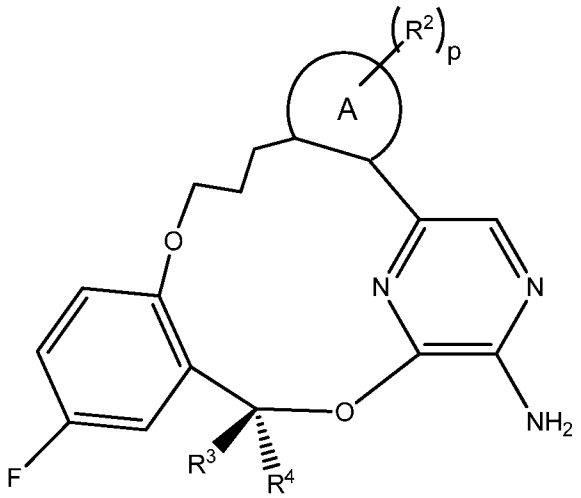
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The embodiments described herein as relevant to compounds of formula (II) and (XII) are also applicable to compounds of formula (XXII), to the extent they are compatible with the definition of R^3 and R^4 in formula (XXII).

In another aspect, the invention provides a compound of the formula (XXIII)



(XXIII)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} are independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

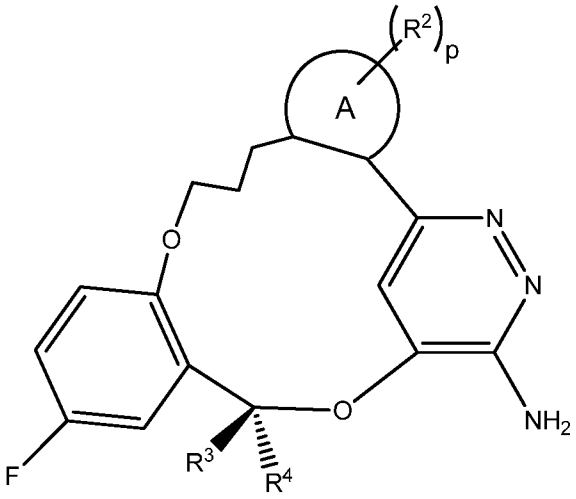
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The embodiments described herein as relevant to compounds of formula (III) and (XIII) are also applicable to compounds of formula (XXIII), to the extent they are compatible with the definition of R^3 and R^4 in formula (XXIII).

In another aspect, the inventions provides a compound of the formula (XXIV)



(XXIV)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} are independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

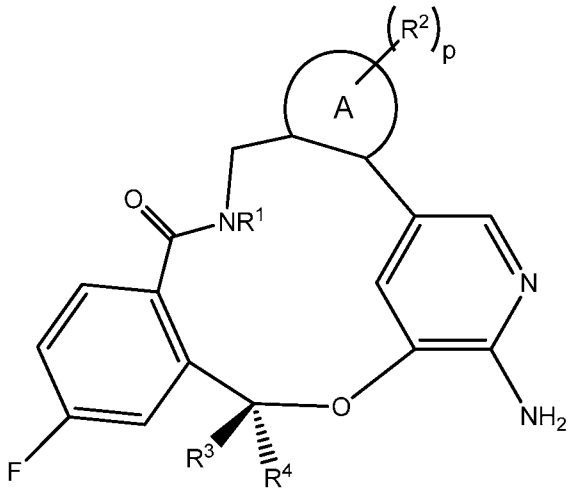
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The embodiments described herein as relevant to compounds of formula (IV) and (XIV) are also applicable to compounds of formula (XXIV), to the extent they are compatible with the definition of R^3 and R^4 in formula (XXIV).

In another aspect, the invention provides a compound of the formula (XXV)



(XXV)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $--C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

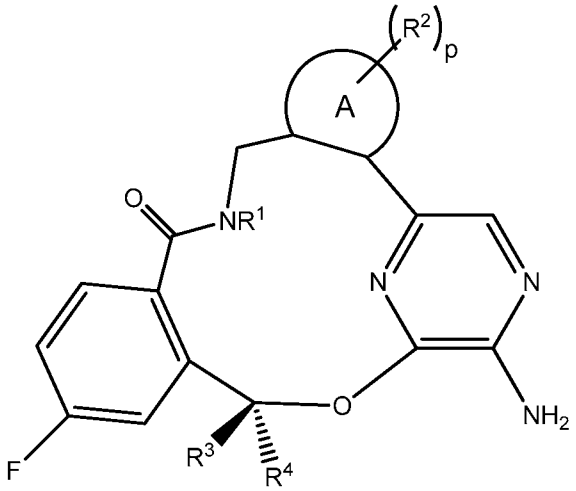
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The embodiments described herein as relevant to compounds of formula (V) and (XV) are also applicable to compounds of formula (XV), to the extent they are compatible with the definition of R^3 and R^4 in formula (XV).

In another aspect, the invention provides a compound of the formula (XXVI)



(XXVI)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

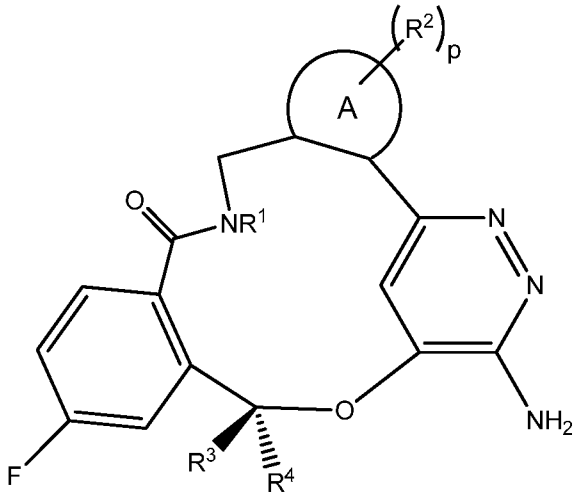
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The embodiments described herein as relevant to compounds of formula (VI) and (XVI) are also applicable to compounds of formula (XVI), to the extent they are compatible with the definition of R^3 and R^4 in formula (XVI).

In another aspect, the invention provides a compound of the formula (XXVII)



(XXVII)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

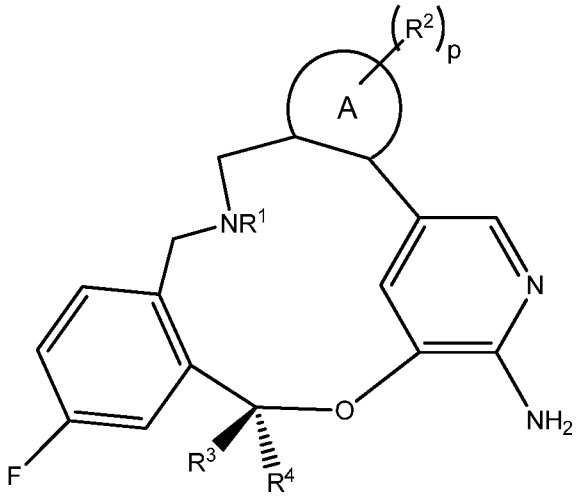
each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3;

each t is independently 0, 1 or 2; or a pharmaceutically acceptable salt thereof.

The embodiments described herein as relevant to compounds of formula (VII) and (XVII) are also applicable to compounds of formula (XVII), to the extent they are compatible with the definition of R^3 and R^4 in formula (XVII).

In another aspect, the invention provides a compound of the formula (XXVIII)



(XXVIII)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

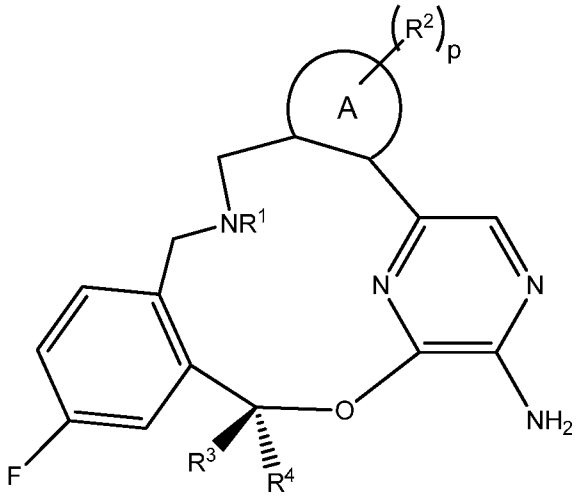
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The embodiments described herein as relevant to compounds of formula (VIII) and (XVIII) are also applicable to compounds of formula (XVIII), to the extent they are compatible with the definition of R^3 and R^4 in formula (XVIII).

In another aspect, the invention provides a compound of the formula (XXIX)



(XXIX)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

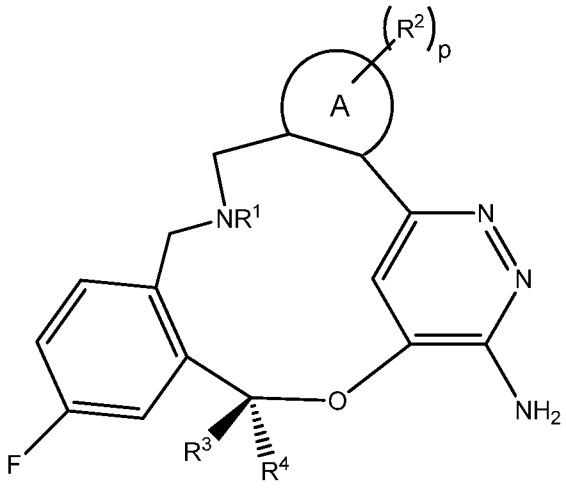
each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The embodiments described herein as relevant to compounds of formula (IX) and (XIX) are also applicable to compounds of formula (XXIX), to the extent they are compatible with the definition of R^3 and R^4 in formula (XXIX).

In another aspect, the invention provides a compound of the formula (XXX)



(XXX)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

The embodiments described herein as relevant to compounds of formula (X) and (XX) are also applicable to compounds of formula (XXX), to the extent they are compatible with the definition of R^3 and R^4 in formula (XXX).

In one embodiment, the invention provides one or more compounds selected from the group consisting of the compounds of Example 1 to Example 137, or a pharmaceutically acceptable salt thereof.

In another embodiment, the invention provides a compound selected from:

(5*R*)-8-amino-3-fluoro-5,17-dimethyl-13-(methylsulfonyl)-16,17-dihydro-7,11-(metheno)dibenzo[*g*,*l*][1,4,10]oxadiazacyclotetradecin-18(5*H*)-one;

(10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile;

(10*R*)-7-amino-12-fluoro-3-methoxy-10,16-dimethyl-16,17-dihydro-8,4-(metheno)isothiazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one;

7-amino-12-fluoro-2,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile;

8-amino-3-fluoro-17-methyl-13-(methylsulfonyl)-16,17-dihydro-7,11-(metheno)dibenzo[*g*,*l*][1,4,10]oxadiazacyclotetradecin-18(5*H*)-one;

7-amino-12-fluoro-1,3,16-trimethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one ;

8-amino-3-fluoro-17-methyl-16,17-dihydro-7,11-(metheno)dibenzo[*g*,*l*][1,4,10]oxadiazacyclotetradecin-18(5*H*)-one;

8-amino-3-fluoro-5,17-dimethyl-16,17-dihydro-7,11- (metheno)dibenzo[*g*,*l*][1,4,10]-oxadiazacyclotetradecin-18(5*H*)-one;

7-amino-16-ethyl-12-fluoro-1,3,10-trimethyl-16,17-dihydro-1H-8,4-(metheno)pyrazolo [4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one;

7-amino-16-cyclopropyl-12-fluoro-1,3,10-trimethyl-16,17-dihydro-1H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one;

7-amino-12-fluoro-1,3,10,16-tetramethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one;

7-amino-3-cyclopropyl-12-fluoro-2,10,16-trimethyl-16,17-dihydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one;

7-amino-3-cyclopropyl-12-fluoro-1,10,16-trimethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one;

7-amino-12-fluoro-3-methoxy-2,10,16-trimethyl-16,17-dihydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one;

7-amino-12-fluoro-3-methoxy-1,10,16-trimethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one;

7-amino-10-ethyl-12-fluoro-3-methoxy-1,16-dimethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one;

7-amino-10-cyclopropyl-12-fluoro-3-methoxy-1,16-dimethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one;

(10*R*)-7-amino-3-ethyl-12-fluoro-10,16-dimethyl-16,17-dihydro-3*H*-8,4-(metheno)pyrazolo[3,4-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one;

7-amino-12-fluoro-1,3,10,16-tetramethyl-16,17-dihydro-1H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one;

8-amino-13-fluoro-4-methoxy-11,17-dimethyl-17,18-dihydro-9,5-(azeno)pyrido[3,4-h][2,5,11]benzoxadiazacyclotetradecin-16(11H)-one;

7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile;

(11*R*)-8-amino-13-fluoro-4-methoxy-11,17-dimethyl-17,18-dihydro-9,5-(metheno)pyrido[3,4-*h*][2,5,11]benzoxadiazacyclotetradecin-16(11*H*)-one;

(5*R*)-3-fluoro-5,17-dimethyl-13-(methylsulfonyl)-5,16,17,18-tetrahydro-7,11-(metheno)dibenzo[*g*,*l*][1,4,10]oxadiazacyclotetradecin-8-amine;

(10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-10,15,16,17-tetrahydro-2*H*-4,8-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile;

12-fluoro-3-methyl-3,16,17,18-tetrahydro-10H-8,4-(metheno)pyrazolo[4,3-e][1,12,9]benzodioxazacyclopentadecin-7-amine;

12-fluoro-3-methyl-1,16,17,18-tetrahydro-10H-8,4-(metheno)pyrazolo[3,4-e][1,12,9]benzodioxazacyclopentadecin-7-amine;

7-amino-12-fluoro-2,16,17,18-tetrahydro-10H-8,4-(metheno)pyrazolo[3,4-e][1,12,9]benzodioxazacyclopentadecine-3-carbonitrile;

7-amino-12-fluoro-16,17-dihydro-1H,10H-8,4-(metheno)pyrazolo[3,4-d][1,11,8]benzodioxazacyclotetradecine-3-carbonitrile; and

(10*R*)-7-amino-12-fluoro-10,16-dimethyl-3-propyl-16,17-dihydro-3*H*-8,4-(metheno)[1,2,3]triazolo[4,5-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one;

or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a pharmaceutical composition comprising a compound of one of the formulae described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical composition comprises two or more pharmaceutically acceptable carriers and/or excipients.

In another aspect, the invention provides a compound of one of the formulae described herein, or a pharmaceutically acceptable salt thereof, for use as a medicament. In one embodiment, the medicament is for use in the treatment of abnormal cell growth in a mammal. In frequent embodiments, the abnormal cell growth is cancer. In one embodiment, the medicament is for use in the treatment of abnormal cell growth mediated by ALK in a mammal. In another embodiment, the medicament is for use in the treatment of abnormal cell growth mediated by an EML4-ALK fusion protein in a mammal. In some such embodiments, the EML4-ALK fusion protein has at least one mutation. In one embodiment, the mutation is L1196M. In another embodiment, the mutation is C1156Y.

In one embodiment, the invention provides a compound of one of the formulae described herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of abnormal cell growth in a mammal. In frequent embodiments, the abnormal cell growth is cancer. In one embodiment, the abnormal cell growth is mediated by ALK. In another embodiment, the abnormal cell growth is mediated by an EML4-ALK fusion protein. In some such embodiments, the EML4-ALK fusion protein has at least one mutation. In one embodiment, the mutation is L1196M. In another embodiment, the mutation is C1156Y.

The invention also provides therapeutic methods and uses comprising administering a compound of the invention, or a pharmaceutically acceptable salt thereof, alone or in combination with another therapeutic or palliative agent to a mammal in need of such treatment. In a preferred embodiment, the mammal is a human. In other embodiments, the mammal is a dog or cat.

In one aspect, the invention provides a method for the treatment of abnormal cell growth in a mammal comprising administering to a mammal a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for the treatment of abnormal cell growth in a mammal comprising administering to a mammal an amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with an amount of an anti-tumor agent, which amounts are together effective in treating said abnormal cell growth. In some embodiments, the anti-tumor agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

In one embodiment, the invention provides a method for the treatment of abnormal cell growth in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of one of the formulae described herein, or a pharmaceutically acceptable salt thereof. In frequent embodiments, the abnormal cell growth is cancer. In one embodiment, the abnormal cell growth is mediated by ALK. In another embodiment, the abnormal cell growth is mediated by an EML4-ALK fusion protein. In some such embodiments, the EML4-ALK fusion protein has at least one mutation. In one embodiment, the mutation is L1196M. In another embodiment, the mutation is C1156Y.

In another aspect, the invention provides a method for the treatment of a disorder mediated by ALK in a mammal comprising administering to the mammal a compound of the invention, or a pharmaceutically acceptable salt thereof, in an amount that is effective for treating said disorder.

The compounds and salts of the present invention inhibit wild-type ALK and/or certain mutant forms of ALK, including EML4-ALK fusion proteins, including EML4-ALK fusion proteins having at least one mutation. In one embodiment, the mutation is L1196M. In one embodiment, the mutation is C1156Y.

In one embodiment, the invention provides a method of treating abnormal cell proliferation in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof. In some such embodiments, the abnormal cell proliferation is cancer. In one embodiment, the cancer is mediated by ALK. In another embodiment, the cancer is mediated by an EML4-ALK fusion protein. In further such embodiments, the EML4-ALK fusion protein has at least one mutation. In one such embodiment, the mutation is L1196M. In another such embodiment, the mutation is C1156Y.

In another aspect, the invention provides a compound of one of the formulae described herein, or pharmaceutically acceptable salt thereof, for use in the treatment of abnormal cell growth in a mammal. In a further aspect, the invention provides the use of a compound of one of the formulae described herein, or pharmaceutically acceptable salt thereof, for the treatment of abnormal cell growth in a mammal.

In yet another aspect, the invention provides the use of a compound of one of the formulae described herein, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of abnormal cell growth.

In frequent embodiments of the methods and uses described herein, the abnormal cell growth is cancer. In some embodiments, the cancer is selected from lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, and combinations thereof.

In another embodiment, the cancer is selected from the group consisting of non-small cell lung cancer (NSCLC), squamous cell carcinoma, hormone-refractory prostate cancer,

papillary renal cell carcinoma, colorectal adenocarcinoma, neuroblastomas, anaplastic large cell lymphoma (ALCL) and gastric cancer.

In some embodiments, the methods described herein further comprise administering to the mammal an amount of an anti-cancer therapeutic agent or a palliative agent, which amounts are together effective in treating said abnormal cell growth. In some such embodiments, one or more anti-cancer therapeutic agent are selected from anti-tumor agents, anti-angiogenesis agents, signal transduction inhibitors and antiproliferative agents, which amounts are together effective in treating said abnormal cell growth.

In other embodiments, the uses described herein comprise the use of a compound of one of the formulae described herein or pharmaceutically acceptable salt thereof, in combination with one or more substances selected from anti-tumor agents, anti-angiogenesis agents, signal transduction inhibitors and antiproliferative agents.

In some embodiments, the medicaments described herein are adapted for use in combination with one or more substances selected from anti-tumor agents, anti-angiogenesis agents, signal transduction inhibitors and antiproliferative agents.

Each of the embodiments of the compounds of the present invention described herein can be combined with one or more other embodiments of the compounds of the present invention described herein not inconsistent with the embodiment(s) with which it is combined. In addition, each of the embodiments describing the invention envisions within its scope the pharmaceutically acceptable salts of the compounds of the invention. Accordingly, the phrase "or a pharmaceutically acceptable salt thereof" is implicit in the description of all compounds described herein.

Brief Description of the Drawings

Figure 1: X-ray crystal structure of Example 1 demonstrating absolute stereochemistry of an (R)-configuration for the compound of Example 1.

Detailed Description of the Invention

The present invention may be understood more readily by reference to the following detailed description of the preferred embodiments of the invention and the Examples included herein. It is to be understood that the terminology used herein is for the purpose of describing specific embodiments only and is not intended to be limiting. It is further to be understood that unless specifically defined herein, the terminology used herein is to be given its traditional meaning as known in the relevant art.

As used herein, the singular form "a", "an", and "the" include plural references unless indicated otherwise. For example, "a" substituent includes one or more substituents.

"Alkyl" refers to a saturated, monovalent aliphatic hydrocarbon radical including straight chain and branched chain groups having the specified number of carbon atoms. Alkyl substituents typically contain 1 to 20 carbon atoms ("C_1-C_{20} alkyl"), preferably 1 to 12 carbon atoms ("C_1-C_{12} alkyl"), more preferably 1 to 8 carbon atoms ("C_1-C_8 alkyl"), or 1 to 6 carbon atoms ("C_1-C_6 alkyl"), or 1 to 4 carbon atoms ("C_1-C_4 alkyl"). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, n-octyl and the like. Alkyl groups may be substituted or unsubstituted. In particular, unless otherwise specified, alkyl groups may be substituted by one or more halo groups, up to the total number of hydrogen atoms present on the alkyl moiety. Thus, C_1-C_4 alkyl includes halogenated alkyl groups, e.g., trifluoromethyl or difluoroethyl (i.e., CF_3 and $-CH_2CHF_2$).

As used herein, "C_1-C_6 alkyl" denotes a straight-chain or branched group containing 1, 2, 3, 4, 5 or 6 carbon atoms. This also applies if they carry substituents or occur as substituents of other radicals, for example in O-(C_1-C_6)alkyl radicals. Examples of suitable C_1-C_6 alkyl radicals are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-buty, n-pentyl, *sec*-pentyl, neopentyl, n-hexyl, *sec*-hexyl, and the like. Examples of suitable O-(C_1-C_6)alkyl radicals are methoxy, ethoxy, *n*-propyloxy, *iso*-propyloxy, *n*-butyloxy, *iso*-butyloxy, *sec*-butyloxy and *tert*-butyloxy, n-pentyloxy, neopentyloxy, hexyloxy, and the like.

Alkyl groups described herein as optionally substituted by may be substituted by one or more substituent groups, which are selected independently unless otherwise indicated. The total number of substituent groups may equal the total number of hydrogen atoms on the alkyl moiety, to the extent such substitution makes chemical sense. Optionally substituted alkyl groups typically contain from 1 to 6 optional substituents, sometimes 1 to 5 optional substituents, preferably from 1 to 4 optional substituents, or more preferably from 1 to 3 optional substituents.

Optional substituent groups suitable for alkyl include, but are not limited to C_3-C_8 cycloalkyl, 3-12 membered heterocyclyl,C_6-C_{12} aryl and 5-12 membered heteroaryl, halo, =O (oxo), =S (thiono), =N-CN, $=N-OR^X$, $=NR^X$, -CN, $-C(O)R^x$, $-CO_2R^x$, $-C(O)NR^xR^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-SO_2NR^xR^y$, $-NO_2$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(O)NR^xR^y$, $-NR^xC(O)OR^x$, $-NR^xSO_2R^y$, $-NR^xSO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$ and $-OC(O)NR^xR^y$; wherein each R^x and R^y is independently H, C_1-C_8 alkyl, C_1-C_8 acyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{12} aryl, or 5-12 membered heteroaryl, or R^x and R^y may be taken together with the N atom to which they are attached to form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl, each optionally containing 1, 2 or 3 additional heteroatoms selected from O, N and S;

each R^x and R^y is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, =O, =S, =N-CN, =N-OR', =NR', -CN, -C(O)R', -CO_2R', -C(O)NR'$_2$, -SR', -SOR', -SO_2R', -SO_2NR'$_2$, -NO_2, -NR'$_2$, -NR'C(O)R', -NR'C(O)NR'$_2$, -NR'C(O)OR', -NR'SO_2R', -NR'SO_2NR'$_2$, -OR', -OC(O)R' and -OC(O)NR'$_2$, wherein each R' is independently H, C_1-C_8 alkyl, C_1-C_8 acyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{12} aryl, or C_5-C_{12} heteroaryl; and wherein each said C_3-C_8 cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{12} aryl and 5-12 membered heteroaryl is optionally substituted as further defined herein.

Typical substituent groups on alkyl include halo, -OH, C_1-C_4 alkoxy, -O-C_6-C_{12} aryl, -CN, =O, -COOR^x, -OC(O)R^x, -C(O)N$R^x R^y$, -NR^xC(O)R^y, –N$R^x R^y$, C_3-C_8 cycloalkyl, C_6-C_{12} aryl, 5-12 membered heteroaryl and 3-12 membered heterocyclyl; where each R^x and R^y is independently H or C_1-C_4 alkyl, or R^x and R^y may be taken together with the N to which they are attached form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl ring, each optionally containing 1, 2 or 3 additional heteroatoms selected from O, N and S; wherein each said C_3-C_8 cycloalkyl, C_6-C_{12} aryl, 5-12 membered heteroaryl and 3-12 membered heterocyclyl is optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo, -OH, =O, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_4 alkoxy-C_1-C_6 alkyl, -CN, -NH_2, -NH(C_1-C_4 alkyl), and -N(C_1-C_4 alkyl)$_2$.

In some embodiments, alkyl is optionally substituted by one or more substituents, and preferably by 1 to 3 substituents, which are independently selected from the group consisting of halo, -OH, C_1-C_4 alkoxy, -O-C_6-C_{12} aryl, -CN, =O, -COOR^x, -OC(O)R^x, -C(O)N$R^x R^y$, -NR^xC(O)R^y, –N$R^x R^y$, C_3-C_8 cycloalkyl, C_6-C_{12} aryl, 5-12 membered heteroaryl and 3-12 membered heterocyclyl; where each R^x and R^y is independently H or C_1-C_4 alkyl, or R^x and R^y may be taken together with the N to which they are attached form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl ring, each optionally containing 1, 2 or 3 additional heteroatoms selected from O, N and S; and each said C_3-C_8 cycloalkyl, C_6-C_{12} aryl, 5-12 membered heteroaryl and 3-12 membered heterocyclyl is optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo, -OH, =O, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_4 alkoxy-C_1-C_6 alkyl, -CN, -NH_2, -NH(C_1-C_4 alkyl) and -N(C_1-C_4 alkyl)$_2$.

In other embodiments, alkyl is optionally substituted by one or more substituent, and preferably by 1 to 3 substituents, independently selected from the group consisting of halo, -OH, C_1-C_4 alkoxy, -CN, –N$R^x R^y$, C_3-C_8 cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{12} aryl and 5-12 membered heteroaryl; where each R^x and R^y is independently H or C_1-C_4 alkyl, or R^x and R^y may be taken together with the N to which they are attached form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl ring, each optionally containing 1, 2 or 3 additional heteroatoms

selected from O, N and S; and where each said cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo, -OH, =O, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_4 alkoxy-C_1-C_6 alkyl, -CN, $-NH_2$, $-NH(C_1$-C_4 alkyl) and $-N(C_1$-C_4 alkyl)$_2$.

In some instances, substituted alkyl groups may be specifically named with reference to the substituent group. For example, "haloalkyl" refers to an alkyl group having the specified number of carbon atoms that is substituted by one or more halo substituents, and typically contain 1-6 carbon atoms and 1, 2 or 3 halo atoms (i.e., "C_1-C_6 haloalkyl"). Thus, a C_1-C_6 haloalkyl group includes trifluoromethyl ($-CF_3$) and difluoromethyl ($-CF_2H$).

Similarly, "hydroxyalkyl" refers to an alkyl group having the specified number of carbon atoms that is substituted by one or more hydroxy substituents, and typically contain 1-6 carbon atoms and 1, 2 or 3 hydroxy (i.e., "C_1-C_6 hydroxyalkyl"). Thus, C_1-C_6 hydroxyalkyl includes hydroxymethyl ($-CH_2OH$) and 2-hydroxyethyl ($-CH_2CH_2OH$).

"Alkoxyalkyl" refers to an alkyl group having the specified number of carbon atoms that is substituted by one or more alkoxy substituents. Alkoxyalkyl groups typically contain 1-6 carbon atoms in the alkyl portion and are substituted by 1, 2 or 3 C_1-C_4 alkyoxy substituents. Such groups are sometimes described herein as C_1-C_4 alkyoxy-C_1-C_6 alkyl.

"Aminoalkyl" refers to alkyl group having the specified number of carbon atoms that is substituted by one or more substituted or unsubstituted amino groups, as such groups are further defined herein. Aminoalkyl groups typically contain 1-6 carbon atoms in the alkyl portion and are substituted by 1, 2 or 3 amino substituents. Thus, a C_1-C_6 aminoalkyl group includes, for example, aminomethyl ($-CH_2NH_2$), *N,N*-dimethylamino-ethyl ($-CH_2CH_2N(CH_3)_2$), 3-(*N*-cyclopropylamino)propyl ($-CH_2CH_2CH_2NH-{}^cPr$) and *N*-pyrrolidinylethyl ($-CH_2CH_2$-N-pyrrolidinyl).

"Alkenyl" refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond. Typically, alkenyl groups have 2 to 20 carbon atoms ("C_2-C_{20} alkenyl"), preferably 2 to 12 carbon atoms ("C_2-C_{12} alkenyl"), more preferably 2 to 8 carbon atoms ("C_2-C_8 alkenyl"), or 2 to 6 carbon atoms ("C_2-C_6 alkenyl"), or 2 to 4 carbon atoms ("C_2-C_4 alkenyl"). Representative examples include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-, 2-, or 3-butenyl, and the like. A "C_2-C_6 alkenyl" denotes a straight-chain or branched group containing 1 to 6 carbon atoms and at least one double bond between two sp^2 hybridized carbon atoms. This also applies if they carry substituents or occur as substituents of other radicals, for example in O-(C_1-C_6)alkenyl radicals. Examples of suitable C_1-C_6 alkyl radicals are *n*-propenyl, *iso*-propenyl, *n*-butenyl, *iso*-butenyl, n-pentenyl, *sec*-pentenyl, n-hexenyl, *sec*-hexenyl, and the like. Alkenyl groups may be unsubstituted or substituted by the same groups that are described herein as suitable for alkyl.

"Alkynyl" refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond. Alkynyl groups have 2 to 20 carbon atoms ("C_2-C_{20} alkynyl"), preferably 2 to 12 carbon atoms ("C_2-C_{12} alkynyl"), more preferably 2 to 8 carbon atoms ("C_2-C_8 alkynyl"), or 2 to 6 carbon atoms ("C_2-C_6 alkynyl"), or 2 to 4 carbon atoms ("C_2-C_4 alkynyl"). Representative examples include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-, 2-, or 3-butynyl, and the like. Alkynyl groups may be unsubstituted or substituted by the same groups that are described herein as suitable for alkyl. A "C_2-C_6 alkynyl" denotes a straight-chain or branched group containing 1 to 6 carbon atoms and at least one triple bond between two sp hybridized carbon atoms. This also applies if they carry substituents or occur as substituents of other radicals, for example in O-(C_1-C_6)alkynyl radicals. Examples of suitable C_1-C_6 alkynyl radicals are propynyl, butynyl, pentynyl, hexynyl, and the like.

"Alkylene" as used herein refers to a divalent hydrocarbyl group having the specified number of carbon atoms which can link two other groups together. Sometimes it refers to –$(CH_2)_n$– where n is 1-8, and preferably n is 1-4. Where specified, an alkylene can also be substituted by other groups and may include one or more degrees of unsaturation (i.e., an alkenylene or alkynlene moiety) or rings. The open valences of an alkylene need not be at opposite ends of the chain. Thus –CH(Me) – and –$C(Me)_2$– are also included within the scope of the term `alkylenes`, as are cyclic groups such as cyclopropan-1,1-diyl and unsaturated groups such as ethylene (-CH=CH-) or propylene (-CH_2-CH=CH-). Where an alkylene group is described as optionally substituted, the substituents include those typically present on alkyl groups as described herein.

"Heteroalkylene" refers to an alkylene group as described above, wherein one or more non-contiguous carbon atoms of the alkylene chain are replaced by -N(R)-, -O- or -$S(O)_q$-, where R is H or C_1-C_4 alkyl and q is 0-2. For example, the group –O-$(CH_2)_{1-4}$- is a 'C_2-C_5'-heteroalkylene group, where one of the carbon atoms of the corresponding alkylene is replaced by O.

"Alkoxy" refers to a monovalent –O-alkyl group, wherein the alkyl portion has the specified number of carbon atoms. Alkoxy groups typically contain 1 to 8 carbon atoms ("C_1-C_8 alkoxy"), or 1 to 6 carbon atoms ("C_1-C_6 alkoxy"), or 1 to 4 carbon atoms ("C_1-C_4 alkoxy"). For example, C_1-C_4 alkoxy includes –OCH_3, -OCH_2CH_3, -$OCH(CH_3)_2$, -$OC(CH_3)_3$, and the like. Such groups may also be referred to herein as methoxy, ethoxy, isopropoxy, *tert*-butyloxy, etc. Alkoxy groups may be unsubstituted or substituted on the alkyl portion by the same groups that are described herein as suitable for alkyl. In particular, alkoxy groups may be substituted by one or more halo groups, up to the total number of hydrogen atoms present on the alkyl portion. Thus,

C_1-C_4 alkoxy includes halogenated alkoxy groups, e.g., trifluoromethoxy and 2,2-difluoroethoxy (i.e., $-OCF_3$ and $-OCH_2CHF_2$).

Similarly, “thioalkoxy” refers to a monovalent –S-alkyl group, wherein the alkyl portion has the specified number of carbon atoms, and may be optionally substituted on the alkyl portion by the same groups that are described herein as suitable for alkyl. For example, a C_1-C_4 thioalkoxy includes $–SCH_3$ and $-SCH_2CH_3$.

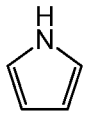
“Halogen” or “halo” refers to fluoro, chloro, bromo and iodo (F, Cl, Br, I). Preferably, halo refers to fluoro or chloro (F or Cl).

"Heteroaryl" or “heteroaromatic” refer to monocyclic or fused bicyclic or polycyclic ring systems having the well-known characteristics of aromaticity that contain the specified number of ring atoms and include at least one heteroatom selected from N, O and S as a ring member in an aromatic ring. The inclusion of a heteroatom permits aromaticity in 5-membered rings as well as 6-membered rings. Typically, heteroaryl groups contain 5 to 20 ring atoms (“5-20 membered heteroaryl”), preferably 5 to 14 ring atoms (“5-14 membered heteroaryl”), and more preferably 5 to 12 ring atoms (“5-12 membered heteroaryl”) or 5 to 6 ring atoms (“5-6 membered heteroaryl”). Heteroaryl rings are attached to the base molecule via a ring atom of the heteroaromatic ring, such that aromaticity is maintained. Thus, 6-membered heteroaryl rings may be attached to the base molecule via a ring C atom, while 5-membered heteroaryl rings may be attached to the base molecule via a ring C or N atom. The heteroaryl group may be unsubstituted or substituted as further described herein. As used herein, "5-6 membered heteroaryl" refers to a monocyclic group of 5 or 6 ring atoms containing one, two or three ring heteroatoms selected from N, O, and S, the remaining ring atoms being C, and, in addition, having a completely conjugated pi-electron system. Substituents on adjacent ring atoms of a 5- or 6-membered heteroaryl may combine to form a fused 5- or 6-membered carbocyclic ring optionally substituted by one or more substituents, such as oxo, C_1-C_6 alkyl, hydroxyl, amino and halogen, or a fused 5- or 6-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, O and $S(O)_p$ (where p is 0, 1 or 2) optionally substituted by one or more substituents, such as oxo, C_1-C_6 alkyl, hydroxyl, amino and halogen. A pharmaceutically acceptable heteroaryl is one that is sufficiently stable to be attached to a compound of the invention, formulated into a pharmaceutical composition and subsequently administered to a patient in need thereof.

Examples of 5-membered heteroaryl rings containing 1, 2 or 3 heteroatoms independently selected from O, N and S, include pyrrolyl, thienyl, furanyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl and thiadiazolyl. Preferred 6-membered heteroaryl rings contain 1 or 2 nitrogen atoms. Examples of 6-membered heteroaryl are pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl. Examples of fused heteroaryl rings

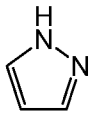
include benzofuran, benzothiophene, indole, benzimidazole, indazole, quinoline, isoquinoline, purine, triazine, naphthryidine and carbazole.

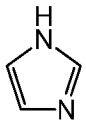
Examples of typical monocyclic heteroaryl groups include, but are not limited to:


pyrrole (pyrrolyl)

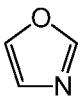

furan (furanyl)


thiophene (thiophenyl)

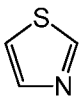

pyrazole (pyrazolyl)

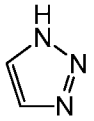

imidazole (imidazolyl)

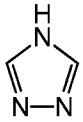

isoxazole (isoxazolyl)

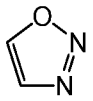

oxazole (oxazolyl)

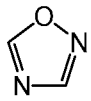

isothiazole (isothiazolyl)


thiazolyl (thiazolyl)


1,2,3-triazole (1,2,3-triazolyl)


1,3,4-triazole (1,3,4-triazolyl)


1-oxa-2,3-diazole (1-oxa-2,3-diazolyl)


1-oxa-2,4-diazole (1-oxa-2,4-diazolyl)

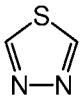

1-oxa-2,5-diazole (1-oxa-2,5-diazolyl)

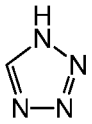

1-oxa-3,4-diazole (1-oxa-3,4-diazolyl)

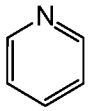

1-thia-2,3-diazole (1-thia-2,3-diazolyl)

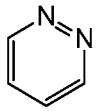

1-thia-2,4-diazole (1-thia-2,4-diazolyl)

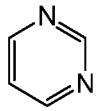

1-thia-2,5-diazole (1-thia-2,5-diazolyl)

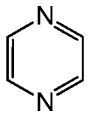

1-thia-3,4-diazole (1-thia-3,4-diazolyl)


tetrazole (tetrazolyl)

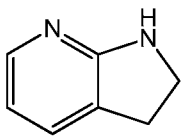

pyridine (pyridinyl)

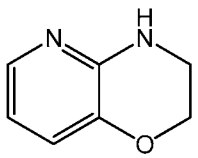

pyridazine (pyridazinyl)

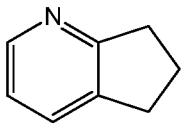

pyrimidine (pyrimidinyl)


pyrazine (pyrazinyl)

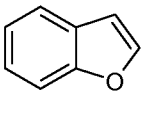
Examples of 6-membered heteroaryl groups having adjacent ring atoms that form a fused heterocyclic ring or a carbocyclic ring include, but are not limited to

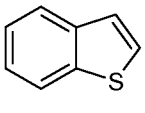

2,3-dihydro-1*H*-pyrrolo [2,3-*b*]pyridinyl

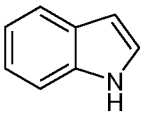

3,4-dihydro-2*H*-pyrido [3,2-*b*][1,4]oxazinyl

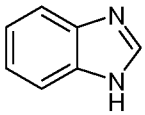

6,7-dihydro-5*H*-cyclopenta [*b*]pyridinyl

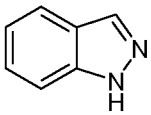
Illustrative examples of fused ring heteroaryl groups include, but are not limited to:

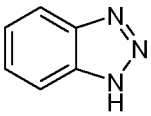

benzofuran
(benzofuranyl)

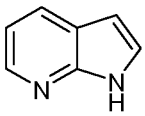

benzothiophene
(benzothiophenyl)

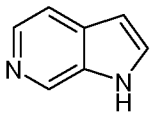

indole
(indolyl)

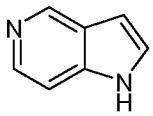

benzimidazole
(benzimidazolyl)

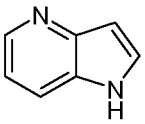

indazole
(indazolyl)

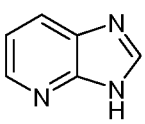

benzotriazole
(benzotriazolyl)

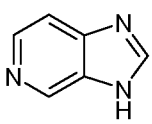

pyrrolo[2,3-b]pyridine
(pyrrolo[2,3-b]pyridinyl)

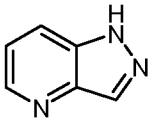

pyrrolo[2,3-c]pyridine
(pyrrolo[2,3-c]pyridinyl)

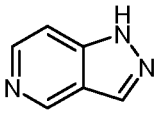

pyrrolo[3,2-c]pyridine
(pyrrolo[3,2-c]pyridinyl)

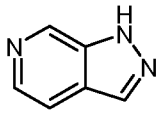

pyrrolo[3,2-b]pyridine
(pyrrolo[3,2-b]pyridinyl)

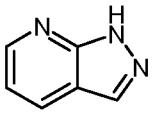

imidazo[4,5-b]pyridine
(imidazo[4,5-b]pyridinyl)

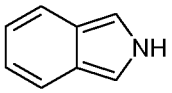

imidazo[4,5-c]pyridine
(imidazo[4,5-c]pyridinyl)

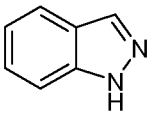

pyrazolo[4,3-d]pyridine
(pyrazolo[4,3-d]pyidinyl)

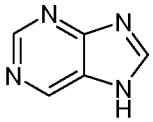

pyrazolo[4,3-c]pyridine
(pyrazolo[4,3-c]pyidinyl)

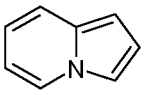

pyrazolo[3,4-c]pyridine
(pyrazolo[3,4-c]pyidinyl)

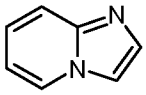

pyrazolo[3,4-b]pyridine
(pyrazolo[3,4-b]pyidinyl)

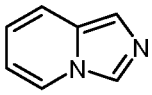

isoindole
(isoindolyl)

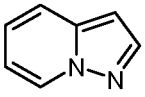

indazole
(indazolyl)

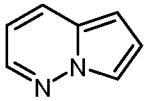

purine
(purinyl)

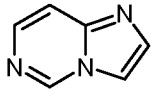

indolizine
(indolininyl)

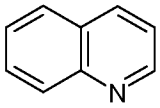

imidazo[1,2-a]pyridine
(imidazo[1,2-a]pyridinyl)

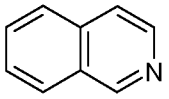

imidazo[1,5-a]pyridine
(imidazo[1,5-a]pyridinyl)

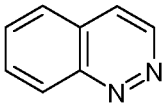

pyrazolo[1,5-a]pyridine
(pyrazolo[1,5-a]pyridinyl)

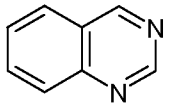

pyrrolo[1,2-b]pyridazine
(pyrrolo[1-2,b]pyridazinyl)

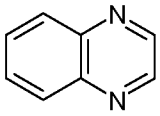

imidazo[1,2-c]pyrimidine
(imidazo[1,2-c]pyrimidinyl)

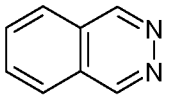

quinoline
(quinolinyl)

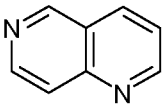

isoquinoline
(isoquinolinyl)

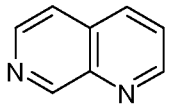

cinnoline
(cinnolinyl)

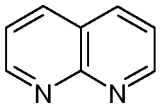

quinazoline
(azaquinazoline)

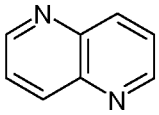

quinoxaline
(quinoxalinyl)

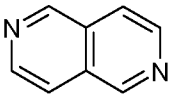

phthalazine
(phthalazinyl)

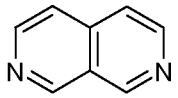

1,6-naphthyridine
(1,6-naphthyridinyl)

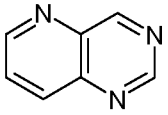

1,7-naphthyridine
(1,7-naphthyridinyl)

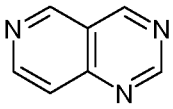

1,8-naphthyridine
(1,8-naphthyridinyl)

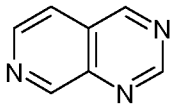

1,5-naphthyridine
(1,5-naphthyridinyl)

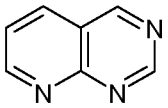

2,6-naphthyridine
(2,6-naphthyridinyl)

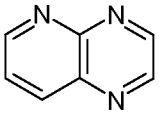

2,7-naphthyridine
(2,7-naphthyridinyl)

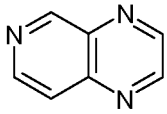

pyrido[3,2-d]pyrimidine
(pyrido[3,2-d]pyrimidinyl)

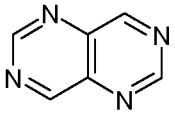

pyrido[4,3-d]pyrimidine
(pyrido[4,3-d]pyrimidinyl)

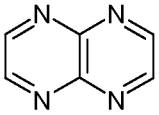

pyrido[3,4-d]pyrimidine
(pyrido[3,4-d]pyrimidinyl)

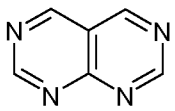

pyrido[2,3-d]pyrimidine
(pyrido[2,3-d]pyrimidinyl)


pyrido[2,3-b]pyrazine
(pyrido[2,3-b]pyrazinyl)


pyrido[3,4-b]pyrazine
(pyrido[3,4-b]pyrazinyl)


pyrimido[5,4-d]pyrimidine
(pyrimido[5,4-d]pyrimidinyl)

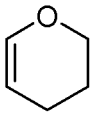

pyrazino[2,3-b]pyrazine
(pyrazino[2,3-b]pyrazinyl)


pyrimido[4,5-d]pyrimidine
(pyrimido[4,5-d]pyrimidinyl)

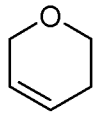
The terms “heteroalicyclic”, "heterocyclyl", or "heterocyclic" may be used interchangeably herein to refer to a non-aromatic, saturated or partially unsaturated ring system containing the specified number of ring atoms, including at least one heteroatom selected from N, O and S as a ring member, wherein the heterocyclic ring is connected to the base molecule via a ring atom, which may be C or N. Heteroalicyclic rings may be fused to one or more other heteroalicyclic or carbocyclic rings, which fused rings may be saturated, partially unsaturated or aromatic. Preferably, heteroalicyclic rings contain 1 to 4 heteroatoms selected from N, O, and S as ring members, and more preferably 1 to 2 ring heteroatoms, provided that such heteroalicyclic rings do not contain two contiguous oxygen atoms. Heteroalicyclic groups may be unsubstituted or

substituted by the same groups that are described herein as suitable for alkyl, aryl or heteroaryl. In addition, ring N atoms may be optionally substituted by groups suitable for an amine, e.g., alkyl, acyl, carbamoyl, sulfonyl substituents, etc., and ring S atoms may be optionally substituted by one or two oxo groups (i.e., $S(O)_p$, where p is 0, 1 or 2). Preferred heteroalicyclic groups include 3-12 membered heteroalicyclic groups in accordance with the definition herein. As used herein, "3-12 membered heteroalicyclic" refers to a monocyclic or bicyclic group having 3 to 12 ring atoms, in which one, two, three or four ring atoms are heteroatoms selected from N, O and $S(O)_p$ (where p is 0, 1, 2) the remaining ring atoms being C. The ring may also have one or more double bonds. However, the ring does not have a completely conjugated pi-electron system. Substituents on two ring carbon atoms may combine to form a 5- or 6-membered bridged ring that is either carbocyclic or heteroalicyclic containing one, two or three ring heteroatoms selected from N, O and $S(O)_p$ (where p is 0, 1 or 2). The heteroalicyclic group is optionally substituted by oxo, hydroxyl, amino, C_1C_6-alkyl and the like.

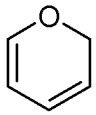
Examples of suitable partially unsaturated heteroalicyclic groups include, but are not limited to:



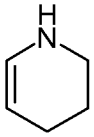
3,4-dihydro-2H-pyran
(3,4-dihydro-2H-pyranyl)



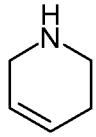
5,6-dihydro-2H-pyran
(5,6-dihydro-2H-pyranyl)



2H-pyran
(2H-pyranyl)

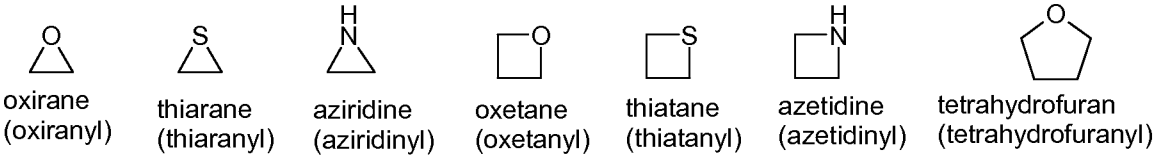


1,2,3,4-tetrahydropyridine
(1,2,3,4-tetrahydropyridinyl)



1,2,5,6-tetrahydropyridine
(1,2,5,6-tetrahydropyridinyl)

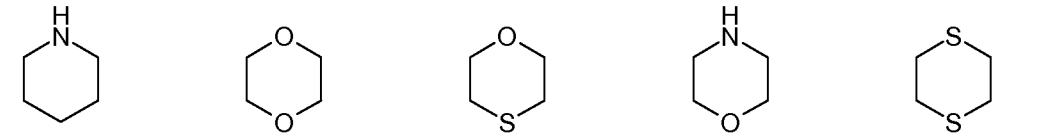
Examples of suitable saturated heteroalicyclic groups include, but are not limited to:



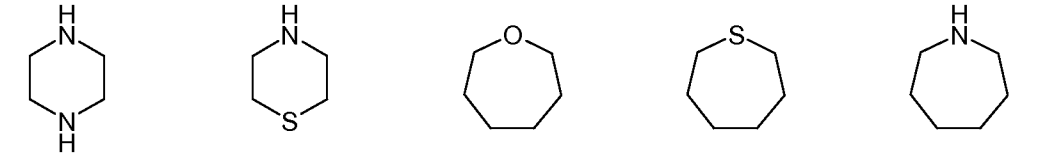
oxirane (oxiranyl) thiarane (thiaranyl) aziridine (aziridinyl) oxetane (oxetanyl) thiatane (thiatanyl) azetidine (azetidinyl) tetrahydrofuran (tetrahydrofuranyl)



tetrahydrothiophene (tetrahydrothiophenyl) pyrrolidine (pyrrolidinyl) tetrahydropyran (tetrahydropyranyl) tetrahydrothiopyran (tetrahydrothiopyranyl)



piperidine (piperidinyl) 1,4-dioxane (1,4-dioxanyl) 1,4-oxathiane (1,4-oxathianyl) morpholine (morpholinyl) 1,4-dithiane (1,4-dithianyl)



piperazine (piperazinyl) 1,4-azathiane (1,4-azathianyl) oxepane (oxepanyl) thiepane (thiepanyl) azepane (azepanyl)



1,4-dioxepane (1,4-dioxepanyl) 1,4-oxathiepane (1,4-oxathiepanyl) 1,4-oxaazepane (1,4-oxaazepanyl) 1,4-dithiepane (1,4-dithiepanyl)



1,4-thieazepane (1,4-thieazepanyl) 1,4-diazepane (1,4-diazepanyl)

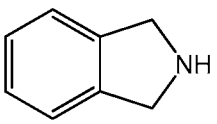
In frequent embodiments, heteroalicyclic groups contain 3-12 ring members, including both carbon and non-carbon heteroatoms, and preferably 4-6 ring members. In certain preferred embodiments, substituent groups comprising 3-12 membered heteroalicyclic groups are selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl

rings, each of which may be optionally substituted to the extent such substitution makes chemical sense.

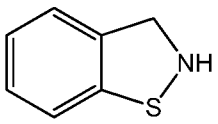
It is understood that no more than two N, O or S atoms are ordinarily connected sequentially, except where an oxo group is attached to N or S to form a nitro or sulfonyl group, or in the case of certain heteroaromatic rings, such as triazine, triazole, tetrazole, oxadiazole, thiadiazole, and the like.

The term "heterocyclylalkyl" may be used to describe a heterocyclic group of the specified size that is connected to the base molecule through an alkylene linker of the specified length. Typically, such groups contain an optionally substituted 3-12 membered heterocycle attached to the base molecule through a C_1-C_4 alkylene linker. Where so indicated, such groups may be optionally substituted on the alkylene portion by the same groups that are described herein as suitable for alkyl groups and on the heterocyclic portion by groups described as suitable for heterocyclic rings.

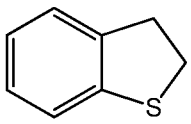
As used herein, "C_6-C_{12} aryl" refers to an all-carbon monocyclic or fused-ring polycyclic groups of 6 to 12 carbon atoms having a completely conjugated pi-electron system. Examples of aryl groups are phenyl and naphthalenyl. The aryl group may be substituted or unsubstituted. Substituents on adjacent ring carbon atoms of a C_6-C_{12} aryl may combine to form a 5- or 6-membered carbocyclic ring optionally substituted by one or more substituents, such as oxo, C_1-C_6 alkyl, hydroxyl, amino and halogen, or a 5- or 6-membered heterocyclic ring containing one, two or three ring heteroatoms selected from N, O and $S(O)_p$ (where p is 0, 1 or 2) optionally substituted by one or more substituents, such as oxo, C_1-C_6 alkyl, hydroxyl, amino and halogen. Examples, without limitation, of aryl groups include phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and tetrahydronaphthyl. The aryl group may be unsubstituted or substituted as further described herein. Additional examples of C_6-C_{10} aryl having two ring carbon atoms that form a fused heterocyclic or carbocyclic ring include but are not limited to:



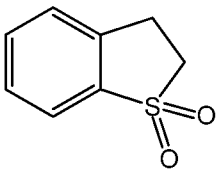
isoindolinyl



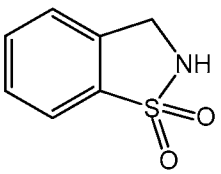
2,3-dihydrobenzo[*d*]isothiazolyl



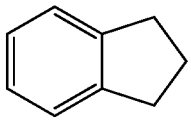
2,3-dihydrobenzo[*b*]thiophenyl



2,3-dihydrobenzo [*b*]thiophene 1,1-dioxide



2,3-dihydrobenzo [*d*]isothiazole 1,1-dioxide



2,3-dihydro-1*H*-indenyl

Aryl, heteroaryl and heteroalicyclic moieties described herein as optionally substituted may be substituted by one or more substituent groups, which are selected independently unless otherwise indicated. The total number of substituent groups may equal the total number of hydrogen atoms on the aryl, heteroaryl or heterocyclyl moiety, to the extent such substitution makes chemical sense and aromaticity is maintained in the case of aryl and heteroaryl rings. Optionally substituted aryl, heteroaryl or heterocyclyl groups typically contain from 1 to 5 optional substituents, sometimes 1 to 4 optional substituents, preferably 1 to 3 optional substituents, or more preferably from 1 to 2 optional substituents.

An "arylene" as used herein refers to a bivalent radical derived from an aromatic hydrocarbon by removal of a hydrogen atom from each of two carbon atoms of the nucleus. In frequent embodiments, the arylene ring is a 1,2-disubstituted or a 1,3--disubstituted arylene. The aryl ring of the arylene moiety may be optionally substituted on open valence positions with groups suitable for an aryl ring, to the extent such substitution is indicated. Preferably, the arylene ring is a C_6-C_{12} arylene ring, for example a 1,2-phenylene or 1,3-phenylene moiety.

Similarly, a "heteroarylene" as used herein refers to a bivalent radical derived from a heteroaromatic ring by removal of a hydrogen atom from each of two carbon or nitrogen atoms of the nucleus. In frequent embodiments, the heteroarylene ring is a 1,2- disubstituted or a 1,3-disubstituted heteroarylene. The heteroaryl ring of the heteroarylene moiety is optionally substituted with groups suitable for an heteroaryl ring, to the extent such substitution is indicated. Preferably, the heteroarylene ring is a 5-12 membered heteroarylene ring, more preferably a 5-6 membered heteroarylene ring, each of which may be optionally substituted.

Optional substituent groups suitable for aryl, heteroaryl and heteroalicyclic rings include, but are not limited to: C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{12} aryl and 5-12 membered heteroaryl; and halo, =O, -CN, $-C(O)R^x$, $-CO_2R^x$, $-C(O)NR^xR^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-SO_2NR^xR^y$, $-NO_2$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(O)NR^xR^y$, $-NR^xC(O)OR^x$, $-NR^xSO_2R^y$, $-NR^xSO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$ and $-OC(O)NR^xR^y$; where each R^x and R^y is independently H, C_1-C_8 alkyl, C_1-C_8 acyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{12} aryl, or 5-12 membered heteroaryl, or R^x and R^y may be taken together with the N atom to which they are attached to form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl, each optionally containing 1, 2 or 3 additional heteroatoms selected from O, N and S; each R^x and R^y is optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, =O, =S, =N-CN, =N-OR', =NR', -CN, -C(O)R', $-CO_2R'$, $-C(O)NR'_2$, -SR', -SOR', $-SO_2R'$, $-SO_2NR'_2$, $-NO_2$, $-NR'_2$, $-NR'C(O)R'$, $-NR'C(O)NR'_2$, $-NR'C(O)OR'$, $-NR'SO_2R'$, $-NR'SO_2NR'_2$, -OR', -OC(O)R' and $-OC(O)NR'_2$, wherein each R' is independently H, C_1-C_8 alkyl, C_1-C_8 acyl, C_2-C_8 alkenyl, C_2-C_8

alkynyl, C_3-C_8 cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{12} aryl, or 5-12 membered heteroaryl; and each said C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{12} aryl and 5-12 membered heteroaryl is optionally substituted as further defined herein.

In typical embodiments, optional substitution on aryl, heteroaryl and heteroalicyclic rings includes one or more substituents, and preferably 1 to 3 substituents, independently selected from the group consisting of halo, C_1-C_8 alkyl, -OH, C_1-C_8 alkoxy, -CN, =O, $-C(O)R^x$, $-COOR^x$, $-OC(O)R^x$, $-C(O)NR^xR^y$, $-NR^xC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-SO_2NR^xR^y$, $-NO_2$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(O)NR^xR^y$, $-NR^xC(O)OR^y$ $-NR^xSO_2R^y$, $-NR^xSO_2NR^xR^y$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, C_3-C_8 cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{12} aryl, 5-12 membered heteroaryl, -O-(C_3-C_8 cycloalkyl),-O-(3-12 membered heterocyclyl), -O-(C_6-C_{12} aryl) and –O-(5-12 membered heteroaryl); where each R^x and R^y is independently H or C_1-C_4 alkyl, or R^x and R^y may be taken together with the N to which they are attached form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl ring, each optionally containing 1, 2 or 3 additional heteroatoms selected from O, N and S; and wherein each said C_1-C_8 alkyl, C_1-C_8 alkoxy, C_3-C_8 cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{12} aryl, 5-12 membered heteroaryl, -O-(C_3-C_8 cycloalkyl),-O-(3-12 membered heterocyclyl), -O-(C_6-C_{12} aryl) and –O-(5-12 membered heteroaryl) that is described as an optional substituent or is part of R^x or R^y is optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo, -OH, =O, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_4 alkoxy-C_1-C_6 alkyl, -CN, $-NH_2$, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$ and N-pyrrolidinyl.

"Cycloalkyl" refers to a non-aromatic, saturated or partially unsaturated carbocyclic ring system containing the specified number of carbon atoms, which may be a monocyclic, bridged or fused bicyclic or polycyclic ring system that is connected to the base molecule through a carbon atom of the cycloalkyl ring. Typically, the cycloalkyl groups of the invention contain 3 to 12 carbon atoms ("C_3-C_{12} cycloalkyl"), preferably 3 to 8 carbon atoms ("C_3-C_8 cycloalkyl"). Representative examples include, e.g., cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cyclohexadiene, cycloheptane, cycloheptatriene, adamantane, and the like. Cycloalkyl groups may be unsubstituted or substituted by the same groups that are described herein as suitable for alkyl. As used herein, "C_3-C_6 cycloalkyl" refers to an all-carbon, monocyclic or fused-ring polycyclic group of 3 to 6 carbon atoms.

"Cycloalkylalkyl" may be used to describe a cycloalkyl ring, typically a C_3-C_8 cycloalkyl, which is connected to the base molecule through an alkylene linker, typically a C_1-C_4 alkylene. Cycloalkylalkyl groups are described by the total number of carbon atoms in the carbocyclic ring and linker, and typically contain from 4-12 carbon atoms ("C_4-C_{12} cycloalkylalkyl"). Thus a

cyclopropylmethyl group is a C_4-cycloalkylalkyl group and a cyclohexylethyl is a C_8-cycloalkylalkyl. Cycloalkylalkyl groups may be unsubstituted or substituted on the cycloalkyl and/or alkylene portions by the same groups that are described herein as suitable for alkyl groups.

An "arylalkyl" group refers to an aryl group as described herein which is linked to the base molecule through an alkylene or similar linker. Arylalkyl groups are described by the total number of carbon atoms in the ring and linker. Thus a benzyl group is a C_7-arylalkyl group and a phenylethyl is a C_8-arylalkyl. Typically, arylalkyl groups contain 7-16 carbon atoms ("C_7-C_{16} arylalkyl"), wherein the aryl portion contains 6-12 carbon atoms and the alkylene portion contains 1-4 carbon atoms. Such groups may also be represented as -C_1-C_4 alkylene-C_6-C_{12} aryl.

"Heteroarylalkyl" refers to a heteroaryl group as described above that is attached to the base molecule through an alkylene linker, and differs from "arylalkyl" in that at least one ring atom of the aromatic moiety is a heteroatom selected from N, O and S. Heteroarylalkyl groups are sometimes described herein according to the total number of non-hydrogen atoms (i.e., C, N, S and O atoms) in the ring and linker combined, excluding substituent groups. Thus, for example, pyridinylmethyl may be referred to as a "C_7"-heteroarylalkyl. Typically, unsubstituted heteroarylalkyl groups contain 6-20 non-hydrogen atoms (including C, N, S and O atoms), wherein the heteroaryl portion typically contains 5-12 atoms and the alkylene portion typically contains 1-4 carbon atoms. Such groups may also be represented as -C_1-C_4 alkylene-5-12 membered heteroaryl.

Similarly, "arylalkoxy" and "heteroarylalkoxy" refer to aryl and heteroaryl groups, attached to the base molecule through a heteroalkylene linker (i.e., -O-alkylene-), wherein the groups are described according to the total number of non-hydrogen atoms (i.e., C, N, S and O atoms) in the ring and linker combined. Thus, -O-CH_2-phenyl and –O-CH_2-pyridinyl groups would be referred to as C_8-arylalkoxy and C_8-heteroarylalkoxy groups, respectively.

Where an arylalkyl, arylalkoxy, heteroarylalkyl or heteroarylalkoxy group is described as optionally substituted, the substituents may be on either the divalent linker portion or on the aryl or heteroaryl portion of the group. The substituents optionally present on the alkylene or heteroalkylene portion are the same as those described above for alkyl or alkoxy groups generally, while the substituents optionally present on the aryl or heteroaryl portion are the same as those described above for aryl or heteroaryl groups generally.

"Hydroxy" refers to an -OH group.

"Acyloxy" refers to a monovalent group –OC(O)alkyl, wherein the alkyl portion has the specified number of carbon atoms (typically C_1-C_8, preferably C_1-C_6 or C_1-C_4) and may be

optionally substituted by groups suitable for alkyl. Thus, C_1-C_4 acyloxy includes an –OC(O)C_1-C_4 alkyl substituent, e.g., -OC(O)CH_3.

“Acylamino” refers to a monovalent group, -NHC(O)alkyl or –NRC(O)alkyl, wherein the alkyl portion has the specified number of carbon atoms (typically C_1-C_8, preferably C_1-C_6 or C_1-C_4) and may be optionally substituted by groups suitable for alkyl. Thus, C_1-C_4 acylamino includes an –NHC(O)C_1-C_4 alkyl substituent, e.g., -NHC(O)CH_3.

“Aryloxy” or “heteroaryloxy” refer to optionally substituted –O-aryl or –O-heteroaryl, in each case where aryl and heteroaryl are as further defined herein.

“Arylamino” or “heteroarylamino” refer to optionally substituted –NH-aryl, -NR-aryl, –NH-heteroaryl or –NR-heteroaryl, in each case where aryl and heteroaryl are as further defined herein and R represents a substituent suitable for an amine, e.g., an alkyl, acyl, carbamoyl or sulfonyl group, or the like.

"Cyano" refers to a -C≡N group.

"Unsubstituted amino" refers to a group $–NH_2$. Where the amino is described as substituted or optionally substituted, the term includes groups of the form $–NR^xR^y$, where each or R^x and R^y is independently H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, acyl, thioacyl, aryl, heteroaryl, cycloalkylalkyl, arylalkyl or heteroarylalkyl, in each case having the specified number of atoms and optionally substituted as described herein. For example, “alkylamino” refers to a group $–NR^xR^y$, wherein one of R^x and R^y is an alkyl moiety and the other is H, and “dialkylamino” refers to $–NR^xR^y$ wherein both of R^x and R^y are alkyl moieties, where the alkyl moieties having the specified number of carbon atoms (e.g., –NH-C_1-C_4 alkyl or –N(C_1-C_4 alkyl)$_2$). Typically, alkyl substituents on amines contain 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms, or more preferably 1 to 4 carbon atoms. The term also includes forms wherein R^x and R^y are taken together with the N atom to which they are attached to form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl ring, each of which may itself be optionally substituted as described herein for heterocyclyl or heteroaryl rings, and which may contain 1 to 3 additional heteroatoms selected from N, O and S as ring members, provided that such rings do not contain two contiguous oxygen atoms.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and the description includes instances where the event or circumstance occurs and instances in which it does not.

The terms “optionally substituted” and “substituted or unsubstituted” may be used interchangeably to indicate that the particular group being described may have no non-hydrogen substituents (i.e., unsubstituted), or the group may have one or more non-hydrogen substituents (i.e., substituted). If not otherwise specified, the total number of substituents that may be

present is equal to the number of H atoms present on the unsubstituted form of the group being described, to the extent that such substitution makes chemical sense. Where an optional substituent is attached via a double bond, such as an oxo (=O) substituent, the group occupies two available valences, so the total number of other substituents that may be included is reduced by two. In the case where optional substituents are selected independently from a list of alternatives, the selected groups may be the same or different.

A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof as an active ingredient, and at least one pharmaceutically acceptable carrier or excipient. The purpose of a pharmaceutical composition is to facilitate administration of a compound to a mammal.

In one aspect, the invention provides a pharmaceutical composition comprising a compound of one of the formulae described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical composition comprises two or more pharmaceutically acceptable carriers and/or excipients.

In some embodiments, the pharmaceutical composition further comprises at least one additional an anti-cancer therapeutic agent or a palliative agent. In some such embodiments, the at least one additional medicinal or pharmaceutical agent is an anti-cancer agent as described below. In some such embodiments, the combination provides an additive, greater than additive, or synergistic anti-cancer effect. In some such embodiments, the one or more additional anti-cancer therapeutic agent is selected from the group consisting of anti-tumor agents, anti-angiogenesis agents, signal transduction inhibitors and antiproliferative agents.

In one aspect, the invention provides a method for the treatment of abnormal cell growth in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for the treatment of abnormal cell growth in a mammal comprising administering to the mammal an amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with an amount of an anti-tumor agent, which amounts are together effective in treating said abnormal cell growth. In some embodiments, the anti-tumor agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

In frequent embodiments of the methods provided herein, the abnormal cell growth is cancer. In some embodiments, the methods provided result in one or more of the following effects: (1) inhibiting cancer cell proliferation; (2) inhibiting cancer cell invasiveness; (3) inducing apoptosis of cancer cells; (4) inhibiting cancer cell metastasis; or (5) inhibiting angiogenesis.

In another aspect, the invention provides a method for the treatment of a disorder mediated by ALK or by an EML4-ALK fusion protein in a mammal, comprising administering to the mammal a compound of the invention, or a pharmaceutically acceptable salt thereof, in an amount that is effective for treating said disorder. In some such embodiments, the EML4-ALK fusion protein has at least one mutation.

The term "mammal" as used herein refers to a human or a non-human animal classified as a mammal. More particularly, the term mammal includes humans, domestic and farm animals, and research, zoo, sports and companion animals, such as household pets and other domesticated animals including, but not limited to, cattle, sheep, ferrets, swine, horses, rabbits, goats, dogs, cats, and the like. In frequent embodiments, the mammal is a human. In some embodiments, the term "subject" may be used to refer to a human. In some other embodiments, the mammal is a dog or cat.

The ALK fusion proteins of particular interest for the present invention are the mutated forms of EML4-ALK. Of particular interest are compounds capable of inhibiting the L1196M mutant EML4-ALK fusion protein and the C1156Y mutant EML4-ALK fusion protein.

The compounds, compositions and methods provided herein are useful for the treatment of cancers including but not limited to cancers of the circulatory system, respiratory tract, gastrointestinal system, genitourinary tract, liver, bone, nervous system, reproductive system, hematologic system, oral cavity, skin, adrenal glands, and other tissues including connective and soft tissue, retroperitoneum and peritoneum, eye, intraocular melanoma, and adnexa, breast, head or/and neck, anal region, thyroid, parathyroid, adrenal gland and other endocrine glands and related structures, secondary and unspecified malignant neoplasm of lymph nodes, secondary malignant neoplasm of respiratory and digestive systems and secondary malignant neoplasm of other sites.

More specifically, examples of cancer when used herein in connection with the present invention include cancer selected from lung cancer, preferably non small cell lung carcinoma (NSCLC), lymphoma, preferably Anaplastic large cells lymphoma, neuroblastoma or soft tissue cancer such as inflammatory myofibroblastic tumor.

Unless indicated otherwise, all references herein to the inventive compounds include references to salts, solvates, hydrates and complexes thereof, and to solvates, hydrates and

complexes of salts thereof, including polymorphs, stereoisomers, and isotopically labeled versions thereof.

Compounds of the invention may exist in the form of pharmaceutically acceptable salts such as, e.g., acid addition salts and base addition salts of the compounds of one of the formulae provided herein. As used herein, the term "pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the parent compound. The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the formulae disclosed herein.

For example, the compounds of the invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to mammals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention can be prepared by treating the base compound with a substantially equivalent amount of the selected mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding an appropriate mineral or organic acid to the solution.

The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Examples of salts include, but are not limited to, acetate, acrylate, benzenesulfonate, benzoate (such as chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, and methoxybenzoate), bicarbonate, bisulfate, bisulfite, bitartrate, borate, bromide, butyne-1,4-dioate, calcium edetate, camsylate, carbonate, chloride, caproate, caprylate, clavulanate, citrate, decanoate, dihydrochloride, dihydrogenphosphate, edetate, edislyate, estolate, esylate,

ethylsuccinate, formate, fumarate, gluceptate, gluconate, glutamate, glycollate, glycollylarsanilate, heptanoate, hexyne-1,6-dioate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, γ-hydroxybutyrate, iodide, isobutyrate, isothionate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, mesylate, metaphosphate, methane-sulfonate, methylsulfate, monohydrogenphosphate, mucate, napsylate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phenylacetates, phenylbutyrate, phenylpropionate, phthalate, phospate/diphosphate, polygalacturonate, propanesulfonate, propionate, propiolate, pyrophosphate, pyrosulfate, salicylate, stearate, subacetate, suberate, succinate, sulfate, sulfonate, sulfite, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

The compounds of the invention that include a basic moiety, such as an amino group, may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

Those compounds of the invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds herein. These salts may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. These salts can also be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of the compounds of the invention that are acidic in nature are those that

form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to, those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium 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).

Salts of the present invention can be prepared according to methods known to those of skill in the art. A pharmaceutically acceptable salt of the inventive compounds can be readily prepared by mixing together solutions of the compound 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 ionization in the salt may vary from completely ionized to almost non-ionized.

It will be understood by those of skill in the art that the compounds of the invention in free base form having a basic functionality may be converted to the acid addition salts by treating with a stoichiometric excess of the appropriate acid. The acid addition salts of the compounds of the invention may be reconverted to the corresponding free base by treating with a stoichiometric excess of a suitable base, such as potassium carbonate or sodium hydroxide, typically in the presence of aqueous solvent, and at a temperature of between about 0° C. and 100° C. The free base form may be isolated by conventional means, such as extraction with an organic solvent. In addition, acid addition salts of the compounds of the invention may be interchanged by taking advantage of differential solubilities of the salts, volatilities or acidities of the acids, or by treating with the appropriately loaded ion exchange resin. For example, the interchange may be affected by the reaction of a salt of the compounds of the invention with a slight stoichiometric excess of an acid of a lower pK than the acid component of the starting salt. This conversion is typically carried out at a temperature between about 0°C and the boiling point of the solvent being used as the medium for the procedure. Similar exchanges are possible with base addition salts, typically via the intermediacy of the free base form.

Pharmaceutically acceptable salts of compounds of the inventionmay be prepared by one or more of the following methods:

(i) by reacting the compound of the invention with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of the invention or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of the invention to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in both unsolvated and solvated forms. When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when the solvent is water. Pharmaceutically acceptable solvates in accordance with the invention include hydrates and solvates wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, d_6-DMSO.

Also included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see Haleblian, *J. Pharm. Sci.*,1975, 64 (8):1269-1288, the disclosure of which is incorporated herein by reference in its entirety.

Hereinafter all references to compounds of the invention include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The compounds of the invention include compounds of the invention as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of the invention.

The invention also relates to prodrugs of the compounds of the formulae provided herein. Thus, certain derivatives of compounds of the invention which may have little or no pharmacological activity themselves can, when administered to a patient, be converted into the inventive compounds, for example, by hydrolytic cleavage. Such derivatives are referred to as

'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association), the disclosures of which are incorporated herein by reference in their entireties.

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the inventive compounds with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985), the disclosure of which is incorporated herein by reference in its entirety.

Some non-limiting examples of prodrugs in accordance with the invention include:

(i) where the compound contains a carboxylic acid functionality (-COOH), an ester thereof, for example, replacement of the hydrogen with (C_1-C_8)alkyl;

(ii) where the compound contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C_1-C_6)alkanoyloxymethyl; and

(iii) where the compound contains a primary or secondary amino functionality (-NH_2 or -NHR where R ≠ H), an amide thereof, for example, replacement of one or both hydrogens with a suitably metabolically labile group, such as an amide, carbamate, urea, phosphonate, sulfonate, etc..

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Finally, certain inventive compounds may themselves act as prodrugs of other of the inventive compounds.

Also included within the scope of the invention are metabolites of compounds of the invention, that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include

(i) where the compound of the invention contains a methyl group, an hydroxymethyl derivative thereof (-CH_3 → -CH_2OH):

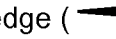
(ii) where the compound of the invention contains an alkoxy group, an hydroxy derivative thereof (-OR → -OH);

(iii) where the compound of the invention contains a tertiary amino group, a secondary amino derivative thereof (-NR^1R^2 → -NHR^1 or -NHR^2);

(iv) where the compound of the invention contains a secondary amino group, a primary derivative thereof (-NHR^1 → -NH_2);

(v) where the compound of the invention contains a phenyl moiety, a phenol derivative thereof (-Ph → -PhOH); and

(vi) where the compound of the invention contains an amide group, a carboxylic acid derivative thereof (-$CONH_2$ → COOH).

The compounds of the formulae provided herein may have asymmetric carbon atoms. The carbon-carbon bonds of the compounds of the invention may be depicted herein using a solid line (———), a solid wedge (), or a dotted wedge (). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers (e.g. specific enantiomers, racemic mixtures, etc.) at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds to asymmetric carbon atoms is meant to indicate that only the stereoisomer shown is meant to be included. It is possible that compounds of the invention may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included. For example, unless stated otherwise, it is intended that the compounds of the invention can exist as enantiomers and diastereomers or as racemates and mixtures thereof. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of the invention and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present.

Compounds of the invention containing one or more asymmetric carbon atoms can exist as two or more stereoisomers, such as racemates, enantiomers, or diastereomers. Stereoisomers of the compounds of the formulae herein can include cis and trans isomers, optical isomers such as (R) and (S) enantiomers, diastereomers, geometric isomers, rotational isomers, atropisomers, conformational isomers, and tautomers of the compounds of the invention, including compounds exhibiting more than one type of isomerism; and mixtures thereof (such as racemates and diastereomeric pairs). 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.

When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

The compounds of the invention may exhibit the phenomena of tautomerism and structural isomerism. For example, the compounds may exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of compounds of the

invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the compounds of the formulae provided.

In addition, some of the compounds of the invention may form atropisomers (e.g., substituted biaryls). Atropisomers are conformational stereoisomers which occur when rotation about a single bond in the molecule is prevented, or greatly slowed, as a result of steric interactions with other parts of the molecule and the substituents at both ends ofthe single bond are unsymmetrical. The interconversion of atropisomers is slow enough to allow separation and isolation under predetermined conditions. The energy barrier to thermal racemization may be determined by the steric hindrance to free rotation of one or more bonds forming a chiral axis.

Where a compound of the invention contains an alkenyl or alkenylene group, geometric *cis*/*trans* (or Z/E) isomers are possible. Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

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 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 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 one skilled in the art.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin 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.

Stereoisomeric conglomerates 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 disclosure of which is incorporated herein by reference in its entirety.

“Enantiomerically pure” as used herein, describes a compound that is present as a single enentiomer and which is described in terms of enantiomeric excess (e.e.). Preferably, wherein

the compound is present as an enantiomer, the enantiomer is present at an enantiomeric excess of greater than or equal to about 80%, more preferably, at an enantiomeric excess of greater than or equal to about 90%, more preferably still, at an enantiomeric excess of greater than or equal to about 95%, more preferably still, at an enantiomeric excess of greater than or equal to about 98%, most preferably, at an enantiomeric excess of greater than or equal to about 99%. Similarly, "diastereomerically pure" as used herein, describes a compound that is present as a diastereomer and which is described in terms of diasteriomeric excess (d.e.). Preferably, wherein the compound is present as a diastereomer, the diastereomer is present at an diastereomeric excess of greater than or equal to about 80%, more preferably, at an diastereomeric excess of greater than or equal to about 90%, more preferably still, at an diastereomeric excess of greater than or equal to about 95%, more preferably still, at an diastereomeric excess of greater than or equal to about 98%, most preferably, at an diastereomeric excess of greater than or equal to about 99%.

The present invention also includes isotopically-labeled compounds, which are identical to those recited in one of the formulae provided, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

Examples of isotopes that may be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as, but not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl. Certain isotopically-labeled compounds of the invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can 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. Isotopically-labeled compounds of the invention may generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting an isotopically-labeled reagent for a non-isotopically-labeled reagent. Pharmaceutically acceptable solvates in accordance with the

invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products, or mixtures thereof. 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.

Therapeutic Methods and Uses

The invention further provides therapeutic methods and uses comprising administering the compounds of the invention, or pharmaceutically acceptable salts thereof, alone or in combination with other therapeutic agents or palliative agents.

In one aspect, the invention provides a method for the treatment of abnormal cell growth in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for the treatment of abnormal cell growth in a mammal comprising administering to the mammal an amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with an amount of an anti-tumor agent, which amounts are together effective in treating said abnormal cell growth. In some such embodiments, the anti-tumor agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

Compounds of the invention include compounds of any of the formulae described herein, including formulae (Φ) and (I)-(XXX), or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for the treatment of abnormal cell growth in a mammal comprising administering to the mammal an amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, that is effective in treating abnormal cell growth.

In still another aspect, the invention provides a method of inhibiting cancer cell proliferation in a mammal, comprising administering to the mammal a compound of the invention, or pharmaceutically acceptable salt thereof, in an amount effective to inhibit cell proliferation.

In another aspect, the invention provides a method of inhibiting cancer cell invasiveness in a mammal, comprising administering to the mammal a compound of the invention, or pharmaceutically acceptable salt thereof, in an amount effective to inhibit cell invasiveness.

In another aspect, the invention provides a method of inducing apoptosis in cancer cells in a mammal, comprising administering to the mammal a compound of the invention, or pharmaceutically acceptable salt thereof, in an amount effective to induce apoptosis.

In a further aspect, the invention provides a method of inducing apoptosis in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of one of the formulae described herein, or pharmaceutically acceptable salt thereof.

In frequent embodiments of the methods provided herein, the abnormal cell growth is cancer, wherein said cancer is selected from the group consisting of basal cell cancer, medulloblastoma cancer, liver cancer, rhabdomyosarcoma, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers.

The compounds of the invention, their pharmaceutically acceptable salts and/or derived forms or composition thereof, are valuable pharmaceutically active compounds, which are suitable for the therapy of numerous disorders in which ALK receptor and/or an ALK fusion protein, e.g., EML4-ALK, is involved or in which inhibition of ALK activity may induce benefit, in particular, cancer.

A further aspect of the invention relates to a compound of the invention, or pharmaceutically acceptable salts, derived forms or compositions thereof, for use as a medicament, and in particular for use in the treatment of diseases where the inhibition of ALK and/or an ALK fusion protein, e.g., EML4-ALK, activity may induce benefit, such as cancer.

A still further aspect of the present invention also relates to the use of the compounds of the invention, or pharmaceutically acceptable salts, derived forms or compositions thereof, for the manufacture of a drug having an ALK inhibitory activity for the treatment of ALK-mediated diseases and/or conditions, in particular the diseases and/or conditions listed above.

A another aspect of the present invention also relates to the use of the compounds of the invention, or pharmaceutically acceptable salts, derived forms or compositions thereof, for the

manufacture of a drug having an EML4-ALK inhibitory activity for the treatment of EML4-ALK mediated diseases and/or conditions, in particular the diseases and/or conditions listed above.

The compounds of the invention, their pharmaceutically acceptable salts and/or derived forms or composition thereof, are valuable pharmaceutically active compounds, which are suitable for the treatment of pain, including acute pain; chronic pain; neuropathic pain; inflammatory pain (including e.g. osteoarthritis pain, rheumatoid arthritis pain); visceral pain; nociceptive pain including post-surgical pain; and mixed pain types involving the viscera, gastrointestinal tract, cranial structures, musculoskeletal system, spine, urogenital system, cardiovascular system and CNS, including cancer pain, back and orofacial pain.

A further aspect of the invention relates to a compound of the invention, or pharmaceutically acceptable salts, derived forms or compositions thereof, for use as a medicament, and in particular for use in the treatment of pain, including acute pain; chronic pain; neuropathic pain; inflammatory pain (including e.g. osteoarthritis pain, rheumatoid arthritis pain); visceral pain; nociceptive pain including post-surgical pain; and mixed pain types involving the viscera, gastrointestinal tract, cranial structures, musculoskeletal system, spine, urogenital system, cardiovascular system and CNS, including cancer pain, back and orofacial pain.

A still further aspect of the present invention also relates to the use of the compounds of the invention, or pharmaceutically acceptable salts, derived forms or compositions thereof, for the manufacture of a drug for treatment of the diseases and/or conditions listed above.

As a consequence, the present invention provides a method to treat a mammal, including a human, with a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt, derived form or pharmaceutical composition thereof. More precisely, the present invention provides a method for the treatment of ALK-mediated cancers in a mammal, including a human, in particular the cancers listed above, comprising administering said mammal with a therapeutically effective amount of a compound of the invention, its pharmaceutically acceptable salts and/or derived forms, or a pharmaceutical composition thereof.

Another embodiment of the present invention of particular interest relates to a method for the treatment of lung cancer in a human in need of such treatment, comprising administering to said human an amount of a compound of the invention, in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of capecitabine, bevacizumab, gemcitabine, docetaxel, paclitaxel, premetrexed disodium, erlotinib, gefitinib, vinorelbine, irinotecan, etoposide, vinblastine, and carboplatin, wherein the amounts of the active agent together with the amounts of the combination anticancer agents is effective in treating lung cancer.

Preferably, the compounds of the invention are selective ALK inhibitors. Preferably, the compounds of the invention are selective inhibitors of the EML4-ALK mutant L1196M. Preferably, the compounds of the invention are selective inhibitors of the EML4-ALK mutant C1156Y.

The term "therapeutically effective amount" as used herein refers to that amount of a compound being administered which will relieve to some extent one or more of the symptoms of the disorder being treated. In reference to the treatment of cancer, a therapeutically effective amount refers to that amount which has the effect of (1) reducing the size of the tumor, (2) inhibiting (that is, slowing to some extent, preferably stopping) tumor metastasis, (3) inhibiting to some extent (that is, slowing to some extent, preferably stopping) tumor growth or tumor invasiveness, and/or (4) relieving to some extent (or, preferably, eliminating) one or more signs or symptoms associated with the cancer.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above. The term “treating” also includes adjuvant and neo-adjuvant treatment of a mammal.

The terms “abnormal cell growth” and “hyperproliferative disorder” are used interchangeably in this application.

“Abnormal cell growth”, as used herein, unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). Abnormal cell growth may be benign (not cancerous), or malignant (cancerous). This includes the abnormal growth of: (1) tumor cells (tumors) that proliferate by expressing ALK or an ALK fusion protein, e.g., EML4-ALK; (2) benign and malignant cells of other proliferative diseases in which ALK or an ALK fusion protein occurs; (3) any tumors that proliferate by aberrant ALK or ALK fusion protein activation; and (4) benign and malignant cells of other proliferative diseases in which aberrant ALK or ALK fusion protein activation occurs.

As used herein “cancer” refers to any malignant and/or invasive growth or tumor caused by abnormal cell growth, including solid tumors named for the type of cells that form them, cancer of blood, bone marrow, or the lymphatic system. Examples of solid tumors include but not limited to sarcomas and carcinomas. Examples of cancers of the blood include but not limited to leukemias, lymphomas and myeloma. The term “cancer” includes but is not limited to a primary cancer that originates at a specific site in the body, a metastatic cancer that has spread from the place in which it started to other parts of the body, a recurrence from the

original primary cancer after remission, and a second primary cancer that is a new primary cancer in a person with a history of previous cancer of different type from latter one.

The compounds of the invention inhibit ALK, and thus are all adapted to therapeutic use as antiproliferative agents (e.g., cancer) or antitumor agent (e.g., effect against solid tumors) in mammals, particularly in humans. In particular, the compounds of the invention are useful in the prevention and treatment of a variety of human hyperproliferative disorders including both malignant and benign abnormal cell growth.

The compounds, compositions and methods provided herein are useful for the treatment of cancers including but not limited to cancers of the:

circulatory system, for example, heart (sarcoma [angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma], myxoma, rhabdomyoma, fibroma, lipoma and teratoma), mediastinum and pleura, and other intrathoracic organs, vascular tumors and tumor-associated vascular tissue;

respiratory tract, for example, nasal cavity and middle ear, accessory sinuses, larynx, trachea, bronchus and lung such as small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma;

gastrointestinal system, for example, esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), gastric, pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma);

genitourinary tract, for example, kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and/or urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma);

liver, for example, hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, pancreatic endocrine tumors (such as pheochromocytoma, insulinoma, vasoactive intestinal peptide tumor, islet cell tumor and glucagonoma);

bone, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma),

multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors;

nervous system, for example, neoplasms of the central nervous system (CNS), primary CNS lymphoma, skull cancer (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain cancer (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma);

reproductive system, for example, gynecological, uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma) and other sites associated with female genital organs; placenta, penis, prostate, testis, and other sites associated with male genital organs;

hematologic system, for example, blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma];

oral cavity, for example, lip, tongue, gum, floor of mouth, palate, and other parts of mouth, parotid gland, and other parts of the salivary glands, tonsil, oropharynx, nasopharynx, pyriform sinus, hypopharynx, and other sites in the lip, oral cavity and pharynx;

skin, for example, malignant melanoma, cutaneous melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, and keloids;

adrenal glands: neuroblastoma; and

other tissues including connective and soft tissue, retroperitoneum and peritoneum, eye, intraocular melanoma, and adnexa, breast, head or/and neck, anal region, thyroid, parathyroid, adrenal gland and other endocrine glands and related structures, secondary and unspecified malignant neoplasm of lymph nodes, secondary malignant neoplasm of respiratory and digestive systems and secondary malignant neoplasm of other sites.

More specifically, examples of cancer when used herein in connection with the present invention include cancer selected from lung cancer (NSCLC and SCLC), cancer of the head or

neck, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, breast cancer, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, non-Hodgkins's lymphoma, spinal axis tumors, or a combination of one or more of the foregoing cancers .

Still more specifically, examples of cancer when used herein in connection with the present invention include cancer selected from lung cancer (NSCLC and SCLC), breast cancer, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, or a combination of one or more of the foregoing cancers.

In one embodiment of the present invention the non-cancerous conditions include such hyperplastic conditions such as benign hyperplasia of the skin (e.g., psoriasis) and benign hyperplasia of the prostate (e.g., BPH).

In another aspect, the invention provides a method for inhibiting cell proliferation, comprising contacting cells with a compound of the invention or a pharmaceutically acceptable salt thereof in an amount effective to inhibit proliferation of the cells.

In another aspect, the invention provides methods for inducing cell apoptosis, comprising contacting cells with a compound described herein in an amount effective to induce apoptosis of the cells.

"Contacting" refers to bringing a compound or pharmaceutically acceptable salt of the invention and a cell expressing ALK together in such a manner that the compound can affect the activity of ALK, either directly or indirectly. Contacting can be accomplished *in vitro* (i.e., in an artificial environment such as, e.g., without limitation, in a test tube or culture medium) or *in vivo* (i.e., within a living organism such as, without limitation, a mouse, rat or rabbit.)

In some embodiments, the cells are in a cell line, such as a cancer cell line. In other embodiments, the cells are in a tissue or tumor, and the tissue or tumor may be in a mammal, including a human.

Dosage Forms and Regimens

Administration of the compounds of the invention may be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration.

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 mammals 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 mammal, 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 regimens 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.

The amount of the compound of the invention administered will be dependent on the mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to about 7 g/day, preferably about 0.1 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than

adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

Formulations and Routes of Administration

As used herein, a "pharmaceutically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

The pharmaceutical acceptable carrier may comprise any conventional pharmaceutical carrier or excipient. The choice of carrier and/or 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.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents (such as hydrates and solvates). 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. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols. 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. Non-limiting examples of materials, therefore, 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.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution suspension, 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.

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 may be suitably buffered, if desired.

The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages.

Pharmaceutical compositions suitable for the delivery of compounds of the invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation can be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995), the disclosure of which is incorporated herein by reference in its entirety.

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 used as fillers in soft or hard capsules and typically include 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), the disclosure of which is incorporated herein by reference in its entirety.

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% 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, pregelatinized starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% 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, pregelatinized 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 include surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents are typically in amounts of from 0.2 wt% to 5 wt% of the tablet, and glidants typically from 0.2 wt% to 1 wt% 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 are present in amounts from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other conventional ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80 wt% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

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 include one or more layers and may be coated or uncoated; or encapsulated.

The formulation of tablets is discussed in detail 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 disclosure of which is incorporated herein by reference in its entirety.

Solid formulations for oral administration 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 are described in U.S. Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles can 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. The disclosures of these references are incorporated herein by reference in their entireties.

Parenteral Administration

The compounds of the invention may also 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 micro needle) 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 lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of the invention 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. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds 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. Examples of such formulations include drug-coated stents and PGLA microspheres.

The compounds 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, fibers, 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, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and micro needle or needle-free (e.g. Powderject™, Bioject™, etc.) injection. The disclosures of these references are incorporated herein by reference in their entireties.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention can 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 pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, 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 include a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurized container, pump, spray, atomizer, or nebulizer contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, 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 micronized 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 homogenization, 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 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 atomizer using electrohydrodynamics to produce a fine mist may contain from 1μg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1μL to 100μL. A typical formulation includes a compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavors, 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 means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing a desired mount of the compound of the invention. The overall daily dose may be administered in a single dose or, more usually, as divided doses throughout the day.

Compounds 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 alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronized 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.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

Other Technologies

Compounds 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 solubilizer. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in PCT

Publication Nos. WO 91/11172, WO 94/02518 and WO 98/55148, the disclosures of which are incorporated herein by reference in their entireties.

Dosage

The amount of the active compound administered will be dependent on the mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is typically in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 0.01 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.07 to about 7000 mg/day, preferably about 0.7 to about 2500 mg/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be used without causing any harmful side effect, with such larger doses typically divided into several smaller doses for administration throughout the day. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein. 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.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus the kit of the invention includes two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically includes directions for administration and may be provided with a memory aid.

Combination Therapy

As used herein, the term “combination therapy” refers to the administration of a compound of the invention together with an at least one additional pharmaceutical or medicinal agent (e.g., an anti-cancer agent), either sequentially or simultaneously.

As noted above, the compounds of the invention may be used in combination with one or more additional anti-cancer agents which are described below. When a combination therapy is used, the one or more additional anti-cancer agents may be administered sequentially or simultaneously with the compound of the invention. In one embodiment, the additional anti-cancer agent is administered to a mammal (e.g., a human) prior to administration of the compound of the invention. In another embodiment, the additional anti-cancer agent is administered to the mammal after administration of the compound of the invention. In another embodiment, the additional anti-cancer agent is administered to the mammal (e.g., a human) simultaneously with the administration of the compound of the invention.

The invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, which comprises an amount of a compound of the invention, as defined above (including hydrates, solvates and polymorphs of said compound or pharmaceutically acceptable salts thereof), in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of anti-angiogenesis agents and signal transduction inhibitors and a pharmaceutically acceptable carrier, wherein the amounts of the active agent and the combination anti-cancer agents when taken as a whole is therapeutically effective for treating said abnormal cell growth.

In one embodiment of the present invention the anti-cancer agent used in conjunction with a compound of the invention and pharmaceutical compositions described herein is an anti-angiogenesis agent (e.g., an agent that stops tumors from developing new blood vessels). Examples of anti-angiogenesis agents include for example VEGF inhibitors, VEGFR inhibitors, TIE-2 inhibitors, PDGFR inhibitors, angiopoetin inhibitors, PKCβ inhibitors, COX-2 (cyclooxygenase II) inhibitors, integrins (alpha-v/beta-3), MMP-2 (matrix-metalloprotienase 2) inhibitors, and MMP-9 (matrix-metalloprotienase 9) inhibitors.

Preferred anti-angiogenesis agents include sunitinib (Sutent™), bevacizumab (Avastin™), axitinib (AG 13736), SU 14813 (*Pfizer*), and AG 13958 (Pfizer).

Additional anti-angiogenesis agents include vatalanib (CGP 79787), Sorafenib (Nexavar™), pegaptanib octasodium (Macugen™), vandetanib (Zactima™), PF-0337210 (Pfizer), SU 14843 (Pfizer), AZD 2171 (AstraZeneca), ranibizumab (Lucentis™), Neovastat™ (AE 941), tetrathiomolybdata (Coprexa™), AMG 706 (Amgen), VEGF Trap (AVE 0005), CEP 7055 (Sanofi-Aventis), XL 880 (Exelixis), telatinib (BAY 57-9352), and CP-868,596 (Pfizer).

Other anti-angiogenesis agents include enzastaurin (LY 317615), midostaurin (CGP 41251), perifosine (KRX 0401), teprenone (Selbex™) and UCN 01 (Kyowa Hakko).

Other examples of anti-angiogenesis agents which can be used in conjunction with a compound of the invention and pharmaceutical compositions described herein include celecoxib (Celebrex™), parecoxib (Dynastat™), deracoxib (SC 59046), lumiracoxib (Preige™), valdecoxib (Bextra™), rofecoxib (Vioxx™), iguratimod (*Careram*™), IP 751 (Invedus), SC-58125 (Pharmacia) and etoricoxib (Arcoxia™).

Other anti-angiogenesis agents include exisulind (Aptosyn™), salsalate (Amigesic™), diflunisal (Dolobid™), ibuprofen (Motrin™), ketoprofen (Orudis™), nabumetone (Relafen™), piroxicam (Feldene™), naproxen (Aleve™, Naprosyn™), diclofenac (Voltaren™), indomethacin (Indocin™), sulindac (Clinoril™), tolmetin (Tolectin™), etodolac (Lodine™), ketorolac (Toradol™), and oxaprozin (Daypro™).

Other anti-angiogenesis agents include ABT 510 (Abbott), apratastat (TMI 005), AZD 8955 (AstraZeneca), incyclinide (Metastat™), and PCK 3145 (Procyon).

Other anti-angiogenesis agents include acitretin (Neotigason™), plitidepsin (aplidine™), cilengtide (EMD 121974), combretastatin A4 (CA4P), fenretinide (*4 HPR)*, halofuginone (Tempostatin™), Panzem™ (2-methoxyestradiol), PF-03446962 (Pfizer), rebimastat *(BMS 275291),* catumaxomab (Removab™), lenalidomide (Revlimid™), squalamine (EVIZON™), thalidomide (Thalomid™), Ukrain™ (NSC 631570), Vitaxin™ (MEDI 522), and zoledronic acid (Zometa™).

In another embodiment the anti-cancer agent is a so called signal transduction inhibitor (e.g., inhibiting the means by which regulatory molecules that govern the fundamental processes of cell growth, differentiation, and survival communicated within the cell). Signal transduction inhibitors include small molecules, antibodies, and antisense molecules. Signal transduction inhibitors include for example kinase inhibitors (e.g., tyrosine kinase inhibitors or serine/threonine kinase inhibitors) and cell cycle inhibitors. More specifically signal transduction inhibitors include, for example, farnesyl protein transferase inhibitors, EGF inhibitor, ErbB-1 (EGFR), ErbB-2, pan erb, IGF1R inhibitors, MEK, c-Kit inhibitors, FLT-3 inhibitors, K-Ras inhibitors, PI3 kinase inhibitors, JAK inhibitors, STAT inhibitors, Raf kinase inhibitors, Akt inhibitors, mTOR inhibitor, P70S6 kinase inhibitors, inhibitors of the WNT pathway and so called multi-targeted kinase inhibitors.

Preferred signal transduction inhibitors include gefitinib (Iressa™), cetuximab (Erbitux™), erlotinib (Tarceva™), trastuzumab (Herceptin™), sunitinib (Sutent™), imatinib (Gleevec™), and PD325901 (Pfizer).

Additional examples of signal transduction inhibitors which may be used in conjunction with a compound of the invention and pharmaceutical compositions described herein include BMS 214662 (Bristol-Myers Squibb), lonafarnib (Sarasar™), pelitrexol (AG 2037), matuzumab (EMD 7200), nimotuzumab (TheraCIM h-R3™), panitumumab (Vectibix™), Vandetanib (Zactima™), pazopanib (SB 786034), ALT 110 (Alteris Therapeutics), BIBW 2992 (Boehringer Ingelheim),and Cervene™ (TP 38).

Other examples of signal transduction inhibitor include PF-2341066 (Pfizer), PF-299804 (Pfizer), canertinib (CI 1033), pertuzumab (Omnitarg™), Lapatinib (Tycerb™), pelitinib (EKB 569), miltefosine (Miltefosin™), BMS 599626 (Bristol-Myers Squibb), Lapuleucel-T (Neuvenge™), NeuVax™ (E75 cancer vaccine), Osidem™ (IDM 1), mubritinib (TAK-165), CP-724,714 (Pfizer), panitumumab (Vectibix™), lapatinib (Tycerb™), PF-299804 (Pfizer), pelitinib (EKB 569), and pertuzumab (Omnitarg™).

Other examples of signal transduction inhibitors include ARRY 142886 (Array Biopharm), everolimus (Certican™), zotarolimus (Endeavor™), temsirolimus (Torisel™), AP 23573 (ARIAD), and VX 680 (Vertex).

Additionally, other signal transduction inhibitors include XL 647 (Exelixis), sorafenib (Nexavar™), LE-AON (Georgetown University), and GI-4000 (Globelmmune).

Other signal transduction inhibitors include ABT 751 (Abbott), alvocidib (flavopiridol), BMS 387032 (Bristol Myers), EM 1421 (Erimos), indisulam (E 7070), seliciclib (CYC 200), BIO 112 (Onc Bio), BMS 387032 (Bristol-Myers Squibb), PD 0332991 (Pfizer), and AG 024322 (Pfizer).

This invention contemplates the use of compounds of the invention together with classical antineoplastic agents. Classical antineoplastic agents include but are not limited to hormonal modulators such as hormonal, anti-hormonal, androgen agonist, androgen antagonist and anti-estrogen therapeutic agents, histone deacetylase (HDAC) inhibitors, gene silencing agents or gene activating agents, ribonucleases, proteosomics, Topoisomerase I inhibitors, Camptothecin derivatives, Topoisomerase II inhibitors, alkylating agents, antimetabolites, poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor, microtubulin inhibitors, antibiotics, plant derived spindle inhibitors, platinum-coordinated compounds, gene therapeutic agents, antisense oligonucleotides, vascular targeting agents (VTAs), and statins

Examples of classical antineoplastic agents used in combination therapy with a compound of the invention, optionally with one or more other agents include, but are not limited to, glucocorticoids, such as dexamethasone, prednisone, prednisolone, methylprednisolone, hydrocortisone, and progestins such as medroxyprogesterone, megestrol acetate (Megace), mifepristone (RU-486), Selective Estrogen Receptor Modulators (SERMs; such as tamoxifen,

raloxifene, lasofoxifene, afimoxifene, arzoxifene, bazedoxifene, fispemifene, ormeloxifene, ospemifene, tesmilifene, toremifene, trilostane and CHF 4227 (Cheisi)), Selective Estrogen-Receptor Downregulators (SERD's; such as fulvestrant), exemestane (Aromasin), anastrozole (Arimidex), atamestane, fadrozole, letrozole (Femara), gonadotropin-releasing hormone (GnRH; also commonly referred to as luteinizing hormone-releasing hormone [LHRH]) agonists such as buserelin (Suprefact), goserelin (Zoladex), leuprorelin (Lupron), and triptorelin (Trelstar), abarelix (Plenaxis), bicalutamide (Casodex), cyproterone, flutamide (Eulexin), megestrol, nilutamide (Nilandron), and osaterone, dutasteride, epristeride, finasteride, Serenoa repens, PHL 00801, abarelix, goserelin, leuprorelin, triptorelin, bicalutamide, tamoxifen, exemestane, anastrozole, fadrozole, formestane, letrozole, and combinations thereof.

Other examples of classical antineoplastic agents used in combination with compounds of the invention include but are not limited to suberolanilide hydroxamic acid (SAHA, Merck Inc./Aton Pharmaceuticals), depsipeptide (FR901228 or FK228), G2M-777, MS-275, pivaloyloxymethyl butyrate and PXD-101; Onconase (ranpirnase),PS-341 (MLN-341), Velcade (bortezomib), 9-aminocamptothecin, belotecan, BN-80915 (Roche), camptothecin, diflomotecan, edotecarin, exatecan (Daiichi), gimatecan, 10-hydroxycamptothecin, irinotecan HCl (Camptosar), lurtotecan, Orathecin (rubitecan, Supergen), SN-38, topotecan, camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, irinotecan, SN-38, edotecarin, topotecan, aclarubicin, adriamycin, amonafide, amrubicin, annamycin, daunorubicin, doxorubicin, elsamitrucin, epirubicin, etoposide, idarubicin, galarubicin, hydroxycarbamide, nemorubicin, novantrone (mitoxantrone), pirarubicin, pixantrone, procarbazine, rebeccamycin, sobuzoxane, tafluposide, valrubicin, Zinecard (dexrazoxane), nitrogen mustard N-oxide, cyclophosphamide, AMD-473, altretamine, AP-5280, apaziquone, brostallicin, bendamustine, busulfan, carboquone, carmustine, chlorambucil, dacarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine, mafosfamide, mechlorethamine, melphalan, mitobronitol, mitolactol, mitomycin C, mitoxatrone, nimustine, ranimustine, temozolomide, thiotepa, and platinum-coordinated alkylating compounds such as cisplatin, Paraplatin (carboplatin), eptaplatin, lobaplatin, nedaplatin, Eloxatin (oxaliplatin, Sanofi), streptozocin, satrplatin, and combinations thereof.

The invention also contemplates the use of the compounds of the invention together with dihydrofolate reductase inhibitors (such as methotrexate and NeuTrexin (trimetresate glucuronate)), purine antagonists (such as 6-mercaptopurine riboside, mercaptopurine, 6-thioguanine, cladribine, clofarabine (Clolar), fludarabine, nelarabine, and raltitrexed), pyrimidine antagonists (such as 5-fluorouracil (5-FU), Alimta (premetrexed disodium, LY231514, MTA), capecitabine (Xeloda™), cytosine arabinoside, Gemzar™ (gemcitabine, Eli Lilly), Tegafur (UFT

Orzel or Uforal and including TS-1 combination of tegafur, gimestat and otostat), doxifluridine, carmofur, cytarabine (including ocfosfate, phosphate stearate, sustained release and liposomal forms), enocitabine, 5-azacitidine (Vidaza), decitabine, and ethynylcytidine) and other antimetabolites such as eflornithine, hydroxyurea, leucovorin, nolatrexed (Thymitaq), triapine, trimetrexate, N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid, AG-014699 (Pfizer Inc.), ABT-472 (Abbott Laboratories), INO-1001 (Inotek Pharmaceuticals), KU-0687 (KuDOS Pharmaceuticals) and GPI 18180 (Guilford Pharm Inc) and combinations thereof.

Other examples of classical antineoplastic cytotoxic agents used in combination therapy with a compound of the invention, optionally with one or more other agents include, but are not limited to, Abraxane (Abraxis BioScience, Inc.), Batabulin (Amgen), EPO 906 (Novartis), Vinflunine (Bristol- Myers Squibb Company), actinomycin D, bleomycin, mitomycin C, neocarzinostatin (Zinostatin), vinblastine, vincristine, vindesine, vinorelbine (Navelbine), docetaxel (Taxotere), Ortataxel, paclitaxel (including Taxoprexin a DHA/paciltaxel conjugate), cisplatin, carboplatin, Nedaplatin, oxaliplatin (Eloxatin), Satraplatin, Camptosar, capecitabine (Xeloda), oxaliplatin (Eloxatin), Taxotere alitretinoin, Canfosfamide (Telcyta™), DMXAA (Antisoma), ibandronic acid, L-asparaginase, pegaspargase (Oncaspar™), Efaproxiral (Efaproxyn™ - radiation therapy)), bexarotene (Targretin™), Tesmilifene (DPPE – enhances efficacy of cytotoxics)), Theratope™ (Biomira), Tretinoin (Vesanoid™), tirapazamine (Trizaone™), motexafin gadolinium (Xcytrin™) Cotara™ (mAb), and NBI-3001 (Protox Therapeutics), polyglutamate-paclitaxel (Xyotax™) and combinations thereof.

Further examples of classical antineoplastic agents used in combination therapy with a compound of the invention, optionally with one or more other agents include, but are not limited to, as Advexin (ING 201), TNFerade (GeneVec, a compound which express TNFalpha in response to radiotherapy), RB94 (Baylor College of Medicine), Genasense (Oblimersen, Genta), Combretastatin A4P (CA4P), Oxi-4503, AVE-8062, ZD-6126, TZT-1027, Atorvastatin (Lipitor, Pfizer Inc.), Provastatin (Pravachol, Bristol-Myers Squibb), Lovastatin (Mevacor, Merck Inc.), Simvastatin (Zocor, Merck Inc.), Fluvastatin (Lescol, Novartis), Cerivastatin (Baycol, Bayer), Rosuvastatin (Crestor, AstraZeneca), Lovostatin, Niacin (Advicor, Kos Pharmaceuticals), Caduet, Lipitor, torcetrapib, and combinations thereof.

Another embodiment of the present invention of particular interest relates to a method for the treatment of breast cancer in a human in need of such treatment, comprising administering to said human an amount of a compound of the invention, in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of trastuzumab,

tamoxifen, docetaxel, paclitaxel, capecitabine, gemcitabine, vinorelbine, exemestane, letrozole and anastrozole.

In one embodiment the invention provides a method of treating colorectal cancer in a mammal, such as a human, in need of such treatment, by administering an amount of a compound of the invention, in combination with one or more (preferably one to three) anti-cancer agents. Examples of particular anti-cancer agents include those typically used in adjuvant chemotherapy, such as FOLFOX, a combination of 5-fluorouracil (5-FU) or capecitabine (Xeloda), leucovorin and oxaliplatin (Eloxatin). Further examples of particular anti-cancer agents include those typically used in chemotherapy for metastatic disease, such as FOLFOX or FOLFOX in combination with bevacizumab (Avastin); and FOLFIRI, a combination of 5-FU or capecitabine, leucovorin and irinotecan (Camptosar). Further examples include 17-DMAG, ABX-EFR, AMG-706, AMT-2003, ANX-510 (CoFactor), aplidine (plitidepsin, Aplidin), Aroplatin, axitinib (AG-13736), AZD-0530, AZD-2171, bacillus Calmette-Guerin (BCG), bevacizumab (Avastin), BIO-117, BIO-145, BMS-184476, BMS-275183, BMS-528664, bortezomib (Velcade), C-1311 (Symadex), cantuzumab mertansine, capecitabine (Xeloda), cetuximab (Erbitux), clofarabine (Clofarex), CMD-193, combretastatin, Cotara, CT-2106, CV-247, decitabine (Dacogen), E-7070, E-7820, edotecarin, EMD-273066, enzastaurin (LY-317615)epothilone B (EPO-906), erlotinib (Tarceva), flavopyridol, GCAN-101, gefitinib (Iressa), huA33, huC242-DM4, imatinib (Gleevec), indisulam, ING-1, irinotecan (CPT-11, Camptosar) ISIS 2503, ixabepilone, lapatinib (Tykerb), mapatumumab (HGS-ETR1), MBT-0206, MEDI-522 (Abregrin), Mitomycin, MK-0457 (VX-680), MLN-8054, NB-1011, NGR-TNF, NV-1020, oblimersen (Genasense, G3139), OncoVex, ONYX 015 (CI-1042), oxaliplatin (Eloxatin), panitumumab (ABX-EGF, Vectibix), pelitinib (EKB-569), pemetrexed (Alimta), PD-325901, PF-0337210, PF-2341066, RAD-001 (Everolimus), RAV-12, Resveratrol, Rexin-G, S-1 (TS-1), seliciclib, SN-38 liposome, Sodium stibogluconate (SSG), sorafenib (Nexavar), SU-14813, sunitinib (Sutent), temsirolimus (CCI 779), tetrathiomolybdate, thalomide, TLK-286 (Telcyta), topotecan (Hycamtin), trabectedin (Yondelis), vatalanib (PTK-787), vorinostat (SAHA, Zolinza), WX-UK1, and ZYC300, wherein the amounts of the active agent together with the amounts of the combination anticancer agents are effective in treating colorectal cancer.

Another embodiment of the present invention of particular interest relates to a method for the treatment of renal cell carcinoma in a human in need of such treatment, comprising administering to said human an amount of a compound of the invention, in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of axitinib (AG 13736), capecitabine (Xeloda), interferon alpha, interleukin-2, bevacizumab (Avastin), gemcitabine (Gemzar), thalidomide, cetuximab (Erbitux), vatalanib (PTK-787),

sunitinib (Sutent™), AG-13736, SU-11248, Tarceva, Iressa, Lapatinib and Gleevec, wherein the amounts of the active agent together with the amounts of the combination anticancer agents is effective in treating renal cell carcinoma.

Another embodiment of the present invention of particular interest relates to a method for the treatment of melanoma in a human in need of such treatment, comprising administering to said human an amount of a compound of the invention, in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of interferon alpha, interleukin-2, temozolomide (Temodar), docetaxel (Taxotere), paclitaxel, Dacarbazine (DTIC), carmustine (also known as BCNU), Cisplatin, vinblastine, tamoxifen, PD-325,901, axitinib (AG 13736), bevacizumab (Avastin), thalidomide, sorafanib, vatalanib (PTK-787), sunitinib (Sutent™), CpG-7909, AG-13736, Iressa, Lapatinib and Gleevec, wherein the amounts of the active agent together with the amounts of the combination anticancer agents is effective in treating melanoma.

Another embodiment of the present invention of particular interest relates to a method for the treatment of lung cancer in a human in need of such treatment, comprising administering to said human an amount of a compound of the invention, in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of capecitabine (Xeloda), axitinib (AG 13736), bevacizumab (Avastin), gemcitabine (Gemzar), docetaxel (Taxotere), paclitaxel, premetrexed disodium (Alimta), Tarceva, Iressa, Vinorelbine, Irinotecan, Etoposide, Vinblastine, sunitinib (Sutent™), and Paraplatin (carboplatin), wherein the amounts of the active agent together with the amounts of the combination anticancer agents is effective in treating lung cancer.

According to another embodiment of the present invention, the compounds of the invention, or pharmaceutically acceptable salts, derived forms or compositions thereof, can also be used as a combination with one or more additional therapeutic agents to be co-administered to a patient to obtain some particularly desired therapeutic end result such as the treatment of central nervous system diseases, cancer and cancer. The second and more additional therapeutic agents may also be a compound of the formula (1), or a pharmaceutically acceptable salt, derived forms or compositions thereof, or may be selected from a different class of therapeutic agents.

As used herein, the terms “co-administration”, “co-administered” and “in combination with”, referring to the compounds of the invention and one or more other therapeutic agents, is intended to mean, and does refer to and include the following:

i. simultaneous administration of such combination of compound(s) of the invention and therapeutic agent(s) to a patient in need of treatment, when such components are

formulated together into a single dosage form which releases said components at substantially the same time to said patient,

ii. substantially simultaneous administration of such combination of compound(s) of the invention and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said patient, whereupon said components are released at substantially the same time to said patient,

iii. sequential administration of such combination compound(s) of the invention and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at consecutive times by said patient with a significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and

iv. sequential administration of such combination of compound(s) of the invention and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components in a controlled manner whereupon they are concurrently, consecutively, and/or overlapingly administered at the same and/or different times by said patient,

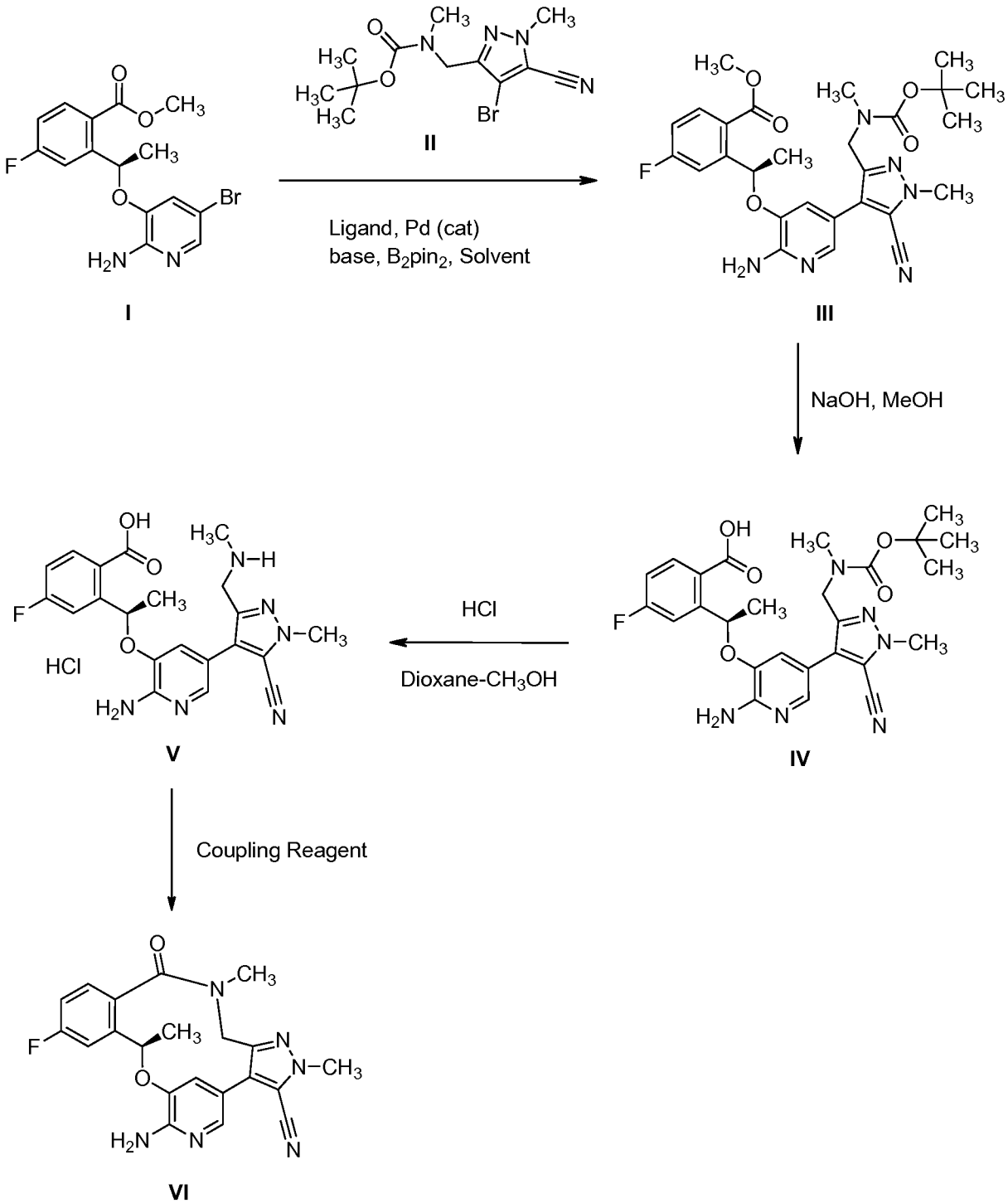
where each part may be administered by either the same or different route.

Synthetic Methods

The compounds of the invention can be prepared by a variety of synthetic methods, as further described and illustrated herein. It will be understood by those of skill in the art that the following general synthetic methods are representative and not intended to be limiting.

Method A

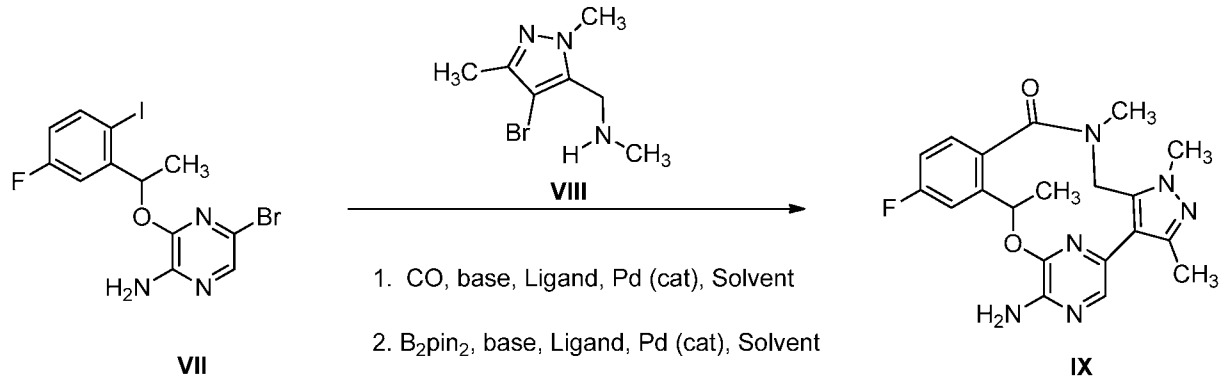
In a general synthetic process, compounds of the general structure represented by compound **VI** are prepared according to **Method A**.



The aryl halide (**I**) may be coupled with aryl halide (**II**) using the Suzuki coupling conditions, where the *in situ* generated boronic acid reacts with the aryl halide to give compound (**III**). The ester group of compound (**III**) may be hydrolyzed using an appropriate base, such as sodium hydroxide, to provide compound (**IV**), and the BOC protecting group may be removed using HCl or TFA to yield compound (**V**). Finally, formation of the lactam may be achieved by using the appropriate coupling reagent such as HATU to yield compound **(VI)**.

Method B

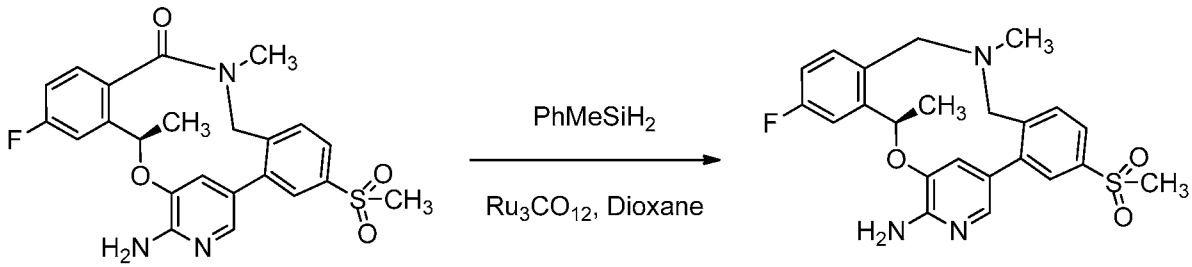
In a general synthetic process, compounds of the general structure represented by compound (**IX**) are prepared according to **Method B**.



In the first step of a two step sequence, regioselective carboamidation of aryl dihalide (**VII**) may be accomplished with amine (**VIII**) in the presence of carbon monoxide and an appropriate palladium catalyst and base. In the second step, Suzuki coupling of the crude amide may be accomplished using diboron pinacol ester and the appropriate palladium catalyst and base to provide the macrocycle (**IX**).

Method C

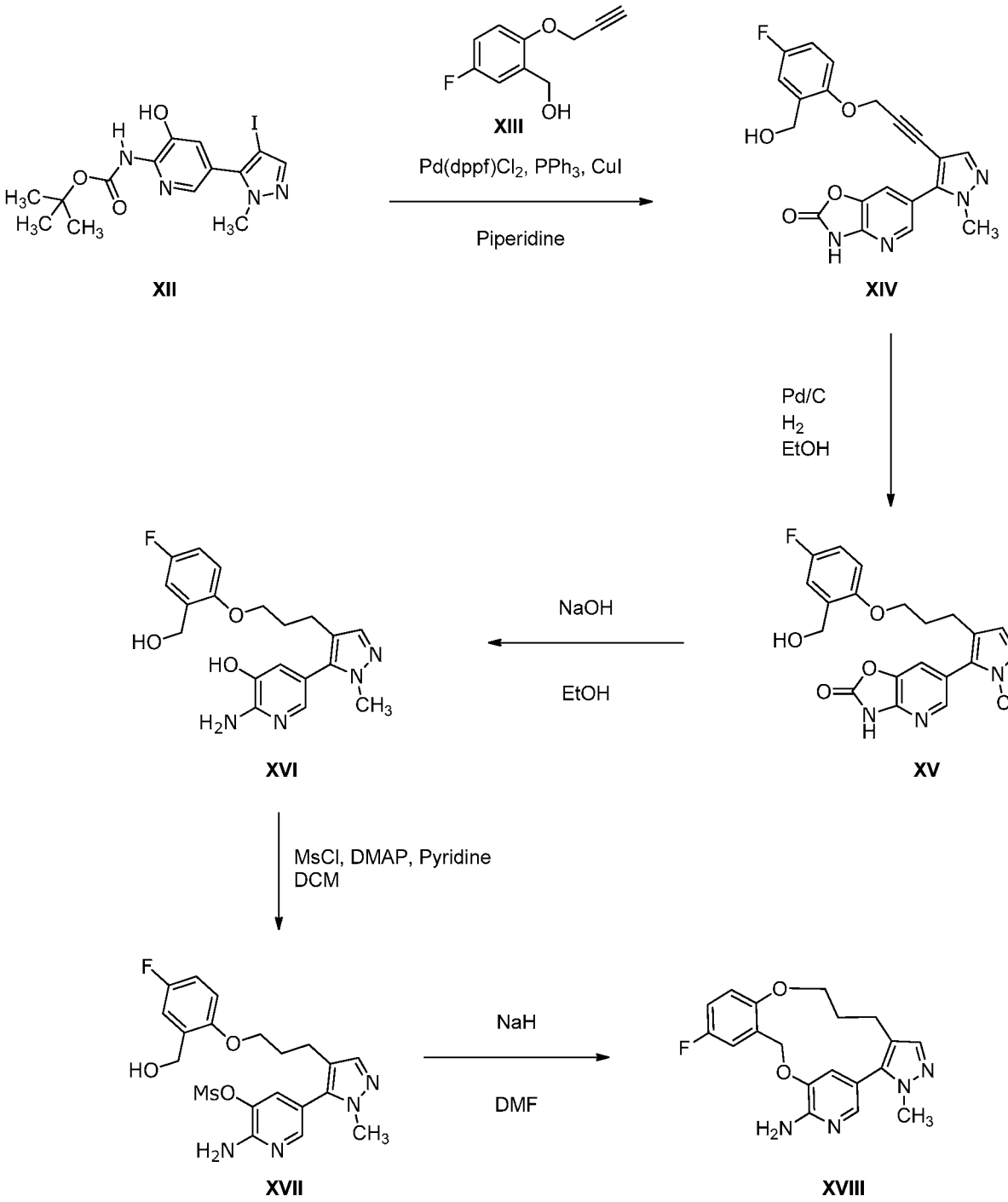
In a general synthetic process, compounds of the general structure represented by compound (**XI**) are prepared according to **Method C**.



The amide (**X**) is reduced by the appropriate reducing reagent, such as a $PhMeSiH_2$ in the presence of a ruthenium catalyst to give compound (**XI**).

Method D

In a general synthetic process, compounds of the general structure represented by compound **(XII)** are prepared according to **Method D**.

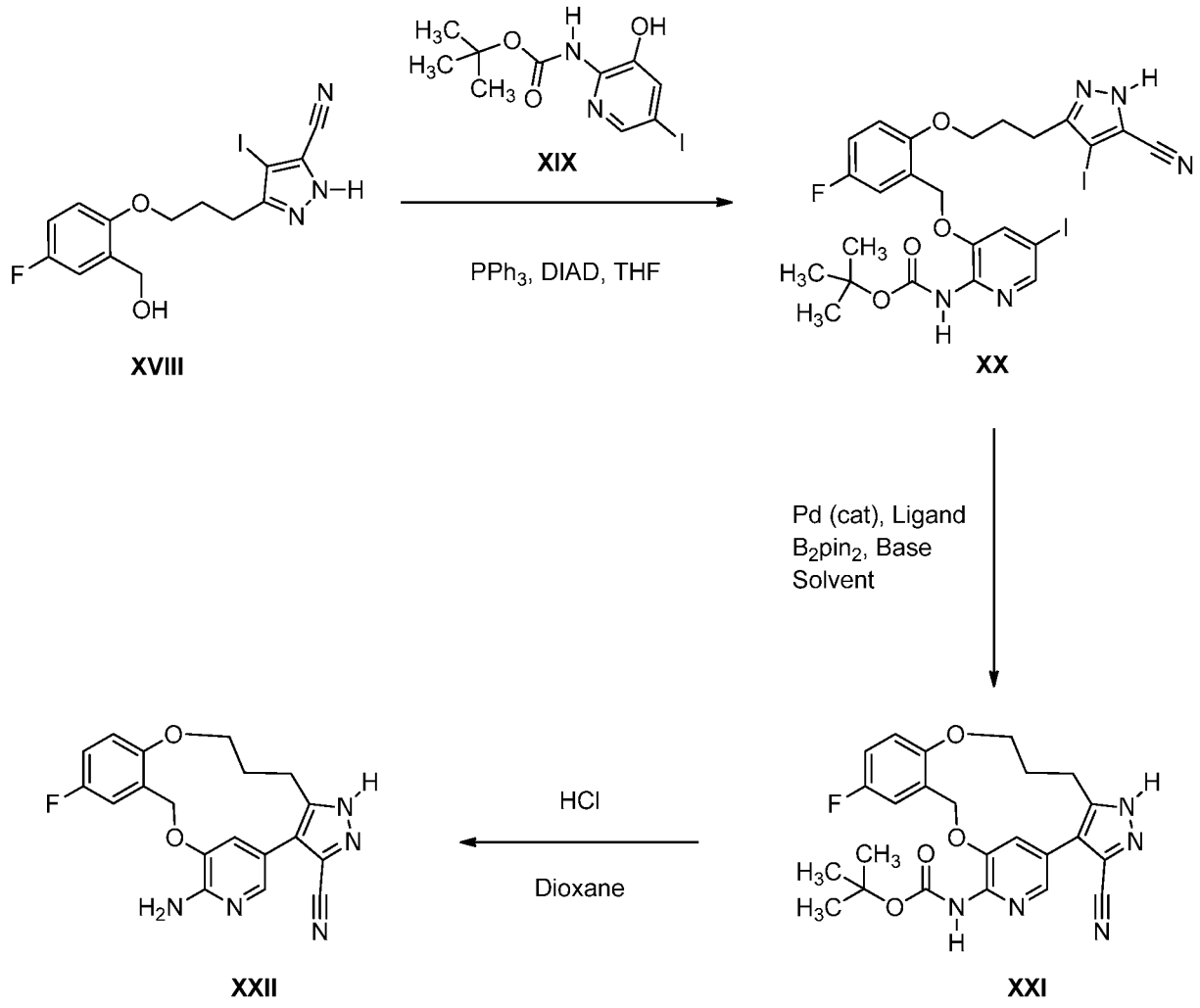


The Sonagashira cross-coupling between aryl halide **(XII)** and alkyne (**XIII**) was accomplished in the presence of the appropriate palladium and copper catalysts and base to provide compound **(XIV)**. The alkyne (**XIV**) may be reduced in an atmosphere of hydrogen in the presence of the appropriate palladium catalyst to provide compound (**XV**). Compound (**XV**) may be deprotected using a suitable base, such as sodium hydroxide, to provide compound (**XVI**). The hydroxyl group of compound **(XVI)** may be converted to a reactive agent, followed by an intramoleculer displacement by the phenoxide to generated **macrocycle (XVIII)**. Thus, **compound (XVI)** may

be treated with mesyl chloride in the presence of a base to provide **compound (XVII)**. The addition of a suitable base, such as sodium hydride, to **compound (XV11)** provides macrocycle (**XVIII**).

Method E

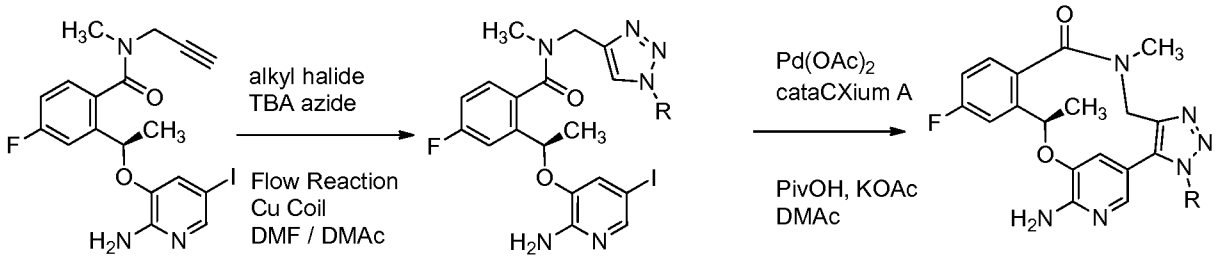
In a general synthetic process, compounds of the general structure represented by compound (**XXI**) are prepared according to **Method E**.



The **phenol (XIX)** may be coupled with **compound (XVIII)** using the Mitsunobu conditions to provide **compound (XX)**. In the second step, intramolecular Suzuki coupling of **compound (XX)** may be accomplished using diboron pinacol ester and the appropriate palladium catalyst and base to provide the **macrocycle (XXI)**. The BOC protecting group of **compound (XXI)** may be removed using HCl to provide **compound (XXII)**.

Method F

In a general synthetic process, compounds of the general structure represented by compound (**XXV**) are prepared according to **Method F**.

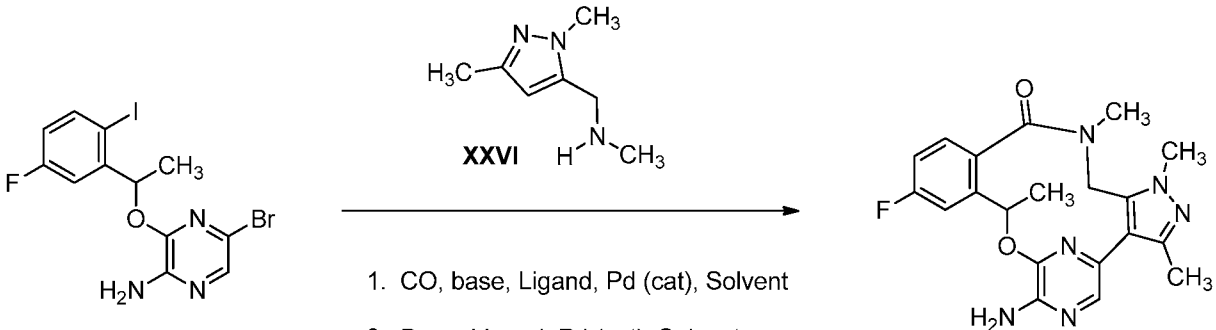


XXIII **XXIV** **XXV**

An alkyl halide may be converted to an alkyl azide, followed by the addition of the alkyne (**XXIII**) and copper to provide **compound (XXIV)**. The 1,4-disubstituted triazole (**XXIV**) may be treated with a palladium catalyst to provide **macrocycle** (**XXV**).

Method G

In a general synthetic process, compounds of the general structure represented by compound (**IX**) are prepared according to **Method G**.

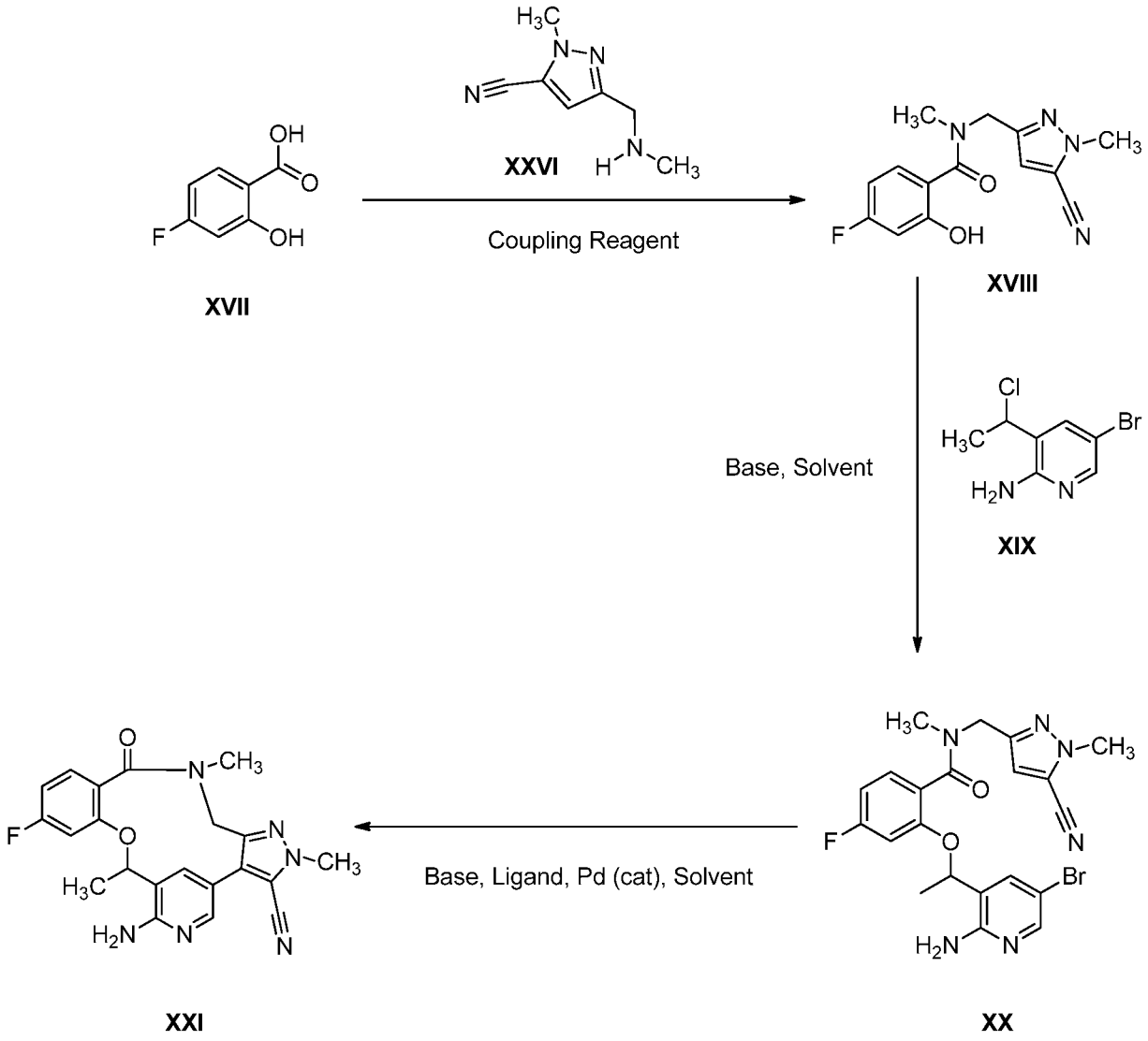


VII **XXVI** **IX**

In the first step of a two step sequence, regioselective carboamidation of aryl dihalide (**VII**) may be accomplished with amine (**XXVI**) in the presence of carbon monoxide and an appropriate palladium catalyst and base. In the second step, a C-H activation reaction on the amide (either crude or purified) may be accomplished using the appropriate palladium catalyst and base to provide the macrocycle (**IX**).

Method H

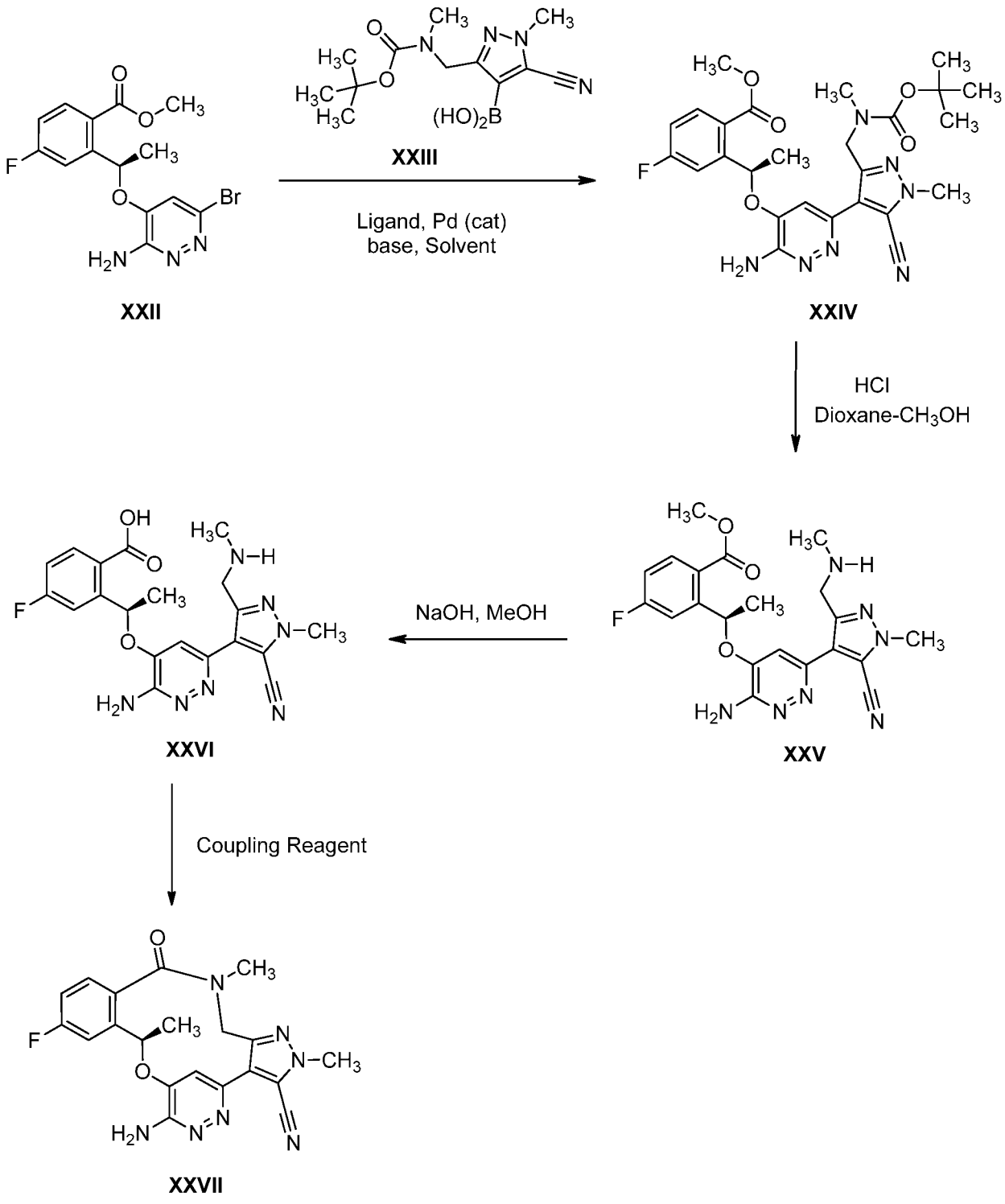
In a general synthetic process, compounds of the general structure represented by compound (**XXI**) are prepared according to **Method H**.



In the first of a three step sequence, amide bond formation of acid (**XVII**) and amine (**XVI**) may be accomplished using a suitable coupling agent, such as HATU, to provide compound (**XVIII**). Nucleophilic displacement of (**XVIII**) with compound (**XIX**) to obtain compound (**XX**) may occur in the presence of a suitable base, such as potassium carbonate. In the final step, a C-H activation reaction on the amide (**XX**) may be accomplished using the appropriate palladium catalyst and base to provide the macrocycle (**XXI**).

Method I

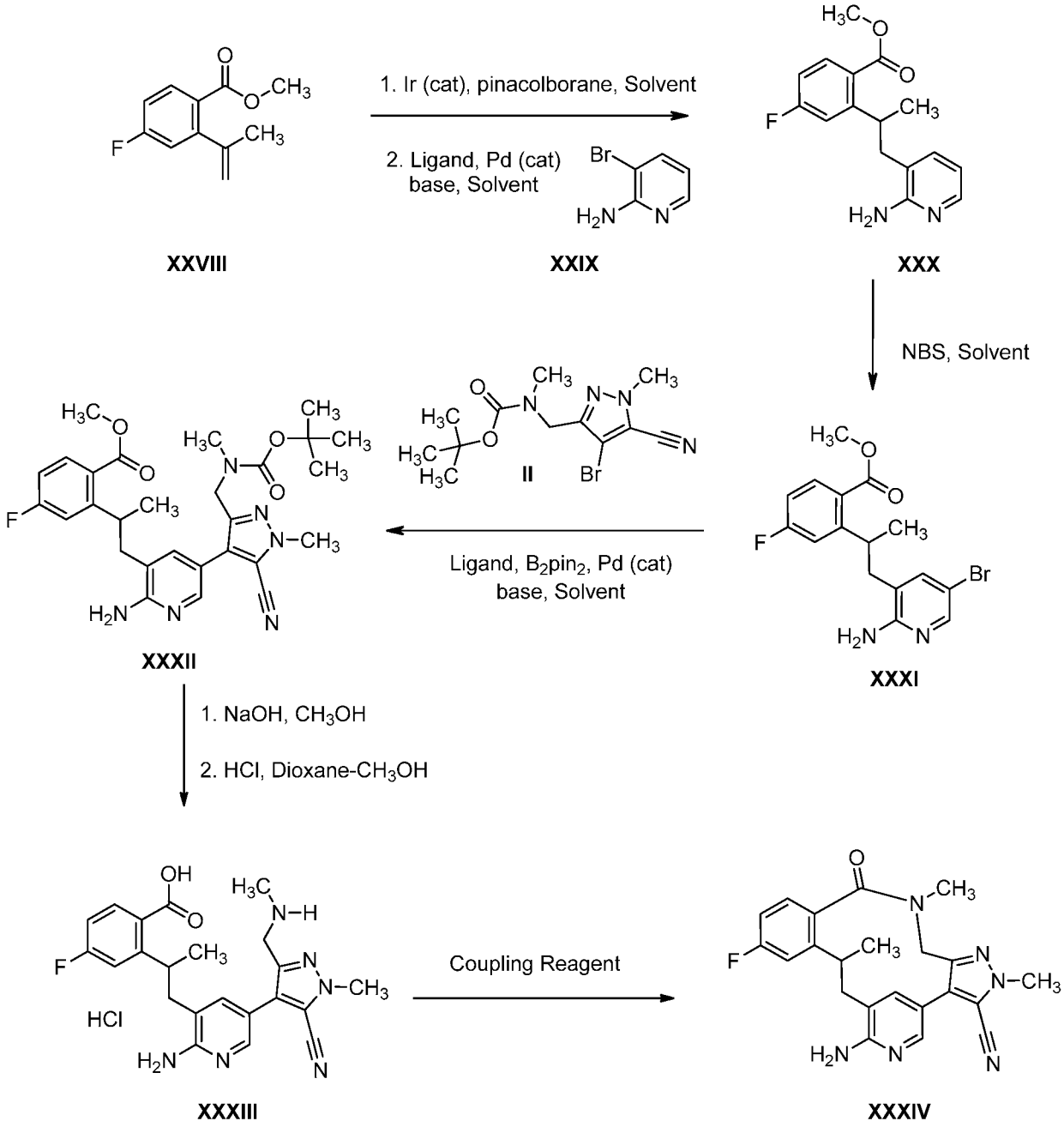
In a general synthetic process, compounds of the general structure represented by compound (**XXVII**) are prepared according to **Method I**.



The aryl halide (**XXII**) may be coupled with boronic acid (**XXIII**) using the Suzuki coupling conditions to give compound (**XXIV**). The BOC protecting group may removed using HCl or TFA to yield compound (**XXV**), and the ester group of compound (**XXV**) may be hydrolyzed using an appropriate base, such as sodium hydroxide, to provide compound (**XXVI**), Finally, formation of the lactam may be achieved by using the appropriate coupling reagent such as HATU to yield compound **(XXVII)**.

Method J

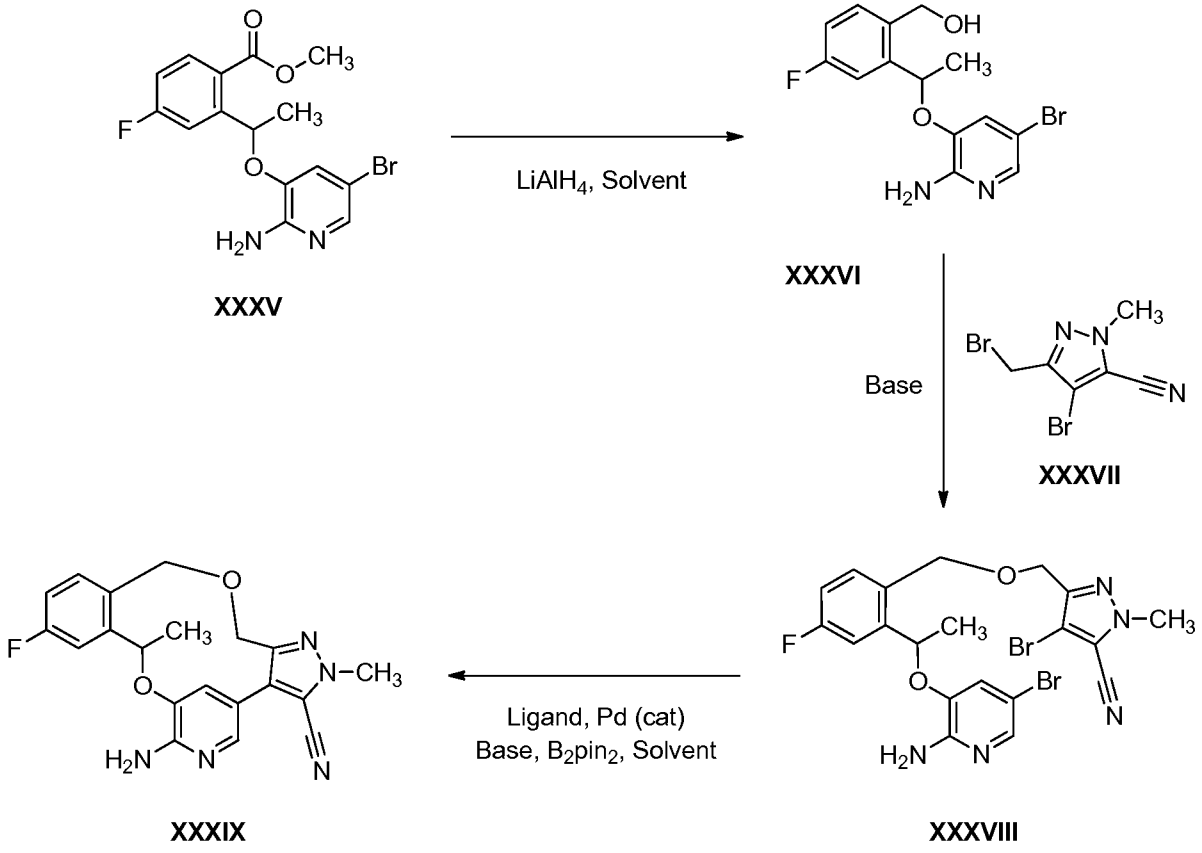
In a general synthetic process, compounds of the general structure represented by compound (**XXXIV**) are prepared according to **Method J**.



Regioselective hydroboration of the alkene (**XXVIII**) may be achieved using pinacol borane, and a suitable catalyst. The boronate species formed may be directly coupled to an aryl halide (**XXIX**) using the Suzuki coupling conditions to give compound (**XXX**). Regioselective halogenation of compound (**XXX**) may be accomplished using a reagent such as NBS to give compound (**XXXI**).The aryl halide (**XXXI**) may be coupled with aryl halide (**II**) using the Suzuki coupling conditions, where the *in situ* generated boronic acid reacts with the aryl halide to give compound (**XXXII**). The ester group of compound (**XXXII**) may be hydrolyzed using an appropriate base, such as sodium hydroxide and then without purification, the BOC protecting group may be removed using HCl or TFA to yield compound (**XXXIII**). Finally, formation of the lactam may be achieved by using the appropriate coupling reagent such as HATU to yield compound **(XXXIV)**.

Method K

In a general synthetic process, compounds of the general structure represented by compound (**XXXIX**) are prepared according to **Method K**.



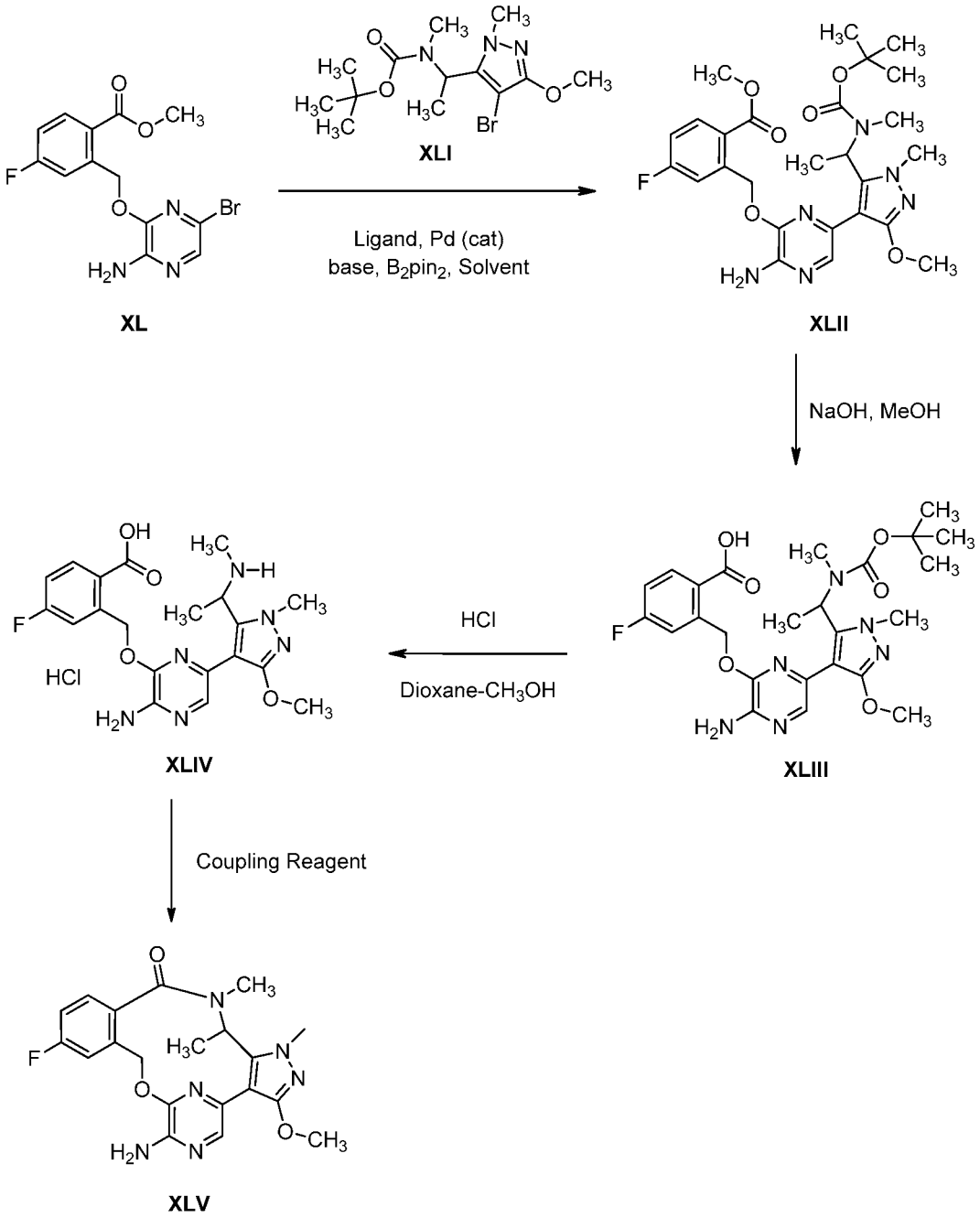
XXXV **XXXVI** **XXXVII** **XXXVIII** **XXXIX**

Reduction of the ester (**XXXV**) to the alcohol (**XXXVI**) may be accomplished with a reducing agent such as LAH. Ether bond formation between alcohol (**XXXVI**) and aryl halide (**XXXVII**)

may occur mediated by a base such as NaH. The aryl dihalide (**XXXVIII**) may be coupled in an intramolecular fashion using the Suzuki coupling conditions, where the *in situ* generated boronic acid generated at one halide reacts with the other halide in the molecule to give compound (**XXXIX**).

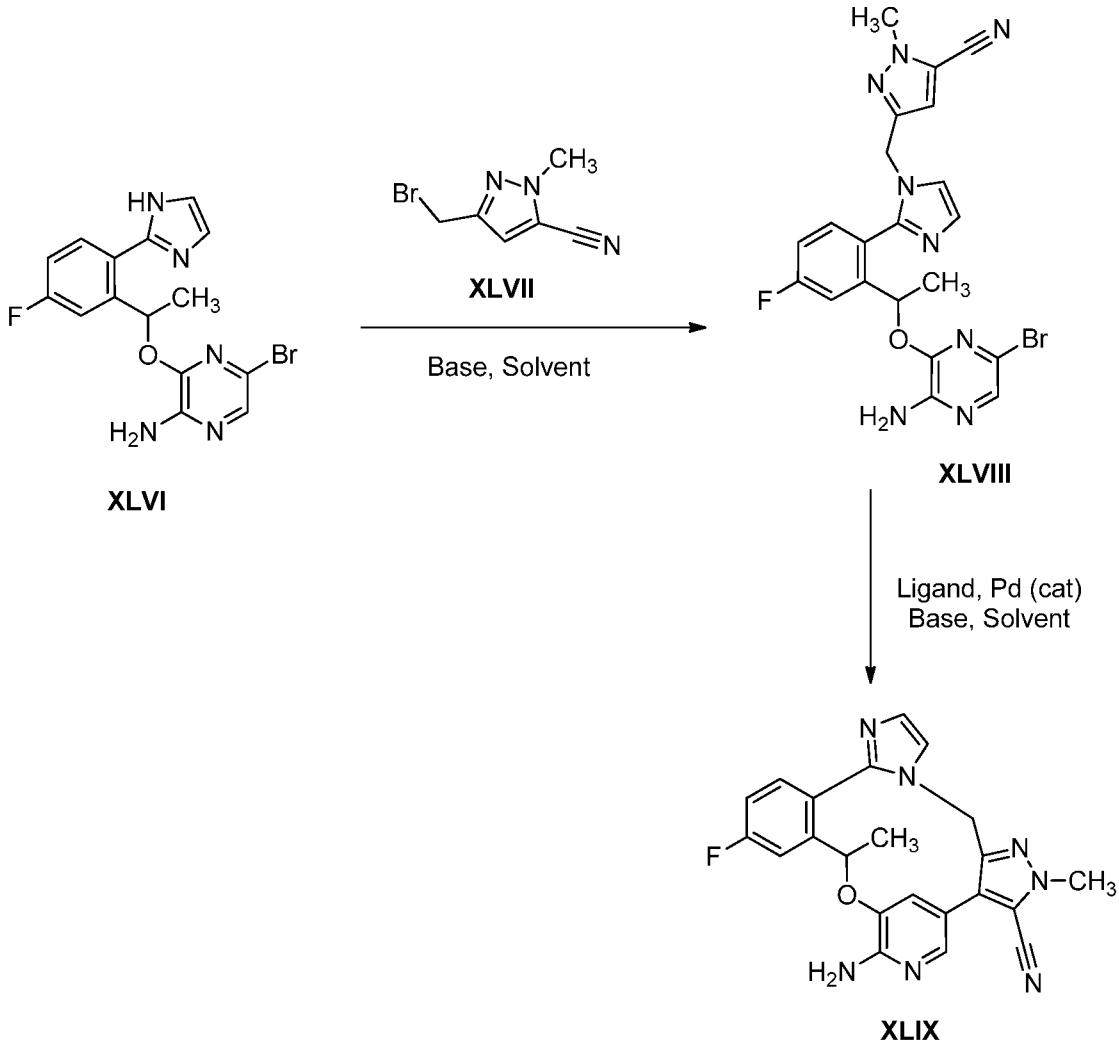
Method L

In a general synthetic process, compounds of the general structure represented by compound (**XLV**) are prepared according to **Method L**.



Method M

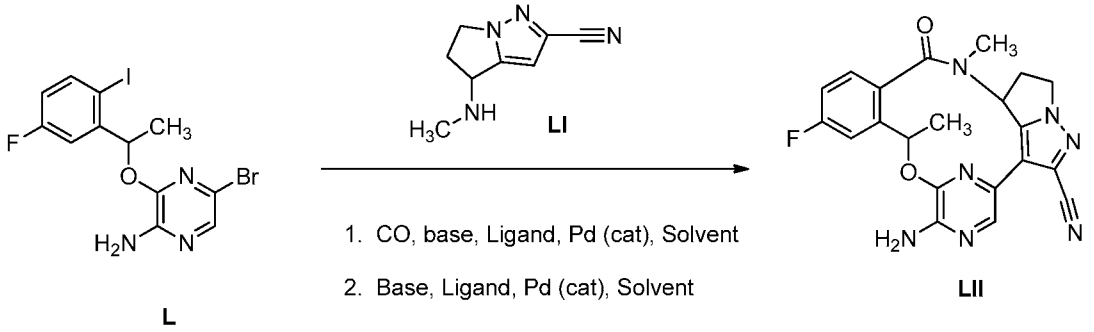
In a general synthetic process, compounds of the general structure represented by compound (**XLIX**) are prepared according to **Method M**.



The symmetrical imidazole (**XLVI**) may be alkylated with the benzylic halide (**XLVII**) in the presence of a suitable base such as K_2CO_3. In the final step, a C-H activation reaction on the amide (**XLVIII**) may be accomplished using the appropriate palladium catalyst and base to provide the macrocycle (**XLIX**).

Method N

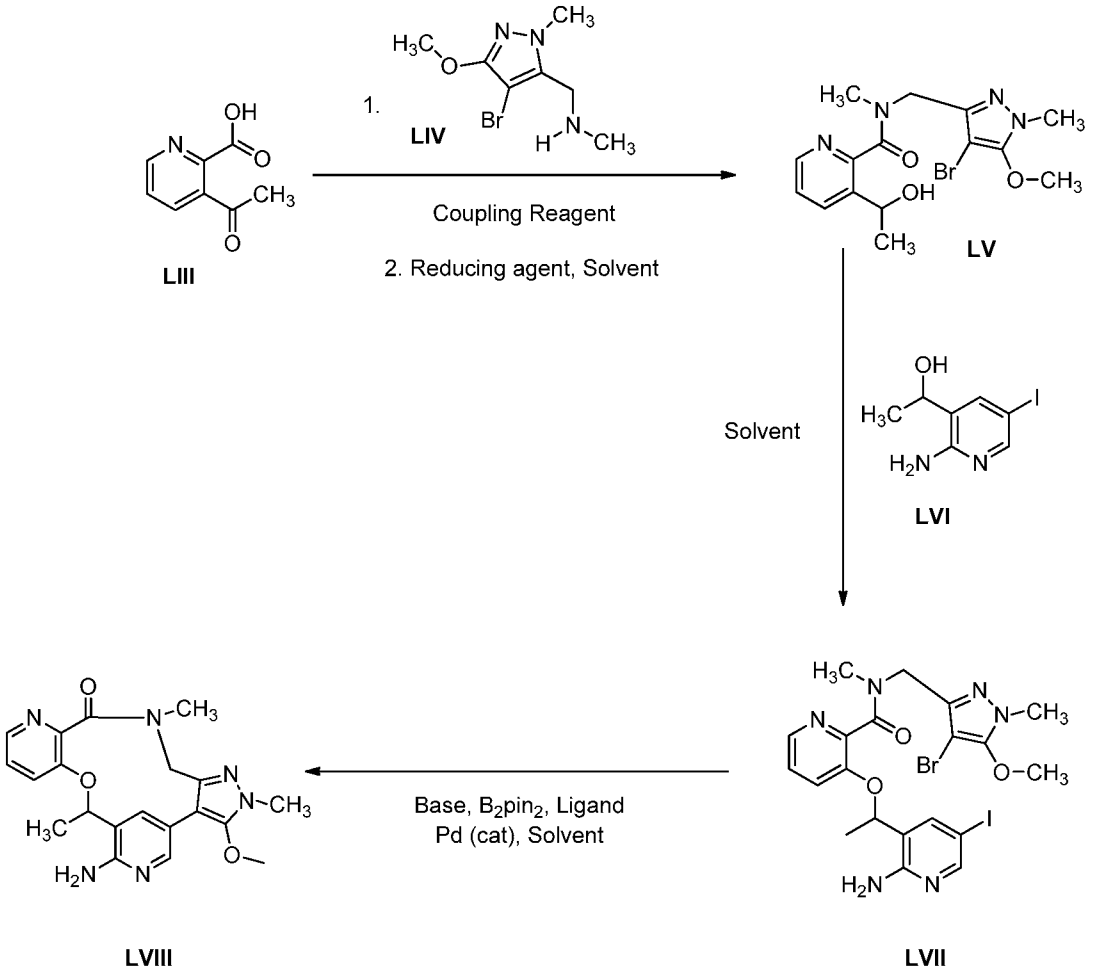
In a general synthetic process, compounds of the general structure represented by compound (**LII**) are prepared according to **Method N**.



In the first step of a two step sequence, regioselective carboamidation of aryl dihalide (**L**) may be accomplished with a bicyclic amine (**LII)** in the presence of carbon monoxide and an appropriate palladium catalyst and base. In the second step, a C-H activation reaction on the amide (either crude or purified) may be accomplished using the appropriate palladium catalyst and base to provide the macrocycle (**LII**).

Method O

In a general synthetic process, compounds of the general structure represented by compound (**LVIII**) are prepared according to **Method N**.



Amide bond formation between acid (**LIII**) and amine (**LIV**) may be accomplished using a suitable coupling agent, such as HATU. Subsequent reduction of the acetophenone functionality to the alcohol (**LV**) may be accomplished using a reagent such as NaBH4. Ether bond formation between (**LV**) and the alcohol (**LVI**) may be accomplished using methodology such as a Mitsunobu reaction to give compound (**LVII**).The aryl dihalide (**LVII**) may be coupled in an intramolecular fashion using the Suzuki coupling conditions, where the *in situ* generated boronic acid generated at one halide reacts with the other halide in the molecule to give compound (**LVIII**).

For some of the steps of the here above described process of preparation of the compounds of the invention, it may be necessary to protect potential reactive functions that are not wished to react, and to cleave said protecting groups in consequence. In such a case, any compatible protecting radical can be used. In particular methods of protection and deprotection such as those described by T.W. GREENE (*Protective Groups in Organic Synthesis*, A. Wiley-Interscience Publication, 1981) or by P. J. Kocienski (*Protecting groups*, Georg Thieme Verlag, 1994), can be used.

All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the examples and preparations hereto. The compounds of the invention as well as intermediates for the preparation thereof can be purified according to various well-known methods, such as for example crystallization or chromatography.

Examples

The Preparations and Examples that follow illustrate the invention but do not limit the invention. All starting materials are available commercially or are described in the literature. All temperatures are in °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 400 MHz NMR spectrometer or a Varian Mercury 400 MHz 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.

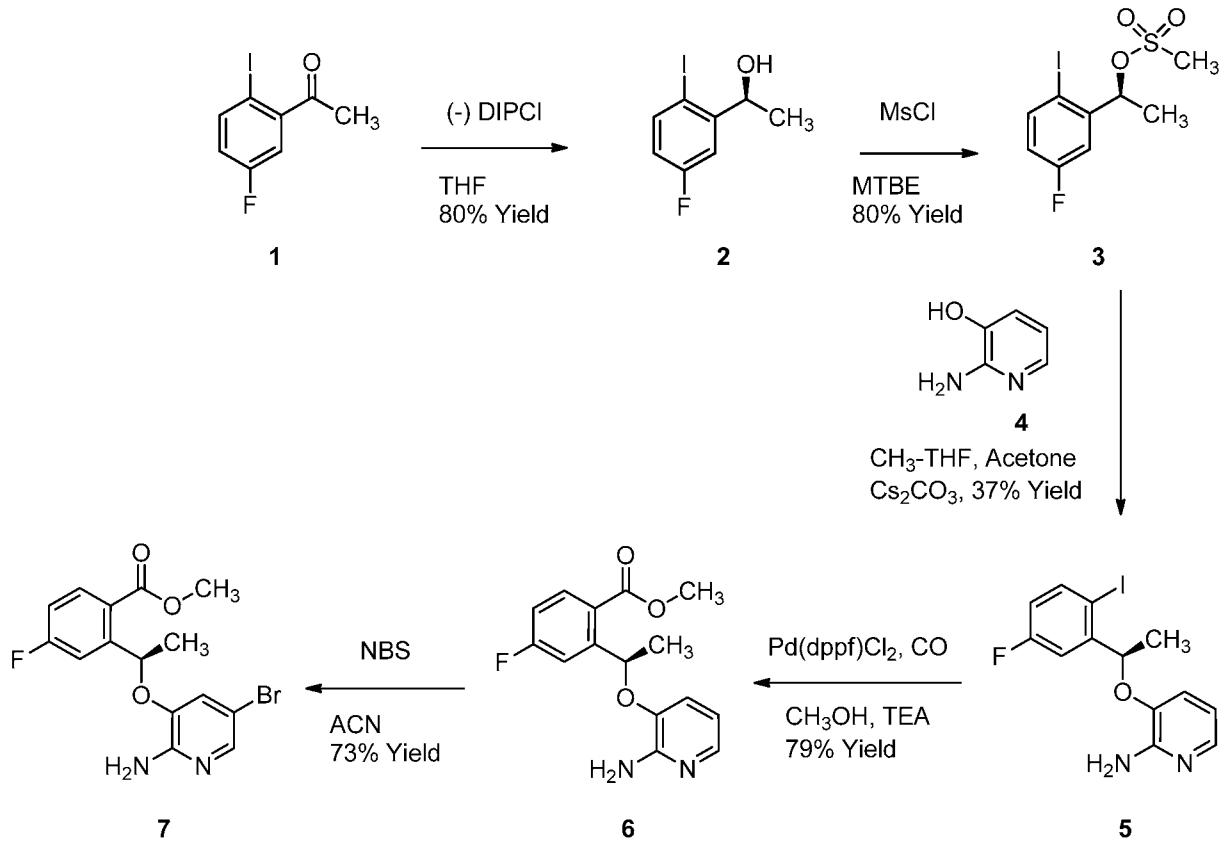
The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions are used:

"Et" means ethyl, "Ac" means acetyl, "Me" means methyl, "Ph" means phenyl, "Boc", "BOC", "t-Boc", or "t-BOC" means tert-butoxycarbonyl, "EtOAc" means ethyl acetate, "TEA", "NEt_3" or "Et_3N" means triethylamine, "THF" means tetrahydrofuran, "MeTHF" means methyltetrahydrofuran, "MeOH" means methanol, "DMSO" means dimethylsulfoxide, "$CDCl_3$" means deuterated chloroform, "TBME" or "MTBE" means methyl t-butyl ether, "DMF" means dimethyl formamide, "DMAP" means 4-dimethylaminopyridine, "dppf" means diphenylphosphino ferrocene, "DME" means ethylene glycol dimethyl ether, "TLC" means thin layer chromatography, "SFC" means supercritical fluid chromatography, "h", "hr" or "hrs" means hours, "min." or "mins." means minutes, "DCM" or "CH_2Cl_2" means methylene chloride, "Et_2O" means diethyl ether, "LC-MS" or "LCMS" means liquid chromatography-mass spectrometry, "MS" means mass spectrometry, "rt" or "RT" means room temperature, "NBS" means N-bromosuccinimide, "MeCN" or "CH_3CN" means acetonitrile, "brine" means saturated aqueous sodium chloride, "HATU" means 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate, "APCI" means atmospheric pressure chemical ionization, "CD_3OD" means deuterated methanol, "$(CD_3)_2SO$" means deuterated dimethyl sulphoxide, "δ" means chemical shift, "d" means doublet, "DAD" means diode array detector, g means grams, "ESCI" means electrospray chemical ionization, "HPLC" means high pressure liquid chromatography, "LRMS" means low resolution mass spectrum, "M" means molar, "m" means multiplet, "mg" or "mgs" means milligrams, "MHz" means mega hertz, "mL" means milliliters, "µL" means microliters, "mmol" means millimoles, "mol" means moles, "NMR" means nuclear magnetic resonance, "q" means quartet, "Rt" means retention time, "s" means singlet, "t" means triplet, "TFA" means trifluoroacetic acid, "SFC" means supercritritcal fluid chromatography, "MeMgBr" means methyl magnesium bromide, "DMSO-d_6" means dueterated dimethylsulfoxide, "DiBAL" or "DIBAL-H" means diisobutylaluminium hydride, "CH_3I" means methyl iodide, "ppm" means parts per million, "mCPBA" means meta-chloroperoxybenzoic acid, "DIPCl" means β-chlorodiisopinocamphenylborane (DIP-Chloride®), "N_2" means nitrogen gas, "MeI" means

methyl iodide, "NBS" means N-bromosuccinimide", "NIS" means N-iodosuccinimide, "DIAD" means diisopropyl azodicarboxylate, "DCE" means 1,2-dichloroethane, "HOBt" means hydroxybenzotriazole, "EDCI" means 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, "CDI" means 1,1'-carbonyldiimidazole, "DMS" means dimethyl sulfide, "DIEA", "DIPEA" or "Hunig's base" means *N*,*N*-diisopropylethylamine, "MsCl" means methanesulfonyl chloride, "AIBN" means azobisisobutyronitrile, "cataCXium" means di(1-adamantyl)-*n*-butylphosphine, "HATU" means 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, "AgOTf" means trifluoromethanesulfonic acid silver salt, "TFAA" means trifluoroacetic acid, "SCX cartridge" means strong cation- exchange column cartridge, and "DMAc" means dimethylacetamide

Preparation of Synthetic Intermediates

Preparation of (*R*)-methyl 2-(1-((2-amino-5-bromopyridin-3-yl)oxy)ethyl)-4-fluorobenzoate (7).



Step 1:

A solution of (-)-DIPCl (57.1 g, 178 mmol) in THF (100 ml) was cooled to -20 to -30 °C. A solution of **compound 1** (31.3 g, 119 mmol) in THF (100 ml) was then added dropwise, *via*

addition funnel (30 min addition). The reaction was left to warm up to RT. After 2 h, the reaction was cooled to -30 °C and another portion of (-)-DIPCl (38.0 g, 119 mmol) was added. After 30 min, the reaction was allowed to warm to RT and after 1 h, the solvents were removed in vacuo and the residue re-dissolved in MTBE (200 ml). A solution of diethanolamine (31 g, 296 mmol) in ethanol/THF (15 ml/30 ml) was added via addition funnel, to the reaction mixture under an ice bath. The formation of a white precipitate was observed. The suspension was heated at reflux for 2 hours then cooled to room temperature, filtered and the mother liquids concentrated *in vacuo*. The residue was suspended in heptane/EtOAc (7:3, 200 ml) and again filtered. This procedure was repeated until no more solids could be observed after the liquids were concentrated. The final yellow oil was purified by column chromatography (eluent: cyclohexane/EtOAc- 99:1 to 96:4). The resulting colorless oil was further purified by recrystallisation from heptanes, to give alcohol **compound 2** (25 g, 80% yield, 99% purity and 96% ee) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, 1 H), 7.32 (dd, 1 H), 6.74 (ddd, 1 H), 4.99 - 5.04 (m, 1 H), 2.01 (d, 1 H), 1.44 (d, 3 H). LCMS-ES: No ionization, Purity 99%. Chiral GC (column CP-Chirasil-DexnCB): 96% ee; Rt (minor) 17.7 minutes and Rt (major) 19.4 minutes.

Step 2:

A solution of **compound 2** (22 g, 83 mmol) in MTBE (350 mL) was cooled under an ice bath and triethylamine (23 mL, 166 mmol) followed by mesyl chloride (9.6 mL, 124 mmol) were added drop-wise. The reaction was then warmed to RT and stirred for 3 h. The reaction mixture was filtered and the solids washed with EtOAc. The mother liquids were concentrated *in vacuo* to give **compound 3** (35 g, 80% yield) as a pale yellow oil. This material was taken into the following step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, 1 H), 7.24 (dd, 1 H), 6.82 (ddd, 1 H), 2.92 (s, 3 H), 1.64 (d, 3 H). LCMS-ES no ionization.

Step 3:

A suspension of Cs_2CO_3 (65 g, 201 mmol) and **compound 4** (13.3 g, 121 mmol) in CH_3-THF (600 mL) and acetone (300 mL) was stirred at RT for 30 minutes then heated at 40 °C before drop-wise addition of a solution of **compound 3** (34.4 g, 80 mmol) in CH_3-THF (300 mL) *via* addition funnel. The resulting mixture was left stirring at 75 - 80 °C for 24 h. The reaction was then filtered through celite with MTBE, the solvents removed *in vacuo* and the residue purified by column chromatography over silica gel which was eluted with cyclohexane/EtOAc (9:1 to 1:1) to give **compound 5** (14.3 g, 39 % yield, 90% ee) as a white solid. The solids were then recrystallised from heptane/EtOAc to give compound **5** (10.8 g, 37% yield, 95% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, 1 H), 7.62 (dd, 1 H), 7.10 (dd, 1 H), 6.75 (ddd, 1 H), 6.44 - 6.51 (m, 2 H), 5.34 - 5.39 (m, 1 H), 4.73 (br s, 2 H), 1.61 (d, 3 H). LCMS-ES *m/z* 359 $[M+H]^+$. HPLC

(Chiralpak IC 4.6 x 250 mm): 95% ee; Rt (minor) 10.4 minutes; Rt (major) 14.7 minutes; eluent: Heptane 80%/IPA 20% with 0.2% DEA, 0.7 mL/min.

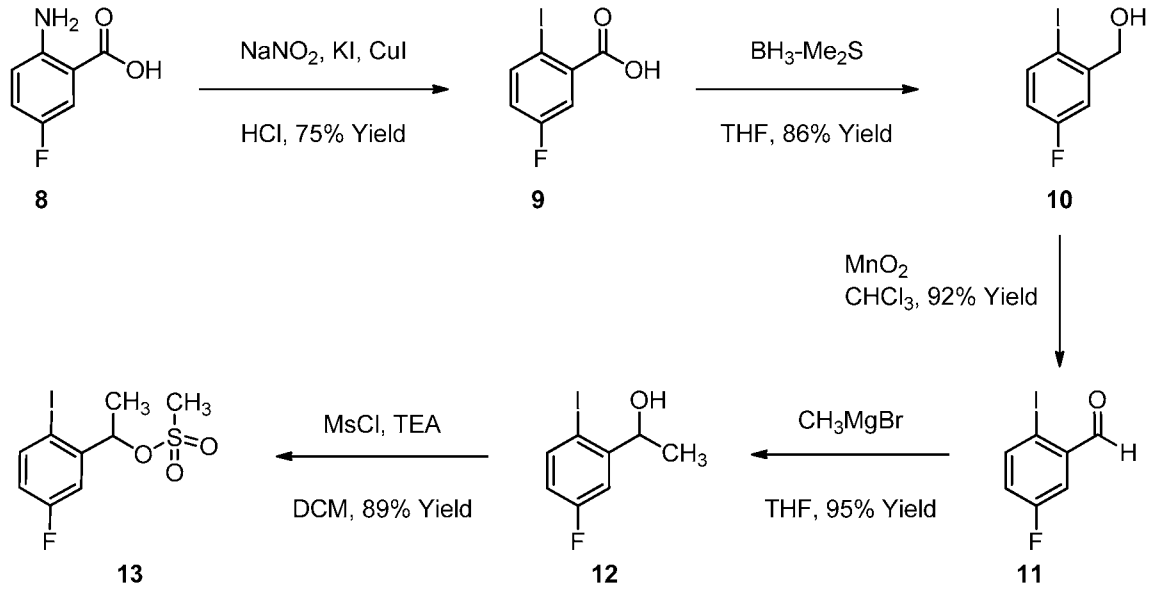
Step 4:

Compound 5 (20 g, 57 mmol) was dissolved in methanol (300 mL), and sequentially treated with triethylamine (15.4 mL, 113 mmol) and $PdCl_2$(dppf) (4.1 g, 5.7 mmol). This mixture was heated at 100 °C for 16 hours, under a 100 psi carbon monoxide atmosphere. LCMS indicated consumption of starting material. The reaction mixture was filtered through a pad of Celite, and the filtrate evaporated to a brown oil. The crude product was purified by flash chromatography over silica gel which was eluted with 50% to 75% ethyl acetate in cyclohexane, affording the pure **product 6** as a brick-red solid (13.0 g, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (d, 3 H), 3.94 (s, 3 H), 4.75 (br s, 2 H), 6.32 (q, 1 H), 6.42 (dd, 1 H), 6.61 (dd, 1 H), 7.00 (ddd, 1 H), 7.28 (dd, 1 H), 7.60 (dd, 1 H), 8.03 (dd, 1 H). LCMS ES *m/z* 291 for $[M+H]^+$.

Step 5:

Compound 6 (13.0 g, 45 mmol) was dissolved in acetonitrile (195 mL), and cooled to <10 °C in an ice water bath. NBS (7.9 g, 45 mmol) was added drop-wise to the cooled reaction mixture as a solution in acetonitrile (195 mL), monitoring the internal temperature to ensure it did not rise above 10 °C. After addition was complete, the mixture was stirred for 15 minutes. TLC (1:1 cyclohexane/ethyl acetate) showed consumption of starting material. The reaction mixture was evaporated, and the residue redissolved in ethyl acetate (400 mL), and washed with 2M aqueous NaOH (2 x 300 mL), and 10% aqueous sodium thiosulfate solution (300 mL). The organic extracts were dried over $MgSO_4$, and evaporated to a red oil (17.6 g). The crude product was purified over silica gel, which was eluted with 10% to 50% ethyl acetate in cyclohexane, which gave **compound 7** (12.0 g, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (d, 3 H), 3.96 (s, 3 H), 4.74 - 4.81 (br s, 2 H), 6.33 (q, 1 H), 6.75 (d, 1 H), 7.03 (ddd, 1 H), 7.25 (dd, 1 H), 7.66 (d, 1 H), 8.06 (dd, 1 H). LCMS ES *m/z* 369/371 $[M+H]^+$. A Chiralpak AD-H (4.6 x 100 mm, 5 micron) column was eluted with 10% MeOH (0.1% DEA) in CO_2 at 120 bar. A flow rate of 5.0 mL/min gave the minor isomer Rt 0.6 minutes and the major isomer Rt 0.8 minutes (99% ee). Optical rotation: $[\alpha]_d^{20}$ = -92.4 deg (c=1.5, MeOH).

Preparation of 1-(5-fluoro-2-iodophenyl)ethyl methanesulfonate (11).



Step 1:

To a solution of **compound 8** (25 g, 0.162 mol) in 2 N HCl solution (350 mL) was added a solution of sodium nitrite (11.2 g, 0.16 mol) in H_2O (150 mL) drop-wise while maintaining the temperature between 0 - 5 °C. After the addition was completed, the mixture was stirred at 0~5 °C for 90 minutes. Then, the mixture was added to a solution of potassium iodide (53 g, 0.32 mol) and copper (I) iodide (15.2 g, 0.081 mol) in H_2O (150 mL) drop-wise with the temperature maintained at ~5 °C. After addition was completed, the mixture was stirred at room temperature for 18 hours after which TLC (EtOAc) indicated that the reaction was complete. The mixture was filtered and the cake dried. The residue was diluted with MTBE (500 mL), refluxed for 20 minutes, and filtered. The filtrate was concentrated to afford **compound 9** as a yellow solid (30 g, 75% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.04 - 8.00 (m, 1 H), 7.59 - 7.56 (m, 1 H), 7.08 - 7.03 (m, 1 H).

Step 2:

To a solution of **compound 9** (67 g, 0.26 mol) in anhydrous THF (500 mL) was added a solution of BH_3•SMe_2 (50.9 mL, 0.51 mol, 1.0 M) in dry THF (150 mL) drop-wise at 0 °C under N_2. After addition was completed, the mixture was stirred at 0 °C for 30 min, and then refluxed for 2 hours. TLC (petroleum ether/EtOAc 1/1) indicated that the reaction was completed. The mixture was quenched with saturated aqueous NH_4Cl solution (300 mL). The volatiles were removed *in vacuo*, and the residue extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 and concentrated to give a residue, which was purified by silica gel chromatography eluting with petroleum ether : EtOAc (50/1 to

25/1) and gave **compound 10** as a white solid (55 g, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.66 (m, 1 H), 7.20 - 7.17 (m, 1 H), 6.72 - 6.67 (m, 1 H), 4.57 (d, 2 H), 1.98 (t, 1 H).

Step 3:

To a mixture of **compound 10** (55 g, 221 mmol) in $CHCl_3$ (500 mL) was added MnO_2 (115 g, 1.33 mol), and the mixture was refluxed for 18 hours. TLC (petroleum ether : EtOAc = 10 : 1) indicated the reaction was completed. The mixture was filtered, and the filtrate was concentrated to afford **compound 11** as a yellow solid (50 g, 97% yield).

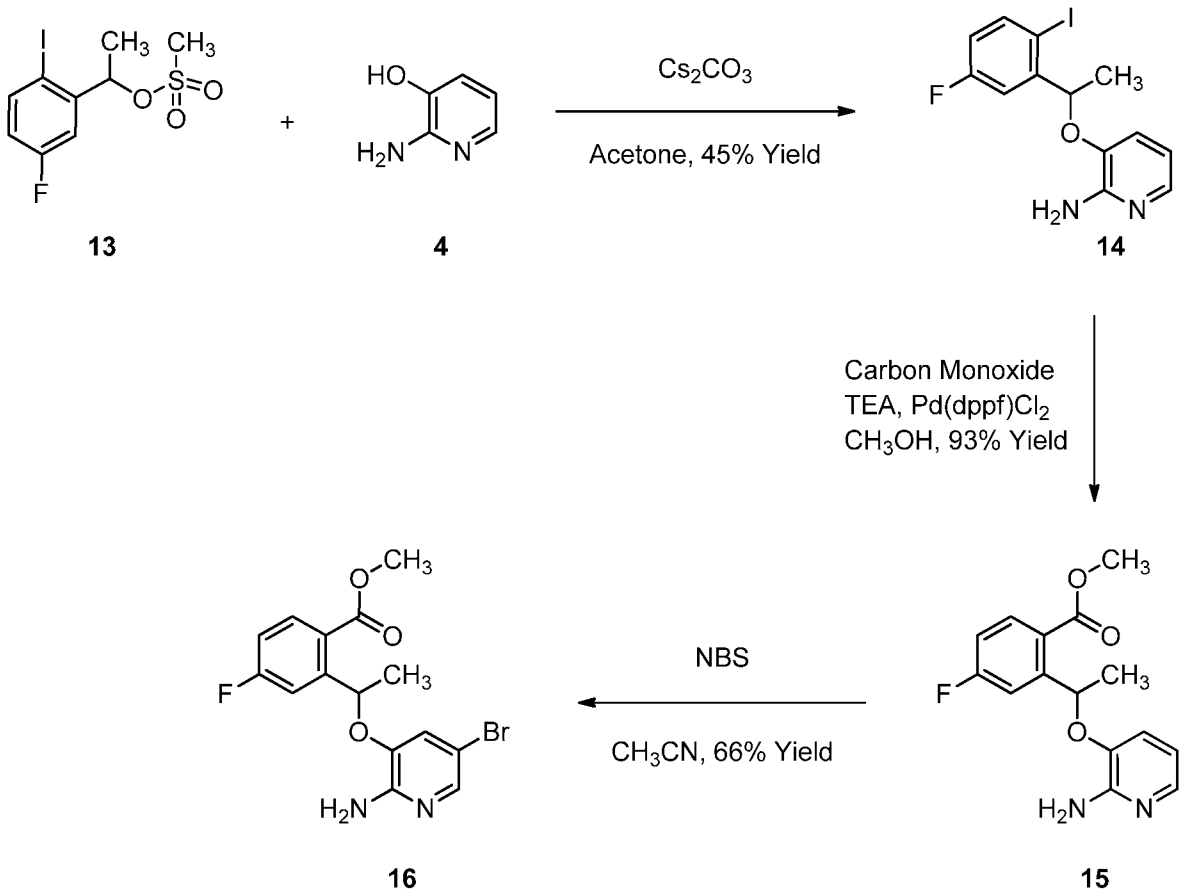
Step 4:

To a solution of **compound 11** (50 g, 200 mmol) in anhydrous THF (500 mL) was added CH_3MgBr (200 mL, 600 mmol, 3 M in diethyl ether) drop-wise at -60 °C under N_2. Once addition was completed, the mixture was warmed to room temperature and stirred for a further 2 hours. TLC (petroleum ether: EtOAc 10:1) indicated the reaction was completed. The mixture was quenched with saturated aqueous NH_4Cl solution (300 mL), and extracted with EtOAc (200 mL × 3). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4 and concentrated *in vacuo* and afforded **compound 12** as a yellow solid (50 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.64 (m, 1 H), 7.27 - 7.24 (m, 1 H), 6.71 - 6.65 (m, 1 H), 4.96 - 4.94 (m, 1 H), 1.38 (d, 3 H).

Step 5:

To a stirred solution of **compound 12** (57 g, 0.213 mol) and TEA (38.5 mL, 0.277 mol) in dry DCM (1 L) was added drop-wise MsCl (35.7 g, 0.213 mol) with the temperature maintained at 0 °C. After the addition was completed, the reaction mixture was stirred at this temperature for 30 minutes and then the mixture was allowed to warm and stirred at room temperature for 3 hours. TLC (petroleum ether/EtOAc 10: 1) indicated the reaction was complete. The reaction mixture was washed sequentially with 1 N HCl (200 mL × 3), saturated aqueous $NaHCO_3$ solution (200 mL × 3) and brine (100 mL × 3), dried over Na_2SO_4 and concentrated *in vacuo* and afforded **compound 13** as yellow oil (65 g, 89% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (1 H, dd), 7.24 (1 H, dd), 6.82 (1 H, td), 5.88 (1 H, q), 2.92 (3 H, s), 1.64 (3 H, d).

Preparation of methyl 2-(1-((2-amino-5-bromopyridin-3-yl)oxy)ethyl)-4-fluorobenzoate (16).



Step 1:

To a stirred suspension of **compound 13** (57 g, 0.16 mol) and **compound 4** (18.1 g, 0.16 mol) in acetone (1 L) was added Cs_2CO_3 (70 g, 0.21 mol) in portions at room temperature. After the addition was completed, the reaction mixture was stirred at room temperature for 15 minutes and then stirred at 45 °C for 18 hours. TLC (petroleum ether/EtOAc=3:1) indicated that the reaction was complete. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to yield a residue, which was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (10:1 to 3:1) and gave **compound 14** as a brown solid (47 g, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 - 7.69 (m, 1 H), 7.54 (d, 1 H), 7.03 (dd, 1 H), 6.71 - 6.68 (m, 1 H), 6.44 - 6.37 (m, 2 H), 5.32 - 5.27 (m, 1 H), 4.68 (br s, 2 H), 1.54 (d, 3 H).

Step 2:

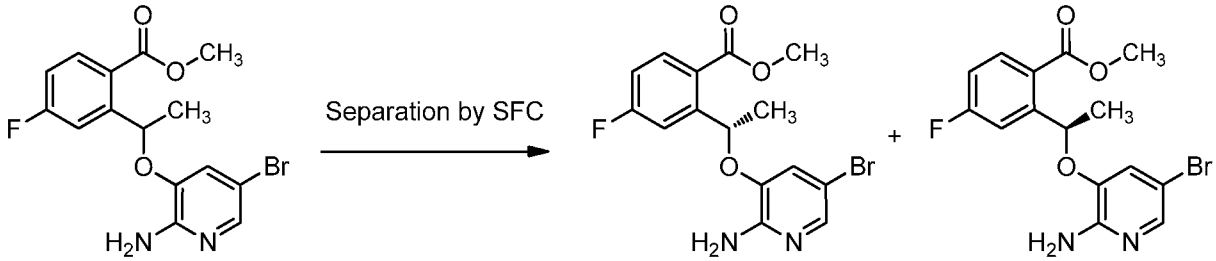
The procedure described in step 4 for **compound 6** was used to prepare **compound 15** (35.5 g, 93% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (1 H, dd), 7.61 (1 H, d), 7.10 (1 H, dd), 6.75 (1 H, td), 6.51 - 6.44 (2 H, m), 5.36 (1 H, q), 4.75 (2 H, br s), 1.61 (3 H, d).

Step 3:

The procedure described in step 5 for **compound 7** was used to prepare **compound 16** (29 g, 66% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (1 H, dd), 7.67 (1 H, d), 7.25 (1 H, dd), 7.03 (1 H,

td), 6.75 (1 H, d), 6.33 (1 H, q), 4.76 (2 H, br s), 3.96 (3 H, s), 1.65 (3 H, d). LCMS *m/z* 181 (styrene fragment from cleavage at the ether bond).

Preparation of (*S*)-methyl 2-(1-((2-amino-5-bromopyridin-3-yl)oxy)ethyl)-4-fluorobenzoate (17) and (*R*)-methyl 2-(1-((2-amino-5-bromopyridin-3-yl)oxy)ethyl)-4-fluorobenzoate (7).



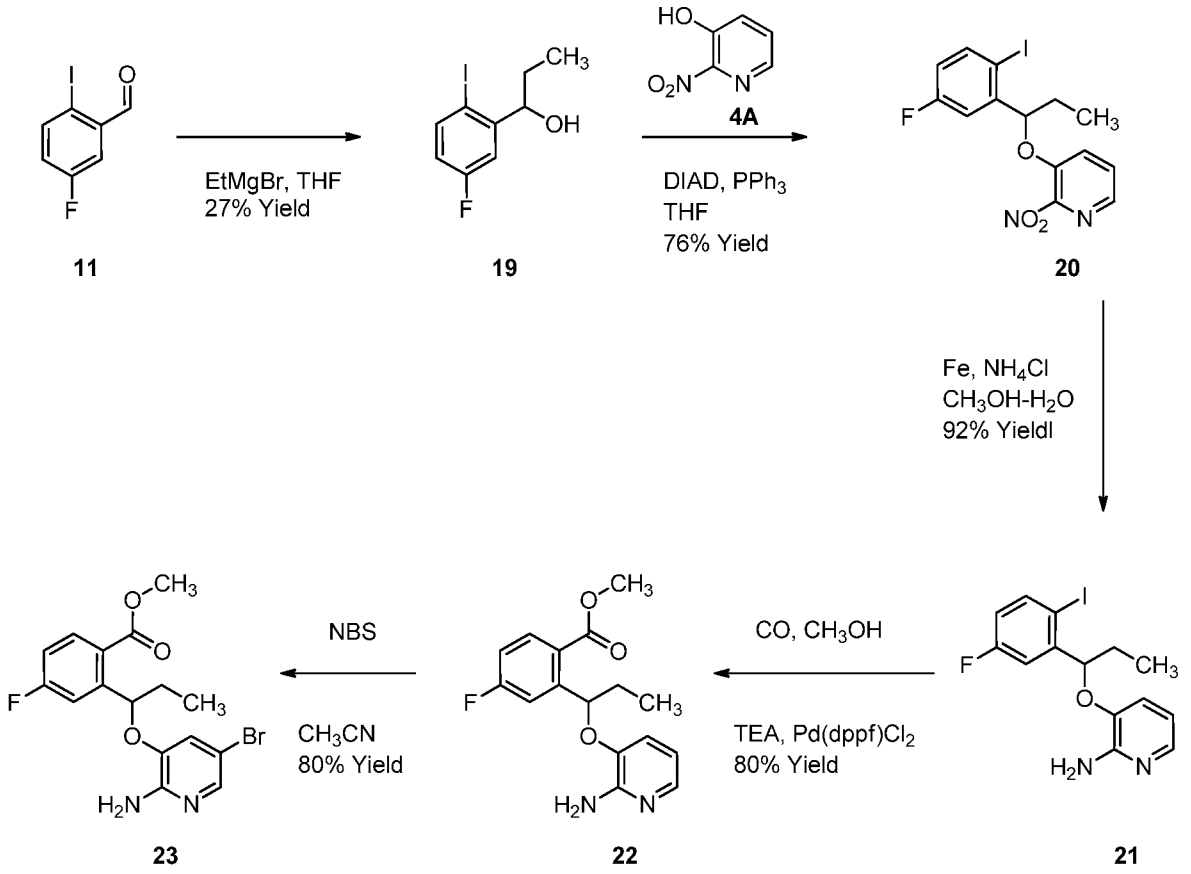
16 17 7

Compound **16** (24 g) was resolved by SFC and gave **compound 17** (Peak 1) (10.6 g, 88% yield) and **compound 7** (Peak 2) (10.2 g, 85% yield) as yellow solids. A Chiralpak AD-H (250 × 4.6 mm I.D., 5 micron particle size) column was eluted with 5% to 40% ethanol (0.05% DEA) in CO_2 at a flow rate of 2.3 mL/min and gave Peak 1 retention time of 4.1 minutes and Peak 2 retention time of 5.8 minutes.

Compound 17 (Peak 1): 99 % ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, 1 H), 7.60 (d, 1 H), 7.18 (t, 1 H), 6.99 - 6.94 (m, 1 H), 6.68 (d, 1 H), 6.28 - 6.24 (dd, 1 H), 4.69 (s, 2 H), 3.89 (s, 3 H), 1.58 (d, 3 H). LCMS *m/z* 369/371 $[M+H]^+$. $[\alpha]_d$= +108.0 deg (c=0.5, MeOH).

Compound 7 (Peak 2): 100% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, 1 H), 7.60 (d, 1 H), 7.18 (t, 1 H), 6.99 - 6.95 (m, 1 H), 6.68 (d, 1 H), 6.24 (dd, 1 H), 4.69 (s, 2 H), 3.89 (s, 3 H), 1.58 (d, 3 H). LCMS *m/z* 369/371 $[M+H]^+$. $[\alpha]_d$= -100.0 deg (c=0.5, MeOH).

Preparation of methyl 2-(1-((2-amino-5-bromopyridin-3-yl)oxy)propyl)-4-fluorobenzoate (23).



Step 1:

To a solution of **compound 11** (40 g, 0.16 mol) in dry THF (400 mL) was added drop-wise EtMgBr (320 mL, 1 M in THF) at 0 °C. After the addition, the resulting mixture was stirred at this temperature for 2 hours. TLC (petroleum ether/EtOAc= 10: 1) indicated the reaction was complete. The reaction mixture was quenched with saturated NH_4Cl (200 mL) at 0 °C and the mixture was extracted with EtOAc (300 mL × 2). The combined organic layers were washed with brine (500 mL × 2), dried over Na_2SO_4 and concentrated. The residue was purified by Biotage (petroleum ether/EtOAc 20:1 to 10:1) to give **compound 19** as light yellow oil (12 g, 27% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 - 7.64 (m, 1 H), 7.20 - 7.17 (m, 1 H), 6.66 (t, 1 H), 4.72 - 4.70 (m, 1 H), 2.20 (s, 1 H), 1.77 - 1.69 (m, 1 H), 1.61 - 1.52 (m, 1 H), 0.98 (t, 3 H).

Step 2:

To a stirred solution of **compound 19** (11g, 0.039 mol), the **compound 4A** (5.5 g, 0.039 mol) and PPh_3 (14 g, 0.055 mol) in anhydrous THF (200 mL) was added drop-wise DIAD (11 g, 0.055 mol) at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 16 hours. TLC (petroleum ether/EtOAc 10: 1) indicated the reaction was complete. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 10:1 to 3:1) to give as a yellow solid **compound 20** (12 g, 76% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, 1 H), 7.83 - 7.81 (m, 1 H), 7.47 - 7.42 (m, 1 H),

7.22 - 7.19 (m, 1 H), 7.09 - 7.07 (m, 1 H), 6.85 - 6.82 (m, 1 H), 5.36 - 5.32 (m, 1 H), 1.88 - 1.85 (m, 1 H), 1.09 (t, 3 H).

Step 3:

A suspension of **compound 20** (12 g, 0.029 mol) and Fe (10 g, 0.18 mol) in methanol (100 mL) and saturated aqueous NH_4Cl (100 mL) was stirred at 80 °C for 2 hours. TLC (petroleum ether/EtOAc=1:1) showed the reaction was complete. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give an aqueous solution, which was extracted with EtOAc (150 mL x 2). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give **compound 21** as a pale brown solid (10 g, 92% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 7.96 - 7.93 (m, 1 H), 7.50 (d, 1 H), 7.34 (d, 1 H), 7.02 (t, 1 H), 6.59 - 6.57 (m, 1 H), 6.41 - 6.40 (m, 1 H), 5.94 (s, 2 H), 5.24 (t, 1 H), 1.96 - 1.85 (m, 2 H), 1.08 (t, 3 H).

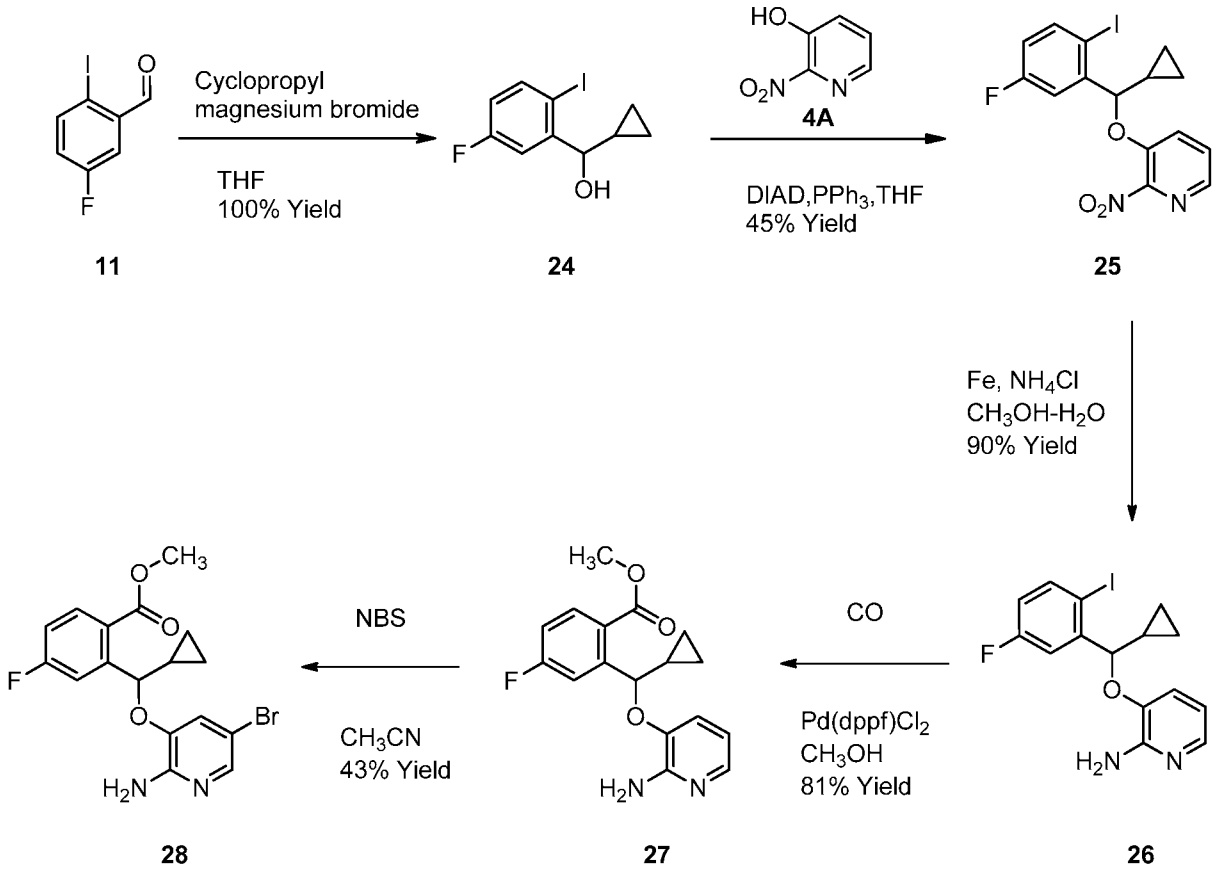
Step 4:

A mixture of **compound 21** (10 g, 0.027 mol), $Pd(dppf)Cl_2$ (2.6 g, 0.0027 mol) and TEA (10 mL, 0.08 mol) in methanol (250 mL) was sealed under CO (2 MPa) at 100 °C for 16 hours. TLC (petroleum ether/EtOAc=1:1) indicated the reaction was complete. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give residue, which was purified by column chromatography on silica gel, (petroleum ether/EtOAc from 5:1 to 2:1) to give **compound 22** as a pale yellow solid (6.5 g, 80% yield).

Step 5:

To a stirred solution of **compound 22** (6.5 g, 0.02 mol) in CH_3CN (50 mL) was added drop-wise a solution of NBS (3.8 g, 0.02 mol) in CH_3CN (40 mL) at 0 °C during a period of 30 minutes. After the addition, the reaction mixture was stirred at this temperature for 30 minutes. TLC (petroleum ether/EtOAc =1:1) indicted the reaction was complete. The mixture was diluted with EtOAc (200 mL), washed with saturated $NaHCO_3$ (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel, which was eluted with petroleum ether/EtOAc (10:1 to 3:1) to give **compound 23** as a pale yellow solid (5.8 g, 76% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 - 7.98 (m, 1 H), 7.59 (s, 1 H), 7.12 (d, 1 H), 6.96 - 6.94 (m, 1 H), 6.69 (s, 1 H), 6.09 - 6.06 (m, 1 H), 4.74 (s, 2 H), 3.89 (s, 3 H), 1.88 - 1.82 (m, 2 H), 1.02 - 096 (m, 3 H). LCMS *m/z* 383/385 $[M+H]^+$.

Preparation of methyl 2-(((2-amino-5-bromopyridin-3-yl)oxy)(cyclopropyl)methyl)-4-fluorobenzoate (28).



Step 1:

The procedure described in step 1 for **compound 23** was used to prepare **compound 24** as a light yellow oil (29 g, 100% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dt, 1 H), 7.21 (dd, 1 H), 6.68 (dt, 1 H), 4.45 (d, 1 H), 4.10 - 4.00 (m, 1 H), 1.97 (s, 1 H), 1.20 - 1.11 (m, 1 H), 0.56 - 0.36 (m, 4 H).

Step 2:

The procedure described in step 2 for **compound 23** was used to prepare **compound 25** as a yellow solid (18 g, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, 1 H), 7.74 (dd, 1 H), 7.32 - 7.29 (m, 1 H), 7.16 - 7.07 (m, 2 H), 6.76 - 6.68 (m, 1 H), 5.22 (d, 1 H), 1.38 - 1.19 (m, 1 H), 0.71 - 0.56 (m, 4 H).

Step 3:

The procedure described in step 3 for **compound 23** was used to prepare **compound 26** as a pale brown solid (15 g, 90% yield).

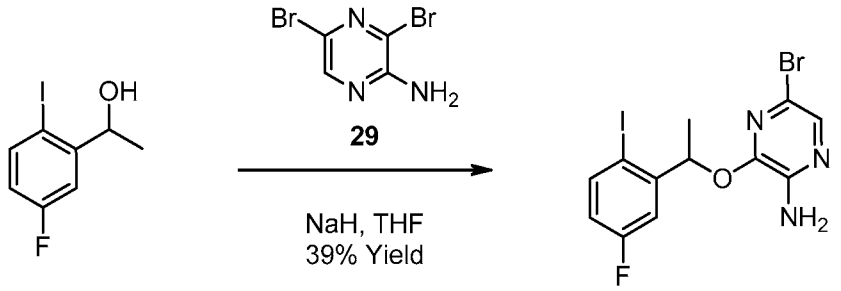
Step 4:

The procedure described in step 4 for **compound 23** was used to prepare **compound 27** as a yellow solid (10 g, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (q, 1 H), 7.59 (d, 1 H), 7.32 - 7.26 (m, 1 H), 7.03 - 6.99 (m, 1 H), 6.74 - 6.72 (m, 1 H), 6.44 - 6.40 (m, 1 H), 6.04 (d, 1 H), 4.73 (s, 2 H), 3.94 (s, 3 H), 1.35 - 1.28 (m, 1 H), 0.62 - 0.52 (m, 4 H).

Step 5:

The procedure described in step 5 for **compound 23** was used to prepare **compound 28** as a pale yellow solid (5.3 g, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 - 7.98 (m, 1 H), 7.49 - 7.45 (m, 2 H), 7.16 - 7.11 (m, 1 H), 6.99 (d, 1 H), 5.90 (q, 1 H), 3.96 (s, 3 H), 1.42 - 1.41 (m, 1 H), 0.69 - 0.68 (m, 1 H), 0.56 - 0.49 (m, 3 H). LCMS *m/z* 395/397 $[M+H]^+$.

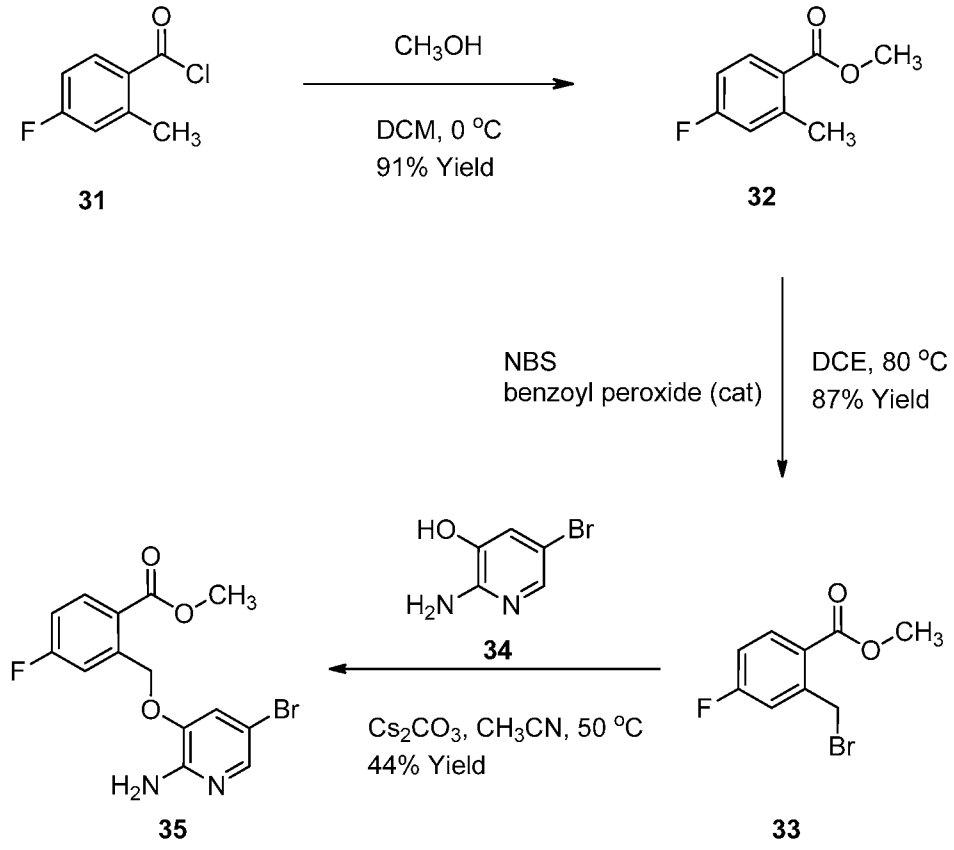
Preparation of 5-bromo-3-(1-(5-fluoro-2-iodophenyl)ethoxy)pyrazin-2-amine (30).



12 **30**

To a solution of **compound 12** (17.8 g, 67.9 mmol) in anhydrous THF (350 mL) was added NaH (2.7 g, 67.9 mmol, 60% in oil) at 0 °C under nitrogen. The mixture was stirred for a further 30 minutes. A solution of **compound 29** (17.1 g, 67.9 mmol) in anhydrous THF (150 mL) was added to the above mixture at 0 °C, and the mixture was refluxed for 18 hours. LCMS indicated that 90% of the starting alcohol had been consumed. The volatiles were removed under reduced pressure, and the residue was diluted with a mixture of H_2O (100 mL) and EtOAc (100 mL). The mixture was filtered, the organic layer removed, and the aqueous layer further extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated to give a residue, which was purified by silica gel column eluting with petroleum ether : EtOAc (30/1 to 20/1) to give **compound 30** as a yellow solid (11.5 g, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.73 (m, 1 H), 7.55 (s, 1 H), 7.04 (d, *J* = 6.8 Hz, 1 H), 6.65 - 6.71 (m, 1 H), 6.10 (q, *J* = 6.4 Hz, 1 H), 4.81 (br s, 2 H), 1.55 (d, *J* = 6.4 Hz, 3 H). LCMS *m/z* 438/440 $[M+H]^+$.

Preparation of methyl 2-(((2-amino-5-bromopyridin-3-yl)oxy)methyl)-4-fluorobenzoate (35).



31 32 33 34 35

Step 1:

To an ice-cooled solution of **compound 31** (24.3 g, 141 mmol) in DCM (300 mL) was added methanol (100 mL) drop-wise over 20 minutes. The reaction mixture was then allowed to warm to room temperature and stirred at room temperature for 2 hours. The reaction was then concentrated *in vacuo* and the residue was dissolved in DCM (200 mL) and then washed with saturated aqueous sodium bicarbonate (150 mL). The organics were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **compound 32** as a colorless oil (19.5 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1 H, m), 6.95 - 6.85 (2 H, m), 3.90 (3 H, s), 2.60 (3 H, s). LCMS ES no ionization.

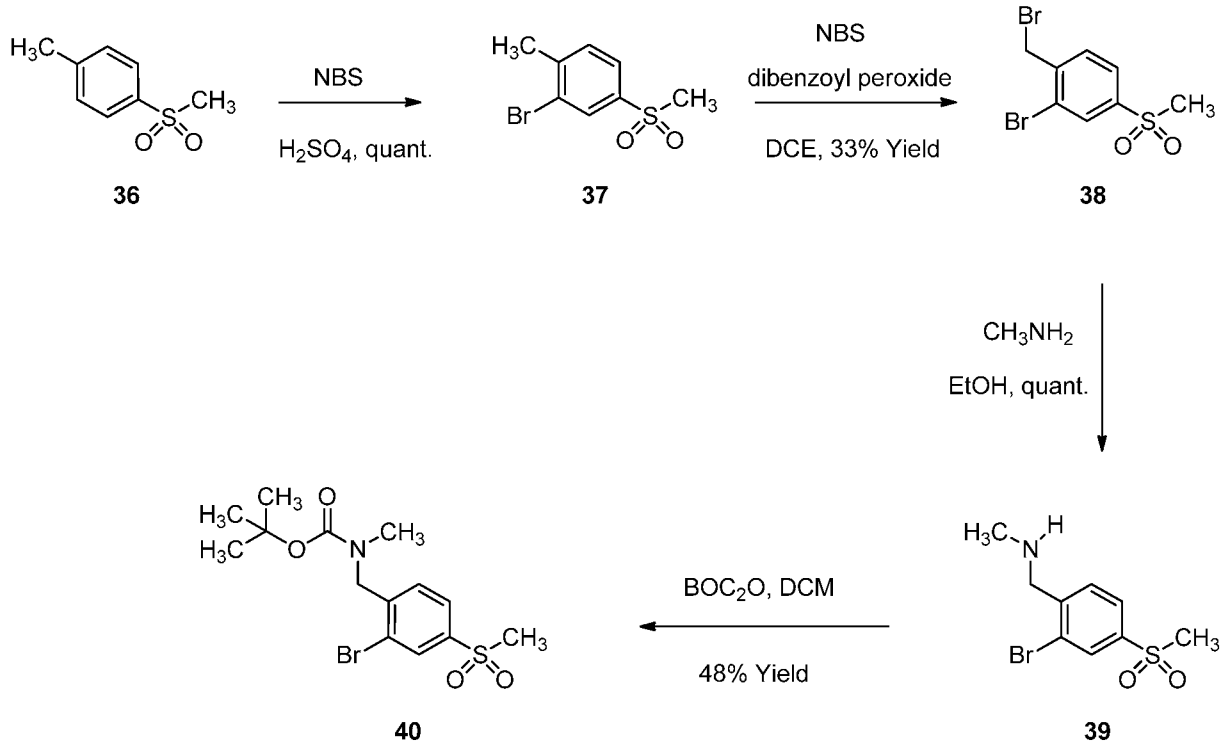
Step 2:

To a solution of **compound 32** (6.3 g, 41.4 mmol) in DCE (100 mL) was added NBS (8.1 g, 46 mmol) followed by a catalytic amount of benzoyl peroxide (200 mg, 0.82 mmol). The reaction was then heated at 80 °C for 8 hrs. The reaction was cooled to room temperature and the precipitated solid was removed by filtration and washed with MTBE. The filtrate was concentrated in vacuo and the residue was partitioned between 2 N NaOH (150 mL) and MTBE (150 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give **compound 33** (8.9 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (1 H, m), 7.20 (1 H, m), 7.10 (1 H, m), 4.90 (2 H, s), 3.95 (3 H, s).

Step 3:

To **compound 33** (15.0 g, 61 mmol) in acetonitrile (150 mL) at room temperature was added **compound 34** (10.9 g, 58 mmol) followed by cesium carbonate (23 g, 69 mmol). The mixture was then heated at 50 °C for 5 hours before cooling to room temperature. The mixture was then concentrated *in vacuo* to remove ~ 80% of the acetonitrile before the residue was partitioned between water (400 mL) and ethyl acetate (400 mL). The two layers were separated and the aqueous layer was re-extracted with ethyl acetate (400 mL). The combined organics were then concentrated in vacuo to give a dark brown solid. (Note that the aqueous layer was still very dark and contained insoluble solids – yield likely to be compromised by the lack of solubility of the product in organic solvents). The solid residue was then slurried in MTBE (300 mL) for 20 minutes and **compound 35** was collected as a dark grey solid (11.5 g, 52% yield. This product was then purified further by column chromatography on silica gel eluting with ethyl acetate and cyclohexane (33% EtOAc to neat EtOAc) to give **compound 35** (9.5 g, 44% yield) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1 H, m), 7.75 (1 H, s), 7.35 (1 H, m), 7.10 (1 H, m), 7.05 (1 H, s), 5.50 (2 H, s), 4.75 (1 H, br s), 3.90 (3 H, s). LCMS ES *m/z* 355/357 $[M+H]^+$.

Preparation of *tert*-butyl 2-bromo-4-(methylsulfonyl)benzyl(methyl)carbamate (40).



Step 1:

To a stirred mixture of NBS (12.0 g, 68 mmol), and **compound 36** (10.0 g, 58 mmol) was added concentrated sulfuric acid (50 mL). The solution initially turned green, after which a pale yellow

color persisted. The solution was stirred for 16 hours at room temperature. The mixture was carefully poured onto ice (400 mL), and then extracted with ethyl acetate (500 mL). The organic layer was washed with 2 M aqueous sodium hydroxide (2x 300 mL), then dried over magnesium sulfate, and evaporated to give **compound 37** as a white solid (14.7 g, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3 H), 3.05 (s, 3 H), 7.43 (d, 1 H), 7.77 (dd, 1 H), 8.10 (d, 1 H).

Step 2:

Compound 37 (10.0 g, 40 mmol) was dissolved in 1,2-dichloroethane (250 mL), followed by addition of NBS (7.1 g, 40 mmol) and dibenzoyl peroxide (970 mg, 4.0 mmol), in small portions. After stirring at 85 °C for 2 hours, TLC (8:2 cyclohexane/ethyl acetate) indicated near-consumption of starting material, and the emergence of a minor spot for dibrominated material. The mixture was allowed to cool, diluted to 500 mL with dichloromethane, and washed with water (2 x 250 mL). The organic layer was dried over $MgSO_4$, and evaporated to a yellow oil. The viscous oil was cooled in an ice bath which gave a solid. Trituration of the solid with diethyl ether gave **compound 38** (4.4 g, 33% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (s, 3 H), 4.60 (s, 2 H), 7.66 (d, 1 H), 7.87 (dd, 1 H), 8.15 (d, 1 H). LCMS ES No ionization of compound **11** evident.

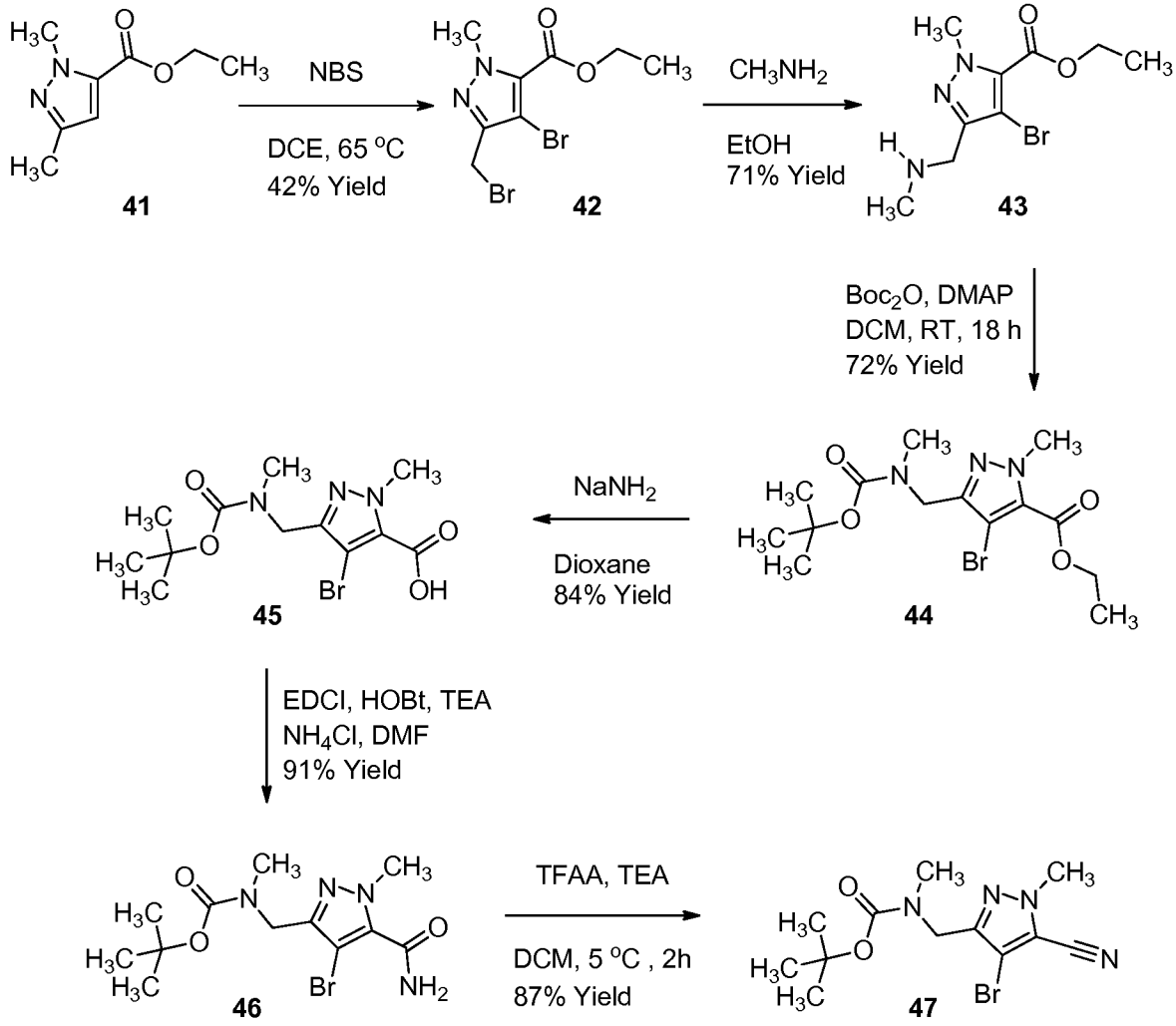
Step 3:

Compound 38 (4.3 g, 13 mmol) was dissolved in methylamine solution (33% solution in ethanol, 100 mL), and stirred at RT for 16 hours. TLC (ethyl acetate) and LCMS indicated consumption of starting material, and the major peak for the product. The mixture was evaporated to **compound 39** as a white solid (3.7 g, quantitative yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 2.49 (s, 3 H), 3.15 (s, 3 H), 3.97 (s, 2 H), 7.71 (d, 1 H), 7.94 (dd, 1 H), 8.16 (d, 1 H). LCMS *m/z* 278/280 $[M+H]^+$.

Step 4:

Compound 39 (3.7 g, 13 mmol) was dissolved in dichloromethane (40 mL), and the mixture cooled to 0 °C. A solution of di(*tert*-butyl) dicarbonate (3.5 g, 16 mmol) in dichloromethane (35 mL) was added dropwise. The ice bath was removed and the mixture stirred for 18 hours at room temperature. LCMS and TLC (1:1 cyclohexane/ethyl acetate) showed consumption of compound **12**, so the reaction was diluted to 150 mL with dichloromethane, and washed with water (2 x 100 mL). Organic extracts were dried over magnesium sulfate, and evaporated to a pale yellow oil. The crude product was purified over silica gel, which was eluted with a gradient of 10% to 20% ethyl acetate in cyclohexane, gave **compound 40** (2.4 g, 48% yield). ^{1}H NMR (400 MHz, methanol-d_4) δ 1.36 - 1.52 (br, 9 H, t-Bu rotamers), 2.95 (s, 3 H), 3.15 (s, 3 H), 4.58 (s, 2 H), 7.40 (d, 1 H), 7.95 (d, 1 H), 8.15 (d, 1 H). LCMS ES *m/z* 378/380 $[M+H]^+$.

Preparation *of tert*-butyl ((4-bromo-5-cyano-1-methyl-1H-pyrazol-3-yl)methyl)-(methyl)carbamate (47).



Step 1:

The procedure described in step 2 for **compound 40** was used to prepare **compound 42** (4.1 g, 42% yield). TLC (EtOAc/Cyclohexane; 1:10; $KMnO_4$): Rf~0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (s, 2 H), 4.41 (q, 2 H), 4.15 (s, 3 H), 1.42 (t, 3 H). LCMS ES *m/z* 324/326/328 $[M+H]^+$.

Step 2:

The procedure described in step 3 for **compound 40** was used to prepare **compound 43** (1.8 g, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (q, 2 H), 4.14 (s, 3 H), 4.05 (s, 2 H), 2.62 (d, 3 H), 1.41 (t, 3 H). LCMS ES *m/z* 276/278 $[M+H]^+$.

Step 3:

The procedure described in step 4 for **compound 40** was used to prepare **compound 44** (1.8 g, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 - 4.44 (m, 2 H), 4.41 (q, 2 H), 4.12 (s, 3 H), 2.82 - 2.79 (m, 3 H), 1.47 (s, 9 H), 1.41 (t, 3 H). LCMS ES *m/z* 376/378 $[M+H]^+$ and 276/278 $[M-BOC]^+$.

Step 4:

Compound 44 (4 g, 11 mmol) was dissolved in dioxane (43 mL). Sodium amide (1 g, 27 mmol) was added in one portion. The reaction mixture was stirred at 100 °C for 24 h. After this time, the solvent was removed under reduced pressure to give a white solid. The material was suspended in EtOAc (100 mL) and washed with 5% citric acid solution (100 mL). The organic phase was separated and washed with water (100 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give **compound 45** as a yellow gum (3.1 g, 84% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.27 (s, 2 H), 3.92 (s, 3 H), 2.70 (s, 3 H), 1.40 (s, 9 H). LCMS ES *m/z* 348/350 $[M+H]^+$ and 248/250 [M-BOC]+.

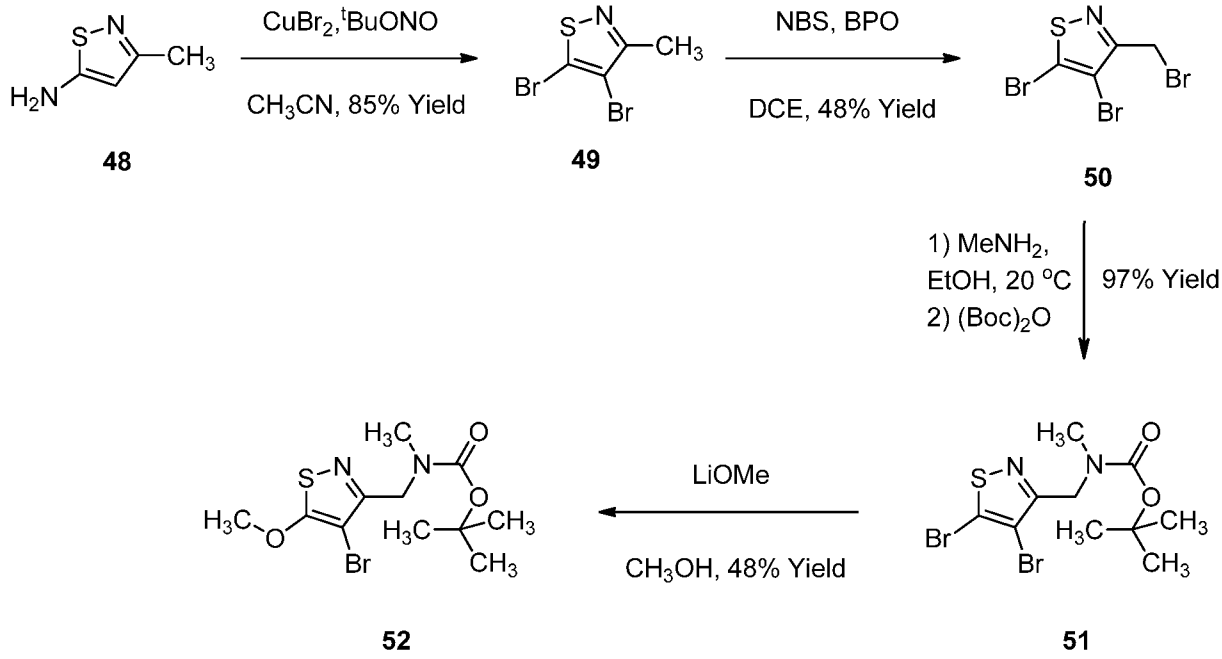
Step 5:

Compound 45 (3 g, 8.6 mmol) was dissolved in DMF (43 mL, 0.2 M). HOBt (1.2 g, 8.6 mmol) was added, followed by ammonium chloride (0.9 g, 17.2 mmol). EDCI (2.5 g, 13 mmol) was then added, followed by TEA (2.4 mL, 17 mmol). The reaction mixture was stirred at room temperature. After 18h, the solvent was removed under reduced pressure to give a yellow oil (8.0 g). The residue was dissolved in EtOAc (7 5mL). The organic phase was washed with $NaHCO_3$ (sat. solution, 70 mL) and then brine (100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to give **compound 46** as a dark yellow oil (2.7 g, 91% yield). This material was used directly in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (br s, 1 H), 5.95 (br s, 1 H), 4.49 (br s, 2 H), 4.16 (s, 3 H), 2.81 (br s, 3 H), 1.47 (s, 9 H). LCMS ES *m/z* 347/349 $[M+H]^+$ and 247/249 $[M-BOC]^+$.

Step 6:

Compound 46 (2.7 g, 7.9 mmol) was dissolved in DCM (80 mL, 0.1 M). TEA (3.3 mL, 23.8 mmol) was then added and the reaction mixture cooled down to -5 °C. Trifluoroacetic anhydride (2.2 mL, 15.8 mmol) in DCM (15 mL) was added dropwise over 30 min. After addition, the reaction mixture was stirred at 0 °C for 1 h. After this time, the solvents were removed under reduced pressure to give a dark yellow oil. This residue was diluted in DCM (100 mL), washed with 5% citric acid, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and the solvents removed *in vacuo* to give a dark yellow oil (2.6 g). The crude product was purified by reverse phase chromatography to give **compound 47** as a yellow oil (2.3 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (br s, 2 H), 4.01 (s, 3 H), 2.83 (br s, 3 H), 1.47 (s, 9 H). LCMS ES *m/z* 331/329 $[M+H]^+$ and 229/231 $[M-BOC]^+$ as the base ion.

Preparation of *tert*-butyl ((4-bromo-5-methoxyisothiazol-3-yl)methyl)(methyl)carbamate (52).



48 **49** **50** **51** **52**

Step 1:

Tert-butyl nitrite (47.4 g, 0.46 mol) was added slowly to a stirred mixture of $CuBr_2$ (103 g, 0.46 mol) and CH_3CN (900 mL) at 0 °C over 2 minutes. After stirring for 5 minutes, the HCl salt of **compound 48** (35 g, 0.23 mol) was added portion-wise as a solid over 20 minutes. During the addition a slight exotherm of 10 °C was noticed but quickly subsided on complete addition of **compound 48**. After complete addition of **compound 48**, the reaction was stirred while slowly warming to room temperature over 20 minutes. HCl (aq, 1 M, 2.5 L) was slowly added with stirring (some frothing and NO_2 gas given-off). The mixture was extracted into diethyl ether (2 x 800 mL). The combined organics were washed with HCl (aq, 1 M, 2 x 1 L), then brine (1 L), dried over Na_2SO_4, and the solvent was removed under reduced pressure, giving **compound 49** as a yellow/orange solid (45 g, 76% yield). TLC: R_f = 0.75 (10% EtOAc in heptanes). ^1H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3 H). LCMS ES no ionization detected.

Step 2:

A mixture of **compound 49** (45 g, 175 mmol), NBS (47 g, 265 mmol) and di-benzoyl peroxide (70% in H_2O, 9.7 g, 40 mmol) in DCE (400 mL) was stirred at reflux for 12 hours. TLC (10% DCM in heptanes) showed approx 50% starting material (R_f = 0.50) and 50% product (R_f = 0.55). An additional portion of NBS (10 g, 56 mmol) was added and the reaction was stirred at reflux for 6 hours. After cooling, the mixture was filtered to remove succinimide and the filtrate

was concentrated. The residue was purified by column chromatography over silica gel, which was eluted with 5% EtOAc in heptanes, giving 50 g of an inseparable mixture consisting of starting material **49** and product **50** and dibromomethyl side product in an approximate ratio of 1 : 2.7 : 1 respectively. Compound **50** was obtained in 48% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.77 (s, 1 H, corresponds to dibromomethyl side product); 4.59 (s, 2 H, corresponds to compound **31**); 2.55 (s, 3 H, corresponds to starting material **30**). LCMS ES no ionization.

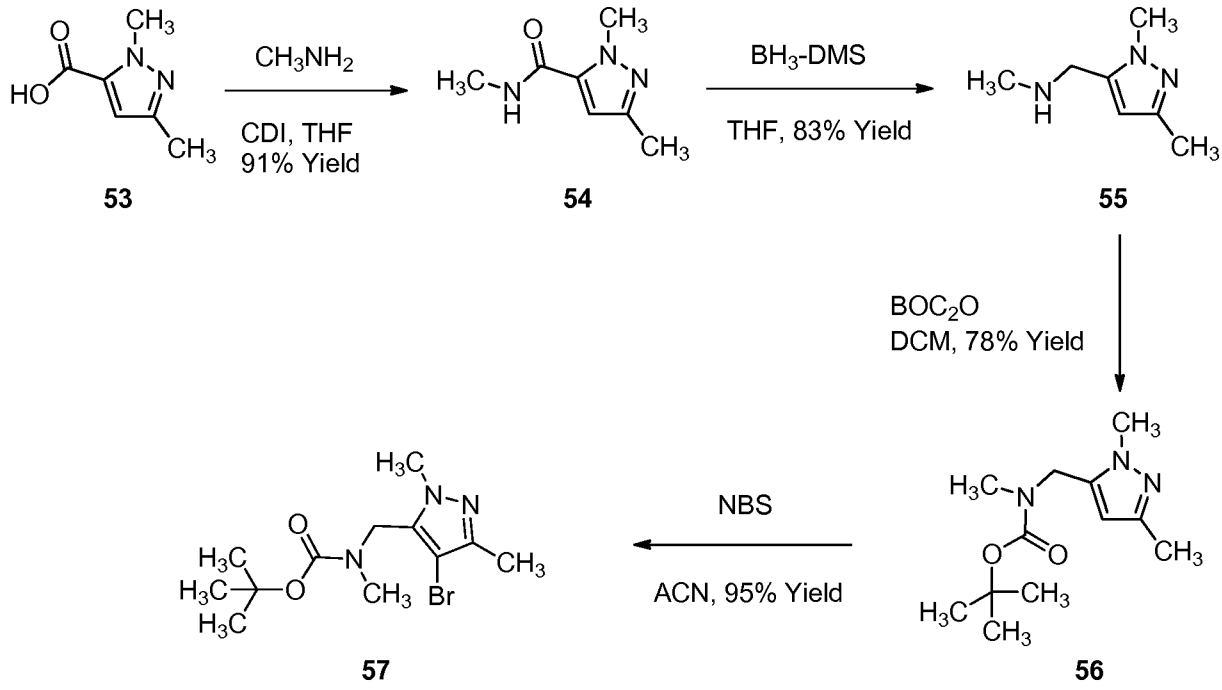
Step 3:

A solution of the mixture obtained from step 2 (50 g, calculated to contain 28 g, 83 mmol of pure compound **31**) in THF (20 mL) was added slowly to a solution of CH_3NH_2 (33% in EtOH, 200 mL, 2.1 mol) diluted with additional EtOH (200 mL) at 0 °C over 10 minutes. After complete addition, the reaction was stirred at 0 °C for 25 minutes. The reaction was then concentrated *in vacuo* to approximately 300 mL volume. Ethanol (150 mL) was added and the mixture was again concentrated to approximately 300 mL in volume. The resulting solution was then cooled to 0 °C and $(BOC)_2O$ (33 g, 150 mmol) was added portion-wise over 5 minutes (CO_2 evolution). After complete addition the mixture was left to stir at 20 °C overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography over silica gel, which was eluted with 10% EtOAc in heptanes, giving **compound 51** as a cream colored solid (32 g, 97% yield). TLC (R_f = 0.30, 10% EtOAc in heptanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 - 4.60 (m, 2 H), 2.90 - 2.99 (m, 3 H), 1.35 - 1.55 (m, 9 H). LCMS ES *m/z* 287 ES $[M\text{-Boc}]^+$.

Step 4:

Lithium (40 mg, 5.7 mmol) was cautiously added to methanol (6 mL), with stirring, in a reaction flask fitted with a reflux condenser. After the lithium dissolved, **compound 51** (350 mg, 0.91 mmol), dissolved in methanol (2 mL), was added in one portion and the resulting solution was stirred at 60 °C for 20 hours. TLC (10% EtOAc in heptanes) showed a major new spot (R_f = 0.20), along with approximately 20% compound **compound 51** (Rf = 0.30) and traces of two other products (R_f's = 0.25 and baseline). After cooling, the reaction (now containing a suspension) was added to water (30 mL) and the mixture was extracted into EtOAc (20 mL). The organic layer was separated, washed with brine (20 mL), dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography over silica gel, which was eluted with 10% EtOAc in heptanes, giving **compound 52** as a pale yellow oil (150 mg, 48% yield). TLC: R_f = 0.20 (10% EtOAc in heptanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 - 4.55 (m, 2 H), 4.04 (s, 3 H), 2.85 - 2.95 (m, 3 H), 1.40 - 1.50 (m, 9 H). LCMS ES *m/z* 237/239 $[M - Boc]^+$.

Preparation of *tert*-butyl ((4-bromo-1,3-dimethyl-1H-pyrazol-5-yl)methyl)(methyl)carbamate (57).



Step 1:

CDI (2.8 g, 17 mmol) was added to a suspension of **compound 53** (2.0 g, 14 mmol) in THF (25 mL) at 20 °C. The mixture was then warmed to 50 °C with stirring for 30 mins (gas evolution). The mixture was then cooled to -10 °C and $MeNH_2$ (2 M in THF, 20 mL, 40.0 mmol) was added in one portion. The ice bath was removed and the reaction was stirred at room temperature for 60 minutes. The mixture was then concentrated and purified by column chromatography over silica gel, which was eluted with 100% EtOAc, giving **compound 54** (2.0 g, 91% yield) as a clear oil. TLC: R_f = 0.60 (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3 H), 2.93 (d, 3 H), 4.09 (s, 3 H), 6.00 (br s, 1 H), 6.12 (s, 1 H). LCMS ES *m/z* 154 $[M+H]^+$.

Step 2:

BH_3·DMS (8.0 g, 105 mmol) was added slowly to a solution of **compound 54** (2.0 g, 13.0 mmol) in THF at -5 °C. After complete addition, the mixture was stirred at 50 °C for 3 hrs, before cooling and stirring at room temperature overnight. The reaction was then cooled to 0 °C and 6 M HCl (30 mL) was added slowly (frothing occured). After complete addition the mixture was stirred at 70 °C for 30 mins, before cooling to 0 °C and basified with NaOH (30% aq solution) to pH 13 (pH paper). The mixture was concentrated under reduced pressure to remove THF and then extracted into DCM (5 x 40 mL). The combined organic layers were dried over Na_2SO_4 and evaporated, which gave **compound 55** (1.5 g, 83% yield). TLC: R_f = 0.20 (98% EtOAc and 2% 7 M NH_3 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3 H), 2.40 (s, 3 H), 3.68 (s, 2 H), 3.78 (s, 3 H), 5.91 (s, 1 H).

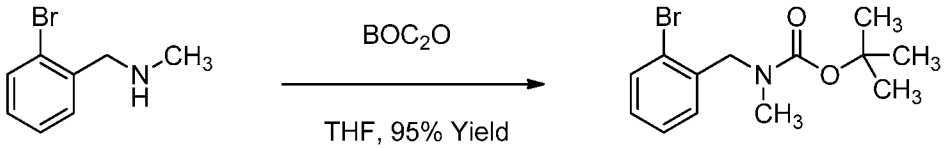
Step 3:

To a solution of **compound 55** (1.5 g, 10.7 mmol) in DCM (30 mL) was added $(BOC)_2O$ (3.27 g, 15 mmol). The mixture was stirred overnight, concentrated under reduced pressure and the residue purified by flash chromatography over silica gel, which was eluted with 30-50% EtOAc in cyclohexane, and gave **compound 56** (2.0 g, 78% yield) as a colorless oil. TLC: Rf = 0.50 (1:1 EtOAc/cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 2.20 (s, 3 H), 2.78 (s, 3 H), 3.78 (s, 3 H), 4.61 (s, 2 H), 5.94 (s, 1 H).

Step 4:

Compound 56 (2.1 g, 8.8 mmol) was dissolved in acetonitrile (31 mL), sodium bicarbonate (0.88 g, 10 mmol) was added and the mixture was cooled to 0 °C. NBS (1.6 g, 9.2 mmol) was added and the reaction mixture was stirred for 1 hour at ~5 °C. LCMS showed consumption of **compound 56**. The reaction mixture was warmed to RT, filtered and concentrated under vacuum to give a yellow oil. MTBE was added and a white solid was observed and filtered. The mother liquors were concentrated and MTBE was added again. The white solid formed was filtered and the mother liquors were washed with a diluted aqueous solution of sodium thiosulfate, water then brine. The solution was dried over $MgSO_4$, filtered and concentrated under vacuum to give **compound 57** as a white solid (2.7 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (s, 2 H), 3.79 (s, 3 H), 2.70 (s, 3 H), 2.20 (s, 3 H), 1.45 (s, 9 H). LCMS ES *m/z* 318/320 $[M+H]^+$.

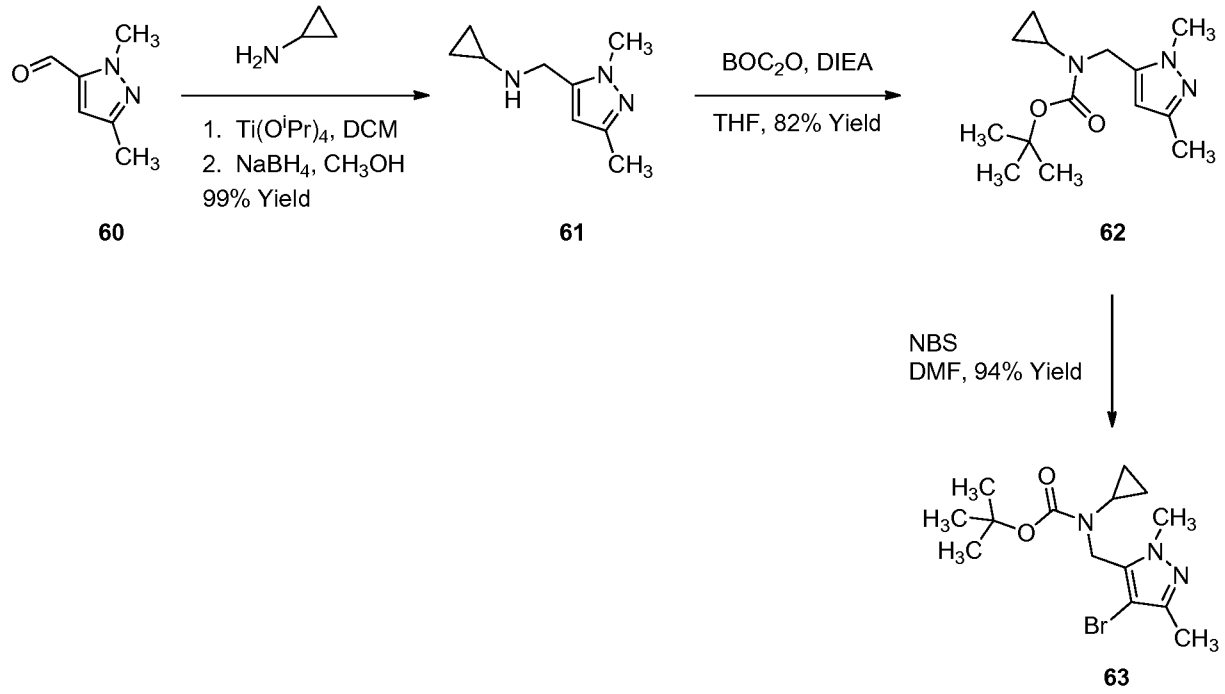
Preparation of *tert*-butyl 2-bromobenzyl(methyl)carbamate (59).



58 **59**

A solution of **compound 58** (2.0 g, 10.0 mmol) and Boc_2O (2.29 g, 10.5 mmol) in THF (40 mL) was stirred at RT for 16 hours. The mixture was then concentrated *in vacuo*. The crude product was purified by flash column chromatography over silica gel, which was eluted with 10% EtOAc in heptanes, and yielded **compound 59** as a colorless oil (2.8 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 1 H), 7.30 (t, 1 H), 7.13 (m, 2 H), 4.53 (br d, 2 H), 2.87 (br s, 3 H), 1.46 (br d, 9 H).

Preparation of *tert*-butyl ((4-bromo-1,3-dimethyl-1H-pyrazol-5-yl)methyl)-(cyclopropyl)carbamate (63).



60 61 62 63

Step 1:

To a solution of **compound 60** (1.00 g, 8.06 mmol) in DCM (80 mL) was added cyclopropyl amine (0.850 mL, 12 mmol) then Ti(O*i*-Pr)$_4$ (4.7 mL, 16 mmol). The solution was stirred at room temperature overnight then MeOH (20 mL) was added followed by $NaBH_4$ (610 mg, 16 mmol) portion wise (gas evolved). The reaction was quenched with saturated $NaHCO_3$, forming white solids. The mixture was filtered through celite then the mother liquor was extracted with EtOAc (2x). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated and gave to give **compound 61** (1.38 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.88 (s, 1 H), 3.68 - 3.66 (m, 2 H), 3.65 (s, 3 H), 2.57 (br. s., 1 H), 2.07 (s, 3 H), 2.06 - 2.01 (m, 1 H), 0.40 - 0.30 (m, 2 H), 0.25 - 0.18 (m, 2 H).

Step 2:

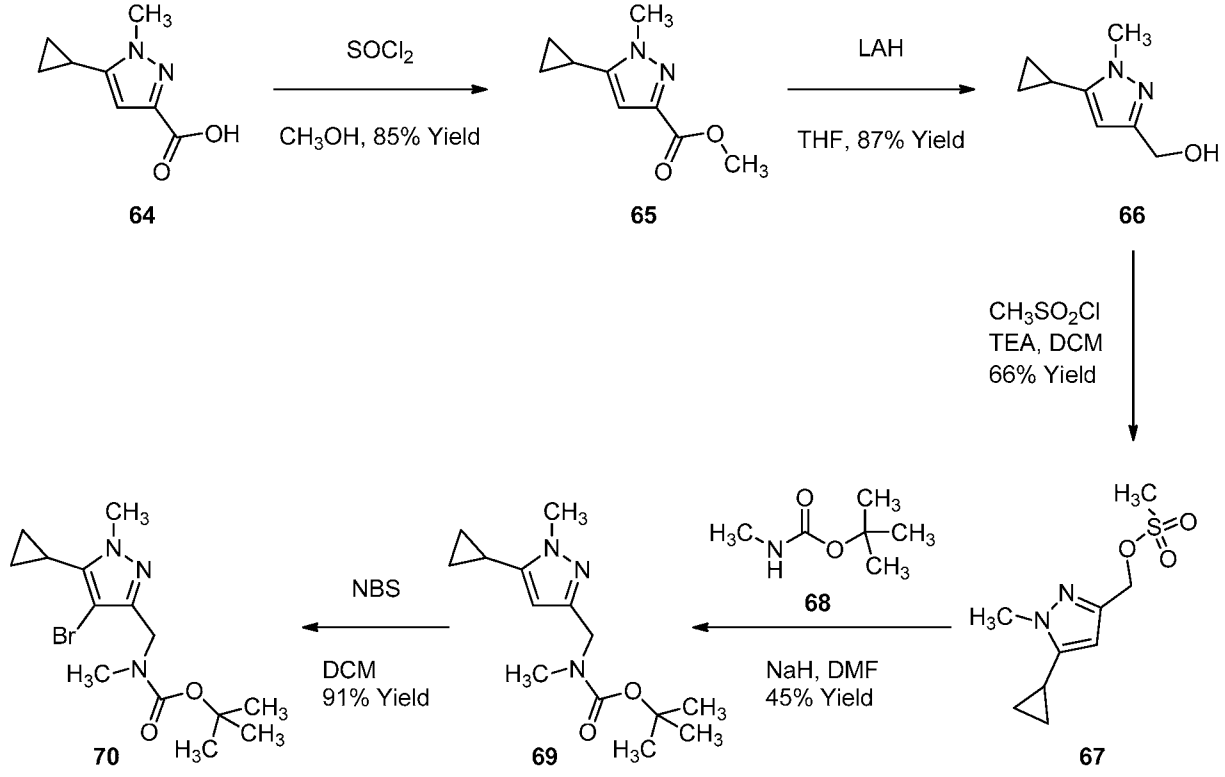
A solution of **compound 61** (1.33 g, 8.06 mmol), DIEA (2.81 mL, 16.1 mmol) and Boc_2O (2.64 g, 12.1 mL) in THF (27 mL) was stirred at room temperature for 2 days. The solution was concentrated and purified by flash chromatography eluting with heptanes/EtOAc (0-50%) to afford **compound 62** (1.75 g, 82% yield over 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.85 (s, 1 H), 4.34 (s, 2 H), 3.68 (s, 3 H), 2.36 (br s, 1 H), 2.08 (s, 3 H), 1.40 (s, 9 H), 0.68 (d, *J* = 6.0 Hz, 2 H), 0.61 (br s, 2 H).

Step 3:

To a solution of **compound 62** (1.75 g, 6.60 mmol) in DMF (44 mL) was added NBS (1.2 g, 6.6 mmol). After 1 hour the solution was diluted with EtOAc, washed with 50% saturated Na_2CO_3 (2x) and brine, dried ($MgSO_4$), filtered and concentrated to give **compound 63** as a yellow gum

(2.14 g, 94% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.45 (s, 2 H), 3.73 (s, 3 H), 2.23 - 2.14 (m, 1 H), 2.09 (s, 3 H), 1.41 (s, 9 H), 0.70 - 0.52 (m, 4 H).

Preparation of *tert*-butyl ((4-bromo-5-cyclopropyl-1-methyl-1H-pyrazol-3-yl)methyl)-(methyl)carbamate (70).



Step 1:

To a solution of **compound 64** (2.9 g, 17.4 mmol) in dry methanol (100 mL) was drop-wise $SOCl_2$ (20 mL) at 0 °C. After addition, the reaction solution was stirred at room temperature for 48 hours. TLC (dichloromethane/methanol 10/1) showed the reaction was completed. The reaction mixture was concentrated *in vacuo* and gave a residue, which was dissolved with EtOAc (200 mL). The organic layer was washed with saturated $NaHCO_3$ (100 mL x 3), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* and gave **compound 65** as pale yellow oil (2.7 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1 H), 4.19 (s, 3 H), 4.12 (s, 3 H), 1.99 - 1.92 (m, 1 H), 1.27 - 1.23 (m, 2 H), 0.94 - 0.91 (m, 2 H).

Step 2:

To a mixture of $LiAlH_4$ (0.85 g, 22.5 mmol) in dry THF (40 mL) was added drop-wise **compound 65** (2.7 g, 15 mmol) in THF (10 mL) at -10 ~ 0 °C. After addition, the reaction mixture was stirred at room temperature for 2 hours. TLC (petroleum ether/EtOAc 1/1) showed the reaction

mixture was completed. The reaction was quenched with 20% aq. NaOH (4 mL). The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified flash chromatography over silica gel which was eluted with petroleum ether/EtOAc (3/1) and gave **compound 66** as a white solid (2.3 g, 87% yield).

Step 3:

To a solution of **compound 66** (2.5 g, 16.4 mmol) and Et_3N (2.48 g, 24.6 mmol) in dry DCM (100 mL) was added drop-wise MsCl (2.13 g, 18.1 mmol) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 3 hours. TLC (petroleum ether/EtOAc 3/1) showed the reaction was complete. The reaction mixture was washed with water (100 mL x 3), saturated $NaHCO_3$ (100 mL x 3), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* and gave **compound 67** as red oil (2.5 g, 66% yield).

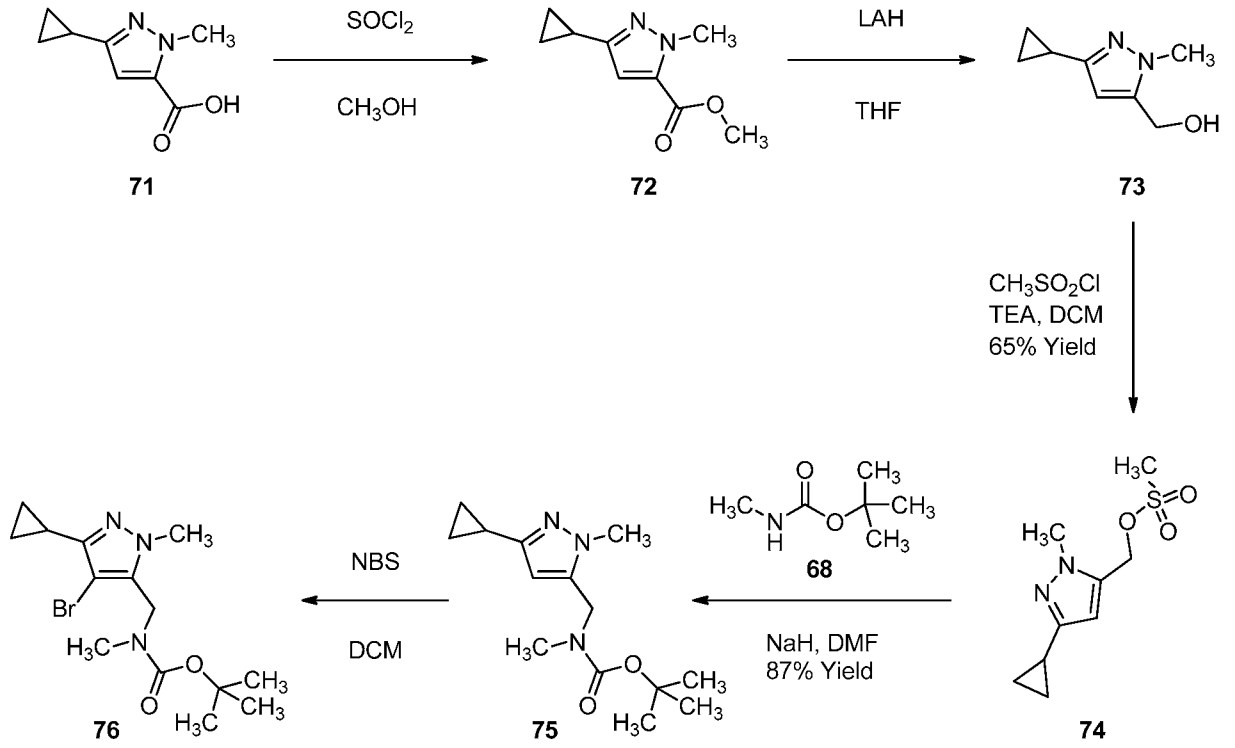
Step 4:

To a solution of the **compound 68** (2.8 g, 21.3 mmol) in dry DMF (40 mL) was added NaH (60% in oil, 0.96 g, 121 mmol) at 0 °C in small portions. After addition, the reaction mixture was stirred at room temperature for 1 hour. **Compound 67** (2.5 g, 10.8 mmol) in DMF (10 mL) was then added drop-wise to the anion at 0 °C. The resulting mixture was then stirred at room temperature overnight. None of **compound 67** was detected by TLC (petroleum ether/EtOAc 3/1). The reaction mixture was poured into ice water (100 mL). The mixture was then extracted with EtOAc (50 mL x 3). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography over silica gel, which was eluted with petroleum ether/EtOAc (3/1) and gave **compound 69** as an off-white solid (1.3 g, 45% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, 1 H), 4.30 (s, 2 H), 3.84 (s, 3 H), 2.82 (s, 3 H), 1.62 - 1.54 (m, 1 H), 1.48 (s, 9 H), 0.96-0.94 (m, 2 H), 0.64 - 0.63 (m, 2 H).

Step 5:

To a solution of **compound 69** (1.2 g, 4.14 mmol) in DCM (50 mL) was incrementally added NBS (0.77 g, 4.35 mmol) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 2 hours. None of **compound 69** was detected by TLC (petroleum ether/EtOAc 3/1). The reaction mixture was washed with saturated $NaHCO_3$ (50 mL x 3), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel which was eluted with petroleum ether/EtOAc (4/1) and gave **compound 70** as pale yellow oil (1.3 g, 91% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 - 4.33 (s, 2 H), 3.79 (s, 3 H), 2.71 (s, 3 H), 1.62 - 1.54 (m, 1 H), 1.41 (s, 9 H), 0.96 - 0.94 (m, 2 H), 0.80 - 0.78 (m, 2 H).

Preparation of *tert*-butyl ((4-bromo-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)methyl)(methyl)carbamate (76).



Step 1:

The procedure described in step 1 for **compound 70** was used to prepare **compound 72**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (s, 1 H), 4.05 (s, 3 H), 3.78 (s, 3 H), 1.83 - 1.81 (m, 1 H), 0.87 - 0.83 (m, 2 H), 0.65 - 0.62 (m, 2 H).

Step 2:

The procedure described in step 2 for **compound 70** was used to prepare **compound 73**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 - 5.77 (d, 1 H), 4.53 (s, 3 H), 3.74 - 3.71 (t, 3 H), 1.83 - 1.77 (m, 3 H), 1.60 (s, 1 H), 0.84 - 0.80 (m, 2 H), 0.61 - 0.57 (m, 2 H).

Step 3:

The procedure described in step 2 for **compound 70** was used to prepare **compound 74** (1.7 g, 65% yield).

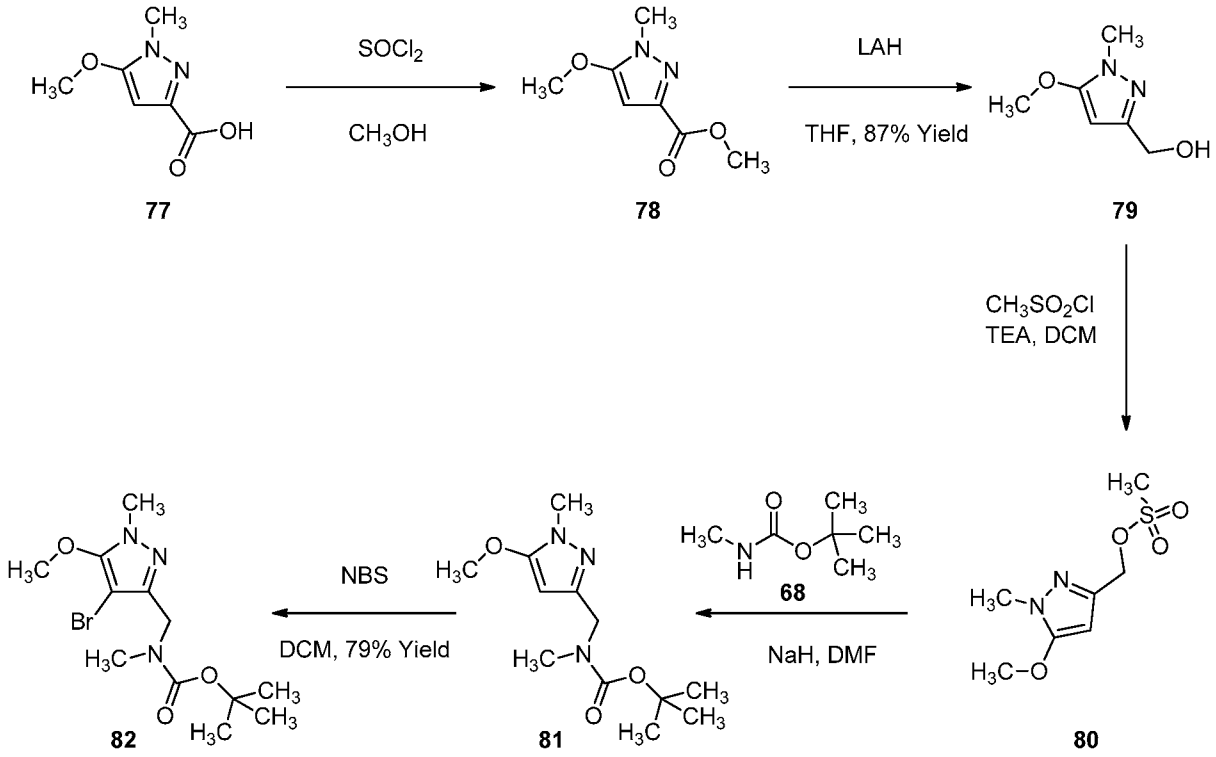
Step 4:

The procedure described in step 4 for **compound 70** was used to prepare **compound 75** (1.6 g, 87% yield).

Step 5:

The procedure described in step 5 for **compound 70** was used to prepare **compound 76**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (s, 2 H), 4.06 - 4.04 (s, 3 H), 2.66 (s, 3 H), 1.77 - 1.76 (m, 1 H), 1.41 (s, 9 H), 0.83 - 0.79 (m, 4 H).

Preparation of *tert*-butyl ((4-bromo-5-methoxy-1-methyl-1H-pyrazol-3-yl)methyl)(methyl)carbamate (82).



Step 1:

The procedure described in step 1 for **compound 70** was used to prepare **compound 78**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1 H), 3.94 - 3.92 (m, 6 H), 3.75 - 3.72 (m, 3 H).

Step 2:

The procedure described in step 2 for **compound 70** was used to prepare **compound 79** (0.6 g, 87% yield).

Step 3:

The procedure described in step 3 for **compound 70** was used to prepare **compound 80**.

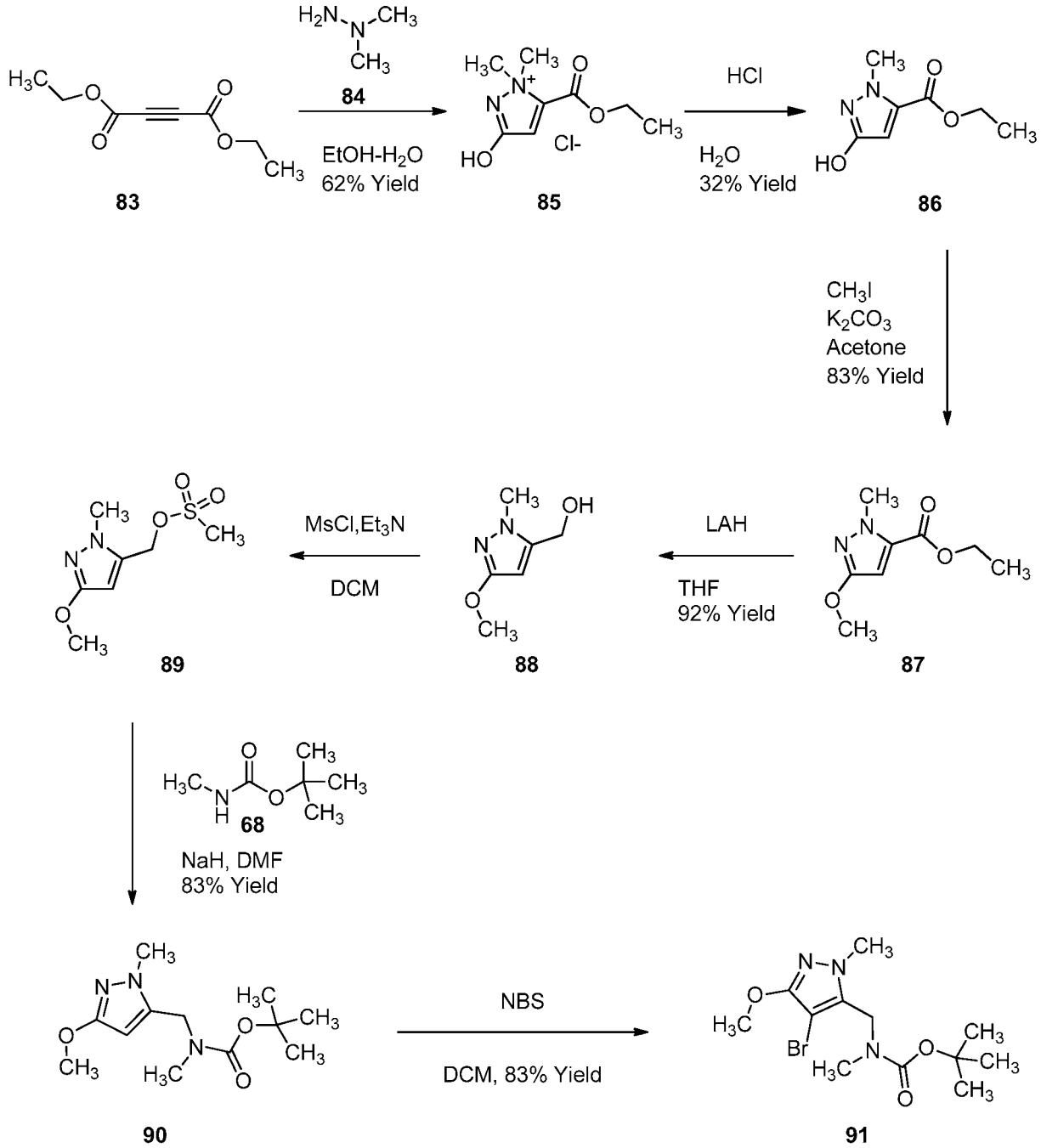
Step 4:

The procedure described in step 4 for **compound 70** was used to prepare **compound 81.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (s, 1 H), 4.27 (s, 2 H), 3.83 (s, 3 H), 3.57 (s, 3 H), 2.82 (s, 3 H), 1.48 (s, 9 H).

Step 5:

The procedure described in step 5 for **compound 70** was used to prepare **compound 82** (3.9 g, 79% yield). LCMS *m/z* 333 $[M+H]^+$.

Preparation of *tert*-butyl ((4-bromo-3-methoxy-1-methyl-1H-pyrazol-5-yl)methyl)(methyl)-carbamate (91).



Step 1:

To a mixture of **compound 83** (10.7 mL, 0.067 mol) in 1:1 EtOH/ H_2O (120 mL) was slowly added at 0 °C a solution of **compound 84** (7.72 g, 0.08 mol) and NaOH (3.2 g, 0.08 mol) in 1:1

EtOH/ H_2O (40 mL). The solution was stirred at 0 °C for 30 min, and warmed to room temperature over for 1 hour. The mixture was concentrated and the residue was partitioned between water (100 mL) and EtOAc (100 mL). The aqueous layer was concentrated and gave **compound 85** as a brown oil (7.6 g, 62% yield).

Step 2:

A mixture of **compound 85** (7.6 g, 41 mmol) in 1 N HCl (75 mL) was stirred at room temperature for 1.5 hours. The mixture was extracted with DCM (50 mL), the aqueous layer was concentrated and gave a residue. The crude product was purified by flash chromatography over silica gel, which was eluted with petroleum ether / EtOAc 6:1) and gave **compound 86** as a white solid (2.2 g, 32% yield).

Step 3:

A mixture of **compound 86** (1.6 g, 9.1 mmol), K_2CO_3 (3.7 g, 27.5 mmol) and methyl iodide (6.5 g, 46 mmol) was heated at reflux for 3 hours. TLC (petroleum ether / EtOAc = 6:1) showed the reaction was complete. The mixture was filtered and the filtrate was concentrated to give a residue. The crude product was purified by flash chromatography over silica gel, which was eluted with petroleum ether / EtOAc (20:1) and gave **compound 87** as a yellow oil (1.4 g, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (s, 1 H), 4.30 (q, 2 H), 4.05 (s, 3 H), 3.83 (s, 3 H), 1.36 (t, 3 H).

Step 4:

The procedure described in step 2 for **compound 70** was used to prepare **compound 88** (1.0 g, 92% yield).

Step 5:

The procedure described in step 3 for **compound 70** was used to prepare **compound 89**.

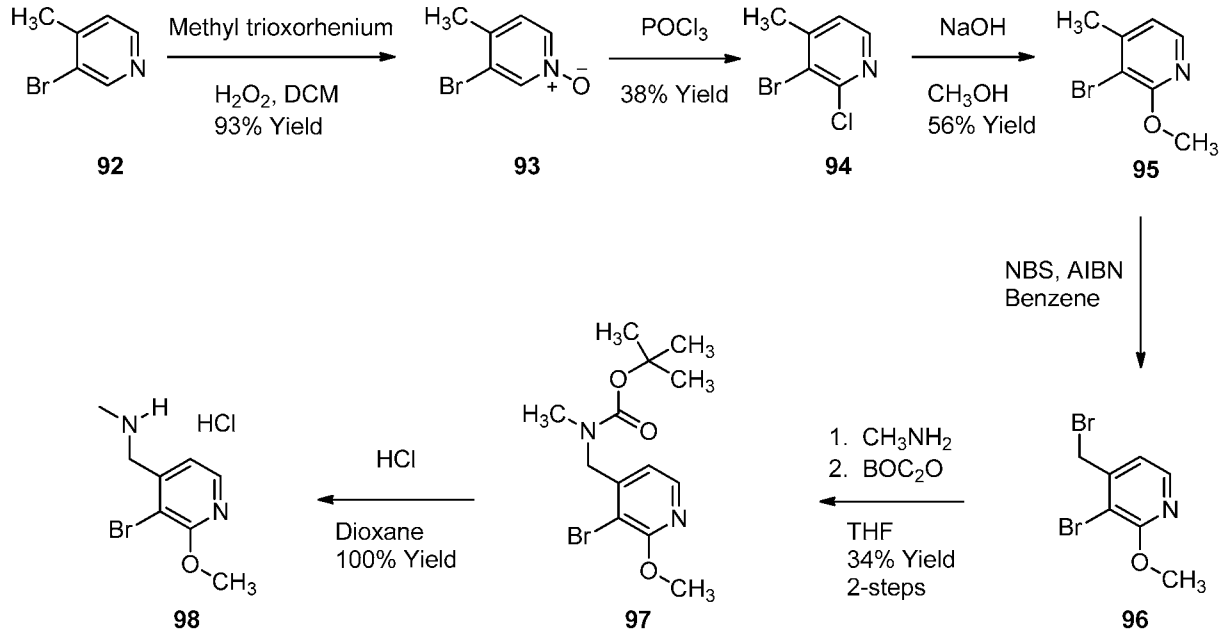
Step 6:

The procedure described in step 4 for **compound 70** was used to prepare **compound 90** (1.5 g, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (s, 1 H), 4.36 (s, 2 H), 3.84 (s, 3 H), 3.67 (s, 3 H), 2.77 (s, 3 H), 1.47 (s, 9 H).

Step 7:

The procedure described in step 5 for **compound 70** was used to prepare **compound 91** (1.3 g, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (s, 2 H), 3.93 (s, 3 H), 3.75 (s, 3 H), 2.73 (s, 3 H), 1.32 (s, 9 H). LCMS *m/z* 335 $[M+H]^+$.

Preparation of 1-(3-bromo-2-methoxypyridin-4-yl)-N-methylmethanamine (98)



Step 1:

To a solution of the **compound 92** (5.0 g, 29 mmol) in DCM (15 mL) was added methyl trioxorhenium (73 mg, 0.29 mmol) followed by H_2O_2 (50% in water, 3.6 mL, 58 mmol). The yellow biphasic mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with DCM (2x). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give **compound 93** as a white solid (5.1 g, 93% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1 H), 8.15 (d, J = 6.5 Hz, 1 H), 7.40 (d, J = 6.5 Hz, 1 H), 2.35 - 2.27 (m, 3 H).

Step 2:

Compound 93 (4.0 g, 21 mmol) was added portion-wise to neat $POCl_3$ (14 mL) at 0 °C resulting in a slurry. The ice bath was removed and the reaction mixture was heated at 70 °C overnight. The majority of the $POCl_3$ was removed in vacuo. Ice was slowly added to the residue followed by the careful addition of 1 N Na_2CO_3. Once the release of CO_2 was complete, the solution was extracted with EtOAc (3x). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography over silica gel which was eluted with heptanes/EtOAc (0-20%) to yield **compound 94** as a white solid (1.65 g, 38% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 4.8 Hz, 1 H), 7.42 (d, J = 4.8 Hz, 1 H), 2.48 - 2.38 (m, 3 H).

Step 3:

In a sealed tube, NaOMe (25% in MeOH, 3.1 mL, 13 mmol) was added to a solution of **compound 94** (1.8 g, 8.7 mmol) in MeOH (17 mL). The reaction was heated at 75 °C for 3 days. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with

saturated NH_4Cl and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography over silica gel, which was eluted with heptanes/EtOAc (0-15%) to afford **compound 95** as a clear oil (991 mg, 56% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, J = 5.0 Hz, 1 H), 6.98 (d, J = 4.8 Hz, 1 H), 3.90 (s, 3 H), 2.35 (s, 3 H).

Step 4:

To a solution of **compound 95** (990 mg, 4.9 mmol) in benzene (33 mL) was added NBS (870 mg, 4.9 mmol) followed by AIBN (40 mg, 0.25 mmol). The mixture was placed in an 80 °C oil bath. After six hours, the reaction was diluted with EtOAc, washed with 1 M Na_2CO_3 and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography eluting with heptanes/EtOAc (0-10%) to afford **compound 96** as an oil (669 mg, 70% pure by NMR). ^1H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 5.0 Hz, 1 H), 7.22 (d, J = 5.0 Hz, 1 H), 4.68 (s, 2 H), 3.93 (s, 3 H).

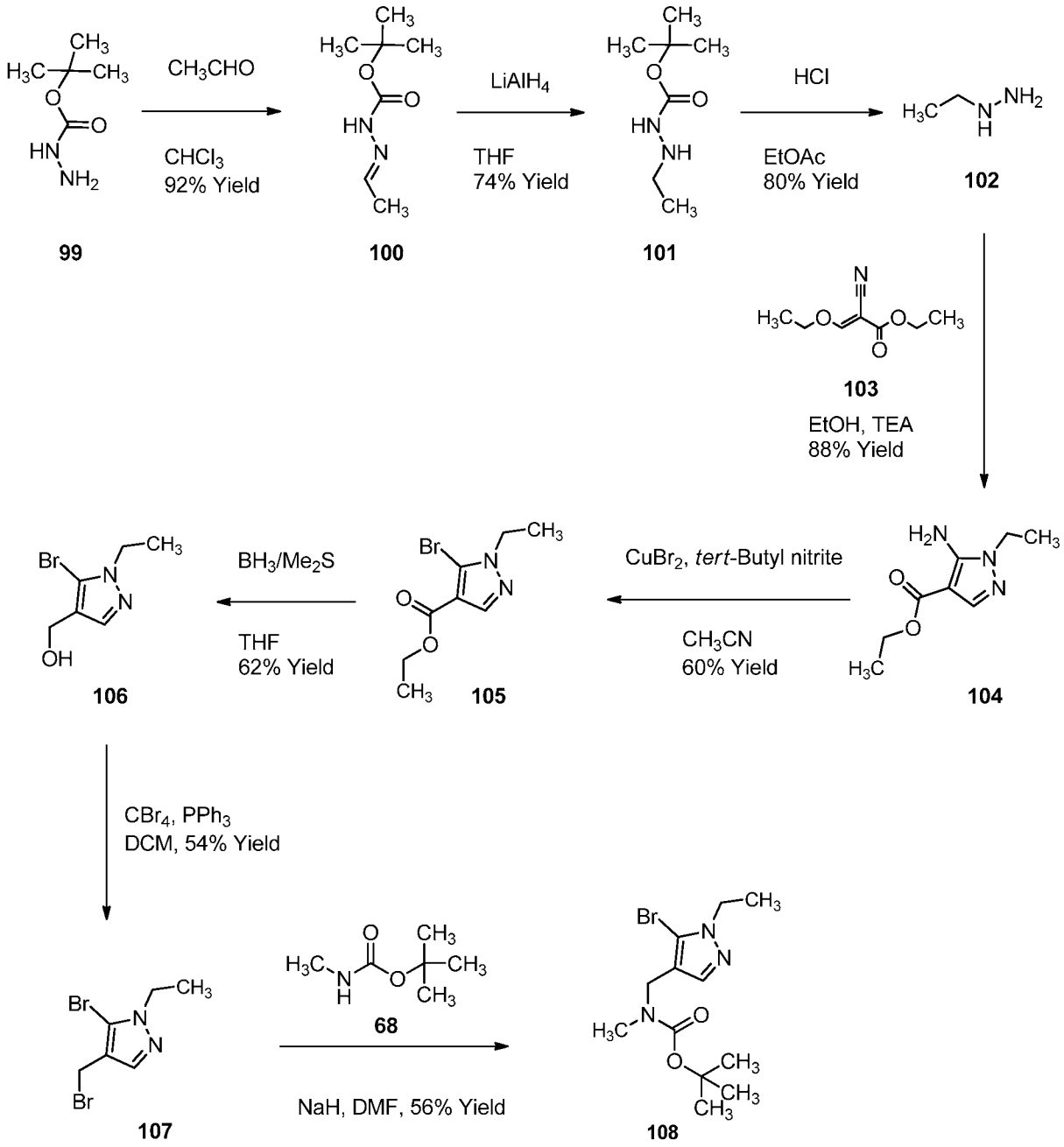
Step 5:

To a solution of **compound 96** (665 mg, 70% pure) in THF (12 mL) was added methyl amine (2 M in THF, 3.5 mL, 6.9 mmol). After 2 hours, Boc_2O (1.5 g, 6.9 mmol) was added. After another 2 hours, the reaction was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with heptanes/EtOAc (0-20%) to afford **compound 97** as a clear gum (552 mg, 34% over 2 steps). ^1H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 5.0 Hz, 1 H), 6.71 (br s, 1 H), 4.42 (s, 2 H), 3.93 (s, 3 H), 2.87 (s, 3 H), 1.56 - 1.16 (m, 9 H).

Step 6:

To a cooled (0 °C) solution of **compound 97** (530 mg, 1.6 mmol) in DCM (8.0 mL) was added HCl (4 N in dioxane, 8 mL). The ice bath was removed and a white precipitate formed. Once complete by LCMS, the mixture was concentrated to afford **compound 98** as a white solid (quantitative).

Preparation of *tert*-butyl ((5-bromo-1-ethyl-1H-pyrazol-4-yl)methyl)(methyl)carbamate (108).



Step 1:

To a stirred solution of **compound 99** (145 g, 1.1 mol) in $CHCl_3$ (1.4 L) was added drop-wise MeCHO (40% in water, 500 g, 4.5 mol) at room temperature. After the addition, the reaction was stirred at room temperature for 24 hours. TLC (petroleum ether/EtOAc = 1/1) showed the reaction was complete. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give **compound 100** as light yellow oil (160 g, 92% yield).

Step 2:

To a stirred suspension of $LiAH_4$ (22.5 g, 0.505 mol) in dry THF (1 L) was added drop-wise a solution of **compound 100** (80 g, 0.505 mol) at -10 °C. After the addition, the reaction mixture was stirred at room temperature for 2 hours. TLC (petroleum ether/EtOAc = 3/1) showed the reaction mixture was complete. The reaction mixture was quenched with saturated NH_4Cl (100 mL) below 0 °C, EtOAc (500 mL) was poured into the above reaction and stirred for 10 minutes. The reaction mixture was filtered and the filtrate was washed with brine (100 mL x 3), dried over Na_2SO_4, concentrated *in vacuo* and gave a residue, which was purified by column chromatography (on silica gel petroleum ether/EtOAc 20/1~10/1) to give **compound 101** as colorless oil (60 g, 74% yield).

Step 3:

To a stirred solution of **compound 101** (60 g, 0.375 mol) in EtOAc (100 mL) was added drop-wise 4 N HCl in EtOAc (200 mL) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 10 hours. TLC (petroleum ether/EtOAc = 3/1) showed the reaction was complete. The reaction mixture was filtered, the cake was collected and dried under reduced pressure to give **compound 102** as a white solid (40 g, 80% yield).

Step 4:

A mixture of **compound 102** (40 g, 0.3 mol) and **compound 103** (56 g, 0.33 mol) and TEA (105 mL, 0.76 mol) in EtOH (500 mL) was refluxed for 24 hours. TLC (petroleum ether/EtOAc = 3/1) showed the reaction was complete. The reaction mixture was concentrated *in vacuo* to get a residue, which was diluted with EtOAc (500 mL). The solution was washed with brine (100 mL x 3), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified by column chromatography over silica gel, which was eluted with petroleum ether/EtOAc (10/1~3/1) to give **compound 104** as a white solid (48 g, 88% yield).

Step 5:

To a stirred solution of *tert*-butyl nitrite (35 mL, 0.31 mol) and $CuBr_2$ (56.3 g, 0.252 mol) in CH_3CN (1 L) was added drop-wise a solution of **compound 104** (38 g, 0.21 mol) at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 3 hours. TLC (petroleum ether/EtOAc = 3/1) showed the reaction was complete. The reaction mixture was poured into 6 N aq. HCl (400 mL) and extracted with DCM (200 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified by column chromatography over silica gel, which was eluted with petroleum ether/EtOAc (20/1~1/1) to give **compound 105** as light yellow oil (35 g, 60% yield).

Step 6:

To a stirred solution of **compound 105** (20 g, 81 mmol) in dry THF (200 mL) was added drop-wise BH_3/Me_2S (1 N, 81 mL, 0.81 mol) at 0 °C. After the addition, the reaction mixture was

stirred at room temperature for 1 hour and subsequently refluxed for 4 hours. TLC (petroleum ether/EtOAc = 3/1) showed the reaction was complete. The reaction mixture was quenched with saturated aqueous NH_4Cl (100 mL) at 0 °C. The mixture was filtered and the filtrate was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified by column chromatography over silica gel, which was eluted with petroleum ether/EtOAc (6/1~3/1) to give **compound 106** as light yellow oil (10 g, 62% yield).

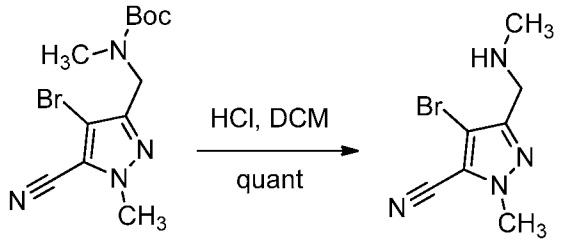
Step 7:

To a stirred solution of **compound 106** (10 g, 48.8 mmol) and PPh_3 (15.4 g, 58.5 mmol) in dry DCM (200 mL) was added drop-wise a solution of CBr_4 (19.3 g, 58.8 mmol) in DCM at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 24 hours. TLC (petroleum ether/EtOAc = 3/1) showed the reaction was complete. The reaction mixture was concentrated *in vacuo* to give a residue, which was purified by column chromatography over silica gel, which was eluted with petroleum ether/EtOAc (50/1~10/1) to give **compound 107** as a white solid (7.0 g, 54% yield).

Step 8:

The procedure described in step 4 for **compound 70** was used to prepare **compound 108** as a colorless oil (4.8 g, 56% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (s, 1 H), 4.28 - 4.25 (m, 2 H), 4.23 (d, 2 H), 2.83 (s, 3 H), 1.50 (s, 9 H), 1.44 - 1.38 (m, 3 H). LCMS *m/z* 318/320 $[M+H]^+$.

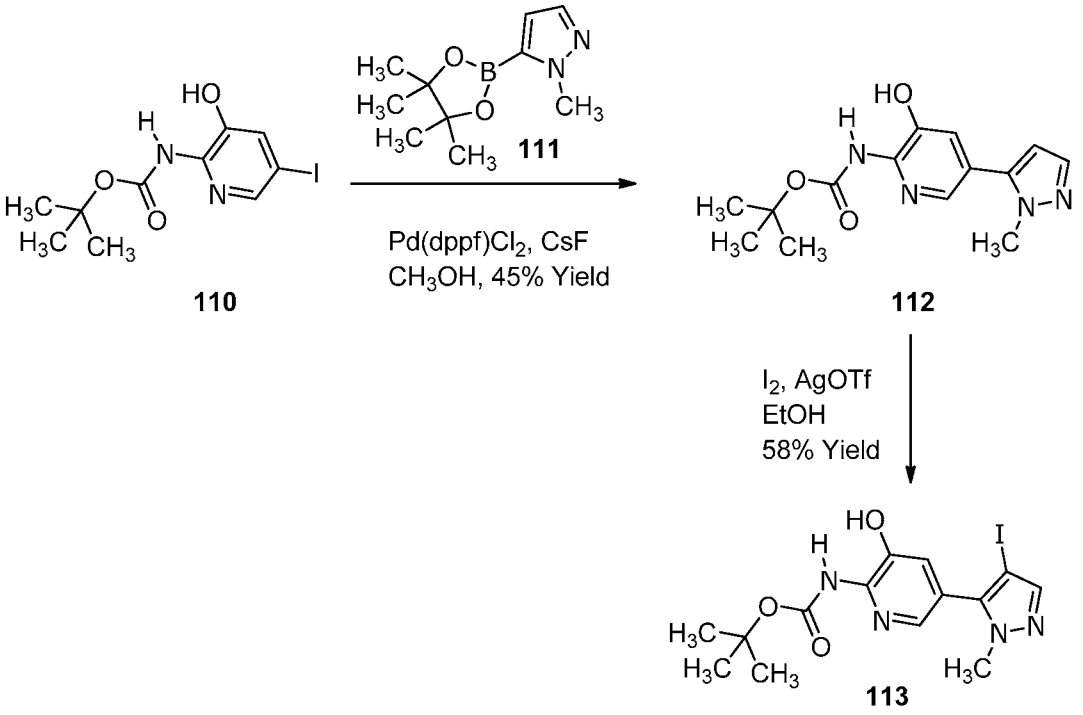
Preparation of 4-bromo-1-methyl-3-[(methylamino)methyl]-1*H*-pyrazole-5-carbonitrile (109)



47 **109**

To a 0 °C solution of **compound 47** (1.0 g, 3.0 mmol) in DCM (15 mL) was added 4 N HCl in dioxane (3.8 mL, 15 mmol). Allowed to stir at room temperature for 3 hours, then concentrated under vacuum to give **compound 109** (810 mg, quantitative) as a white solid.

Preparation of *tert*-butyl (3-hydroxy-5-(4-iodo-1-methyl-1H-pyrazol-5-yl)pyridin-2-yl)carbamate (113).



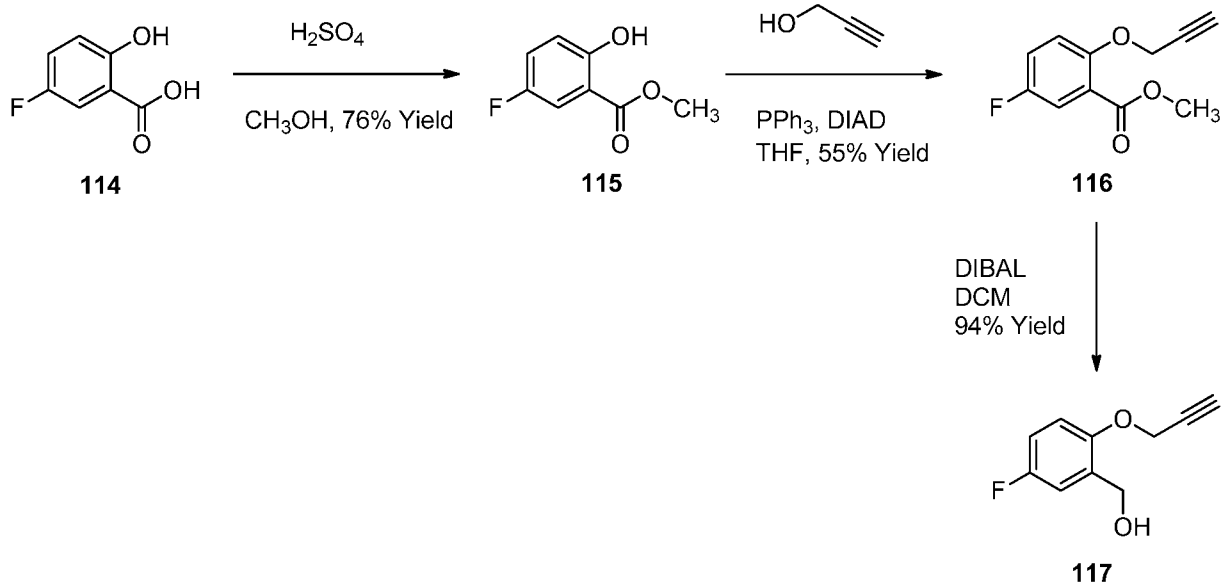
Step 1:

To a mixture of **compound 110** and **compound 111** in MeOH was added 2 M CsF in water. The mixture was bubbled with nitrogen for 5 minutes then $PdCl_2$dppf 1:1 with CH_2Cl_2 was added. The reaction was heated at 60 °C overnight then diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography eluting with heptanes/EtOAc (0-75%). The fractions containing the desired product were concentrated and the product was crashed out using DCM/Et_2O to give **compound 112** (960 mg, 45% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (s, 9 H) 3.85 (s, 3 H) 6.44 (s, 1 H) 7.31 (s, 1 H) 7.48 (s, 1 H) 7.99 (s, 1 H) 9.02 (s, 1 H) 10.12 (s, 1 H).

Step 2:

To a mixture of **compound 112** (960 mg, 3.3 mmol) and AgOTf (850 mg, 3.3 mmol) in EtOH (30 mL) was added a solution of I_2 (0.25 M in EtOH, 13 mL, 3.31 mmol). After 1 hour, additional AgOTf (425 mg, 1.66 mmol) and I_2 (0.25 M in EtOH, 6.6 mL, 1.66 mmol) were added. Once LCMS showed the reaction was complete, the mixture was filtered and the mother liquor was diluted with EtOAc, washed with 1 N Na_2CO_3, saturated $Na_2S_2O_3$/water, and brine. The combined aqueous layers were neutralized with 4 N HCl and extracted with DCM (2x). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography of silica gel, which was eluted with heptanes/EtOAc (0-100%) and gave **compound 113** as a cream solid (800 mg, 58% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47 (s, 9 H), 3.80 (s, 3 H), 7.25 (d, J = 2.0 Hz, 1 H), 7.63 (s, 1 H), 7.89 (d, J = 2.0 Hz, 1 H), 9.02 (s, 1 H), 10.28 (br s, 1 H).

Preparation of (5-fluoro-2-(prop-2-yn-1-yloxy)phenyl)methanol (117).



114 **115** **116** **117**

Step 1:

To a solution of **compound 114** (2.5 g, 16 mmol) in methanol (32 mL) was added sulfuric acid (2.0 mL, 21 mmol). The solution was heated at reflux overnight, cooled to room temperature and concentrated. The residue was dissolved in EtOAc, washed with saturated $NaHCO_3$ (3x), brine, dried ($MgSO_4$), filtered and concentrated to give **compound 115** as to a cream solid (2.1 g, 76% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.89 (s, 3 H), 7.01 (dd, *J* = 9.1, 4.5 Hz, 1 H), 7.40 (td, *J* = 8.6, 3.2 Hz, 1 H), 7.45 - 7.54 (m, 1 H), 10.28 (s, 1H).

Step 2:

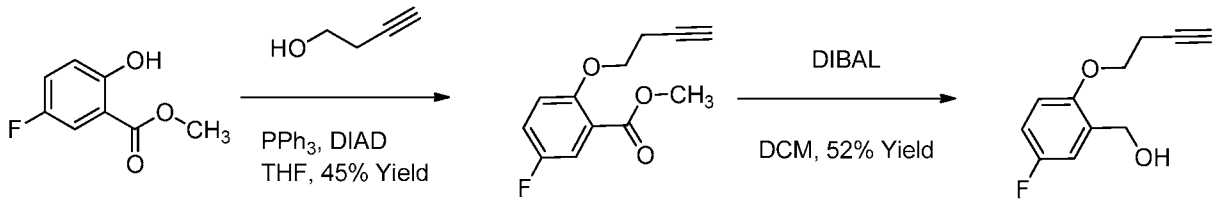
To a solution of **compound 115** (2.1 g, 12 mmol), propargyl alcohol (830 µL, 14 mmol), and triphenylphosphine (4.8 g, 18 mmol) in THF (31 mL) was added TEA (1.7 mL, 12 mmol) followed by DIAD (3.7 mL, 18 mmol). The solution was stirred at room temperature overnight and concentrated. The residue was purified by flash chromatography eluting with heptanes/EtOAc (0-30%) to give **compound 116** as a needle like solid (1.4 g, 55% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.51 - 3.64 (m, 1 H), 3.80 (s, 3 H), 4.86 (d, *J* = 2.3 Hz, 2 H), 7.25 (dd, *J* = 9.1, 4.3 Hz, 1 H), 7.38 - 7.55 (m, 2 H).

Step 3:

To a cooled (-78 °C) solution of **compound 116** (1.4 g, 6.7 mmol) in DCM (34 mL) was added DiBAL (1 M in hexanes, 18.5 mL, 18.5 mmol) drop-wise *via* a syringe pump at ~1 mL/min. The reaction was quenched with MeOH (10 mL) at -78 °C. The dry ice bath was removed, then saturated sodium potassium tartrate (40 mL) was added and the reaction mixture was diluted with EtOAc (50 mL). The mixture was stirred at room temperature for 2 hours then diluted with

EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to give **compound 117** as a clear oil (1.1 g, 94% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.55 (t, *J* = 2.4 Hz, 1 H), 4.48 (d, *J* = 5.8 Hz, 2 H), 4.79 (d, *J* = 2.3 Hz, 2 H), 5.20 (t, *J* = 5.7 Hz, 1 H), 7.03 (dd, *J* = 6.2, 1.6 Hz, 2 H), 7.13 - 7.21 (m, 1 H).

Preparation of (2-(but-3-yn-1-yloxy)-5-fluorophenyl)methanol (120).



118 **119** **120**

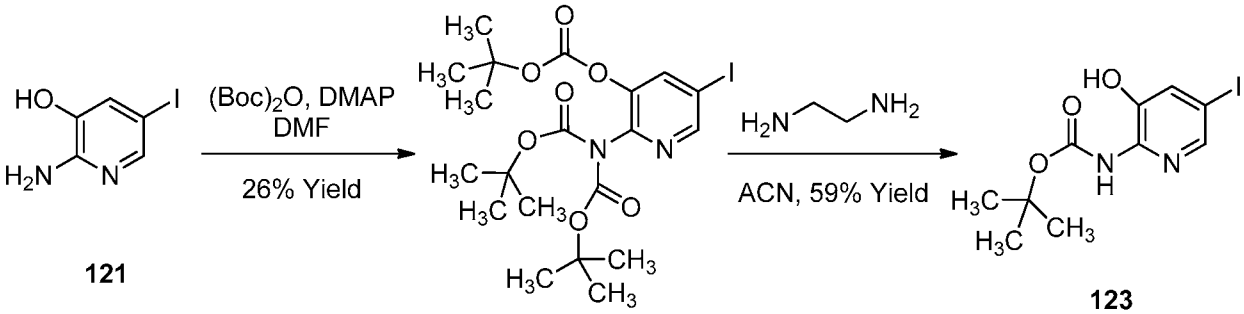
Step 1:

The procedure described in step 2 for **compound 117** was used to prepare **compound 119** (13 g, 45% yield).

Step 2:

The procedure described in step 3 for **compound 117** was used to prepare **compound 120** (13 g, 52% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.20 - 7.17 (m, 1 H), 7.05 - 6.96 (m, 2 H), 5.20 (t, 1 H), 4.54 (t, 2 H), 4.08 (t, 2 H), 2.90 (t, 1 H), 2.66 - 2.62 (m, 2 H). LCMS *m/z* 176 $[M - OH]^+$.

Preparation of (3-Hydroxy-5-iodo-pyridin-2-yl)-carbamic acid tert-butyl ester (123)



121 **122** **123**

Step 1:

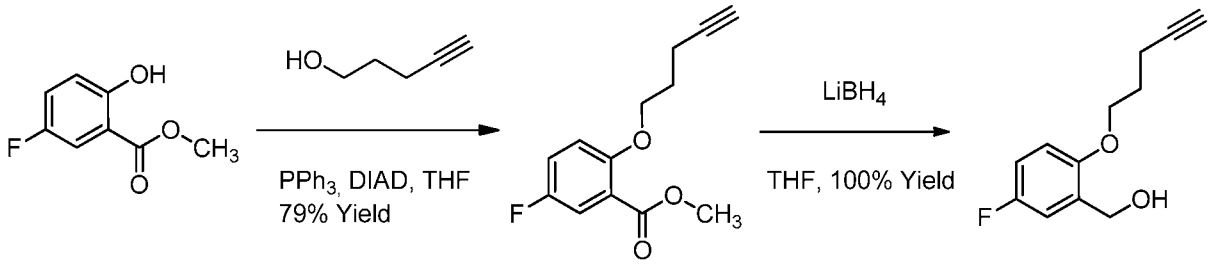
A mixture of 2-amino-5-iodopyridin-3-ol **compound 121**(623 mg, 2.64 mmol), 4-dimethaminopyridine (64.5 mg, 0.528 mmol), and Di-tert-butyl dicarbonate (1.73g, 7.92 mmol) in DMF (7.5 mL) was stirred at RT overnight. The mixture was diluted with EtOAc, washed with sat'd aq. bicarbonate (2x), brine, dried over magnesium sulfate, filtered and concentrated to dryness. The residue was Purified by flash chromatography (ISCO 40g cartridge) using a

gradient to 0-35% EtOAC/heptane as eluent to give **compound 122** (372 mg, 26.3%) as a gum. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 8.62 (d, *J*=1.77 Hz, 1 H) 8.36 (d, *J*=1.77 Hz, 1 H), 1.48 (2, 9H), 1.39 (s, 18 H)

Step 2:

A mixture of **compound 122** (106 mg, 0.98 mmol) and N,N-diethylenediamine (30.6 µL, 0.218 mmol)) in Acetonitrile (1 mL) was stirred at RT for 5 hr. Starting material was still evident by LCMS. More N,N-diethylenediamne (28 µL, 0.198 mmol) was added. After stirring at RT for another 1 hr, LCMS indicated reaction was complete. The mixture was concentrated to dryness and the residue purified by flash chromatography using a gradient of 0-50% dichloromethane/heptane as eluent to obtain **compound 123** as a white solid in 59% yield. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 10.29 (br. s., 1 H), 8.83 (s, 1 H), 8.00 (d, *J*=1.52 Hz, 1 H), 7.48 (d, *J*=1.77 Hz, 1 H), 1.43 (s, 9 H).

Preparation of (5-fluoro-2-(pent-4-yn-1-yloxy)phenyl)methanol (125).



118 **124** **125**

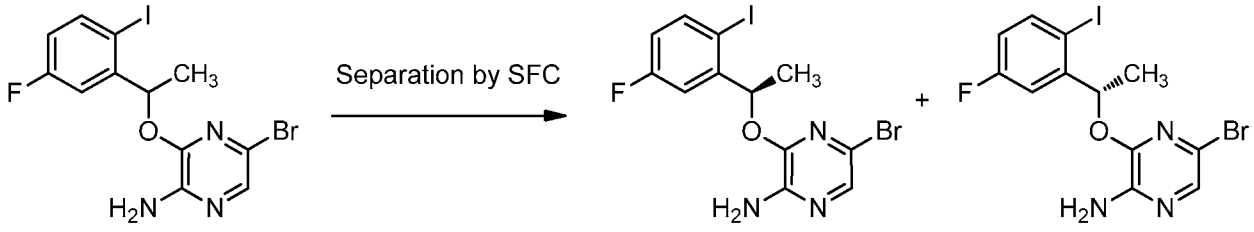
Step 1:

The procedure described in step 2 for **compound 117** was used to prepare **compound 124** (10.0 g, 79% yield).

Step 2:

To a stirred solution of **compound 124** (9.0 g, 38.1 mmol) in dry THF (180 mL) was added portion-wise $LiBH_4$ (2.1 g, 95.2 mmol) at 0 °C under nitrogen. After the addition, the mixture was stirred at 50 °C for 5 hours. TLC (petroleum ether/EtOAc = 6: 1) indicated the reaction was complete. The mixture was cooled to 0 °C, and water (50 mL) was added drop-wise. The aqueous layer was extracted with EtOAc (150 mL × 2). The combined organic extracts were washed with brine (150 mL × 2), dried over Na_2SO_4 and concentrated to give a residue, which was purified by column chromatography on silica gel (petroleum ether / EtOAc = 15:1) to give **compound 125** as yellow oil (9.0 g, 100% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22 - 7.19 (m, 1 H), 7.08 - 6.98 (m, 2 H), 5.23 (t, 1 H), 4.55 (t, 2 H), 4.08 (t, 2 H), 2.88 (t, 1 H), 2.40 - 2.38 (m, 2 H), 1.97 - 1.91 (m, 2 H). LCMS *m/z* 191 $[M - OH]^+$.

SFC separation of 5-bromo-3-[1-(5-fluoro-2-iodophenyl)ethoxy]pyrazin-2-amine (30) into 5-bromo-3-[(1*R*)-1-(5-fluoro-2-iodophenyl)ethoxy]pyrazin-2-amine (126) and 5-bromo-3-[(1*S*)-1-(5-fluoro-2-iodophenyl)ethoxy]pyrazin-2-amine (127)



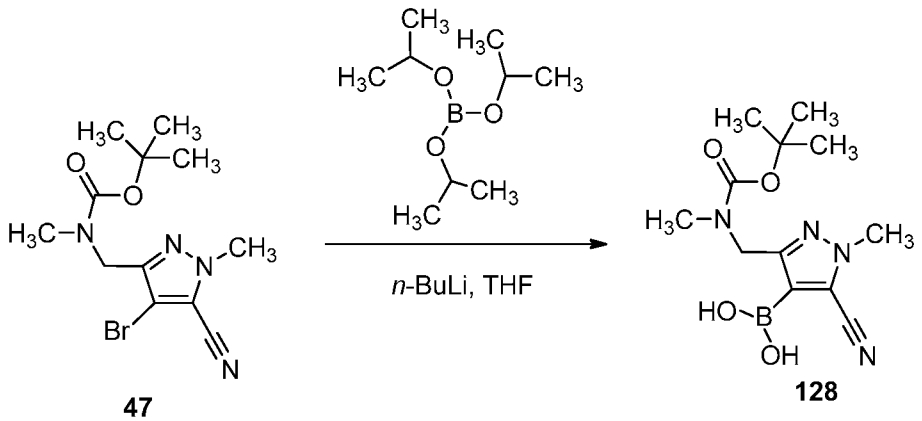
30 **126** **127**

Compound **30** (18 g) was resolved by SFC and gave **compound 126** (Peak 1) (7.75 g, 86%) and **compound 127** (Peak 2) (7.72 g, 85%) as yellow solids. A Chiralpak AD-H (250 × 4.6 mm I.D., 5 micron particle size) column was eluted with 15% methanol in CO_2 @ 140 bar at a flow rate of 3 mL/min and gave Peak 1 retention time of 3.76 minutes and Peak 2 retention time of 4.51 minutes.

Compound 126 (Peak 1): 99 % ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (dd, *J* = 5.8, 8.8 Hz, 1 H), 7.61 - 7.54 (m, 2 H), 6.98 (dt, *J* = 3.0, 8.6 Hz, 1 H), 6.71 (s, 2 H), 6.18 - 6.04 (m,1 H), 1.53 (d, *J* = 6.3 Hz, 1 H). LCMS *m/z* 437/439 $[M+H]^+$.

Compound 127 (Peak 2): > 98% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (dd, *J* = 5.8, 8.8 Hz, 1 H), 7.62 - 7.54 (m, 2 H), 6.97 (dt, *J* = 3.1, 8.5 Hz, 1 H), 6.71 (s, 2 H), 6.17 - 6.04 (m,1 H), 1.52 (d, *J* = 6.5 Hz, 3 H). LCMS *m/z* 437/439 $[M+H]^+$.

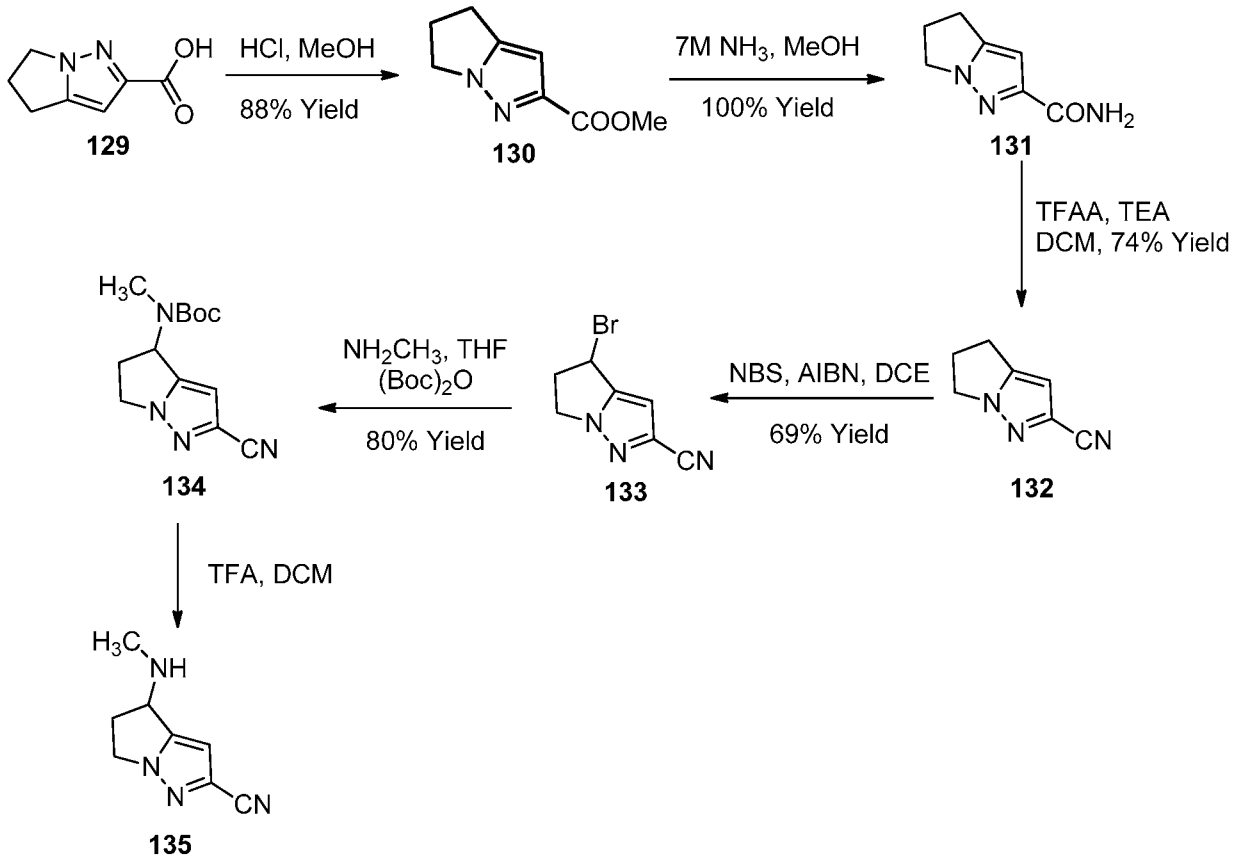
Preparation of (3-{[(tert-butoxycarbonyl)(methyl)amino]methyl}-5-cyano-1-methyl-1H-pyrazol-4-yl)boronic acid (128)



47 **128**

To a solution of compound **47** (800 mg, 2.43 mmol) in anhydrous THF (30 mL) at -78 °C was added *n*-BuLi (1.2 mL, 2.5M in hexanes, 3.2 mmol) dropwise *via* a syringe. The mixture turned orange in color and was stirred at -78 °C for 30 minutes. A solution of triisopropyl borate (0.85 mL, 3.64 mmol) in THF (5 mL) was added dropwise *via* an addition funnel. The resulting mixture was stirred at -78 °C for 30 minutes. 1N HCl (6 mL) was added dropwise and the cooling bath removed. The mixture was allowed to warm to room temperature. The mixture was partitioned between EtOAc/brine, and extracted with EtOAc. The combined organics were dried ($MgSO_4$) and reduced to minimum volume to give 738 mg of a residue, which was taken up in MeOH (17.2 mL) to provide a 0.14M solution of compound **128**, which was used without further purification.

Preparation of 4-(methylamino)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole-2-carbonitrile (135)



Step 1:

A solution of **compound 129** (284 mg, 1.87 mmol) in MeOH (10 mL) was treated with 4 drops of conc. HCl. The reaction was heated at 50 °C for 24 hours. The reaction was concentrated, and partitioned between EtOAc and saturated aqueous $NaHCO_3$. The reaction was extracted with

EtOAc, and the combined organics dried (Na_2SO_4), and concentrated to give compound **130** (273 mg, 88%) as an off white solid. LCMS ES *m/z* 167 $[M+H]^+$.

Step 2:

A mixture of **compound 130** (273 mg, 1.64 mmol) in 7M NH3 in MeOH (5 mL) was heated at 80 °C in a sealed tube for 20 hours. The reaction was concentrated to an off-white solid, which was re-dissolved in 7M NH3 in MeOH (5 mL), and heated for a further 60 hours. The reaction was concentrated to give **compound 131** (276 mg, 100%) as a brownish solid, which was used in the next step without further purification. LCMS ES *m/z* 152 $[M+H]^+$.

Step 3:

To a suspension of **compound 131** (248 mg, 1.64 mmol) in DCM (10 mL) was added TEA (0.686 mL, 4.92 mmol). The resulting mixture was cooled to 0 °C and TFAA (0.456 mL, 3.28 mmol) was added. After 1.5 hours, LCMS showed the reaction was completed. The reaction was concentrated, and purified by column chromatography over silica gel (0-50% EtOAc/heptane) to give 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole-2-carbonitrile, **compound 132** (168 mg, 74%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.70 (s, 1 H) 4.13 - 4.21 (m, 2 H) 2.89 (t, *J* = 7.33 Hz, 2 H), 2.53 - 2.62 (m, 2 H).

Step 4:

Compound 132 (165 mg, 1.24 mmol), NBS (451 mg, 2.51 mmol), and AIBN (10.2 mg, 0.062 mmol) were combined in DCE (8 mL), and the reaction was heated at 85 °C for 60 hours. The reaction was concentrated to give a cream solid. Water (10 mL) was added, and the aqueous extracted with EtOAc (2x). The organics were dried (Na2SO4), concentrated and purified by column chromatography over silica gel (0-30% EtOAc/heptanes) to give **compound 133** (182 mg, 69%) as a thick orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1 H) 5.35 (dd, *J* = 6.82, 1.77 Hz, 1 H) 4.35 - 4.46 (m, 1 H) 4.21 - 4.29 (m, 1 H) 3.28 (ddt, *J* = 14.81, 8.32, 8.32 Hz, 1 H) 2.95 (ddt, *J* = 14.59, 6.76, 1.96 Hz, 1 H).

Step 5:

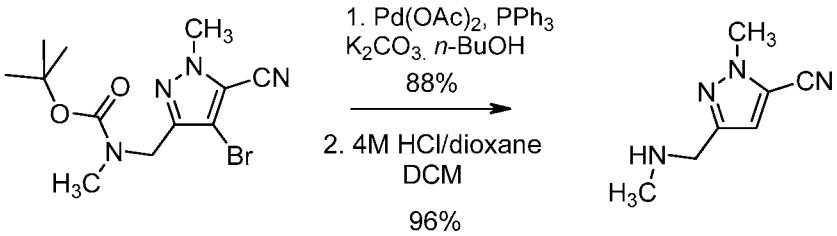
To a cooled solution of **compound 133** (182 mg, 0.858 mmol) in THF (8 mL) was added 2M NH_2CH_3 in THF (1.27 mL). The mixture was stirred at 50 °C for 14 hours. LCMS shows ~50% completion. A further 4 mL of 2M NH_2CH_3 in THF was added, and the resulting mixture was heated at 50 °C for 16 hours. The reaction was allowed to cool, $(Boc)_2O$ (281 mg, 1.29 mmol) was added, and the reaction stirred at room temperature for 18 hours. The reaction was concentrated, and partitioned between water and EtOAc. The organic phase separated, dried (Na_2SO_4), and concentrated to give a brown residue, which was purified by column chromatography over silica gel (0-50% EtOAc/heptane) to give **compound 134** (180 mg, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (d, *J* = 0.76 Hz, 1 H) 5.53 - 5.82 (m, 1 H)

4.33 (ddd, *J* = 11.68, 9.28, 4.55 Hz, 1 H) 4.13 (ddd, *J* = 11.75, 8.72, 6.82 Hz, 1 H) 2.98 (dtd, *J* = 13.58, 8.94, , 4.67 Hz, 1 H) 2.64 (br. s., 3 H) 2.49 (d, *J* = 5.56 Hz, 1 H) 1.43 (s, 9 H). LCMS ES *m/z* 263 $[M+H]^+$.

Step 6:

To a solution of **compound 134** (180 mg, 0.686 mmol) in DCM (2 mL) was added TFA (2 mL). The reaction was complete after 1 hour. It was concentrated to give **compound 135** (237 mg) as a thick yellow oil, which was used without further purification. LCMS ES *m/z* 163 $[M+H]^+$.

Preparation of 1-Methyl-3-((methylamino)methyl)-1*H*-pyrazole-5-carbonitrile (137)



Compound 47 **137**

Step 1:

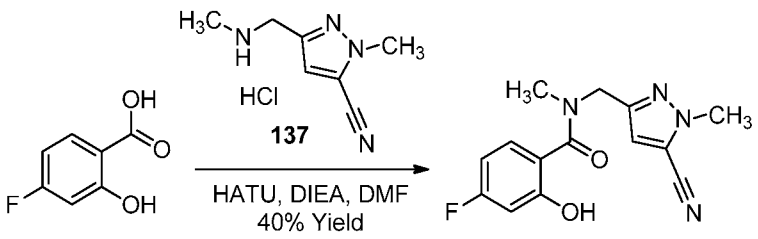
A suspension of **compound 47** (118 g, 358 mmol) in *n*-butanol (1.20 L) was degassed and placed under nitrogen. K_2CO_3 (99.0 g, 716 mmol), triphenylphosphine (18.7 g, 71.3 mmol) and palladium (II) acetate (4.00 g, 17.8 mmol) were then added and the mixture was heated for 4 hours, reaching 80°C after 1 hour, and achieving reflux after 3 hours. The mixture was allowed to cool to room temperature then diluted with EtOAc (1 L) and washed with water (1 L) and brine (1 L). The organic layer was dried ($MgSO_4$) and filtered. On standing overnight a small amount of precipitate was given and so the mixture was filtered and then concentrated *in vacuo* to give 117.4 g of brown oil. Purification by column chromatography over silica gel (10-30% EtOAc/heptane) gave Boc-protected intermediate **compound 137A** as a yellow oil (74.8 g, 83.5%). Impure fractions were combined to give 5.98 g of yellow oil that were purified further by column chromatography over silica gel eluting with 10% EtOAc in heptane increasing polarity to pure EtOAc. This gave a further 3.92 g of **compound 137A** as a yellow oil (4.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 4.38 (s, 2H), 4.01 (s, 3H), 2.84 (s, 3H), 1.47 (s, 9H). LCMS ES *m/z* 251 [M+H]+.

Step 2:

A solution of **compound 137** (78.7 g, 314 mmol) in dichloromethane (400 mL) was cooled to 0°C under nitrogen and a 4M solution of HCl in dioxane (400 mL, 1.6 mol) was added over 5 minutes. After stirring at 0°C for 30 minutes the mixture was allowed to warm to room temperature and stirred for a further 3 hours. The reaction mixture was concentrated to

approximately 150 mL, cooled and filtered, washing with TBME 100 mL). The residue was air dried to give **compound 137** as a colourless crystalline solid (56.12 g, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 2H), 7.31 (s, 1H), 4.13 (s, 2H), 4.03 (s, 3H), 2.52 (s, 3H). LCMS ES *m/z* 151[M+H]$^+$.

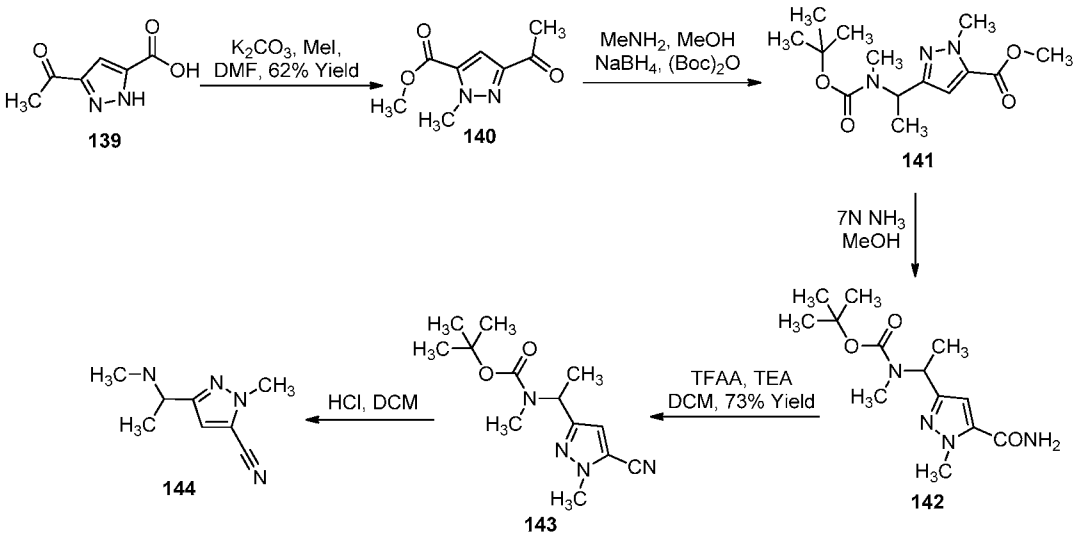
Preparation of *N*-[(5-cyano-1-methyl-1*H*-pyrazol-3-yl)methyl]-4-fluoro-2-hydroxy-*N*-methylbenzamide (138)



136 138

To a solution of 4-fluoro-2-hydroxybenzoic acid **136** (500 mg, 3.2 mmol), (5-cyano-1-methyl-1*H*-pyrazol-3-yl)-*N*-methylmethanaminium chloride **137** (600 mg, 3.2 mmol), and HATU (1.4 g, 3.5 mmol) in DMF (21 mL) was added DIEA (2.8 mL, 16 mmol). After stirring at room temperature for 14 hours, the solution was concentrated and purified by column chromatography over silica gel eluting with heptane/ethyl acetate(0-75%) to afford **compound 138** (370 mg, 40%) as a semi-solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 10.08 (s, 1 H) 7.19 (m, 1 H) 6.94 (s, 1 H) 6.70 - 6.59 (m, 2 H) 4.52 (s, 2 H) 3.98 (d, *J* = 0.8 Hz, 3 H) 2.86 (s, 3 H). LCMS APCI *m/z* 298 [M+H]$^+$.

Preparation of 1-methyl-3-[1-(methylamino)ethyl]-1H-pyrazole-5-carbonitrile (144)



139 140 141 142 143 144

Step 1:

To a stirred suspension of **compound 139** (200 mg, 1.3 mmol), potassium carbonate (450 mg, 3.26 mmol) in DMF (5 mL) was added methyl iodide (456 mg, 3.21 mmol) in a dropwise fashion at room temperature. The vessel was sealed, and the mixture was heated at 50 °C for 1 hour. LCMS indicates complete consumption of starting material and 2 products in a ~ 3 : 1 ratio. The mixture was partitioned between EtOAc/brine. The aqueous layer was extracted with EtOAc. The combined organics were washed with water (2x), brine (1x), dried over $MgSO_4$ and reduced to minimum volume. The residue was purified by column chromatography over silica gel using a gradient of 10-75% EtOAc/heptane as eluent. Two isomers were isolated with the major isomer being **compound 140** (146 mg white solid, 62 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1 H) 4.25 (s, 3 H) 3.91 (s, 3 H) 2.59 (s, 3 H). Minor regioisomer (49 mg, 21%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1 H) 4.24 (s, 3 H) 3.96 (s, 3 H) 2.56 (s, 3 H).

Step 2:

To a solution of **compound 140** (1.13 g, 6.2 mmol) in methanol (50 mL) was added methylamine solution (3.8 mL, 2 M in THF, 7.6 mmol). was allowed to stir at room temperature for 20 hours. To the reaction mixture was added $NaBH_4$ (235 mg, 6.21 mmol). A vigorous gas evolution was initially observed, which ceased after ~30 minutes. LCMS indicated complete conversion to the amine. To the resulting mixture was added $(Boc)_2O$ (2 g, 9.1 mmol) and the mixture was stirred at room temperature for 18 hours. The mixture was concentrated to dryness. The residue was purified by column chromatography over silica gel using a gradient of 10-75% EtOAc/heptane as eluent. The desired fractions were combined and concentrated to give **compound 141** (1.6 g, ~85% pure) as an oil. This material was carried directly into the next step without further purification.^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 6.67 (s, 1 H) 5.26 (q, *J* = 7.05 Hz, 1 H) 4.05 (s, 3 H) 3.84 (s, 3 H) 2.60 (s, 3 H) 1.43 (d, *J* = 7.30 Hz, 12 H).

Step 3:

Compound 141 (1.6 g, 5.4 mmol) was dissolved in 7M ammonia in methanol (20 mL). The vessel was sealed, and the mixture was heated at 50 °C for 5 days. LCMS indicated complete conversion to the desired product. The mixture was concentrated to give **compound 142** (1.496 g ~85% pure) as a gum. This material was carried directly into the next step without further purification. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 7.38 (br. s., 2 H) 6.69 (s, 1 H) 5.26 (q, *J*=6.97 Hz, 1 H) 4.01 (s, 3 H) 2.60 (s, 3 H) 1.44 (s, 9 H) 1.41 (d, *J*=7.05 Hz, 3 H).

Step 4:

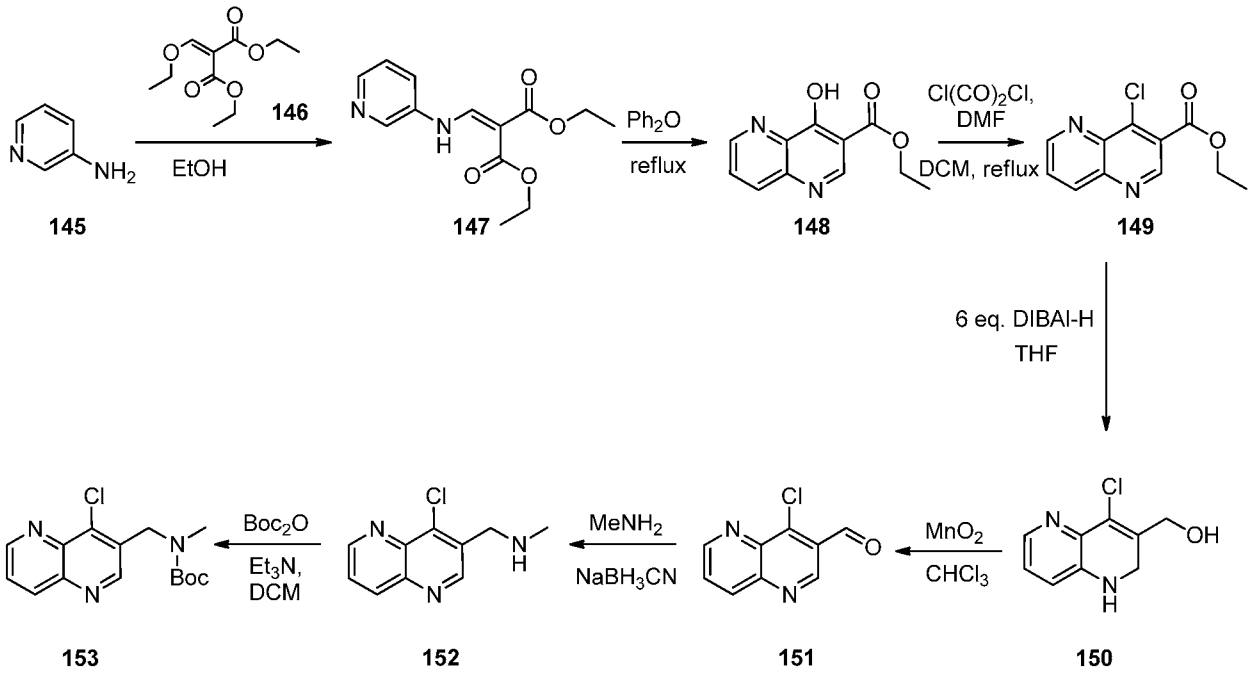
To a suspension of **compound 142** (1.496g, 5.3 mmol) in dichloromethane (20 mL) was added triethylamine (2.2 mL, 15.9 mmol). The resulting suspension was cooled to -10 °C and a solution of trifluoroacetic anhydride (1.5 mL, 10.6 mmol) in dichloromethane (10 mL) was added

dropwise over 20 minutes. After the addition was complete, the reaction mixture was stirred at 0 °C for 1 hour. The mixture was partitioned between dichloromethane and aqueous $NaHCO_3$. The aqueous layer was extracted with dichloromethane (2x). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated to give a dark yellow oil. The residue was purified by column chromatography over silica gel using a gradient of 10-75% EtOAc/heptane as eluent. The desired fractions were concentrated to give **compound 143** (1.026 g, 73%) as a white solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 6.90 (s, 1 H) 5.27 (q, *J*=7.13 Hz, 1 H) 3.97 (s, 3 H) 2.61 (s, 3 H) 1.37 - 1.51 (m, 12 H).

Step 5:

To a solution of **compound 143** (300 mg, 1.14 mmol) in dichloromethane (4.5 mL) was added a solution of HCl in dioxane (4M, 4.5 mL). After stirring at room temperature for 1 hour, the resulting solution was reduced to minimum volume. The residue was concentrated from toluene and dried at 50 °C in a vacuum oven for 1.5 hours to give **compound 144** (228 mg, quant) as a white solid. The material was carried directly into the next step without purification. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 9.39 (br. s., 2 H) 7.30 (s, 1 H) 4.42 (q, *J*=6.88 Hz, 1 H) 4.03 (s, 3 H) 2.46 (s, 3 H) 1.59 (d, *J*=6.80 Hz, 3 H).

Preparation of *tert*-butyl [(4-chloro-1,5-naphthyridin-3-yl)methyl]methylcarbamate (153)



Step 1:

A mixture of **compound 145** (35 g, 0.372 mol) and **compound 146** (96.5 g, 0.447 mol) in EtOH (300 mL) was refluxed overnight. TLC (PE/EtOAc 1/1) showed the reaction was completed. The reaction mixture was concentrated *in vacuo* to give residue. Petroleum ether (200 mL) was added, and then stirred at room temperature for 30 minutes. The mixture was filtered to give **compound 147** (95 g, 97%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03-11.00 (d, 1H), 8.50-8.41 (m, 3H), 7.49-7.47 (d, 1H), 7.34-7.30 (m, 1H), 4.35-4.20 (m, 4H), 1.62-1.18 (m, 6H).

Step 2:

To a refluxing solvent of Ph_2O (200 mL) was added in portions **compound 147** (30 g, 0.113 mol). After addition, the resulting mixture was stirred between 250~260 °C for 30 minutes. TLC (PE/EtOAc 1/1) showed the starting material was consumed completely. The reaction mixture was cooled to room temperature, and then poured into EtOAc (200 mL). The mixture was filtered and the wet cake was washed with EtOH (50 mL), EtOAc (50 mL) and petroleum ether (50 mL) to give **compound 148** (11 g, 45%) as a brown solid.

Step 3:

To a suspension of **compound 148** (12 g, 55 mmol) and DMF (5 mL) in DCM (200 mL) was added dropwise oxalyl chloride (20 mL) below 0 °C. After addition, the resulting mixture was refluxed for three hours. TLC (PE/EtOAc 3/1) showed the reaction was completed. The reaction mixture was poured into ice-water carefully. The mixture was concentrated *in vacuo* to remove DCM. The mixture was extracted with MTBE (500 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified *via* column chromatography (silica gel, PE/EtOAc 5/1) to give **compound 149** (6 g, 46%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 9.17-9.16 (d, 1H), 8.49-8.16 (d, 1H), 7.81-7.78 (t, 1H), 4.56-4.51 (q, 2H), 1.50-1.47 (m, 3H).

Step 4:

To a solution of **compound 149** (4 g, 16.9 mmol) in dry THF (100 mL) was added dropwise DIBAL-H (101.4 mL, 101.4 mmol, 1M in toluene) below 0 °C. After addition, the resulting mixture was stirred at this temperature for 3 hours. TLC (PE/EtOAc 1/1) showed the reaction was completed. The reaction mixture was quenched with saturated aq. Na_2SO_4 (100 mL) below 0 °C and stirred at this temperature for 30 minutes and then at room temperature for 30 minutes. The mixture was filtered. The wet cake was washed with EtOAc (100 mL x 5). The combined filtrates were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified via crystallization from DCM (10 mL) to give **compound 150** (2.5 g, 75.1%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.95 (d, 1H), 6.94-6.91 (m, 1H), 6.75-6.68 (t, 1H), 4.51 (s, 2H), 4.42 (s, 2H), 3.79-3.71 (brs, 1H), 1.70-1.63 (brs, 1H)

Step 5:

A mixture of **compound 150** (2.5 g, 12.7 mmol) and MnO2 (10 g, 115 mmol) in CHCl3 (100 mL) was refluxed overnight. TLC (PE/EtOAc 1/1) showed the reaction was completed. The reaction mixture was filtered and the wet cake was washed with DCM (20 mL x 5). The combined filtrates were dried over Na_2SO_4 and concentrated *in vacuo* to give **compound 151** (2.1 g, 86%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.80 (s, 1H), 9.45 (s, 1H), 9.19-9.11 (m, 1H), 8.51-8.44 (m, 1H), 7.86-7.79 (m, 1H).

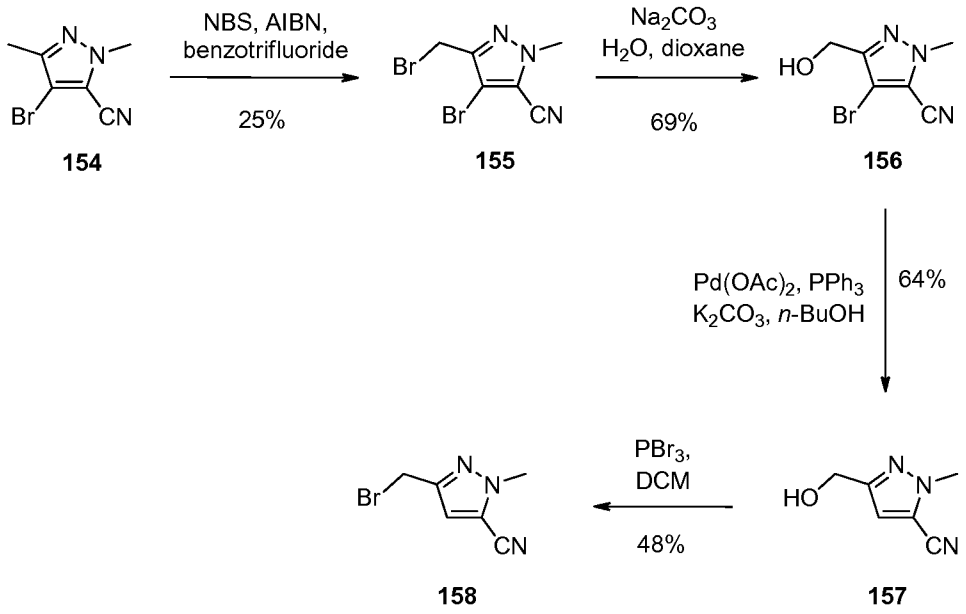
Step 6:

A mixture of **compound 151**(2.7 g, 14.02 mmol), $MeNH_2$.HCl (1.9 g, 28.04 mmol), $MgSO_4$ (5 g) and Et_3N (2.83 g, 158.04 mmol) in methanol (50 mL) was stirred at room temperature overnight. $NaBH_3CN$ (2.5 g, 42.06 mmol) was then added to above mixture and then stirred at room temperature for 4 hours. TLC (PE/EtOAc 1/1) showed the reaction was completed. The reaction mixture was concentrated *in vacuo* to give crude **compound 152**, which was used for next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11-9.10 (d, 1H), 9.02 (s, 1H), 8.46-8.44 (d, 1H), 7.73-7.70 (m, 1H), 4.19 (s, 2H), 2.55 (s, 3H).

Step 7:

To a solution of crude **compound 152** (~ 14.02 mmol) and $(Boc)_2O$ (6.1 g, 28.06 mmol) in DCM (100 mL) was added dropwise Et_3N (2.86 g, 28.04 mmol) at room temperature overnight. After addition, the resulting mixture was stirred at room temperature for 1 hour. TLC (PE/EtOAc 3/1) showed the reaction was completed. The reaction mixture was concentrated *in vacuo* to give residue, which was purified by column chromatography over silica gel (PE/EtOAc 3/1, Rf, 0.15) to give **compound 153** (1.7 g, 36% over two steps) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10-9.09 (d, 1H), 8.88-8.86 (d, 1H), 8.45-8.43 (d, 1H), 7.72-7.71 (m, 1H), 4.87-4.83 (d, 2H), 2.99-2.93 (d, 3H), 1.51-1.47 (d, 9H). LCMS *m/z* 308 $[M+H]^+$.

Preparation of 3-(bromomethyl)-1-methyl-1*H*-pyrazole-5-carbonitrile (158)



Step 1:

Compound 154 (25.0 g, 124.9 mmol) was dissolved in benzotrifluoride (300 mL) and NBS (31.1 g, 174.9 mmol) and AIBN (0.25 g, 1.53 mmol) were added at 45 °C. The temperature was then increased to 80 °C and heated for one hour. Additional AIBN (0.25 g, 1.53 mmol) was added and heating continued overnight. The reaction was cooled to room temperature and the solvent removed under vacuum to give a yellow gum. The gum was taken up in DCM (300 mL) and the remaining solids removed by filtration. The filtrate was concentrated and cold MeOH added to the yellow oil. After standing at 0 oC for two hours, the resultant colourless solid was collected by filtration and washed with cold MeOH (2 x 20 mL). The solid was then recrystallised from methylcyclohexane to give **compound 155** as a colourless solid (9.4 g, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (s, 2H), 4.05 (s, 3H).

Step 2:

Compound 155 (16.0 g, 57.36 mmol) was dissolved in dioxane (200 mL) and a solution of Na_2CO_3 (30.4 g, 286.8 mmol) in H_2O (200 mL) added, and the biphasic mixture heated at 60 °C for 16 hours. The reaction mixture was cooled to room temperature and the dioxane removed under vacuum. The residue was partitioned between DCM (150 mL) and brine (100 mL) and the phases separated. The aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated to give a yellow oil. The crude oil was purified by column chromatography over silica hel (1:3 EtOAc:heptane to 1:1 EtOAc:heptane) to give **compound 156** as a colourless solid (8.60 g, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (d, *J* = 6.1 Hz, 2H), 4.04 (s, 3H), 1.99 (t, *J* = 6.1 Hz, 1H).

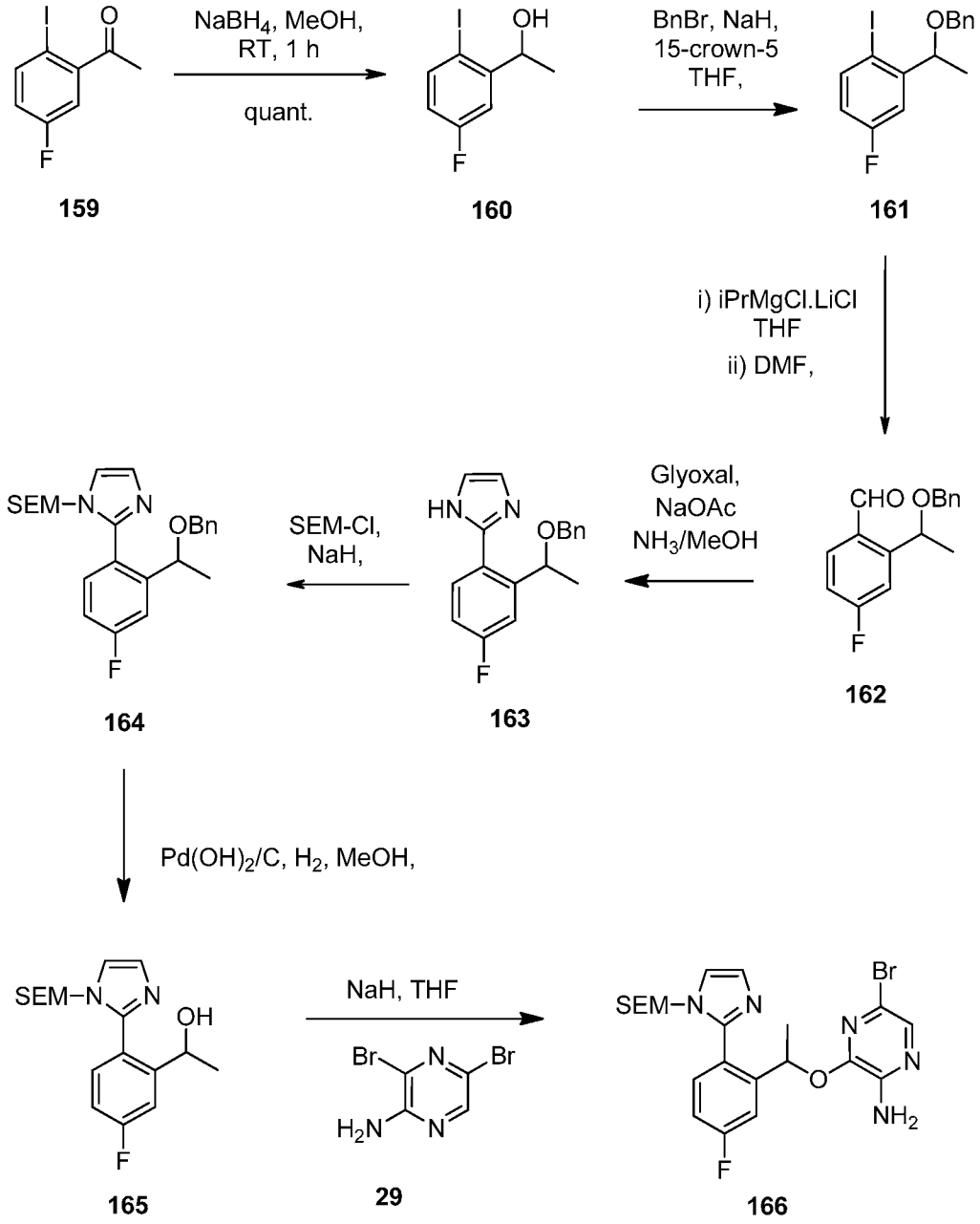
Step 3:

Compound 156 (8.60 g, 39.81 mmol) was dissolved in *n*-butanol (90 mL) and PPh_3 (2.09 g, 7.97 mmol), $Pd(OAc)_2$ (440 mg, 1.96 mol) and K_2CO_3 (11.0 g, 79.6 mmol) were added, and the reaction mixture heated at reflux for 4 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc (150 mL) and washed with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was dried over $MgSO_4$, and concentrated to give a yellow oil. The crude oil was purified by column chromatography over silica gel (1:1 EtOAc : heptane) to give **compound 157** as a colourless solid (3.49 g, 64%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.68 (d, *J* = 6.1 Hz, 2H), 4.04 (s, 3H), 1.99 (t, *J* = 6.1 Hz, 1H).

Step 4:

Compound 157 (3.47 g, 25.30 mmol) was dissolved in DCM (50 mL) and cooled to 0 °C. PBr_3 (3.12 mL, 32.89 mmol) was added dropwise to give a white suspension which was stirred at room temperature overnight. The resultant solution containing a pale yellow gum was diluted with DCM (30 mL) and quenched by the careful addition of H_2O (20 mL) and neutralised with saturated $NaHCO_3$ solution. The phases were separated and the aqueous phase extracted with DCM (2 x 60 mL). The combined DCM extracts were dried over $MgSO_4$ and concentrated to give a yellow oil. The crude oil was purified by column chromatography over silica gel (1:1 DCM : heptane) to give **compound 158** as a colourless oil (2.43 g, 48% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 1H), 4.43 (s, 2H), 4.03 (s, 3H).

Preparation of 5-bromo-3-{1-[5-fluoro-2-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-imidazol-2-yl)phenyl]ethoxy}pyrazin-2-amine (166)



Step 1:

The reaction was performed in 2 batches of 50 g each for portionwise addition of $NaBH_4$). To a cooled (ice bath) solution of **compound 159** (100 g, 379 mmol) in THF (800 ml) and MeOH (400 mL), $NaBH_4$ (28.7 g, 757 mmol) was added portionwise (2 g each) during a 2 hour period (strong gas evolution was observed). The reaction was stirred at room temperature for 3 hours. TLC analysis indicated completion. The reaction was quenched with aqueous NH_4Cl (300 mL). The mixture was extracted with EtOAc (500 mL), the organics separated and again washed with NH_4Cl (300 mL), water (1x 300 mL) then brine (1x 400 mL). The combined organics were dried

($MgSO_4$), and the solvents removed *in vacuo* to give **compound 160** (104.1 g, quant) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (dd, *J* = 8.6, 5.7 Hz, 1H), 7.31 (dd, *J* = 10.4, 3.2 Hz, 1H), 6.92 (td, *J* = 8.4, 3.2 Hz, 1H), 5.55 (d, *J* = 4.1 Hz, 1H), 4.71-4.76 (m, 1H), 1.26 (d, *J* = 6.3 Hz, 3H).

Step 2:

A solution of **compound 160** (119.7 g, 450 mmol) in THF (300 mL) was added *via* addition funnel to an ice-cooled suspension of NaH (60% wt, 19.8 g, 495 mmol) in THF (500 mL) (time of addition - ~1 hour). 15-crown-5 r (13.3 ml, 67.5 mmol) was added and the reaction allowed to warm to room temperature. After 2 hours, a solution of BnBr (51 mL, 427 mmol) in THF (300 mL) was added (~20 min, small exotherm observed up to ~40 °C). The reaction mixture was left stirring at room temperature overnight then quenched with NH_4Cl (200 mL). The mixture was diluted with EtOAc (200 mL), the organics were separated then again washed with NH_4Cl (200 mL), water (300 mL) then brine (2x 300 mL). The combined organics were dried ($MgSO_4$), the solvents removed in vacuo to give an orange oil that was purified by column chromatography (eluent: Heptane/EtOAc – 99:1 to 8:2) to give **compound 161** (144.3 g, 90%) as a colourless liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (dd, *J* = 8.7, 5.7 Hz, 1H), 7.53 – 7.24 (m, 6H), 7.00 (td, *J* = 8.5, 3.1 Hz, 1H), 4.63 (qd, *J* = 6.4, 1.5 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 11.9 Hz, 1H), 1.34 (d, *J* = 6.4 Hz, 3H).

Step 3:

A solution of **compound 161** (50 g, 140 mmol) in THF (500 mL) was cooled to -45 °C (internal T). A solution of *i*-PrMgCl.LiCl (1.3 M in THF, 121 mL, 160 mmol) was added *via* addition funnel (~20 min addition period) keeping the reaction internal T between -40 and -50 °C. After stirring for 1 hour, a white suspension had formed. After another hour, a solution of DMF (15.5 mL, 201 mmol) in THF (100 mL) was added (~30 min addition). The resulting clear reaction mixture was allowed to warm slowly to room temperature. After 16 hours, the reaction was diluted with EtOAc (200 mL), washed with NH_4Cl (3x 300 mL) then brine (2x 400 mL). The combined organics were dried with $MgSO_4$ and the solvents removed *in vacuo* to give 2-(1-(benzyloxy)ethyl)-4-fluorobenzaldehyde **compound 162** (37.9 g, quant) as a pale yellow oil that was used in the following step without further purification.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.02 (dd, *J* = 8.6, 5.9 Hz, 1H), 7.62 – 7.16 (m, 8H), 5.61 – 5.38 (m, 1H), 4.41 (s, 2H), 1.42 (d, *J* = 6.4 Hz, 3H).

Step 4:

Glyoxal (88.2 mL, 771.6 ml) followed by NaOAc (95.5 g, 701.5 mmol) were added to a cooled (ice bath) solution of **compound 162** (38.22 g, 140.3 mmol) in MeOH (100 mL). After stirring for 5 min, a 7N NH_3 in MeOH solution (425 mL) was added and the resulting mixture stirred at 0 °C

for another 10 min before being sealed in an autoclave and heated at 120 °C for 5 hours. The reaction was then cooled to room temperature, the solvents removed *in vacuo* to give a black paste that was redissolved in DCM (600 mL) then washed with a 1:1 NH_4Cl/1M HCl aqueous solution (2x 500 mL) then brine (1x 500 mL). The combined organics were dried ($MgSO_4$), the solvents removed *in vacuo* and the residue (adsorbed on celite) was purified by column chromatography (eluent: Heptane/EtOAc – 9:1 to 1:1). The brown solids isolated were further purified by slurring in minimum amount of EtOAc followed by filtration. After drying *in vacuo*, **compound 163** (16.2 g, 39%) was isolated as off-white solids. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 7.62 (s, 1H), 7.40 (dd, *J* = 10.4, 2.7 Hz, 1H), 7.35 – 7.19 (m, 8H), 5.47 (s, 1H), 4.43 – 4.12 (m, 2H), 1.40 (d, *J* = 5.1 Hz, 3H). LCMS ES *m/z* 297 $[M+H]^+$.

Step 5:

NaH (60% wt, 2.23 g, 55.7 mmol) was added portionwise to a cooled (ice bath) solution of **compound 163** (14 g, 47.2 mmol) in THF (250 mL). The mixture was stirred for 30 minutes before SEM-Cl (9.28 mL, 55.7 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature. After 6 hours, the reaction was placed under an ice bath then quenched by slow addition of water (150 mL) then diluted with EtOAc. The phases were separated and the aqueous layer again extracted with EtOAc (2x 100 mL). The combined organics were dried ($MgSO_4$) and the solvents removed in vacuo to give a residue that was purified by column chromatography (eluent: Heptane/EtOAc – 7:3 to 1:1) to give **compound 164** (32 g, 70%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36-7.49 (m, 2H), 7.34 – 7.18 (m, 7H), 7.04 (d, *J* = 1.3 Hz, 1H), 5.22 – 5.05 (m, 2H), 4.57 (qd, *J* = 6.4, 1.6 Hz, 1H), 4.37 – 4.12 (m, 2H), 3.54 – 3.38 (m, 2H), 1.33 (d, *J* = 6.4 Hz, 3H), 0.85 – 0.63 (m, 2H), -0.08 (s, 9H). LCMS APCI *m/z* 427 $[M+H]^+$.

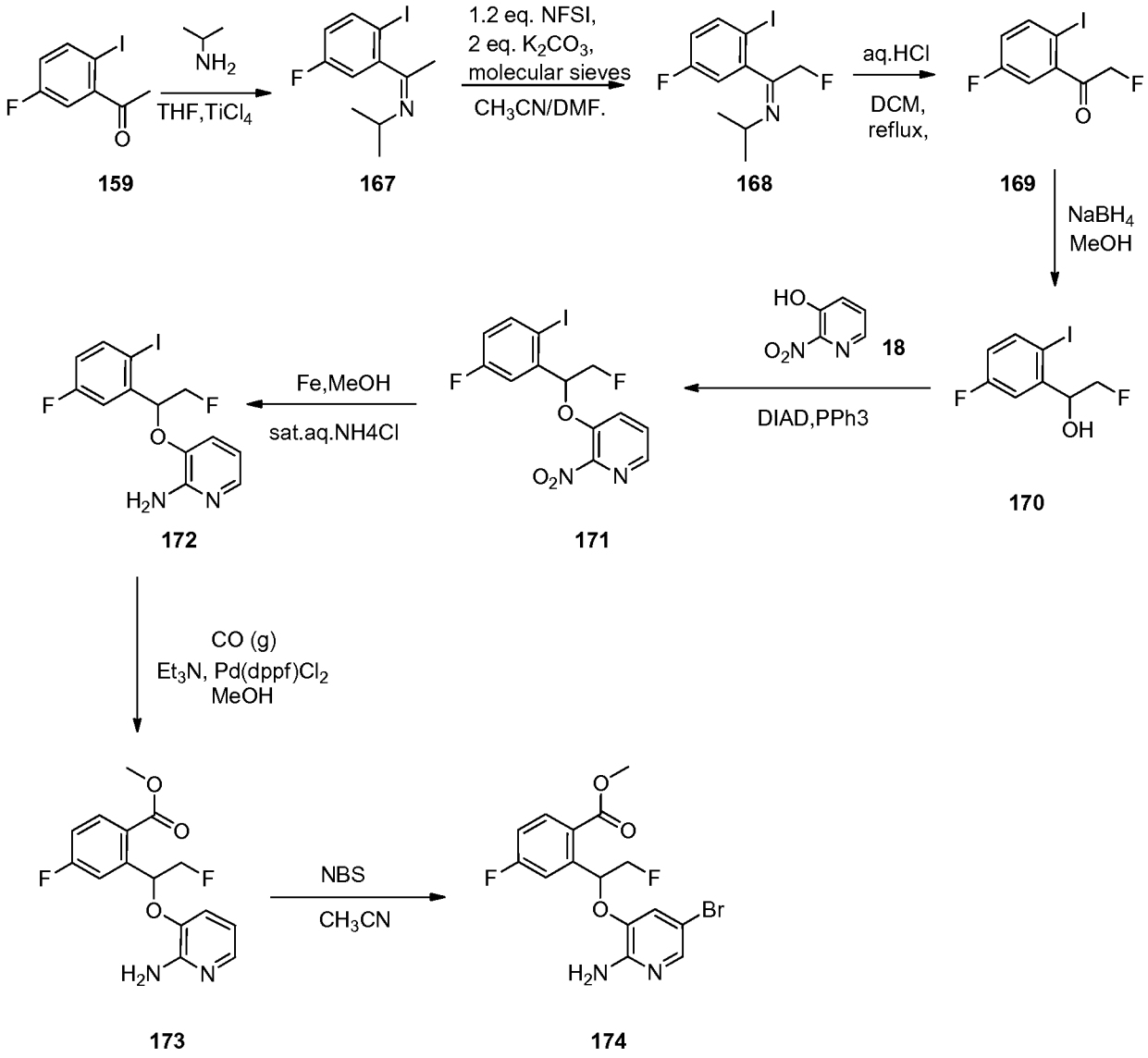
Step 6:

To a stirred solution of **compound 164** (24 g, 56.3 mmol) in MeOH (375 mL) was added 20% wt. $Pd(OH)_2$/C (5 g), and the resulting mixture was heated at 50 °C under an atmosphere of H_2 (30 psi) for 6 hours then at room temperature for 16 hours. The reaction mixture was filtered through a pad of celite washing the filtrates with MeOH. The mother liquids were concentrated *in vacuo* and the resulting residue was purified by column chromatography (eluent: Heptane/EtOAc – 3:1 to 1:1) to give **compound 165** (18.19 g, 96%) as a pale yellow oil. This material was taken into the following step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, *J* = 1.4 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.16 (td, *J* = 8.4, 2.8 Hz, 1H), 7.05 (d, *J* = 1.3 Hz, 1H), 5.40 (d, *J* = 4.5 Hz, 1H), 4.68-4.74 (m, 1H), 3.41 (dd, *J* = 9.0, 7.3 Hz, 2H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.83 – 0.73 (m, 2H), -0.06 (s, 9H). LCMS APCI *m/z* 337 $[M+H]^+$.

Step 7:

A solution of **compound 165** (18.19 g, 54.06) in THF (200 mL) was cooled under an ice bath before NaH (60% wt, 2.59 g, 64.87 mmol) was added (in 3 portions). After stirring for 30 minutes, the reaction was allowed to warm to room temperature. A solution of **compound 29** (16.4 g, 64.87 mmol) in THF (50 mL) was added *via* addition funnel. The reaction mixture was heated at 60 °C for 16 hours then cooled to room temperature. The mixture was diluted with EtOAc (300 mL) then washed with water (2x 300 mL). The organics were dried ($MgSO_4$) and the solvents removed in vacuo to give crude dark solids. These were purified by column chromatography over silica gel (eluent: Heptane/EtOAc – 9:1 to 1:1) to give **compound 166** (19.36 g, 70%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (dd, *J* = 10.3, 2.8 Hz, 1H), 7.63 – 7.49 (m, 3H), 7.29 (td, *J* = 8.5, 2.8 Hz, 1H), 7.15 (d, *J* = 1.3 Hz, 1H), 6.71 (s, 2H), 6.08 – 5.89 (m, 1H), 5.32 (d, *J* = 10.9 Hz, 1H), 5.16 (d, *J* = 10.9 Hz, 1H), 3.66 – 3.48 (m, 2H), 1.65 (d, *J* = 6.4 Hz, 3H), 0.85 (ddd, *J* = 10.1, 6.2, 2.5 Hz, 2H), -0.00 (s, 9H). LCMS APCI *m/z* 508/509 $[M+H]^+$.

Preparation of methyl 2-{1-[(2-amino-5-bromopyridin-3-yl)oxy]-2-fluoroethyl}-4-fluorobenzoate (174)



Step 1:

To a solution of **compound 159** (40 g, 0.153 mol) and isopropylamine (36.2 g, 0.613 mol) in dry THF (500 mL) was added $TiCl_4$ (10 mL) drop-wise at 0 °C. After addition the mixture was stirred at room temperature for 2 hours. TLC (petroleum ether/EtOAc 10/1) showed the reaction was complete. The mixture was filtered. The filtrate was poured into 0.5 M NaOH solution (500 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated to give **compound 167** (43 g, 93.5%) as yellow oil.

Step 2:

To a mixture of NFSI (25 g, 79.4 mmol) K_2CO_3 (18.4 g, 132.4 mmol) and 4Å molecular sieves (25 g) in dry CH_3CN/DMF (250 mL/50 mL) was stirred at 0 °C under nitrogen.for 15 minutes.

Compound 167 (20 g, 66.2 mmol) was added to the mixture. After addition, the reaction mixture was stirred at room temperature for two days. TLC (petroleum ether/EtOAc = 10: 1) indicated 90% of **compound 167** was consumed. Et_3N (5 mL) was added to reaction mixture at 0 °C, and the mixture was stirred for another 15 minutes. The mixture was filtered. The filtrate was poured to 0.5 M NaOH solution (300 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried over Na_2SO_4, and concentrated to give **compound 168** (20 g, 95%) as brown oil which was used directly without further purification.

Step 3:

To a solution of **compound 168** (27.8 g, 86.3 mmol) in CH_2Cl_2/H_2O (250 mL/200 mL) was added concentrated HCl (50 mL). After addition the mixture was refluxed for 1 hour. TLC (petroleum ether: EtOAc = 50:1) showed the reaction was complete. The mixture was cooled to room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (200 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated. The residue was purified by reverse phase preparative HPLC to give **compound 169** (13 g, 54%) as a yellow solid.

Step 4:

To a solution of **compound 169** (13 g, 45.9 mmol) in MeOH (100 mL) was added $NaBH_4$ (3.4 g, 91.9 mol) in portions at 0 °C. After addition, the mixture was stirred at room temperature for 2 hours. TLC (petroleum ether: EtOAc = 10:1) showed the reaction was complete. The mixture was concentrated The residue was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried over Na_2SO_4, and concentrated to give **compound 170** (13 g, 100%) as yellow oil.

Step 5:

To a stirred solution of **compound 170** (4.5g, 15.8 mmol), **compound 18** (2.23 g, 15.8 mmol) and PPh_3 (5.59 g, 22 mmol) in anhydrous THF (80 mL) was added drop-wise DIAD (4.4 g, 0.22 mmol) at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 2 hours. TLC (petroleum ether/EtOAc 3: 1) indicated the reaction was complete. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 20:1 to 10:1) to give **compound 171** (5 g, 78 %) as a yellow solid.

Step 6:

A suspension of **compound 171** (6 g, 14.7 mmol) and Fe (3.3 g, 59 mmol) in MeOH (80 mL) and saturated aqueous NH_4Cl (80 mL) was refluxed for 2 hours. TLC (petroleum ether/EtOAc = 2:1) showed the reaction was complete. The reaction mixture was filtered and the filtrate was

concentrated to give an aqueous solution, which was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel eluting with petroleum ether/EtOAc 6/1 ~ 3/1 to give **compound 172** (5 g, 91%) as a yellow solid.

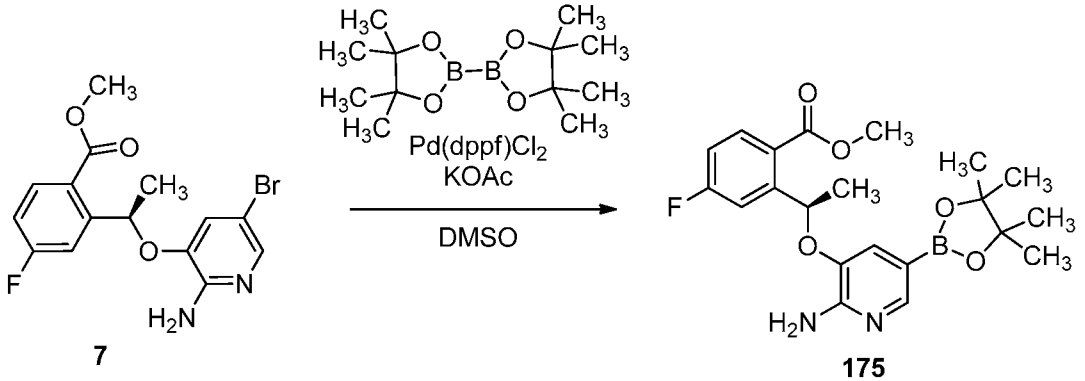
Step 7:

A mixture of **compound 172** (5 g, 13.3 mmol), $Pd(dppf)Cl_2$ (1.15 g, 1.33 mmol) and TEA (2.65g, 26.5 mmol) in methanol (100 mL) was sealed under CO (4 bar) at 100 °C for 16 hours. TLC (petroleum ether/EtOAc=1:1) indicated the reaction was complete. The reaction mixture was filtered and the filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel, (petroleum ether/EtOAc from 8:1 to 6:1) to give **compound 173** (3.5 g, 84%) as a pale brown solid.

Step 8:

To a stirred solution of **compound 173** (3.5 g, 11.3 mmol) in CH_3CN (50 mL) was added dropwise a solution of NBS (2 g, 11.3 mmol) in CH_3CN (30 mL) at 0 °C. After the addition, the reaction mixture was stirred at this temperature for 30 minutes. TLC (petroleum ether/EtOAc =1:1) indicted the reaction was complete. The mixture was diluted with EtOAc (200 mL), washed with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel (petroleum ether/EtOAc 3:1) to give **compound 174** (3.5 g, 79 %) as a pale brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17-8.22 (m, 1H), 7.77 (s, 1H), 7.37-7.40 (d, 1H), 7.14-7.19 (m, 1H), 6.78 (s, 1H), 6.45-6.51 (m, 1H), 4.85-4.9 (s, 2H), 4.59-4.76 (m, 2H), 4.01(s, 3H). LCMS *m/z* 388 $[M+H]^+$.

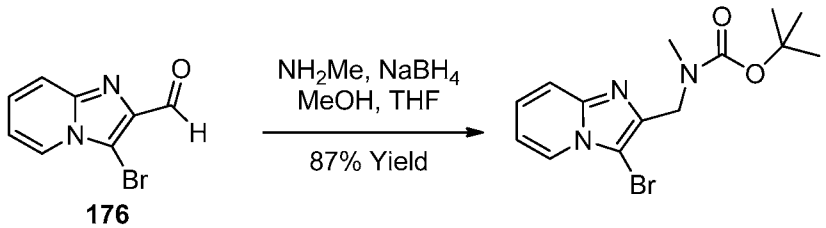
Preparation of methyl 2-[(1*R*)-1-{[2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl]oxy}ethyl]-4-fluorobenzoate (175)



7 175

The procedure described in step 1 for **Example 45** was used to prepare **compound 175**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.94 (dd, *J* = 8.80, 5.87 Hz, 1 H), 7.74 (s, 1 H), 7.68 (dd, *J* = 10.56, 2.35 Hz, 1 H), 7.25 (td, *J* = 8.36, 2.64 Hz, 1 H), 6.87 (s, 1 H), 6.36 (s, 2 H), 6.26 (q, *J* = 6.46 Hz, 1 H), 3.91 (s, 3 H), 1.57 (d, *J* = 5.87 Hz, 3 H), 1.21 (d, J = 5.87 Hz, 12 H).

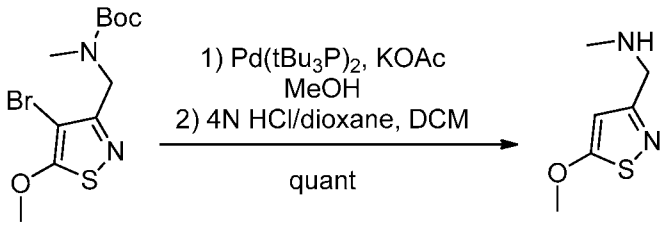
Preparation of *tert*-butyl [(3-bromoimidazo[1,2-*a*]pyridin-2-yl)methyl]methylcarbamate (177)



176 **177**

To a solution of **compound 176** (0.5g, 2.22 mmol), in MeOH (20 mL) was added a methyl amine solution (2M in THF, 1.33 mL, 2.67 mmol). The resulting mixture was stirred at RT for 1 hr. To the reaction mixture was added $NaBH_4$ (84 mg, 2.22 mmol). Vigorous gas evolution was observed. Gas evolution ceased after 30 minutes. LCMS indicates complete conversion to the amine. Di-tert-butyl dicarbonate (735 mg, 3.33mmol) was added and mixture was stirred at RT for 18h. LCMS shows complete conversion to desired product. The solution was concentrated, and the residue was purified by Biotage (40+S cartridge) using a gradient of 10-75% EtOAc/heptane as eluent to give **compound 177** (654 mg, 86.5 %) as an oil. HNMR taken at 80°C . ^{1}H NMR (400 MHz. **80°C**, DMSO-d_6) δ ppm 8.21 - 8.44 (m, 1 H), 7.50 - 7.64 (m, 1 H), 7.27 - 7.43 (m, 1 H), 6.96 - 7.14 (m, 1 H), 4.54 (s, 2 H), 2.86 (s, 3 H), 1.42 (s, 8 H).

Preparation of 1-(5-methoxy-1,2-thiazol-3-yl)-*N*-methylmethanamine (178)

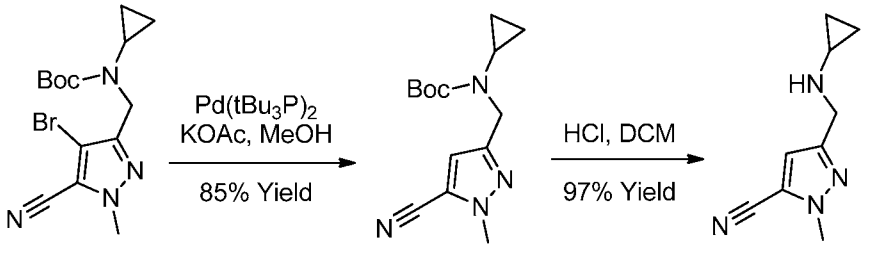


52 **178**

In a sealed 20 ml microwave vial, a solution of **compound 52** (340 mg, 1.01 mmol), KOAc (297 mg, 3.02 mmol) and $Pd(P^tBu_3)_2$ (52.7 mg, 0.101 mmol) in MeOH (5 mL) was heated in the microwave for 45 min at 100 °C. Diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was dissolved in DCM (2.50 mL) then 4 N HCl in dioxane (2.52 mL, 10.1 mmol) was added. The reaction was stirred at room

temperature and concentrated under vacuum to give **compound 178** (196 mg, quantitave) as a solid. ^{1}H NMR (400MHz ,DMSO-d6) δ 9.46 (br. s., 2 H), 6.92 (s, 1 H), 4.15 (s, 2 H), 4.00 (s, 3 H), 2.58 (s, 3 H).

Preparation of 3-[(cyclopropylamino)methyl]-1-methyl-1*H*-pyrazole-5-carbonitrile (181).



179 **180** **181**

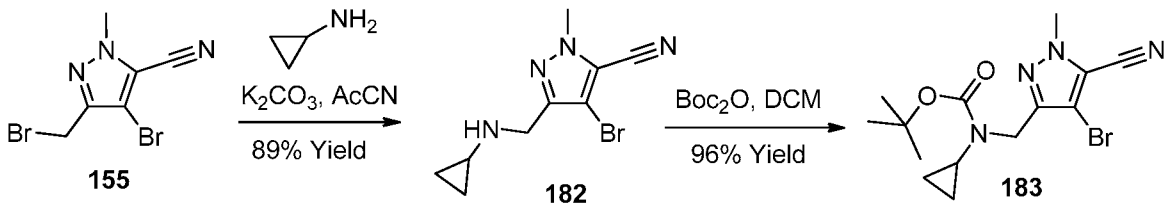
Step 1:

To a solution of **compound 179** (1.50 g, 4.22 mmol) in degassed MeOH was added KOAc (1.24 g, 3.00 mmol) and $Pd(tBu_3P)_2$ (220 mg, 0.10 mmol). Heated to 120 °C in the microwave for 1 hour. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by column chromatography (0-40% EtOAc/heptanes) to give **compound 180** (990 mg, 85%) as a clear oil. ^{1}H NMR (400MHz ,DMSO-d6) δ 6.91 (s, 1 H), 4.31 (s, 2 H), 3.96 (s, 3 H), 2.49 - 2.43 (m, 1 H), 1.39 (s, 9 H), 0.72 - 0.53 (m, 4 H)

Step 2:

To a solution of **compound 180** (990 mg, 3.58 mmol) in DCM (9 mL) was added 4 N HCl in dioxane (8.96 mL, 35.8 mmol). The suspension was stirred for 2 hours at room temperature, then the reaction mixture concentrated under vacuum to give **compound 181** (739 mg, 97%) as a white solid ^{1}H NMR (400MHz ,DMSO-d6) δ 9.72 (br. s., 2 H), 7.33 (s, 1 H), 4.22 (s, 2 H), 4.03 (s, 3 H), 2.66 (tt, *J* = 3.8, 7.4 Hz, 1 H), 0.95 - 0.83 (m, 2 H),0.77 - 0.66 (m, 2 H).

Preparation of *tert*-butyl [(4-bromo-5-cyano-1-methyl-1*H*-pyrazol-3-yl)methyl]cyclopropyl-carbamate (183).



155 **182** **183**

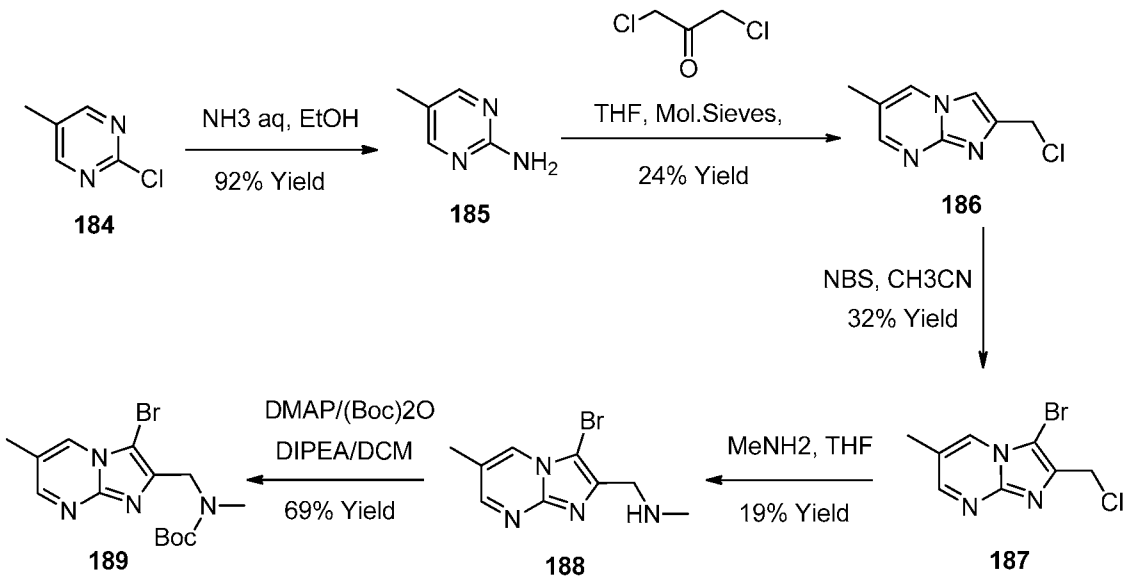
Step 1:

Cyclopropylamine (31.07 g, 544 mmol) was diluted in acetonitrile (30 ml) then potassium carbonate (8.4 g, 61 mmol) was added, followed by **compound 155** (8.5 g, 279 mmol) dissolved in acetonitrile (30 ml). The reaction mixture was stirred at room temperature during 18 hours. To the reaction mixture was added EtOAc (400 ml) and water (80 ml). The phases were separated then the organic phase was evaporated to remove the excess of cyclopropylamine. To the crude compound was added EtOAc (400 ml) and an aqueous solution of HCl 1 M (80 ml). The aqueous phase was put to pH 7 with an aqueous solution of NaOH 1M and extracted with EtOAc (3*400ml). The organic phases were combined, dried over MgSO4, filtered and the solvents were removed under reduced pressure to give **compound 182** as a pale yellow solid (6.95 g, 89% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 3.99 (s, 3H), 3.68 (s, 2H), 2.05 (tt, 1H, J = 6.65, 3.53 Hz), 0.34 (td, 2H, J = 4.06, 6.43 Hz), 0.23 - 0.19 (m, 2H), [M+H]+= 257.06 – 258.14 (1/1)

Step 2:

Compound 182 (6.95 g, 27.2 mmol, 1 eq.) was dissolved in dichloromethane (90 ml, 0.3 M) then Boc anhydride (5.94 g, 27.2 mmol, 1 eq.) was added in small portion. The reaction mixture was stirred at room temperature during 60 hours.The solvents were removed in vacuo. The crude material was combined with the smaller scale reaction (792 mg) and purified by flash chromatography to give **compound 183** as a white solid (10.29 g, 96% yield, 97% purity by LC-MS). ^{1}H NMR (400 MHz, DMSO-d6) δ 4.35 (s, 2H), 3.99 (s, 3H), 2.42 (tt, J = 6.6, 4.0 Hz, 1H), 1.37 (s, 8H), 0.63 (ddt, J = 5.1, 3.4, 2.1 Hz, 4H). [M+H-Boc]= 255.01 – 256.99 (1/1).

Preparation of tert-butyl((3-bromo-6-methylimidazo[1,2-a]pyrimidin-2-yl)methyl)(methyl)-carbamate (189).



Step 1:

To a solution of **compound 184** (10.0 g, 77.79 mmol) in IMS (100 mL) was added aqueous ammonia (35%, 100 ml). The reaction mixture was transferred to a sealed bomb and heated at 200 °C for 4 h. The reaction mixture was allowed to cool to room temperature and was concentrated to remove most of the solvent and water (25 mL) added. The solid obtained was filtered and dried under vacuum to give the desired **compound 185** as off-white solid (7.85 g, 92% yield).^{1}H NMR (400 MHz, DMSO-d6) δ 8.06 (s, 2H), 6.30 (s, 2H), 2.03 (s, 3H). LCMS *m/z* 110 $[M+H]^+$.

Step 2:

The reaction was done in two batches using 1 g and 9.36 g of **compound 185** and the crude material obtained from both batches was combined for purification. To a slurry of **compound 185** (9.36 g, 85.82 mmol) in dry THF (250 mL) was added dichloroacetone (21.80 g, 171.64 mmol) and 4A° molecular sieves (25 g). The reaction mixture was heated at 90 °C for 3 days, then the reaction mixture was concentrated and the resulting residue dissolved in water (200 mL). The solution was treated with solid K_2CO_3 (10 g) and stirred for 10 min before extraction with ethyl acetate (3 x 400 mL). The combined ethyl acetate extracts were washed with brine (100 mL) and concentrated to give the crude product as thick brown oil. The aqueous phase was subjected to liquid-liquid extraction with DCM (500 mL) and the resulting product obtained was combined with the crude oil obtained from the ethyl acetate extractions for purification. Purification by silica gel column chromatography using 0.5% - 1% MeOH in DCM furnished **compound 186** as off-white solid (4.2 g, 24% yield).^{1}H NMR (400 MHz, Chloroform-d) δ 8.44 (d, *J* = 2.4 Hz, 1H), 8.23 (dd, *J* = 2.4, 1.2 Hz, 1H), 7.56 (d, *J* = 0.8 Hz, 1H), 4.79 (d, *J* = 0.8 Hz, 2H), 2.37 (d, *J* = 1.1 Hz, 3H). LCMS *m/z* 182 $[M+H]^+$.

Step 3:

The reaction was done in two batches using 2.0 g and 2.2 g of **compound 186** and the crude material obtained from both batches was combined for purification. To a solution of **compound 186** (2.0 g, 11.01 mmol) in acetonitrile (30 mL) was added NBS (2.14 g, 12.0 mmol) and the reaction stirred at room temperature overnight. The solvent was removed under vacuum and the combined crude product was dissolved in EtOAc (100 mL). The solid which precipitated was removed by filtration and the filtrate was evaporated to give the crude product as light yellow gum. Purification of the crude by silica gel column chromatography using 0.5% MeOH in DCM furnished the pure **compound 187** as an off-white solid (1.9 g, 32% yield).^{1}H NMR (400 MHz, Chloroform-d) δ 8.47 (d, *J* = 2.4 Hz, 1H), 8.14 (dd, *J* = 2.4, 1.2 Hz, 1H), 4.78 (s, 2H), 2.44 (s, 3H). LCMS *m/z* 260/262 $[M+H]^+$.

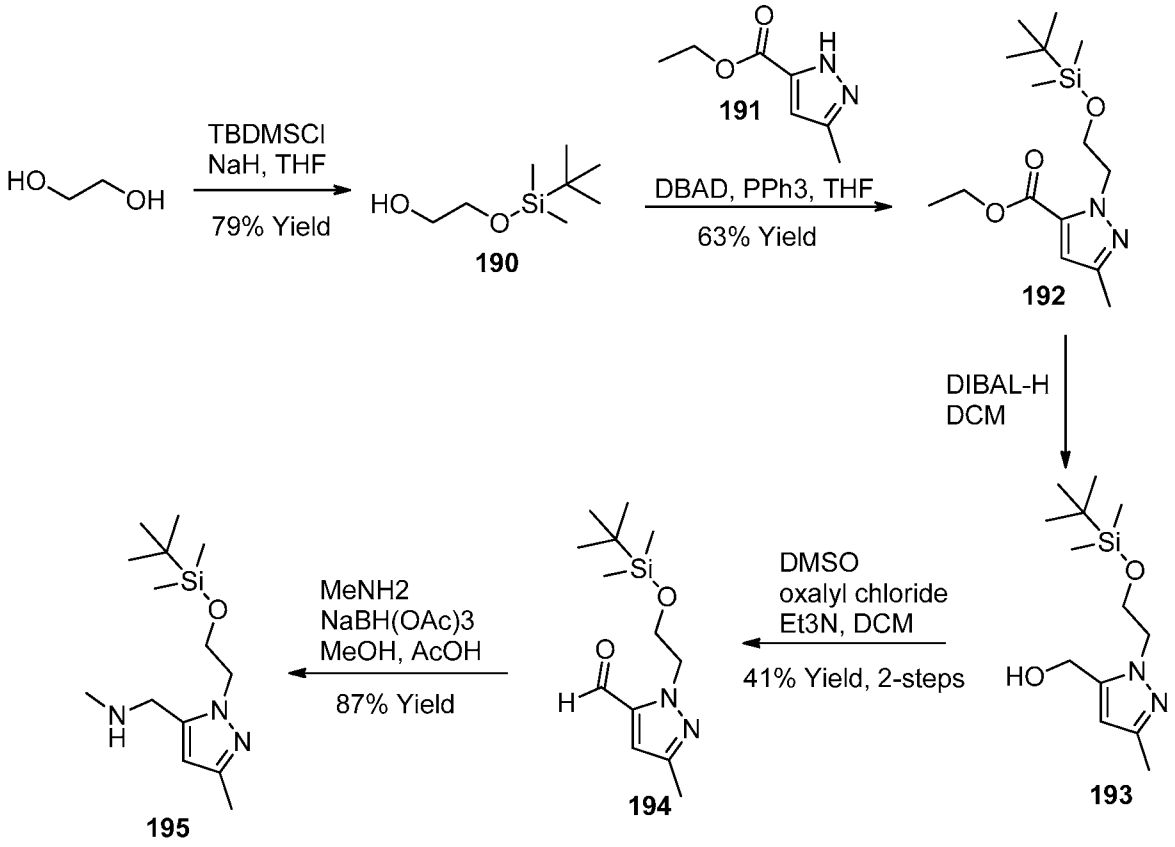
Step 4:

To a suspension of **compound 187** (1.68 g, 6.45 mmol) in THF (20 mL) being heated at 60 °C, was slowly added a solution of methyl amine in THF (2M, 53.2 mL, 96.75 mmol) over a period of 30 min using a syringe pump. Once the addition was complete, the reaction was heated at 60 °C for 4h. The crude product obtained after concentration of the reaction mixture, was purified by flash silica gel column chromatography using 10% MeOH in DCM along with 0.1% of 35% aqueous ammonia. The product obtained was found to contain a small amount of undesired dimer and so was further purified by reverse phase using a CH_3CN/H_2O solvent gradient. The product thus obtained was contaminated with a trace of impurity and was purified again by flash silica gel column chromatography using 4% MeOH in DCM (containing 7N ammonia) to furnish **compound 188** as a yellow solid (254 mg, 15% yield).^{1}H NMR (400 MHz, Methanol-d4) δ 8.89 – 8.22 (m, 2H), 3.88 (s, 2H), 2.45 (d, *J* = 1.1 Hz, 3H), 2.42 (s, 3H). LCMS *m/z* 255/257 $[M+H]^+$.

Step 5:

To a solution of **compound 188** (250 mg, 0.980 mmol), DIEA (0.512 mL, 2.94 mmol) and DMAP (23.9 mg, 0.196 mmol) in DCM (4 mL) was added $(Boc)_2O$ (856 mg, 3.92 mmol) at 0 °C. The mixture was stirred at RT for overnight. It was concentrated and purified by ISCO (24g) using 0% - 75% EtOAc/Heptanes to give **compound 189** as a gum (241 mg, 69% yield). ^{1}H NMR (400MHz, DMSO-d6) δ 8.59 (s, 1H), 8.48 (d, *J*=2.3 Hz, 1H), 4.52 (s, 2H), 2.85 (br. s., 3H), 2.37 (s, 3H), 1.39 (d, *J*=15.9 Hz, 9H). LCMS *m/z* 355/357 $[M+H]^+$.

Preparation of 1-[1-(2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl)-3-methyl-1*H*-pyrazol-5-yl]-*N*-methylmethanamine (195).



Step 1:

Under inert atmosphere at 0 °C (ice/water bath), to a suspension of NaH (60% in mineral oil, 6.44 g, 0.161 mol) (internal T=4 °C) was added ethylene glycol (10.0 g, 0.161 mol). The internal temperature after addition was 6 °C. The reaction was stirred for 45 minutes in ice/water bath (internal T= 4 °C). tert-butylchlorodimethylsilane (29.121 g, 0.161 mol) was added portionwise over 15 minutes keeping the temperature below 10 °C. After addition of tert-butylchlorodimethylsilane the reaction mixture was allowed to warm to room temperature and stirred for 2.5 hours. The reaction was then quenched by addition of NaHCO3 sat solution (250 mL) and water (100 mL). The mixture was extracted with TBME (250 mLX2), the combined organics were washed with brine (250 mL), dried over Na_2SO_4, filtered and reduced to dryness to give a yellow oil. The crude was purified by filtration on silica pad using heptanes/EtOAc (gradient elution 95/5 then 9/1, 8/2, 7/3). The correct fractions were combined and reduced to dryness to give **compound 190** as colourless oil (22.5 g, 79%). ^{1}H NMR(400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.82 (s, 9H), 2.00 (t, 1H), 3.54-3.58 (m, 2H), 3.62-3.64 (m, 2H).

Step 2:

Under an inert atmosphere, to a solution of **compound 191** (20.00 g, 129.7 mmol), 2-((tert-butyldimethylsilyl)oxy)ethanol **190** (27.45 g, 155.7 mmol) and triphenylphosphine (40.83 g, 155.7 mmol) in THF (400 mL) cooled to 0 °C was added dropwise a solution of DBAD (35.85 g, 155.7

mmol) in THF (200 mL) over 1 hour. After stirring for 3 hours at room temperature, 0.1 equiv of 2-((tert-butyldimethylsilyl)oxy)ethanol (2.2 g, 12.48 mmol) was added. The reaction mixture was stirred for another 18 hours then concentrated. The resulting yellow oil was triturated with heptane (1 L) forming a white solid which was removed by filtration. The filtrate was concentrated and the oily residue was purified by column chromatography (silica, 2% to 6% EtOAc in heptane) yielding **compound 192** as a pale yellow oil (25.47 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.78 (s, 9H), 1.33 (t, 3H), 2.25 (s, 3H), 3.89 (t, 2H), 4.29 (q, 2H), 4.63 (t, 2H), 6.57 (s, 1H), [MH]+ 313.

Step 3:

Under an inert atmosphere, to a solution of **compound 192** (24.8 g, 79.4 mmol) in DCM (600 mL) cooled to – 78 °C was added dropwise DIBAL-H (1M solution in DCM, 250 mL, 250 mmol). After stirring for 1 hour at – 78 °C, the reaction mixture was quenched with methanol (60 mL) then warmed to room temperature. Water and brine were added forming a grey precipitate. Attempt at performing an extraction was not successful as both phases were hard to visualize. The reaction mixture was then filtered over celite and washed with large amounts of DCM (4 L). The water layer was separated and the organic phase was dried (Na_2SO_4) and concentrated to give **compound 193** as an oil (20 g) which was used as it is in the next step. ^{1}H NMR (400 MHz, CDCl3) δ 0.04 (s, 6H), 0.79 (s, 9H), 2.23 (s, 3H), 3.96 (t, 2H), 4.22 (t, 2H), 4.55 (d, 2H), 5.97 (s, 1H), [MH]+ 271.

Step 4:

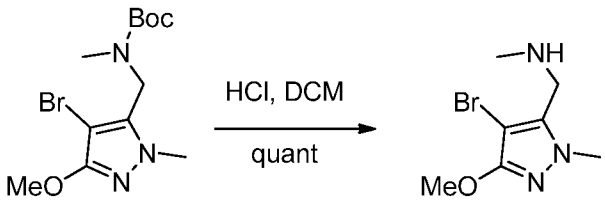
Under an inert atmosphere, to a solution of oxalyl chloride (8.70 mL, 103 mmol) in DCM (188 mL) cooled to – 78 °C was added over 30 min a solution of DMSO (14.4 mL, 205 mmol) in DCM (75 mL). The reaction mixture was stirred for 30 min at – 78°C then a solution of **compound 193** (20 g) in DCM (188 mL) was added dropwise. The reaction mixture was stirred for 1.25 hours at – 78 °C followed by the dropwise addition of triethylamine (66.0 mL, 474 mmol). The reaction was warmed to room temperature and water (600 mL) was added. The phases were separated and the aqueous layer was extracted with DCM (3 x 500 mL). The combined organics were dried (Na_2SO_4) and concentrated. The resulting oily residue was purified by column chromatography (silica, 0% to 2% EtOAc in DCM) to give **compound 194** as a pale yellow oil (8.75 g, 41% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.78 (s, 9H), 2.29 (s, 3H), 3.90 (t, 2H), 4.56 (t, 2H), 6.63 (s, 1H), 9.80 (s, 1H), [MH]+ 269.

Step 5:

Under an inert atmosphere, to a solution of **compound 194** (11.15 g, 41.54 mmol) and methylamine (33% w/w in EtOH, 14.77 g, 157.22 mmol) in methanol (280 mL) was added acetic acid (2.50 mL, 41.54 mmol) dropwise. The reaction mixture was stirred at room temperature for

1.3 hours, cooled to 0 °C, treated with $NaBH(OAc)_3$ (13.2 g, 62.31 mmol) then stirred at room temperature for 18 hours. After this time, some amine (3.90 mg, 41.92 mmol) was added followed by $NaBH(OAc)_3$ (8.80 g, 41.5 mmol) 30 minutes later. The reaction mixture was stirred for another 40 minutes, concentrated, taken up in EtOAc (375 mL) and washed with sat. aq. $NaHCO_3$ (275 mL) and brine (200 mL). The organic layer was dried (Na_2SO_4) and concentrated. The resulting oily residue was purified by column chromatography (neutralized silica, 0% to 6% 7N NH_3/MeOH in DCM) to give **compound 195** (10.3 g, 87%).^{1}H NMR (400 MHz, CDCl3) δ 0.10 (s, 6H), 0.80 (s, 9H), 1.60 (br, 1H), 2.20 (s, 3H), 2.42 (s, 3H), 3.71 (s, 2H), 3.92 (t, 2H), 4.11 (t, 2H), 5.88 (s, 1H), MH]+ 284.

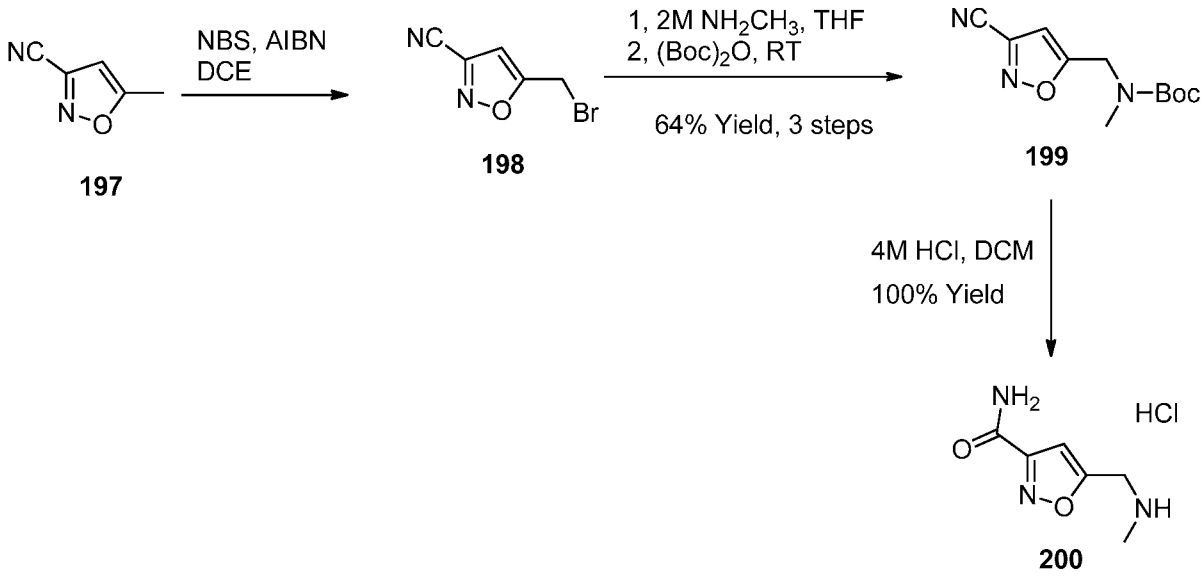
Preparation of 1-(4-bromo-3-methoxy-1-methyl-1*H*-pyrazol-5-yl)-*N*-methylmethanamine (196)



91 **196**

To a solution of **compound 91** (1613 mg, 4.826 mmol) in DCM (10 ml) was added 4N HCl in dioxane.(10 ml). The solution was allowed to stir at room temperature for2 hours, then the reaction mixture was concentrated to give **compound 196** (1357 mg, 104%) as a yellow solid.

Preparation of 5-((methylamino)methyl)isoxazole-3-carboxamide (200)



197 **198** **199** **200**

Step 1:

To a solution of **compound 197** (800 mg, 7.40 mmol) in DCE (30 mL) was added NBS (2.79 g, 15.5 mmol) and AIBN (60.8 mg, 0.375 mmol).The reaction stirred at 85 °C for overnight. Concentrate to give the cream solid. Water (20 mL) was added, and extracted with EtOAc (30 mL × 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to give **compound 198**(1.44 g, 2.90 mmol) as an off-white semi-solid, which was taken into the next step without further purification.

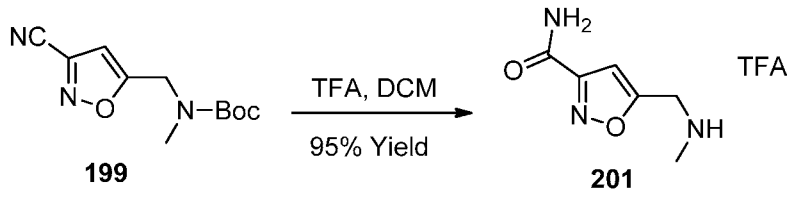
Step 2:

To a solution of **compound 198** (1.44 g, 2.90 mml) in THF (15 mL) was cooled to 0 °C, 2M NH_2CH_3 in THF (4.36 mL, 8.73 mmol) was added. The mixture was stirred at 0 °C for 2.5 h. $(Boc)_2O$ (635 mg, 2.91 mmol) was added. Let it go for overnight at RT. LCMS shows the new peak and the staring material. 380 mg of $(Boc)_2O$ was added. The resulting mixture was stirred at RT for 3h. LCMS shows the new peak was growing. After another 2 h, no any progress was found by LCMS. 283 mg of $(Boc)_2O$ was added. It was stirred at RT for overnight. Solvent removed in *vacuo* and the reaction partitioned between water and EtOAc (50ml/50ml). The organic phase separated, dried over Na_2SO_4, and concentrated. It was purified by ISCO with 0-40% EtOAc/Heptane to give **compound 199** as a colorless oil (445 mg, 64% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (br. s., 9 H) 2.98 (s, 3 H) 4.60 (br. s., 2 H) 6.56 (br. s., 1 H).

Step 3:

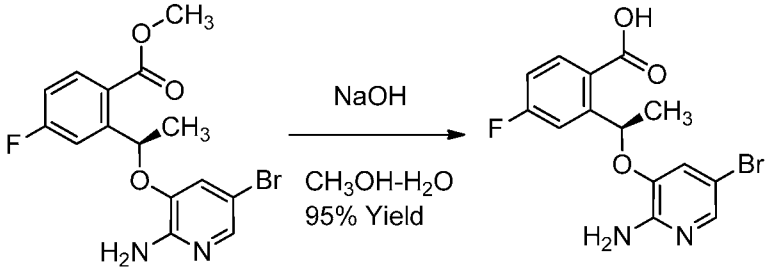
To a solution of **compound 199** (445 mg, 1.88 mmol) in DCM (5 mL) was added 4M HCl in dioxane (5 mL) dropwise. The reaction was complete after 2 hours by LCMS. It was concentrated and dried over a vacuum oven at 60 °C for overnight to give **compound 200** HCl salt as a white solid (333 mg, 100% yield). ^1H NMR (400 MHz, DMSO-*d6*) δ 2.59 (s, 3 H) 4.44 (s, 2 H) 7.00 (s, 1 H) 7.90 (br. s., 1 H) 8.21 (br. s., 1 H) 9.77 (br. s., 2 H). LCMS *m/z* 156 $[M+H]^+$.

Preparation of 5-[(methylamino)methyl]-1,2-oxazole-3-carbonitrile (201)



To a solution of **compound 199** (850 mg, 2.90 mmol) in DCM (3 mL) was added TFA (3 mL, 38.9 mmol) dropwise. The reaction was complete after 1.5 hours by LCMS. It was concentrated and dried over a vacuum oven at 60 °C overnight to give **compound 201** as a brown gum (686 mg, 95% yield).

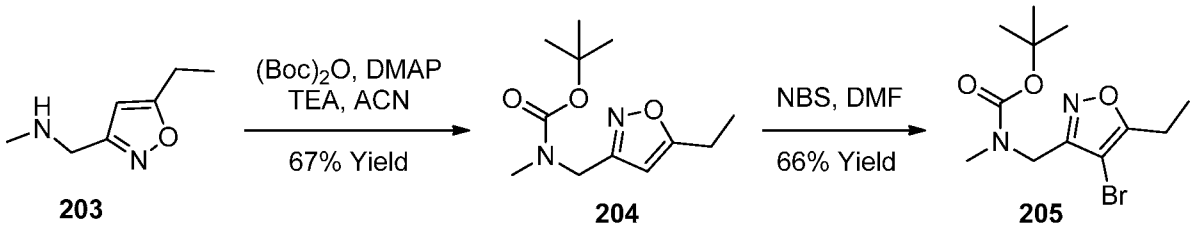
Preparation of 2-{(1*R*)-1-[(2-amino-5-bromopyridin-3-yl)oxy]ethyl}-4-fluorobenzoic acid (202)



7 **202**

The procedure described in step 2 for **Example 41** was used to prepare **compound 202** (731 mg, 95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (br. s., 1 H) 7.97 (dd, *J*=8.59, 6.06 Hz, 1 H) 7.47 - 7.64 (m, 2 H) 7.18 - 7.30 (m, 1 H) 6.87 (s, 1 H) 6.20 - 6.48 (m, 3 H) 1.58 (d, *J*=6.32 Hz, 3 H).

Preparation of *tert*-butyl [(4-bromo-5-ethyl-1,2-oxazol-3-yl)methyl]methylcarbamate (205).



203 **204** **205**

Step 1:

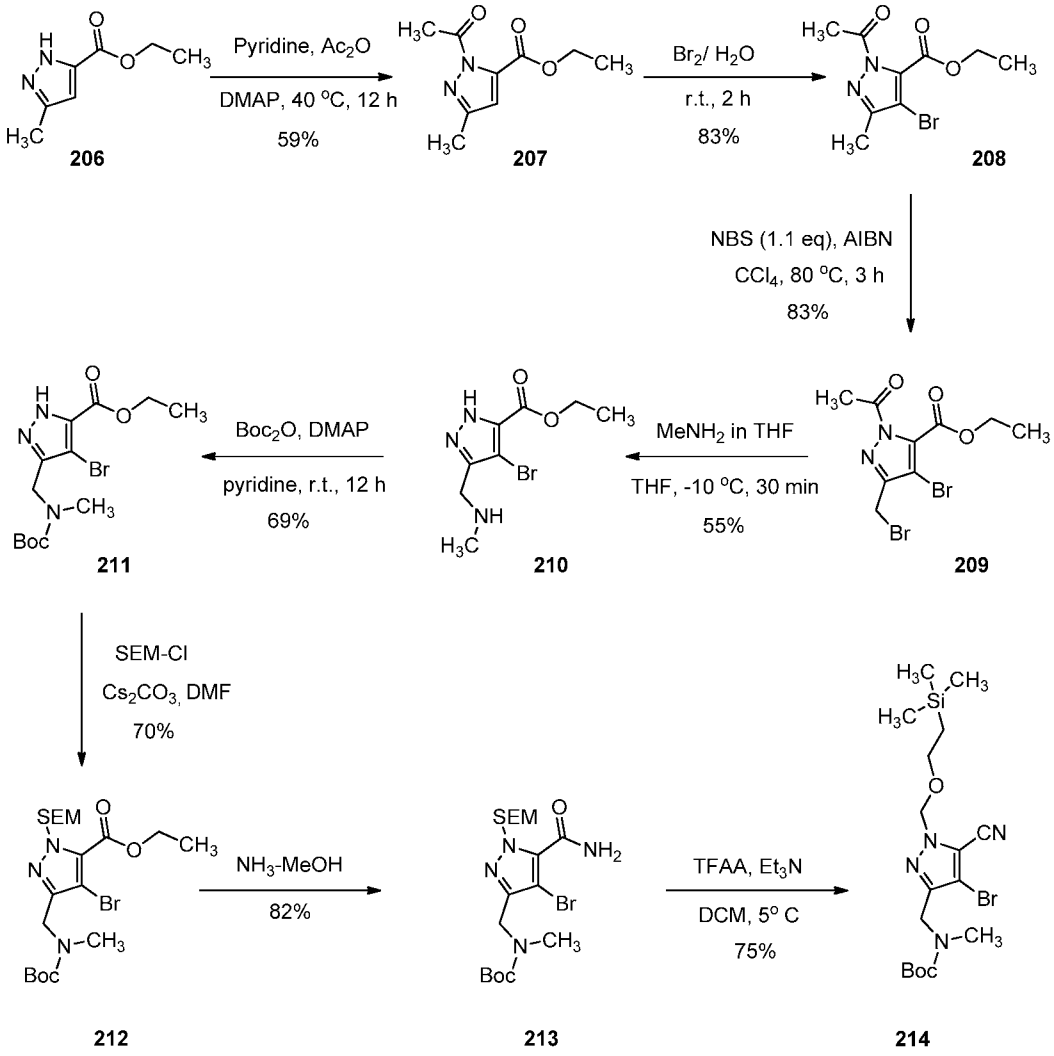
To a 0 °C suspension of **compound 203** (1.81 g, 12.9 mmol), TEA (9.10 mL, 64.6 mmol), and DMAP (0.315 g, 2.58 mmol) in ACN (50 mL) was added di-t-butyl-dicarbonate (3.38 g, 15.5 mmol). The reaction mixture was allowed to stir at room temperature for 2 hours. Water and EtOAc were added to the reaction mixture. The aqueous layer was extracted by 2x EtOAc. The organic layer was washed by brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography (2 to 30 % EtOAc/Heptane) to give **compound 204** (2.09 g, 67%) as a colorless oil. ^{1}H NMR (400 MHz, METHANOL-d4) δ 1.28 (t, J=7.58 Hz, 3 H) 1.47 (br. s., 9 H) 2.77 (q, J=7.58 Hz, 2 H) 2.88 (s, 3 H) 4.42 (s, 2 H) 6.04 (s, 1 H).

Step 2:

To a solution of **compound 204** (500 mg, 2.08 mmol) in DMF (2.2 mL) was added N-bromosuccinimide (444mg, 2.50 mmol). The reaction mixture was heated to 60 °C for 1 hour. EtOAc (22 mL) was added to the reaction mixture, then washed with water (1 x 22 mL), and brine (22 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography (3% to 30% EtOAc/Heptane) to

give **compound 205** (441 mg, 66%) as a colorless oil. ^{1}H NMR (400 MHz, METHANOL-d_4) δ 1.28 (t, *J*=7.71 Hz, 3 H) 1.48 (s, 4 H) 1.43 (s, 5 H) 2.82 (q, *J*=7.66 Hz, 2 H) 2.89 (s, 3 H) 4.50 (s, 2 H).

Synthesis of *tert*-butyl ((4-bromo-5-cyano-1-((-2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3- yl)methyl)carbamate (Compound 214)



206 207 208 209 210 211 212 213 214

Step 1:

To a solution of **compound 206** (120 g, 0.779 mol) in pyridine (800 mL) was added Ac_2O (400 mL) and then a catalytic amount of DMAP (13 g, 0.106 mol) at room temperature. The resulting mixture was stirred at room temperature for 12 hours. TLC (Petroleum ether/EtOAc = 3:1) showed the reaction was complete. The mixture was concentrated *in vacuo* to give the residue, which was partitioned between CH_2Cl_2 (1 L) and H_2O (200 mL). The organic layer was separated, washed with brine (100 mL) and dried over Na_2SO_4, concentrated *in vacuo* to give the crude product. The crude product was purified by column chromatography over silica gel

(Petroleum ether/EtOAc = 10:1) to obtain **compound 207** (90 g, 59%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 1H), 4.40-4.35 (q, 2H), 2.74 (s, 3H), 2.57 (s, 3H), 1.39-1.35 (t, 3H)

Step 2:

To a suspension of **compound 207** (50 g, 0.255 mol) in H_2O (1.5 L) was added dropwise Br_2 (44 g, 0.281 mol) at room temperature. The resulting mixture was stirred at room temperature for 3 hours. TLC (Petroleum ether/EtOAc = 5:1) showed the reaction was complete. The mixture was extracted with EtOAc (500 mL x 3). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ (200 mL), H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* give the crude product, which was purified by re-crystallization from petroleum ether/EtOAc (5:1, 120 mL) to obtain **compound 208** (58 g, 83%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47-4.42 (q, 2H), 2.77 (s, 3H), 2.63 (s, 3H), 1.44-1.40 (t, 3H)

Step 3:

To a suspension of **compound 208** (56 g, 0.204 mol) in CCl_4 (800 mL) was added NBS (40 g, 0.225 mol) and AIBN (9.6 g) at room temperature under a nitrogen atmosphere. The resulting mixture was heated at reflux for 3 hours. TLC (Petroleum ether/EtOAc = 3:1) showed the reaction was complete. The mixture was cooled to room temperature and then filtered, and the solids washed with CH_2Cl_2 (200 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ solution (100 mL x 2), H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was re-crystallized from petroleum ether/EtOAc (5:1, 120 mL) to obtain **compound 209** (60 g, 83%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (s, 2H), 4.48-4.42 (q, 2H), 2.80 (s, 3H), 1.45-1.41 (t, 3H)

Step 4:

To a solution of **compound 209** (59 g, 0.167 mol) in THF (300 mL) was added dropwise CH_3NH_2 in THF (2 N, 419 mL, 0.835 mol) at -10 °C. The resulting mixture was stirred at -10 °C for 30 minutes. TLC (Petroleum ether/EtOAc = 3:1) showed the reaction was complete. The mixture was filtered, and the filtrate was concentrated *in vacuo* at 25 °C for 20 minutes and then at higher temperature to give the crude product, which was purified by column chromatography over silica gel (CH_2Cl_2/MeOH = 100:1~20:1, R_f = 0.3 in CH_2Cl_2/MeOH = 10:1) to obtain **compound 210** (24 g, 55%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.55 (br, 2H), 6.85 (s, 1H), 5.29 (s, 0.62H, residual CH_2Cl_2), 4.36-4.31 (q, 2H), 4.21 (s, 2H), 3.49 (s, 1.56H, residual MeOH), 2.68 (s, 3H), 1.37-1.24 (t, 3H).

Step 5:

To a solution of **compound 210** (24 g, 0.092 mol) in pyridine (300 mL) was added DMAP (5.66 g, 0.046 mol) and Boc_2O (29.81 g, 0.138 mol) at room temperature. The resulting mixture was stirred at room temperature overnight. TLC (Petroleum ether/EtOAc = 3:1) showed the reaction

was complete. The mixture was concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (Petroleum ether/EtOAc= 10:1~2:1) to give **compound 211** (23 g, 69%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44-4.38 (m, 4H), 2.91 (s, 3H), 1.49 (s, 9H), 1.25-1.24 (t, 3H)

Step 6:

To a suspension of **compound 211** (23 g, 0.0637 mol) in anhydrous DMF (400 mL) was added Cs_2CO_3 (46.8 g, 0.14 mol) at room temperature. The resulting mixture was stirred at room temperature for 30 minutes. After 30 minutes, SEM-Cl (24.39 g, 0.146 mol) was added into the mixture. The resulting mixture was stirred at room temperature for 2 hours. TLC (Petroleum ether/EtOAc = 3:1) showed the reaction was complete. The mixture was diluted with EtOAc (1 L) and brine (200 mL). The organic layer was separated and washed with H_2O (200 mL x 2), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (Petroleum ether/EtOAc = 10:1) to obtain **compound 212** (22 g, 70%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.76 (s, 1H), 4.72-4.65 (m, 2H), 4.47-4.40 (q, 2H), 3.55-3.51 (m, 2H), 2.95-2.76 (m, 3H), 1.49 (s, 9H), 1.43-1.39 (t, 3H), 0.96-0.85 (m, 2H), 0-0.05 (m, 9H).

Step 7:

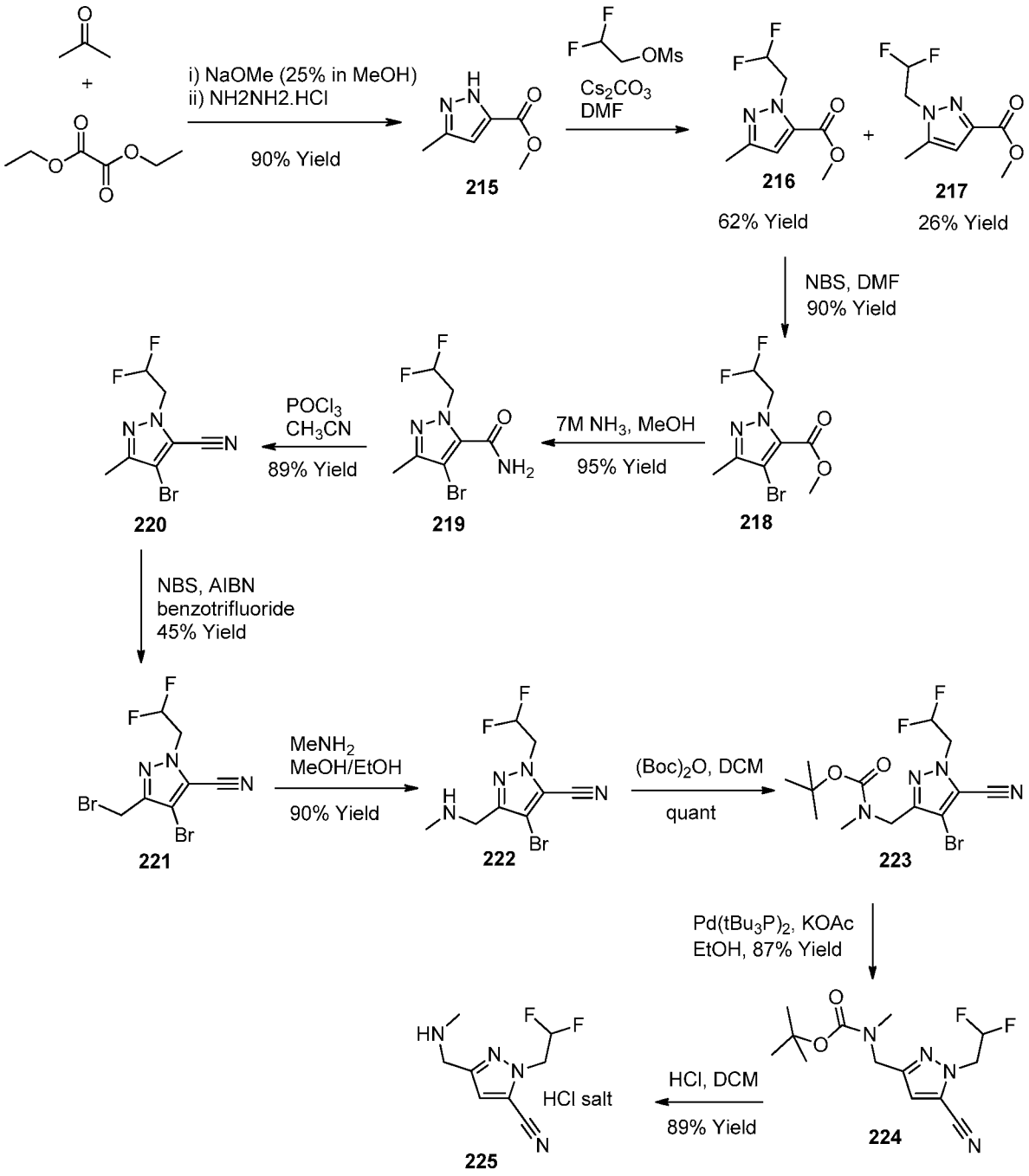
A solution of **compound 212** (22 g, 0.0448 mol) in NH_3-MeOH (5 N, 350 mL) was heated at 60 °C for 12 hours in a sealed tube. TLC (Petroleum ether/EtOAc = 1:1) showed the reaction was complete. The mixture was concentrated *in vacuo* to give the residue, which was partitioned between CH_2Cl_2 (200 mL) and citric acid (2 N, 30 mL). The organic layer was separated and washed with aqueous $NaHCO_3$ (2 N, 30 mL), brine (20 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (Petroleum ether/EtOAc = 5:1~3:1) to obtain **compound 213** (17 g, 82%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 5.80 (s, 1H), 5.75 (s, 1H), 4.53-4.48 (m, 2H), 3.62-3.55 (m, 2H), 2.83-2.77 (m, 2H), 1.48 (s, 9H), 0.93-0.87 (m, 2H), 0 (s, 9H)

Step 8:

To a solution of **compound 213** (16 g, 0.0346 mol) in anhydrous CH_2Cl_2 (250 mL) was added Et_3N (14.4 mL, 0.104 mol) and then TFAA (9.6 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours. TLC (Petroleum ether/EtOAc = 3:1) showed the reaction was complete. The mixture was concentrated *in vacuo* to give the crude product, which was partitioned between CH_2Cl_2 (150 mL) and citric acid (40 mL, 2 N). The organic layer was separated, washed with aqueous $NaHCO_3$ (2 N, 50 mL), brine (20 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel

(Petroleum ether/EtOAc = 50:1) to give **compound 214** (11.5 g, 74.8%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (s, 2H), 4.61-4.42 (m, 2H), 3.63-3.51 (m, 2H), 2.83-2.79 (m, 2H), 1.47 (s, 9H), 0.95-0.86 (m, 2H), 0 (s, 9H). LC-MS *m/z* 468 $[M+Na]^+$.

Preparation of *tert*-butyl {[4-bromo-5-cyano-1-(2,2-difluoroethyl)-1*H*-pyrazol-3-yl]methyl}methylcarbamate (225)



Step 1:

To a 5 litre flask fitted with an overhead stirrer was added NaOMe solution (25% in MeOH, 500 mL, 2.31 mol) under an N_2 atmosphere. To this was added MeOH (1.50 L) followed by a solution of diethyl oxalate (337 g, 2.31 mol) in acetone (168 mL, 2.31 mol) slowly over 50 mins (after 35 mins the reaction had set solid so a further 500 mL of MeOH was added). On complete addition the thick pale yellow reaction mixture was allowed to stand at room temperature for 2 days under N_2. The reaction was then cooled to 0 °C with stirring and conc 37% aq HCl (190 mL, 2.31 mol) was slowly added followed by slow addition hydrazine monohydrate (112 mL, 2.31 mol) over 60 mins, maintaining a internal reaction temperature of less than 20 °C. The reaction was then stirred at room temperature overnight. The reaction was then filtered through celite, washing the pad with MeOH (200 mL). The solvent was removed to a very low volume and the residue was partitioned between EtOAc (2.5 L) and water/brine (2.0 L, 1:1). The organic phase was collected and the aq phase extracted with additional EtOAc (500 mL). The combined organics were washed with brine 1.0 L), dried over Na_2SO_4 and evaporated to dryness, giving **compound 215** (226 g, 70%) as a cream colored solid. 1H NMR (400 MHz, Chloroform-d) δ 11.64 (s, 1H), 6.58 (d, J = 0.8 Hz, 1H), 3.89 (s, 3H), 2.37 (d, J = 0.7 Hz, 3H), [MH]+ 140.99.

Step 2:

A mixture of **compound 215** (30.8 g, 0.22 mol), 2,2-difluoroethyl methanesulfonate (38.0 g, 0.24 mol) and Cs_2CO_3 (94.3 g, 0.29 mol) in DMF (150 mL) was stirred at 80 °C for 3.5 hours. After cooling, the reaction was diluted with EtOAc (200 mL) and water (800 mL). The organic was collected and the aqueous was extracted with EtOAc (2 x 300 mL). The combined organics were washed with water (500 mL), brine (500 mL), dried (Na_2SO_4) and evaporated. Purification by flash chromatography (20% to 50% EtOAc in heptanes) gave **compound 216** (28 g, 62%) and **compound 217** (12 g, 26%).

Compound 216: 1H NMR (400 MHz, Chloroform-d) δ 6.64 (s, 1H), 6.09 (tt, J = 55.9, 4.5 Hz, 1H), 4.87 (td, J = 13.1, 4.5 Hz, 2H), 3.86 (s, 3H), 2.26 (s, 3H).

Compound 217: 1H NMR (400 MHz, Chloroform-d) δ 6.55 (s, 1H), 6.09 (tt, J = 55.5, 4.5 Hz, 1H), 4.41 (td, J = 13.1, 4.5 Hz, 2H), 3.86 (s, 3H), 2.30 (s, 3H), [MH]+ 205.06.

Step 3:

NBS (32.0 g, 180 mmol) was added to a solution of **compound 216** (35.0 g, 172 mmol) in DMF (100 mL) and stirred at 20 °C for 20 hr. Water (200 mL) and 2% aq $NaHSO_4$ (150 mL) was added and the mixture was stirred for 10 mins, then extracted into EtOAc/heptanes (2:1, 400 mL). The organic layer was separated and washed with brine (200 mL), dried (Na_2SO_4) and evaporated, giving **compound 218** (41 g, 90%) as an oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.36

(tt, J = 55.0, 3.8 Hz, 1H), 4.90 (td, J = 14.6, 3.8 Hz, 2H), 3.88 (s, 3H), 2.20 (s, 3H), [MH]+ 283 and 285 (100%).

Step 4:

A mixture of **compound 218** (41 g, 0.145 mol) and 7M NH_3 in MeOH (500 mL) was stirred at 25 °C for 5 days. The reaction mixture was then evaporated giving **compound 219** (37 g, 95%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.04 (s, 1H), 7.77 (s, 1H), 6.31 (tt, J = 55.1, 3.7 Hz, 1H), 4.74 (td, J = 15.0, 3.7 Hz, 2H), 2.16 (s, 3H), [MH]+ 268 and 270 (100%).

Step 5:

POCl3 (74 g, 0.483 mol) was added to a solution of **compound 219** (37 g, 0.138 mol) in acetonitrile (250 mL) at 25 °C. The reaction was then stirred at reflux for 6 hours. After cooling, the reaction was slowly poured into water (1000 mL) while controlling the exotherm by keeping the mixture below 40 °C by addition of ice to the aqueous as needed. After stirring for 5 minutes and no further exotherm was noted, the mixture was extracted into EtOAc/heptanes (1:1, 500 mL). The organic layer was separated and washed with saturated aq $NaHCO_3$ (200 mL), dried (Na_2SO_4) and evaporated, giving **compound 220** (27 g, 78%) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.43 (tt, J = 53.9, 2.9 Hz, 1H), 4.81 (td, J = 15.9, 2.8 Hz, 2H), 2.23 (s, 3H).

Step 6:

A mixture of **compound 220** (15 g, 60 mmol), NBS (14.95 g, 84 mmol) and AIBN (492 mg, 3.0 mmol) in benzotrifluoride (200 mL) was stirred at 80 °C for 12 hours. After cooling, the mixture was filtered through a short pad of silica gel and the filter cake was washed with toluene (20 mL). The filtrate was evaporated, giving **compound 221** (9.0 g, 45% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.72 – 6.21 (m, 1H), 5.03 – 4.72 (m, 2H), 4.64 (s, 2H).

Step 7:

A solution of **compound 221** (18 g, 27.4 mmol) in EtOH (50 mL) was slowly added to a solution of $MeNH_2$ (40% in MeOH, 56 mL, 0.55 mol) in additional EtOH (50 mL) at 0 °C over 15 mins. After complete addition the reaction was stirred at 0 °C for 2 hours. The mixture was then concentrated under vacuo to approx 50 mL in volume. EtOH (50 mL) was added and the mixture was again concentrated under vacuo to approx 40 mL volume. 1M aq HCl (90 mL) was added, followed by TBME (150 mL) and the mixture was stirred vigorously for 5 minutes. The aqueous layer was collected and washed once more with TBME (100 mL). The aqueous layer was collected and basified to approx pH 12-13 (pH paper) using conc aq NH_3. The resulting mixture was extracted into DCM (3 x 150 mL). The organics were dried (Na_2SO_4) and evaporated, giving **compound 222** (6.8 g, 90%) as a pale brown oil which solidified on standing. ^{1}H NMR (400

MHz, DMSO-d6) δ 6.44 (tt, J = 53.8, 2.8 Hz, 1H), 4.84 (td, J = 15.9, 2.8 Hz, 2H), 3.63 (s, 2H), 2.24 (s, 3H), [MH]+ 279.0 and 281.0 (60%).

Step 8:

Di-tert-butyl dicarbonate (5.6 g, 25.6 mmol) was added portionwise (solid) to a solution of **compound 222** (6.8 g, 24.4 mmol) in DCM (100 mL) at 20 °C over 5 minutes. The mixture was then concentrated under vacuo and the residue purified by flash chromatography (20% EtOAc in heptane) giving **compound 223** (9.24 g, quant) as an oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.44 (tt, J = 53.7, 2.7 Hz, 1H), 4.86 (td, J = 16.0, 2.7 Hz, 2H), 4.42 (s, 2H), 2.78 (s, 3H), 1.47 – 1.28 (m, 9H), [MH-Boc]+ 268 and 270 (40%).

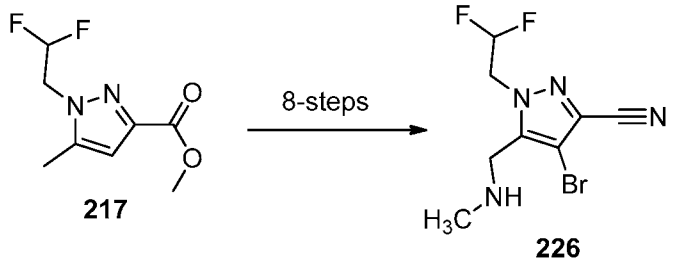
Step 9:

$Pd(t\text{-}Bu_3P)_2$ (240 mg) was added in one portion to a mixture of **compound 223** (1.80 g, 4.75 mmol), KOAc (1.39 g, 14.3 mmol) and de-gassed IMS (95% EtOH, 18.0 mL). The mixture was then stirred under microwave irradiation (120 °C) for 60 mins. After cooling, the mixture was concentrated and purified by column chromatography (30% EtOAc in heptanes) giving **compound 224** (1.25 g, 87%) as an oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.08 (s, 1H), 6.42 (tt, J = 54.0, 2.9 Hz, 1H), 4.80 (td, J = 15.8, 2.9 Hz, 2H), 4.36 (s, 2H), 2.79 (s, 3H), 1.38 (s, 9H), [MH-Boc]+ 201.06.

Step 10:

HCl (4M in dioxane, 5.0 mL) was added to a solution of **compound 224** (1.40 g, 4.66 mmol) and the mixture was stirred at 25 °C overnight. The mixture was concentrated under vacuum and the residue was slurried with EtOAc (10mL) and collected by filtration. **Compound 225** (980 mg, 89%) was obtained as the hydrochloride salt (cream coloured solid). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.47 (s, 2H), 7.44 (s, 1H), 6.46 (tt, J = 53.8, 2.8 Hz, 1H), 4.88 (td, J = 16.0, 2.7 Hz, 2H), 4.18 (s, 2H), 2.54 (s, 3H), [MH]+ 201.11.

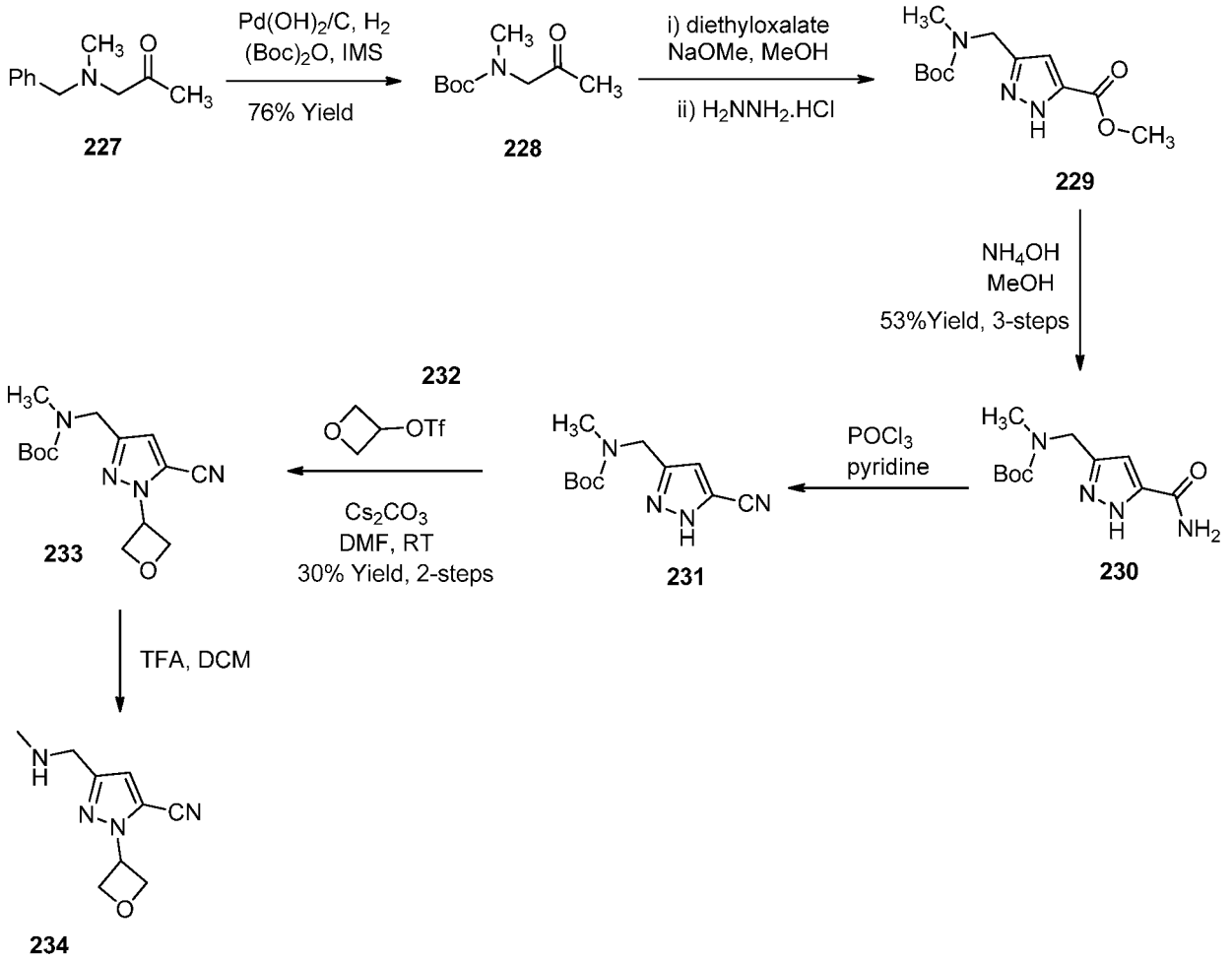
Preparation of *tert*-butyl {[4-bromo-5-cyano-1-(2,2-difluoroethyl)-1*H*-pyrazol-3-yl]methyl}methylcarbamate (226)



217 **226**

The procedures described in steps 3-10 for **compound 225** were used to prepare **compound 226** (30% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.57 (s, 2H), 7.30 (s, 1H), 6.47 (tt, J = 54.2, 3.4 Hz, 1H), 4.96 (td, J = 15.2, 3.4 Hz, 2H), 4.36 (s, 2H), 2.59 (s, 3H), [MH + CH3CN]+ 242.04.

Synthesis of *tert*-butyl ((5-cyano-1-oxetan-3-yl)-1*H*-pyrazol-3-yl)methyl)(methyl) carbamate (Compound 234)



Step 1:

Compound 227 (45.3 g, 0.256 mol) was dissolved in IMS (475 mL) and $(Boc)_2O$ (58.6 g, 0.269 mol) and $Pd(OH)_2/C$ (4.0 g, 9 wt%) were added. The reaction mixture was then stirred at room temperature under a hydrogen atmosphere (50 psi) for three hours before being heated at 50 °C for a further two hours. After cooling to room temperature the reaction mixture was filtered through celite, eluting with additional IMS and the filtrate concentrated to give a brown oil. The majority of the crude material (43.2 g) was purified by flash chromatography over silica gel (10% to 30% EtOAc in heptanes) to give **compound 228** as a yellow oil (29.5 g, 76% yield, > 95% purity by 1H NMR). 1H NMR indicates a ~1:1.1 mixture of tautomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 2H), 3.90 (s, 2H), 2.92 (s, 3H), 2.89 (s, 3H), 2.12 (s, 6H), 1.47 (s, 9H), 1.42 (s, 9H).

Step 2:

A solution of 5.4M NaOMe in MeOH (29.2 mL, 0.157 mol) was diluted with further MeOH (150 mL) and stirred at room temperature under nitrogen. A solution of **compound 228** (29.5 g, 0.157 mol) and diethyloxalate (21.3 mL, 0.157 mol) in MeOH (40 mL) was added from a dropping funnel over 10 minutes and the resultant yellow reaction mixture heated to 50 °C. After 3 hours, additional diethyloxalate (2 mL, 0.015 mol) and NaOMe solution (2 mL, 0.011 mol) were added and heating continued for a further 30 minutes. The reaction was cooled to 5-10 °C and hydrazine monohydrochloride (10.7 g, 0.157 mol) added in portions over 10 minutes, maintaining the temperature in this range. The reaction was then left to warm to room temperature and was stirred for 60 hours. H2O (200 mL) and brine (100 mL) were added to the reaction mixture before being extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO4 and concentrated to give **compound 229** as a yellow oil, which was used without purification (43.2 g). ^{1}H NMR (400 MHz, CDCl3) δ 6.72 (s, 1H), 4.47 – 4.32 (m, 2H), 3.91 (s, 3H), 2.86 (s, 3H), 1.47 (s, 9H). LC-MS ES m/z 268 [M+H]+.

Step 3:

Compound 229 (21.1 g, 78.3 mmol) was dissolved in MeOH (60 mL) and 33% aqueous NH_3 solution (100 mL) added before the reaction solution was stirred at room temperature overnight. The volume of MeOH was reduced under vacuum, until a precipitate just started to form. The mixture was left to crystallise and the precipitate collected by filtration, washed with H_2O (2 x 30 mL) and thoroughly dried in a vacuum oven (40 °C, overnight) to give a tautomeric mixture (~1:1) of **compound 230** as an off-white solid (10.4 g, 53% yield over two steps). ^{1}H NMR indicates a ~1:1.2 mixture of tautomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.27 (s, 1H), 13.11 (s, 1H), 7.91 (s, 1H), 7.55 – 7.33 (m, 2H), 7.15 (s, 1H), 6.68 (d, J = 2.0 Hz, 1H), 6.43 (d, J = 1.9 Hz, 1H), 4.37 (s, 2H), 4.30 (s, 2H), 2.79 (s, 3H), 2.75 (s, 3H),1.41 (s, 18H). LC-MS ES *m/z* 252 $[M+H]^+$.

Step 4:

Compound 230 (10.5 g, 41.3 mmol) was dissolved in pyridine (105 mL) and $POCl_3$ (9.6 mL, 103.2 mmol) was added slowly from a dropping funnel, maintaining the temperature around 15 °C using an ice/H_2O cooling bath. The reaction mixture was stirred for 90 minutes, during which time it turned yellow and then a darker brown color. In portions, the mixture was then poured into H_2O (250 mL), maintaining the temperature around 30 °C by the addition of ice. Once hydrolysed, the mixture was extracted with EtOAc (3 x 100 mL) and the combined organic extracts washed with saturated aqueous $NaHCO_3$ solution (150 mL) before being dried over $MgSO_4$ and concentrated. The residue was azeotroped with toluene (3 x 100 mL) and then

heptanes (3 x 100 mL) to remove residual pyridine to give **compound 231** as a brown gum which was used without purification (9.1 g, >85% purity by 1H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (s, 1H), 4.31 (s, 2H), 2.89 (s, 3H), 1.48 (s, 9H). LC-MS ES *m/z* 235 $[M+H]^+$.

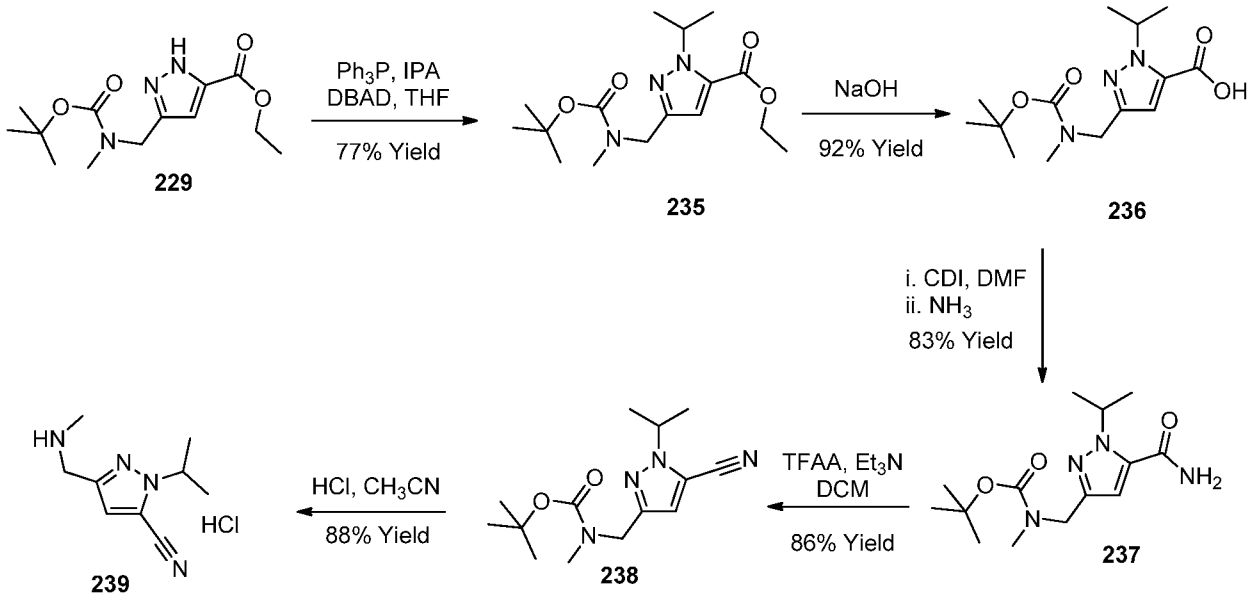
Step 5:

Crude **compound 231** (9.1 g) was dissolved in DMF (85 mL) under nitrogen and Cs_2CO_3 (37.6 g) was added. A solution of oxetan-3-yl trifluoromethanesulfonate **232** (9.5 g) in DMF (15 mL) was then added slowly from a dropping funnel, maintaining the temperature between 15-20 °C After complete addition, the reaction mixture was stirred for 90 minutes before being diluted with H_2O (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated to give a brown residue. The crude material was purified by flash chromatography over silica gel (1:2 EtOAc;heptanes then 1:1 EtOAc:heptanes) to give **compound 233** as a yellow oil (4.00 g, 30% yield over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) 7.14 – 6.89 (m, 1H), 5.71 (tt, *J* = 7.6, 6.0 Hz, 1H), 4.96 (t, *J* = 7.2 Hz, 2H), 4.88 (t, *J* = 6.5 Hz, 2H), 4.41 (s, 2H), 2.81 (s, 3H), 1.47 – 1.34 (m, 9H). Further elution afforded the regioisomeric pyrazole as a colorless solid (3.28 g, 25% yield over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.93 (s, 1H), 5.77 (s, 1H), 4.91 – 4.81 (m, 4H), 4.47 (s, 2H), 2.72 (s, 3H), 1.41 (s, 9H).

Step 6:

Compound 233 (0.50 g, 1.71 mmol) was dissolved in DCM (5 mL) and cooled in an ice-water bath under nitrogen. TFA (5 mL) was then added and the reaction mixture was stirred for two hours, during which it warmed to room temperature. The reaction was concentrated and residual TFA removed from the residue by co-evaporation with DCM (2 x 10 mL) and then toluene (2 x 10 mL). The TFA salt of **compound 234** was obtained as a yellow gum (0.85 g). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.00 (s, 2H), 7.25 (s, 1H), 5.78 (tt, J = 7.6, 5.9 Hz, 1H), 5.00 (t, J = 7.2 Hz, 2H), 4.89 (t, J = 6.4 Hz, 2H), 4.27 (t, J = 5.6 Hz, 2H), 2.61 (t, J = 5.2 Hz, 3H).

Preparation of 3-[(methylamino)methyl]-1-(propan-2-yl)-1*H*-pyrazole-5-carbonitrile hydrochloride (1:1) (239)



Step 1:

Di tertbutylazodicarboxylate (6.5 g, 28.2 mmol) was added portionwise (solid) to a solution of **compound 229** (8.0 g, 28.2 mmol), Ph_3P (7.4 g, 28.2 mmol) and isopropanol (2.55 g, 42.5 mmol) in THF (80 mL) at 0 °C over 5 minutes. The reaction was then stirred at 0 °C to 20 °C over 2 hours. The reaction was then concentrated and the residue purified by flash chromatography (10% to 40% EtOAc in heptanes) giving **compound 235** (7.1 g, 77%). ^{1}H NMR (400 MHz, DMSO-d6) δ 6.63 (d, J = 15.6 Hz, 1H), 5.36 (hept, J = 6.6 Hz, 1H), 4.37 – 4.23 (m, 4H), 2.76 (s, 3H), 1.39 (t, J = 5.6 Hz, 15H), 1.29 (t, J = 7.1 Hz, 3H), [MH]+ 326.12.

Step 2:

NaOH (3.4 g, 87.3 mmol) was dissolved in water (6.0 mL) and the solution was added to a solution of **compound 235** in MeOH and the reaction was stirred at 25 °C for 2 hours. The mixture was then diluted with water (250 mL) and acidified to approx pH 2 (pH paper) using 5% aq $NaHSO_4$. The mixture was then extracted into EtOAc (2 x 120 mL). The organic layers were washed with brine (100mL), dried (Na_2SO_4) and evaporated, giving **compound 236** (6.0 g, 92%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 13.26 (s, 1H), 6.58 (d, J = 11.4 Hz, 1H), 5.42 (hept, J = 6.6 Hz, 1H), 4.30 (s, 2H), 2.76 (s, 3H), 1.38 (m, 15H), [MH]+ 298.07.

Step 3:

Carbonyldiimidazole (3.56 g, 22.0 mmol) was added to a solution of **compound 236** in DMF (35 mL) at room temperature. After stirring for 45 minutes, the reaction was cooled to 0 °C and ammonia gas was bubbled through the mixture for 10 minutes. The reaction was then allowed to stir for 2 hours at room temperature, before dilution with water (250 mL). The mixture was extracted into EtOAc (2 x 100 mL). The combined organics were washed with brine (200 mL), dried (Na_2SO_4) and evaporated, giving **compound 237** (4.9 g, 83%) as an oil which set to a

solid on standing. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (s, 1H), 7.44 (s, 1H), 6.65 (s, 1H), 5.51 (hept, J = 6.6 Hz, 1H), 4.38 – 4.24 (m, 2H), 2.76 (s, 3H), 1.40 (d, J = 4.1 Hz, 9H), 1.34 (d, J = 6.6 Hz, 6H), [MH]+ 297.11.

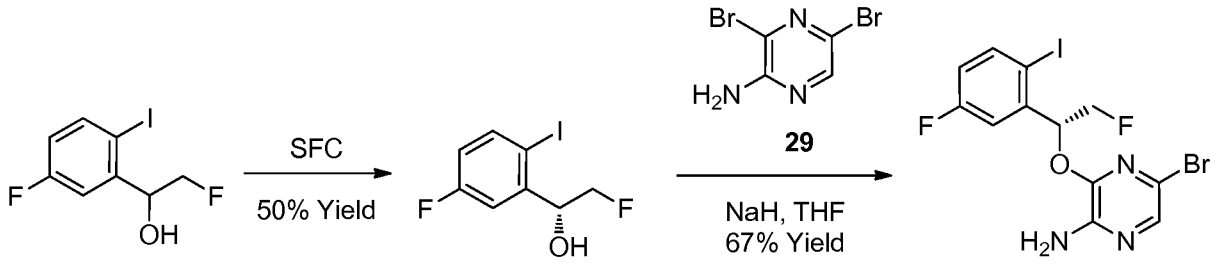
Step 4:

A solution of trifluoroacetic anhydride in DCM (50 mL) was added slowly to a solution of **compound 237** (4.90 g, 16.55 mmol) and Et_3N (5.10 g, 50.0 mmol) in DCM (50 mL) at 0 °C over 10 minutes. The reaction was stirred at 0 °C for 60 minutes, before addition of water (100 mL) and stirred for 10 minutes. The organic layer was separated, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (20% EtOAc in heptanes), giving **compound 238** (3.95 g, 86%) as a colourless oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.95 (d, J = 15.2 Hz, 1H), 4.72 (hept, J = 6.6 Hz, 1H), 4.34 (s, 2H), 2.78 (s, 3H), 1.45 (d, J = 6.6 Hz, 6H), 1.43 – 1.34 (m, 9H), [MH-Boc]+ 179.14.

Step 5:

HCl (4M in dioxane, 5.0 mL) was added to a solution of **compound 238** (3.90 g, 14.0 mmol) in CH_3CN and stirred at 50 °C for 60 mins. After cooling, the reaction was concentrated, then EtOAc (35 mL) was added and the mixture was filtered to collect **compound 239** (2.20 g, 88%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.49 (s, 2H), 7.34 (s, 1H), 4.79 (hept, J = 6.6 Hz, 1H), 4.16 (s, 2H), 2.53 (s, 3H), 1.47 (d, J = 6.6 Hz, 6H), [MH]+ 179.14.

Preparation of 5-bromo-3-[(1*R*)-2-fluoro-1-(5-fluoro-2-iodophenyl)ethoxy]pyrazin-2-amine (241)



Step 1:

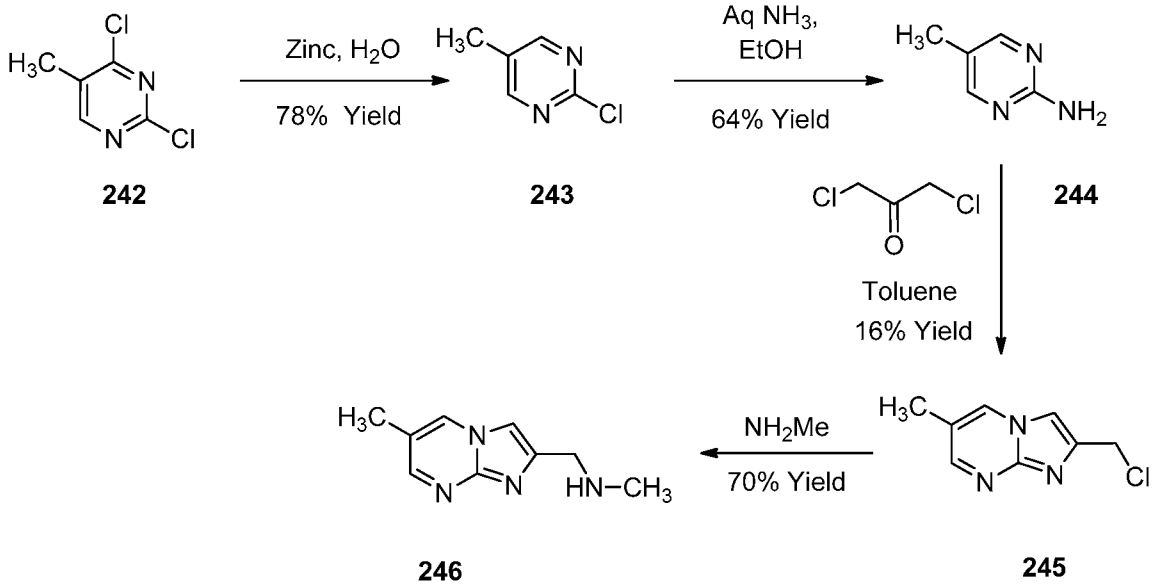
Compound 170 was separated by preparative SFC to give pure **compound 240** (4 g, 50%) as yellow oil. ^{1}H NMR (400 MHz, CDCl3): δ 7.75-7.78 (m, 1H), 7.34-7.37 (m, 1H), 6.79-6.84 (m, 1H), 5.17-5.24 (m, 1H), 4.57-4.70 (m, 1H), 4.17-4.34 (m, 1H), 2.652-2.658 (s, 1H).

Step 2:

To a solution of **compound 240** (3 g, 10.6 mmol) in anhydrous THF (100 mL) was added NaH (464 mg, 11.6 mmol, 60% in oil) at 0 °C under N2, and the mixture was stirred for another 30

min. A solution of compound 12 (2.141 g, 8.5 mmol) in dry THF (10 mL) was added to the above mixture at 0 °C, and the mixture was refluxed for 10 hours. THF was remover under reduced pressure, and the residue was dilute with H_2O (100 mL)/EtOAc (100 mL). The mixture was filtered, and the filtrated was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated to give residue which was purified by silica gel column eluting with petroleum ether : EtOAc = 60/1 ~ 10/1 to give **compound 241** (2.6 g, 67%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.84 (m, 1H), 7.67 (s, 1H), 7.09-7.12 (d, 1H), 6.79-6.84(t, 1H), 6.35-6.42 (q, 1H), 4.91 (s, 2H), 4.59-4.81 (m, 2H), [M+H]+ 457.8.

Synthesis of N-methyl-1-(6-methylimidazo[1,2-a]pyrimidin-2-yl)methanamine (Compound 246)



Step 1:

A suspension of **compound 242** (50.0 g, 307 mmol) and freshly activated (acid washed) Zn (59.8 g, 920 mmol) in water (500 mL) was heated at reflux for 3 hours. TLC showed consumption of SM. The reaction mixture was cooled to room temperature, filtered through a pad of celite, and rinsed with CH_2Cl_2 (500 mL). The phases of the filtrate were separated and the organic phase was washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated under vacuum carefully to give **compound 243** as a beige powder (30.6 g, 78% yield, 95% purity by ^{1}H NMR).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, *J* = 0.9 Hz, 2H), 2.27 (t, *J* = 0.8 Hz, 3H).

Step 2:

Compound 243 (30.6 g, 239 mmol) was dissolved in ethanol (300 mL) and aqueous ammonia (35%, 300 mL). The solution was set in a reaction bomb and heated at 200 °C for 6 hours, cooled at room temperature, then left opened at this temperature for 72 hours. The ethanol had evaporated, and aqueous ammonia was added again (35%, 200 mL). The solution was heated at 200 °C for 22 hours then cooled to room temperature. The mixture was concentrated under vacuum then water (50 mL) was added and the suspension obtained filtered. The beige powder obtained was dried in a vacuum oven for 20 hours to give pure **compound 244** (16.7 g, 64% yield, >95% purity by ^{1}H NMR). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 2H), 6.33 (s, 2H), 2.03 (s, 3H). LC-MS *m/z* 109 $[M+H]^+$.

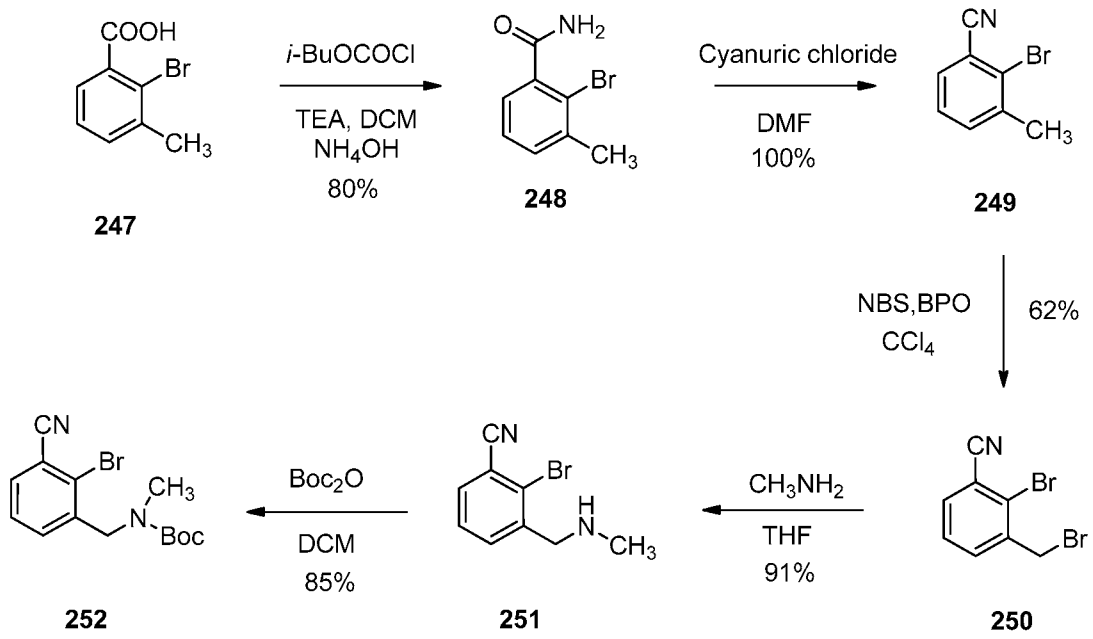
Step 3:

Compound 244 (5.0 g, 45.9 mmol) and dichloroacetone (29.1 g, 229.3 mmol) were mixed with toluene (1 L). The flask was equipped with a Dean-Stark apparatus and the mixture was heated at 155 °C for 1 hour (as soon as refluxing toluene was observed on top of the Dean-Stark). The reaction was cooled to room temperature and CH_2Cl_2 (500 mL) and silica were added. The mixture obtained was put directly on top of a column chromatography and purified by this way (eluents CH_2Cl_2/MeOH from 100:0 to 80:20). The fractions containing **compound 245** were combined, concentrated under vacuum and purified by SCX-2 column. The fractions containing the expected **compound 245** were purified again by column chromatography over silica gel (eluents CH_2Cl_2/MeOH from 100:0 to 95:5) to give the expected **compound 245** as pale yellow oil (1.4 g, 16% yield, 95% purity by LC-MS). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (dq, J = 2.3, 1.1 Hz, 1H), 8.45 (d, J = 2.4 Hz, 1H), 7.88 (s, 1H), 4.85 (d, J = 0.6 Hz, 2H), 2.29 (d, J = 1.1 Hz, 3H). LC-MS *m/z* 182/184 $[M+H]^+$.

Step 4:

Compound 245 (1.4 g, 7.7 mmol) was dissolved in CH_2Cl_2 (70 mL) and this solution was added to a solution of N-methylamine in MeOH/THF (2 M, 145 mL, MeOH/THF = 1:4). The flask was sealed and the yellow solution was stirred at room temperature for 24 hours. TLC showed consumption of SM. A solution of HCl in dioxane (1 mL, 4 M) was added dropwise to the solution. The mixture was concentrated then CH_2Cl_2 (10 mL) was added. The suspension obtained was filtered to give a beige solid containing the hydrochloride salt of both the expected amine and of N-methyl amine. The solids were dissolved in MeOH (150 mL) and Amberlyst A-26 (40 mL) was added. The mixture was concentrated *in vacuo*, and then filtered. The filtrate was concentrated to give **compound 246** (500 mg, 37% yield, 99% purity by LC-MS). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (dq, *J* = 2.3, 1.1 Hz, 1H), 8.35 (d, *J* = 2.4 Hz, 1H), 7.65 (s, 1H), 3.73 (d, *J* = 0.8 Hz, 2H), 2.32 (s, 3H), 2.28 (d, *J* = 1.0 Hz, 3H). LC-MS *m/z* 177 $[M+H]^+$.

Preparation of *tert*-butyl-2-bromo-3-cyanobenzyl(methyl)carbamate (Compound 252)



Step 1:

To a solution of **compound 247** (15 g, 69.8 mmol) in CH2Cl2 (100 mL) was added TEA (7.76 g, 76.7 mol) and *iso*-butylchloroformate (10.4 g, 76.7 mmol) at 0 °C. After the addition, the mixture was stirred at 0 °C for 30 minutes, TLC (CH_2Cl_2 / MeOH = 10:1) showed the reaction was completed. Then, $NH_3 \cdot H_2O$ (27.9 g, 0.28 mol, 35% in H_2O) was added to the mixture 0 °C. The resulting mixture was stirred at this temperature for 30 minutes. TLC (petroleum ether / EtOAc = 8:1) showed the reaction was completed. The mixture was poured into ice-water (200 mL). The solid was filtered and the wet cake was washed with H_2O (50 mL), dried to give **compound 248** (12 g, 80%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (brs, 1H), 7.55 (brs, 1H), 7.35 (m, 1H), 7.30 (m, 1H), 7.15 (m, 1H), 2.38 (s, 3H).

Step 2:

To a solution of compound **248** (12 g, 56.1 mmol) in DMF (100 mL) was added a solution of cyanuric chloride (15.47 g, 84.1 mol) in DMF (50 mL) at 0 °C under a nitrogen atmosphere. After the addition, the mixture was stirred at room temperature overnight. TLC (petroleum ether / EtOAc = 1:1) showed the reaction was completed. The mixture was poured into water (500 mL) and extracted with EtOAc (200 mL x 2). The combined organic layers were washed with saturated aqueous Na_2CO_3 (200 mL x 2), brine (200 mL x 4), dried over Na_2SO_4 and concentrated to give **compound 249** (11 g, 100%).as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.45 (m, 2H), 7.33-7.29 (m, 1H), 2.47 (s, 3H)

Step 3:

A mixture of **compound 249** (11 g, 56.1 mmol), NBS (10 g, 56.1 mmol) and BPO (81 mg, 0.34 mmol) in CCl_4 (150 mL) was heated at reflux overnight. TLC (petroleum ether / EtOAc = 5:1) showed the reaction was completed. The mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography over silica gel (petroleum ether / EtOAc = 20:1) to yield **compound 250** (9.6 g, 62%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.67 (d, 1H), 7.63-7.61 (d, 1H), 7.45-7.41 (t, 1H), 4.61 (s, 2H)

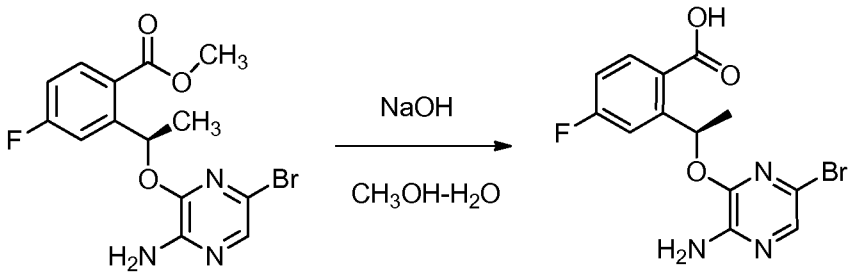
Step 4:

To a solution of **compound 250** (11.9 g, 43.3 mmol) in THF (100 mL) was added a solution of methylamine (2M in THF, 215 mL, 0.43 mol) at -10 °C ~ 0 °C under a nitrogen atmosphere. After the addition, the mixture was allowed to warm to room temperature and stirred for 2 hours. TLC (petroleum ether / EtOAc = 5:1) showed the reaction was completed. The mixture was diluted with water (200 mL), and extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated to give **compound 251** (8.9 g, 91%).as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.65 (d, 1H), 7.58-7.56 (d, 1H), 7.43-7.39 (t, 1H), 3.87 (s, 2H), 2.47 (s, 3H).

Step 5:

To a solution of **compound 251** (8.7 g, 38.6 mmol) in CH_2Cl_2 (100 mL) were added TEA (11.7 g, 0.11 mol) and Boc_2O (8.9 g, 40.5 mmol) at room temperature. The mixture was stirred at room temperature for 3 hours. TLC (CH_2Cl_2 / MeOH = 10:1) showed the reaction was completed. The mixture was concentrated and purified by column chromatography over silica gel (petroleum ether / EtOAc = 40:1) to yield **compound 252** (10.71 g, 85%) as a colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 1H), 7.45-7.38 (m, 2H), 4.56-4.50 (m, 2H), 2.93-2.89 (m, 3H), 1.52-1.40 (m, 9H). MS *m/z* 347 $[M+Na]^+$.

Preparation of 2-{(1*R*)-1-[(3-amino-6-bromopyrazin-2-yl)oxy]ethyl}-4-fluorobenzoic acid (254)

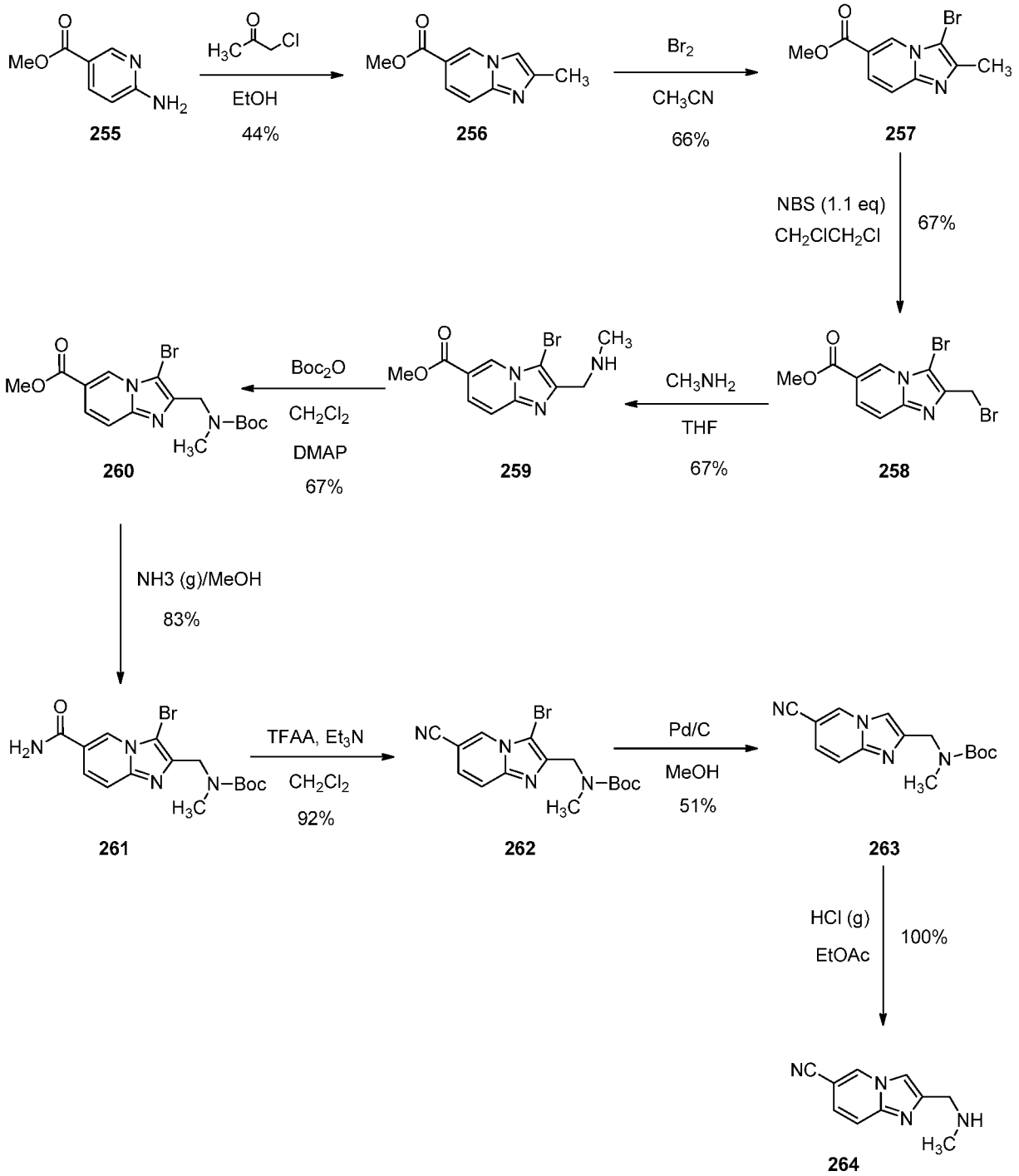


253 **254**

The procedure described in step 2 for **Example 41** was used to prepare **compound 254** (0.56 g, 89% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (dd, J = 8.7, 6.0 Hz, 1H), 7.67 (dd, J = 10.5,

2.7 Hz, 1H), 7.52 (s, 1H), 7.19 (td, J = 8.4, 2.7 Hz, 1H), 6.88 (q, J = 6.4 Hz, 1H), 6.68 (s, 2H), 1.57 (d, J = 6.3 Hz, 3H), [MH]+ 356.03 (8%) and 357.95 (8%).

Preparation of 2-((methylamino)methyl)imidazo[1,2-a]pyridine-6-carbonitrile (264)



Step 1:

A mixture of **compound 255** (50 g, 0.329 mmol) and 1-chloropropane-2-one (448.4 g, 4.87 mol) in EtOH (150 mL) was heated at reflux for 24 hours. TLC (Petroleum ether/EtOAc = 1:1) showed

that approximately half of **compound 255** remained. No change was observed after reflux for a further 12 hours. The mixture was concentrated *in vacuo* to give the residue, which was dissolved in CH_2Cl_2 (200 mL), washed with aqueous $NaHCO_3$ solution (2 N, 50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/EtOAc = 2:1~1:1) to obtain **compound 256** (18 g, 44%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.67-7.65 (m, 1H), 7.81-7.48 (m, 1H), 7.41 (s, 1H), 3.94 (s, 1H), 2.47 (s, 1H)

Step 2:

To a solution of **compound 256** (16 g, 0.089 mol) in CH_3CN (400 mL) was added Br_2 (15.62 g, 0.098 mol) at room temperature. The resulting mixture was stirred at room temperature for 1 hour. TLC (EtOAc) showed the reaction was complete. The mixture was diluted with CH_2Cl_2 (500 mL) and then washed with saturated aqueous $NaHCO_3$ solution (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/CH_2Cl_2 = 2:1~1:1) to obtain **compound 257** (15 g, 66%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.44-8.42 (m, 1H), 8.37-8.34 (m, 1H), 4.07 (s, 3H), 2.74 (s, 3H).

Step 3:

To a mixture of **compound 257** (16 g, 0.0625 mol) and NBS (9.95 g, 0.05625 mol) in CH_2ClCH_2Cl (375 mL) was added AIBN (1.025 g, 0.00625 mol) at room temperature under a nitrogen atmosphere. The resulting mixture was heated at reflux for 2 hours. TLC (Petroleum ether/EtOAc = 3:1) showed most of **compound 257** had been consumed. The mixture was cooled to room temperature and washed with saturated aqueous $NaHCO_3$ solution (50 mL), brine (50 mL) and dried over Na_2SO_4, concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/EtOAc = 4:1~1:1) and then re-crystallized from petroleum ether/EtOAc (5:1, 30 mL) to **compound 258** (14 g, 67%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.85-8.75 (m, 1H), 7.88-7.80 (m, 1H), 7.62-7.55 (m, 1H), 4.67 (s, 2H), 4.00 (s, 3H).

Step 4:

To a solution of **compound 258** (14 g, 41.92 mmol) in anhydrous THF (200 mL) was added methylamine in THF (520 mL, 1.048 mol, 2 M in THF) over one minute. The resulting mixture was stirred at 0 °C for 1 hour and then at room temperature for 1 hour. TLC (Petroleum ether/EtOAc = 3:1) showed most of **compound 258** had been consumed. The mixture was concentrated *in vacuo* at 25 °C for 20 minutes and then at higher temperature to give the crude product, which was purified by column chromatography over silica gel, (petroleum ether/EtOAc = 1:1~CH_2Cl_2/MeOH = 50:1) to obtain **compound 259** (8.4 g, 67%) as a yellow solid. ^1H NMR

(400 MHz, $CDCl_3$) δ 8.85 (m, 1H), 7.84-7.81 (m, 1H), 7.60-7.52 (m, 1H), 4.18-4.15 (s, 2H), 4.00 (s, 3H), 2.65 (s, 3H)

Step 5:

To a suspension of **compound 259** (8.4 g, 28.28 mmol) in CH2Cl2 (250 mL) was added Boc_2O (12.5 g, 56.56 mmol) and DMAP (3.47 g, 28.28 mmol) at room temperature. The resulting mixture was stirred at room temperature for 12 hours. TLC (CH_2Cl_2/MeOH = 20:1) showed the reaction was complete. The mixture was concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/EtOAc= 10:1~5:1) to obtain **compound 260** (7.5 g, 67%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.80-7.78 (m, 1H), 7.59-7.56 (m, 1H), 4.68 (s, 2H), 4.00 (s, 3H), 3.95 (s, 3H), 1.50 (s, 9H)

Step 6:

The reaction was run in 3 x 1 g batches: A solution of **compound 260** (1 g, 2.519 mmol) in NH_3(g)/MeOH (7 N, 70 mL) was sealed and heated at 80 °C for 12 hours. TLC (Petroleum ether/EtOAc = 1:1) showed the reaction was complete. The reactions were combined, and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/EtOAc = 5:1~1:1) to obtain **compound 261** (2.4 g, 83%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.90 (s, 1H), 7.90-7.82 (m, 1H), 7.65-7.55 (m, 1H), 4.65 (s, 2H), 2.95-2.84 (m, 3H), 1.45 (s, 9H)

Step 7:

To a solution of **compound 261** (2.4 g, 6.28 mmol) in anhydrous CH_2Cl_2 (50 mL) was added Et_3N (2.6 mL, 18.85 mmol) and then in a dropwise manner TFAA (1.73 mL, 12.57 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2 hours. TLC (Petroleum ether/EtOAc = 1:1) showed the reaction was complete. The mixture was concentrated *in vacuo* to give the residue, which was partitioned between CH_2Cl_2 (100 mL) and brine (20 mL). The organic layer was separated, washed with critic acid (1 N, 10 mL), saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/EtOAc = 5:1~1:1) to obtain **compound 262** (2.1 g, 92%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.68-7.65 (m, 1H), 7.35-7.26 (m, 1H), 4.66 (s, 2H), 2.93 (s, 3H), 1.47 (s, 9H). LCMS *m/z* 308 $[M-55]^+$.

Step 8:

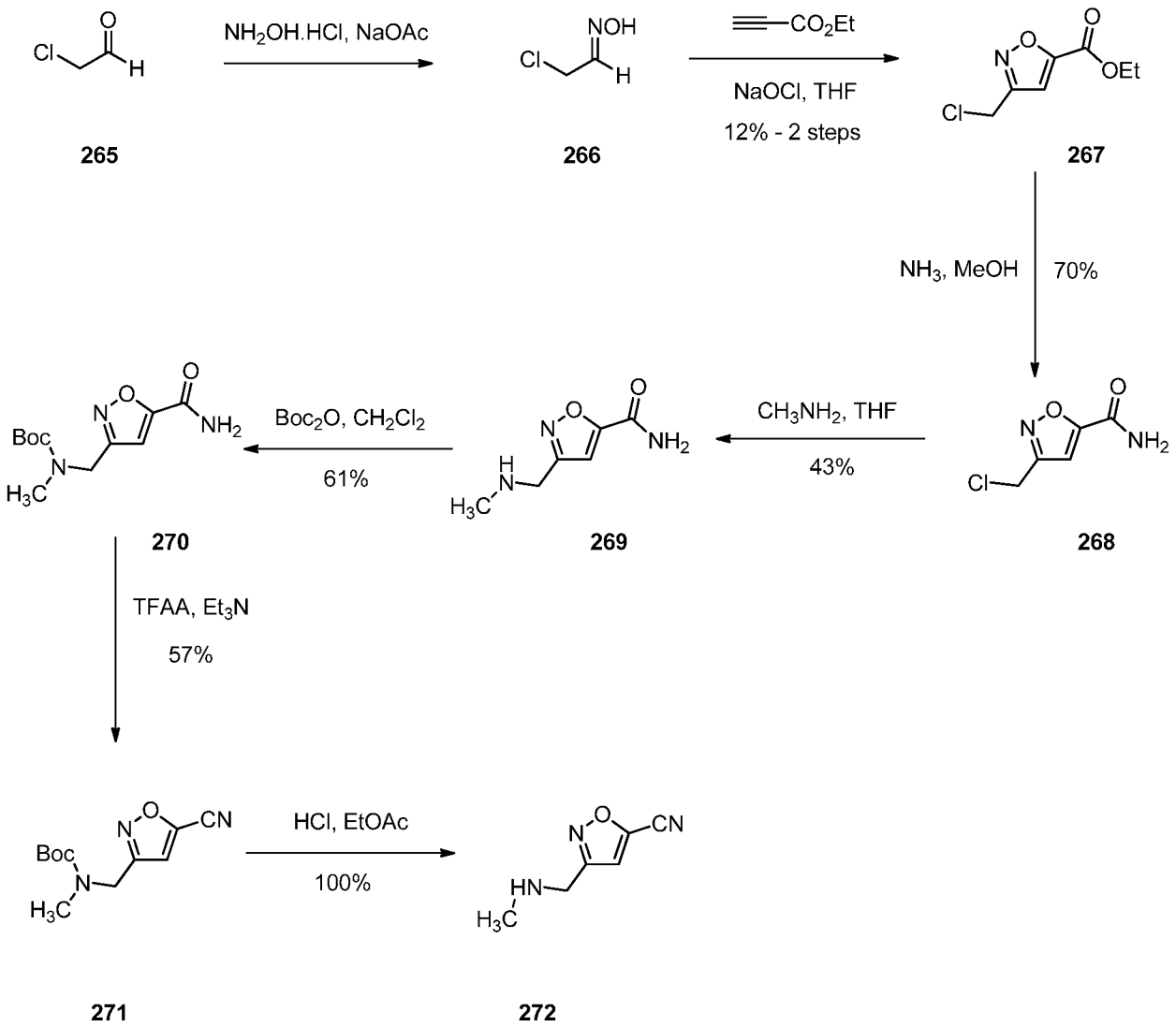
To a solution of **compound 262** (0.45 g, 1.23 mmol) in MeOH (80 mL) was added Pd/C (150 mg) at room temperature. The resulting mixture was purged with H_2 three times and stirred under a pressure of H_2 (15 psi) at room temperature for 2 hours. TLC (Petroleum ether/EtOAc = 3:1) showed the reaction was complete. The mixture was filtered and washed with MeOH (30

mL). The filtrate was concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel, (petroleum ether/EtOAc = 5:1) to give **compound 263** (0.18 g, 51%) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.52 (s, 1H), 7.64-7.50 (m, 2H), 7.27 (s, 1H), 4.59 (s, 2H), 2.98 (s, 3H), 1.50 (s, 9H)

Step 9:

To a solution of **compound 263** (0.18 g, 0.627 mmol) in CH_2Cl_2 (10 mL) was added HCl (g)/EtOAc (7 N, 20 mL) at room temperature. The resulting mixture was stirred at room temperature for 12 h. The mixture was concentrated *in vacuo* to give **compound 264** (0.15 g, 100%) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 9.48 (s, 1H), 8.48 (s, 1H), 8.15-8.05 (m, 2H), 4.58 (s, 2H), 2.85 (s, 3H)

Preparation of 3-((methylamino)methyl)isoxazole-5-carbonitrile (Compound 272)



Step 1:

To a stirred solution of **compound 265** (52 g, 0.64 mol) in H_2O (830 mL) was added $NH_2OH.HCl$ (50 g, 0.71 mol) and NaOAc (59 g, 0.71 mol) at room temperature. After the addition, the mixture was stirred at room temperature for 1 hour. Then, the solution was extracted with MTBE (2 x 500 mL), the combined organic layers washed with brine (200 mL x 3), dried over Na_2SO_4, and concentrated to give crude **compound 266** (40 g) as a light yellow oil, which was used in the next step without purification.

Step 2:

To a stirred solution of **compound 266** (40 g, 0.437 mol) in THF (150 mL) was added dropwise ethyl propiolate (50 mL, 0.5 mol) at 0 °C. NaOCl (10%, 1.5 L) was added dropwise to the above mixture at 0 °C. After the addition, the mixture was stirred at room temperature for 18 hours. The mixture was concentrated to remove THF, extracted with EtOAc (2 x 500 mL). The combined organic layers were washed with brine (200 mL x 3), dried over Na_2SO_4, and concentrated to give a residue, which was purified by column chromatography over silica. gel. (Rf ~ 0.5, petroleum ether/EtOAc = 10:1-5:1) to give **compound 267** (11 g, 12.2 %) as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 4.64 (s, 2H), 4.49-4.41 (m, 2H), 11.46-1.43 (t, 3H).

Step 3:

To a stirred solution of NH_3 (g) in MeOH (12N, 100 mL) was added **compound 267** (11 g, 0.058 mol) at 0 °C. After the addition, the mixture was stirred at room temperature for 10 minutess. TLC (Petroleum ether/EtOAc = 1:1) indicated the reaction was complete. The mixture was concentrated to give a residue, which was purified by column chromatography over silica. gel (Rf = 0.2, petroleum ether/EtOAc = 1:1-2:1) to give **compound 268** (6.5 g, 70 %) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.2 (s, 1H), 5.74 (s, 1H), 4.63 (s, 2H),

Step 4:

This reaction was run in 3 x 2 g batches. A mixture of **compound 268** (2 g, 13 mmol) and methylamine (2M in THF, 15 mL) was heated in a sealed vessel at 110 °C for 18 hours. TLC (EtOAc) indicated the reaction was complete. The reactions were combined, filtered and the filtrates were concentrated to give crude **compound 269** (2.5 g, 43%) as a yellow solid. ^1H NMR (400 MHz, Methanol-d_4) δ 7.00 (s, 1H), 3.89-3.88 (s, 1H), 2.44 (s, 3H)

Step 5:

To a stirred solution of **compound 269** (2.5 g, 16 mmol) and Boc_2O (5.2 g, 24 mmol) in dry THF (30 mL) was added TEA (3.2 g, 32 mol) at 0 °C. After the addition, the mixture was stirred at room temperature for 2 hours. TLC (petroleum ether/EtOAc =1:1) indicated the reaction was complete. The mixture was concentrated to give a residue, which was purified by column chromatography over silica. Gel (Rf = 0.46, petroleum ether/EtOAc = 3:1) to give **compound**

270 (2.5 g, 61 %) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.51 (s, 1H), 6.02 (s, 1H), 4.52 (s, 2H), 2.89-2.86 (s, 3H), 1.47 (s, 9H)

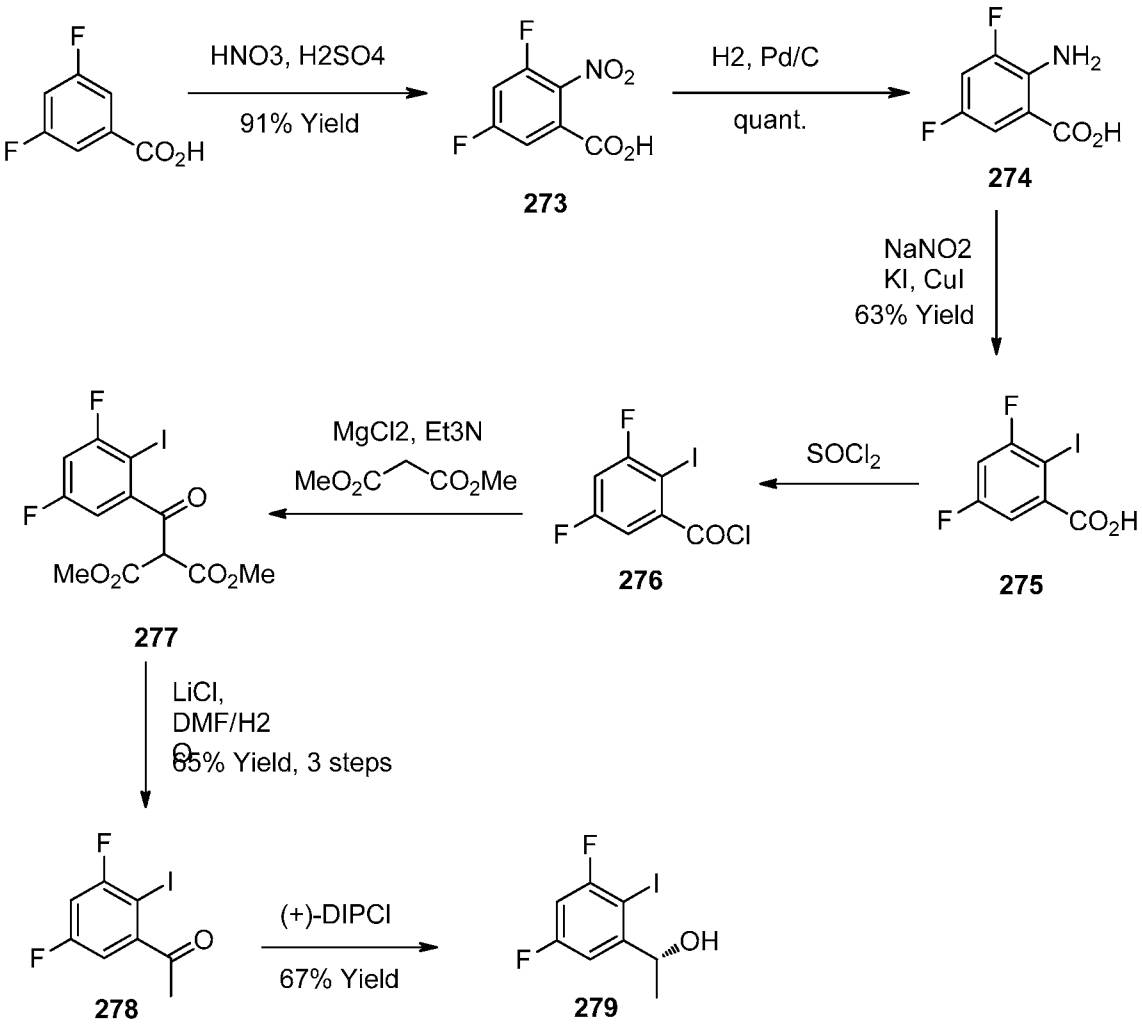
Step 6:

To a stirred solution of **compound 270** (2.5 g, 10 mmol) and TEA (4.2 mL, 30 mmol) in dry DCM (30 mL) was added TFAA (4.32 g, 20 mol) at 0 °C under a nitrogen atmosphere. After the addition, the mixture was stirred at 0 °C for 12 hours. TLC (petroleum ether/EtOAc =3:1) indicated the reaction was complete. The mixture was washed with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL x 2), dried over Na_2SO_4, and concentrated to give a residue, which was purified by column chromatography over silica. gel (Rf = 0.4, petroleum ether/EtOAc = 10:1) to give **compound 271** (1.3 g, 56.5 %) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 4.52 (s, 2H), 2.87 (s, 3H), 1.47 (s, 9H)

Step 7:

To a stirred solution of **compound 271** (1.3 g, 5.5 mmol) in EtOAc (2 mL) was added HCl (g)/EtOAc (6N, 10 mL) at room temperature. After the addition, the mixture was stirred at room temperature for 2 hours. TLC (petroleum ether/EtOAc =1:1) indicated the reaction was complete. The mixture was concentrated to give **compound 272** (1 g, 100%) as the hydrochloride salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 2H), 7.85 (s, 1H), 4.43 (s, 2H), 2.63 (s, 3H).

Preparation of (1*R*)-1-(3,5-difluoro-2-iodophenyl)ethanol (Compound 279)



Step 1:

3,5-difluorobenzoic acid (80 g, 506 mmol) and sulfuric acid (250 ml) were stirred at room temperature for one hour. Then nitric acid (90 ml) was added, keeping the internal temperature below 45C with a water bath. The mixture was left at room temperature overnight. The reaction was poured slowly into ice and the resulting solid was filtered and washed with cold water to give **compound 273** as a white solid (93.0 g, 91% yield). This material was taken into the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.01(ddd, J=10.9, 8.5, 2.8 Hz, 1H), 7.71(dt, J= 8.4, 2.2 Hz, 1H).

Step 2:

Compound 273 (80 g, 394 mmol) and palladium on carbon (9 g, 10% wt) in EtOAc (900 ml) were stirred at room temperature under an atmosphere of H2 (50 bar) for 4 hours. The reaction mixture was filtered on a pad of silica and celite and the solvent removed in vacuo to give **compound 274** as a pale yellow solid (67.39 g, 99% yield, ~95% purity-NMR). This material

was taken into the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.39 (ddd, J= 11.5, 8.4, 3.0Hz, 1H), 7.3 (ddd, J=9.6, 3.0, 1.8 Hz, 1H)

Step 3:

The **compound 274** (53.8 g, 311 mmol) was dissolved in an aqueous solution of HCl (2M, 800 ml) and cooled to 0-5 C. Sodium nitrite (21.44 g, 311mmol) was dissolved in water (344 ml) and added to the previous solution over a period of 15 minutes. This mixture was stirred at 0-5 C for 2 hours then transferred to a conical flask and kept cold. In a new round bottom flask was added potassium iodide (103.25 g, 622 mmol) and copper iodide (29.61 g, 156mmol) in water (344 ml). This mixture was cooled at 0-5C then the previous mixture was added slowly. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The suspension was filtered and the resulting solid was slurried in ethyl acetate (860 ml) for 1 hour. This solution was filtered again and the mother liquors were washed with sodium metabisulfate (10%, 4*600ml) and brine (600ml). After drying on MgSO4 and removal of the solvents in vacuo, **Compound 275** was isolated as a pale yellow solid (55.35 g, 63% yield, 90% purity-NMR).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (ddd, J=8.5, 2.9, 1.5 Hz, 1H), 7.07 (J=7.8, 2.8 Hz, 1H), [M-H+]-282.74.

Step 4:

Thionyl chloride (142 ml, 1940 mmol) was added to **compound 275** (55.0 g, 194 mmol) and the mixture was heated at 80 °C for 3.5 hours. The reaction was then cooled to room temperature and thionyl chloride was removed under reduced pressure and then azeotroped with toluene. **compound 276** was isolated as an orange oil (56 g, quantitative).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 (ddd, J=8.4, 2.8, 1.4 Hz, 1H), 7.09 (td, J= 7.7, 2.8 Hz, 1H), [M+H+]-298.

Step 5:

This reaction was set up in 7 batches of 5 g each of **compound 276**. Magnesium chloride (2.35 g, 24.6 mmol) and diethyl malonate (3.95 g, 24.6 mmol) were suspended in acetonitrile (50 ml). The resulting mixture was cooled to 0 C then triethylamine (3.42 ml, 24.6 mmol) was added dropwise at 0 C and the reaction stirred during 45 min at 0 C. A solution of **compound 276** (5 g, 16.4 mmol) in acetonitrile (20ml) was added quickly to this mixture at 0 C.The solution was warmed to room temperature and stirred for 3 hours. The solvents were removed under reduced pressure and the residue was diluted with EtOAc (350ml) and an aqueous solution of HCl (1M, 300 ml). The aqueous phase was washed with EtOAc (3*300 ml) then the organic phases were combined, dried over MgSO4, filtered and the solvents removed under reduced pressure to give **compound 277** as an orange oil (combined crude 68.9 g) ^{1}H NMR (400 MHz, DMSO-d6) δ 7.49-7.43 (m, 1H), 7.22 (ddd, J= 8.5, 2.7, 1.2 Hz, 1H), 4.11-3.99 (m, 4H), 1.99 (s, 1H), 1.20 (m, 6H); [M-H+]= 424.89, 426.14, 426.92 (10/1).

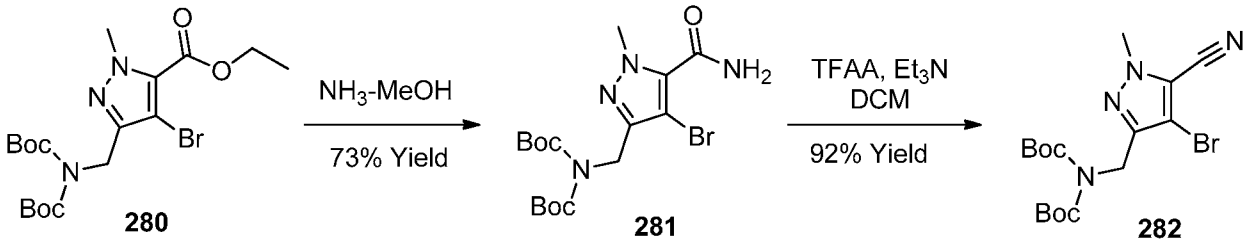
Step 6:

This reaction was set up in 2 batches which were combined prior to work up (37.6 g + 31.34 g). **Compound 277** (37.6 g, 88.2 mol) and lithium chloride (3.74 g, 88.2 mmol) were dissolved in DMF (170 ml) and water (17 ml) and heated at 100 C for 4 hours. The reaction was allowed to cool to RT then water (150 ml) and TBME (150 ml) were added. The phases were separated and the aqueous layer was washed with TBME (3*150 ml). The organic phases were combined and washed with water (500 ml), dried over MgSO4, filtered then evaporated under reduced pressure. The residue was purified by dry flash chromatography (eluent: Hept/EtOAc 98:2 to 9:1) to give **compound 278** as an orange solid (21.34 g, 65% yield over 3 steps, 88% pure by LCMS). ^{1}H NMR (400 MHz, DMSO-d6) δ 7.53-7.51 (m, 1H), 7.50-7.48 (m, 1H), 2.57 (s, 3H), [M-F+MeCN]= 293.03, 293.79(1/10).

Step 7:

A solution of (+)DIP-Cl (17.1 g, 53.2 mmol) in THF(24 ml) was cooled to -35 °C. Then a solution of **compound 278** (7.5 g, 26.5 mmol) in THF (20 ml) was added dropwise keeping the internal temperature of the reacton between -35 and -30C. The reaction was allowed to warm to room temperature and stirred for 12 hours. TLC analysis confirmed the reaction was complete. The solvents were removed in vacuo and the residue was diluted in TBME (64.5 ml). A mixture of diethanolamine (9.16 g, 87.45 mmol) in ethanol/THF (3.75 ml / 7.5 ml) was added. The reaction mixture was stirred for 3 hours at reflux then cooled to room temperature and filtered. The mother liquids were concentrated in vacuo and the resulting residue was purified by column chromatography (eluent: Hep/EtOAc 99:1 to 9:1). The colourless oil obtained was further purified by recrystallisation from heptane to give **compound 279** as a white solid (5.02 g, 67% yield, 95% pure by NMR, 99% ee-chiral GC analysis). ^{1}HNMR (400 MHz, d6-DMSO) δ 7.28-7.12 (m, 2H), 5.64 (d, J= 4.2 Hz, 1H), 4.86 (q, J= 6.4 Hz, 1H), 1.27 (d, J+ 6.4 Hz, 3H), [M-F+H2O-H+]-279.12/280.92 (1:1), HPLC (CP-chiralsil-dex- CB column): 99% ee; Rt(minor)- 18.23 min; Rt(major)-18.55min; 40C to 225C at 6C per minute.

Preparation of di-*tert*-butyl [(4-bromo-5-cyano-1-methyl-1*H*-pyrazol-3-yl)methyl]imido-dicarbonate (Compound 282)



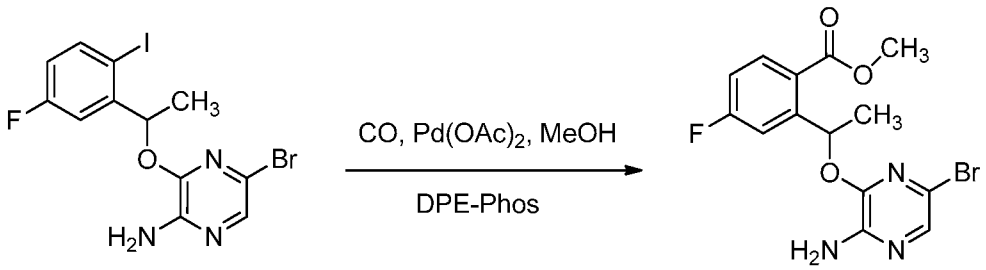
Step 1:

A solution of **compound 280** (10 g, 0.21 mol) in NH_3(g)/MeOH (150 mL) was was stirred at 45 °C overnight in a sealed tube. TLC (petroleum ether/EtOAc = 3: 1) indicated the consumption of compound 9. The reaction mixture was concentrated. The residue was re-crystallized from CH_2Cl_2/petroleum ether to give **compound 281** (6.6 g, 72.6%) as a pale brown solid.^{1}H NMR (400 MHz, DMSO) δ 8.00 (s, 1H),7.82 (s, 1H), 4.64 (s, 2H), 3.85 (s, 3H), 1.38 (s, 18H)

Step 2:

To a mixture of **compound 281** (58 g, 20.5 mol) and Et_3N (4.6 g, 45.6 mmol) in dry CH_2Cl_2 (100 mL) was added TFAA (6.4 g, 30.5 mol) drop-wise at 0 ~ -5 °C. After addition, the mixrue was stirred at 0 °C for 1.5 hour. TLC (petroleum ether: EtOAc = 1:1) showed the reaction was complete. The mixture was diluted with CH_2Cl_2 (100 mL), Washed with 5% citric acid (50 mL), sat. $NaHCO_3$ (50 mL), and brine (50 mL), dried over sodium sulfate and concentrated. The residue was purified by biotage (petroleum ether/EtOAc 6/1, Rf = 0.5) to give **compound 282** (5.8 g, 92.2%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.797 (s, 2H), 3.988 (s, 3H), 1.481 (s, 18H). LC-MS: m/z for C16H23BrN4O4 [M+Na]+ 439.2.

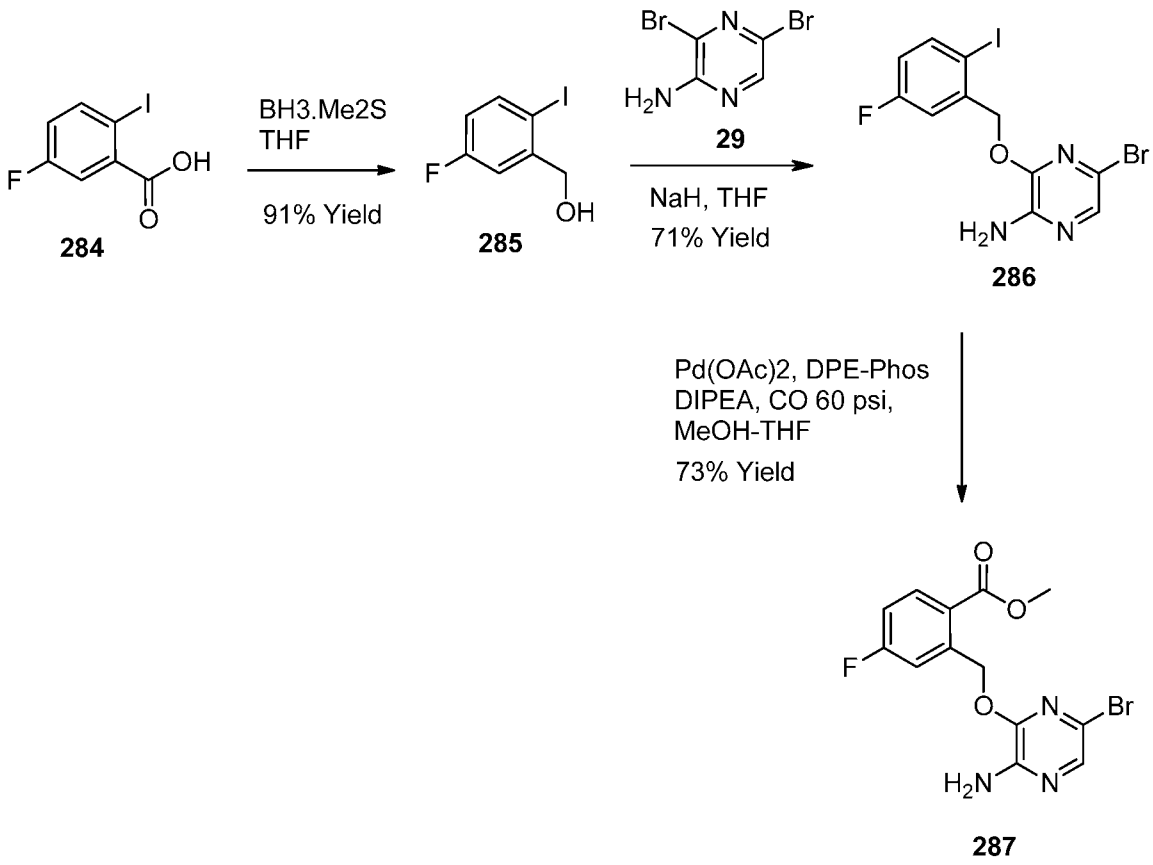
Preparation of methyl 2-{1-[(3-amino-6-bromopyrazin-2-yl)oxy]ethyl}-4-fluorobenzoate (283).



30 **283**

The procedure described in step 1 for **Example 89** was used to prepare **compound 283.**

Preparation of methyl 2-{[(3-amino-6-bromopyrazin-2-yl)oxy]methyl}-4-fluorobenzoate (Compound 287)



284 285 29 286 287

Step 1:

Compound 284 (5.00 g, 18.80mmol) was dissolved in THF (50mL) and cooled to 0°C under nitrogen. Borane-dimethylsulphide (3.57mL, 37.60mmol) was added dropwise with stirring and the reaction mixture warmed to room temperature. Stirred at room temperature for 16 hours. The reaction mixture was carefully quenched by pouring onto ice and adding 10% aqueous K_2CO_3 solution (50mL). The mixture was extracted with DCM (2 x 50mL) and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo to give **compound 285** as a colorless solid (4.80g, 91% yield). 1H NMR (400 MHz, CDCl3): δ 7.68 (dd, 1H, J = Hz), 7.19 (dd, 1H, J = Hz), 6.70 (td, 1H, J = Hz), 4.57 (d, 2H, J = Hz), 1.95 (t, 1H, J = Hz).

Step 2:

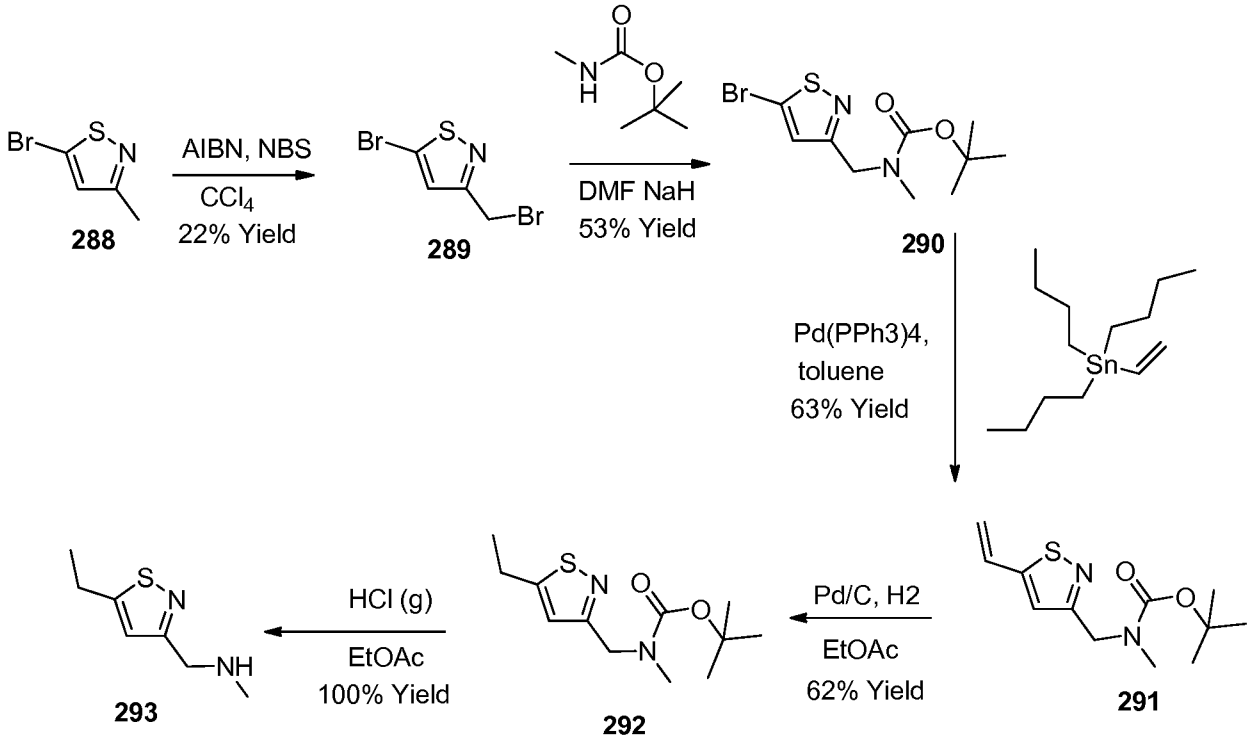
Compound 285 (4.80g, 19.05mmol) was dissolved in dry THF (80mL) and cooled to 0°C under nitrogen. NaH (60% dispersion in mineral oil, 831mg, 20.77mmol) was added in portions and the mixture stirred for 30 minutes room temperature. Cooled back down to 0°C and added a solution of 3,5-dibromopyrazin-2-amine (4.38g, 17.31mmol) in THF (40mL). The reaction mixture was then heated at reflux for 18 hours. After cooling to room temperature, the mixture was evaporated in vacuum to give a dark brown oil. To this oil was added 10% aq. K_2CO_3 solution (100mL) and extracted with EtOAc (3 x 100mL). The combined organic extracts were washed with brine (100mL), dried over $MgSO_4$ and evaporated in vacuum to give a fawn solid.

This was purified by flash chromatography eluting with DCM:heptanes 3:1 and then DCM to give **compound 286** as a pale yellow solid (5.80g, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, 1H, J = 8.7, 5.5 Hz), 7.70 (s, 1H), 7.21 (dd, 1H, J = 9.7, 3.0 Hz), 6.84 (td, 1H, J = 8.3, 3.0 Hz), 5.38 (s, 2H), 4.82 (br. s, 2H); [MH+]-425.80.

Step 3:

Compound 286 (5.20g, 12.26mmol) was partially suspended in MeOH (50mL) and THF (25mL) added to dissolve in a reaction bomb. DIPEA (10.61mL, 61.30mmol), DPE-Phos (792mg, 12mol%) and $Pd(OAc)_2$ (165mg, 6 mol%) were added. The reaction bomb was filled with CO (60 psi) and the reaction mixture heated to 40°C for 3 hours. The reaction was cooled to ambient and then evaporated in vacuum to give a mauve solid. This solid was triturated in hot DCM, then cooled before filtering off a yellow solid of essentially pure compound 4 (2.65g, 61% yield). The filtrate was purified by flash chromatography eluting with 25-33% EtOAc in heptanes to give more of **compound 287** as a pale brown solid (540mg 12% yield). A total of 3.19g was obtained (73% yield). ^{1}H NMR (400 MHz, CDCl3): δ 8.06 (dd, 1H, J = 8.7, 5.9 Hz), 7.69 (s, 1H), 7.24 (dd, 1H, J = 9.9, 2.6 Hz), 7.08 (ddd, 1H, J = 8.7, 7.8, 2.7 Hz), 5.82 (s, 2H), 4.81 (br. s, 2H), 3.90 (s, 3H), [MH+]-358.02.

Preparation of 1-(5-ethyl-1,2-thiazol-3-yl)-N-methylmethanamine (293).



Step 1:

A mixture of **compound 288** (13 g, 73 mmol), AIBN (1.19 g, 7.3 mmol) and NBS (32.5 g, 182.5 mmol) in chloroform (200 mL) was refluxed under nitrogen for 24 hours. The reaction mixture was concentrated in vacuo to give the residue, which was purified by column chromatography on silica gel eluting with petroleum ether/EtOAc 200/1 to give **compound 289** (4 g, 21.5%) as yellow oil.

Step 2:

To a stirred solution of *tert*-butyl methylcarbamate (2.4 g, 18.7 mmol) in DMF (30 mL) was added NaH (0.75 g, 17.8 mmol, 60% in mineral oil) at 0 °C under nitrogen. After addition, the reaction mixture was stirred at 0 °C for 1 hour. **Compound 289** (4 g, 15.6 mmol) was added to the mixture at 0 °C and the mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with H2O (100 mL) and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried over Na2SO4 and concentrated. The residue was purified by column chromatography on silica gel eluting with petroleum ether/ EtOAc 20/1 to give **compound 290** (2.5 g, 53.2%) as yellow oil.

Step 3:

A mixture of **compound 290** (2.5 g, 8.2 mmol), tributyl(ethenyl)stannane (3.7 g, 12.3 mmol) and $Pd(PPh_3)_4$ (0.474 g, 0.41 mmol) in dry toluene (30 mL) was refluxed under nitrogen for 4 hours. The reaction mixture was concentrated in vacuo to give the residue, which was purified by column chromatography on silica gel eluting with petroleum ether/EtOAc 50/1~10/1 to give **compound 291** (1.6 g, 62.5%) as yellow oil.

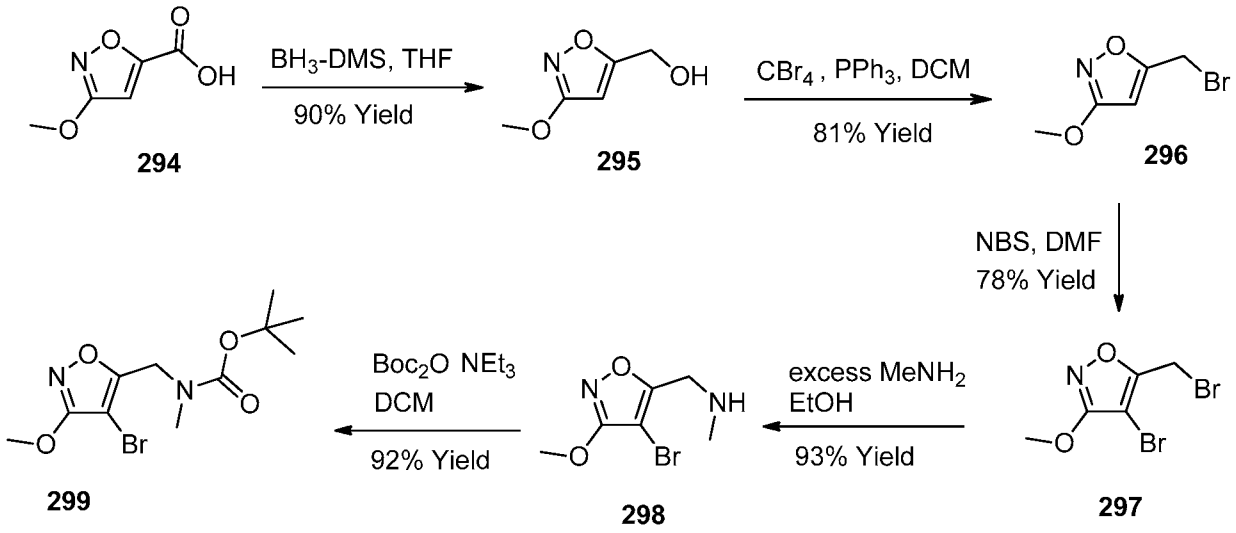
Step 4:

A mixture of **compound 291** (1.6 g, 6.3 mmol) and Pd/C (180 mg) in EtOAc (30 mL) was stirred at 30 °C under hydrogen for 16 hours. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give a residue, which was purified by column chromatography on silica gel eluting with petroleum ether/ EtOAc 50/1~10/1 to give **compound 292** (1.0 g, 62.1%) as light yellow oil. ^{1}H NMR (400 MHz, MeOD): δ 6.973 (s, 1H), 4.50 (s, 2H), 2.96-3.0 (q, 2H), 2.93-2.91 (t, 3H), 1.53 (s, 9H), 1.35-1.28 (t, 3H) LC-MS: 127144-146-P m/z for C12H20N2O2S [M-boc+H]+ 157.0

Step 5:

To a solution of **compound 292** (0.42 g, 1.6 mmol) in EtOAc (10 mL) was added dropwise HCl (g)/ EtOAc (5 mL) and stirred at room temperature for 5 hours. The mixture was concentrated to give **compound 293** as a yellow solid (0.32 g, 100%). ^{1}H NMR (400 MHz, D2O): δ 7.17 (s, 1H), 4.33 (s, 2H), 2.98-2.92 (q, 2H), 2.77 (s, 3H), 1.32-1.29 (t, 3H).

Preparation of *tert*-butyl [(4-bromo-3-methoxy-1,2-oxazol-5-yl)methyl]methylcarbamate (299).



Step 1:

To a solution of 3-methoxyisoxazole-5-carboxylic acid **294** (7.6g , 53.14mmol) in anhydrous tetrahydrofuran (80ml) at 0 °C under nitrogen,was added dropwise over 10 minutes a solution of borane-dimethylsulfide complex (5.18g, 6.47ml, 69.0 mmol) in THF (30ml). The mixture was allowed to warm to room temperature, and then heated to 60 °C for 2 hours, then cooled to room temperature. The mixture was carefully quenched by the dropwise addition of 10 ml water, stirred for 10 minutes, then extracted with EtOAc (2 x 80ml), dried over Na_2SO_4, filtered and the solvent removed under vacuum to afford **compound 295** as a pale yellow oil (6.0g, 88%). ^{1}H NMR (400 MHz, d6-DMSO): δ 6.087 (s, 1H), 4.438 (s, 2H), 5.60 (br.s, 1H), 3.867 (s, 3H), [M+H 130.03].

Step 2:

To a solution of **compound 295** (411mg, 3.18 mmol) in dichloromethane (5ml) at 0 °C under nitrogen, was added triphenylphosphine (833mg, 3.18 mmol) and carbontetrabromide (1.029g, 3.10 mmol) (which had been freshly dried by azeotroping 3 times with toluene). The mixture, which had turned orange, was stirred at 0 °C for 1 hour, then allowed to warm to room temperature. The mixture was concentrated by the removal of solvent under vacuum, and then purified by flash column chromatography eluting with 3:1 heptane:EtOAc which yielded the **compound 296** as a colourless oil (486mg, 81%). ^{1}H NMR (400 MHz, d6-DMSO): δ 6.350 (s, 1H), 4.696 (s, 2H), 3.889 (s, 3H, [M+H 192.2 and 194.2].

Step 3:

To a solution of **compound 296** (4.4g, 23 mmol) in anhydrous dimethylformamide (20ml) was added at room temperature N-bromosuccinimide (4.1g, 23.1 mmol), and mixture warmed to 45

°C for 2 hours. Further N-bromosuccinimide (2.0g, 11.3 mmol) was added, and mixture stirred at 45 °C for 2 hours. Further N-bromosuccinimide (1.3g, 7.4 mmol) was added, and mixture stirred overnight at room temperature. Further N-bromosuccinimide (1.1g, 11.3 mmol) was added, and mixture stirred at 45 °C overnight. The mixture was concentrated by the removal of solvent under vacuum, then extracted with EtOAc (2 x 100ml), the organic layer was washed with water (50ml), brine (20ml), dried over Na_2SO_4, filtered and the solvent removed under vacuum. The residue was added to 0.9g of impure product from another identical reaction and was purified by flash column chromatography eluting with 100:0 – 80:20 heptane:EtOAc , which yielded the **compound 297** as a colourless oil, which later crystallised on standing to a colourless solid (5.66g , 91% - however taking into account added material to column, calculated yield 78%). ^{1}H NMR (400 MHz, d6-DMSO): δ 4.72 (s, 2H), 3.98 (s, 3H).

Step 4:

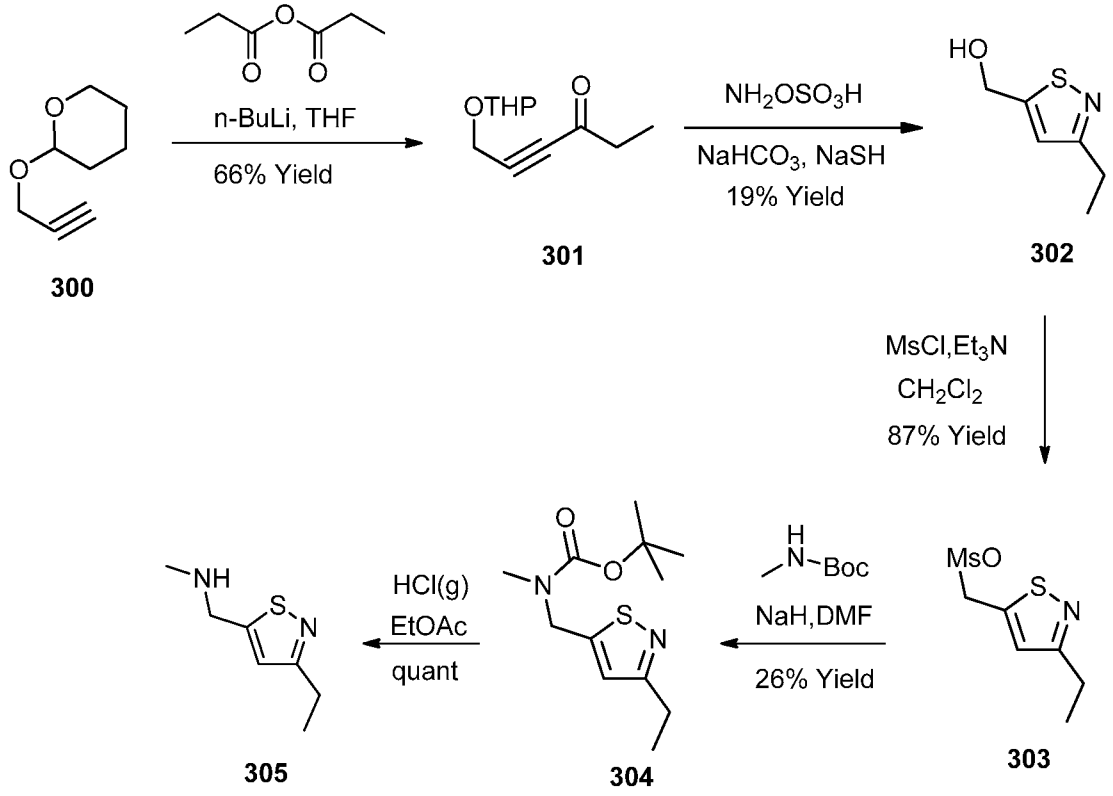
To a solution of methylamine 33% in ethanol (77ml, 653 mmol) at 0 °C under nitrogen, was added dropwise over 10 minutes a solution of **compound 297** in ethanol (20ml), and the mixture was allowed to warm to room temperature overnight. The mixture was concentrated by the removal of solvent under vacuum, then saturated aqueous sodium hydrogen carbonate was added (20 ml), then the mixture extracted with EtOAc (100ml), dried over Na_2SO_4, filtered and the solvent removed under vacuum to give **compound 298** as pale yellow oil 4.5g (93.5%).

^{1}H NMR (400 MHz, d6-DMSO): δ 3.956 (s, 3H), 3.686 (s, 2H), 2.287 (br.s, 1H), 2.234 (s, 3H), [M+H 220.95 and 222.95].

Step 5:

To a solution of **compound 298** (4.5g, 20.4 mmol) in dichloromethane at room temperature under nitrogen was added triethylamine (2.12g, 2.92 ml, 21 mmol), then portionwise over 3 minutes di-tert-butyldicarbonate (4.58g, 21 mmol). Very mild effervescence was observed. The mixture was stirred at room temperature under nitrogen for 3 hours. The mixture was concentrated by the removal of solvent under vacuum, azeotroped with 150ml heptane, then the residue was partitioned between EtOAc (100ml) and water (20ml). The organic layer was dried over Na_2SO_4, filtered and the solvent removed under vacuum to give **compound 299** (6g, 92% yield).

Preparation of 1-(3-ethyl-1,2-thiazol-5-yl)-*N*-methylmethanamine (305).



Step 1:

A solution of **compound 300** (55 g, 0.39mol) in dry THF (600 mL) was added n-BuLi (157 mL, 0.39 mol, 2.5 M) drop wise at -70 °C under N2. After addition, the mixture was stirred at -70 °C for 1 hour. The mixture was warmed to -20 °C, and stirred at this temperature for 20 min. The reaction mixture was cooled to -70 °C, and transferred via a double-ended needle to a solution of propanoic anhydride (61.3 g, 0.47 mol) in dry THF (400 mL) also kept at -70 °C. The reaction mixture was allowed to warm to room temperature slowly, and stirred at room temperature overnight. The reaction mixture was diluted with saturated NH_4Cl solution (500 mL) and EtOAc (500 mL), and separated. The aqueous layer was extracted with EtOAc (500 mL × 3). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, and concentrated. The residue was distilled under reduced pressure to give **compound 301** (50 g, 65.7%) as yellow oil.

Step 2:

To a mixture of **compound 301** (58 g, 0.296 mol) in H_2O (1 L) was added NH_2OSO_3H (36.78 g, 0.326 mol) at 0 °C, and the mixture was stirred at room temperature for 4 hours. $NaHCO_3$ (27.38 g, 0.326 mol) was added to the mixture carefully. Then NaSH (24.86 g, 0.444mol) was added, and the mixture was refluxed overnight. TLC (petroleum ether: EtOAc = 3:1) showed the reaction was complete. The mixture was filtered. The filtrate was extracted with EtOAc (500 mL × 3). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, and

concentrated. The residue was purified with silica gel column eluting with petroleum ether/ EtOAc 15/1 ~ 10/1 to give **compound 302** (8 g, 19%) as brown oil.

Step 3:

To a solution of **compound 302** (8 g, 55.9 mmol) and Et_3N (16.9 g, 0.168 mol) in dry CH_2Cl_2 (100 mL) was added MsCl (8.32 g, 72.7 mmol) drop-wise at 0 °C. After addition the mixture was stirred at room temperature for 2 hours. TLC (petroleum ether: EtOAc = 3:1) showed the reaction was complete. The mixture was diluted with EtOAc (250 mL), and filtered. The filtrate was washed with brine (50 mL), dried over Na_2SO_4, and concentrated to give **compound 303** (11 g, 87%) as brown liquid.

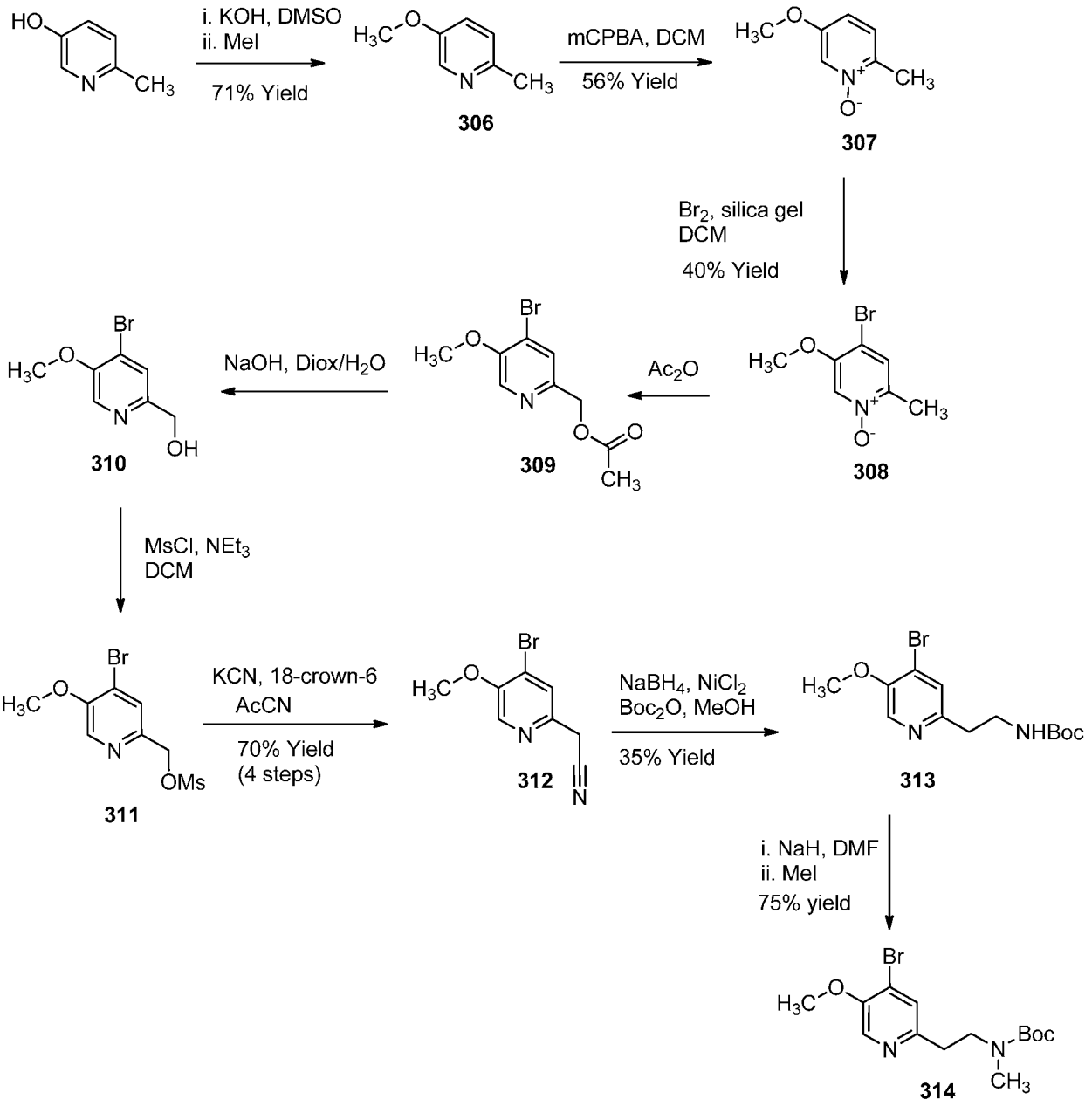
Step 4:

To a solution of *tert*-butyl methylcarbamate (11 g, 90.5mmol) in dry DMF (100 mL) was added NaH (3.6 g, 90.5 mmol, 60% in oil) in portions at 0 °C under N_2. After addition, the reaction mixture was stirred at 0 °C for 30 min. **Compound 303** (10 g, 45.2 mmol) was added to the mixture at 0 °C, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with H_2O (100 mL)), and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried over Na_2SO_4 and concentrated. The residue was purified by prep.HPLC under basic conditions to give **compound 304** (3 g, 26%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 6.926 (s, 1H), 4.626 (s, 2H), 2.94 (s, 3H), 2.84-2.86 (q, 2H), 1.53 (s, 9H), 1.33-1.36 (t, 3H), [M+H]+ 257.

Step 5:

To a solution of **compound 304** (0.42 g, 1.6 mmol) in EtOAc (10 mL) was added dropwise HCl (g)/ EtOAc (5 mL) and stirred at room temperature for 8 hours. The mixture was concentrated to give **compound 305** (0.32 g, 100%) as a white solid. ^1H NMR (400 MHz, D_2O): δ 7.30 (s, 1H), 4.51 (s, 2H), 2.81-2.75 (q, 2H), 2.72 (s, 3H), 1.222-1.18 (t, 3H).

Preparation of *tert*-butyl [2-(4-bromo-5-methoxypyridin-2-yl)ethyl]methyl-carbamate (314).



Step 1:

KOH (141 g, 2.52 mol) was added to a solution of 2-methyl-3-hydroxy pyridine (55.0 g, 0.50 mol) in DMSO (840 mL). The mixture was stirred at room temperature for 1 hour (KOH not fully dissolved) then was cooled at 0°C. MeI (34.6 mL, 0.55 mol) was added drop wise then the reaction was stirred at room temperature for 18 hours. Water (1.25 L) was added slowly to the reaction mixture. The aqueous phase was extracted with MTBE (3 x 500 mL) then EtOAc (3 x 400 mL). The aqueous phase was saturated with NaCl then extracted again with EtOAc (3 x 200 mL). Organic phases were combined, dried over $MgSO_4$, filtered and concentrated carefully under vacuum (product is volatile). The oil obtained was purified by column chromatography (eluent: heptanes:EtOAc form 1:1 to 0:1) to give **compound 306** (44.1 g, 71% yield). ^1H NMR

(400 MHz, DMSO-d_6) δ 8.14 (d, J = 3.1 Hz, 1H), 7.27 (dd, J = 8.5, 3.1 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 3.78 (s, 3H), 2.38 (s, 3H).

Step 2:

To a solution of **compound 306** (44.1 g, 358 mmol) in DCM (890 mL) was added Na_2SO_4 (76.2 g, 537 mmol). The mixture was stirred at room temperature for 15 min then mCPBA (88.0 g, 358 mmol) was added portion wise (exothermic process). The reaction was stirred at room temperature for 20 hours. An additional amount of mCPBA (8.0 g, 36 mmol) was added and the mixture was stirred at room temperature for 3 hours. The reaction was filtered then washed with 1 M KOH (500 mL). The aqueous phase was extracted with DCM (3 x 200 mL) then the organic phases were combined, dried over $MgSO_4$, filtered and concentrated under vacuum. The oil obtained was dissolved in DCM (600 mL) then Na_2SO_4 (17 g) was added followed by the addition of mCPBA (8.0 g). The mixture was stirred at room temperature for 20 hours then washed with an 1 M KOH (500 mL). The aqueous phase was saturated with NaCl and extracted with DCM (3 x 300 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under vacuum to give **compound 307** as a white solid (28.7 g, 56% yield,). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.96 (dd, J = 8.8, 2.5 Hz, 1H), 3.78 (s, 3H), 2.27 (s, 3H).

Step 3:

Water (100 mL) was added drop wise to silica gel (280 g). The mixture was stirred 30 min at RT to obtain a fluffy powder. DCM (420 mL) was added, the mixture was stirred to obtain an homogeneous suspension then a solution of **compound 307** (27.7 g, 199 mmol) in DCM (275 mL) was added. After obtaining an homogeneous suspension, a solution of Br_2 in DCM (1 M, 285 mL, 199 mmol) was added drop wise over 30 min. The mixture was stirred at room temperature for 18 hours. An additional portion of silica gel (100 g) and a solution of Br_2 in DCM (1 M, 142 mL, 100 mmol) were added. The mixture was stirred at room temperature for 8 hours then the same amount of silica gel and of Br_2 solution were added. The mixture was stirred at room temperature for 18 hours then filtered. The pad of silica was rinsed with EtOAc (500 mL) then with a mixture DCM/MeOH (8:2, 400 mL). The mother liquors were concentrated under vacuum, redissolved into DCM (500 mL) and this solution was washed with a 10% aqueous solution of sodium metabisulfite (250 mL). The phases were separated. The aqueous phase was saturated with NaCl then carefully extracted with DCM (8 x 150 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The oil obtained was purified quickly by column chromatography (eluents: EtOAc/MeOH from 15:1 to 8:1). The solids isolated (27 g, mixture between 4-bromo and 2-bromo pyridine ~6:4) were suspended in EtOAc (100 mL) and triturated for 1 hour. The solid was filtered (white powder, 24 g) then slurried in DCM (100 mL)

and stirred at reflux for 2 hours. The suspension was cooled to room temperature and the solid was filtered to give **compound 308**. The mother liquors were concentrated and slurried in DCM and the trituration was repeated to give a second batch of **compound 308** (white powder, 14.9 g, 34% yield). The remaining mix fractions (8.0 g, 1:1 mixture) was purified by column chromatography (eluents: EtOAc/MeOH from 15:1 to 8:1) to give an additional **compound 308** as a white powder (2.6 g, 6% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J = 2.3 Hz, 1H), 7.79 (d, J = 2.6 Hz, 1H), 3.88 (s, 3H), 2.27 (s, 3H).

Step 4:

Compound 308 (2.8 g, 13 mmol) was dissolved in Ac_2O (24 mL) and the solution was heated at 60°C for 18 hours. The mixture was concentrated under vacuum. Cyclohexane (50 mL) was added and the mixture was concentrated under vacuum. This was repeated 3 times. The oil obtained was dissolved in EtOAc (150 mL) and the solution was washed with a saturated aqueous solution of $NaHCO_3$ (100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under vacuum to give crude **compound 309** which was used in the next step without further purification (light brown crystals, 3.18 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.70 (s, 1H), 5.06 (s, 2H), 3.97 (s, 3H), 2.09 (s, 3H).

Step 5:

Compound 309 (3.2 g, 12 mmol) was dissolved in dioxane (86 mL) then an aqueous solution of NaOH (2 M, 28 mL) was added. The mixture was stirred at room temperature for 18 hours. The solution was acidified with a 1 M aqueous HCl solution until pH 7. The aqueous phase was extracted with EtOAc (3 x 150 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated to give **compound 310** as a pale yellow oil (2.5 g) which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.64 (s, 1H), 5.43 (t, J = 6.0 Hz, 1H), 4.49 (d, J = 5.6 Hz, 2H), 3.95 (s, 3H).

Step 6:

Compound 310 (2.5 g, 12 mmol) was dissolved in DCM (80 mL) then triethylamine (2.0 mL, 15 mmol) was added and the solution was cooled at 0 °C. Methanesulfonyl chloride (1.0 mL, 13 mmol) was added drop wise and the mixture was stirred at 0 °C for 1 hour. Water (100 mL) was added carefully to the cooled solution. After leaving it to room temperature for 30 min, the phases were separated and the aqueous phase was extracted with DCM (2 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under vacuum (rotavapor bath at RT) to give **compound 311** as a brown oil (3.4 g) which was used directly in the next step (degradation observed if kept at room temperature for 24 hours). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.83 (s, 1H), 5.23 (s, 2H), 4.00 (s, 3H), 3.27 (s, 3H).

Step 7:

Compound 311 (3.4 g, 12 mmol) was dissolved in ACN (8.5 mL) and 18-crown-6 (4.8 g, 18 mmol) then KCN (1.0 g, 15 mmol) were added. The mixture was heated at 50 °C for 1.5 hour then was cooled to RT. An aqueous solution of NaOH (1 M, 200 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). Organic phases were combined, dried over $MgSO_4$, filtered and concentrated under vacuum. The oil obtained was purified by column chromatography (eluents heptane/etOAc from 3:1 to 1:1) to give **compound 312** as a beige solid (2.5 g, 70% yield over 4 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.71 (s, 1H), 4.13 (s, 2H), 3.97 (s, 3H).

Step 8:

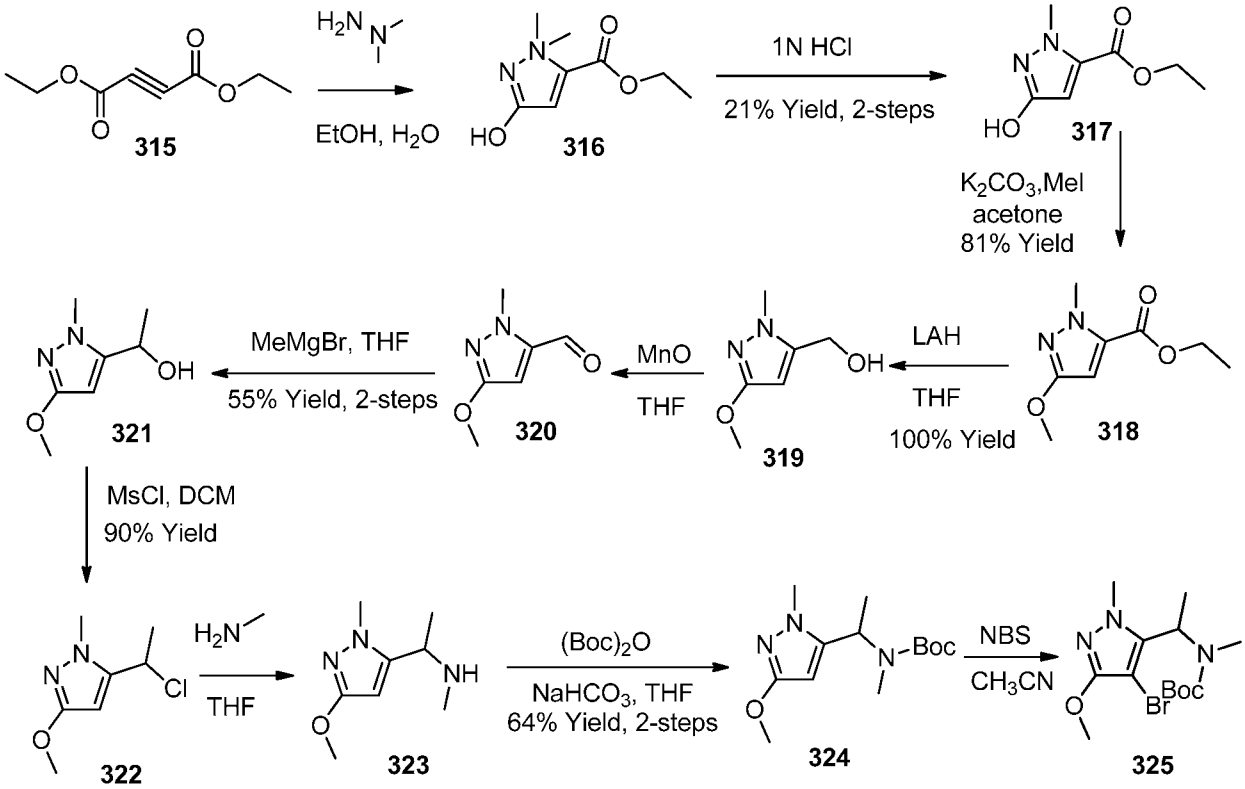
Compound 312 (2.0 g, 8.8 mmol) was dissolved in MeOH (135 mL) and $NiCl_2.6H_2O$ (0.21 g, 0.88 mmol) then Boc_2O (3.9 g, 18 mmol) were added. The mixture was cooled at -10 °C then $NaBH_4$ (1.0 g, 27 mmol) was added portion wise over 9 hours. Diethylenetriamine (2 mL) was added and the mixture was stirred at room temperature for 18 hours. The mixture was concentrated under vacuum then EtOAc (100 mL) was added. The solution was washed with a saturated aqueous solution of $NaHCO_3$ (100 mL). Phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under vaccum. The oil obtained was purified by reverse phase chromatography (eluents H_2O/AcCN from 95:5 to 5:95). **Compound 313** was obtained as colorless oil (1.0 g, 35% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.51 (s, 1H), 6.85-6.81 (m, 1H), 3.96 (s, 3H), 3.24-3.20 (m, 2H), 2.80-2.76 (m, 2H), 1.38 (s, 9H).

Step 9:

Compound 313 (1.0 g, 3.0 mmol) was dissolved in DMF (135 mL). The solution was cooled at 0°C then NaH (60% in oil, 180 mg, 4.5 mmol) was added portion wise over 10 min. The mixture was stirred at 0 °C for 1 hour then MeI (0.19 mL, 3.0 mmol) was added drop wise over 10 min. The mixture was stirred at room temperature for 3 hours. The solution was cooled again at 0 °C then H_2O (100 mL) was added carefully. The mixture was extracted with Et_2O (3 x 150 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The oil obtained was combined with two other samples (starting from 100 mg each) and was purified by column chromatography (eluents heptanes/EtOAc from 3:1 to 1:1). 10% of SM was observed so the previous sample was dissolved in DMF (30 mL), the solution was cooled to 0 °C then NaH (37 mg, 1.0 mmol) was added portion wise. The mixture was stirred at 0 °C for 1 hour then MeI (29 µL, 0.45 mmol) was added. The mixture was stirred at room temperature for 2 hours then was cooled at 0 °C. Water (50 mL) was added carefully and was extracted with Et_2O (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated to give

compound 314 as a pale yellow oil (920 mg, 75% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.54 (s, 1H), 3.92 (s, 3H), 3.54-3.36 (m, 2H), 2.84 (t, J = 6.8 Hz, 2H), 2.74 (s, 3H), 1.48-1.11 (m, 9H).

Preparation of *tert*-butyl [1-(4-bromo-3-methoxy-1-methyl-1*H*-pyrazol-5-yl)ethyl]methylcarbamate (325).



Step 1:

A mixture of **compound 315** (55 mL, 0.35 mol) in 1:1 EtOH/ H2O (600 mL) was slowly added at 0 °C a solution of 1,1-dimethylhydrazine (25.74 g, 0.44 mol w/w 40% in water) in 1:1 EtOH/ H2O (200 mL). The solution was stirred at 0 °C for 30 mins, then allowed to warm to room temperature for 1h. The mixture was concentrated and the residue was partitioned between water (300 mL) and EtOAc (300 mL). The aqueous layer was concentrated to give **compound 316**, which was used for next step directly.

Step 2:

A mixture of **compound 316** in 1N HCl (200 mL) was stirred at room temperature for 1.5 h. The mixture was extracted with DCM (150 mL), the aqueous layer was concentrated to give the residue, which was purified by column chromatography (silica gel, petroleum ether / EtOAc = 6:1) to yield **compound 317** (13 g, 21%) as a white solid. $_1$H NMR (400 MHz, $CDCl_3$): δ 6.148 (s, 1H), 4.34-4.26 (m, 2H), 3.99 (s, 3H), 1.38-1.30 (m, 3H)

Step 3:

A mixture of **compound 317** (4 g, 23.5 mmol), K2CO3 (9.7 g, 70.5 mmol) and MeI (16.8 g, 0.11 mol) were heated to reflux for 3 hours. TLC (petroleum ether / EtOAc = 6:1) showed the reaction was complete. The mixture was filtered and the filtrate was concentrated to give the residue, which was purification by column chromatography (silica gel, petroleum ether / EtOAc = 20:1) to yield **compound 318** (3.5g, 81%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.18 (s, 1H), 4.34-4.29 (q, 2H), 4.05 (s, 3H), 3.83 (s, 3H), 1.38-1.34 (t, 3H).

Step 4:

To a mixture of **compound 318** (2 g, 11.5 mmol) in THF (50 mL) was added LiAlH4 (0.52 g, 13.8 mmol) in portions at 0 °C. After the addition, the reaction mixture was stirred at room temperature overnight. TLC (petroleum ether/EtOAc 1/1) showed the reaction mixture was complete. The reaction mixture was quenched with 20% aq. NaOH (4 mL). The mixture was filtered and the filtrate was concentrated in vacuo to give **compound 319** (1.7 g, ~100 %) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.58 (s, 1H), 4.55 (s, 2H), 4.83 (s, 3H), 3.65 (s, 3H).

Step 5:

A solution of **compound 319** (2 g, 14.3 mmol), MnO2 (6.2 g, 71.4 mmol) in dry THF (50 mL) was heated to reflux overnight. TLC (petroleum ether/EtOAc 6/1) showed the reaction mixture was complete. The reaction mixture was filtered and the filtrate (**compound 320**) was used for next step directly.

Step 6:

To a solution of **compound 320** (~14.3 mmol) in dry THF (100 mL) was added MeMgBr (24 mL, 71.4 mmol, 3.0M) at -50 °C. After the addition, the reaction mixture was stirred at room temperature for 15 hours. TLC (petroleum ether/EtOAc 6/1) showed the reaction mixture was completed. The reaction mixture was quenched with sat.NH4Cl (20 mL). The mixture was then extracted with EtOAc (100 mL x 3). The combined extracts were washed with brine (100 mL x 2), dried over Na2SO4 and concentrated in vacuo to give the residue, which was purified via column chromatography (silica gel, petroleum ether/EtOAc 10/1) to give **compound 321** (1.2g, 55 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.58-5.57 (d, 1H), 4.84-4.80 (q, 1H), 3.83 (s, 3H), 3.73-3.72 (d, 3H), 2.03-2.02 (bs, 1H), 1.55-1.53 (d, 3H).

Step 7:

To a solution of **compound 321** (1.2 g, 7.6 mmol) and Et3N (1.1 g, 11.4 mmol) in dry DCM (30 mL) was added dropwise MsCl (1.3 g, 11.4 mmol) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 12 hours. TLC (petroleum ether/EtOAc 1/1) showed the reaction mixture was complete. The reaction mixture was washed with brine (20 mL), dried over Na2SO4 and concentrated in vacuo to give crude the residue, which was purified by column

chromatography (silica gel, petroleum ether/EtOAc 20/1) to give **compound 322** (1.2 g, 90 %) as a yellow oil. ^{1}H NMR (400 MHz, CDCl3): δ 5.61 (s, 1H), 5.04-4.99 (q, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 1.88-1.86 (d, 3H).

Step 8:

A solution of **compound 322** (0.3 g, 1.72 mmol) in a solution of CH3NH2 (20 mL, 2M in THF) was heated to 80 °C in a sealed tube for 12 hours. TLC (petroleum ether/EtOAc 6/1) showed the reaction mixture was complete. The **compound 323** was used for next step directly.

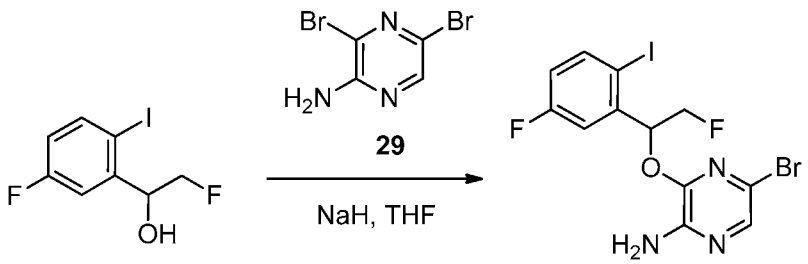
Step 9:

To a mixture of **compound 323** in DCM (20 mL) was added Et3N (347 mg, 3.44 mmol) and (Boc)2O (743 mg, 3.44 mmol), the mixture was stirred at room temperature overnight. TLC (petroleum ether/EtOAc 6/1) showed the reaction mixture was complete. The reaction mixture was partitioned between water (20 mL) and DCM (50 mL). The separated organic layer was washed with brine (50 mL), dried over Na2SO4 and concentrated in vacuo to give the residue, which was purified by column chromatography (silica gel, petroleum ether/EtOAc 20/1) to give **compound 324** (300 mg, 64% in two steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (s, 1H), 5.47 (br, 1H), 3.83 (s, 3H), 3.62 (s, 3H), 2.54 (s, 3H), 1.48 (s, 9H); LCMS: m/z for C13H23N3O3 270.3 [M+H]+.

Step 10:

To a solution of **compound 324** (2.1 g, 7.78 mmol) in DCM (20 mL) was added in portions NBS (1.46 g, 8.16 mmol) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 2 hours. TLC (petroleum ether/EtOAc 6/1) showed the reaction mixture was completed. The reaction mixture was washed with sat. NaHCO3 (30 mL x 4), brine (30 mL), dried over Na2SO4 and concentrated in vacuo to give **compound 325** (2.5 g, 91 %) as yellow oil. ^{1}H NMR (400 MHz, CDCl3): δ 5.79 (s, 1H), 3.92 (s, 3H), 3.68 (s, 3H), 2.70 (s, 3H), 1.66-1.64 (d, 3H), 1.47 (s, 9H).

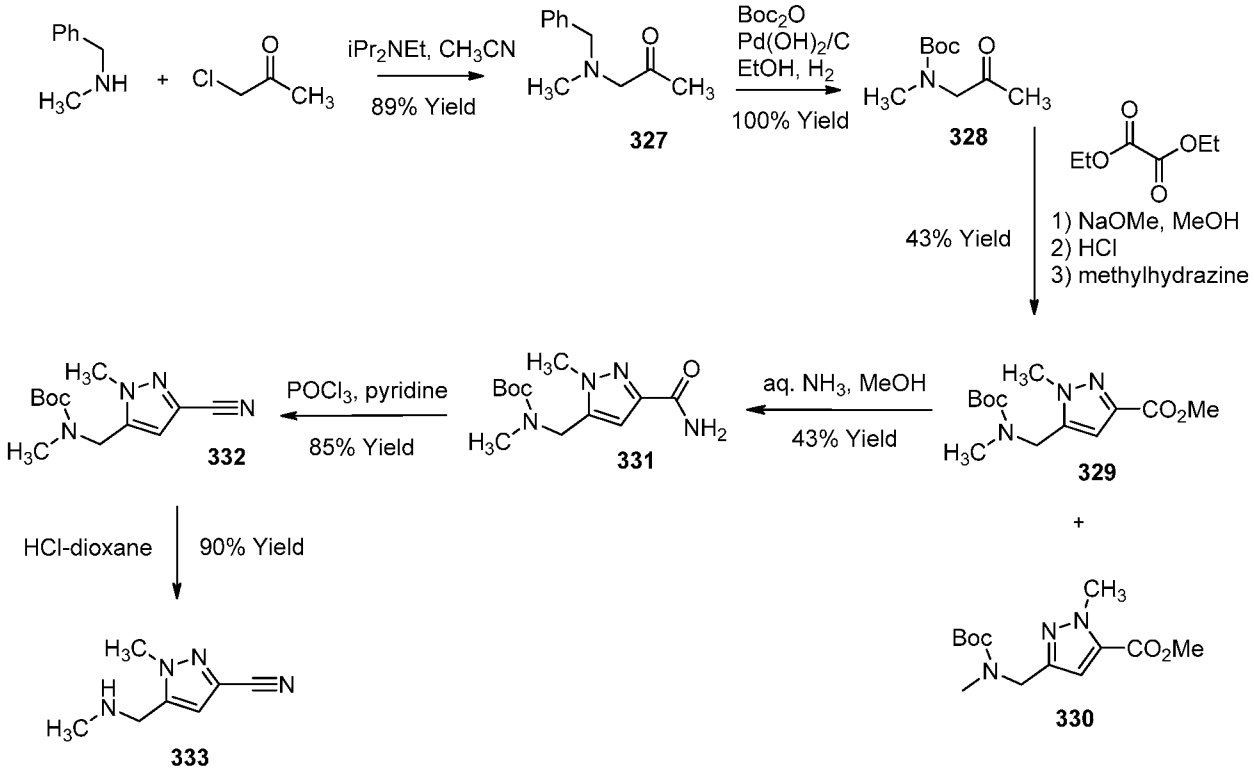
Preparation of 5-bromo-3-[2-fluoro-1-(5-fluoro-2-iodophenyl)ethoxy]pyrazin-2-amine (326).



170 **326**

The procedure described in step 2 for **compound 241** was used to prepare **compound 326.**

Preparation of 1-methyl-5-[(methylamino)methyl]-1*H*-pyrazole-3-carbonitrile (333).



Step 1:

Chloroacetone (207 mL, 2.59 mol) was added drop wise over 45 min to a solution of DIEA (410 mL, 310 g, 2.40 mol) and N-methylbenzylamine (286 g, 2.36 mol) in acetonitrile (1500 mL), maintaining the temperature at between 18 and 20°C by gentle cooling with a cold water bath. Once addition was complete the cooling bath was left in place for a further 30 min before being removed. Stirring was continued for a further 5.5 h, during which time the internal reaction temperature rose to 27°C over 1 hour, plateaued for 2 hours and then slowly dropped. The reaction mixture was concentrated in vacuo to approximately 1 L then left to stand overnight. Crystalline precipitate was removed by filtration, washing with acetonitrile (50 mL) and the filtrate was concentrated in vacuo. The concentrated filtrate was taken up in EtOAc (1 L) and filtered through a short silica pad (1200 mL silica) washing with further EtOAc (2 x 1L). The filtrate was concentrated in vacuo to give **compound 327** as an orange-brown oil (374 g, 89%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.22 (m, 5H), 3.59 (s, 2H), 3.16 (s, 2H), 2.30 (s, 3H), 2.14 (s, 3H).

Step 2:

Palladium hydroxide on carbon (20%, 36 g) and di-tertbutyl dicarbonate (565 g, 2.59 mol) were added to a solution of **compound 327** (439 g, 2.48 mol) in ethanol (3.25 L) and the mixture was

hydrogenated at 50°C and 50 psi pressure of H_2 for 8 hours. Heating was stopped and the reaction was left under hydrogen over the weekend. Catalyst was removed by filtering through Celite, washing with methanol, and the solvent was removed in vacuo to give **compound 328** as a brown oil containing a small amount of suspended solid (476.5 g). This material was used without further purification. ^{1}H NMR (400 MHz, Chloroform-d) 2 rotamers δ 4.00 and 3.90 (2 x s, 2H), 2.92 and 2.88 (2 x s, 2H), 2.12 (s, 3H), 1.47 and 1.42 (2 x s, 9H).

Step 3:

A mixture of diethyl oxalate (187 mL, 1.38 mol) and **compound 328** (258 g, 1.38 mol) in MeOH (200 mL) was added drop wise over 30 min to a solution of NaOMe in MeOH (5.38 M, 257 mL, 1.38 mol) in MeOH (1800 mL). Once then addition was complete the reaction was heated to 55°C and stirred for 2 hours. The reaction was then heated at 65°C for 30 min before being cooled to -7°C. A solution of methylhydrazine hydrochloride in MeOH (preformed by the dropwise addition of conc. HCl [115 mL, 1.38 mol] to an ice cooled solution of methylhydrazine [72.7 mL, 63.6 g, 1.38 mol] in MeOH [100 mL]) was then added drop wise so that the temperature was kept below -5°C. Once addition was complete the reaction was allowed to warm slowly to room temperature and stirred overnight. The reaction mixture was filtered and concentrated in vacuo. The brown semi-solid mass was then taken up in 10% DCM in heptane (500 mL + 250 mL to wash) filtered and combined with the material from a second reaction (207 g tert-butyl methyl(2-oxopropyl)carbamate, 1.10 mol). The combined filtrates were applied to the top of a dry flash column (3.7 L silica) and the column was eluted with heptanes/EtOAc (5-25%) to give **compounds 329 and 330** (3:1 ratio). **Compound 329**: (302 g, 43%). ^{1}H NMR (400 MHz, DMSO-d6) δ 6.65 (s, 1H), 4.30 (s, 2H), 4.04 (s, 3H), 3.82 (s, 3H), 2.76 (s, 3H), 1.40 (s, 9H).

Step 4:

Compound 330 (7.55 g, 26.6 mmol) was dissolved in MeOH (7 mL) then an aqueous solution of ammonia (35%, 70 mL) was added. The solution was stirred at room temperature for 18 hours. The suspension formed was filtered and the white solid isolated was dried to give **compound 331** (3.4 g, 43% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (s, 1H), 7.17 (s, 1H), 6.49 (s, 1H), 4.46 (s, 2H), 3.81 (s, 3H), 2.76 (s, 3H), 1.41 (s, 9H).

Step 5:

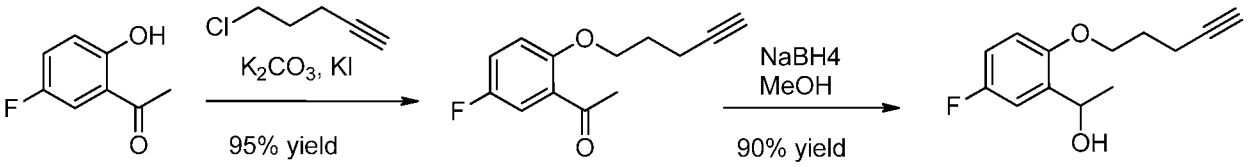
Compound 331 (3.4 g, 13 mmol) was dissolved in pyridine (34 mL) and the solution was cooled at 0°C. $POCl_3$ (2.32 mL, 25.4 mmol) was added drop wise maintaining the temperature less than 25 °C. The mixture was then stirred at 0°C for additional 5 minutes and then at RT for 20 minutes. The reaction was quenched by adding water (200 mL) slowly. The temperature of the mixture was kept below 30 °C by adding ice. At the end of the addition, the mixture was stirred at RT for 40 minutes then extracted with EtOAc (3 x 200 mL). The organic phases were

combined, washed with an aqueous saturated solution of $NaHCO_3$ (200 mL) then brine (200 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The brown oil obtained was purified by column chromatography to give **compound 332** as yellow oil (2.71 g, 85% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 6.84 (s, 1H), 4.49 (s, 2H), 3.87 (s, 3H), 2.77 (s, 3H), 1.40 (s, 9H).

Step 6:

Compound 332 (2.71 g, 10.8 mmol) was dissolved in DCM (15 mL) and the solution was cooled at 0°C. HCl (4 M in dioxane, 15 mL, 60 mmol) was added drop wise, the solution was stirred at 0°C for 10 minutes then at room temperature for 3 hours. The suspension obtained was concentrated under vacuum until obtaining half of the initial volume. The suspension was filtered, the solids were rinsed with DCM (10 mL) and dried to give **compound 333** hydrochloride as a white solid (1.80 g, 90% yield). ^1H NMR (400 MHz, Methanol-d_4) δ 6.99 (s, 1H), 4.42 (s, 2H), 4.03 (s, 3H), 2.81 (s, 3H).

Preparation of 1-[5-fluoro-2-(pent-4-yn-1-yloxy)phenyl]ethanol (336).



334 **335** **336**

Step 1:

1-(5-fluoro-2-hydroxyphenyl)ethanone **334** (5.0 g, 32.5 mmol), K_2CO_3 (8.96 g, 64.9 mmol) and KI (8.08 g, 48.7 mmol) were mixed in DMF (150 mL). 5-chloropent-1-yne (5.15 mL, 48.7 mmol) was added and the mixture was heated at 80 °C for 18 hours. LC-MS showed full conversion. The mixture was cooled at RT and EtOAc (1 L) was added then washed with water (6 x 200 mL). The organic phase was dried over MgSO4, filtered and concentrated under vacuum. The oil obtained was purified by column chromatography (eluents heptanes/EtOAc from 6:1 to 3:1) to give **compound 335** as pale yellow oil (6.82 g, 95% yield, 100% purity by LC-MS). ^1H NMR (400 MHz, DMSO-d6) δ 7.45 – 7.31 (m, 2H), 7.20 (dd, J = 9.1, 4.2 Hz, 1H), 4.15 (t, J = 6.1 Hz, 2H), 2.83 (t, J = 2.7 Hz, 1H), 2.55 (s, 3H), 2.37 (td, J = 7.1, 2.7 Hz, 2H), 2.10 – 1.85 (m, 2H).

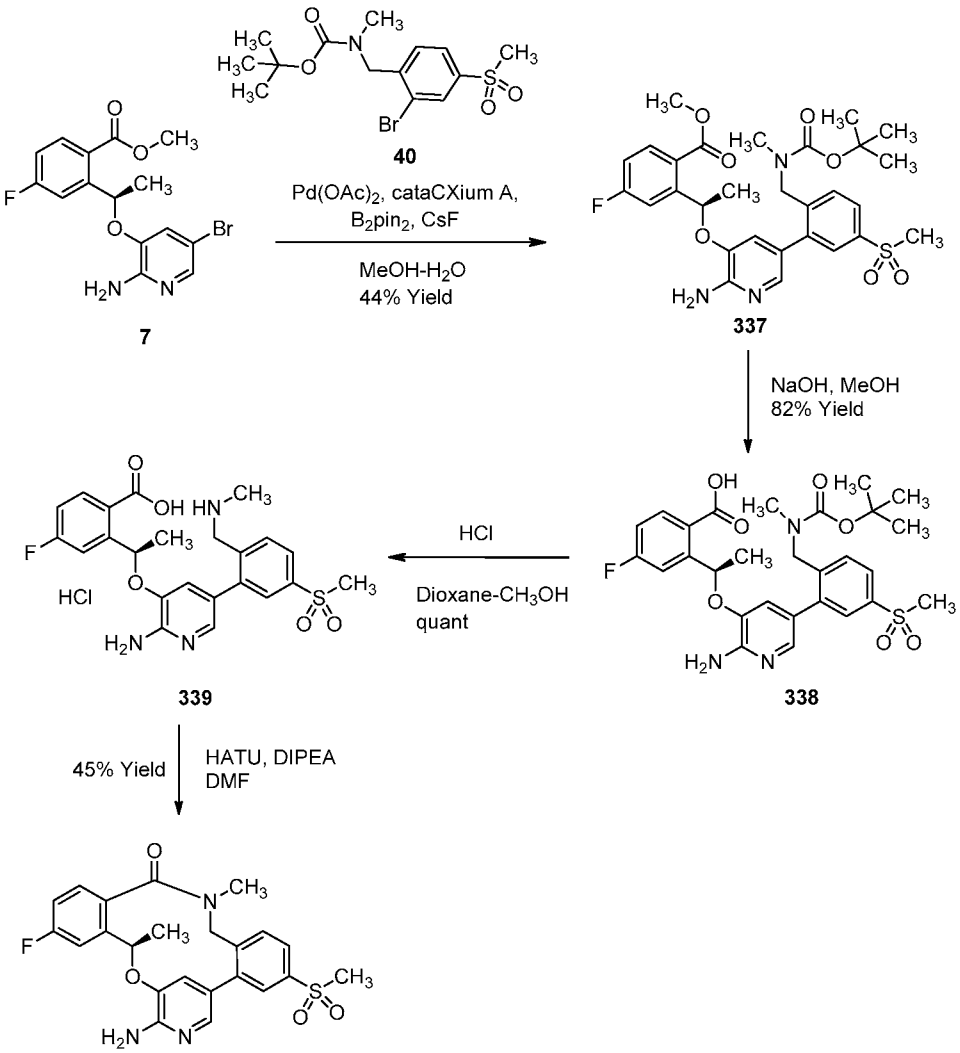
Step 2:

Compound 335 (6.62 g, 30.1 mmol) was dissolved in MeOH (120 mL). The solution was cooled at 0 °C and NaBH4 (1.47 g, 39.1 mmol) was added portion wise. The mixture was stirred at 0 °C for 1 hour the RT for 30 minutes. TLC showed full completion. Water (300 mL) was added slowly to the mixture and was extracted with EtOAc (2 x 200 mL). The organic phases were combined, dried over MgSO4, filtered and concentrated under vacuum. The oil obtained was purified by column chromatography (eluents heptanes/EtOAc from 9:1 to 3:1) to give **compound 336** as

pale yellow oil (6.04 g, 90% yield, 97% purity by LC-MS). ^{1}H NMR (400 MHz, DMSO-d6) δ 7.17 (dd, J = 9.7, 3.1 Hz, 1H), 7.05 – 6.85 (m, 2H), 5.13 (d, J = 3.9 Hz, 1H), 4.95 (p, J = 6.2 Hz, 1H), 4.12 – 3.91 (m, 2H), 2.81 (t, J = 2.7 Hz, 1H), 2.34 (td, J = 7.1, 2.7 Hz, 2H), 1.96 – 1.84 (m, 2H), 1.26 (d, J = 6.3 Hz, 3H).

Examples

Preparation of (5*R*)-8-amino-3-fluoro-5,17-dimethyl-13-(methylsulfonyl)-16,17-dihydro-7,11-(metheno)dibenzo[*g*,*l*][1,4,10]oxadiazacyclotetradecin-18(5*H*)-one (Example 1).



Step 1:

Palladium (II) acetate (70 mg, 0.31 mmol) and cataCXium® A (221 mg, 0.62 mmol) were mixed together in toluene (2.5 mL, de-gassed) and the resulting solution was added *via* pipette to a stirred solution of **compound 7** (1.10 g, 3.1 mmol), bis-pinacolato diboron (1.6 g, 6.2 mmol) and

CsF (1.87 g, 12.4 mmol) in MeOH/H2O (4:1, 24 mL, de-gassed) at 50 °C. After 4 - 5 minutes, the reaction became dark grey/brown in color and a solution of **compound 40** (900 mg, 2.4 mmol) in methanol (5 mL, de-gassed) was added all at once. The resulting mixture was then stirred at reflux for 3 hrs, by which time TLC (EtOAc/cyclohexane 6:4) had shown complete consumption of both aryl bromides and conversion to a major new more polar spot (Rf = 0.35). After cooling to room temperature, the mixture was diluted with EtOAc (150 mL) and washed with water (100 mL), then brine (100 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography over silica gel, which was eluted with 6:4 EtOAc/cyclohexane, and gave **compound 110** as a light brown foam (950 mg). TLC: Rf = 0.35 (EtOAc/cyclohexane 6:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, 1 H, *J* = 9.1, 6.1 Hz), 7.83 - 7.84 (m, 1 H), 7.63 (d, 1 H, *J* = 2.1 Hz), 7.56 - 7.59 (m, 1 H), 7.34 - 7.37 (m, 1 H), 6.97 - 7.04 (m, 2 H), 6.58 - 6.61 (m, 1 H), 6.39 - 6.45 (m, 1 H), 4.98 (br s, 2 H), 4.05 - 4.30 (m, 2 H), 3.84 (br s, 3 H), 3.05 (br s, 3 H), 2.54 - 2.68 (m, 3 H), 1.67 (d, 3 H, *J* = 6.3 Hz), 1.32 - 1.51 (m, 9 H). LCMS ES *m/z* 588 $[M+H]^+$.

Step 2:

To a solution of **compound 337** (65% purity, 1.1 g, assumed 1.2 mmol) in MeOH (25 mL) was added NaOH (1.2 g, 30 mmol) and the mixture was stirred at room temperature overnight. The reaction was diluted with water (60 mL) and washed with MTBE (60 mL). The aqueous layer was then acidified carefully with 1 M aq HCl to approx pH 4 (pH paper). Sodium chloride (10 g) was added to the mixture and the mixture was extracted with EtOAc (80 mL). The organic layer was separated, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography over silica gel which was eluted with 2% AcOH in EtOAc, giving **compound 338** (550 mg, 82% yield) as an off white foam. TLC: Rf = 0.5 (2% AcOH in EtOAc). ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (dd, 1 H, *J* = 8.2, 5.8 Hz), 7.88 (dd, 1 H, *J* = 8.0, 1.7 Hz), 7.62 (s, 1 H), 7.40 - 7.44 (m, 2 H), 7.34 (dd, 1 H, *J* = 10.1, 2.7 Hz), 7.05 - 7.09 (m, 1 H), 6.90 - 6.83 (m, 1 H), 6.53 (br s, 1 H), 4.00 - 4.33 (m, 2 H), 3.12 (s, 3 H), 2.55 - 2.75 (m, 3 H), 1.70 (d, 3 H, *J* = 6.55 Hz), 1.25 - 1.48 (m, 9 H). LCMS ES *m/z* 574 $[M+H]^+$.

Step 3:

A solution of HCl in dioxane (4 M, 5.0 mL) was added to a solution of **compound 338** (550 mg, 0.96 mmol) in dioxane/MeOH (4:1, 15 mL) and the reaction was stirred at room temperature overnight. The reaction mixture was then concentrated to dryness under reduced pressure. The residue was taken-up in MeOH (50 mL) and toluene (100 mL) was added and the mixture was then again evaporated to dryness, which gave **compound 339** as an off white solid (500 mg, assumed quantitative yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (dd, 1 H, *J* = 8.0, 2.0 Hz), 8.06 (dd, 1 H, *J* = 8.9, 5.9 Hz), 7.85 (d, 1 H, *J* = 8.0 Hz), 7.78 (d, 1 H, *J* = 2.0 Hz), 7.56 (d, 1 H, *J*

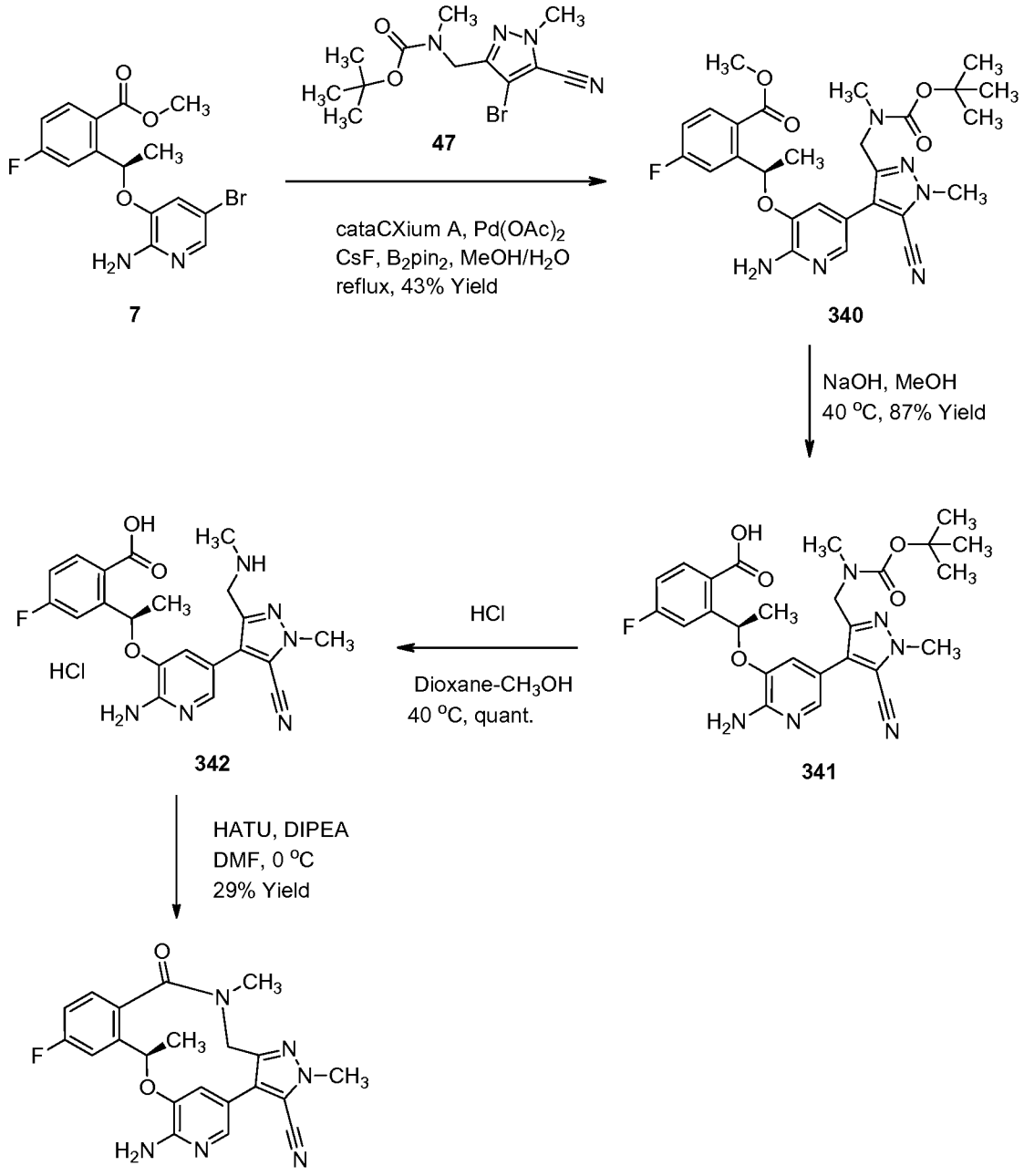
= 1.7 Hz), 7.48 (dd, 1 H, *J* = 9.9, 2.7 Hz), 7.26 (d, 1 H, *J* = 1.7 Hz), 7.19 (dt, 1 H, *J* = 8.31, 2.85 Hz), 6.70 (q, 1 H, *J* = 6.5 Hz), 4.19 (d, 1 H, *J*= 14.5 Hz), 4.13 (d, 1 H, *J* = 14.6 Hz), 3.17 (s, 3 H), 2.61 (s, 3 H), 1.76 (d, 3 H, *J* = 6.0 Hz). LCMS ES *m/z* 474 $[M+H]^+$.

Step 4:

A solution of **compound 339** (500 mg, assumed 0.96 mmol) as the HCl salt and DIPEA (2.0 g, 15.5 mmol) in DMF (6.0 mL) and THF (1.0 mL) was added drop-wise to a solution of HATU (510 mg, 1.34 mmol) in DMF (6.0 mL) at 0 °C over 35 minutes. After complete addition, the mixture was stirred at 0 °C for a further 60 mins. Water (100 mL) was added and the mixture was extracted into EtOAc (2 x 50 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL), dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel, which was eluted with 100% EtOAc, giving a sticky solid. The solids were dissolved in acetonitrile (2.5 mL) and MTBE (30 mL) was added slowly with good stirring to precipitate the product. After stirring for 20 minutes, the mixture was filtered, and **Example 1** was collected as a cream colored solid (200 mg, 45% yield). TLC: R_f = 0.5 (100% EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 - 7.92 (m, 3 H), 7.69 (dd, 1 H, *J* = 10.4, 2.8 Hz), 7.51 (d, 1 H, *J* = 2.0 Hz), 7.36 (dd, 1 H, *J* = 8.8, 6.0 Hz), 7.14 (dt, 1 H, *J* = 8.4, 2.4 Hz), 7.09 (d, 1 H, 2.0 Hz), 6.13 (s, 2H), 5.71 - 5.67 (m, 1 H), 4.45 (d, 1 H, *J* = 13.2 Hz), 4.22 (d, 1 H, *J* = 13.2 Hz), 3.29 (s, 3 H), 3.01 (s, 3 H), 1.69 (d, 3 H, *J* = 6.4 Hz). LCMS ES *m/z* 456 $[M+H]^+$.

Crystals of **Example 1** were grown by vapor diffusion of pentane into an ethanol solution, and data were collected in a nitrogen gas stream at 120(2) K. See Figure 1.

Preparation of (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 2).



Example 2

Step 1:

Palladium (II) acetate (53 mg, 0.24 mmol) and cataCXium® A (180 mg, 0.5 mmol) were mixed together in toluene (1.5 mL, de-gassed) and the resulting solution was added *via* pipette to a stirred solution of **compound 7** (0.9 g, 2.4 mmol), **compound 47** (1.0 g, 3.0 mmol) bis-pinacolato diboron (0.9 g, 3.6 mmol) and CsF (1.9 g, 12.6 mmol) in MeOH/H_2O (9:1, 12 mL, de-gassed) at 60 °C. The resulting mixture was then stirred at reflux for 3 hrs. A further portion of Palladium (II) acetate (26 mg, 0.12 mmol) and cataCXium® A (90 mg, 0.25 mmol) in toluene (1.5 mL, de-gassed) was added, and the yellow reaction mixture stirred at 60 °C overnight. After

cooling to room temperature, the mixture was diluted with EtOAc (150 mL) and filtered through celite. The filtrate was washed with water (100 mL), then brine (100 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography over silica gel, which was eluted with 1:1 EtOAc/cyclohexane, and gave **compound 340** as a yellow oil (570 mg, 43% yield). TLC (Rf = 0.40, 1:1 EtOAc/cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 1 H), 7.65 (s, 1 H), 7.27 (dd,1 H, *J* = 9.9, 2.7 Hz), 7.01 (m, 1 H), 6.68 (m, 1 H), 6.40 (m, 1 H), 4.90 (br s, 2 H), 4.20 - 4.30 (m, 2 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 2.55 - 2.85 (m, 3 H), 1.68 (d, 3 H, *J* = 6.6 Hz), 1.24 (s, 9 H). LCMS ES *m/z* 539 $[M+H]^+$.

Step 2:

To a solution of **compound 340** (69% purity, 0.95 g, assumed 1.05 mmol) in MeOH (20 mL) was added a solution NaOH (1.0 g, 25 mmol) in water (2 mL). The mixture was stirred at 40 °C for 3.5 hours. The reaction was diluted with water (80 mL), concentrated by 20 mL to remove MeOH on the rotorvap, and washed with MTBE (100 mL). The aqueous layer was then acidified carefully with 1 M aq HCl to approx pH 2 (pH paper). Sodium chloride (15 g) was added to the mixture and the mixture was extracted with EtOAc (100 mL). The organic layer was separated, dried (Na_2SO_4) and evaporated to give **compound 341** as a pale yellow solid (480 mg, 87% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.05 (m, 1 H), 7.45 (s, 1 H), 7.37 (dd,1 H, *J* = 10.4, 2.8 Hz), 7.10 (dt, 1 H, *J* = 8.5, 2.4 Hz), 6.50 - 6.60 (m, 2 H), 4.05 - 4.30 (m, 2 H), 3.99 (s, 3 H), 2.60 - 2.80 (m, 3 H), 1.72 (d, 3 H, *J* = 6.5 Hz). LCMS ES *m/z* 525 $[M+H]^+$.

Step 3:

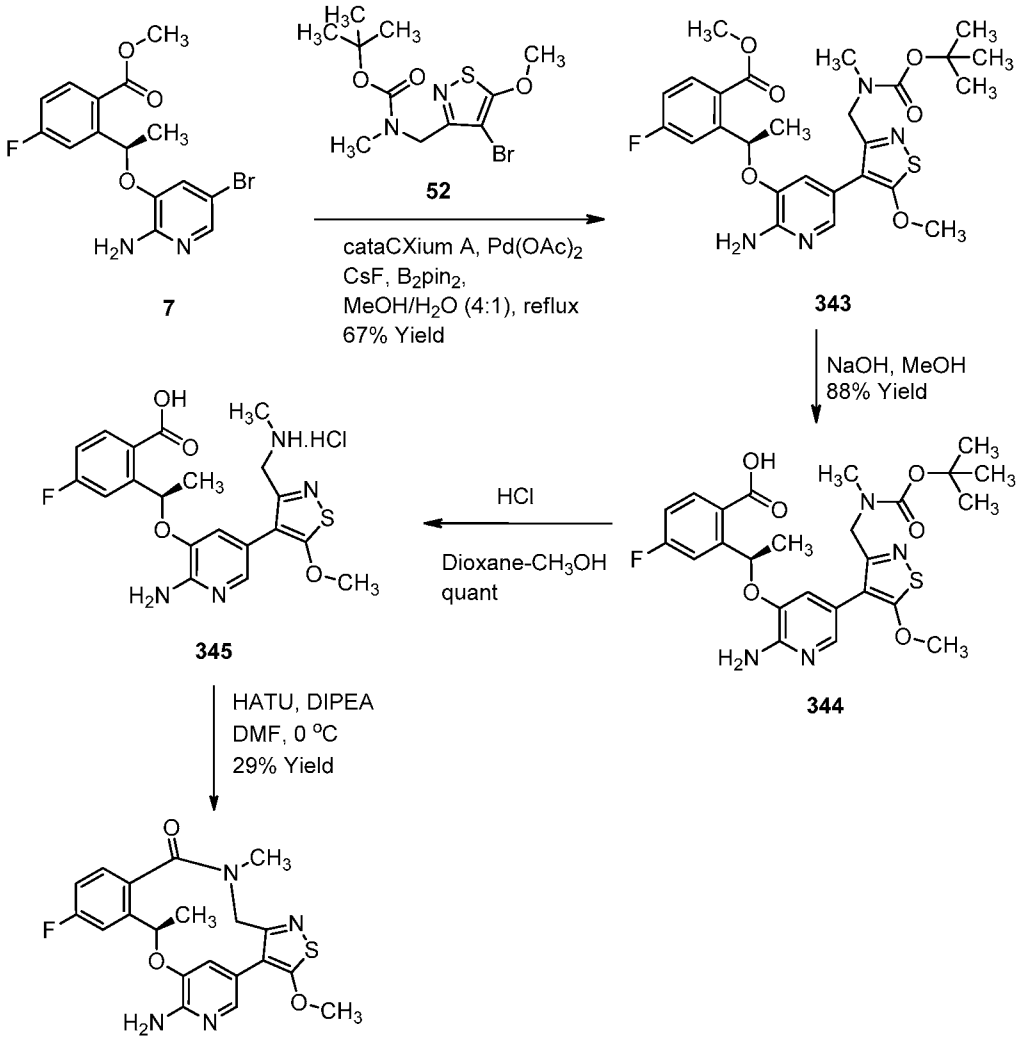
A solution of HCl in dioxane (4 M, 6.0 mL) was added to a solution of **compound 341** (480 mg, 0.91 mmol) in MeOH (6 mL) and the reaction was stirred at 40 °C for 2.5 hours. The reaction mixture was then concentrated to dryness under reduced pressure. The residue was taken-up in MeOH (50 mL) and acetonitrile (100 mL) was added and the mixture was then again evaporated to dryness, to give **compound 342** as an off white solid (400 mg, 87% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.07 (dd, 1 H, *J* = 8.9. 5.9 Hz), 7.51 (d, 1 H, *J* = 1.7 Hz), 7.42 (dd, 1 H, *J* = 9.8, 2.6 Hz), 7.23 (d, 1 H, *J* = 1.6 Hz), 7.16 (dt, 1 H, *J* = 8.5, 2.7 Hz), 6.73 (dd, 1 H, *J* = 11.9, 6.9 Hz), 4.22 (d, 1 H, *J* = 14.7 Hz), 4.14 (d, 1 H, *J* = 14.7 Hz), 4.07 (s, 3 H), 2.75 (s, 3 H), 1.75 (d, 3 H, *J* = 5.5 Hz). LCMS ES *m/z* 425 $[M+H]^+$.

Step 4:

A solution of **compound 342** (400 mg, assumed 0.91 mmol) as the HCl salt and DIPEA (1.17 g, 9.1 mmol) in DMF (5.0 mL) and THF (0.5 mL) was added drop-wise to a solution of HATU (482 mg, 1.27 mmol) in DMF (10.0 mL) at 0 °C over 30 minutes. After complete addition, the mixture was stirred at 0 °C for a further 30 mins. Water (70 mL) was added and the mixture was extracted into EtOAc (2 x 60 mL). The combined organics were washed with saturated aqueous

$NaHCO_3$ (2 x 100 mL), brine (100 mL), dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography over silica gel, which was eluted with 70% EtOAc/cyclohexane giving 205mg of a pale yellow residue (semi-solid). The solids were dissolved in MTBE (7 mL) and cyclohexane (20 mL) was added slowly with good stirring to precipitate the product. After stirring for 30 minutes, the mixture was filtered, and **Example 2** was collected as a white solid (110 mg, 29% yield). TLC (Rf = 0.40, 70% EtOAc in cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, 1 H, *J* = 2.0 Hz), 7.30 (dd, 1 H, *J* = 9.6, 2.4 Hz), 7.21 (dd, 1 H, *J* = 8.4, 5.6 Hz), 6.99 (dt, 1 H, *J* = 8.0, 2.8 Hz), 6.86 (d, 1 H, *J* = 1.2 Hz), 5.75 - 5.71 (m, 1 H), 4.84 (s, 2 H), 4.45 (d, 1 H, *J* = 14.4 Hz), 4.35 (d ,1 H, *J* = 14.4 Hz), 4.07 (s, 3 H), 3.13 (s, 3 H), 1.79 (d, 3 H, *J* = 6.4Hz). LCMS ES *m/z* 407 $[M+H]^+$.

Preparation of (10*R*)-7-amino-12-fluoro-3-methoxy-10,16-dimethyl-16,17-dihydro-8,4-(metheno)isothiazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 3).



Step 1:

The procedure described in step 1 for **Example 1** was used to prepare **compound 343** (1.3 g, 67% Yield). TLC (R_f = 0.30, 1:1 EtOAc/cyclohexane). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (m, 1 H), 7.52 (dd, 1 H, *J* = 10.4, 3.0 Hz), 7.41 (m, 1 H),7.25 (m, 1 H), 6.60 (m, 1 H), 6.20 (m, 1 H), 6.00 - 6.05 (m, 2 H), 4.00 - 4.25 (m, 2 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 2.70 - 2.78 (m, 3 H), 1.60 (d, 3 H, *J* = 6.7 Hz),1.08 - 1.38 (m, 9 H). LCMS ES *m/z* 547 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 1** was used to prepare **compound 344** (600 mg, 88% yield). TLC: R_f = 0.25 (EtOAc + 1% AcOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 - 8.10 (m, 3 H), 7.50 - 7.60 (m, 2 H), 7.25 (m, 1 H), 6.95 - 7.10 (m, 1 H), 6.52 (m, 1 H), 4.10 - 4.40 (m, 2 H), 3.91 (s, 3 H), 2.50 - 2.75 (m, 3 H), 1.65 (d, 3 H), 1.08 - 1.30 (m, 9 H). LCMS ES *m/z* 533 $[M+H]^+$.

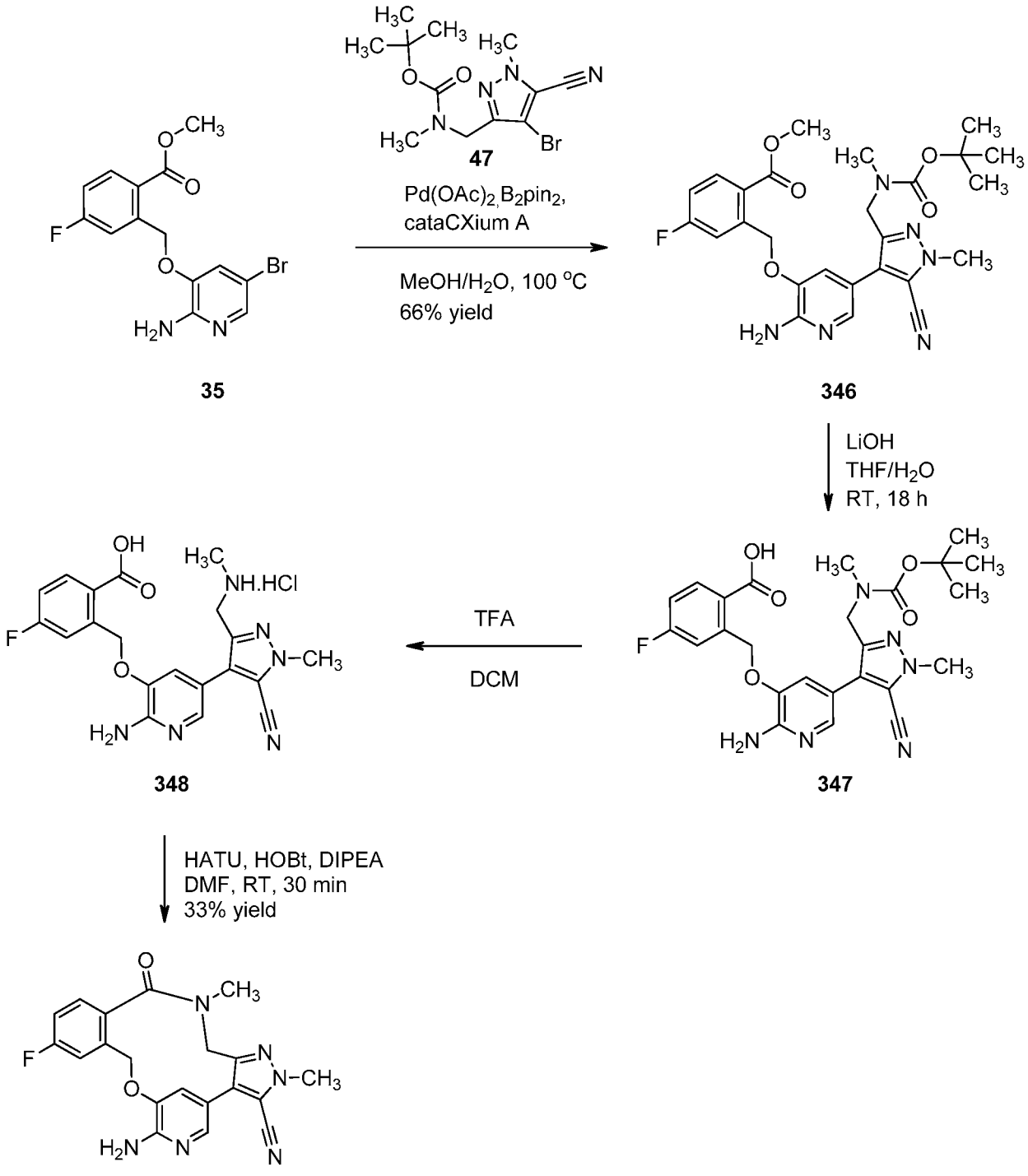
Step 3:

The procedure described in step 3 for **Example 1** was used to prepare **compound 345** (540 mg, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (br s, 2 H), 8.10 - 8.30 (m, 2 H), 8.03 (dd, 1 H, *J* = 9.4, 6.8 Hz), 7.65 (m, 1 H), 7.56 (dd, 1 H, *J* = 11.1, 2.6 Hz), 7.28 (dt, 1 H, *J* = 7.9, 2.8 Hz), 7.10 (s, 1 H), 6.52 (q, 1 H, *J* = 6.7 Hz), 4.00 - 4.20 (m, 2 H), 3.94 (s, 3 H), 2.54 - 2.57 (m, 3 H), 1.66 (d, 3 H, *J* = 6.1 Hz). LCMS ES *m/z* 433 $[M+H]^+$.

Step 4:

The procedure described in step 4 for **Example 1** was used to prepare **Example 3** (130 mg, 29% yield). TLC (R_f = 0.40, 100% EtOAc). ^{1}H NMR (400 MHz, DMSOd_6) δ 7.63 (dd, 1 H, *J* = 12.0, 4.0 Hz), 7.50 (d, 1 H, *J* = 1.6 Hz), 7.42 (dd,1 H, *J* = 8.4, 5.6 Hz), 7.13 (dt, 1 H, *J* = 8.4, 2.8 Hz), 6.82 (d, 1 H, *J* = 1.6 Hz), 5.96 (s, 2 H), 5.66 - 5.62 (m, 1 H), 4.31 (d, 1 H, *J* = 13.5 Hz), 4.18 (d, 1 H, *J* =13.5 Hz), 4.05 (s, 3 H), 3.03 (s, 3 H), 1.67 (d, 3 H, *J* = 6.4 Hz). LCMS ES *m/z* 415 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-2,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 4).



Example 4

Step 1:

The procedure described in step 1 for **Example 1** was used to prepare **compound 346** (232 mg, 54% Yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 - 8.12 (m, 2 H), 7.69 - 7.75 (m, 1 H), 7.36 (dd, 1 H), 7.07 (td, 1 H), 5.56 (br s, 2 H), 5.07 (br s, 0.2 H), 4.94 (br s, 1.8 H), 4.50 (br s, 2 H), 4.02 (s, 3 H), 3.90 (s, 3 H), 2.71 (br s, 3 H), 1.35 (br s, 9 H). LCMS ES *m/z* 525 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 1** was used to prepare **compound 347**, where LiOH was used instead of NaOH (210 mg, quantitative yield). LCMS ES *m/z* 511 $[M+H]^+$.

Step 3:

Compound 347 (210 mg, ~0.44 mmol) was dissolved in DCM (6 mL) and TFA (0.12 mL, 1.6 mmol) was added. The mixture was stirred at RT for 18 hours. TFA (0.06 mL, 0.8 mmol) was added and the mixture was stirred at RT for 2 hours. LCMS showed consumption of **compound 347**. The reaction was concentrated under vacuum and diethyl ether (3 mL) and MTBE (3 mL) were added. The mixture was stirred at RT for 1 hour and decanted. The mother liquors were removed and the white solids obtained were dried under vacuum to give **compound 348** (216 mg, quantitative yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 - 8.13 (m, 1 H), 7.66 (br s, 1 H), 7.58 - 7.49 (m, 2 H), 7.26 - 7.18 (m, 1 H), 5.80 - 5.77 (m, 2 H), 4.30 (s, 1 H), 4.11 (s, 2 H), 4.05 (s, 1 H), 3.21 (s, 3 H), 2.77 (s, 3 H). LCMS ES *m/z* 411 $[M+H]^+$.

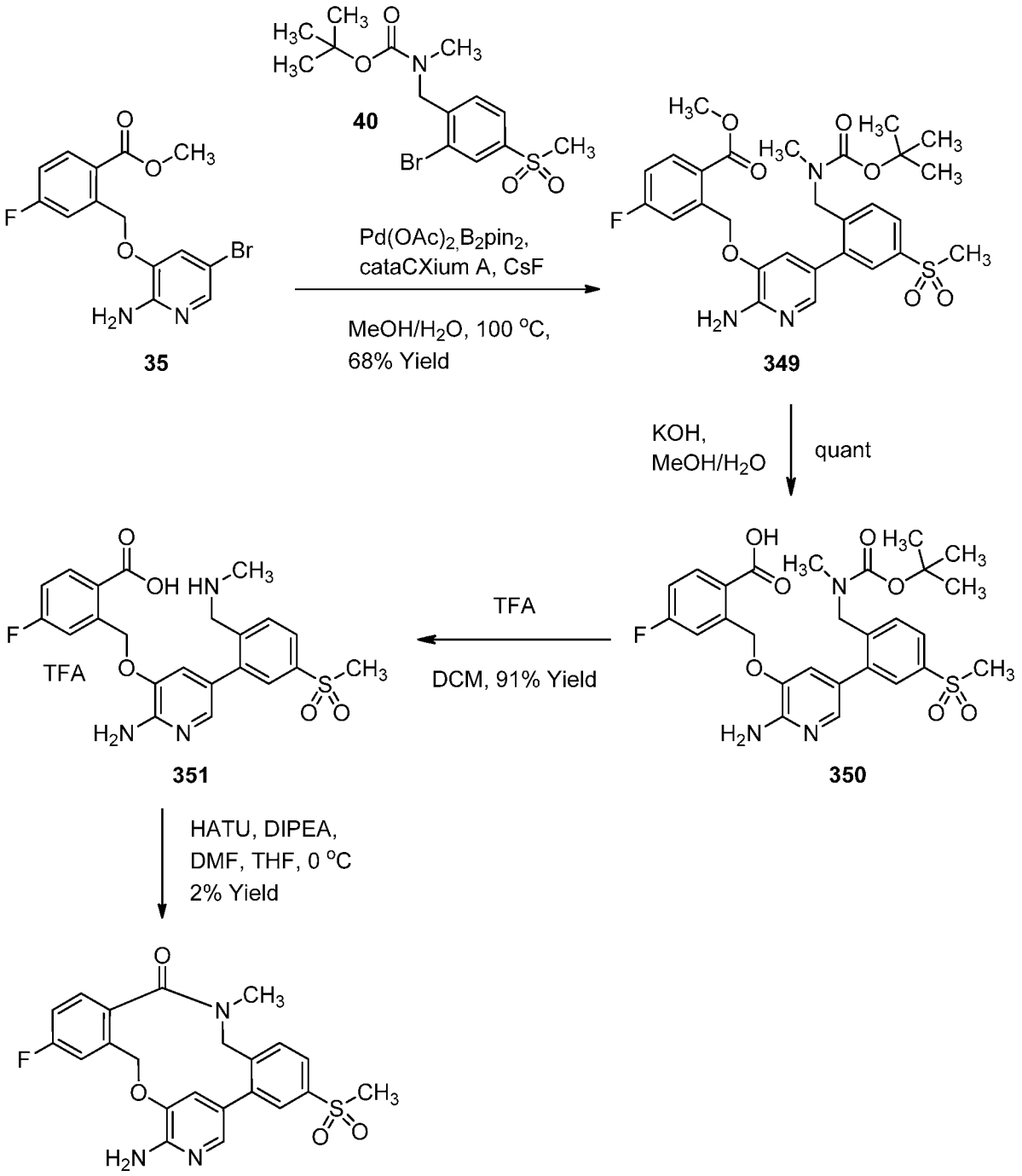
Step 4:

HATU (380 mg, 0.99 mmol) and HOBt (20 mg, cat.) were dissolved in DMF (10 mL). A solution of **compound 348** (210 mg, ~0.33 mmol) and DIPEA (0.42 mL, 2.31 mmol) in DMF (10 mL) was added dropwise over 25 min. At the end of the addition, LCMS showed consumption of the SM. Brine (100 mL) was added and extracted with ethyl acetate (6 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography over silica gel, which was eluted with cyclohexane and ethyl acetate (1:1 to 0:1), gave **Example 4** (45 mg, 35% yield over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 1 H, *J* = 1.6 Hz), 7.34 (dd, 1 H, *J* = 9.2, 2.4 Hz), 7.22 - 7.27 (m, 1 H), 7.02 (td, 1 H, *J* = 8.4, 2.8 Hz), 6.84 (d, 1 H, *J* = 2.0 Hz), 5.49 (dd, 1 H, *J* = 13.6, 1.6 Hz), 5.23 (d, 1 H, *J* = 13.6 Hz), 4.88 (br s, 2 H), 4.48 (d, 1 H, *J* = 14.4 Hz), 4.38 (d, 1 H, *J* = 14.4 Hz), 4.07 (s, 3 H), 3.12 (s, 3 H). LCMS ES *m/z* 393 $[M+H]^+$. The analytical chiral separation by SFC was performed using a Chiralpak OD-H (4.6 mm x 250 mm column , 5 micron particle size), which was eluted with 30% MeOH in CO_2 held at 35 °C at 140 bar. A flow rate of 3 mL/minutes gave $Rt_{(Peak\ 1)}$ = 4.3 minutes ($[\alpha]_d^{20}$= -121.4° (C=0.23, MeOH) and $Rt_{(Peak\ 2)}$ = 5.4 minutes ($[\alpha]_d^{20}$= 103.3° (C=0.23, MeOH).

Example 4a (Atropisomer peak 1): 91.6% ee. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.45 - 7.63 (3 H, m), 7.17 - 7.27 (1 H, m), 6.77 (1 H, s), 6.20 (2 H, br s), 5.29 (1 H, d, *J* = 14.3 Hz), 5.24 (1 H, d, *J* = 13.2 Hz), 4.46 (1 H, d, *J* = 14.2 Hz), 4.23 (1 H, d, *J* = 15.3 Hz), 4.02 (3 H, s), 2.97 (3 H, s).

Example 4b (Atropisomer peak 2): 89.6% ee. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.45 - 7.62 (3 H, m), 7.18 - 7.27 (1 H, m), 6.77 (1 H, s), 6.20 (2 H, br s), 5.30 (1 H, d, *J* = 14.3 Hz), 5.24 (1 H, d, *J* = 13.2 Hz), 4.46 (1 H, d, *J* = 14.2 Hz), 4.23 (1 H, d, *J* = 14.2 Hz), 4.02 (3 H, s), 2.97 (3 H, s).

Preparation of 8-amino-3-fluoro-17-methyl-13-(methylsulfonyl)-16,17-dihydro-7,11-(metheno)dibenzo[*g*,*l*][1,4,10]oxadiazacyclotetradecin-18(5*H*)-one (Example 5).



Example 5

Step 1:

The procedure described in step 1 for **Example 1** was used to prepare **compound 349** (312 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, 1 H, *J* = 8.4, 5.8 Hz), 7.89 (dd, 1 H, *J* = 8.0, 1.6 Hz), 7.77 (d, 1 H, *J* = 2.0 Hz), 7.63 (br s, 1 H), 7.43 (d, 1 H, *J* = 8.4 Hz), 7.39 (br d, 1 H,

J = 10.0 Hz), 7.08 (dt, 1 H, *J* = 8.4, 2.4 Hz), 6.86 - 6.89 (m, 1 H), 5.55 (s, 2 H), 4.92 (br s, 2 H), 4.34 - 4.42 (m, 2 H), 3.89 (s, 3 H), 3.08 (s, 3 H), 2.68 - 2.76 (m, 3 H), 1.38 - 1.47 (m, 9 H). LCMS ES *m/z* 574 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 1** was used to prepare **compound 350**, where KOH was used instead of NaOH (200 mg, 67% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (dd, 1 H, *J* = 8.8, 6.0 Hz), 7.98 (dd, 1 H, *J* = 7.6, 2.0 Hz), 7.78 (d, 1 H, *J* = 2.0 Hz), 7.63 - 7.70 (m, 2 H), 7.46 - 7.50 (m, 2 H), 7.29 (dt, 1 H, *J* = 2.8, 8.4 Hz), 5.65 (s, 2 H), 5.39 - 4.41 (m, 2 H), 3.25 (s, 3 H), 2.66 (br s, 3 H), 1.25 - 1.36 (m, 9 H). LCMS ES *m/z* 560 $[M+H]^+$.

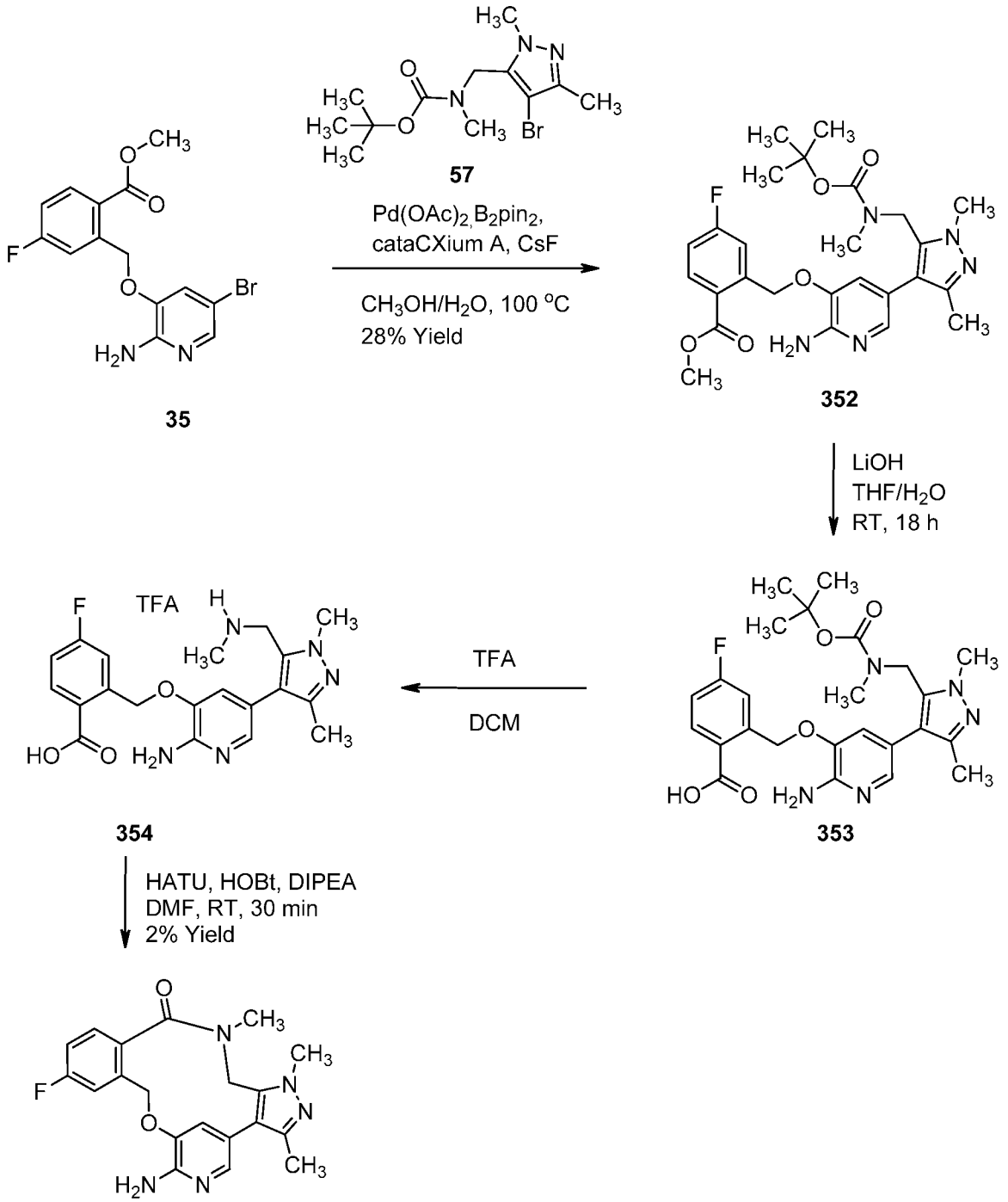
Step 3:

The procedure described in step 3 for **Example 4** was used to prepare **compound 351** (170 mg, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 - 9.32 (m, 2 H), 8.02 - 8.09 (m, 3 H), 7.88 (d, 1 H, *J* = 2.0 Hz), 7.70 - 7.73 (m, 2 H), 7.54 (s, 1 H), 7.30 - 7.33 (m,1 H), 5.65 (s, 2 H), 4.13 - 4.15 (m, 2 H), 3.30 (s, 3 H), 3.17 (s, 3 H). LCMS ES *m/z* 460 $[M+H]^+$.

Step 4:

A solution of **compound 351** (527 mg, 1.1 mmol) and DIPEA (2.24 mL, 15.9 mmol) in DMF (9 mL) and THF (1 mL) at -10 °C was added drop-wise over 10 minutes to a stirred solution of HATU (566 mg, 1.5 mmol) in DMF (9 mL) cooled under an ice/NaCl/MeOH bath. LCMS showed complete consumption of **compound 351**. Water (30 mL) and EtOAc (30 mL) were added and the mixture saturated by addition of NaCl. The phases were separated and the aqueous layer was again extracted with EtOAc (3 x 30 mL). The organic layers were combined, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was purified by column chromatography over silica gel, which was eluted with EtOAc/heptane (8:2 to 1:0 then EtOAc/MeOH 9:1) to give a fraction containing **Example 5** (110 mg, ~70% purity but contaminated with DMF) and a more polar fraction (major component of the crude mixture, 83 mg, white solid, $[M+H]^+$ 883) likely to be the cyclised dimer. The former fraction was further purified by reverse phase chromatography to give **Example 5** as a white solid (10 mg, 2% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, 1 H, *J* = 2.0 Hz), 7.92 (dd, 1 H, *J* = 8.0, 2.0 Hz), 7.65 (d, 1 H, *J* = 8.0 Hz), 7.59 (d, 1 H, *J* = 2.0 Hz), 7.33 (dd, 1 H, *J* = 9.2, 2.8 Hz), 7.21 (dd, 1 H, *J* = 8.6, 5.4 Hz), 7.11 (d, 1 H, *J* = 1.6 Hz), 7.00 (dt, 1 H, *J* = 8.4, 2.4 Hz), 5.59 (dd, 1 H, *J* = 13.6, 2.0 Hz), 5.22 (d, 1 H, *J* = 13.6 Hz), 4.84 (br s, 2 H), 4.63 (d, 1 H, *J* = 13.2 Hz), 4.28 (d, 1 H, *J* = 13.2 Hz), 3.12 (s, 3 H), 3.11 (s, 3 H).

Preparation of 7-amino-12-fluoro-1,3,16-trimethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 6).



Example 6

Step 1:

The procedure described in step 1 for **Example 1** was used to prepare **compound 352** (350 mg, 28% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, 1 H, *J* = 8.8, 6.0 Hz), 7.55 (s, 1 H), 7.35 (dd, 1 H, *J* = 10.0, 2.8 Hz), 7.06 (td, 1 H, *J* = 8.4, 2.4 Hz), 6.74 (d, 1 H, *J* = 1.6 Hz), 5.54 (s, 2 H), 4.81 (s, 2 H), 4.40 (s, 2 H), 3.89 (s, 3 H), 3.79 (s, 3 H), 2.45 (s, 3 H), 2.10 (s, 3 H), 1.45 (s, 9 H). LCMS ES *m/z* 514 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 1** was used to prepare **compound 353**, where LiOH was used instead of NaOH (310 mg, 88% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 - 7.85 (m, 1 H), 7.36 (s, 1 H), 7.24 (dd,1 H, *J* = 10.0, 2.4 Hz), 6.99 (td, 1 H, *J*= 8.4, 2.4 Hz), 6.87 (s, 1 H), 5.60 (s, 2 H), 4.37 (s, 2 H), 3.75 (s, 3 H), 2.40 (s, 3 H), 2.04 - 2.00 (m, 3 H), 1.42 (s, 9 H). LCMS ES *m/z* 500 $[M+H]^+$.

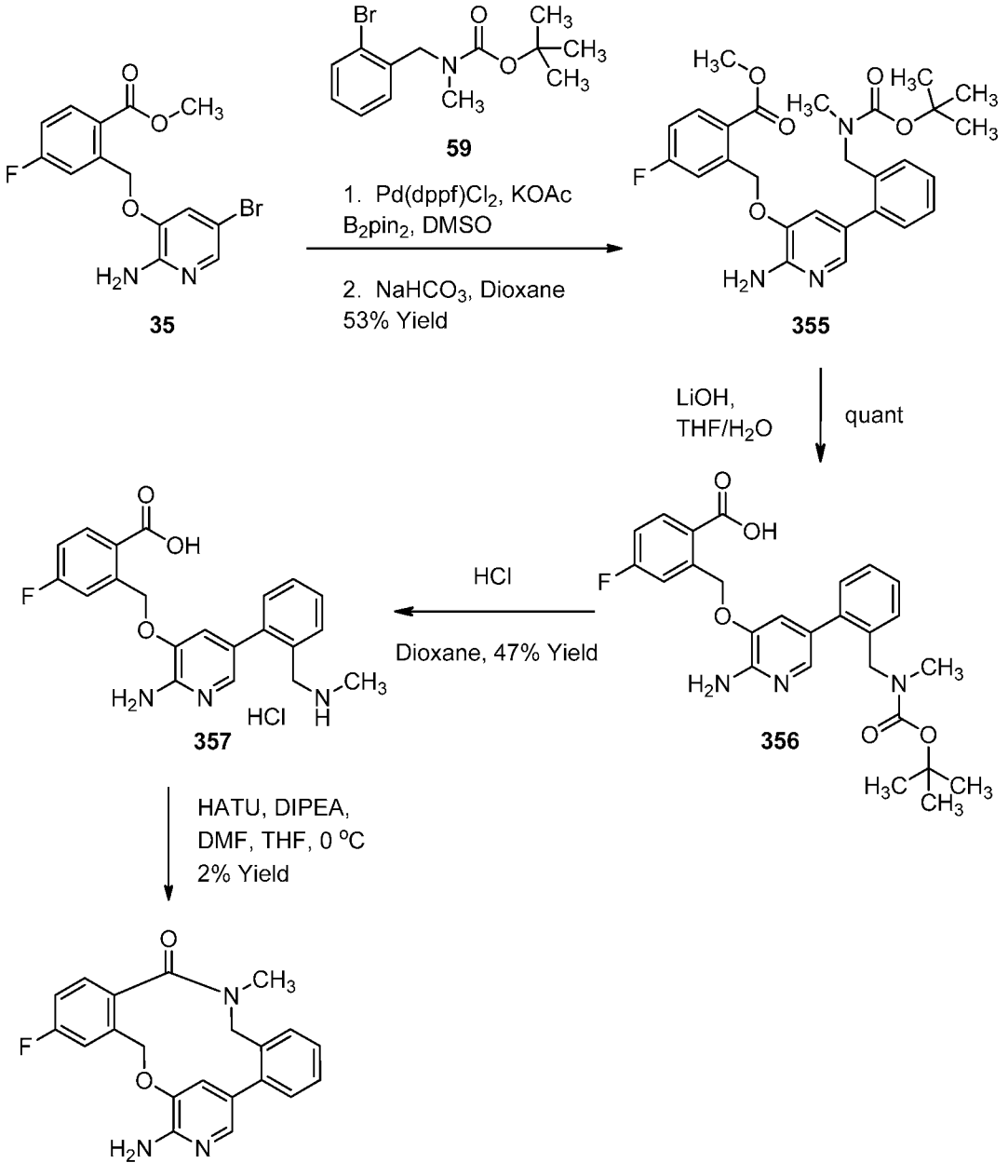
Step 3:

The procedure described in step 3 for **Example 4** was used to prepare **compound 354** (408 mg, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (br s, 2 H), 8.06 (dd, 1 H, *J* = 8.4, 6.0 Hz), 7.67 (dd, 1 H, *J* = 10.0, 2.4 Hz), 7.57 (d, 1 H, *J* = 1.6 Hz), 7.26 - 7.35 (m, 2 H), 5.65 (s, 2 H), 4.20 (br s, 2 H), 3.86 (s, 3 H), 2.44 (br s, 3 H), 2.05 (s, 3 H). LCMS ES *m/z* 400 $[M+H]^+$.

Step 4:

The procedure described in step 4 for **Example 4,** performed at 0 °C, was used to prepare compound **Example 6** (130 mg, 29% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (dd, 1 H, *J* = 9.6, 2.4 Hz), 7.44 - 7.38 (m, 2 H), 7.22 (td, 1 H, *J* = 8.4, 2.8 Hz), 6.73 (d, 1 H, *J* = 1.6 Hz), 5.82 (br s, 2 H), 5.30 (d, 1 H, *J* = 13.6 Hz), 5.17 (d, 1 H, *J* = 13.6 Hz), 4.65 (d, 1 H, *J* = 15.2 Hz), 4.20 (d, 1 H, *J* = 15.2 Hz), 3.89 (s, 3 H), 2.97 (s, 3 H), 2.54 (s, 1 H), 2.22 (s, 3 H). LCMS ES *m/z* 382 $[M+H]^+$.

Preparation of 8-amino-3-fluoro-17-methyl-16,17-dihydro-7,11-(metheno)dibenzo[*g*,*l*]-[1,4,10]oxadiazacyclotetradecin-18(5*H*)-one (Example 7).



Example 7

Step 1:

To a degassed solution of **compound 35** (350 mg, 0.99 mmol), bis(neopentylglycolato)diboron (289 mg, 1.3 mmol) and KOAc (339 mg, 3.4 mmol) in DMSO (10 mL) was added $Pd(dppf)Cl_2$ (80 mg, 0.1 mmol). The resulting mixture was stirred at 75 °C for 1 h. LCMS analysis indicated that the boronic acid intermediate was formed. After cooling to RT, **compound 59** (311 mg, 1.03 mmol) and $NaHCO_3$ (aq) (1 M solution, 3.0 mL, 3.0 mmol) and dioxane (10 mL) were added. The mixture was degassed, followed by the addition of $Pd(dppf)Cl_2$ (80 mg, 0.1 mmol). The resulting mixture was stirred at 80 °C for 2 hours and concentrated *in vacuo*, ethyl acetate (100 mL) and water (150 mL) were added and then partitioned. The aqueous was extracted with

EtOAc (2 x 100 mL), and the combined organic layers were washed with brine (400 mL), dried over $MgSO_4$, and then concentrated *in vacuo*. Purification by flash column chromatography over silica gel, which was eluted with 1% MeOH and 10% heptane in DCM, gave **compound 355** as a yellow solid (260 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, 1 H), 7.66 (s, 1 H), 7.16 - 7.30 (m, 5 H), 7.05 (ddd, 1 H), 6.86 (d, 1 H), 5.53 (s, 2 H), 4.80 (br s, 2H), 4.33 (br s, 2 H), 3.96 (s, 3 H), 2.63 (br d, 3 H), 1.42 (br d, 9 H). LCMS ES *m/z* 440 $[M-^tBu]^+$.

Step 2:

The procedure described in step 2 for **Example 1** was used to prepare **compound 356**, where LiOH was used instead of NaOH (123 mg, quantitative yield). LCMS ES *m/z* 482 $[M+H]^+$.

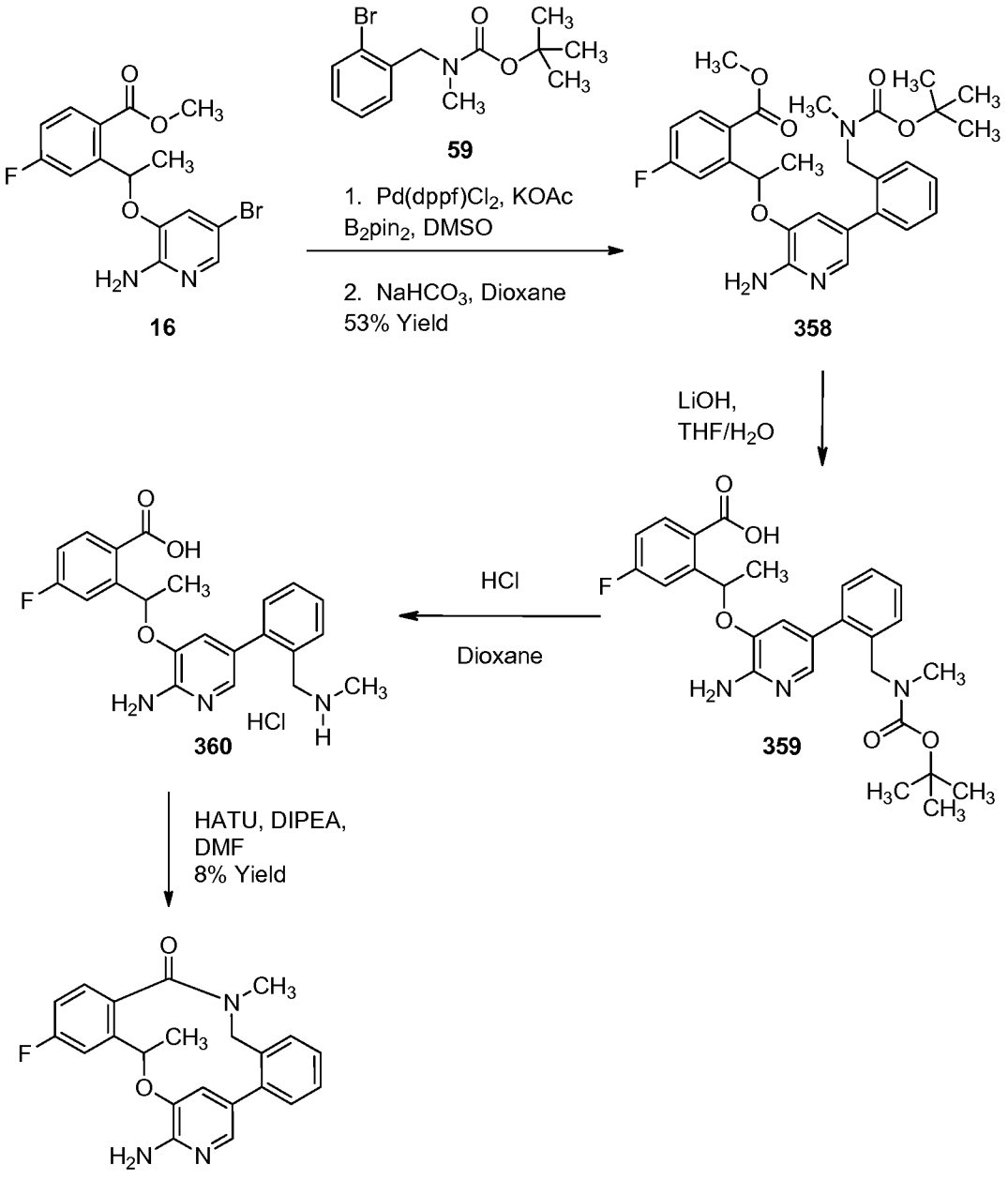
Step 3:

The procedure described in step 3 for **Example 1** was used to prepare **compound 357** (36 mg, 47% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (dd, 1 H), 7.63 (m, 1 H), 7.45 (m, 3 H), 7.32 (m, 2 H), 7.22 (d, 1 H), 7.02 (ddd, 1 H), 5.55 (s, 2 H), 4.08 (s, 2 H), 2.56 (s, 3 H). LCMS ES *m/z* 383 $[M+H]^+$.

Step 4:

To a suspension of **compound 357** (36 mg, 0.09 mmol) in DMF (6 mL) was added DIPEA (84 µL, 0.48 mmol) followed by HATU (72 mg, 0.19 mmol). The resulting solution was stirred at room temperature for 30 minutes. LCMS analysis indicated that a mixture of the desired product and a dimer was formed (ratio 2:1). After being concentrated *in vacuo*, the residue was purified by reverse phase prep-HPLC (water/MeCN gradient, 30 min run), to yield **Example 7** as a brown solid (14 mg, 41% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (m, 2 H), 7.37 - 7.45 (m, 5 H), 7.15 (d, 1 H), 7.10 (ddd, 1 H), 5.53 (d, 1 H), 5.24 (d, 1 H), 4.47 (d, 1 H), 4.38 (d, 1 H), 3.10 (s, 3 H). LCMS ES *m/z* 364 $[M+H]^+$.

Preparation of 8-amino-3-fluoro-5,17-dimethyl-16,17-dihydro-7,11- (metheno)dibenzo[*g*,*l*]-[1,4,10]-oxadiazacyclotetradecin-18(5*H*)-one (Example 8).



Example 8

Step 1:

The procedure described in step 1 for **Example 7** was used to prepare **compound 358** (820 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, 1 H), 7.54 (br s, 1 H), 7.34 - 7.18 (m, 4 H), 7.07 (dd, 1 H), 6.99 (br s, 1 H), 6.62 - 6.49 (m, 1 H), 6.44 - 6.32 (m, 1 H), 4.86 (br s, 2 H), 4.11 - 4.02 (m, 2 H), 3.86 (br s, 3 H), 2.60 - 2.45 (m, 3 H), 1.67 (d, 3 H), 1.55 - 1.31 (m, 9 H). LCMS ES *m/z* 510 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 1** was used to prepare **compound 359**, where LiOH was used instead of NaOH (629 mg, quantitative yield). LCMS ES *m/z* 496 $[M+H]^+$.

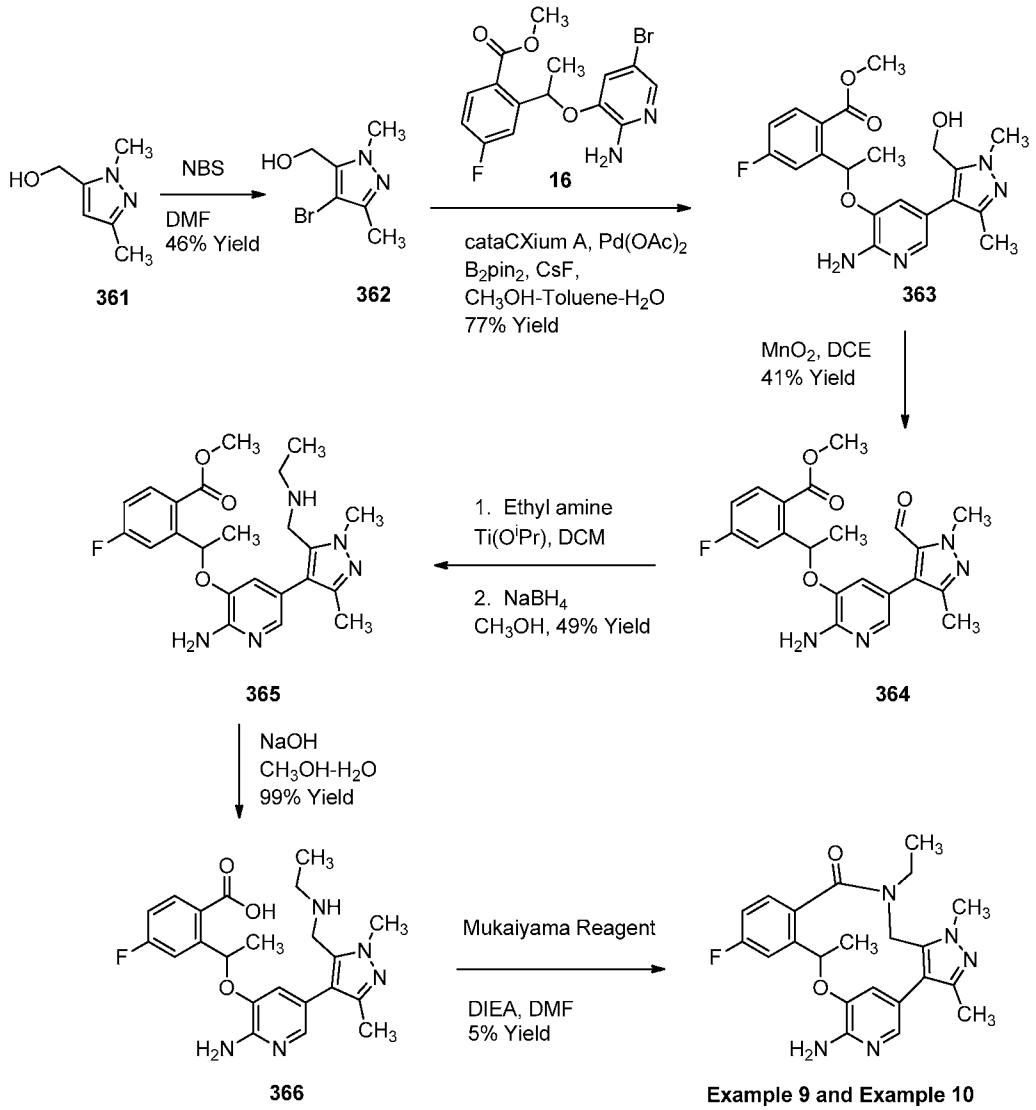
Step 3:

The procedure described in step 3 for **Example 1** was used to prepare **compound 360** (810 mg, quantitative yield). LCMS ES *m/z* 396 $[M+H]^+$.

Step 4:

The procedure described in step 4 for **Example 7** was used to prepare **Example 8** (49 mg, 8% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 1 H, *J* = 2.0 Hz), 7.48 - 7.32 (m, 4 H), 7.28 (dd,1 H, *J* = 10.0, 2.8 Hz), 7.17 - 7.13 (m, 2 H), 6.94 (td, 1 H, *J* = 8.0, 2.4 Hz), 5.83 (qd, 1 H, *J* = 6.0, 2.0 Hz), 4.75 (br s, 2 H), 4.50 (d, 1 H, *J* = 13.2 Hz), 4.16 (d, 1 H, *J* = 13.6 Hz), 3.12 (s, 3 H), 1.78 (d, 3 H, *J* = 6.4 Hz). LCMS ES *m/z* 378 $[M+H]^+$.

Preparation of 7-amino-16-ethyl-12-fluoro-1,3,10-trimethyl-16,17-dihydro-1H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 9 and Example 10).



Step 1:

To a solution of **compound 361** (1.0 g, 7.9 mmol) in DMF (53 mL) was added NBS (1.4 g, 7.9 mmol). The solution was stirred at room temperature overnight then concentrated. To the solid was added 1 N Na_2CO_3 (10 mL) and the mixture was concentrated to remove water. The solid was slurried in DCM/MeOH and filtered. The mother liquor was concentrated and purified by flash chromatography over silica gel, which was eluted with DCM/7 N NH_3 in MeOH (0-10%) to give **compound 362** (749 mg, 46% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.31 (t, *J* = 5.4 Hz, 1 H), 4.43 (d, *J* = 5.3 Hz, 2 H), 3.77 (s, 3 H), 2.08 (s, 3 H).

Step 2:

In a sealed tube, a mixture of **compound 16** (500 mg, 1.35 mmol), **compound 362** (555 mg, 2.03 mmol), diboron pinacol ester (1.38 g, 5.42 mmol) and cesium fluoride (1.03 g, 6.77 mmol) in MeOH (9.0 mL) and water (0.90 mL) was heated at 60 °C and bubbled with nitrogen. A solution of $Pd(OAc)_2$ (30 mg, 0.14 mmol) and di(1-adamantyl)-*n*-butylphosphine (100 mg, 0. 72 mmol) in toluene (0.5 mL) was added and the mixture was heated at 100 °C. After ~6 hours, the mixture was cooled to room temperature and diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography over silica gel, which was eluted with DCM/ MeOH (0-9%) and gave **compound 363** as a yellow gum (433 mg, 77% yield). LCMS ES *m/z* 415 $[M+H]^+$.

Step 3:

To a solution of **compound 363** (560 mg, 1.35 mmol) in DCE (13.5 mL) was added MnO_2 (1.2 g, 10.0 mmol). The reaction was heated at 50 °C overnight. The mixture was filtered and the mother liquor was concentrated and purified by flash chromatography over silica gel, which was eluted with heptanes/EtOAc (0-75%) and gave **compound 364** (226 mg, 41% yield over 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1 H), 7.94 (dd, *J* = 5.9, 8.7 Hz, 1 H), 7.55 (dd, *J* = 2.6, 10.4 Hz, 1 H), 7.50 (d, *J* = 1.8 Hz, 1 H), 7.26 (dt, *J* = 2.8, 8.4 Hz, 1 H), 6.71 (d, *J* = 1.8 Hz, 1 H), 6.25 (q, *J* = 6.1 Hz, 1 H), 6.16 (s, 2 H), 4.00 (s, 3 H), 3.84 (s, 3 H), 1.92 (s, 3 H), 1.62 (d, *J* = 6.3 Hz, 3 H). LCMS ES *m/z* 413 $[M+H]^+$.

Step 4:

A solution of the **compound 364** (226 mg, 0.548 mmol) in DCM (5.5 mL) was added ethyl amine (2 M in THF, 548 µL, 1.10 mmol) followed by $Ti(O^iPr)_4$ (642 µL, 2.19 mmol). After 1 hour, MeOH (2.0 mL) and $NaBH_4$ (104 mg, 2.74 mmol) were added (gas evolved). The reaction was quenched with water, and white solids formed. The mixture was filtered through celite and the mother liquor was diluted with EtOAc, washed with saturated NH_4Cl and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography over silica gel, which was eluted with heptanes/EtOAc (0-100%) followed by MeOH/DCM (0-10%) and

gave **compound 365** (119 mg, 49% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (dd, *J* = 6.0, 8.8 Hz, 1 H), 7.52 (dd, *J* = 2.5, 10.3 Hz, 1 H), 7.42 (d, *J* = 1.8 Hz, 1 H), 7.25 (dt, *J* = 2.8, 8.4 Hz, 1 H), 6.58 (d, *J* = 1.5 Hz, 1 H), 6.22 (q, *J* = 6.0 Hz, 1 H), 5.86 (s, 2 H), 3.86 (s, 3 H), 3.72 (s, 3 H), 3.48 - 3.35 (m, 2 H), 2.32 (q, *J* = 7.1 Hz, 2 H), 1.83 (s, 3 H), 1.79 (br s, 1 H), 1.61 (d, *J* = 6.3 Hz, 3 H), 0.88 (t, *J* = 7.1 Hz, 3 H). LCMS ES *m/z* 442 $[M+H]^+$.

Step 5:

To a solution **compound 365** (115 mg, 0.26 mmol) in MeOH (520 µL) was added 15% NaOH (68 µL, 0.26 mmol). The reaction was heated at 50 °C. Once complete by LCMS, the reaction was concentrated to afford the sodium salt of **compound 366** (116 mg, 99% yield).

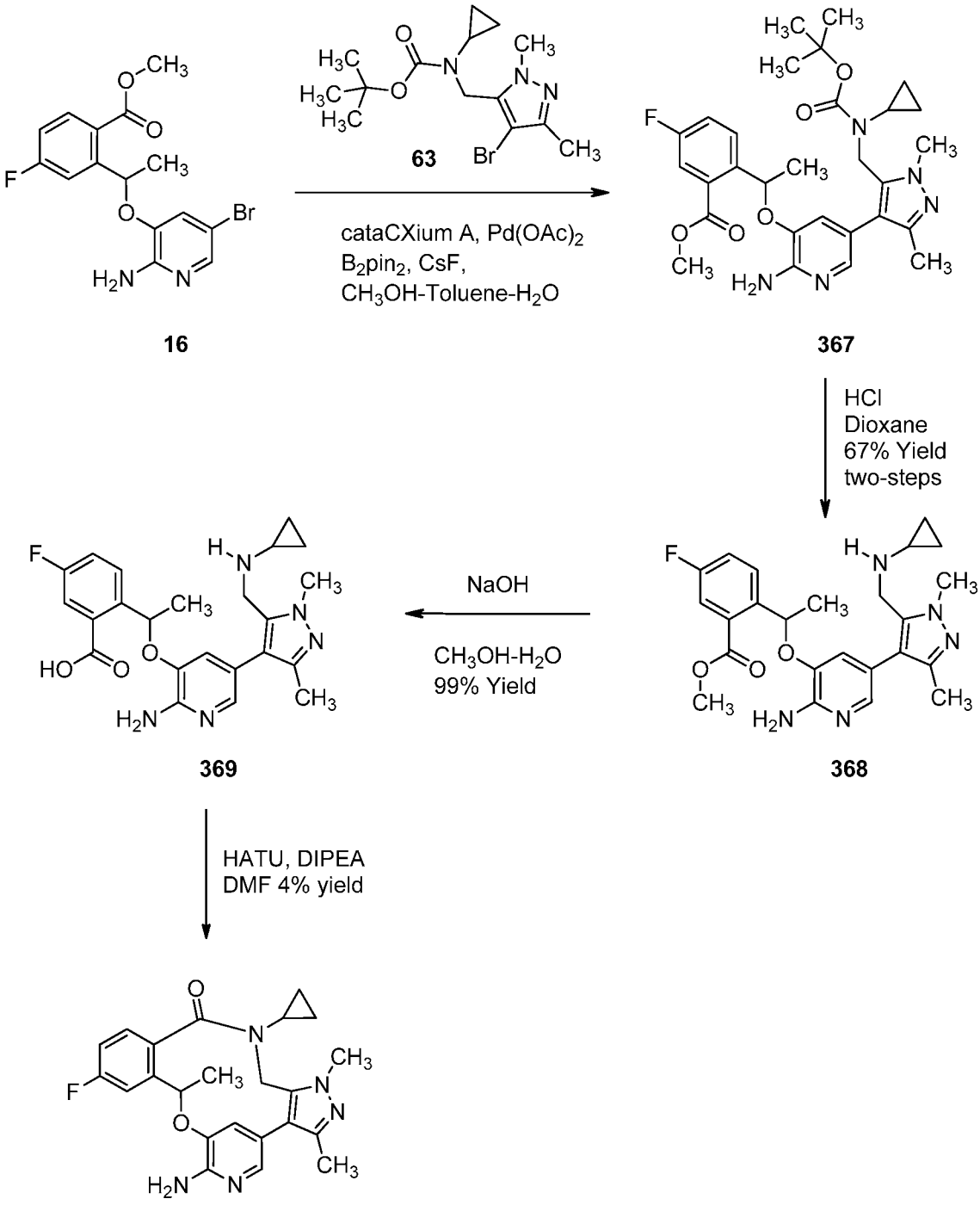
Step 6:

To a solution of sodium salt of **compound 366** (90 mg, 0.20 mmol) in DMF (13 mL) was added DIEA (70 µL, 0.40 mmol) followed by 2-chloro-1-methyl pyridinium iodide (57 mg, 0.22 mmol). After 30 min the reaction was concentrated and purified by flash chromatography over silica gel, which was eluted with DCM/MeOH (0-10%) followed by chiral separation by SFC to afford both enantiomers of the title compound. The analytical chiral separation by SFC was performed using a Regis Whelk-01 (*S,S*) column (4.6 mm x 100 mm column, 5 micron particle size), which was eluted with 30% MeOH in CO_2 held at 25 °C at 140 bar. A flow rate of 5 mL/min gave $Rt_{(Peak\ 1)}$ = 1.28 minutes and $Rt_{(Peak\ 2)}$ = 1.78 minutes.

Example 9 (Peak 1): 3.7 mg, >98% ee, 4.5% yield. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.59 (dd, *J* = 2.5, 10.4 Hz, 1 H), 7.37 (s, 1 H), 7.34 (dd, *J* = 5.6, 8.4 Hz, 1 H), 7.16 (dt, *J* = 2.5, 8.4 Hz, 1 H), 6.83 (s, 1 H), 5.80 (s, 2 H), 5.60 (d, *J* = 6.4 Hz, 1 H), 4.68 (d, *J* = 15.3 Hz, 1 H), 4.07 (d, *J* = 15.5 Hz, 1 H), 3.87 (s, 3 H), 3.37 (d, *J* = 6.9 Hz, 1 H), 2.19 (s, 3 H), 1.66 (d, *J* = 6.4 Hz, 3 H), 1.02 (t, *J* = 7.0 Hz, 3 H). LCMS ES *m/z* 410 $[M+H]^+$.

Example 10 (Peak 2): 4.0 mg, 90% ee, 4.9% yield. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.59 (dd, *J* = 2.5, 10.2 Hz, 1 H), 7.37 (s, 1 H), 7.34 (dd, *J* = 5.6, 8.4 Hz, 1 H), 7.16 (d, *J* = 2.5 Hz, 1 H), 6.83 (d, *J* = 1.3 Hz, 1 H), 5.80 (s, 2 H), 5.60 (d, *J* = 5.6 Hz, 1 H), 4.68 (d, *J* = 15.3 Hz, 1 H), 4.07 (d, *J* = 15.5 Hz, 1 H), 3.87 (s, 3 H), 2.19 (s, 3 H), 1.66 (d, *J* = 6.1 Hz, 3 H), 1.02 (t, *J* = 7.0 Hz, 3 H). LCMS *m/z* 410 $[M+H]^+$.

Synthesis of 7-amino-16-cyclopropyl-12-fluoro-1,3,10-trimethyl-16,17-dihydro-1H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 11 and Example 12).



Example 11 and Example 12

Step 1:

The procedure described in step 2 for **Example 9** and **10** was used to prepare **compound 367** (191 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.89 (dd, J = 5.8, 8.8 Hz, 1 H), 7.49 (dd, J = 2.4, 10.4 Hz, 1 H), 7.32 (s, 1 H), 7.20 (dt, J = 2.4, 8.5 Hz, 1 H), 6.49 (s, 1 H), 6.22 (q, J = 6.0 Hz, 1 H), 5.89 (s, 2 H), 4.34 (d, J = 15.9 Hz, 1 H), 4.07 (d, J = 15.6 Hz, 1 H), 3.85 (s, 3 H), 3.66 (s, 3 H), 1.87 (s, 3 H), 1.69 (br. s., 1 H), 1.61 (d, J = 6.3 Hz, 3 H), 1.35 (s, 9 H), 0.09 - 0.15 (m, 4 H).

LCMS ES *m/z* 554 $[M+H]^+$.

Step 2:

To a solution of **compound 367** (191 mg) in DCM (1.7 mL) was added HCl (4 N in dioxane, 1.7 mL). Diluted with EtOAc washed with saturated $NaHCO_3$ (2x) and brine, dried ($MgSO_4$), filtered, and concentrated. Purified by flash chromatography eluting with heptanes/EtOAc (50-100%) then DCM/MeOH (0-10%) to afford **compound 368** (104 mg, 67% yield over 2 steps). ^1H NMR (DMSO-d_6, 400 MHz) δ 7.95 (dd, *J* = 5.8, 8.8 Hz, 1 H), 7.52 (dd, *J* = 2.6, 10.2 Hz, 1 H), 7.44 (d, *J* = 1.0 Hz, 1 H), 7.24 (dt, *J* = 2.8, 8.3 Hz, 1 H), 6.57 (s, 1 H), 6.22 (q, *J* = 6.1 Hz, 1 H), 5.86 (s, 2 H), 3.85 (s, 3 H), 3.69 (s, 3 H), 3.48 (s, 2 H), 2.40 (br. s., 1 H), 1.82 (s, 4 H), 1.60 (d, *J* = 6.3 Hz, 3 H), 0.24 - 0.15 (m, 2 H), 0.11 - 0.04 (m, 2 H). LCMS ES *m/z* 454 $[M+H]^+$.

Step 3:

The procedure described in step 5 for **Example 9** and **10** was used to prepare **compound 369** (105 mg of the sodium salt).

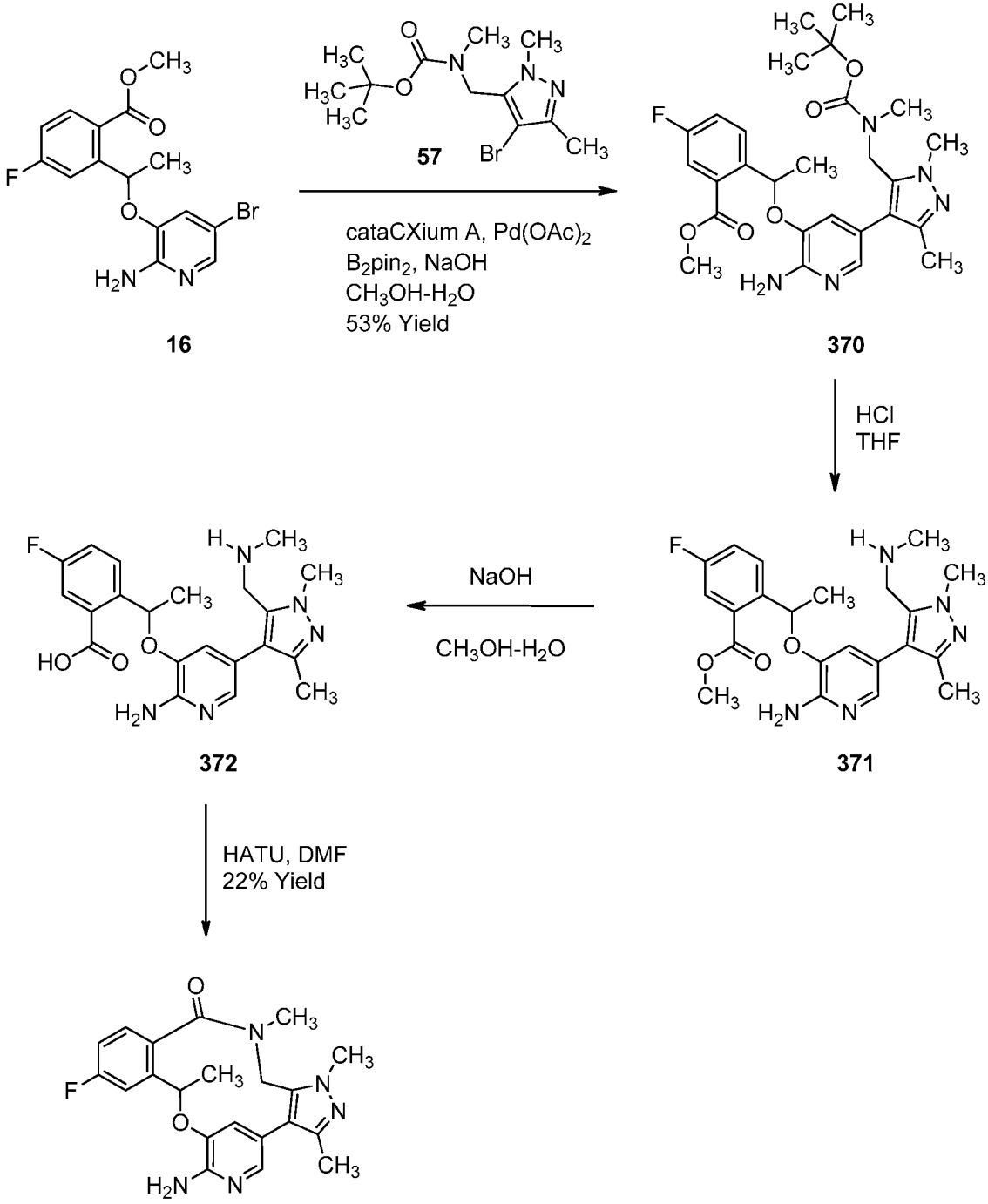
Step 4:

The procedure described in step 6 for **Example 9** and **10** was used to prepare **Examples 11** and **12.** The analytical chiral separation by SFC was performed using a Regis Whelk-01 (*S,S*) 4.6 mm x 100 mm column (5 micron particle size) which was eluted with 30% MeOH in CO_2 held at 35 ºC at 120 bar. The flow rate of 5 mL/min gave $Rt_{(Peak\ 1)}$ = 1.69 minutes and $Rt_{(Peak\ 2)}$ = 2.73 minutes.

Example 11 (Peak 2): 1.8 mg; 85% ee, 2% yield. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.57 (dd, *J* = 2.5, 10.4 Hz, 1 H), 7.37 - 7.32 (m, 2 H), 7.13 (dt, *J* = 2.8, 8.4 Hz, 1 H), 6.74 (s, 1 H), 5.80 - 5.75 (m, 2 H), 5.70 - 5.64 (m, 1 H), 4.64 (d, *J* = 15.3 Hz, 1 H), 4.09 (d, *J* = 15.0 Hz, 1 H), 3.91 (s, 3 H), 2.44 - 2.39 (m, 1 H), 2.19 (s, 3 H), 1.65 (d, *J* = 6.1 Hz, 3 H), 1.10 (br. s, 1 H), 0.97 - 0.91 (m, 1 H), 0.86 - 0.77 (m, 2 H). LCMS ES *m/z* 422 $[M+H]^+$.

Example 12 (Peak 1): 2.2 mg; 85% ee, 2% yield. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.57 (d, *J* = 9.7 Hz, 1 H), 7.37 - 7.32 (m, 2 H), 7.13 (t, *J* = 8.4 Hz, 1 H), 6.74 (s, 1 H), 5.77 (s, 2 H), 5.70 - 5.64 (m, 1 H), 4.64 (d, *J* = 15.3 Hz, 1 H), 4.09 (d, *J* = 15.5 Hz, 1 H), 3.91 (s, 3 H), 2.44 - 2.39 (m, 1 H), 2.19 (s, 3 H), 1.65 (d, *J* = 5.8 Hz, 3 H), 1.13 - 1.06 (m, 1 H), 0.98 - 0.90 (m, *J* = 6.9 Hz, 1 H), 0.82 (br s, 2 H). LCMS ES *m/z* 422 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-1,3,10,16-tetramethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 13 and Example 14).



Example 13 and Example 14

Step 1:

To a solution of **compound 57** (689 mg, 2.2 mmol) and **compound 16** (400 mg, 1.1 mmol) and bis pinacol ester (825 mg, 3.25 mmol) in MeOH (11.6 mL) was added 1 N NaOH in water (2.2 mL, 2.2 mmol). The reaction mixture was purged with nitrogen. Next, $Pd(OAc)_2$ (30.3 mg, 0.14 mmol) and di(1-adamantyl)-*n*-butylphosphine (4 mg, 0.14 mmol) were sequentially added and the reaction mixture was purged with nitrogen. The reaction mixture was heated at 80 °C in an

oil bath over night, and cooled to room temperature. The reaction mixture was filtered through a celite pad and washed with MeOH. The resulting solution was concentrated and purified *via* reversed phase chromatography and gave **compound 370** as an oil (300 mg, 53% yield). LCMS *m/z* 528 $[M+H]^+$.

Step 2:

To **compound 370** (50 mg, 0.09 mmol) in THF (3 mL) was added 0.5 mL of 38% HCl at room temperature. The reaction mixture formed two layers. The reaction mixture was heated in microwave at 60 °C for 30 minutes which gave **compound 371.**

Step 3:

Compound 371 was cooled to room temperature and to the reaction mixture was added 50% NaOH (approximately 1.0 mL) until pH ~12, and MeOH (3 mL). After heating at 60 °C for 30 min in an oil bath, the reaction was concentrated and lyophilized overnight and gave **compound 372**. The assumed theoretical yield was 39 mg.

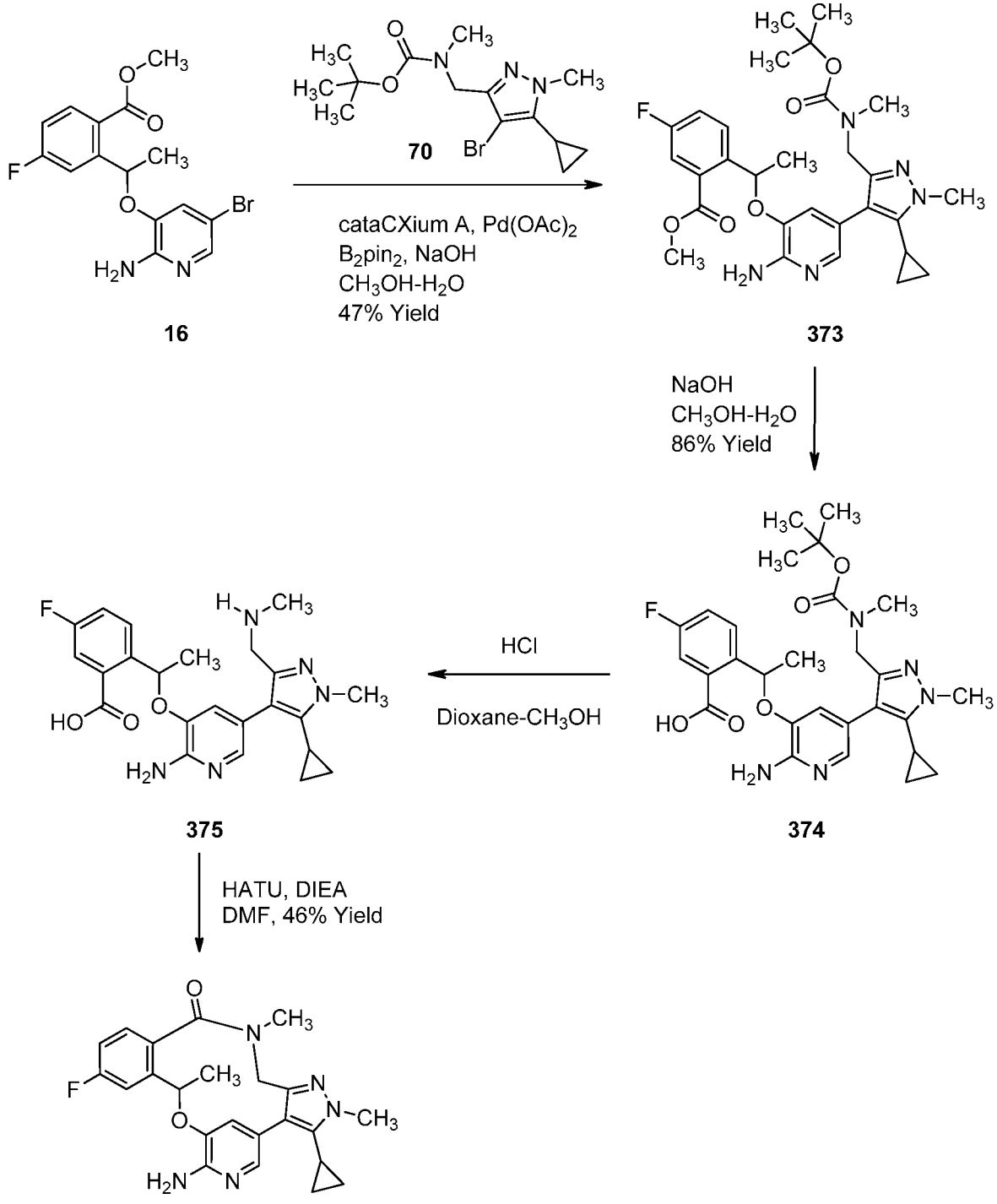
Step 4:

To a reaction mixture containing **compound 372** (39 mg, 0.09 mmol) in anhydrous DMF (3 mL) at pH ~10 was added HATU (72 mg, 0.18 mmol) and stirred at room temperature. After 4 hours, LCMS of the reaction mixture showed completed conversion to the desired product. The reaction mixture was diluted with MeOH and filtered through a celite pad and concentrated. After reversed phase purification using ammonium acetate as additive, the desired product was obtained as a solid (8 mg 22% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.59 - 7.63 (m, 1 H), 7.36 - 7.41 (m, 2 H), 7.17 (d, *J* = 2.5 Hz, 1 H), 6.75 (s, 1 H), 5.81 (s, 2 H), 5.50 - 5.64 (m, 1 H), 4.61 (d, *J* = 14.9 Hz, 1 H), 4.08 (d, *J* = 15.2 Hz, 1 H), 3.87 (s, 3 H), 2.98 (s, 3 H), 2.20 (s, 3 H), 1.65 (d, *J* = 6.4 Hz, 3 H). The analytical chiral separation by SFC was performed using a Chiralcel OD-3 (4.6 mm x 100 mm column, 3 micron particle size) which was eluted with 30% MeOH in CO_2 held at 25 °C at 120 bar. The flow rate of 5 mL/min gave $Rt_{(Peak\ 1)}$ = 0.75 minutes and $Rt_{(Peak\ 2)}$ = 1.3 minutes.

Example 13 (Peak 1): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (dd, *J* = 2.5, 10.3 Hz, 1 H), 7.33 - 7.43 (m, 2 H), 7.15 - 7.23 (m, 1 H), 6.76 (d, *J* = 1.5 Hz, 1 H), 5.81 (s, 2 H), 5.60 (br s, 1 H), 4.62 (d, *J* = 15.1 Hz, 1 H), 4.08 (d, *J* = 15.1 Hz, 1 H), 3.88 (s, 3 H), 2.99 (s, 3 H), 2.21 (s, 3 H), 1.65 (d, *J* = 6.0 Hz, 3 H).

Example 14 (Peak 2): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 - 7.65 (m, 1 H), 7.33 - 7.44 (m, 2 H), 7.12 - 7.23 (m, 1 H), 6.76 (s, 1 H), 5.80 (s, 2 H), 5.61 (br. s, 1 H), 4.62 (d, *J* = 15.4 Hz, 1 H), 4.09 (d, *J* = 15.1 Hz, 1 H), 3.88 (s, 3 H), 2.99 (s, 3 H), 2.21 (s, 3 H), 1.66 (d, *J* = 6.0 Hz, 3 H).

Preparation of 7-amino-3-cyclopropyl-12-fluoro-2,10,16-trimethyl-16,17-dihydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 15 and Example 16).



Example 15 and Example 16

Step 1:

The procedure described in step 1 for **Example 13** and **14** was used to prepare **compound 373** (380 mg, 43% yield). LCMS *m/z* 554 $[M+H]^+$.

Step 2:

A mixture of **compound 373** (380 mg, 0.557 mmol) and NaOH (0.55 g, 13.74 mmol) in methanol (10 mL) and water (10 mL) was stirred at 40 °C for 3 hours. None of the **compound 374** was detected by LCMS. The reaction mixture was concentrated under reduced pressure and the resultant residue was dissolved in water (20 mL). The aqueous layer was extracted with MTBE (20 mL). The organic layer was discarded and the aqueous layer was acidified with 6 N HCl to pH ~5. The mixture was saturated with solid NaCl and extracted with EtOAc (30 mL x 5). The combined EtOAc layers were dried over Na_2SO_4 and concentrated *in vacuo* and gave **compound 374** as a yellow solid (320 mg, 86% yield). LCMS *m/z* 540 $[M+H]^+$.

Step 3:

To a solution of **compound 374** (320 mg, 0.515 mmol) in methanol (5 mL) was added drop-wise ~ 4 M HCl in dioxane (10 mL). The reaction mixture was stirred at 40 °C for 3 hours. None of **compound 147** was detected by LCMS. The reaction mixture was concentrated under reduced pressure and the resultant residue was dissolved in toluene and concentrated. This was repeated two times and gave **compound 375**. LCMS *m/z* 440 $[M+H]^+$.

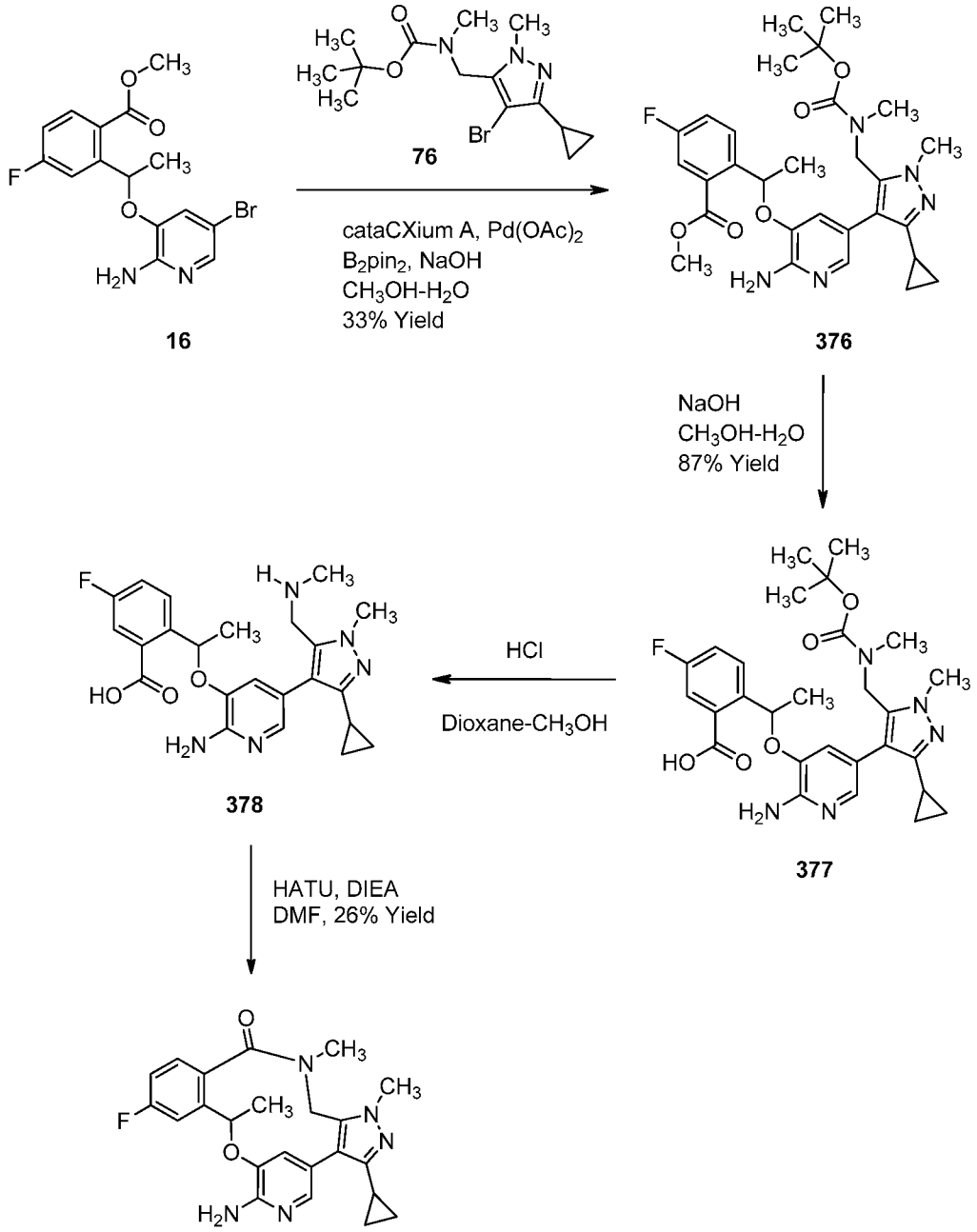
Step 4:

To a solution of HATU (338 mg, 0.89 mmol) in DMF (70 mL) was added drop-wise a solution of **compound 375** (0.515 mmol) and DIPEA (1.2 g, 9.5 mmol) in DMF (20 mL) at 0 °C. After addition, the resulting mixture was stirred at 0 °C for 1 hour. None of the **compound 375** was detected by LCMS. The mixture was poured into ice water (50 mL) and the aqueous layer was extracted with EtOAc (40 mL x 5). The combined EtOAc layers were washed with brine (20 mL x 5), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel which was eluted with EtOAc and gave pure a mixture of **Example 15 and Example 16** as an off-white solid (100 mg, 46% yield). The analytical chiral separation was performed by SFC on a Chiralpak AS-H (150 x 4.6 mm I.D., 5 micron particle size), which was eluted with 5-40% ethanol (0.05% DEA) in CO_2. The flow rate of 3 mL/min gave $Rt_{(Peak\ 1)}$ = 3.08 minutes and $Rt_{(Peak\ 2)}$ = 3.47 minutes. The racemic mixture was purified by preparative SFC and gave peak 1 as a white solid (27 mg) and as a white solid peak 2 (22 mg).

Example 16 (Peak 1): 98% ee. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.42 - 7.39 (m, 2 H), 7.29 (dd, 1 H), 7.00 (dd, 1 H), 6.77 (s, 1 H), 5.63 - 5.58 (m, 1 H), 4.22 (q, 2 H), 3.84 (s, 3 H), 2.99 (s, 3 H), 1.78 - 1.72 (m, 1 H), 1.68 - 1.67 (d, 3 H), 0.98 - 0.94 (m, 1 H), 0.86 - 0.82 (m, 1 H), 0.46 - 0.42 (m, 1 H), 0.28 - 0.24 (m, 1 H). LCMS *m/z* 422 $[M+H]^+$.

Example 15 (Peak 2): 100% ee. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.42 - 7.39 (m, 2 H), 7.29 (dd, 1 H), 7.00 (dd, 1 H), 6.77 (s, 1 H), 5.63 - 5.58 (m, 1 H), 4.22 (q, 2 H), 3.84 (s, 3 H), 2.99 (s, 3 H), 1.78 - 1.72 (m, 1 H), 1.68 - 1.67 (d, 3 H), 0.98 - 0.94 (m, 1 H), 0.86 - 0.82 (m, 1 H), 0.46 - 0.42 (m, 1 H), 0.28 - 0.24 (m, 1 H). LCMS *m/z* 422 $[M+H]^+$.

Preparation of 7-amino-3-cyclopropyl-12-fluoro-1,10,16-trimethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 17 and Example 18).



Example 17 and Example 18

Step 1:

The procedure described in step 1 for **Example 13** and **14** was used to prepare **compound 376** (495 mg, 33% yield). LCMS *m/z* 554 $[M+H]^+$.

Step 2:

The procedure described in step 3 for **Example 13** and **14** was used to prepare **compound 377** (420 mg, 87% yield). LCMS *m/z* 540 $[M+H]^+$.

Step 3:

The procedure described in step 2 for **Example 13** and **14** was used to prepare **compound 378**. LCMS *m/z* 439 $[M+H]^+$.

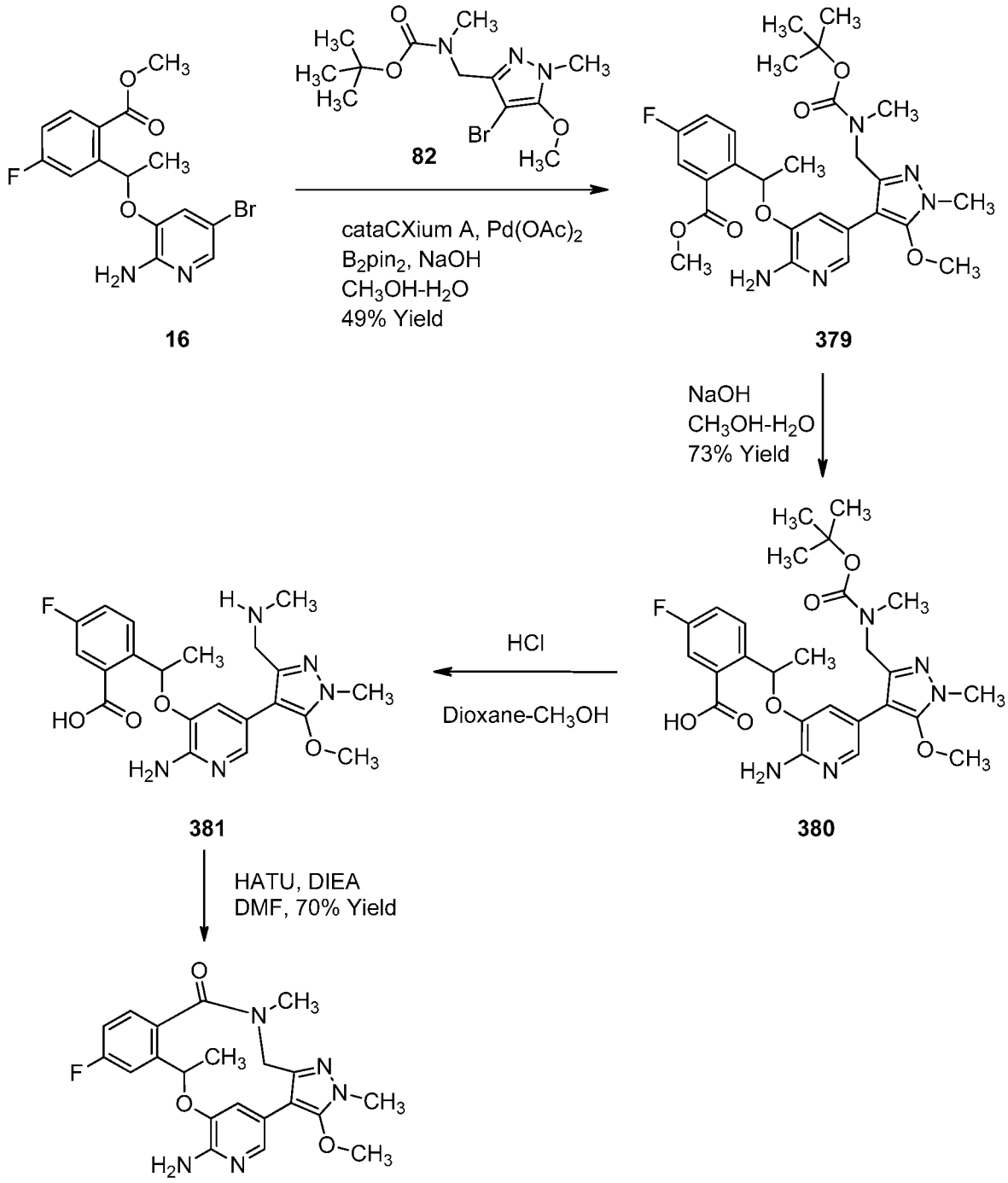
Step 4:

To a solution of HATU (520 mg, 1.4 mmol) in DMF (100 mL) was added drop-wise a solution of **compound 378** (0.91 mmol) and DIPEA (1.88 g, 14.6 mmol) in DMF (20 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 1 hour. None of **compound 378** was detected by LCMS. The mixture was poured into ice water (50 mL) and the aqueous layer was extracted with EtOAc (40 mL x 5). The combined EtOAc layers were washed with brine (20 mL x 5), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography over silica gel, which was eluted with EtOAc and gave a mixture of **Example 17 and Example 18** as a dark solid (100 mg, 26% yield). The analytical chiral separation was performed by SFC on a Chiralcel (50 x 4.6 mm I.D., 3 micron particle size), which was eluted with 5-40% methanol (0.05% DEA) in CO_2. The flow rate of 4 mL/min gave $Rt_{(Peak\ 1)}$ = 1.47 min and $Rt_{(Peak\ 2)}$ = 1.74 min. The racemic mixture was separated by preparative SFC and gave peak 1 as a white solid (30 mg) and peak 2 as a white solid (39 mg).

Example 17 (Peak 1): 93.7% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 - 7.75 (m, 1 H), 7.25 (dd, 1 H), 7.10 (dd, 1 H), 693 - 6.90 (m, 1 H), 6.80 (m, 1 H), 5.70 - 5.68 (s, 1 H), 4.54 (s, 2 H), 4.40 (d, 1 H), 4.22 (d, 1 H), 3.85 (s, 3 H), 3.06 (s, 3 H), 1.85 (m, 1 H), 1.70 (d, 3 H), 1.02 - 1.01 (m, 1 H), 0.95 - 0.93 (m, 1 H), 0.81 - 0.79 (m, 1 H), 0.63 (m, 1 H). LCMS *m/z* 422 $[M+H]^+$.

Example 18 (Peak 2): 94.6% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 7.22 (dd, 1 H), 7.18 (dd, 1 H), 693 - 6.90 (m, 1 H), 6.81 (m, 1 H), 5.70 - 5.68 (s, 1 H), 4.67 (s, 2 H), 4.32 (d, 1 H), 4.26 (d, 1 H), 3.85 (s, 3 H), 3.06 (s, 3 H), 1.85 (m, 1 H), 1.70 (d, 3 H), 1.02 - 1.01 (m, 1 H), 0.95 - 0.93 (m, 1 H), 0.81 - 0.79 (m, 1 H), 0.63 (m, 1 H). LCMS *m/z* 422 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-3-methoxy-2,10,16-trimethyl-16,17-dihydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 19 and Example 20).



Example 19 and Example 20

Step 1:

The procedure described in step 1 for **Example 13** and **14** was used to prepare **compound 379** (1.0 g, 49% yield). LCMS *m/z* 544 $[M+H]^+$.

Step 2:

The procedure described in step 3 for **Example 13** and **14** was used to prepare **compound 380** (700 mg, 73% yield). LCMS *m/z* 540 $[M+H]^+$.

Step 3:

The procedure described in step 3 for **Example 15** and **16** was used to prepare **compound 381**. LCMS *m/z* 430 $[M+H]^+$.

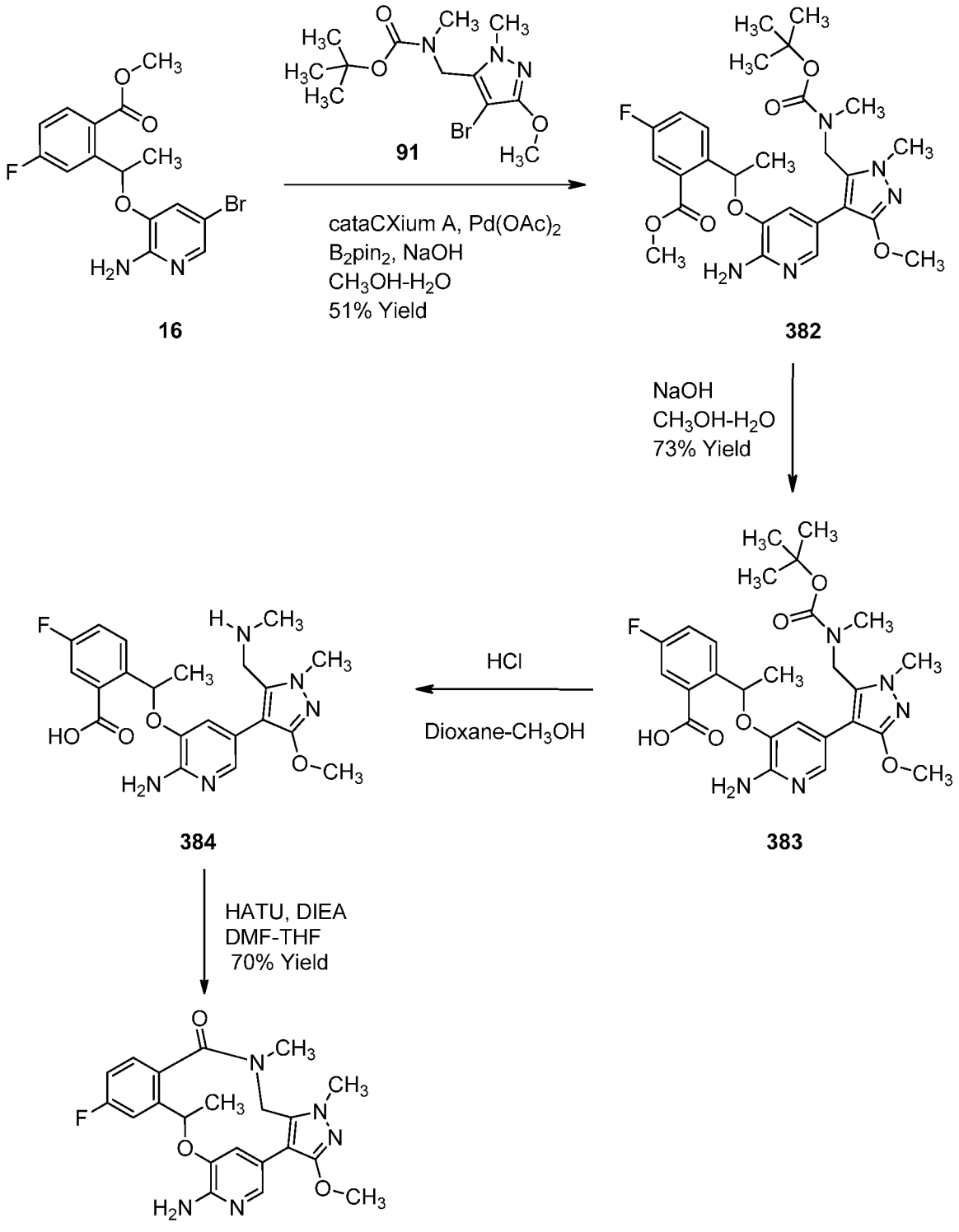
Step 4:

To a solution of HATU (710 mg, 1.85 mmol) in DMF (30 mL) was added drop-wise a solution of **compound 381** (1.32 mmol) and DIPEA (2.7 g, 21.1 mmol) in DMF (30 mL) and THF (6 mL) at 0 °C. After addition, the resulting mixture was stirred at the same temperature for 1 hour. LCMS showed the reaction was complete. The mixture was poured into ice water (100 mL), and the aqueous layer was extracted with EtOAc (60 mL x 5). The combined EtOAc layers were washed with brine (50 mL x 5), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified by column chromatography over silica gel, which was eluted with DCM/MeOH = 15:1 (Rf = 0.3) and gave a mixture of **Example 19 and Example 20** as a yellow solid (390 mg, 70% yield). The analytical chiral separation was performed by SFC on a Chiralpak AD-3 (150 x 4.6 mm I.D., 3 micron particle size), which was eluted with 5-40% methanol (0.05% DEA) in CO_2. $Rt_{(Peak\ 1)}$ = 4.85 minutes and $Rt_{(Peak\ 2)}$ = 5.79 minutes. The racemic mixture was separated by preparative SFC to give Peak 1 as a white solid (130 mg) and peak 2 as a white solid (128 mg).

Example 19 (Peak 1): 100% ee. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.41 - 7.38 (m, 2 H), 7.30 (dd, 1 H), 7.00 (dd, 1 H), 6.80 (s, 1H), 5.64 - 5.60 (m, 1 H), 4.26 (d, 1 H), 4.12 (d, 1 H), 3.73 (s, 3 H), 3.56 (s, 3 H), 3.02 (s, 3 H), 1.68 (d, 3 H). LCMS *m/z* 412 $[M+H]^+$.

Example 20 (Peak 2): 98.2% ee. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.41 - 7.38 (m, 2 H), 7.30 (dd, 1 H), 7.00 (dd, 1 H), 6.80 (s, 1 H), 5.64 - 5.60 (m, 1 H), 4.26 (d, 1 H), 4.12 (d, 1 H), 3.73 (s, 3 H), 3.61 (s, 3 H), 3.02 (s, 3 H), 1.68 (d, 3 H). LCMS *m/z* 412 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-3-methoxy-1,10,16-trimethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 21 and Example 22).



Example 21 and Example 22

Step 1:

The procedure described in step 1 for **Example 13** and **14** was used to prepare **compound 382** as a brown oil (300 mg, 51% yield). LCMS *m/z* 544 $[M+H]^+$.

Step 2:

The procedure described in step 3 for **Example 13** and **14** was used to prepare **compound 383** as a yellow solid (320 mg, 73% yield). LCMS *m/z* 529 $[M+H]^+$.

Step 3:

The procedure described in step 2 for **Example 15** and **16** was used to prepare **compound 384**. LCMS *m/z* 430 [M+H]+.

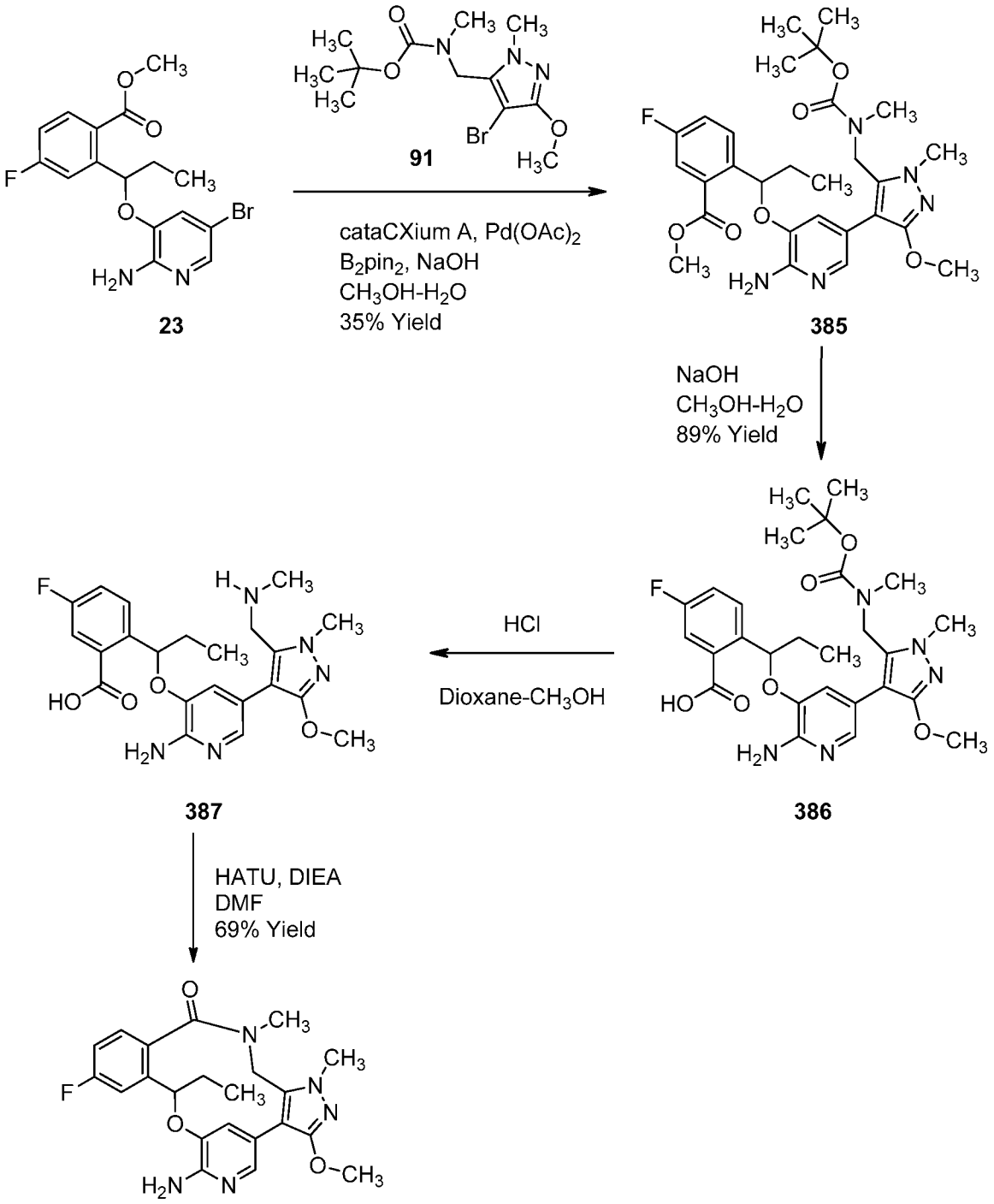
Step 4:

To a solution of HATU (280 mg, 0.74 mmol) in DMF (25 mL) was added drop-wise a solution of **compound 384** (0.53 mmol) and DIPEA (1.09 g, 8.48 mmol) in DMF (25 mL) and THF (5 mL) at 0 °C. The mixture was stirred at same temperature for 1 hour. LCMS showed the reaction was complete. The mixture was poured into ice water (100 mL) and the aqueous later was extracted with EtOAc (60 mL x 5). The combined EtOAc layers were washed with brine (50 mL x 5), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, which was purified via Biotage (DCM/MeOH = 15:1, Rf=0.3) to give a mixture of **Example 21** and **Example 22** as a yellow solid (170 mg, 78%). The analytical chiral separation was performed by SFC on a Chiralcel OD-3 (50 x 4.6 mm I.D., 3 micron particle size), which was eluted with 5-40% methanol (0.05% DEA) in CO_2. $Rt_{(Peak\ 1)}$ = 1.44 minutes and $Rt_{(Peak\ 2)}$ = 1.59 minutes. The racemic mixture was separated by preparative SFC and gave Peak 1 as a white solid (62 mg) and Peak 2 as a white solid (72 mg).

Example 21 (Peak 1): 96.6% ee. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.62 (d, 1 H), 7.50 (dd, 1 H), 7.43 (dd, 1 H), 7.16 - 7.11 (m, 1 H), 6.90 (d, 1 H), 5.64 - 5.60 (m, 1 H), 4.84 (d, 1 H), 4.37 (d, 1 H), 3.92 (d, 6 H), 3.17 (s, 3 H), 1.78 (d, 3 H). LCMS *m/z* 412 $[M+H]^+$.

Example 22 (Peak 2): 96.9% ee. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.61 (d, 1 H), 7.50 (dd, 1 H), 7.42 (dd, 1 H), 7.15 - 7.10 (m, 1 H), 6.90 (d, 1 H), 5.68 - 5.64 (m, 1 H), 4.82 (d, 1 H), 4.36 (d, 1 H), 3.90 (d, 6 H), 3.15 (s, 3 H), 1.78 (d, 3 H). LCMS *m/z* 412 $[M+H]^+$.

Preparation of 7-amino-10-ethyl-12-fluoro-3-methoxy-1,16-dimethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 23 and Example 24).



Example 23 and Example 24

Step 1:

The procedure described in step 1 for **Example 13** and **14** was used to prepare **compound 385** as a brown solid (470 mg, 35% yield).

Step 2:

The procedure described in step 3 for **Example 13** and **14** was used to prepare **compound 386** as a pale yellow solid (410 mg, 89% yield).

Step 3:

The procedure described in step 2 for **Example 15** and **16** was used to prepare **compound 387** as a pale yellow solid (410 mg, quantitative).

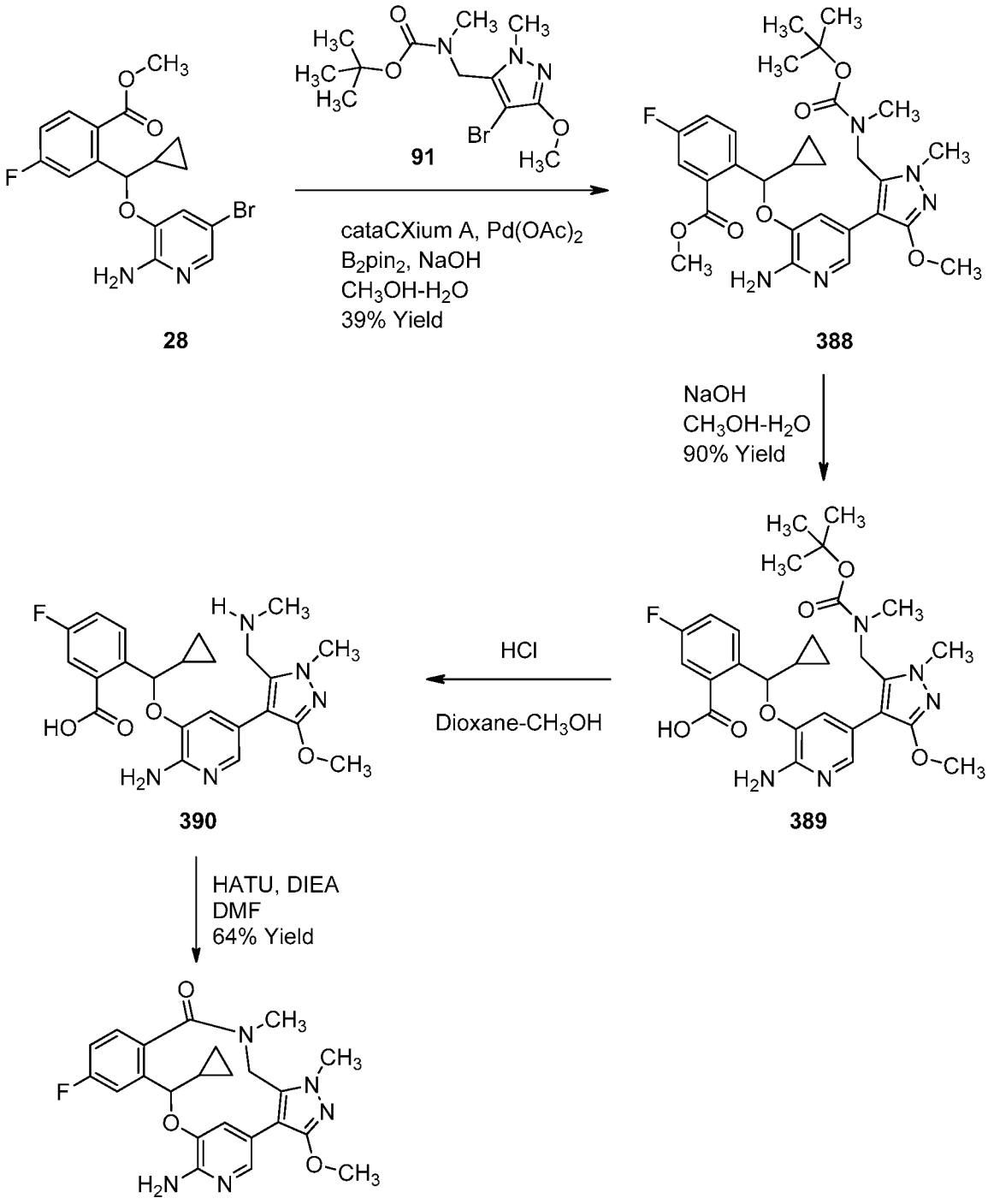
Step 4:

To a solution of HATU (399 mg, 1.05 mmol) in DMF (80 mL) was added drop-wise a solution of **compound 387** (0.75 mmol) and DIPEA (1.4 g, 11.3 mmol) in DMF (20 mL) at 0 °C. After addition, the resulting mixture was stirred at same temperature for 1 hour. LCMS showed the reaction was complete. The mixture was poured into ice water (100 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined EtOAc layers were washed with H_2O (40 mL x 2), brine (40 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified *via* Biotage (CH_2Cl_2/MeOH from 15:1 to 10:1) to give **Example 23** and **Example 24** as an off-white solid (220 mg, 69% yield). The analytical chiral separation was performed by SFC on a Chiralcel AD-H (250 x 4.6 mm I.D., 5 micron particle size), which was eluted with 5-40% ethanol (0.05% DEA) in CO_2. A flow rate of 2.3 ml/min gave $Rt_{(Peak\ 1)}$ = 7.6 minutes and $Rt_{(Peak\ 2)}$ = 8.7 minutes. The racemic mixture was separated by preparative SFC to give Peak 1 as an off-white solid (65 mg) and peak 2 as an off-white solid (79 mg).

Example 23 (Peak 1): 99.0% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1 H), 7.28 (m, 1 H), 7.19 - 7.17 (m, 1 H), 7.01 - 6.98 (m, 1 H), 6.90 (s, 1 H), 5.41 - 5.38 (m, 1 H), 4.76 (m, 2 H), 4.44 (d, 1 H), 4.28 (d, 1 H), 3.93 (s, 3 H), 3.72 (s, 3 H), 3.13 (s, 3 H), 2.26 - 2.16 (m, 1 H), 2.04 - 1.97 (m, 1 H), 1.05 (t, 3 H). LCMS *m/z* 426 $[M+H]^+$.

Example 24 (Peak 2): 94.4% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1 H), 7.27 (m, 1 H), 7.17 - 7.15 (m, 1 H), 6.94 - 6.90 (m, 1 H), 6.72 (s, 1 H), 5.35 - 5.32 (m, 1 H), 4.63 (s, 2 H), 4.38 (d, 1 H), 4.21 (d, 1 H), 3.87 (s, 3 H), 3.66 (s, 3 H), 3.08 (s, 3 H), 2.21 - 2.09 (m, 1 H), 1.97 - 1.92 (m, 1 H), 1.02 (t, 3 H). LCMS *m/z* 426 $[M+H]^+$.

Preparation of 7-amino-10-cyclopropyl-12-fluoro-3-methoxy-1,16-dimethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 25 and Example 26).



Example 25 and Example 26

Step 1:

The procedure described in step 1 for **Example 13** and **14** was used to prepare **compound 388** as a pale brown solid (550 mg, 39% yield).

Step 2:

The procedure described in step 2 for **Example 13** and **14** was used to prepare **compound 389** as a pale yellow solid (482 mg, 90% yield).

Step 3:

The procedure described in step 3 for **Example 13** and **14** was used to prepare **compound 390** as a pale yellow solid (480 mg, quantitative).

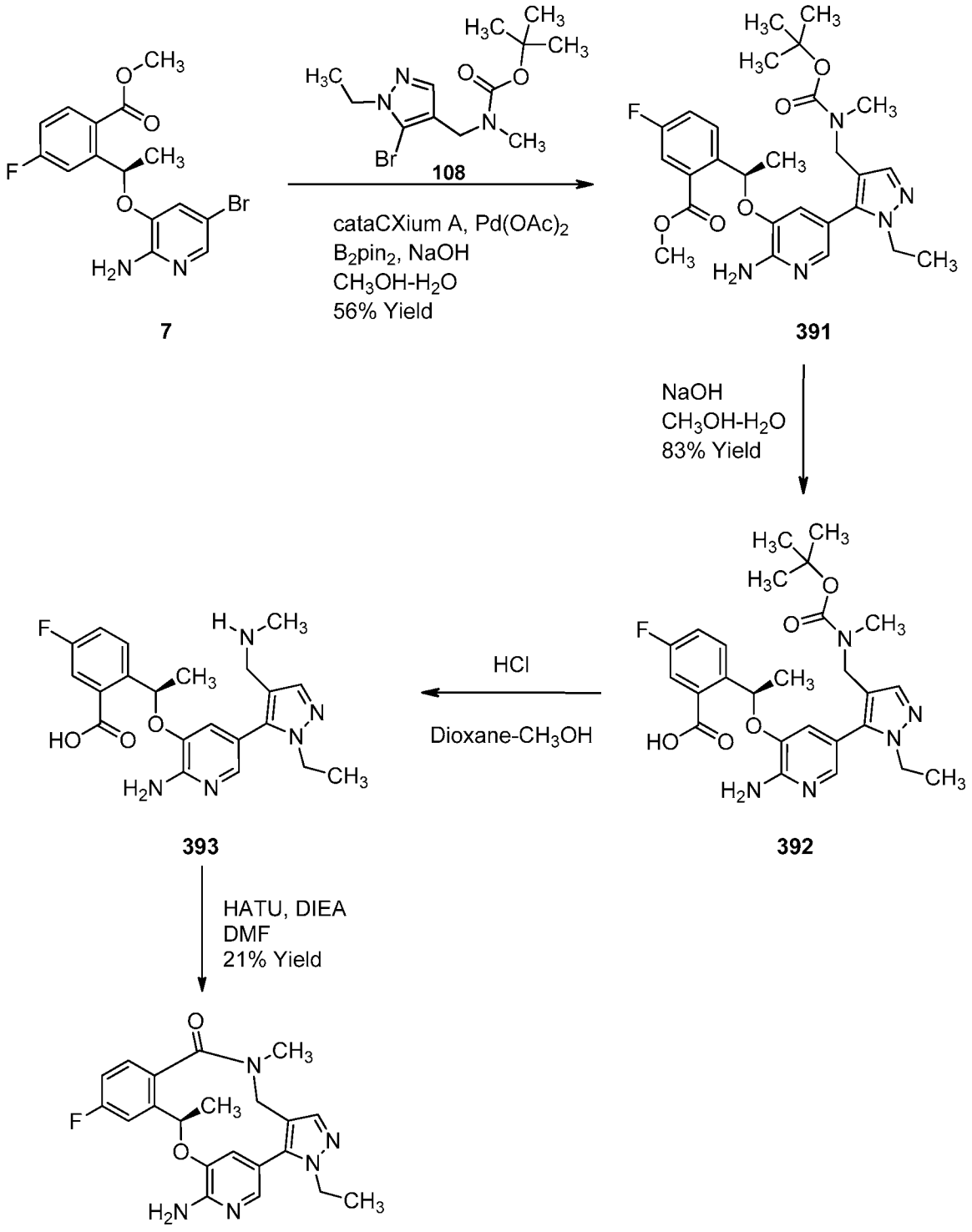
Step 4:

To a solution of HATU (456 mg, 1.2 mmol) in DMF (80 mL) was added drop-wise a solution of **compound 390** (0.86 mmol) and DIPEA (1.6 g, 12.4 mmol) in DMF (20 mL) at 0 °C. After addition, the resulting mixture was stirred at same temperature for 1 hour. LCMS showed the reaction was complete. The mixture was poured into ice water (100 mL). The mixture was extracted with EtOAc (60 mL x 2). The combined EtOAc layers were washed with H_2O (50 mL x 2), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified *via* Biotage (CH_2Cl_2/MeOH from 15:1 to 10:1) to give a mixture of **Example 25 and Example 26** as an off-white solid (240 mg, 64% yield). The analytical chiral separation was performed by SFC on a Chiralcel AD-H (250 x 4.6 mm I.D., 5 micron particle size), which was eluted with 5-40% ethanol (0.05% DEA) in CO_2. A flow rate of 2.3 mL/min gave $Rt_{(Peak\ 1)}$ = 8.1 minutes and $Rt_{(Peak\ 2)}$ = 9.1 minutes. The racemic mixture was separated by preparative SFC to give Peak 1 as an off-white solid (75 mg) and Peak 2 as an off-white solid (76 mg).

Example 25 (Peak 1): 100% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 7.35 - 7.32 (m, 1 H), 7.16 - 7.12 (m, 1 H), 6.95 - 6.92 (m, 1 H), 6.60 (s, 1 H), 4.65 - 4.61 (m, 3 H), 4.35 (d, 1 H), 4.20 (d, 1 H), 3.86 (s, 3 H), 3.73 (s, 3 H), 3.06 (s, 3 H), 1.41 - 1.36 (m, 1 H), 0.85 - 0.82 (m, 2 H), 0.60 - 0.52 (m, 2 H). LCMS *m/z* 438 $[M+H]^+$

Example 26 (Peak 2): 94.8% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1 H), 7.34 - 7.32 (m, 1 H), 7.15 - 7.12 (m, 1 H), 6.96 - 6.93 (m, 1 H), 6.61 (s, 1 H), 4.64 - 4.62 (m, 3 H), 4.34 (d, 1 H), 4.20 (d, 1 H), 3.85 (s, 3 H), 3.71 (s, 3 H), 3.04 (s, 3 H), 1.42 - 1.37 (m, 1 H), 0.84 - 0.81 (m, 2 H), 0.61 - 0.53 (m, 2 H). LCMS *m/z* 438 $[M+H]^+$.

Preparation of (10*R*)-7-amino-3-ethyl-12-fluoro-10,16-dimethyl-16,17-dihydro-3*H*-8,4-(metheno)pyrazolo[3,4-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 27).



Example 27

Step 1:

The procedure described in step 1 for **Example 13** and **14** was used to prepare **compound 391** as a brown solid (400 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 - 7.95 (m, 1 H), 7.45 (s, 1 H), 7.39 (s, 1 H), 7.18 - 7.15 (m, 1 H), 6.94 (d, 1 H), 6.38 (s, 1 H), 6.33 (d, 1 H), 4.93 (s, 2

H), 3.84 (d, 2 H), 3.71 (d, 3 H), 3.69 - 3.67 (m, 2 H), 2.34 (s, 3 H), 1.62 (d, 3 H), 1.36 (s, 9 H), 1.07 (t, 3 H).

Step 2:

The procedure described in step 2 for **Example 13** and **14** was used to prepare **compound 392** as a yellow solid (320 mg, 83% yield). LCMS *m/z* 514 $[M+H]^+$.

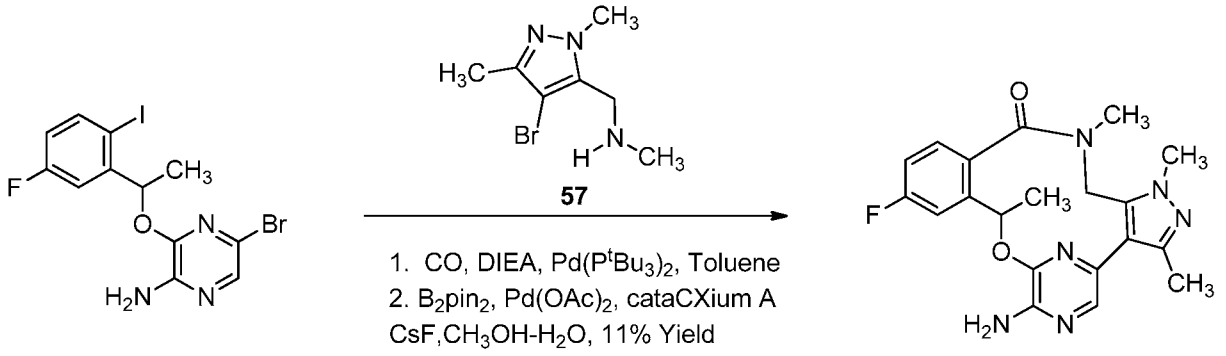
Step 3:

The procedure described in step 3 for **Example 13** and **14** was used to prepare **compound 393** as a pale yellow solid (320 mg, quantitative).

Step 4:

To a solution of HATU (684 mg, 1.8 mmol) in DMF (60 mL) was added drop-wise a solution of **compound 393** (0.62 mmol) and DIPEA (2.5 g, 19.2 mmol) in DMF (20 mL) at 0 °C. After the addition, the resulting mixture was stirred at room temperature for 1 hour. LCMS showed the reaction was complete. The mixture was poured into ice water (50 mL). The aqueous layer was extracted with EtOAc (40 mL x 5). The combined EtOAc layers were washed with brine (20 mL x 5), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography over silica gel, which was eluted with petroleum ether/EtOAc (2:1~1:2), and gave **Example 27** as a pink solid (52 mg, 21% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.48 (d, 1 H), 7.21 (s, 1 H), 7.19 (s, 1 H), 7.10 (d, 1 H), 6.85 (m, 1 H), 5.79 (s, 1 H), 4.94 (s, 2 H), 4.19 - 4.16 (m, 2 H), 4.11 (m, 2 H), 3.05 (s, 3 H), 1.72 (d, 3 H), 1.39 (t, 3 H). LCMS *m/z* 396 $[M+H]^+$. Analysis by chiral chromatography using Chiralcel OD-3 (150 × 4.6 mm I.D., 3 micron particle size) and eluting with methanol (5% to 40% with 0.05% DEA) in CO_2 at a flow rate of 2.5mL/min gave a retention time of 6.23 minutes (100% ee).

Preparation of 7-amino-12-fluoro-1,3,10,16-tetramethyl-16,17-dihydro-1H-8,4-(azeno)-pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 28 and Example 29).



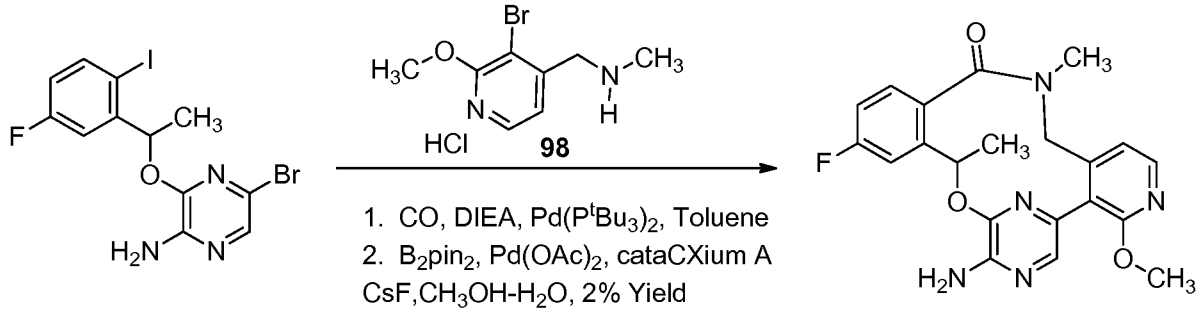
30 **Example 28 and Example 29**

To a solution of **compound 30** (266 mg, 0.607 mmol), **compound 57** (166 mg, 0.759) and DIEA (211 µL, 1.21 mmol) in toluene (60 mL) was added $Pd(P^tBu_3)_2$ (32 mg, 0.61 mmol). The reaction mixture was heated at 100 °C under 4 bar CO overnight then concentrated. The residue was taken-up in MeOH (12 mL) and water (1.3 mL) and added to a vial containing diboron pinacol ester (771 mg, 3.04 mmol) and CsF (461 mg, 3.04 mmol). The vial was sealed and the reaction mixture was bubbled with nitrogen before adding a solution of $Pd(OAc)_2$ (14 mg, 0.61 mmol) and di(1-adamantyl)-n-butylphosphine (45 mg, 0.12 mmol) in toluene (0.5 mL). After heating for 30 min at 60 °C, the temperature was increased to 90 °C for 6 hours. The reaction was allowed to stand at room temperature overnight then additional $Pd(OAc)_2$ (14 mg, 0.61 mmol) and di(1-adamantyl)-n-butylphosphine (45 mg, 0.12 mmol) in toluene (0.5 mL) were added. After heating for 2 hours at 100 °C, the reaction mixture was cooled to room temperature and filtered. The mother liquor was diluted with EtOAc, washed with water (2x) and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography eluting with DCM/MeOH (0-8%) followed by a second column eluting with heptanes/EtOAc (50-100%) then DCM/MeOH (0-6%), and finally chiral separation by SFC to afford both enantiomers of the title compound. The chiral separation was performed by SFC on a Chiralcel OD-H (4.6 mm x 250 mm, 5 micron particle size) column which was eluted with 25% MeOH in CO_2 held at 25 ºC at 140 bar. A flow rate of 3.0 mL/min gave Peak 1 $Rt_{(Peak\ 1)}$ = 4.23 min ($[\alpha]_d^{20}$= -77.1° (C=0.23, MeOH), and Peak 2 $Rt_{(Peak\ 2)}$ = 5.60 min ($[\alpha]_d^{20}$= +78.6° (C=0.24, MeOH).

Example 28 (Peak 1): 14 mg, >99% ee, 6% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (s, 1 H), 7.51 - 7.46 (m, 1 H), 7.36 (dd, *J* = 5.8, 8.3 Hz, 1 H), 7.17 (dt, *J* = 2.5, 8.6 Hz, 1 H), 6.29 (s, 2 H), 5.95 - 5.84 (m, 1 H), 4.47 (d, *J* = 14.7 Hz, 1 H), 4.27 (d, *J* = 14.4 Hz, 1 H), 3.87 (s, 3 H), 2.87 (s, 3 H), 2.26 (s, 3 H), 1.62 (d, *J* = 6.6 Hz, 3 H). LCMS ES *m/z* 397 $[M+H]^+$.

Example 29 (Peak 2): 13 mg, 99% ee, 5% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (s, 1 H), 7.49 (dd, *J* = 2.7, 10.2 Hz, 1 H), 7.36 (dd, *J* = 5.7, 8.5 Hz, 1 H), 7.17 (dt, *J* = 2.5, 8.5 Hz, 1 H), 6.29 (s, 2 H), 5.95 - 5.82 (m, 1 H), 4.47 (d, *J* = 14.7 Hz, 1 H), 4.27 (d, *J* = 14.4 Hz, 1 H), 3.87 (s, 3 H), 2.87 (s, 3 H), 2.26 (s, 3 H), 1.62 (d, *J* = 6.6 Hz, 3 H). LCMS ES *m/z* 397 $[M+H]^+$.

Preparation of 8-amino-13-fluoro-4-methoxy-11,17-dimethyl-17,18-dihydro-9,5-(azeno)pyrido[3,4-h][2,5,11]benzoxadiazacyclotetradecin-16(11H)-one (Example 30 and Example 31).



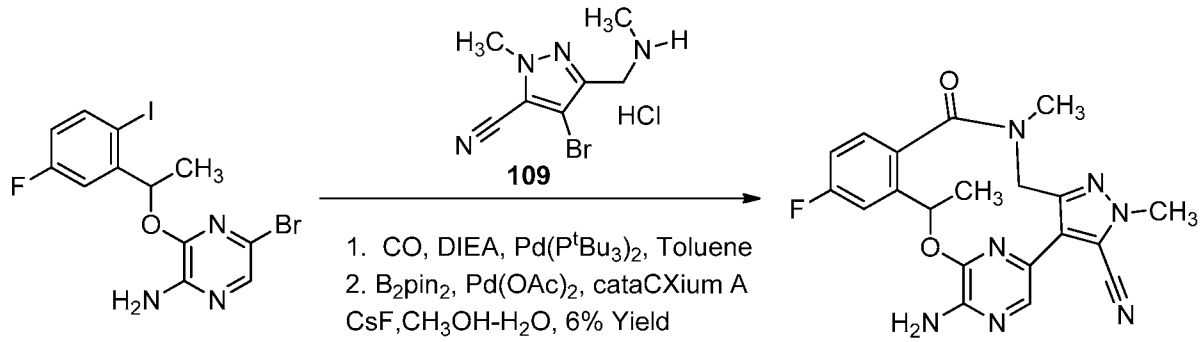
30 **Example 30 and Example 31**

The procedure described for **Example 28** was used to prepare **Example 30 and Example 31.** The analytical chiral separation was performed by SFC on a Chiralcel OD-H (4.6 x 250 mm, 5 micron particle size), which was eluted with 25% methanol in CO_2 at 140 bar. A flow rate of 3.0 mL/min gave $Rt_{(Peak\ 1)}$ = 4.4 minutes and $Rt_{(Peak\ 2)}$ = 5.3 minutes.

Example 30 (Peak 1): 4 mg; >98% ee, 1% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, *J* = 5.3 Hz, 1 H), 7.66 (s, 1 H), 7.63 (dd, *J* = 2.5, 10.3 Hz, 1 H), 7.28 (dd, *J* = 5.8, 8.6 Hz, 1 H), 7.22 (d, *J* = 5.3 Hz, 1 H), 7.11 (dt, *J* = 2.6, 8.5 Hz, 1 H), 6.52 (s, 2 H), 6.08 - 5.98 (m, 1 H), 4.20 (d, *J* = 12.4 Hz, 1 H), 4.16 (d, *J* = 12.1 Hz, 1 H), 3.82 (s, 3 H), 2.89 (s, 3 H), 1.65 (d, *J* = 6.5 Hz, 3 H). LCMS ES *m/z* 410 $[M+H]^+$.

Example 31 (Peak 2): 3 mg, ~80% ee, 1% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, *J* = 5.0 Hz, 1 H), 7.65 (s, 1 H), 7.62 (dd, *J* = 2.6, 10.2 Hz, 1 H), 7.28 (dd, *J* = 5.7, 8.4 Hz, 1 H), 7.22 (d, *J* = 5.0 Hz, 1 H), 7.15 - 7.06 (m, 1 H), 6.51 (s, 2 H), 6.07 - 5.97 (m, 1 H), 4.20 (d, *J* = 12.3 Hz, 1 H), 4.16 (d, *J* = 12.4 Hz, 1 H), 3.82 (s, 3 H), 2.88 (s, 3 H), 1.65 (d, *J* = 6.5 Hz, 3 H). LCMS ES *m/z* 410 $[M+H]^+$.

Synthesis of 7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 32 and Example 33).



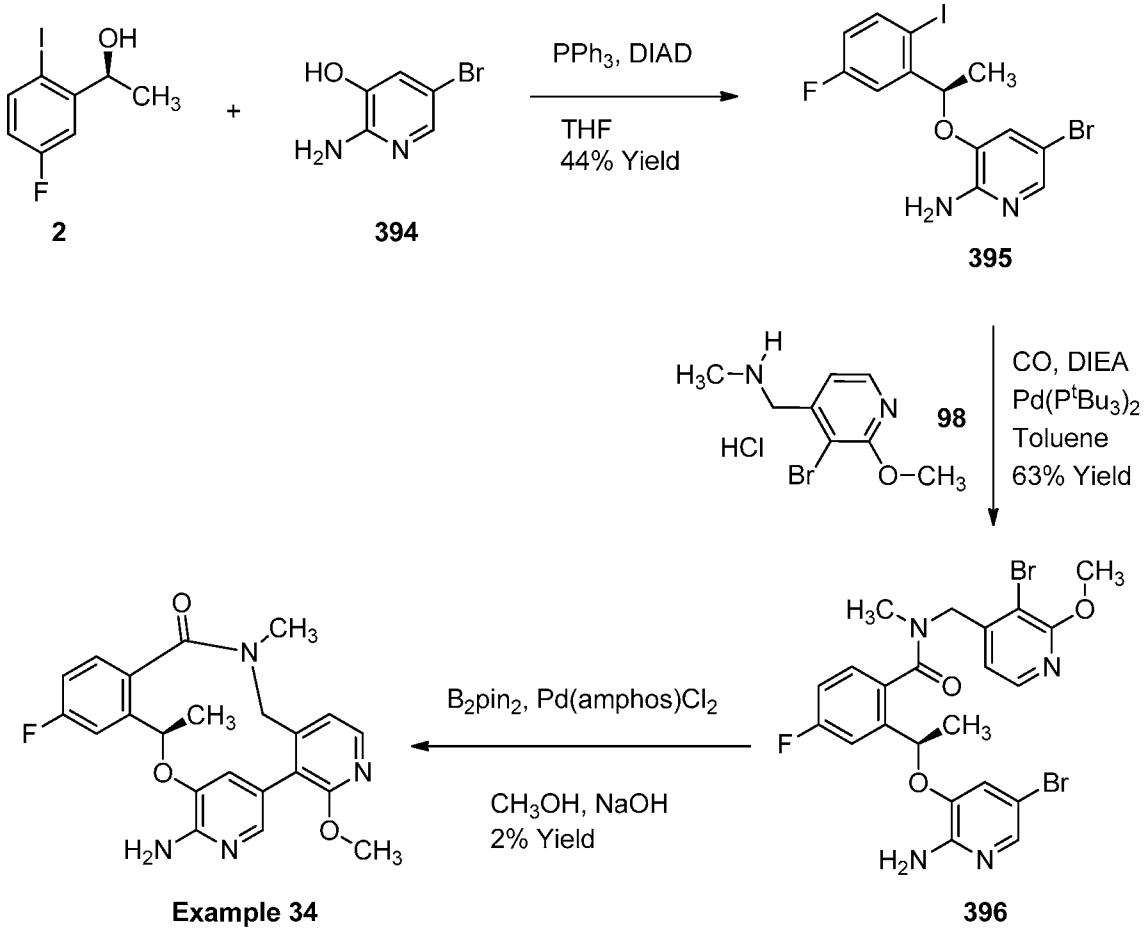
30 **Example 32 and Example 33**

The procedure described for **Example 28** and **29** was used to prepare **Example 32 and Example 33.** The analytical chiral separation was performed by SFC on a Regis Whelk-01 (*R, R*) (4.6 x 250 mm, 5 micron particle size), which was eluted with 20% methanol in CO_2 at 140 bar. A flow rate of 3.0 mL/min gave $Rt_{(Peak\ 1)}$ = 4.5 minutes and $Rt_{(Peak\ 2)}$ = 6.6 minutes.

Example 32 (Peak 1): 8 mg; >99% ee, 3% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1 H), 7.47 (dd, *J* = 2.8, 10.1 Hz, 1 H), 7.41 (dd, *J* = 5.7, 8.4 Hz, 1 H), 7.16 (dt, *J* = 2.8, 8.6 Hz, 1 H), 6.72 (s, 2 H), 5.97 - 5.81 (m, 1 H), 4.30 (AB q, *J* = 13.9 Hz, 1 H), 4.03 (s, 3 H), 2.89 (s, 3 H), 1.64 (d, *J* = 6.5 Hz, 3 H). LCMS *m/z* 408 $[M+H]^+$.

Example 33 (Peak 2): 10 mg, 96% ee, 3% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (1 H, s), 7.47 (1 H, dd, *J* = 10.0, 2.7 Hz), 7.41 (1 H, dd, *J* = 8.3, 5.8 Hz), 7.16 (1 H, td, *J* = 8.5, 2.7 Hz), 6.74 (2 H, s), 5.84 - 5.98 (1 H, m), 4.31 (2 H, AB q, *J* = 13.7 Hz), 4.03 (4 H, s), 2.89 (3 H, s), 1.64 (3 H, d, *J* = 6.6 Hz). LCMS *m/z* 408 $[M+H]^+$.

Preparation of (11*R*)-8-amino-13-fluoro-4-methoxy-11,17-dimethyl-17,18-dihydro-9,5-(metheno)pyrido[3,4-*h*][2,5,11]benzoxadiazacyclotetradecin-16(11*H*)-one (Example 34).



2 **394** **395** **98** **396** **Example 34**

Step 1:

To a solution of both **compound 2** (338 mg, 1.27 mmol), **compound 394** (200 mg, 1.06 mmol) and triphenylphosphine (333 mg, 1.27 mmol) in THF (11 mL) was added DIAD (260 µL, 1.27 mmol). The solution was dark brown. After 30 minutes at room temperature, LCMS showed mostly product. The solvent was removed under reduced pressure and the crude product was purified by column chromatography over silica gel, which was eluted with 0 - 13% EtOAc-DCM, which gave **compound 395** as a yellow gum (205 mg, 44% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (dd, *J* = 5.7, 8.7 Hz, 1 H), 7.54 (d, *J* = 2.0 Hz, 1 H), 7.42 (dd, *J* = 3.0, 10.1 Hz, 1 H), 6.99 (dt, *J* = 3.0, 8.6 Hz, 1 H), 6.75 (d, *J* = 2.0 Hz, 1 H), 6.18 (s, 2 H), 5.45 (q, *J* = 6.1 Hz, 1 H), 1.54 (d, *J* = 6.3 Hz, 3 H). LCMS ES *m/z* 437/439.

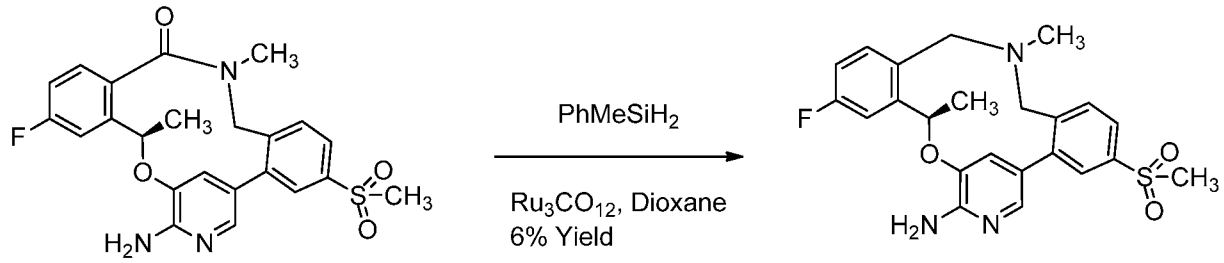
Step 2:

A mixture of **compound 395** (200 mg, 0.46 mmol), **compound 98** (135 mg, 0.50 mmol), DIEA (0.32 mL, 1.8 mmol) and Pd(P*t*-Bu$_3$)$_2$ (24 mg, 0.05 mmol) in toluene (42 mL) was heated at 85 °C in an atmosphere of carbon monoxide at 4 bar. After 18 hours, the reaction mixture was concentrated and purified by column chromatography over silica, which was eluted with 0-100% EtOAc-heptane and gave **compound 396** (165 mg, 63% yield). LCMS ES *m/z* 566/568/571.

Step 3:

A mixture of **compound 396** (165 mg, 0.29 mol), diboron pinacol ester (368 mg, 1.45 mmol), sodium hydroxide (58 mg, 1.45 mmol) and Pd(amphos)Cl$_2$ (20 mg, 0.03 mmol) in methanol (10 mL) was degassed and purged with nitrogen. The mixture was heated at 100 °C for 18 hours and cooled to room temperature. The crude reaction mixture was diluted with EtOAc and sequentially washed with water and brine. The organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel, which was eluted with 0-100% EtOAc-heptane followed by purification by reversed phase chromatography which gave **Example 34** (3 mg, 2% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, *J* = 5.0 Hz, 1 H), 7.72 (dd, *J* = 2.5, 10.3 Hz, 1 H), 7.44 (d, *J* = 1.8 Hz, 1 H), 7.29 (dd, *J* = 5.7, 8.4 Hz, 1H), 7.22 (d, *J* = 5.3 Hz, 1 H), 7.09 (dt, *J* = 2.5, 8.4 Hz, 1 H), 6.96 (s, 1 H), 5.95 (s, 2 H), 5.73 - 5.61 (m, *J* = 6.0 Hz, 1 H), 4.26 (d, *J* = 12.8 Hz, 1 H), 4.04 (d, *J* = 12.8 Hz, 1 H), 3.81 (s, 3 H), 2.99 (s, 3 H), 1.68 (d, *J* = 6.0 Hz, 3 H). LCMS m/z 409 $[M+H]^+$.

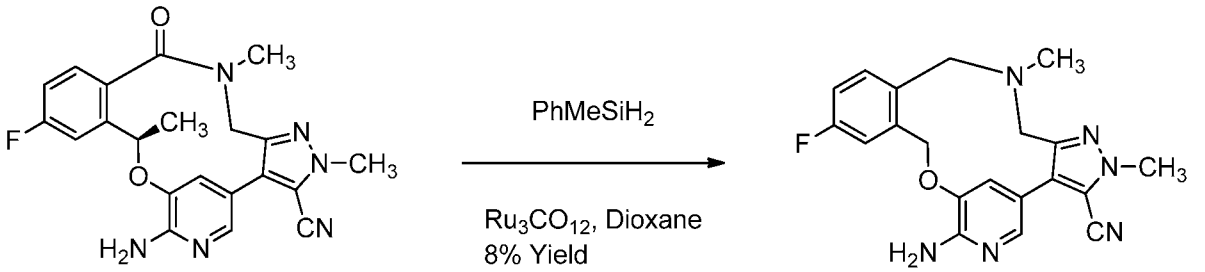
Preparation of (5*R*)-3-fluoro-5,17-dimethyl-13-(methylsulfonyl)-5,16,17,18-tetrahydro-7,11-(metheno)dibenzo[*g,l*][1,4,10]oxadiazacyclotetradecin-8-amine (Example 35).



Example 1 **Example 35**

To a stirred solution of **Example 1** (18.2 mg, 0.04 mmol) in dry dioxane (4 mL) was added Ru_3CO_{12} (4.0 mg, 0.006 mmol) followed by $PhMeSiH_2$ (200 µL, 1.6 mmol). The reaction was stirred overnight at 90 °C for 18 hours. After 18 hours the reaction was concentrated to 1 mL and purified by reversed phase preparative chromatography and gave **Example 35** (1 mg, 6% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.51 (m, 1 H), 7.87 (d, *J* = 2 Hz, 1 H), 7.76 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.56 (m, 1 H), 7.36 (m, 2 H), 7.19 (dd, *J* = 8.3, 6.0 Hz, 1 H), 6.97 (dt, *J* = 8.3, 2.8 Hz, 1 H), 6.08 (br s, 2 H), 6.00 (q, *J* = 6.4 Hz, 1 H), 4.33 (d, *J* = 10.2 Hz, 2 H), 3.17 (s, 2 H), 2.80 (d, *J* = 10.2 Hz, 1 H), 2.53 (s, 3 H), 2.35 (s, 3 H), 1.65 (d, *J* = 6.4 Hz, 3 H). LCMS *m/z* 442 $[M+H]^+$.

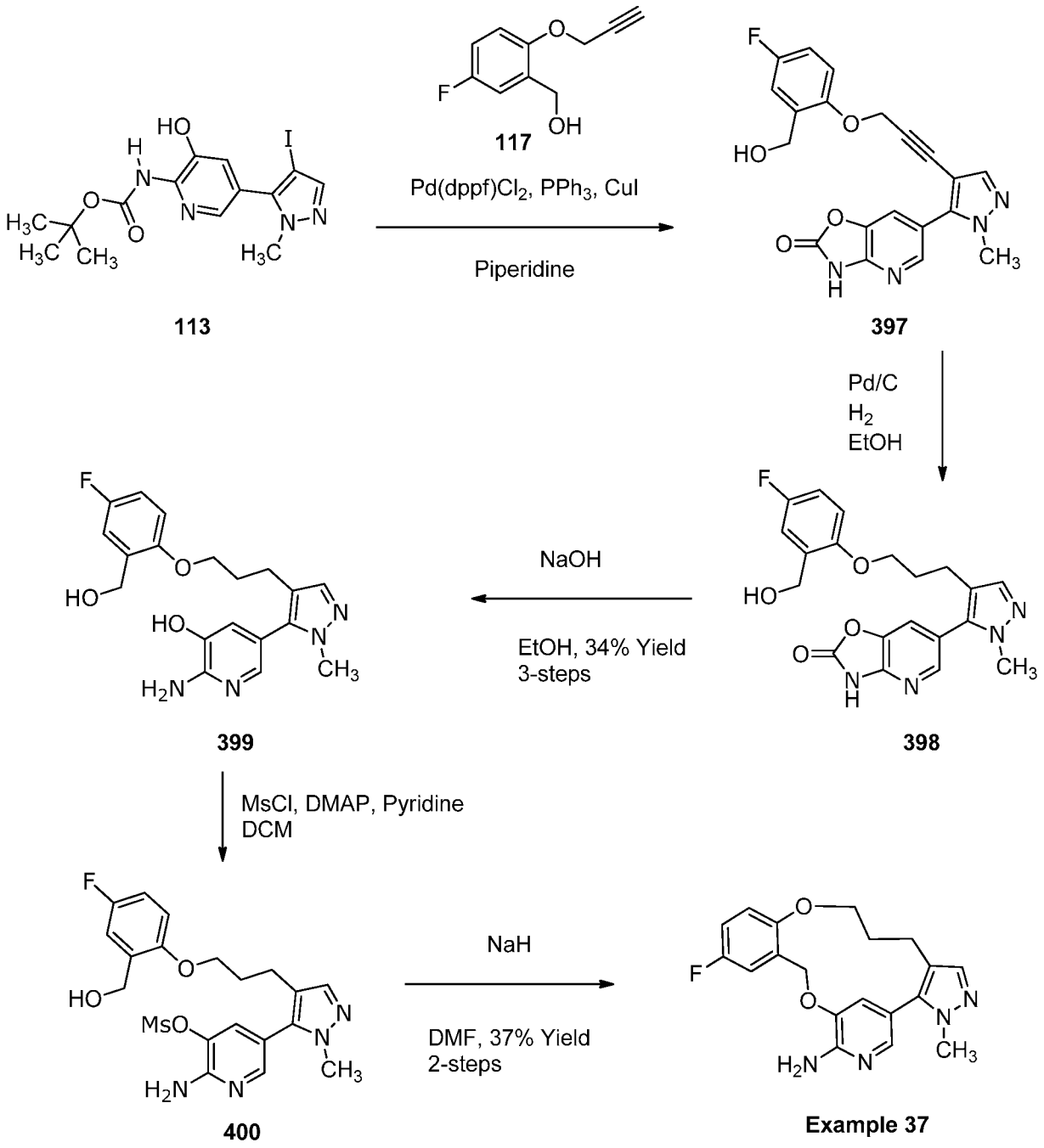
Preparation of (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-10,15,16,17-tetrahydro-2*H*-4,8-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 36).



Example 2 **Example 36**

The procedure described for **Example 2** was used to prepare compound **Example 36** (3 mg, 8%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.64 (m, 1 H), 7.61 (m, 1 H), 7.42 (m, 1 H), 7.24 (m, 1 H), 6.98 (m, 2 H), 6.09 (br s, 2 H), 5.88 (q, *J* = 6.4 Hz, 1 H), 4.33 (d, *J* = 15.5 Hz, 2 H), 3.26 (d, *J* = 15.5 Hz, 2 H), 3.16 (d, *J* = 13.8 Hz, 2 H), 2.94 (d, *J* = 13.8 Hz, 2 H), 3.34 (s, 3 H), 1.65 (d, *J* = 6.4 Hz 3 H). LCMS *m/z* 393 $[M+H]^+$.

Synthesis of 12-fluoro-3-methyl-3,16,17,18-tetrahydro-10H-8,4-(metheno)pyrazolo[4,3-e][1,12,9]benzodioxazacyclopentadecin-7-amine (Example 37).



Step 1:

A mixture of **compound 174** (270 mg, 0.65 mmol), **compound 117** (176 mg, 0.974 mmol), cuprous iodide (6 mg, 0.032 mmol), triphenylphosphine (17 mg, 0.065 mmol) and $PdCl_2(PPh_3)_2$ (23 mg, 0.032 mmol) in neat piperidine (4.3 mL) was bubbled with nitrogen then heated at 80 °C. After 5 hours, the reaction mixture was diluted with EtOAc, washed with saturated NH_4Cl (2x) and brine, dried ($MgSO_4$), filtered and concentrated. The material was purified by flash chromatography over silica gel, which was eluted with DCM/MeOH (0 - 5%) to give **compound 397**.

Step 2:

To a solution of **compound 397** (0.65 mmol) in EtOH (50 mL) was added $Pd(OH)_2$ (50 mg). The mixture was heated at 50 °C at 3-4 bar of hydrogen for 18 hrs. The reaction mixture was filtered through celite and the mother liquor was concentrated to give **compound 398**.

Step 3:

Compound 398 was dissolved in EtOH (5 mL) then 15% NaOH (5 mL) was added and the solution was heated at 85 °C overnight. The reaction was neutralized with 1 N HCl and extracted with EtOAc (3x). Saturated $NaHCO_3$ was added to the aqueous layer which was extracted with EtOAc (2x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography over silica gel, which was eluted with DCM/MeOH (0-10%) to give **compound 399** (82 mg, 34% yield over 3 steps). ^1H NMR (400 MHz, DMSO-d_6) δ 1.85 (q, *J* = 6.9 Hz, 2 H), 2.42 - 2.49 (m, 2 H), 3.64 (s, 3 H), 3.87 (t, *J* = 6.2 Hz, 2 H), 4.43 (br s, 2 H), 5.11 (br. s, 1 H), 5.75 (s, 2 H), 6.80 (d, *J* = 1.5 Hz, 1 H), 6.83 (dd, *J* = 9.1, 4.5 Hz, 1 H), 6.89 - 7.00 (m, 1 H), 7.12 (dd, *J* = 9.6, 3.0 Hz, 1 H), 7.33 (s, 1 H), 7.41 (s, 1 H), 9.72 (br s, 1 H). LCMS *m/z* 373 $[M+H]^+$.

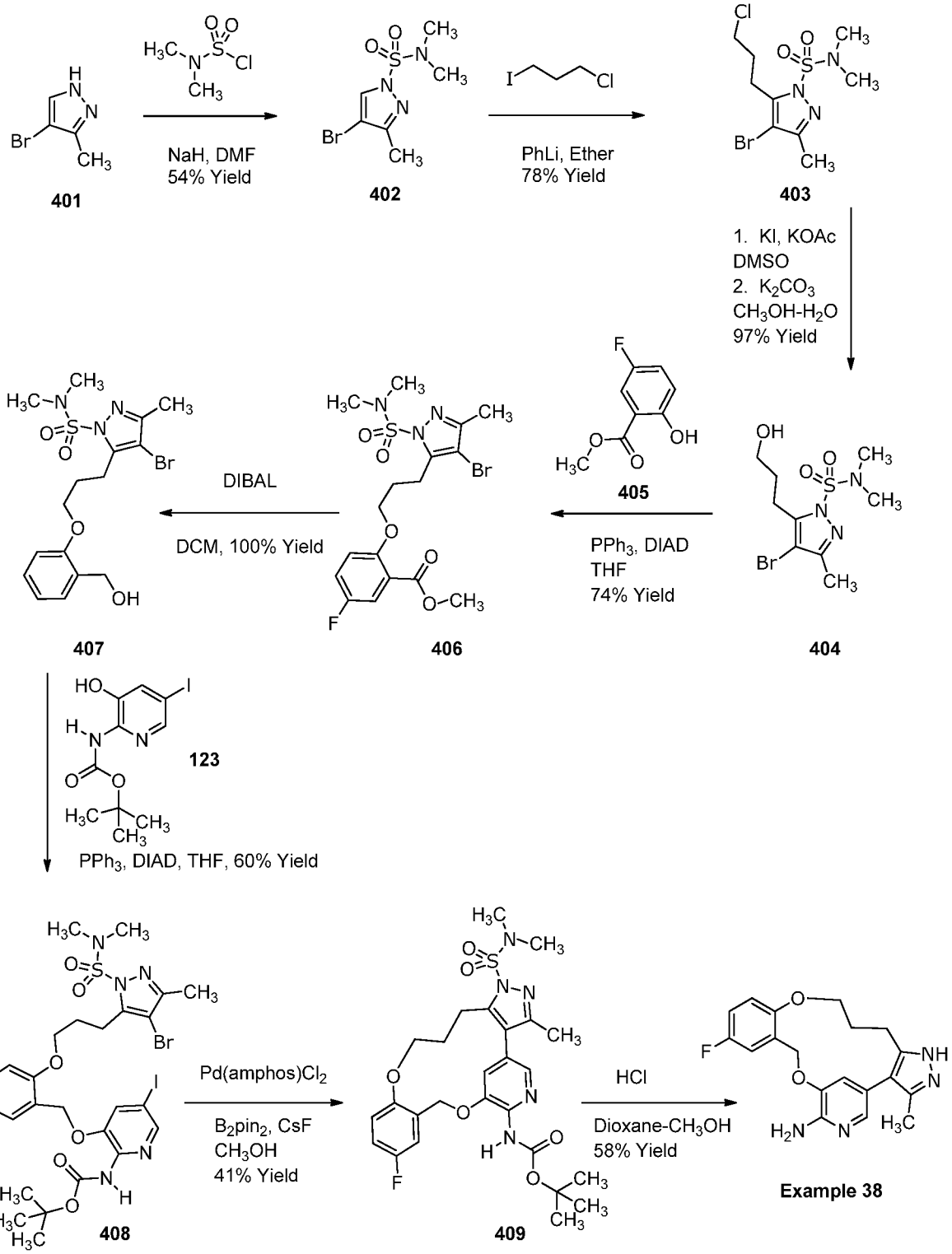
Step 4:

To a cooled (0 °C) solution of **compound 399** (80 mg, 0.22 mmol), DMAP (1.3 mg, 0.011 mmol), and pyridine (200 µL, 2.5 mmol) in DCM (1.4 mL) was added a solution of MsCl (17 µL, 0.22 mmol) in DCM (0.5 mL). After 1 hour the reaction was diluted with EtOAc, washed with saturated NH_4Cl (2x) and brine, dried ($MgSO_4$), filtered and concentrated to give **compound 400** (96 mg).

Step 5:

To a solution of **compound 400** (96 mg, 0.21 mmol) in DMF (4.1 mL) was added NaH (60% dispersion on mineral oil, 9.1 mg, 0.23 mmol). The reaction mixture was heated at 50 °C for 30 minutes then diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography over silica gel, which was eluted with DCM/MeOH (0-10%) to give **Example 37** (27 mg, 37% yield over 2 steps). ^1H NMR (400 MHz, DMSO-d_6) δ 2.04 - 2.20 (m, 2 H), 2.65 (t, *J* = 6.8 Hz, 2 H), 3.78 (s, 3 H), 3.97 - 4.14 (m, 2 H), 5.22 (s, 2 H), 5.68 (br s, 2 H), 6.99 - 7.16 (m, 2 H), 7.25 - 7.36 (m, 2 H), 7.38 (s, 1 H), 7.65 (d, *J* = 1.5 Hz, 1 H). LCMS 355 $[M+H]^+$.

Preparation of 12-fluoro-3-methyl-1,16,17,18-tetrahydro-10H-8,4-(metheno)pyrazolo[3,4-e][1,12,9]benzodioxazacyclopentadecin-7-amine (Example 38).



Step 1:

To a cooled (0 °C) solution of **compound 401** (2.50 g, 15.5 mmol) in DMF (40 mL) was added NaH (60% dispersion on mineral oil, 745 mg, 18.6 mmol). After 30 min a solution of *N,N*-dimethylsulfamoyl chloride (1.67 mL, 15.5 mmol) in DMF (5 mL) was added. The reaction

mixture was gradually warmed to room temperature and stirred for 5 hours. The reaction was quenched with saturated NH_4Cl and diluted with EtOAc. The organic layer was sequentially washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel which was eluted with heptanes/EtOAc (0-30%) and gave **compound 402** as a white waxy solid (2.3 g, 54% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1 H), 2.85 (s, 6 H), 2.23 (s, 3 H).

Step 2:

To a cooled (-78 °C) solution of **compound 402** (2.3 g, 8.4 mmol) in Et_2O (25.5 mL) was added drop-wise phenyl lithium (1.8 M in dibutyl ether, 5.2 mL, 9.3 mmol) keeping the internal temperature less than -65 °C. A white precipitate formed and the mixture became thick. The mixture was warmed to 0 °C and stirred for 30 minutes, and cooled back down to -78 °C and a solution of 1-chloro-3-iodopropane (2.7 mL, 25.3 mmol) in THF (5.0 mL) was added. The reaction was warmed to room temperature and stirred overnight. The solution was diluted with EtOAc, washed sequentially with saturated NH_4Cl and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel which was eluted with heptanes/EtOAc (0-20%) and gave **compound 403** as a clear gum (2.3 g, 78% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.67 (t, J = 6.3 Hz, 2 H), 3.03 - 2.97 (m, 2 H), 2.95 (s, 6 H), 2.20 (s, 3 H), 2.07 - 1.93 (m, 2 H).

Step 3:

A mixture of **compound 403** (1.82 g, 5.28 mmol), potassium iodide (544 mg, 3.27 mmol), and potassium acetate (1.04 g, 10.6 mmol) in DMSO (13.2 mL) was heated at 80 °C overnight. The reaction mixture was diluted with EtOAc, washed with water (2x) and brine, then concentrated to obtain a gum. The residue was dissolved in methanol (26 mL) then water (870 µL) and K_2CO_3 (737 mg, 5.33 mmol) were added. After 30 minutes the reaction was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated to give **compound 404** as a faint yellowish-orange gum (1.67 g, 97% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.57 (t, J = 5.3 Hz, 1 H), 3.47 - 3.37 (m, 2 H), 2.94 (s, 6 H), 2.89 - 2.82 (m, 2 H), 2.19 (s, 3 H), 1.77 - 1.58 (m, 2 H).

Step 4:

To a solution of the **compound 404** (1.1 g, 3.37 mmol), **compound 405** (602 mg, 3.54 mmol), and triphenylphosphine (1.11 g, 4.22 mmol) in THF (16.9 mL) was added DIAD (859 µL, 4.22 mmol) drop-wise, very slowly over 1.5 hours. After stirring at room temperature overnight the reaction was concentrated and purified by flash chromatography eluting with heptanes/EtOAc (0-30%) to give **compound 406** as a clear gum (1.2 g, 74 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 - 2.05 (m, 2 H), 2.19 (s, 3 H), 2.95 (s, 6 H), 3.04 (dd, J = 8.6, 6.8 Hz, 2 H), 3.81 (s, 3

H), 4.04 (t, *J* = 5.8 Hz, 2 H), 7.15 (dd, *J* = 9.2, 4.4 Hz, 1 H), 7.38 (m, 1 H), 7.44 (dd, *J* = 8.8, 3.3 Hz, 1 H).

Step 5:

To a cooled (-78 °C) solution of the **compound 406** (1.2 g, 2.51 mmol) in DCM (12.5 mL) was added DiBAL (1 M in hexanes, 6.27 mL, 6.27 mmol) drop-wise. Once the addition was complete the reaction was quenched with methanol at -78 °C. The ice bath was removed, saturated sodium potassium tartrate (5 mL) was added, and the flask was filled with EtOAc. Once a clear solution formed, the biphasic mixture was washed with water and brined, dried ($MgSO_4$), filtered and concentrated to give **compound 407** as a clear gum (1.2 g, 100% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ .95 - 2.05 (m, 2 H), 2.14 - 2.23 (m, 3 H), 2.87 - 2.99 (m, 6 H), 2.98 - 3.09 (m, 2 H), 3.91 - 4.01 (m, 2 H), 4.50 (d, *J* = 5.8 Hz, 2 H), 5.15 (t, *J* = 5.7 Hz, 1 H), 6.83 - 6.92 (m, 1 H), 6.92 - 7.03 (m, 1 H), 7.14 (dd, *J* = 9.6, 3.3 Hz, 1 H).

Step 6:

To a solution of **compound 407** (660 mg, 1.47), **compound 123** (493 mg, 1.47 mmol) and triphenyphosphine (481 mg, 1.83 mmol) in THF (9.8 mL) was added DIAD drop-wise over 1 hour. After stirring at room temperature for 1 hour, the solution was concentrated and purified by flash chromatography eluting with heptanes/EtOAc (0-40%) to yield **compound 408** (660 mg, 60% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.40 (s, 9 H), 1.98 - 2.10 (m, 2 H), 2.19 (s, 3 H), 2.96 (s, 6 H), 3.02 - 3.12 (m, 2 H), 4.07 (t, *J* = 5.5 Hz, 2 H), 5.12 (s, 2 H), 6.98 - 7.06 (m, 1 H), 7.13 (td, *J* = 8.7, 3.3 Hz, 1 H), 7.36 (dd, *J* = 9.2, 3.2 Hz, 1 H), 7.78 (d, *J*=1.8 Hz, 1 H), 8.16 (d, *J* = 1.8 Hz, 1 H), 9.01 (s, 1 H).

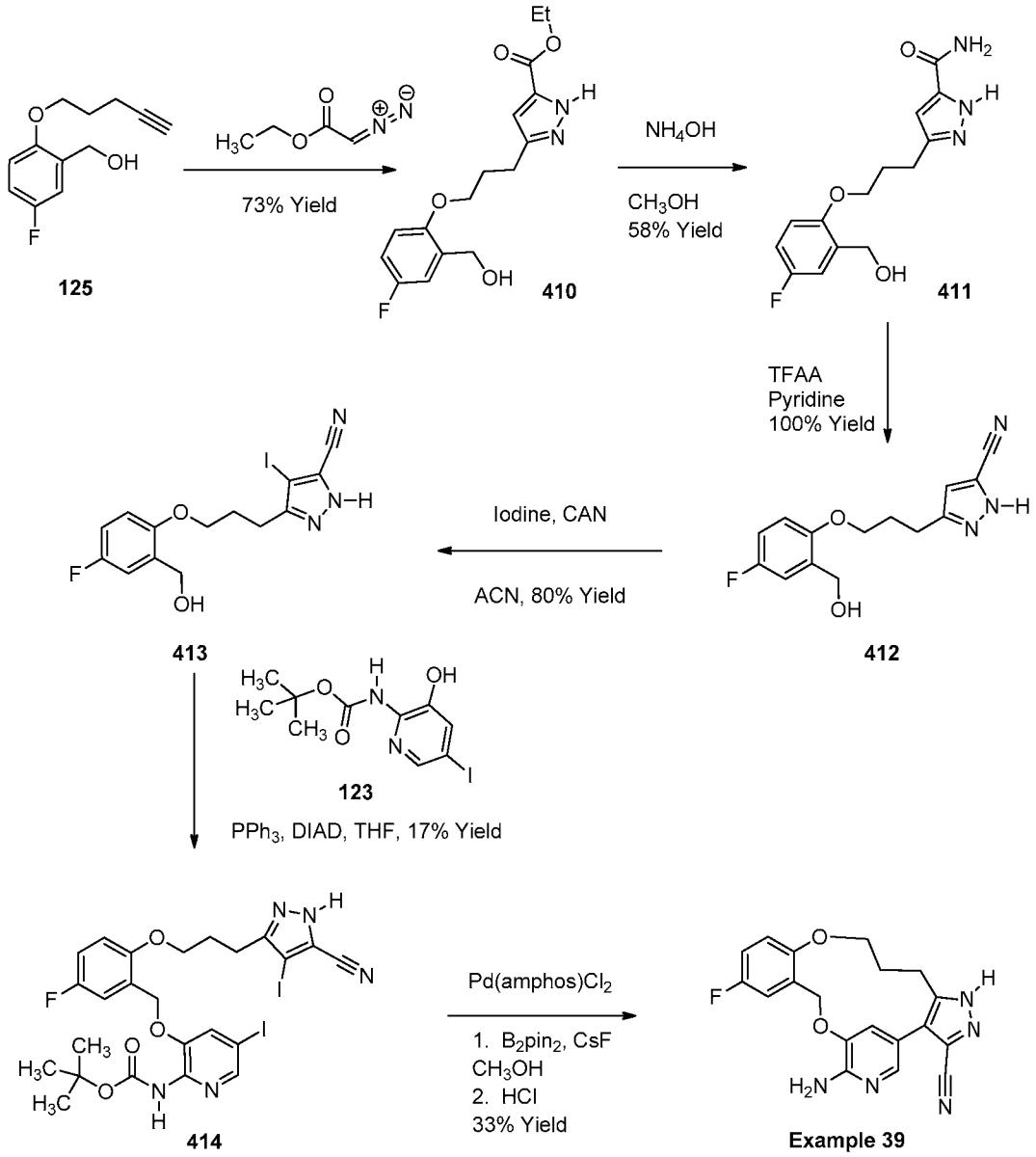
Step 7:

A warm (60 °C) solution of **compound 408** (569 mg, 0.740 mmol), diboron pinacol ester (752 mg, 2.96 mmol), and 1 N cesium fluoride (3.7 mL) in MeOH (37 mL) was bubbled with nitrogen. A solution of bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)-dichloropalladium (II) (79 mg, 0.11 mmol) in toluene (0.5 mL) was added. The mixture was heated at 60 °C for 30 minutes then diluted with EtOAc, washed with brine (2x), dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography eluting with DCM/MeOH (0-6%). The fractions containing the desired product were concentrated and the resultant solids was slurring in 25% EtOAc/heptanes. The solids were collected by vacuum filtration to yield **compound 409** as a cream solid (170 mg, 41% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46 (s, 9 H), 2.31 (s, 5 H), 2.91 - 3.06 (m, 8 H), 4.19 (br s, 2 H), 5.29 (br s, 2 H), 7.04 - 7.23 (m, 2 H), 7.39 (dd, *J* = 8.9, 2.9 Hz, 1 H), 7.69 (d, *J* = 1.5 Hz, 1 H), 7.94 (d, *J* = 1.5 Hz, 1 H), 8.85 (s, 1 H).

Step 8:

To a solution of **compound 409** (170 mg, 0.303 mmol) in dioxane (3.0 ml) was added HCl (4 N in dioxane,1.52 mL, 6.06 mmol). Methanol (0.5 mL) was added and the solution was heated at 40 °C. After 4 hour, the reaction mixture was diluted with EtOAc, washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$), filtered, concentrated. The residue was slurried in DCM and the solids were collected by vacuum filtration to give **Example 38** as a white solid (62 mg, 58% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.19 (s, 5 H), 2.71 - 2.98 (m, 2 H), 4.04 (br s, 2 H), 5.18 (br s, 2 H), 5.56 (s, 2 H), 6.99 - 7.16 (m, 2 H), 7.19 - 7.35 (m, 2 H), 7.48 (s, 1 H), 12.32 (br s, 1 H). LCMS *m/z* 355 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-2,16,17,18-tetrahydro-10H-8,4-(metheno)pyrazolo[3,4-e][1,12,9]benzodioxazacyclopentadecine-3-carbonitrile (Example 39).



Step 1:

Ethyl diazoacetate (2.44 mL, 23.5 mmol) and **compound 125** (4.45 g, 21.4 mmol) were heated at 100 °C in a sealed tube for 2 days. The crude product was purified by flash chromatography eluting with heptanes/EtOAc (0-75%) to give **compound 410** as the major regioisomeric pyrazole (5.0 g, 4:1 mixture of regioisomers, 73% yield).

Step 2:

In a sealed tube a solution of **compound 410** (5.0 g, 16 mmol) in MeOH (31 mL) was heated at 60 °C for 1 hour. Ammonium hydroxide was added and the solution was heated at 60 °C overnight. The reaction mixture was cooled to 0 °C and the solids were collected by vacuum filtration to give a single regioisomer of **compound 411** (2.7 g, 58% yield).

Step 3:

To a cooled (0° C) mixture of **compound 411** (1.50 g, 5.11 mmol) in pyridine (26 mL) was added TFAA (2.87 mL, 20.5 mmol) drop-wise. After 1 hour at 0 °C the solution was diluted with EtOAc, washed with saturated $NaHCO_3$ (2x), brine, 1 N HCl (2x), brine, dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in 20% MeOH/DCM and passed through an SCX cartridge and the mother liquor was concentrated to give **compound 412** (1.4 g, 100% yield). ^{1}H NMR (400 MHz ,DMSO-d_6) δ 13.71 (br s, 1 H), 7.14 (dd, *J* = 3.1, 9.4 Hz, 1 H), 7.03 - 6.94 (m, 1 H), 6.94 - 6.88 (m, 1 H), 6.76 (s, 1 H), 4.48 (s, 2 H), 3.96 (t, *J* = 6.0 Hz, 2 H), 2.82 (t, *J* = 7.7 Hz, 2 H), 2.12 - 1.96 (m, 2 H).

Step 4:

To a solution of **compound 412** (1.4 g, 5.1 mmol) and cerium ammonium nitrate (1.95 g, 3.56 mmol) in ACN (45 mL) was added a solution of iodine (904 mg, 3.56 mmol) in ACN (5 mL). The reaction was heated at 60 °C and stirred for 2 hours. The reaction mixture was diluted with EtOAc, washed with saturated $Na_2S_2O_3$ (2x) and brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography eluting with heptanes/EtOAc (0-50%) to give **compound 413** (1.2 g, 80% pure) which contains 20% of the aldehyde. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.15 (dd, *J* = 3.1, 9.4 Hz, 1 H), 7.02 - 6.94 (m, 1 H), 6.91 - 6.87 (m, 1 H), 4.50 (s, 2 H), 3.94 (t, *J* = 5.9 Hz, 2 H), 2.81 (t, *J* = 7.6 Hz, 2 H), 2.08 - 1.99 (m, 2 H).

Step 5:

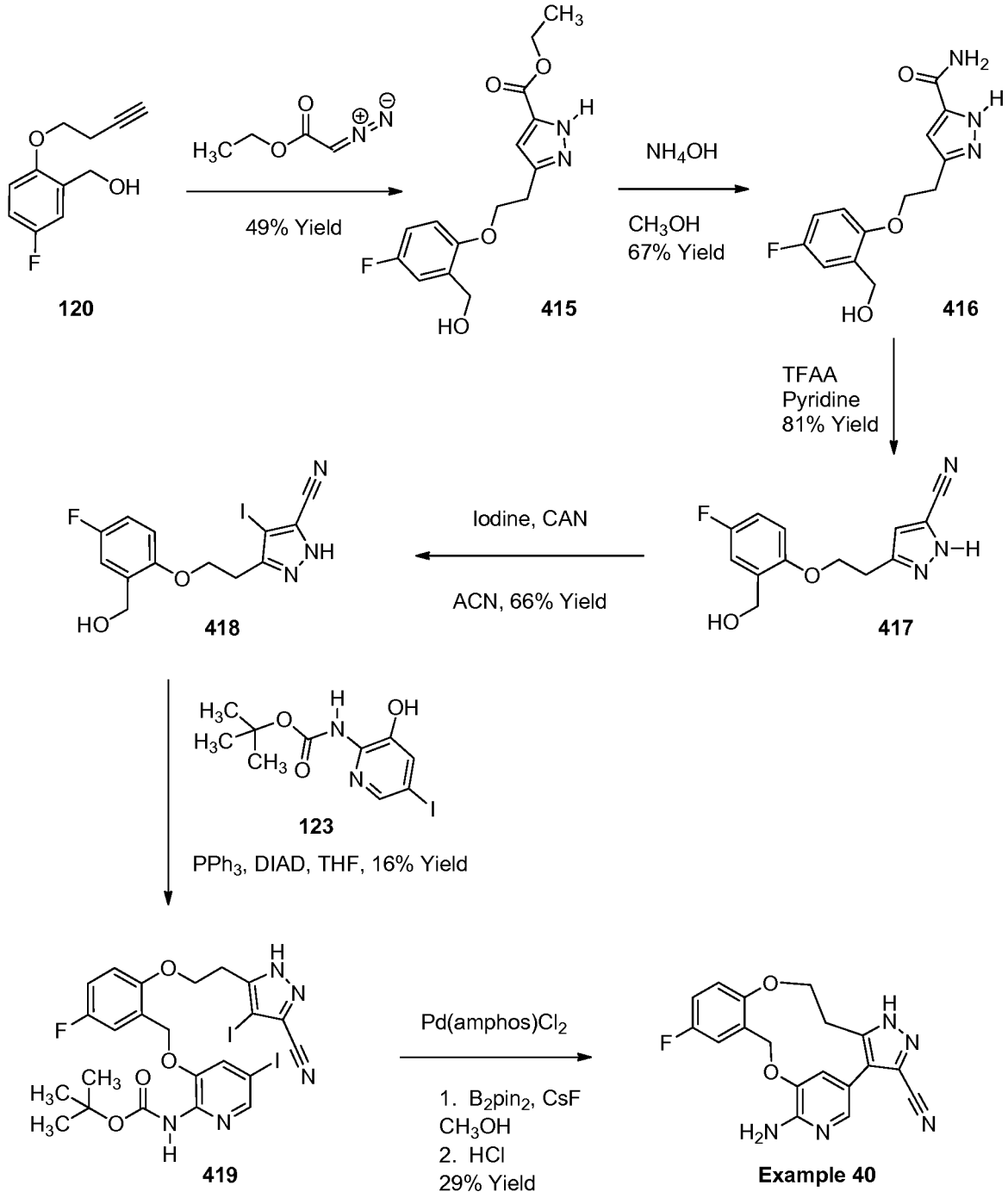
To a solution of **compound 413** (500 mg, 80% pure, 1.0 mmol), **compound 123** (340 mg, 1.0 mmol) and triphenylphosphine (327 mg, 1.25 mmol) in THF (6.7 mL) was added DIAD (254 µL, 1.25 mmol) drop-wise over 1 hour. Once the reaction was complete by LCMS, the solution was concentrated and purified by flash chromatography eluting with heptanes/EtOAc (0 - 50%). The

fractions containing the desired product were concentrated and the solids were triturated with Et_2O to give **compound 414** (125 mg, 17% yield). ^1H NMR (400 MHz ,DMSO-d_6) δ 1.40 (s, 9 H), 1.99 - 2.15 (m, 2 H), 2.85 (t, *J* = 7.4 Hz, 2 H), 4.02 (t, *J* = 5.7 Hz, 2 H), 5.12 (s, 2 H), 7.02 (dd, *J* = 9.2, 4.4 Hz, 1 H), 7.13 (td, *J* = 8.8, 3.2 Hz, 1 H), 7.35 (dd, *J* = 9.2, 3.2 Hz, 1 H), 7.80 (d, *J* = 1.5 Hz, 1 H), 8.15 (d, *J* = 1.5 Hz, 1 H), 9.00 (s, 1 H), 14.14 (br s, 1 H).

Step 6:

In a sealed vial a mixture of **compound 414** (120 mg, 0.17 mmol), diboron pinacol ester (212 mg, 0.84 mmol), and cesium fluoride (127 mg, 0.835 mmol) in MeOH (8.4 mL) and water (0.80 mL) was bubbled with nitrogen. A solution of bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium (II) (18 mg, 0.025 mmol) in toluene (0.5 mL) was added. The mixture was heated at 60 °C for 1 hour then diluted with EtOAc, washed with brine (2x), dried (Na_2SO_4), filtered, concentrated. The residue was dissolved in DCM (1 mL) and HCl was added (4 N in dioxane, 1 mL, 4.2 mmol). After stirring at room temperature overnight, the reaction was concentrated and purified by flash chromatography eluting with DCM/7 N NH_3 MeOH (0-6%). The fractions containing the desired product were concentrated and the resultant solids were triturated with Et_2O to give **Example 39** (20 mg, 33% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 2.23 (br s, 2 H), 3.03 (br s, 2 H), 3.55 - 4.55 (m, 2 H), 5.21 (br s, 2 H), 5.90 (s, 2 H), 7.04 - 7.16 (m, 2 H), 7.30 (dd, *J* = 8.9, 2.4 Hz, 1 H), 7.38 (d, *J* = 2.0 Hz, 1 H), 7.75 (d, *J* = 1.8 Hz, 1 H), 13.88 (br s, 1 H). LCMS *m/z* 366 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-16,17-dihydro-1H,10H-8,4-(metheno)pyrazolo-[3,4-d][1,11,8]benzodioxazacyclotetradecine-3-carbonitrile (Example 40).



Step 1:

The procedure described in step 1 for **Example 39** was used to prepare **compound 415** (1.6 g, 49% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (t, J = 7.0 Hz, 3 H), 3.07 (br. s, 2 H), 4.13 - 4.22 (m, 2 H), 4.25 (d, J = 6.6 Hz, 2 H), 4.40 (s, 2 H), 4.95 - 5.34 (m, 1 H), 6.63 (br. s, 1 H), 6.89 - 7.06 (m, 2 H), 7.13 (dd, J = 9.4, 2.6 Hz, 1 H), 13.29 (br s, 1 H).

Step 2:

The procedure described in step 2 for **Example 39** was used to prepare **Compound 416** (930 mg, 67% yield). ^{1}H NMR (400 MHz ,DMSO-d_6) δ 12.97 (br s, 1 H), 7.38 (br s, 1 H), 7.18 - 7.05 (m, 2 H), 7.02 - 6.90 (m, 2 H), 6.49 (s, 1 H), 5.19 (t, *J* = 5.4 Hz, 1 H), 4.41 (d, *J* = 5.0 Hz, 2 H), 4.18 (t, *J* = 6.4 Hz, 2 H), 3.06 (t, *J* = 5.9 Hz, 2 H).

Step 3:

The procedure described in step 3 for **Example 39** was used to prepare **Compound 417** (700 mg, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.10 (t, *J* = 6.2 Hz, 2 H), 4.19 (t, *J* = 6.3 Hz, 2 H), 4.37 (s, 2 H), 6.82 (s, 1 H), 6.91 - 7.05 (m, 2 H), 7.13 (dd, *J* = 9.6, 3.0 Hz, 1 H), 13.77 (br s, 1 H).

Step 4:

The procedure described in step 4 for **Example 39** was used to prepare **Compound 418** (630 mg, 66% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.10 (t, *J* = 6.2 Hz, 2 H), 4.20 (t, *J* = 6.2 Hz, 2 H), 4.34 (s, 2 H), 6.91 - 7.05 (m, 2 H), 7.13 (dd, *J* = 9.4, 3.2 Hz, 1 H).

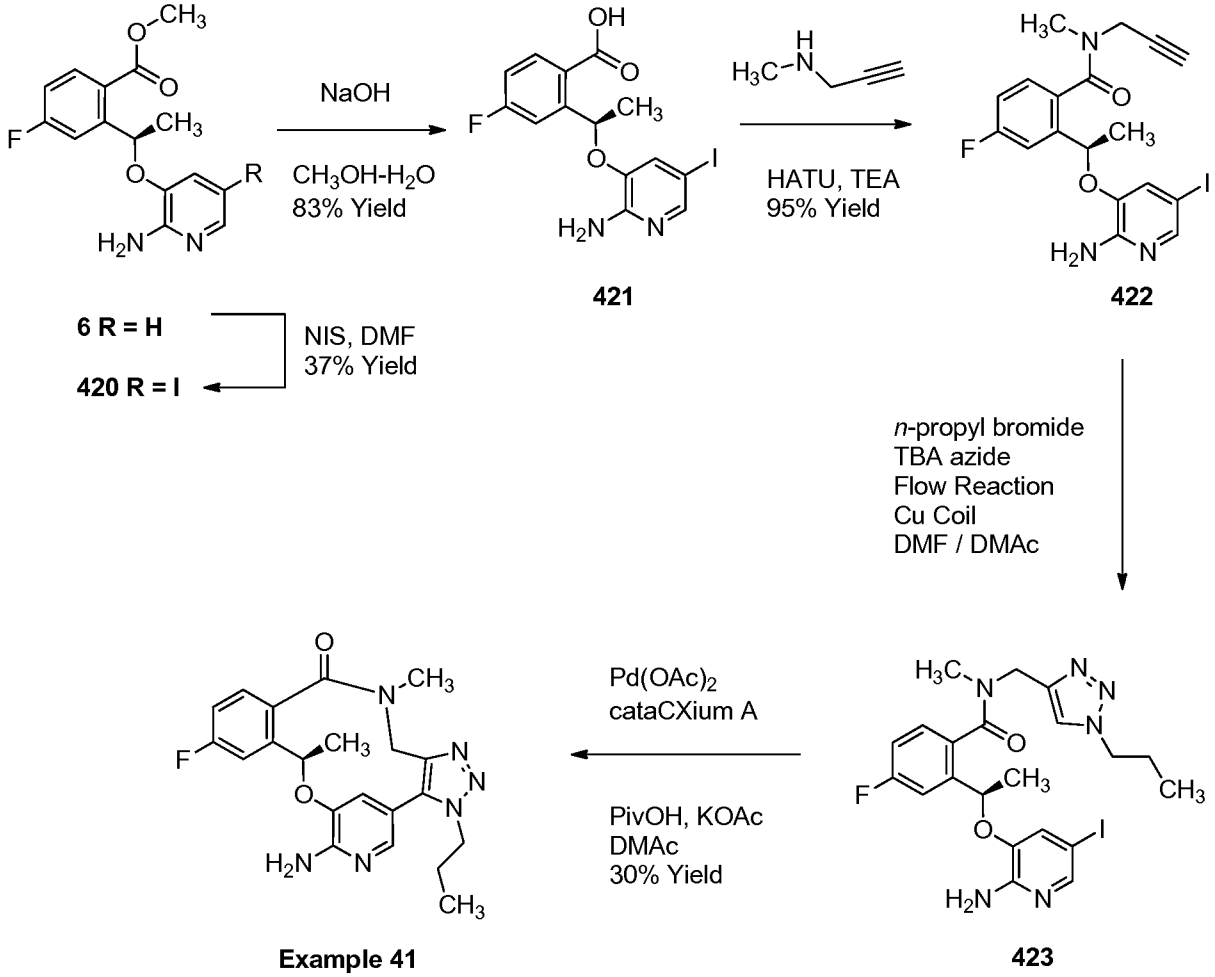
Step 5:

The procedure described in step 5 for **Example 39** was used to prepare **Compound 419** (180 mg, 16% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41 (s, 9 H) 3.16 (t, *J* = 6.2 Hz, 2 H) 4.25 (t, *J* = 6.3 Hz, 2 H) 5.00 (s, 2 H) 6.96 - 7.19 (m, 2 H) 7.33 (dd, *J* = 9.3, 3.0 Hz, 1 H) 7.74 (d, *J* = 1.8 Hz, 1 H) 8.17 (d, *J* = 1.8 Hz, 1 H) 9.03 (s, 1 H) 14.23 (br s, 1 H).

Step 6:

The procedure described in step 6 for **Example 39** was used to prepare **Example 40** (25 mg, 29% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.06 - 3.17 (m, 2 H), 4.51 (br s, 2 H), 5.19 (br s, 2 H), 5.54 (br s, 2 H), 7.02 - 7.19 (m, 2 H), 7.37 (dd, *J* = 9.1, 3.0 Hz, 1 H), 7.67 (d, *J* = 1.8 Hz, 1 H), 7.86 (d, *J* = 1.8 Hz, 1 H), 13.46 (s, 1 H). LCMS ES *m/z* 352 $[M+H]^+$.

Preparation of (10*R*)-7-amino-12-fluoro-10,16-dimethyl-3-propyl-16,17-dihydro-3*H*-8,4-(metheno)[1,2,3]triazolo[4,5-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 41).



Step 1:

Compound 6 (7.6 g, 26.2 mmol) was dissolved in DMF (76 mL) to give a brown solution which was cooled to -5 °C under a nitrogen atmosphere. *N*-iodosuccinimide (5.9 g, 26.2 mmol) was added in portions (7 portions) with no noticeable exotherm detected. After warming to room temperature, a TLC (50% EtOAc/heptane) showed **compound 6** was present. The reaction mixture was re-cooled to 0 °C and more NIS (5.6 g, 24.9 mmol) was added over 2.5 h. The reaction was quenched with 10% aqueous sodium thiosulphate (50 mL) and saturated sodium bicarbonate (30 mL). The brown mixture was evaporated to a residue (ca. 60 mL) which was partitioned between EtOAc (200 mL) and 10% aqueous sodium thiosulphate (200 mL). After separation, the organic was washed with saturated aqueous sodium bicarbonate (100 mL) and then brine (100 mL). The aqueous layer was back extracted with EtOAc (50 mL). The combined EtOAc layers were dried over $MgSO_4$, filtered and evaporated to give a brown oily residue (ca. 7 g). The crude product was absorbed onto silica and purified by column chromatography (eluent: 20 to 40% EtOAc/heptane) and gave **compound 420** as a brown solid (4.0 g, 37% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (1 H, m), 7.57 (2 H, m), 7.21 (1 H, t),

6.91 (1 H, s), 6.13 (1 H, m), 6.10 (2 H, s), 3.85 (3 H, s), 1.51 (3 H, d). LCMS ES *m/z* 417 $[M+H]^+$.

Step 2:

To a solution of **compound 420** (400 mg, 0.961 mmol) in MeOH, was added 2 M NaOH (1.0 mL, 2.0 mmol). The mixture was stirred at room temperature. After 6 hours, the reaction was only ~20% complete by LCMS. Additional 4 M NaOH (1.0 mL, 4.0 mmol) was added. The mixture was stirred at room temperature. After 11 h, the reaction was complete. About 70% of the solvent was removed under reduced pressure and the residue was adjusted to pH = ~7 with 2 N HCl. The precipitate was collected through filtration and rinsed with MeOH/water to afford **compound 421** as a solid (321 mg, 83% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.56 (d, *J* = 6.3 Hz, 3 H), 6.19 (br s, 2 H), 6.33 (q, *J* = 6.4 Hz, 1 H), 6.93 (d, *J* = 1.5 Hz, 1 H), 7.23 (td, *J* = 8.5, 2.8 Hz, 1 H), 7.54 (dd, *J* = 10.4, 2.5 Hz, 1 H), 7.61 (d, *J* = 1.8 Hz, 1 H), 7.97 (dd, *J* = 8.7, 5.9 Hz, 1 H), 13.42 (br s, 1 H). LCMS APCI *m/z* 403 $[M+H]^+$.

Step 2:

To a solution of **compound 421** (300 mg, 0.746 mmol), the *N*-methyl propargyl amine (57 mg, 0.82 mmol), DIEA (289 mg, 2.24 mmol) in DMF (3 mL) was added HATU (340 mg, 0.895). The resulting mixture was stirred at room temperature. After 1.5 h, the reaction was only ~15% complete. The reaction mixture was heated up to 55 °C. After 1 h, the reaction was complete. The solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed with water, saturated $NaHCO_3$ and brine. The organic layer was filtered, concentrated and purified by flash chromatography over silica gel, which was eluted with 3% to 50% EtOAc/heptane, and gave **compound 422** as a light brown gum (323 mg, 95% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.54 (d, *J* = 6.3 Hz, 3 H), 2.85 (s, 3 H), 3.07 (s, 1 H), 4.33 - 4.40 (m, 2 H), 5.35 - 5.50 (m, 1 H), 6.12 (s, 1 H), 7.17 - 7.28 (m, 1 H), 7.30 - 7.37 (m, 1 H), 7.50 (d, *J* = 8.1 Hz, 1 H), 7.62 (d, *J* = 1.8 Hz, 1 H). LCMS APCI *m/z* 454 $[M+H]^+$.

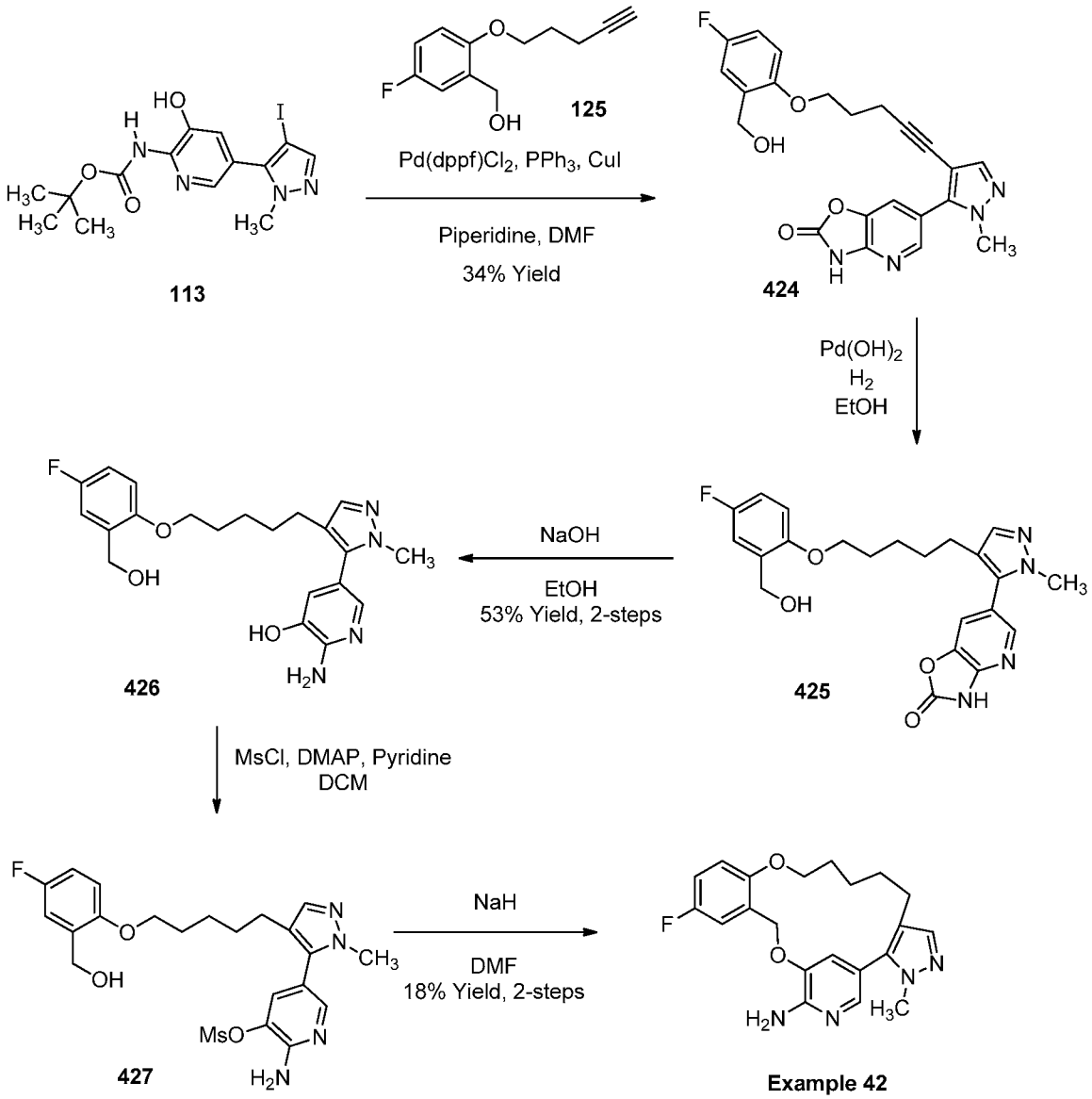
Step 3:

To a stirred solution of 1-bromopropane (0.4 mmol) in DMAc (200 µL) was added tetrabutylammonium azide (0.4 mmol) drop-wise (200 µL/min) as a solution in DMF (400 µL). To this solution was then added **compound 422** (91 mg, 0.2 mmol) drop-wise (200 µL/min) as a solution in DMAc (200 µL). After 30 seconds the reaction segment (800µL) was injected into a flow reactor device and passed through a coil of copper tubing for 3 minutes at 150 °C. The reaction segment was then cooled and collected by a UV (280 nm) triggered fraction collector. LCMS analysis of this segment showed the presence of the desired mass ion for **compound 423**. LCMS *m/z* 539 $[M+H]^+$. The solvent was removed under a purge of N_2 at 50°C and used crude in the subsequent step.

Step 4:

To **compound 423** (108 mg, 0.2 mmol) was added dry, degassed DMAc (3 mL), $Pd(OAc)_2$ (0.0021 mmol), cataCXium® A (0.0042 mmol), Pivalic Acid (0.0067 mmol) and KOAc (0.167 mmol) under controlled glove box conditions (<50 ppm O_2, <50 ppm H_2O). The reaction mixture was stirred at 110 °C for 18 hours. After cooling to room temperature, the reaction mixture was diluted with water and EtOAc. The organic layer was collected and washed with saturated $NaHCO_3$ and water. The organic layer was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel, which was eluted with 30-90% EtOAc-heptane and gave unpure product. The sample was re-purified by reverse phase chromatography which gave **Example 41** as a white solid (16 mg, 30% Yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 - 7.72 (m, 2 H), 7.44 (dd, *J* = 5.7, 8.5 Hz, 1 H), 7.16 (dt, *J* = 2.8, 8.5 Hz, 1 H), 6.77 (s, 1 H), 6.33 (s, 2 H), 5.65 (q, *J* = 7.2, 3.6 Hz, 1 H), 4.51 (d, *J* = 14.4 Hz, 1 H), 4.29 - 4.43 (m, 2 H), 4.15 (d, *J* = 14.7 Hz, 1 H), 2.99 (s, 3 H), 1.73 - 1.83 (m, 2 H), 1.67 (d, *J* = 6.1 Hz, 3 H), 0.78 (t, *J* = 7.3 Hz, 3 H). LCMS APCI *m/z* 412 $[M+H]^+$.

Preparation of 12-fluoro-1-methyl-1,4,5,6,7,8-hexahydro-14H-16,20-(metheno) pyrazolo[4,3-g][1,14,11]benzodioxazacycloheptadecin-17-amine (Example 42).



Step 1:

A mixture of **compound 113** (300 mg, 0.72 mmol), **compound 125** (300 mg, 1.4 mmol), cuprous iodide (6.9 mg, 0.036 mmol), triphenyl phosphine (9.4 mg, 0.036 mmol) and $PdCl_2(PPh_3)_2$ (50.5 mg, 0.072 mmol) in a mixture of DMF (4.81 mL) and piperidine (4.81 mL) was bubbled with nitrogen, and then heated in an oil bath to 90 °C. After 4 hours, the reaction was allowed to cool, and diluted with ethyl acetate. The solution was washed with saturated aqueous NH_4Cl (3 x), brine, and the organics dried over $MgSO_4$. The solution was filtered, concentrated, and the residue subjected to column chromatography over silica gel (50-100% EA/heptane) to afford **compound 424** (102 mg, 34%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.69 (br. s., 1 H), 8.22 (d, *J* =1.77 Hz, 1 H), 7.88 (d, *J* =1.77 Hz, 1 H), 7.64 (s, 1 H), 7.12 (dd, *J* = 9.35, 3.28 Hz, 1 H), 6.90 - 6.99 (m, 1 H), 6.82, (dd, *J* = 8.84, 4.55 Hz, 1 H),

5.12 (br. s., 1 H), 4.45 (br. s., 2 H), 3.96 (t, *J* = 6.06 Hz, 2 H), 3.80 (s, 3 H), 1.88 (quin, J= 6.51 Hz, 2 H). LCMS *m/z* 423 $[M+H]^+$.

Step 2:

Compound 424 (100 mg, 0.237 mmol) was dissolved in ethanol (0.5 mL), and palladium hydroxide 25 mg, 20% on carbon) added. The mixture was flushed with nitrogen, followed by being pressurized under 3-4 bar of hydrogen. The reaction was agitated, and heated to 60 °C for 12 hours. The reaction vessel was allowed to cool, and LCMS indicated that the major product was the desired accompanied by minor amounts of the ethyl carbamate. The reaction was filtered through a celite cartridge to remove the catalyst, and washed with methanol. The filtrate was concentrated, and to the residue (**compound 425)** added 2N aqueous NaOH (2 mL), and methanol (0.8 mL). The reaction was heated to 90 °C for 4 hours, allowed to cool, and stirred for a further 48 hours. The mixture was diluted with EtOAc, and washed with saturated aqueous NH_4Cl. The aqueous was adjusted to pH 6 using 4N HCl, and further extracted with EtOAc. The organics were dried over $MgSO_4$, concentrated, and purified by column chromatography over silica gel (0-10% MeOH/DCM) to afford **compound 426** (5mg, 53%) as a colorless solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.72 (br. s., 1 H), 7.40 (d, *J* = 1.76 Hz, 1 H), 7.31 (s, 1 H), 7.12 (dd, *J* = 9.57, 3.27 Hz, 1 H), 6.93 - 7.02 (m, 1 H), 6.83 - 6.92 (m, 1 H), 6.79 (d, *J* =1.76 Hz, 1 H), 5.75 (s, 2 H), 5.13 (br. s., 1 H), 4.45 (s, 2 H), 3.88 (t, *J* = 6.42 Hz, 2 H), 3.63 (s, 3 H), 2.31 (t, *J* = 7.55 Hz, 2 H), 1.56 - 1.69 (m, 2 H), 1.41 - 1.56 (m, 2 H), 1.27 - 1.41 (m, 2 H). LCMS *m/z* 401 $[M+H]^+$.

Step 3:

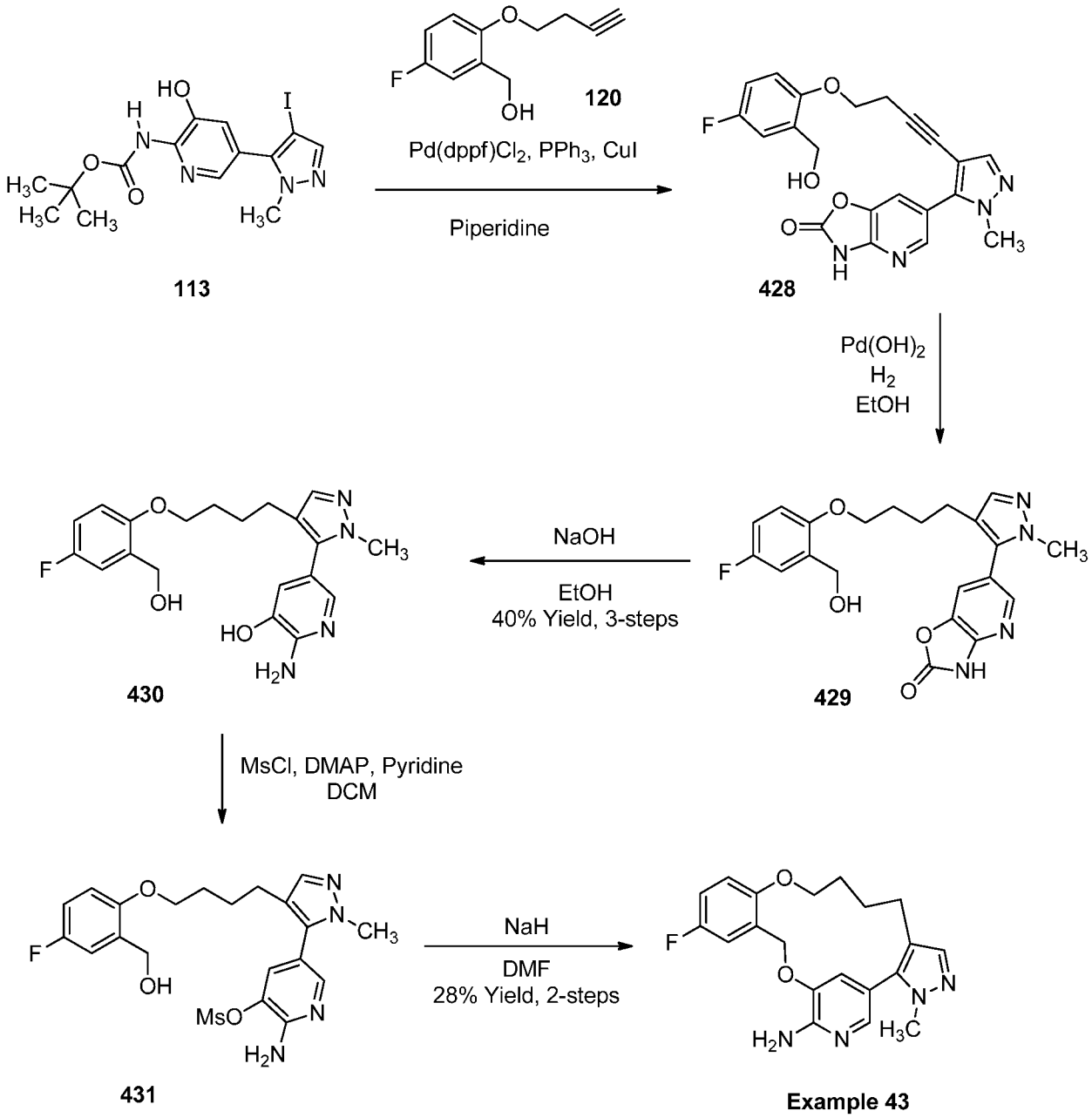
To a cooled 0 °C solution of **compound 426** in DCM (500 µL) was added TEA (20.9 µL, 0.15 mmol), and a catalytic amount of DMAP (0.6 mg), followed by a solution of MsCl (9.7 µl, 0.125 mmol) in DCM (250 µL). The reaction was allowed to slowly warm to room temperature, and after one hour, LCMS indicated that the desired product was the major component formed. The reaction was diluted with DCM, and washed with water. The organics were dried ($MgSO_4$), filtered and concentrated. After being dried overnight under high vacuum, **compound 427** (53 mg, 89%), was isolated as a light foamy solid, which was used without purification in the cyclization step. LCMS *m/z* 479 $[M+H]^+$.

Step 4:

To a solution of the **compound 427** (50 mg, 0.1 mmol) in DMF (2.08 mL) was added NaH (5.6 mg, 0.15 mmol, 60% dispersion). The reaction was heated to 50 °C for 3 hours. A further portion of NaH (5 mg) was added, and the reaction heated for a further hour. The reaction was diluted with EtOAc, washed with saturated aqueous NH_4Cl/water mixture, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography over silica gel (0-

10% MeOH/DCM) to afford **Example 42** (6 mg, 20%) as a yellow cream solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (s, 1 H), 7.23 - 7.30 (m, 2 H), 7.02 - 7.10 (m, 1 H), 6.95 - 7.02 (m, 1 H), 6.86 (s, 1 H), 5.77 (br. s., 2 H), 5.26 (s, 2 H), 4.01 (t, *J* = 5.41 Hz, 2 H), 3.65 (s, 3 H), 2.30 (t, *J* = 6.29 Hz, 2 H), 1.68 (m, *J* = 5.29 Hz, 2 H) 1.41 - 1.58 (m, 4 H). LCMS APCI *m/z* 383 $[M+H]^+$.

Preparation of 12-fluoro-3-methyl-16,17,18,19-tetrahydro-3*H*,10*H*-8,4-(metheno)-pyrazolo[4,3-*f*][1,13,10]benzodioxazacyclohexadecin-7-amine (Example 43)



Step 1:

A mixture of **compound 113** (400 mg, 0.96 mmol), **compound 120** (233 mg, 1.2 mmol), cuprous iodide (9.1 mg, 0.048 mmol), triphenyl phosphine (25.2 mg, 0.096 mmol) and $PdCl_2(PPh_3)_2$ (33.7 mg, 0.048 mmol) in piperidne (6.4 mL) was bubbled with nitrogen, and then heated in an oil bath to 90 °C. After 4 hours, the reaction was allowed to cool, and diluted with EtOAc. The solution was washed with saturated aqueous NH_4Cl (3x), brine, and the organics dried over $MgSO_4$. The solution was filtered, concentrated, and the residue subjected to column chromatography over silica gel (0-10% MeOH/DCM) to afford **compound 428** as a gummy solid contaminated with excess piperidine. This material was used without further purification in the following step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1 H), 8.06 (d, *J* = 2.01 Hz, 1 H), 7.64 (s, 1 H) 7.45 (d, *J* = 1.76 Hz, 1 H), 7.13 (dd, *J* = 9.32, 2.77 Hz, 1 H), 6.92 - 7.01 (m, 2 H), 5.13 (br. s., 1 H), 4.48 (d, *J*= 2.27 Hz, 2 H), 4.06 (t, *J* =6.67 Hz, 2 H), 3.82 (s, 3 H), 2.78 (t, *J* =6 .55 Hz, 2 H). LCMS *m/z* 409 $[M+H]^+$.

Step 2:

Compound 428 (400 mg, 0.979 mmol) was dissolved in ethanol (9.8 mL), and palladium hydroxide (40 mg, 20% on carbon) added. The mixture was flushed with nitrogen, followed by being pressurized under 3-4 bar of hydrogen. The reaction was agitated, and heated to 50 °C for 18 hours. The reaction vessel was allowed to cool, and LCMS indicated that the major product was the desired accompanied by minor amounts of the ethyl carbamate. The reaction was filtered through a celite cartridge to remove the catalyst, and washed with methanol. The filtrate was concentrated, dissolved in ethanol (10 mL), and 15% aqueous NaOH (7.83 mL) was added. The reaction was heated to 85 °C for 12 hours, and allowed to cool. The mixture was neutralized with 1N aqueous HCl, and extracted with EtOAc. The organics were dried over $MgSO_4$, concentrated, and purified by column chromatography over silica gel (0-10% MeOH/DCM) to afford **compound 430** (151 mg, 40%) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (br. s., 1 H), 7.41(d, *J* = 1.76 Hz, 1 H), 7.33 (s, 1 H), 7.12 (dd, *J* = 9.44, 3.15 Hz, 1 H), 6.91 - 7.02 (m, 1 H), 6.85 (dd, *J* = 8.81, 4.53 Hz, 1 H), 6.79 (d, *J* = 2.01 Hz, 1 H), 5.75 (s, 2 H), 5.13 (br. s.,1 H), 4.45 (s, 2 H), 3.87 (t, *J* = 6.04 Hz, 2 H), 3.64 (s, 3 H), 2.35 (t, *J* = 7.30 Hz, 2 H), 1.47 - 1.74 (m, 4 H). LCMS *m/z* 387 $[M+H]^+$.

Step 3:

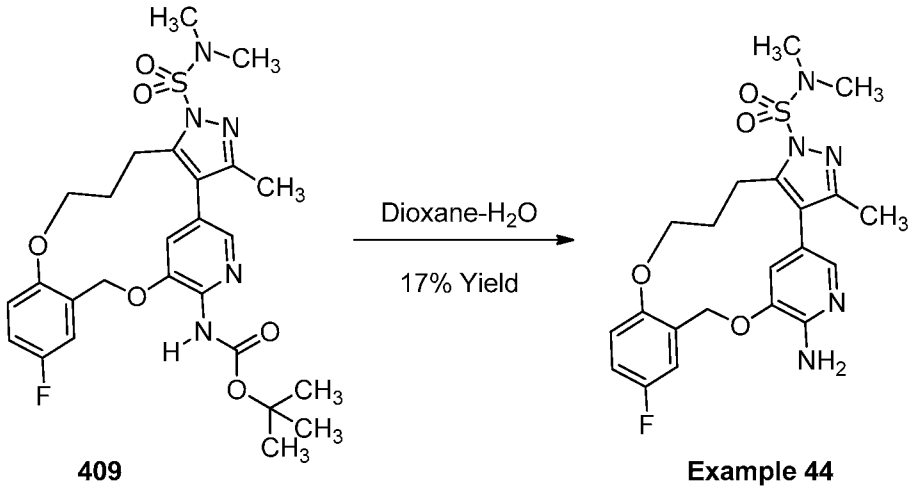
To a cooled 0 °C solution of **compound 430** (150 mg, 0.388 mmol) in DCM (2 mL) was added TEA (65 µL, 0.47 mmol), and a catalytic amount of DMAP (2-3 mg), followed by a solution of MsCl (30 µL, 0.39 mmol) in DCM (0.5 mL). The reaction was allowed to slowly warm to room temperature. After 2 hours, pyridine (2 mL), and MsCl (15 µL, 0.2 mmol) were added to the reaction, which was allowed to stir for a further hour. The reaction was diluted with EtOAc, and washed with saturated aqueous NH_4Cl and brine. The organics were dried ($MgSO_4$), filtered

and concentrated. After being dried overnight under high vacuum, **compound 431** (156 mg, 86%), was isolated as an orange gum, which was used without purification in the cyclization step.

Step 4:

To a solution of the **compound 431** (156 mg, 0.34 mmol) in DMF (2.08 mL) was added NaH (13.4 mg, 0.34 mmol, 60% dispersion). The reaction was heated to 50 °C for 2 hours. The reaction was diluted with EtOAc, washed with saturated aqueous NH_4Cl/water mixture, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography over silica gel (0-8% MeOH/DCM) to afford **Example 43** (40mg, 32%) as a yellow cream solid. ^{1}H NMR (400 MHz, 80 °C, DMSO-d_6) δ 7.50 - 7.57 (m, 2 H), 7.29 - 7.33 (m, 2 H), 7.01 - 7.09 (m, 1 H), 6.92 - 7.00 (m, 1 H), 5.77 (br. s., 2 H), 5.28 (s, 2 H), 4.02 (t, *J* = 5.54 Hz, 2 H), 3.69 (s, 3 H), 2.18 - 2.34 (m, 2 H), 1.71 - 1.89 (m, 4 H). LCMS APCI *m/z* 369 $[M+H]^+$.

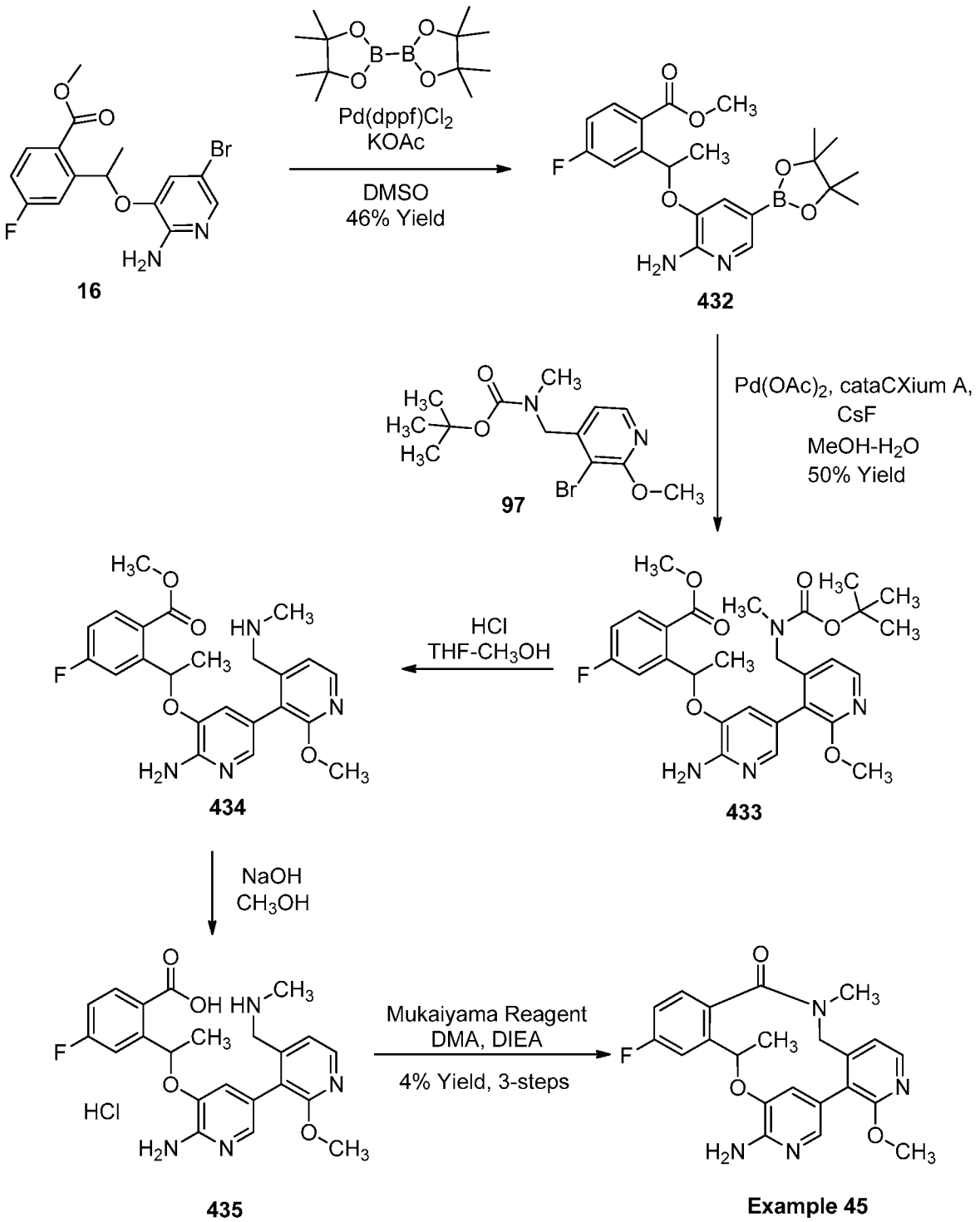
Preparation of 7-amino-12-fluoro-*N*,*N*,3-trimethyl-17,18-dihydro-10*H*-8,4-(metheno)-pyrazolo[3,4-e][1,12,9]benzodioxazacyclopentadecine-1(16*H*)-sulfonamide (Example 44)



409 **Example 44**

Compound 409 (30 mg, 0.053 mmol) was dissolved in dioxane/water (500 µL/50 µL), and heated to 100 °C for 14 hours. The reaction was concentrated, and purified by column chromatography over silica gel (0-60% EtOAc/DCM), followed by reverse phase HPLC to afford **Example 44** (13 mmol, 17% - determined by ELSD analysis of DMSO solution), which was submitted directly for screening. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.51 (d, *J* = 1.65 Hz, 1 H), 7.37 (dd, *J* =8.78, 2.74 Hz, 1 H), 7.33 (d, *J*=1.65 Hz, 1 H), 7.07 - 7.17 (m, 2 H), 5.85 (s, 2H), 5.22 (s, 2 H), 4.18 (m, *J* = 4.94 Hz, 2 H), 2.96 (s, 6 H), 2.88 (br. s., 2 H), 2.30 (s, 2 H), 2.24 (s, 3 H). LCMS ES *m/z* 462 $[M+H]^+$.

Preparation of 8-amino-13-fluoro-4-methoxy-11,17-dimethyl-17,18-dihydro-9,5-(metheno)pyrido[3,4-*h*][2,5,11]benzoxadiazacyclotetradecin-16(11*H*)-one (Example 45)



Step 1:

A mixture of bromo starting material **compound 16** (1.364 g, 3.70 mmol,), bis(pinacolato)diboron (1.44 g, 5.54 mmol), KOAc (1.27 g, 12.9 mmol), $Pd(dppf)Cl_2$ (272 mg,

0.333 mmol) and anhydrous DMSO (17 mL) was stirred at room temperature for 10 minutes to obtain a dark orange suspension. The mixture was then heated to 80 °C for 5 hours. EtOAc was added to the mixture followed by Si-Thiol. The suspension was allowed to cool to room temperature with stirring. After 30 minutes, the mixture was filtered and the solids were washed with EtOAc. The filtrate (clear dark orange) was further diluted with EtOAc and washed with water (2x) and then brine. The aqueous layers were back extracted with EtOAc (2x). The organic layers were combined and washed with 1M HCl. The aqueous layers were collected and then cooled to 0 °C and neutralized with 10 M NaOH (aq) to pH = 7. The suspension was then extracted with EtOAc and the organic layers were combined and washed with brine. The organic layer was then dried (Na_2SO_4), filtered, and concentrated to give 1.42 g of crude material as a brown solid. The material was dissolved in a *minimal* amount of EtOAc and then heptane was added. A precipitate formed. The mixture was allowed to sit for 1 hour, and then filtered and washed with heptane to provide **compound 432** (702.2 mg, 46%) as a light-brown solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.94 (dd, *J* = 8.80, 5.87 Hz, 1 H), 7.74 (s, 1 H), 7.68 (dd, *J* = 10.56, 2.35 Hz, 1 H), 7.25 (td, *J* = 8.36, 2.64 Hz, 1 H), 6.87 (s, 1 H), 6.36 (s, 2 H), 6.26 (q, *J* = 6.46 Hz, 1 H), 3.91 (s, 3 H), 1.57 (d, *J* = 5.87 Hz, 3 H), 1.21 (d, J = 5.87 Hz, 12 H).

Step 2:

To a microwave vial was added **compound 97** (100 mg, 0.3 mmol), **compound 432** (189 mg, 0.45 mmol). cesium fluoride (138 mg, 0.91 mmol), cataCXium A (12.9 mg, 0.036 mmol), palladium acetate (8.1 mg, 0.036 mmol), methanol (3 mL) and water (0.3 mL). The reaction mixture was degassed, and the vial sealed, and heated to 80 °C for 2 hours. The mixture was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography over silica gel (20-50% EtOAc/Heptane, then 5-10% MeOH/EtOAc) to afford **compound 433** (82 mg, 50%) as a brown gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 - 8.10 (m, 2 H), 7.46 (d, *J* = 13.64 Hz, 1 H), 7.27 - 7.35 (m, 1 H), 7.00 (t, *J* = 7.33 Hz, 1 H), 6.75 (d, *J* = 5.31 Hz, 1 H), 6.51 (br. s., 1 H), 6.30 - 6.37 (m, 1 H), 4.96 (br. s., 2 H), 3.87 (s, 3 H), 3.66 - 3.77 (m, 3 H), 2.53 - 2.68 (m, 3 H), 1.63 - 1.69 (m, 3 H), 1.41 (br. s., 9 H). LCMS *m/z* 541 $[M+H]^+$.

Step 3:

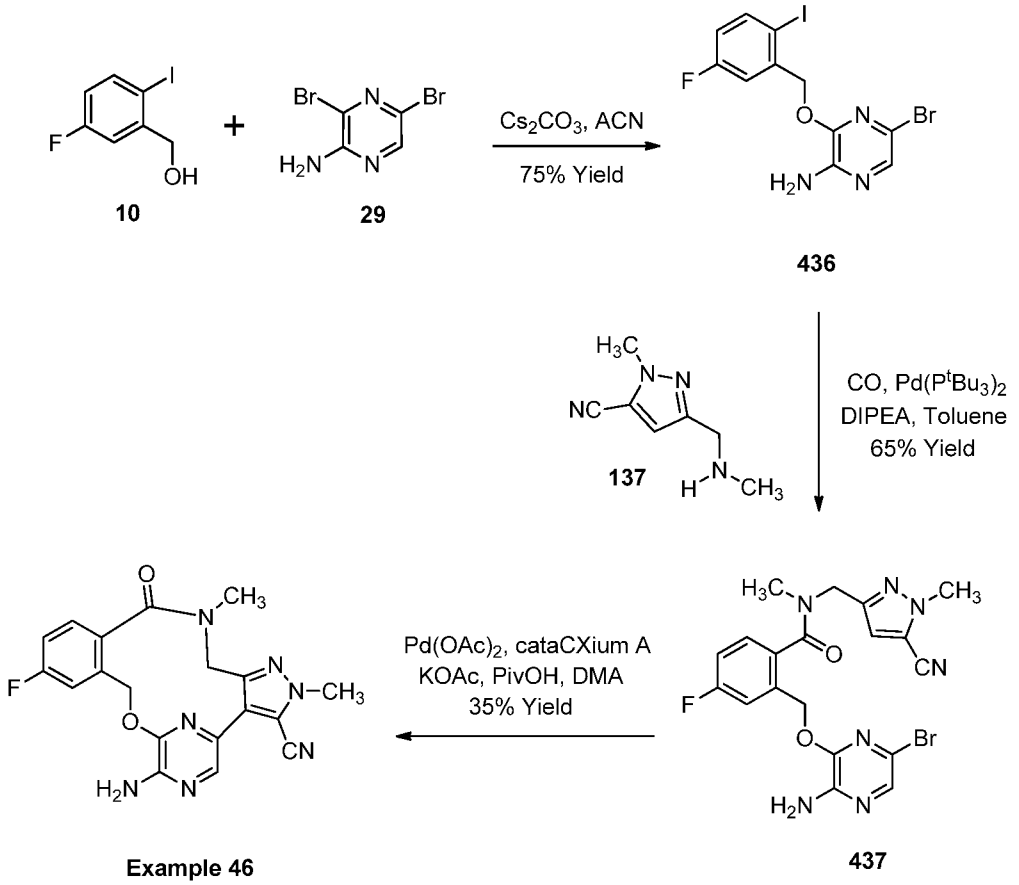
Compound 433 (82 mg, 0.15 mmol) was dissolved in THF (1 mL) and MeOH (0.3 mL), before 38% HCl (0.1 mL) was added. The reaction was heated using an oil bath at 50 °C for 4 hours. The reaction was allowed to cool to room temperature, and 50% aqueous NaOH was added until the pH reached 12 (~0.2 mL). 0.3 mL of MeOH was added, and the reaction heated at 50 °C for 1 hour. The reaction was concentrated, and subjected to lyophilization. The solid was filtered, and washed with EtOAc, followed by MeOH/CH_2Cl_2, and the filtrates concentrated to

give **compound 435** (126 mg) as a white solid, which was used in the following step without further purification.

Step 4:

Compound 435 (65 mg, 0.15 mmol) was dissolved in DMA (15 mL), and the solution was cooled to 0 °C. DIEA (53 µL, 0.3 mmol) was added, followed by CMPI (43.1 mg, 0.17 mmol), and the mixture was stirred at 0 °C for 30 minutes. The reaction mixture was diluted with water, and subjected to lyophilization. The solid was washed with EtOAc and MeOH/CH_2Cl_2, the filtrates concentrated, and purified by reverse phase HPLC to afford **Example 45** (2.38 mg, 4%) as an off-white solid. ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.03 - 8.15 (m, 1 H), 7.59 (dd, *J* = 10.11, 2.53 Hz, 1 H), 7.53 (d, *J* = 2.02 Hz, 1 H), 7.31 (dd, *J* = 8.46, 5.68 Hz, 1 H), 7.19 (s, 1 H), 6.96 - 7.06 (m, 2 H), 5.76 - 5.85 (m, 1 H), 5.47 (s, 1 H), 4.28 (s, 2 H), 3.79 - 3.87 (m, 3 H), 3.06 (s, 3 H), 1.69 - 1.74 (m, 3 H). LCMS APCI *m/z* 409 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-2,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(azeno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 46)



Step 1:

Compound 10 (1.89 g, 7.5 mmol), **compound 29** (2.28 g, 9 mmol), and cesium carbonate (6.11 g, 18.7 mmol) were combined in acetonitrile (75 mL), and heated at 80°C for 18 hours. The crude suspension was added to brine (400 mL) and the resulting rust colored solids were collected by filtration and rinsed with water. The partially dried solids were recrystallized from hot acetonitrile (~200 mL) to afford **compound 436** (2.37 g, 75%) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (dd, 1 H), 7.58 - 7.69 (m, 2 H), 7.05 (td, *J* = 8.65, 3.24 Hz, 1 H), 6.69 (s, 2 H), 5.27 (s, 2 H). LCMS *m/z* 423/425 $[M+H]^+$.

Step 2:

Compound 436 (450 mg, 1.06 mmol), **compound 137** (155 mg, 0.30 mmol), DIEA (0.578 mL, 3.32 mmol) and Pd (P^tBu_3)$_2$ (43.3 mg, 0.083 mmol) were dissolved in toluene (40 mL) in a stainless steel bomb, and heated to 85 °C under 4 bar CO pressure for 15 hours. The mixture was concentrated and purified by column chromatography over silica gel (25-100% EtOAc/heptane) to afford **compound 437** (255 mg, 65%) as a yellow solid. ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ ppm 7.64 (s, 1 H), 7.51 (dd, *J* = 10.20, 2.64 Hz, 1 H), 7.40 (dd, *J* = 8.31, 5.79 Hz, 1 H), 7.15 - 7.32 (m, 1 H), 6.94 (s, 1 H), 6.23 (br. s., 2 H), 5.34 (s, 2 H), 4.13 - 4.83 (m, 2 H), 3.95 (s, 3 H), 2.87 (br. s., 3 H). LCMS *m/z* 474/476 $[M+H]^+$.

Step 3:

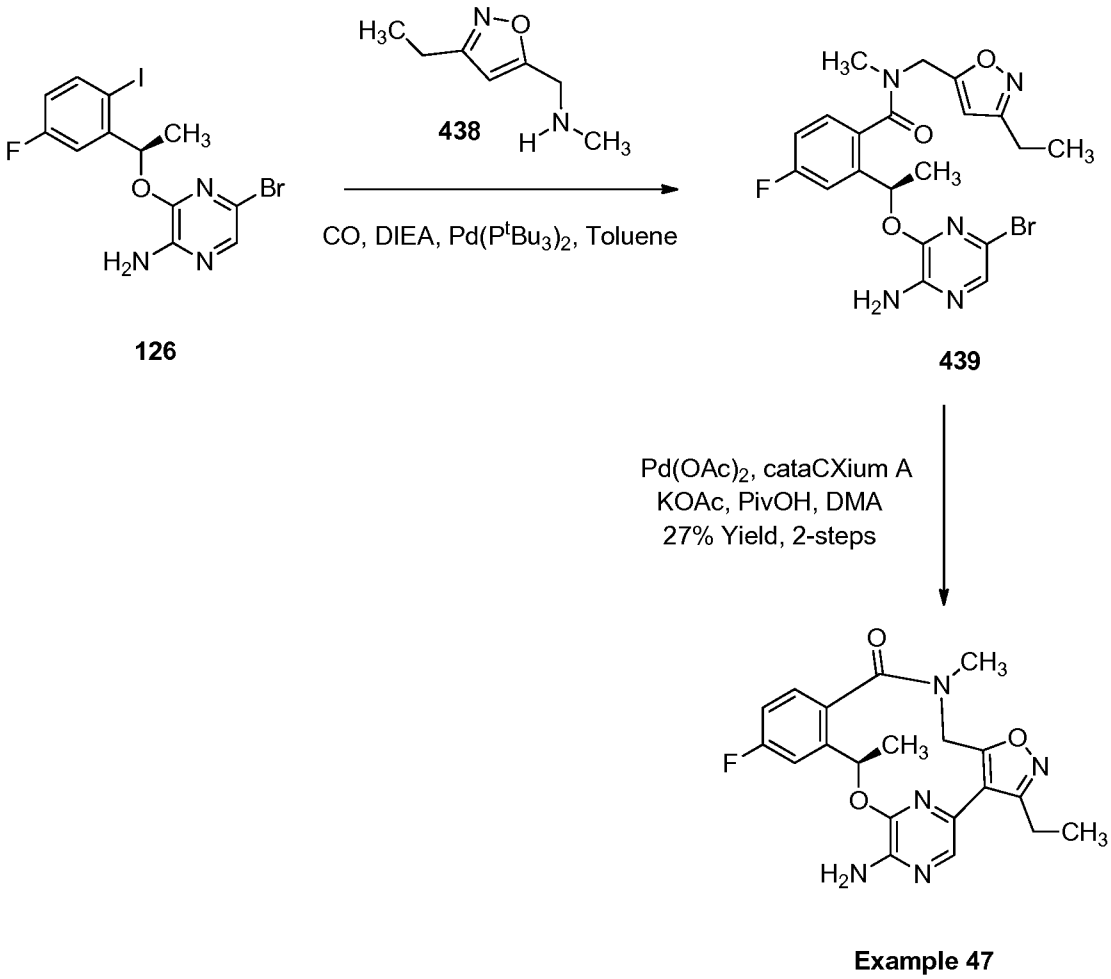
Compound 437 (125 mg, 0.264 mmol), cataCXium A (29.2 mg, 0.079 mmol), palladium acetate (9 mg, 0.04 mmol), KOAc (130 mg, 1.32 mmol), and pivalic acid (8.1 mg, 0.079 mmol) were dissolved in DMA (5.29 mL) in a microwave vial. The vial was flushed with nitrogen, and heated in the microwave at 150 °C for 1 hour. The mixture was diluted with water, and the solids removed by filtration. The aqueous was extracted with EtOAc, washed with brine. The solids were combined with the organics, and dried over $MgSO_4$. The organics were filtered, and concentrated. The residue was purified by column chromatography over silica gel (25-100% 3:1 DCM in heptanes/5% MeOH in EtOAc). Trituration of the product containing fractions with MTBE afforded **Example 46** (36 mg, 35%) as a colorless solid as a mixture of atropisomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (s, 1 H), 7.35 - 7.53 (m, 2 H), 7.19 (td, *J* = 8.50, 2.64 Hz, 1 H), 6.75 (s, 2 H), 5.57 (dd, *J*= 12.46, 1.64 Hz, 1 H), 5.10 (d, *J* = 12.59 Hz, 1 H), 4.23 - 4.50 (m, 2 H), 4.04 (s, 3 H), 2.88 (s, 3 H). LCMS APCI *m/z* 394 $[M+H]^+$.

The analytical chiral separation by SFC was performed using a Chiralpak OD-H (4.6 mm x 250 mm column , 5 micron particle size), which was eluted with 30% MeOH in CO_2 held at 35 °C at 140 bar. A flow rate of 3 mL/minutes gave $Rt_{(Peak\ 1)}$ = 4.85 minutes and $Rt_{(Peak\ 2)}$ = 5.79 minutes.

Example 46 (Atropisomer peak 1): 99% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 1 H), 7.37 - 7.56 (m, 2 H), 7.19 (td, *J* = 8.46, 2.78 Hz, 1 H), 6.77 (s, 2 H), 5.57 (dd, *J* = 12.51, 1.64 Hz, 1 H), 5.10 (d, *J* = 12.38 Hz, 1 H), 4.25 - 4.41 (m, 2 H), 4.04 (s, 3 H), 2.88 (s, 3 H).

Example 46 (Atropisomer peak 2): 96% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.79 (s, 1 H), 7.37 - 7.53 (m, 2 H), 7.19 (td, *J* = 8.53, 2.65 Hz, 1 H), 6.77 (s, 2 H), 5.57 (dd, *J* = 12.38, 1.52 Hz, 1 H), 5.10 (d, *J* = 12.63 Hz, 1 H), 4.24 - 4.47 (m, 2 H), 4.04 (s, 3 H), 2.88 (s, 3 H).

Preparation of (10*R*)-7-amino-3-ethyl-12-fluoro-10,16-dimethyl-16,17-dihydro-8,4-(azeno)[1,2]oxazolo[4,5-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 47)



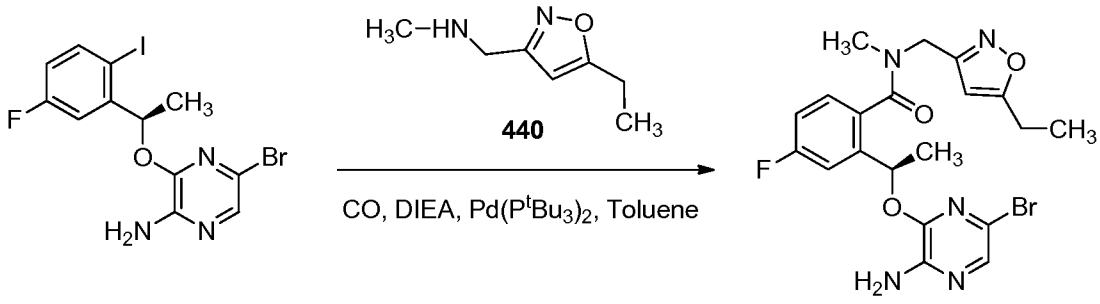
Step 1:

Compound 126 (286 mg, 0.653 mmol), **compound 438** (115 mg, 0.653 mmol), DIEA (0.455 mL, 2.61 mmol), Pd (P^tBu_3)$_2$ (33.9 mg, 0.05 mmol) were dissolved in toluene (20 mL) in a stainless steel vessel. The reactor was pressurized to 4 bar of CO, and heated to 85 °C for 14 hours. The reaction mixture was diluted with EtOAc, washed with water, saturated aqueous NH_4Cl, and brine. The organics were dried ($MgSO_4$), and concentrated. The residue of **compound 439** was used in the next step without further purification.

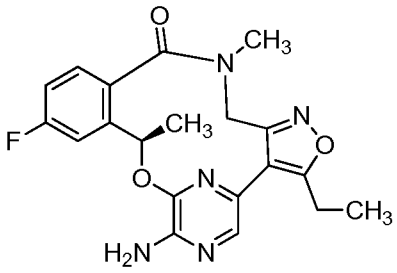
Step 2:

Compound 439 (312 mg, 0.653mmol), KOAc (320 mg, 3.26mmol), pivalic acid (16.8 mg, 0.163 mmol) were combined in DMF (4.35 mL) and the solution purged with nitrogen. $Pd(OAc)_2$ (14.6 mg, 0.065 mmol) and cataCXium A (48.4 mg, 0.131mmol) were then added, and the reaction heated to 150 °C for 45 minutes in the microwave. The reaction was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Purification by reverse phase HPLC afforded **Example 47** (71mg, 27%) as a colorless solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 - 7.25 (m, 3 H), 7.08 (dt, *J* = 2.6, 8.2 Hz, 1 H), 6.30 - 6.22 (m, 1 H), 4.57 (d, *J* = 13.6 Hz, 1 H),4.41 (d, *J* = 13.4 Hz, 1 H), 3.12 (s, 3 H), 3.01 - 2.77 (m, 2 H), 1.84 (d, *J* = 6.6 Hz, 3 H), 1.39 (t, *J* = 7.6 Hz, 3 H). LCMS APCI *m/z* 398 $[M+H]^+$.

Preparation of (10*R*)-7-amino-3-ethyl-12-fluoro-10,16-dimethyl-16,17-dihydro-8,4-(azeno)[1,2]oxazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 48)



$Pd(OAc)_2$, cataCXium A
KOAc, PivOH, DMF
24% Yield, 2-steps



Example 48

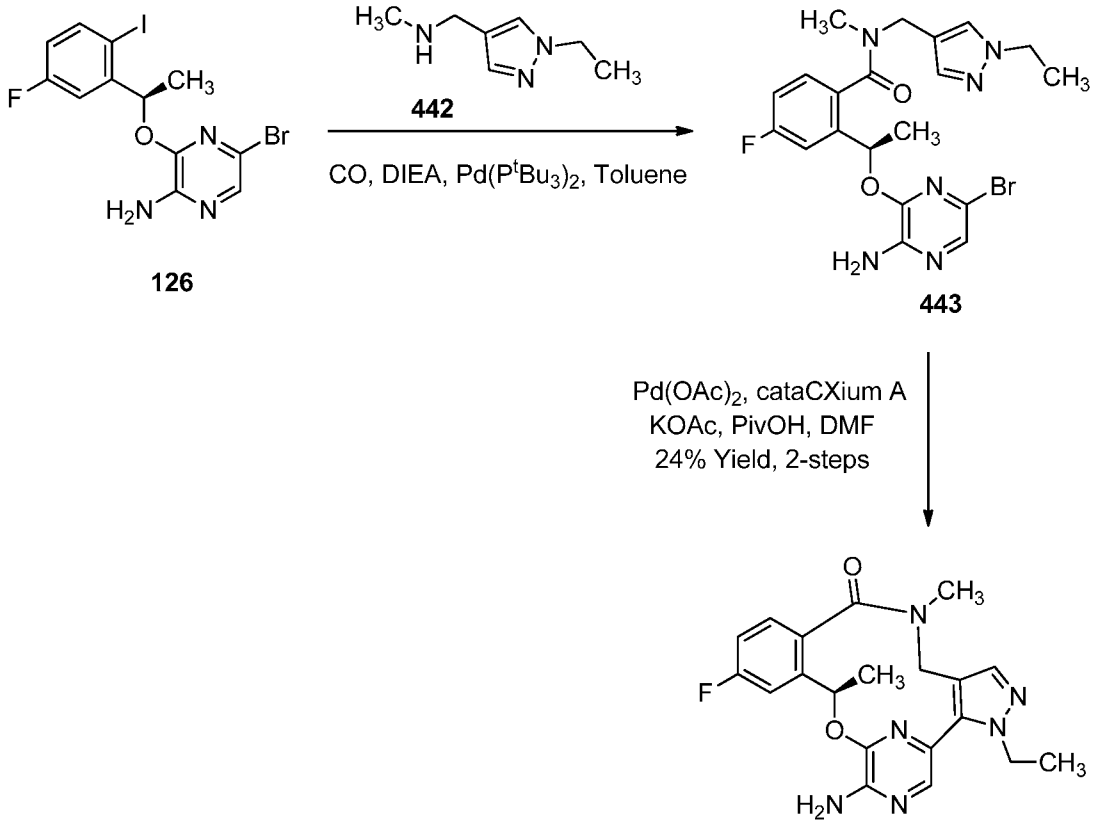
Step 1:

Compound 126 (285 mg, 0.650 mmol), **compound 440** (115 mg, 0.650 mmol), DIEA (0.453 ml, 2.61 mmol), Pd (P^tBu_3)$_2$ (33.9 mg, 0.05 mmol) were dissolved in toluene (20 mL) in a stainless steel vessel. The reactor was pressurized to 4 bar of CO, and heated to 85 °C for 14 hours. The reaction mixture was diluted with EtOAc, washed with water, saturated aqueous NH_4Cl, and brine. The organics were dried ($MgSO_4$), and concentrated. The residue of **compound 441** was used in the next step without further purification.

Step 2:

Compound 441 (311 mg, 0.650 mmol), KOAc (320 mg, 3.26 mmol), pivalic acid (16.8 mg, 0.163 mmol) were combined in DMF (5 mL) and the solution purged with nitrogen. $Pd(OAc)_2$ (14.6 mg, 0.065 mmol) and cataCXium A (48.6 mg, 0.131 mmol) were then added, and the reaction heated to 150°C for 45 minutes in the microwave. The reaction was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Purification by reverse phase HPLC afforded **Example 48** (62 mg, 24%) as a colorless solid. ^{1}H NMR (400 MHz ,$CDCl_3$) δ 7.66 (s, 1 H), 7.31 - 7.27 (m, 1 H), 7.21 (dd, *J* = 5.5, 8.4 Hz, 1 H), 7.01 (dt, *J* = 2.6, 8.3 Hz, 1 H), 6.16 -6.03 (m, 1 H), 5.01 (br. s., 2 H), 4.67 (d, *J* = 14.1 Hz, 1 H), 4.33 (d, *J* = 14.1 Hz, 1 H), 3.11 (s, 3 H), 2.95 - 2.75 (m, 2 H), 1.76 (d, *J* = 6.6 Hz, 3 H),1.34 (t, *J* = 7.5 Hz, 3 H). LCMS APCI *m/z* 398 $[M+H]^+$.

Preparation of (10*R*)-7-amino-3-ethyl-12-fluoro-10,16-dimethyl-16,17-dihydro-3*H*-8,4-(azeno)pyrazolo[3,4-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 49)



Example 49

Step 1:

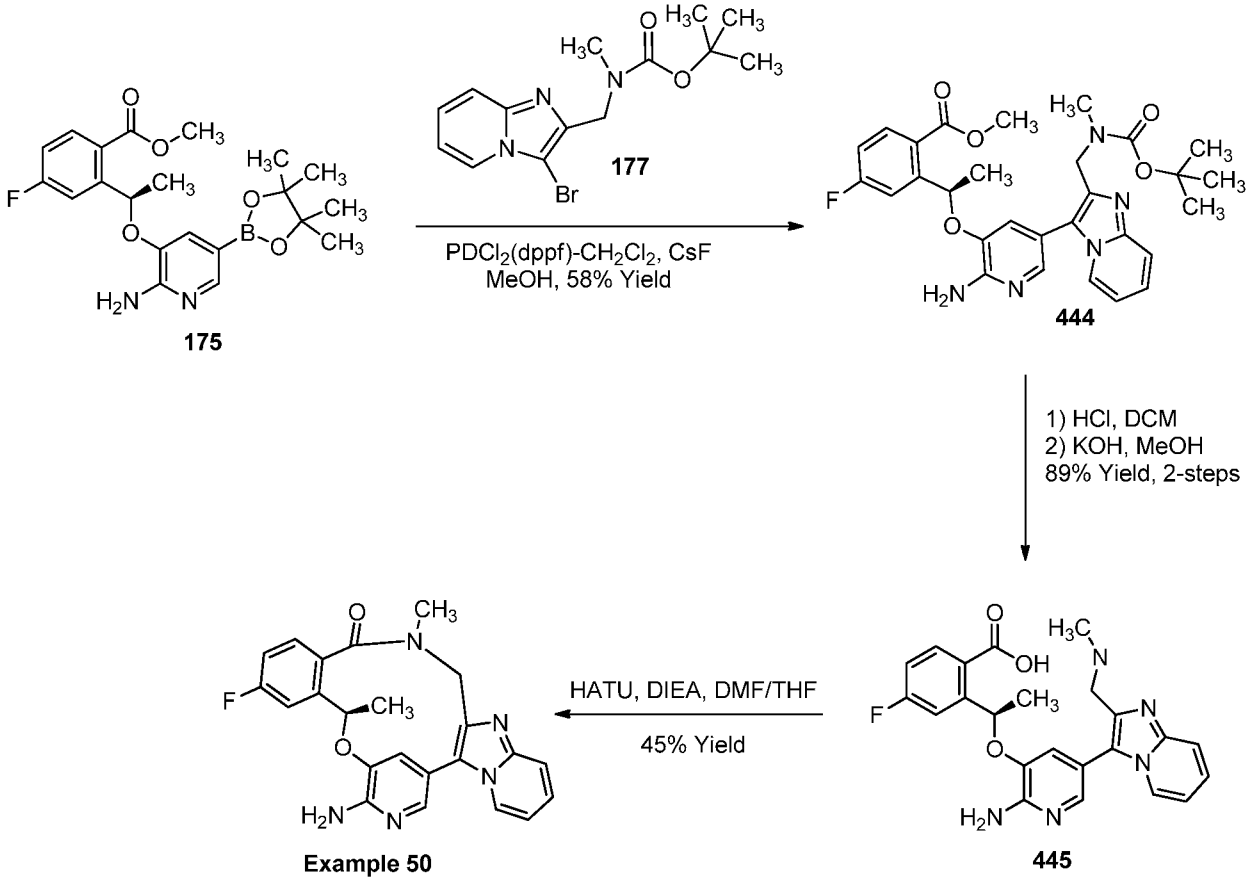
Compound 126 (314 mg, 0.718 mmol), **compound 442** (100 mg, 0.718 mmol), DIEA (0.5 mL, 2.87 mmol), Pd ($P^tBu_3)_2$ (37.5 mg, 0.072 mmol) were dissolved in toluene (20 mL) in a stainless steel vessel. The reactor was pressurized to 4 bar of CO, and heated to 85 °C for 14 hours. The reaction mixture was diluted with EtOAc, washed with water, saturated aqueous NH_4Cl, and brine. The organics were dried ($MgSO_4$), and concentrated. The residue of **compound 443** was used in the next step without further purification. LCMS *m/z* 477/479 $[M+H]^+$.

Step 2:

Compound 443 (258 mg, 0.540 mmol), KOAc (265 mg, 2.7 mmol), pivalic acid (13.9 mg, 0.135 mmol) were combined in DMF (4 mL) and the solution purged with nitrogen. $Pd(OAc)_2$ (12.1 mg, 0.054 mmol) and cataCXium A (39.9 mg, 0.108 mmol) were then added, and the reaction heated to 150 °C for 30 minutes in the microwave. The reaction was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Purification by reverse phase HPLC afforded **Example 49** (52 mg, 24%) as a colorless solid. ^1H NMR (400 MHz , DMSO-d_6) δ 7.67 (s, 1 H), 7.60 (s, 1 H), 7.54 (dd, *J* = 2.6, 10.1 Hz, 1 H), 7.31 (dd, *J* = 5.7, 8.4 Hz, 1 H), 7.12 (dt, *J* = 2.6, 8.5Hz, 1 H), 6.75 (s, 2 H), 6.09 - 5.96 (m, 1 H), 4.20 - 4.13 (m, 2 H),

4.13 - 4.04 (m, 2 H), 2.90 (s, 3 H), 1.64 (d, *J* = 6.6 Hz, 3 H), 1.33 (t, *J* = 7.2 Hz, 3H). LCMS APCI *m/z* 397 $[M+H]^+$.

Preparation of (5*R*)-8-amino-3-fluoro-5,19-dimethyl-18,19-dihydro-7,11-(metheno)pyrido-[2',1':2,3]imidazo[4,5-*h*][2,5,11]benzoxadiazacyclotetradecin-20(5*H*)-one (Example 50)



Step 1:

A mixture of **compound 175** (355 mg, 0.852 mmol), **compound 177** (348 mg, 1.02 mmol) and CsF (388 mg, 2.56 mmol). in MeOH (10 mL) was purged with nitrogen prior to the addition of $PdCl_2(dppf).CH_2Cl_2$ (35.1 mg, 0.043 mmol). The reaction was heated at 120 °C in the microwave for 1 hour, and then partitioned between EtOAc and brine. The aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried ($MgSO_4$) and reduced to minimum volume. The residue was purified by column chromatography over silica gel (0-10% MeOH : 10% aqueous NH_4OH/DCM : EtOAc, 1:1) to afford **compound 444** (272 mg, 58%) of the product as a pale orange foam. LCMS *m/z* 550 $[M+H]^+$.

Step 2:

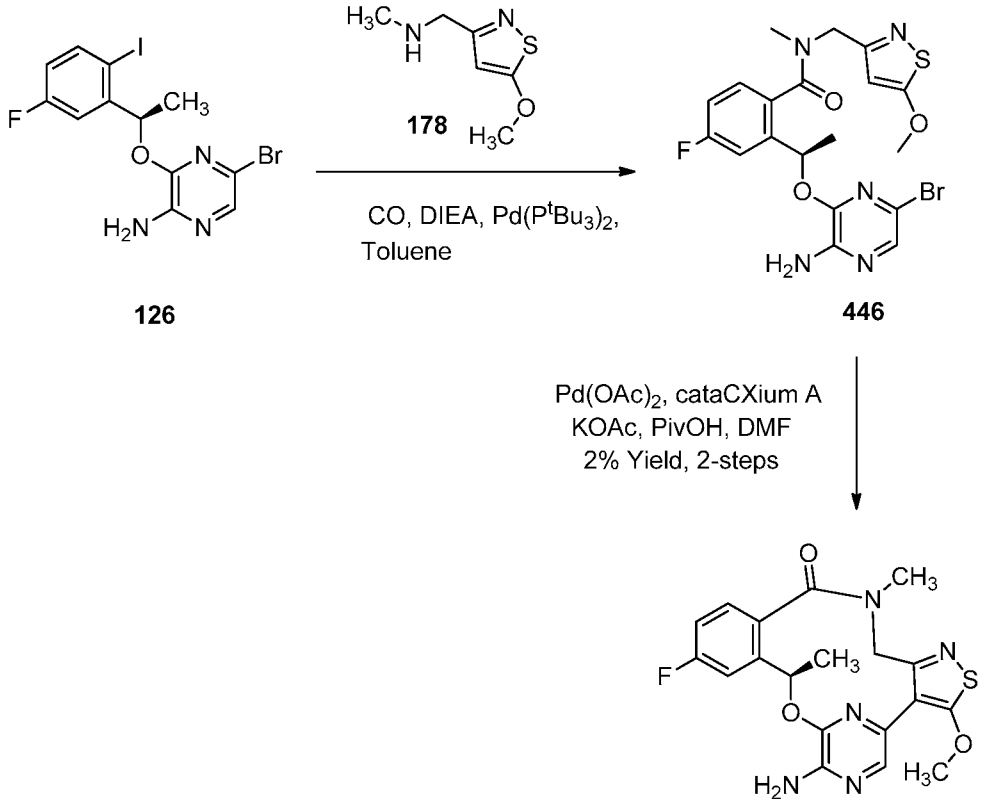
To a solution of **compound 444** (440 mg, 0.801 mmol) in DCM (4 mL) was added HCl (4 mL, 4M in dioxane, 20 mmol). The mixture quickly became cloudy and formed a suspension. The

reaction mixture was stirred at room temperature for 4 hours, and then stripped to dryness. The residue azeotroped with MTBE, and dried in a vacuum oven at ~50 °C for 1 hour to give a pale orange solid. The solid was dissolved in MeOH (8 mL) and solid KOH (378 mg, 6.74 mmol) was added. The resulting suspension was stirred at 50 °C overnight. The pH of the resulting suspension was adjusted to 5-6 by drop-wise addition of 6N HCl. The reaction was filtered, and the filtrate concentrated *in vacuo*. The residue was azeotroped with toluene to afford a brown solid, which was dried in the vacuum over at 50 °C for 1 hour to afford **compound 445** (401 mg, 89%), which was used without purification.

Step 3:

To a solution of HATU (439 mg, 1.12 mmol) in DMF /THF(20 mL/4 mL) at 0 °C was added in a dropwise manner a solution of **compound 445** (348 mg, 0.8 mmol) and DIEA (0.7 mL, 4 mmol) in DMF /THF (20 mL/4 mL). The addition took 35 minutes. After addition, the resulting mixture was stirred at 0 °C for 20 minutes. The mixture was poured into aqueous $NaHCO_3$ (400 mL). The mixture was filtered, and filtrate was extracted with EtOAc (3x). The combined EtOAc layers were washed with water, (2x), brine (1x), dried over $MgSO_4$ and concentrated *in vacuo* to give a residue, which was purified by column chromatography over silica gel (0-10% Methanol/DCM:EtOAc 1:1). The desired fractions were concentrated *in vacuo* to give a residue, which was triturated with MTBE to afford **Example 50** (164 mg, 45%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, 1 H), 7.79 (d, *J* = 1.52 Hz, 1 H), 7.59 - 7.70 (m, 2 H), 7.46 (dd, *J* = 8.59, 5.81 Hz, 1 H), 7.28 (ddd, *J* = 9.03, 6.76, 1.14 Hz, 1 H), 7.17 (td, *J* = 8.46, 2.78 Hz, 1 H), 6.94 (td, *J* = 6.82, 1.01 Hz, 1 H), 6.89 (d, *J* = 1.52 Hz, 1 H), 6.18 (s, 2 H), 5.62 - 5.82 (m, 1 H), 4.47 (d, *J* = 13.89 Hz, 1 H), 4.31 (d, *J* = 13.89 Hz, 1 H), 3.06 (s, 3 H), 1.69 (d, *J* = 6.32 Hz, 3 H). LCMS APCI *m/z* 418 $[M+H]^+$.

Preparation of (10*R*)-7-amino-12-fluoro-3-methoxy-10,16-dimethyl-16,17-dihydro-8,4-(azeno)[1,2]thiazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 51)



Example 51

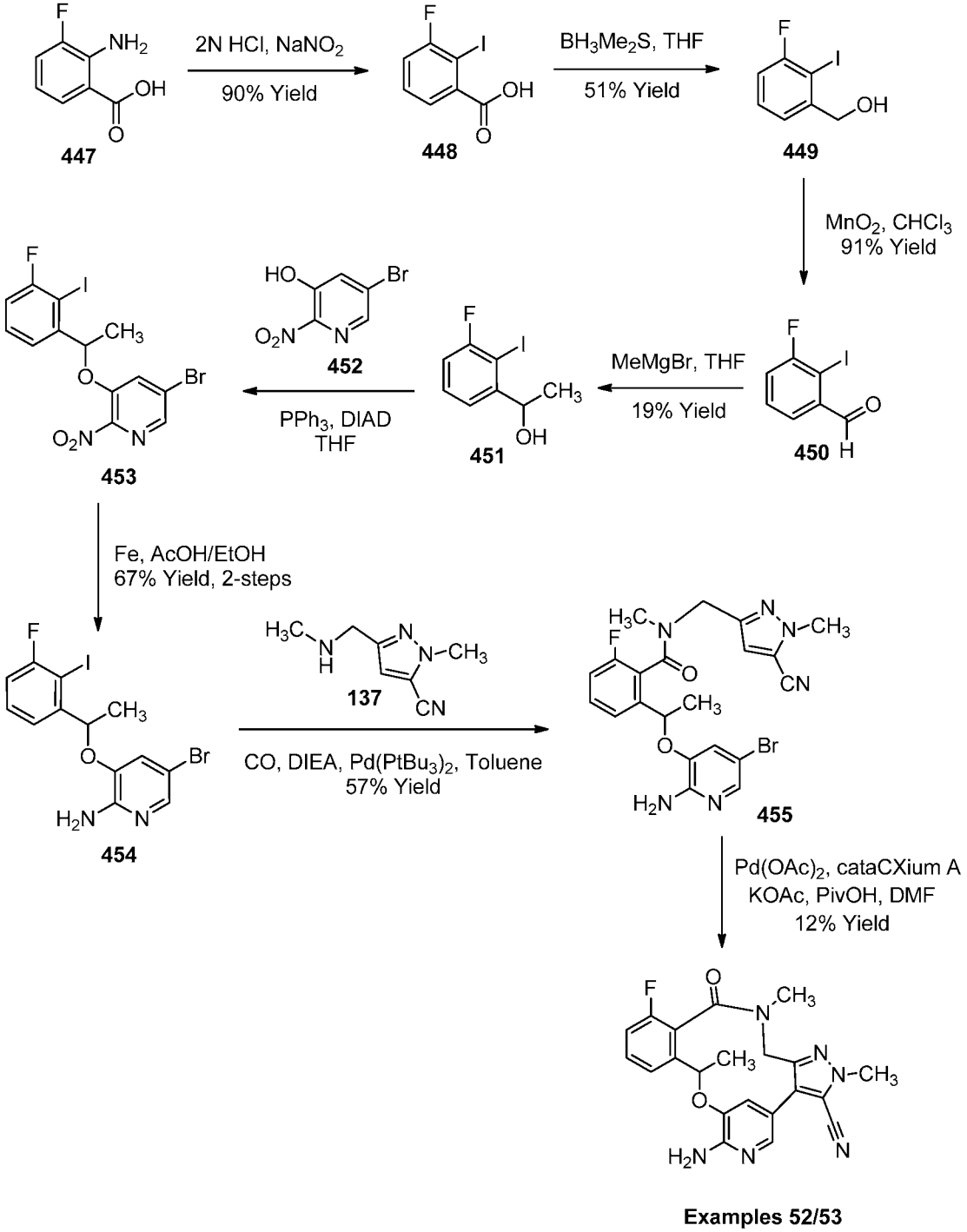
Step 1:

Compound 126 (442 mg, 1.01 mmol), **compound 178** (197 mg, 1.01 mmol), DIPEA (0.704 mL, 4.04 mmol), Pd ($P^tBu_3)_2$ (52.7 mg, 0.101 mmol) were dissolved in toluene (20 mL) in a stainless steel vessel. The reactor was pressurized to 4 bar of CO, and heated to 85 °C for 14 hours. The reaction mixture was diluted with EtOAc, washed with water, saturated aqueous NH_4Cl, and brine. The organics were dried ($MgSO_4$), and concentrated. The residue of **compound 446** was used in the next step without further purification. LCMS APCI *m/z* 497 $[M+H]^+$.

Step 2:

Compound 446 (440 mg, 0.886 mmol), KOAc (435 mg, 4.43 mmol), pivalic acid (22.9 mg, 0.222 mmol) were combined in DMF (9 mL) and the solution purged with nitrogen. $Pd(OAc)_2$ (20 mg, 0.089 mmol) and cataCXium A (65.4 mg, 0.177 mmol) were then added, and the reaction heated to 120 °C for 60 minutes in the microwave. The reaction was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Purification by reverse phase HPLC afforded **Example 51** (5.2mg, 2%) as a colorless solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.71 (s, 1 H), 7.51 (dd, *J* = 2.5, 10.1 Hz, 1 H), 7.38 (dd, *J* = 5.8, 8.6 Hz, 1 H), 7.14 (dt, *J* = 2.5, 8.6 Hz, 1 H), 6.50 (s, 2 H), 5.99 - 5.85 (m, 1 H), 4.36 (d, *J* = 12.8 Hz, 1 H), 4.18 (d, *J* = 12.8 Hz, 1 H), 4.08 (s, 3 H), 2.94 (s, 3 H), 1.63 (d, *J* = 6.5 Hz, 3 H). LCMS APCI *m/z* 416 $[M+H]^+$.

Preparation of 7-amino-14-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 52 and 53)



Examples 52/53

Step 1:

To a cooled (0 °C) solution of **compound 447** (2.5 g, 166 mmol) in 2N aqueous HCl (32 mL) was added a solution of $NaNO_2$ (1.14 g, 16.1 mmol) in water 16 mL, maintaining the internal temperature at 0-5 °C. After the addition was complete, the mixture was stirred at 0 °C

for 1.5 hours This solution was then added dropwise (maintaining the internal T <10 °C), to a mixture of KI (5.35 g, 32.2 mmol) and CuI (1.54 g, 8.06 mmol) in water (16 mL). The ice bath was removed and the reaction was stirred overnight. The mixture was filtered, and the resulting solids were slurried in MTBE and heated to 40 °C for 1 hour. The solids were filtered again, then and the filtrates concentrated to give **compound 448** (3.86 g, 90%) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.51 (br. s., 1 H), 7.53 - 7.44 (m, 2 H), 7.43 - 7.32 (m, 1 H).

Step 2:

To a cooled (0 °C) solution of the **compound 448** (3.8 g, 14 mmol) in THF (30 mL) was added BH_3 Me_2S (28.6 mL. 1M in THF, 28.6 mmol). The ice bath was removed and the solution was heated to 60 °C for three hours. The reaction was cooled to room temperature, and quenched with saturated aqueous NH_4Cl. The reaction was extracted with EtOAc (2x), and the combined organics washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography over silica gel (0-50% EtOAc/heptanes) to afford **compound 449** (1.82 g, 51%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (dt, *J* = 5.9, 7.9 Hz, 1 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.14 (t, *J* = 8.1 Hz, 1 H), 5.53 (t, *J* = 5.7 Hz, 1 H), 4.45 (d, *J* = 5.0 Hz, 2 H).

Step 3:

To a solution of the **compound 449** (1.82 g, 7.22 mmol) in $CHCl_3$ (40 mL) was added activated MnO_2 (3.77 g, 43.3 mmol). The mixture was heated to 50 °C overnight, filtered through a glass filter, and concentrated to afford **compound 450** (1.65g, 91%) as a yellow solid, which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1 H), 7.66 - 7.61 (m, 1 H), 7.61 - 7.56 (m, 2 H).

Step 4:

To a cooled (-78 °C) solution of **compound 450** (1.65 g, 6.6 mmol) in THF (33 mL) was added MeMgBr (6.6 mL, 3 M in diethyl ether, 19.8 mmol). The reaction was stirred for 2 hours, quenched with saturated aqueous NH_4Cl, and then extracted with EtOAc (2x). The organics were dried over $MgSO_4$, filtered and concentrated to an orange brown gum. This residue was purified by column chromatography over silica gel (0-25% EtOAc/heptane) to afford **compound 451** (330 mg, 19%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 - 7.34 (m, 2 H), 7.13 (dt, *J* = 1.8, 7.9 Hz, 1 H), 5.49 (d, *J* = 4.3 Hz, 1 H), 4.90 - 4.81 (m, 1 H), 1.27 (d, *J* =6.3 Hz, 3 H).

Step 5:

To a solution of **compound 452** (302 mg, 1.38 mmol) and **compound 451** (333 mg, 1.25 mmol) in THF (6 mL) was added a solution of PPh_3 (410 mg, 1.56 mmol) and DIAD (330 mg, 1.56 mmol) in THF (6 mL). The reaction was stirred at room temperature for 12 hours, concentrated and purified by column chromatography over silica gel (0-25% EtOAc/heptane) to afford

compound 453 (379 mg, 69%) as a colorless solid. The material contained 10-15% of reduced DIAD, but was used without further purification in the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, *J* = 1.8 Hz, 1 H), 7.87 (d, *J* = 1.8 Hz, 1 H), 7.48 (dt, *J* = 5.9, 8.0 Hz, 1 H), 7.30 - 7.23 (m, 2 H), 5.92 (q, *J* = 6.3 Hz, 1 H), 1.61 (d, *J* = 6.3 Hz, 3 H).

Step 6:

A mixture of **compound 453** (379 mg, 0.811 mmol) and iron (453 mg, 8.11 mmol) in AcOH/EtOH (5.4 mL/5.4 mL) was heated to 80 °C. The reaction was complete after 1.5 hours. Water was added, and the reaction neutralized with solid Na_2CO_3. The reaction was extracted with EtOAc (2x), dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography over silica gel (0-50% EtOAc/heptane) to afford **compound 454** (235 mg, 67%) as a white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.52 (d, *J* = 2.0 Hz, 1 H), 7.47 - 7.37 (m, 1 H), 7.32 (dd, *J* = 1.5, 7.8 Hz, 1 H), 7.20 (dt, *J* = 1.5, 8.1 Hz, 1 H), 6.68 (d, *J* = 2.0 Hz, 1 H), 6.14 (s, 2 H), 5.54 (q, *J* = 6.4 Hz, 1 H), 1.56 (d, *J* = 6.3 Hz, 3 H). LCMS *m/z* 436/438 $[M+H]^+$.

Step 7:

Compound 454 (230 mg, 0.526 mmol), **compound 137** (103 mg, 0.552 mmol), DIEA (0.366 mL, 2.1 mmol), $Pd(P^tBu_3)_2$ (27.6 mg, 0.053 mmol) were dissolved in toluene (20 mL) in a stainless steel vessel. The reactor was pressurized to 4 bar of CO, and heated to 85 °C for 14 hours. The reaction mixture was shown not to be complete, and $Pd(P^tBu_3)_2$ (27.6 mg, 0.053 mmol) was again added, and the reaction heated at 85 °C under 4 bar of CO for a further 4 hours. The reaction was diluted with EtOAc, washed with water, saturated aqueous NH_4Cl, and brine. The organics were dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography over silica gel (0-75% EtOAc/heptane, then 0-10% MeOH/DCM) to afford **compound 455** (198 mg, 57%) as a yellow solid.

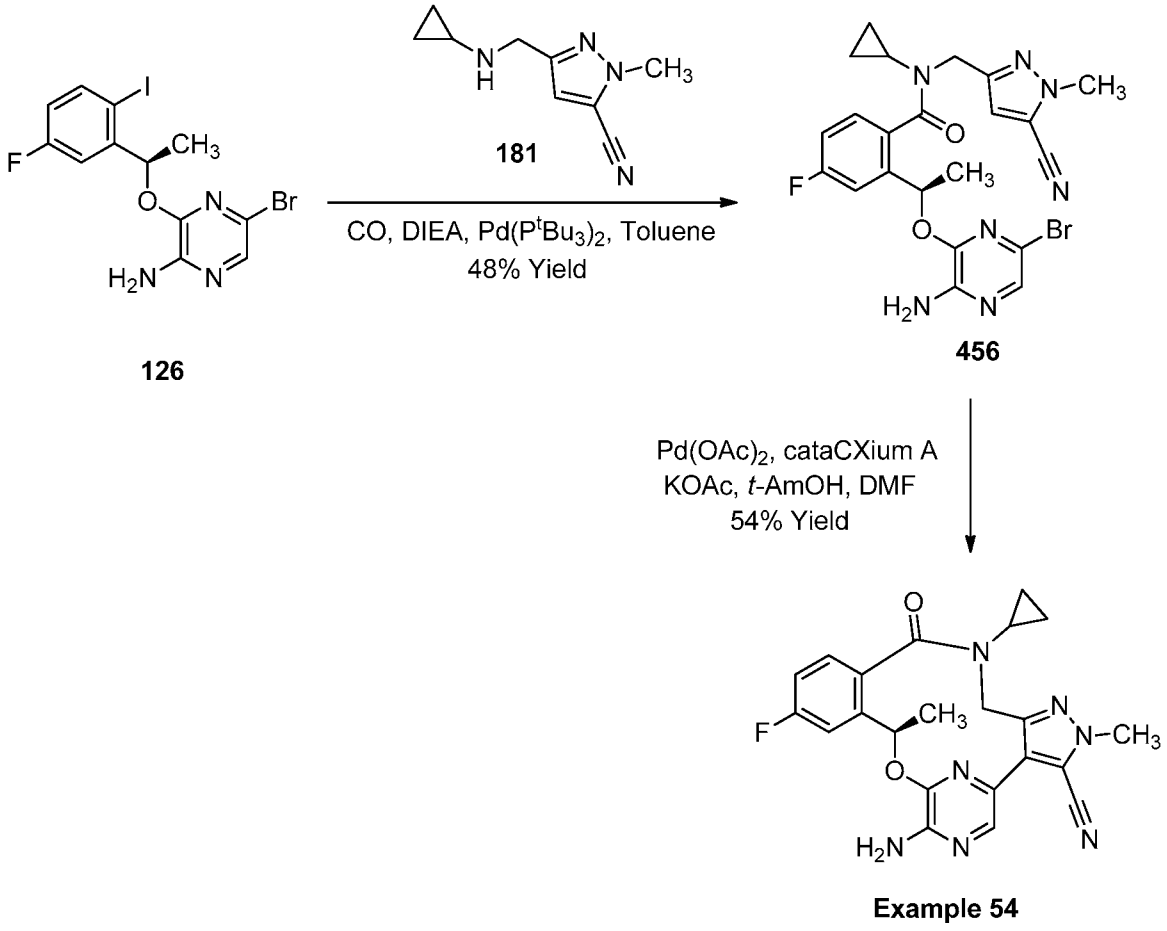
Step 8:

Compound 455 (198 mg, 0.406 mmol), KOAc (199 mg, 2.03 mmol), pivalic acid (10.5 mg, 0.102 mmol) were combined in *t*-amylalcohol (6.44 mL) and water (7.3 µL). The solution purged with nitrogen. $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and cataCXium A (18.9 mg, 0.0510 mmol) were then added, and the reaction heated to 150 °C for 60 minutes in the microwave. The reaction was diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography over silica gel (0-10% MeOH/DCM) to afford **Examples 52** and **53** as a mixture of enantiomers (20 mg, 12%), which were subjected to chiral separation by SFC to afford both enantiomers of the title **compound**. The analytical chiral separation by SFC was performed using a Regis Whelk-01 (*R,R*) column (4.6 mm x 250 mm column, 5 micron particle size), which was eluted with 20% MeOH in CO_2 held at 25 °C at 140 bar. A flow rate of 3 mL/min gave $Rt_{(Peak\ 1)}$ = 1.28 minutes and $Rt_{(Peak\ 2)}$ = 1.78 minutes.

Example 52 (Peak 1): 5.56 mg, >99% ee, 8.3% yield. ^{1}H NMR (400MHz ,DMSO-d_6) δ 7.66 - 7.46 (m, 3 H), 7.22 (t, *J* = 8.6 Hz, 1 H), 6.90 (s, 1 H), 6.18 (s, 2 H), 5.55 (q, *J* = 5.9 Hz, 1 H), 4.36 (d, *J* =14.1 Hz, 1 H), 4.24 - 4.16 (m, 1 H), 4.04 (s, 3 H), 3.02 (s, 3 H), 1.67 (d, *J* = 6.0 Hz, 3 H). LCMS ES *m/z* 407 $[M+H]^+$.

Example 53 (Peak 2): 5.06 mg, 90% ee, 7.6% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 - 7.55 (m, 2 H), 7.54 - 7.47 (m, 1 H), 7.22 (t, *J* = 8.8 Hz, 1 H), 6.90 (s, 1 H), 6.18 (s, 2 H), 5.55 (q, *J* = 6.1Hz, 1 H), 4.36 (d, *J* = 14.1 Hz, 1 H), 4.24 - 4.15 (m, 1 H), 4.04 (s, 2 H), 3.02 (s, 2 H), 1.67 (d, *J* = 6.3 Hz, 2 H). LCMS ES *m/z* 407 $[M+H]^+$.

Preparation of (10*R*)-7-amino-16-cyclopropyl-12-fluoro-2,10-dimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(azeno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 54)



Step 1:

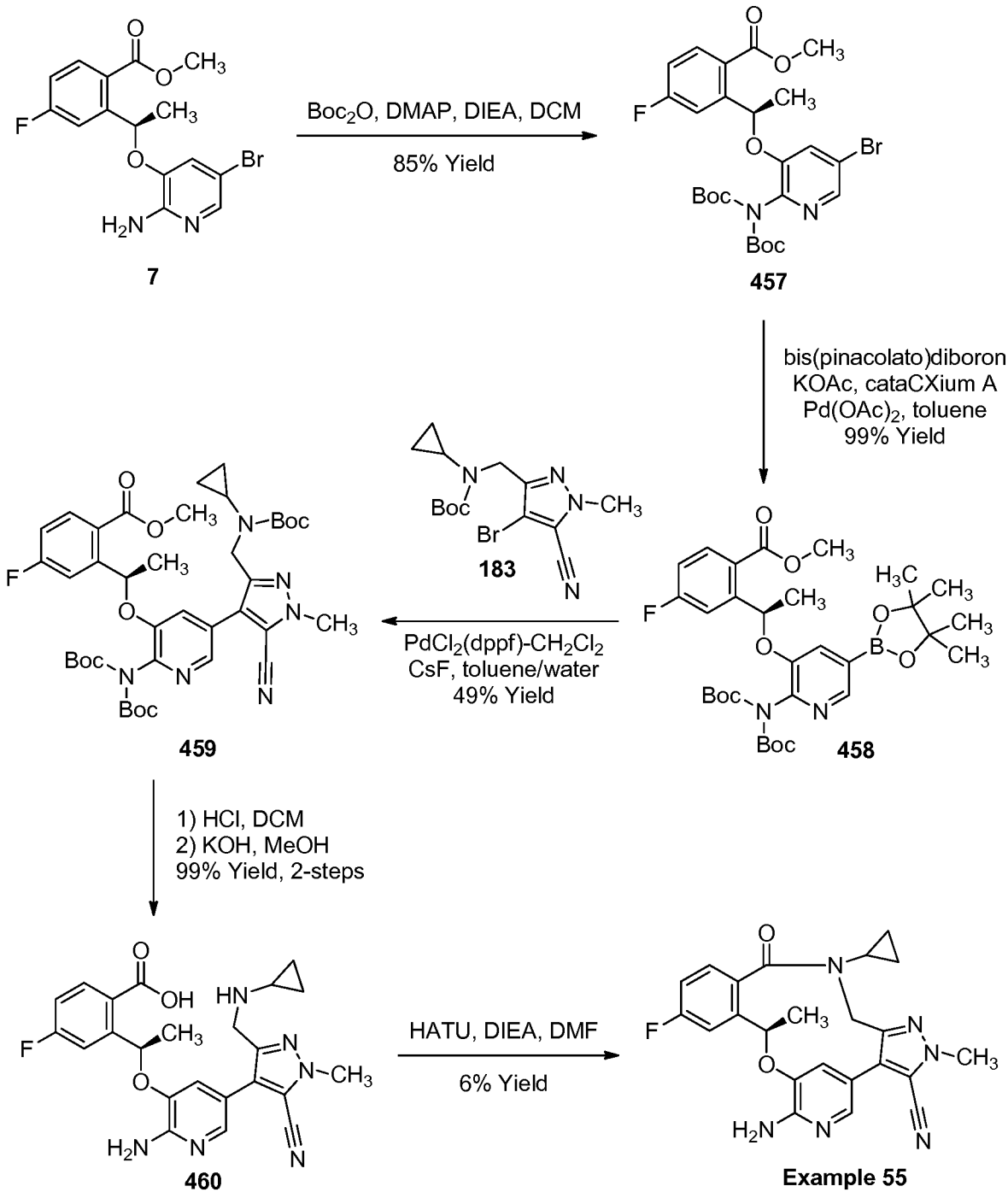
Compound 126 (300 mg, 0.685 mmol), **compound 181** (146 mg, 0.685 mmol), DIEA (0.597 mL, 3.42 mmol), Pd (P^tBu_3)$_2$ (36 mg, 0.069 mmol) were dissolved in toluene (20 mL) in a stainless steel vessel. The reactor was pressurized to 4 bar of CO, and heated to 85 °C for 14 hours. The reaction mixture was concentrated, and subjected to column chromatography over

silica gel (0-75% EtOAc/heptane) to afford **compound 456** (168 mg, 48%) as a cream solid. ^{1}H NMR (400 MHz ,80°C, DMSO-d_6) δ 7.63 - 7.50 (m, 2 H), 7.47 - 7.36 (m, 1 H), 7.14 (dt, *J* = 2.8, 8.6 Hz, 1 H), 7.01 (s, 1 H), 6.41 (br. s., 2 H), 6.17(d, *J* = 5.5 Hz, 1 H), 4.74 - 4.48 (m, 2 H), 3.97 (s, 3 H), 2.83 (br. s., 1 H), 1.59 (d, *J* = 6.5 Hz, 3 H), 0.57 (br. s., 4 H).

Step 2:

A mixture of **compound 456** (165 mg), pivalic acid (9.9 mg, 0.096 mmol) and KOAc (158 mg, 1.6mmol) in *t*-AmOH (8.68 mL) with 1 drop of water added was purged with nitrogen for 10 minutes. CataCXium A (35.5 mg, 0.096 mmol) and $Pd(OAc)_2$ (10.8 mg, 0.048 mmol) were added, and the vial heated to 140 °C for 1 hour in the microwave. The reaction was concentrated, and purified by column chromatography over silica gel (0-100% EtOAc/heptane). Fractions containing the desired product were slurried in water, filtered and dried in the vacuum oven to afford **Example 54** (75 mg, 54%) as a cream solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (s, 1 H), 7.47 (dd, *J* = 2.5, 10.1 Hz, 1 H), 7.31 (dd, *J* = 5.8, 8.6 Hz, 1 H), 7.12 (dt, *J* = 2.6, 8.5 Hz, 1 H), 6.71 (s, 2 H), 6.16 - 6.05 (m, 1 H), 4.33 - 4.26 (m, 1 H), 4.22 - 4.15 (m, 1 H), 4.02 (s, 3 H), 2.16 - 2.06 (m, 1 H), 1.66 (d, *J* = 6.5 Hz, 3 H), 1.11 -1.00 (m, 1 H), 0.97 - 0.84 (m, 1 H), 0.81 - 0.71 (m, 1 H), 0.70 - 0.61 (m, 1 H). LCMS APCI *m/z* 434 $[M+H]^+$.

Preparation of (10*R*)-7-amino-16-cyclopropyl-12-fluoro-2,10-dimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 55)



Step 1:

To a solution of **compound 7** (30 g, 81.3mmol) in DCM (325 mL) was added DIEA (42.5 mL, 244 mmol), DMAP (1.99 g, 16.3 mmol) and $(Boc)_2O$ (53.2 g, 244 mmol). The reaction was stirred overnight, and then concentrated. Purification by column chromatography over silica gel (0-25% EtOAc/heptane) afforded **compound 457** (39.3g, 85%) as a viscous gum. ^1H NMR (400 MHz, 30 °C, DMSO-d_6) δ 8.16 (d, J = 2.0 Hz, 1 H), 8.00 (dd, J = 5.9, 8.7 Hz, 1 H), 7.53 (d, J =

2.0 Hz, 1 H), 7.35 - 7.25 (m, 2 H), 6.38 -6.26 (m, 1 H), 3.91 (s, 3 H), 1.55 (d, *J* = 6.3 Hz, 3 H), 1.38 (s, 18 H). LCMS APCI *m/z* 469 $[M - Boc]^+$.

Step 2:

A mixture of the **compound 457** (22 g, 39 mmol), bis(pinacolato)diboron (10.8 g, 42.5 mmol) and KOAc (11.4 g, 116 mmol) in toluene (260 mL) was bubbled with nitrogen for 30 min before addition of cataCXium A (1.43g, 3.86mmol) and $Pd(OAc)_2$ (434mg, 1.93mmol). The reaction was heated to 100 °C using an oil bath for 16 hours. The reaction was allowed to cool, and diluted with EtOAc. The organics were washed with water (2x) and brine, dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography over silica gel (0-10% MeOH/DCM) afforded **compound 458** (24.9 g, 99%) as a yellow viscous gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, *J* = 1.3 Hz, 1 H), 8.01 (dd, *J* = 6.0, 8.8 Hz, 1 H), 7.92 (s, 1 H), 7.37 (s, 1 H), 7.36 - 7.25 (m, 2 H), 6.38 (q, *J* = 6.0 Hz, 1 H), 3.92 (s, 3 H), 1.54 (d, *J* = 6.3 Hz, 3 H), 1.37 (s, 18 H), 1.27 (d, *J* = 5.5 Hz, 12 H).

Step 3:

A mixture of **compound 458** (684 mg, 0.887 mmol), **compound 183** (315 mg, 0.887 mmol), and cesium fluoride (404 mg, 2.66 mmol) in toluene/water (6 mL/0.2 mL) were flushed with nitrogen. $PdCl_2$(dppf).CH_2Cl_2 (73 mg, 0.089 mmol) was added, and the mixture heated to reflux for 16 hours. The reaction was cooled, diluted with EtOAc, washed with water and brine, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography over silica gel (0-50% EtOAc/heptane) afforded **compound 459** (332 mg, 49%) as a glassy solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, *J* = 2.0 Hz, 1 H), 7.98 (dd, *J* = 5.8, 8.8 Hz, 1 H), 7.36 (dd, *J* = 2.8, 10.3 Hz, 1 H), 7.27 - 7.19 (m, 2 H), 6.35 (q, *J* = 6.0 Hz, 1 H), 4.36 - 4.26 (m, 1 H), 4.18 - 4.10 (m, 1 H), 4.01 (s, 3 H), 3.90 (s, 3 H), 2.43 - 2.33 (m, 1 H), 1.61 (d, *J* = 6.3 Hz, 3 H), 1.43 (s, 18 H), 1.30 (s, 9 H), 0.61 - 0.35 (m, 4 H).

Step 4:

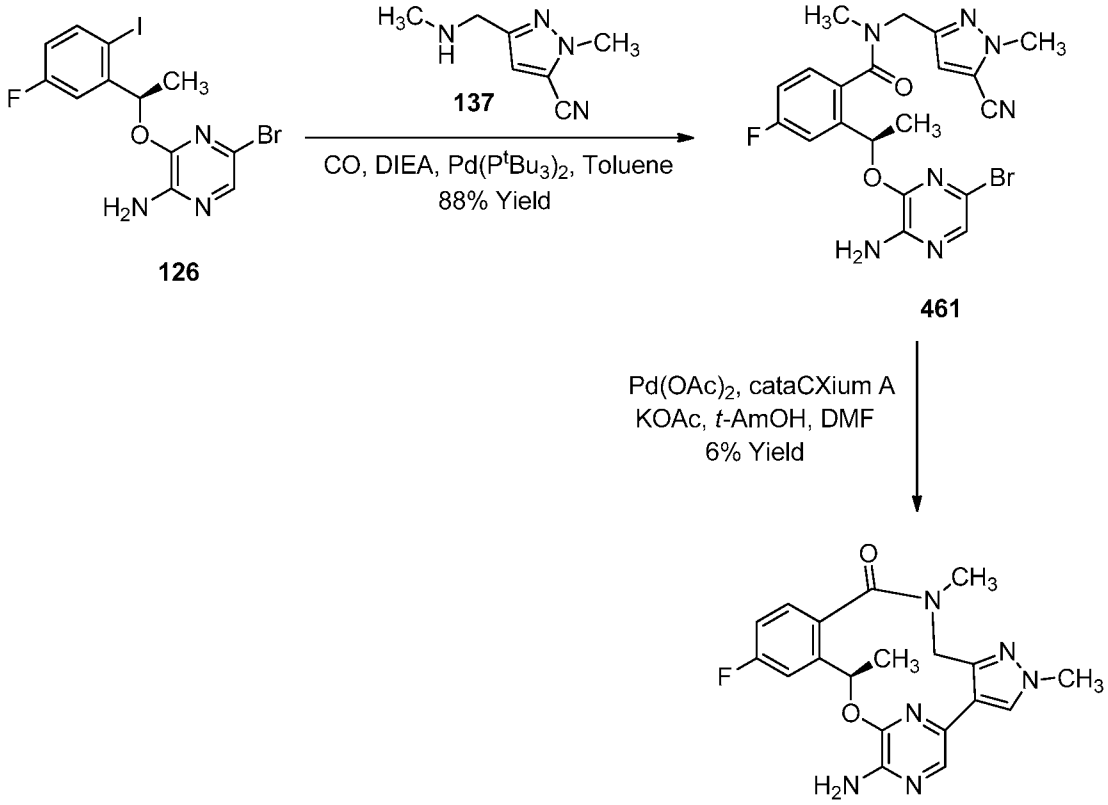
To a cooled (0 °C) solution of the **compound 459** (330 mg, 0.431 mmol) in DCM (2.16 mL) was added HCl (2.16 mL, 4M in dioxane, 8.63 mmol). The reaction was stirred at room temperature for 2 hours then concentrated. The residue was dissolved in MeOH (2 mL), and KOH (0.242 g, 4.31 mmol) added. The reaction was heated at 50 °C for 48 hours. After being cooled to 0 °C, the reaction was neutralized with concentrated HCl. The solids were filtered, and the filtrate concentrated and dried in the vacuum oven. This residue was dissolved in methanol, filtered again, concentrated and dried to afford **compound 460** (272 mg, 99%), which was used without further purification. LCMS APCI *m/z* 451 $[M+H]^+$.

Step 5:

To a cooled (0 °C) solution of HATU (186 mg, 0.474 mmol) in DMF (8.5 mL) was added in a dropwise fashion a solution of **compound 460** (200 mg, 0.431 mmol) and DIEA (375 µL, 2.16 mmol) in DMF (8.5 mL). On completion of addition, the reaction was allowed to warm to room temperature, and stirred for 14 hours. The reaction was then concentrated, and the residue dissolved in EtOAc. The organics were washed with saturated aqueous Na_2CO_3 (2x) and brine, dried ($MgSO_4$), filtered and concentrated. The reaction was purified by column chromatography over silica gel (25-100% EtOAc/heptane). Fractions containing the desired product were concentrated, and slurried in water. The solids were filtered, and dried in the vacuum oven overnight to afford **Example 55** (11 mg, 6%) as a cream solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.60 (dd, *J* = 2.6, 10.2 Hz, 1 H), 7.56 (d, *J* = 1.8 Hz, 1 H), 7.39 (dd, *J* = 5.8, 8.6 Hz, 1 H), 7.15 (dt, *J* = 2.5, 8.4Hz, 1 H), 6.74 (d, *J* = 1.3 Hz, 1 H), 6.17 (s, 2 H), 5.86 - 5.70 (m, 1 H), 4.47 (d, *J* = 14.4 Hz, 1 H), 4.06 - 3.98 (m, 4 H), 2.40 - 2.23 (m, 1 H), 1.69 (d, *J* = 6.3 Hz, 3 H), 1.19 - 1.08 (m, 1 H), 0.99 - 0.87 (m, 1 H), 0.79 (td, *J* = 7.2, 14.5 Hz, 1 H), 0.75 - 0.64 (m, 1 H). LCMS APCI *m/z* 433 $[M+H]^+$.

Preparation of (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-16,17-dihydro-2*H*-8,4-(azeno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one

(Example 56)



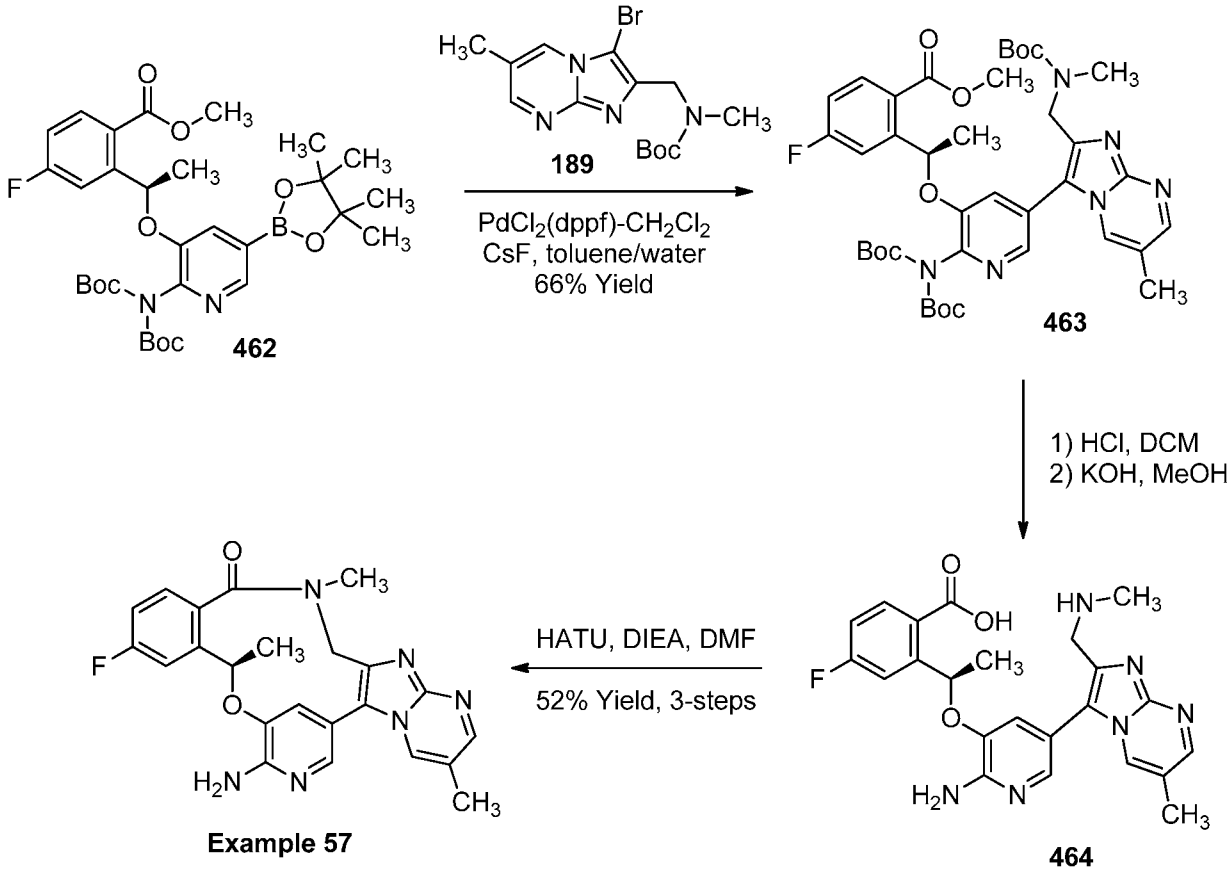
Step 1:

A mixture of **compound 126** (8.5 g, 19 mmol), **compound 137** (3.69 g, 19.8 mmol), DIEA (13.5 mL, 77.6 mmol) and $Pd(P^tBu_3)_2$ (1.01 g, 1.94 mmol) in toluene (320 mL) was heated to 85 °C under 4 bar of CO pressure for 4 hours. The reaction was cooled, concentrated, and purified by column chromatography over silica gel (0-60% EtOAc/heptane) to afford **compound 461** (8.25 g, 88%) as a white solid. LCMS APCI *m/z* 488/490 $[M+H]^+$.

Step 2:

Compound 461 (10.23 g, 20.95 mmol), KOAc (10.3 g, 105 mmol), cataCXium A (968 mg, 2.62 mmol), and $Pd(OAc)_2$ (294 mg, 1.31 mmol) were combined with *t*-amylalcohol (300 mL) in a 500 mL stainless steel vessel. The reaction was sealed, and heated to 120 °C for 16 hours. The reaction was allowed to cool, and the vessel opened. The mixture was diluted with EtOAc, washed with water, dried (Na_2SO_4), and the solvent evaporated. The residue was purified by column chromatography over silica gel (1-6% MeOH/EtOAc) to afford **Example 56** (415 mg, 6%) as a yellow solid. ^1H NMR (400MHz, $CDCl_3$) δ 7.60 (s, 1 H), 7.55 (s, 1 H), 7.18 - 7.30 (m, 2 H), 6.97 (td, *J* = 8.27, 2.65 Hz, 1 H), 6.07 (dd, *J* = 6.57, 1.77 Hz, 1 H), 4.95 (s, 2 H), 4.60 (d, *J* = 13.39 Hz, 1 H), 4.20 (d, *J* = 13.14 Hz, 1 H), 3.91 (s, 3 H), 3.04 (s, 3 H), 1.38 (d, *J* = 12.38 Hz, 3 H). LCMS APCI *m/z* 383 $[M+H]^+$.

Preparation of (5*R*)-8-amino-3-fluoro-5,14,19-trimethyl-18,19-dihydro-7,11-(metheno)-pyrimido[2',1':2,3]imidazo[4,5-*h*][2,5,11]benzoxadiazacyclotetradecin-20(5*H*)-one (Example 57)



Step 1:

Compound 462 (489 mg, 0.56 mmol), **compound 189** (197 mg, 0.56 mmol), cesium fluoride (253 mg, 1.66 mmol) were combined in toluene/water (3.7 mL/370 µL), and nitrogen was flushed through the mixture. $PdCl_2(dppf).CH_2Cl_2$ (45.7 mg, 0.056 mmol) was added, and the reaction mixture refluxed for 14 hours. The reaction was allowed to cool, diluted with EtOAc, washed with water (2x) and brine, dried ($MgSO_4$) filtered and concentrated. Purification by column chromatography over silica gel (0-100% EtOAc/heptane) afforded **compound 463** (280 mg, 66%) as a viscous gum. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.20 (s, 2H), 7.97 (dd, *J* = 6.2, 8.7 Hz, 1H), 7.44 - 7.33 (m, 2H), 7.28 - 7.21 (m, 1H), 6.41 - 6.30 (m,1H), 4.45 - 4.25 (m, 2H), 3.82 (s, 3H), 2.74 (s, 3H), 2.28 (s, 3H), 1.61 (d, *J* = 6.3 Hz, 3H), 1.47 (s, 18H), 1.30 (br. s., 9H).

Step 2:

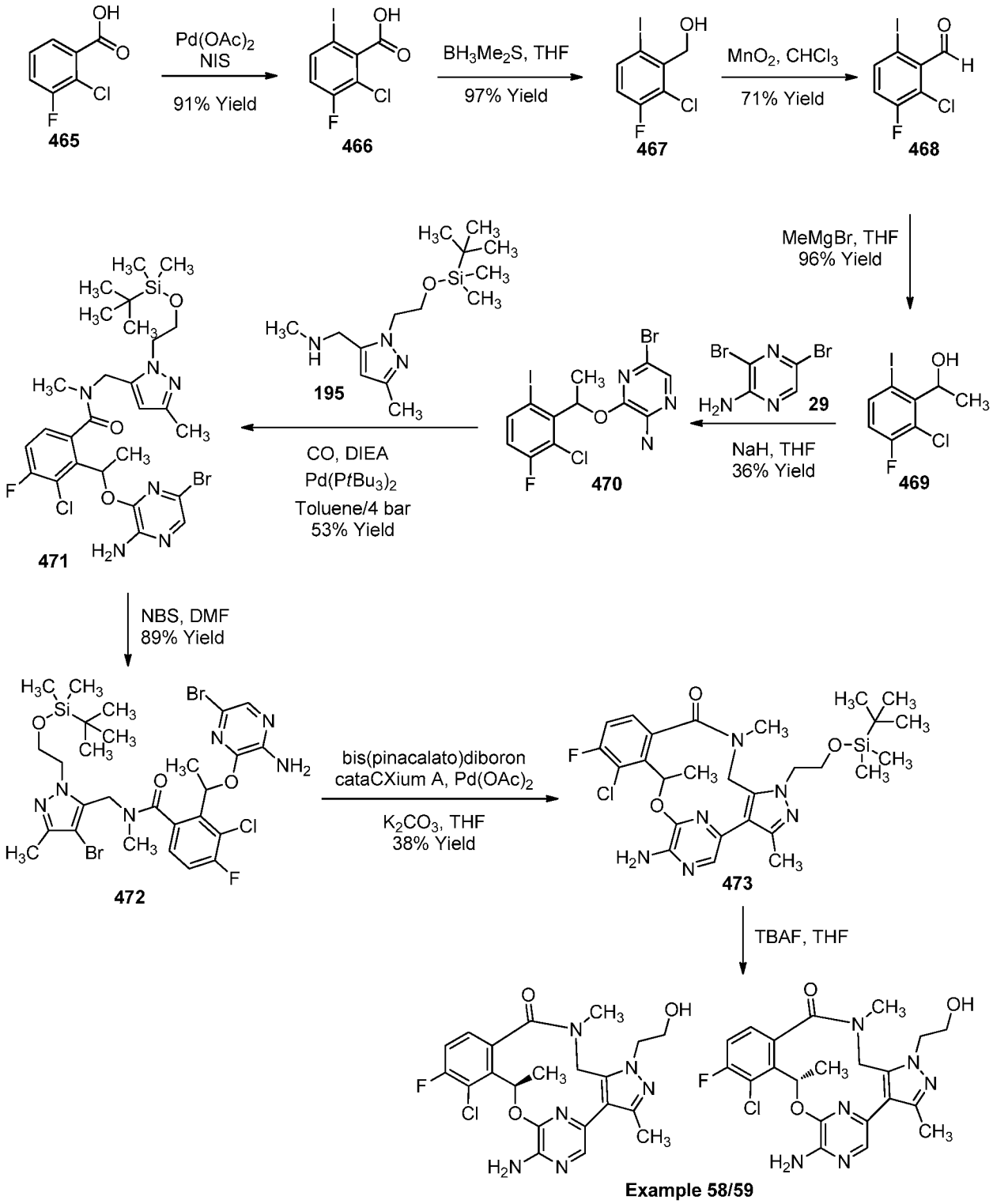
Compound 463 (280 mg, 0.37 mmol) was dissolved in DCM (2 mL), and HCl (2 mL, 4M in dioxane, 7.32 mmol) was added. The reaction was stirred for 38 hours at room temperature. The reaction was then concentrated, the residue dissolved in methanol (2 mL), and KOH (0.205 g, 3.66 mmol) added. The reaction was heated to 60 °C for 6 hours, cooled and neutralized with concentrated HCl. The solids were filtered, and the filtrate concentrated, and dried overnight in

the vacuum oven to afford **compound 307** as an orange-brown solid, which was used without further purification.

Step 3:

To a cooled (0°C) solution of HATU (158 mg, 0.403 mmol) in DMF (7.3 mL) was added a solution of **compound 464** (165 mg, 0.366 mmol) and DIEA (0.319 mL, 1.83 mmol in DMF (7.3 mL). The reaction was allowed to warm to room temperature, and stirred for 14 hours. The mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl (3x), saturated aqueous Na_2CO_3 (3x), brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography over silica gel (25-100% EtOAc/heptane then 0-10% MeOH/DCM) to afford **Example 57** (83 mg, 52%) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.79 (dd, *J* = 1.2, 2.1 Hz, 1H), 8.45 (d, *J* = 2.2 Hz, 1H), 7.82 (d, *J*=1.7 Hz, 1H), 7.66 (dd, *J* = 2.6, 10.3 Hz, 1H), 7.47(dd, *J* = 5.8, 8.5 Hz, 1H), 7.17 (dt, *J* = 2.7, 8.4 Hz, 1H), 6.88 (d, *J* = 1.6 Hz, 1H), 6.22 (s, 2H), 5.73 - 5.63 (m, 1H), 4.50 (d, *J* = 13.9 Hz, 1H), 4.31 (d, *J* = 13.8 Hz, 1H), 3.06 (s, 3H), 2.31 (s, 3H), 1.69 (d, *J*=6.2 Hz, 3H). LCMS APCI *m/z* 433 $[M+H]^+$.

Preparation of (10*R*)-7-amino-11-chloro-12-fluoro-1-(2-hydroxyethyl)-3,10,16-trimethyl-16,17-dihydro-1*H*-8,4-(azeno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one/(10*S*)-7-amino-11-chloro-12-fluoro-1-(2-hydroxyethyl)-3,10,16-trimethyl-16,17-dihydro-1*H*-8,4-(azeno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 58 and 59)



Example 58/59

Step 1:

$Pd(OAc)_2$ (642 mg, 2.86 mmol) was added to a degassed solution of **compound 465** (4.99 g, 28.61 mmol) and NIS (7.08 g, 31.5 mmol) in DMF (143 mL). The resulting solution was stirred at 100 °C for 24 hours. The reaction was filtered, diluted with EtOAc, and the combined organics washed with water (3x), brine (2x) and dried (Na_2SO_4). The solution was filtered, concentrated,

and the residue purified by column chromatography over silica gel (0-100% EtOAc/heptane) to afford **compound 466** (7.9 g, 91%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 4.58, 8.74 Hz, 1H), 7.00 (t, J = 8.56 Hz, 1H).

Step 2:

To a solution of **compound 466** (7.26 g, 24.16 mmol) in dry THF (100 mL) was added a solution of BH_3•SMe_2 (5.32 mL, 10 M in THF, 53.2 mmol) in a dropwise fashion at 0 °C under nitrogen. After the addition was complete, the mixture was stirred at 0 °C for 30 minutes, and then refluxed overnight. The mixture was quenched with saturated aqueous NH_4Cl solution, and the reaction diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The reaction was purified by column chromatography over silica gel (0-30% EtOAc/heptane) to afford **compound 467** (6.7 g, 97%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 5.07, 8.74 Hz, 1H), 6.90 (t, *J* = 8.50 Hz, 1H), 5.00 (d, *J* = 6.97 Hz, 2H), 2.11 (t, *J* = 7.03 Hz, 1H).

Step 3:

To a solution of **compound 467** (6.67 g, 23.35 mmol) in CHCl3 (60 mL) was added activated MnO_2 (135 g, 140 mmol), and the reaction was refluxed (70 °C) for 18 hours. The reaction was not complete, and a further portion of MnO_2 (9 g) and $CHCl_3$ (5 mL) was added. The reaction was refluxed for a further 12 hours. The reaction was cooled, filtered, and the solids washed with DCM. The organics were dried (Na_2SO_4), filtered and concentrated to afford a yellow solid. This was purified by column chromatography over silica gel (0-20% EtOAc/heptane) to afford **compound 468** (4.73 g, 71%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.91 (dd, *J* = 4.77, 8.68 Hz, 1H), 7.07 (t, *J* = 8.44 Hz, 1H).

Step 4:

To a solution of the **compound 468** (4.72 g, 16.59 mmol) in dry THF (70 mL) was added MeMgBr (6.08 mL, 3M in diethyl ether, 18.3 mmol) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 10 minutes, and allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography over silica gel (0-30% EtOAc/heptane) to afford **compound 469** (4.8 g, 96%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 5.26, 8.68 Hz, 1H), 6.81 (t, *J* = 8.50 Hz, 1H), 5.39 (dd, *J* = 6.97, 8.93 Hz, 1H), 2.85 (s, 1H), 1.62 (d, *J* = 6.85 Hz, 3H).

Step 5:

To a solution of the alcohol **469** (4.76 g, 15.85 mmol) in THF (16 mL) was added NaH (697mg, 17.4 mmol, 60% dispersion). The reaction was stirred for 30 minutes, and then the pyrazine **29** (3.81 g, 15.1 mmol) was added as a solid. The reaction was stirred at 55 °C for 4 hours. The

reaction was allowed to cool, diluted with water, and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated. Trituration with diethyl ether afforded **compound 470** (2.8 g, 37%) as a white solid. The mother liquors were combined, concentrated, and purified by column chromatography over silica gel (0-20% EtOAc/heptane). Trituration of the product containing fractions with diethyl ether afforded a second crop of **compound 470** (2.7 g, 36%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.86 (m, 1H), 7.61 (s, 1H), 6.82 (t, *J* = 8.72 Hz, 1H), 6.47-6.60 (m, *J* = 6.10 Hz, 1H), 4.91 (br. s., 2H), 1.80 (d, *J* = 6.82 Hz, 3H).

Step 6:

Compound 470 (2.97 g, 6.29 mmol), the pyrazole **195** (1.87 g, 6.61 mmol), DIEA (4.39 mL, 25.2 mmol), and $Pd(P^tBu_3)_2$ (161 mg, 0.315 mmol) were combined in toluene (63 mL) in a stainless steel vessel. The reaction was heated to 85 °C under 4 bar CO pressure for 16 hours. The vessel was then allowed to cool, and the reaction filtered. The filtrate was concentrated, and the residue subjected to column chromatography over silica gel (0-100% EtOAc/heptane) to afford **compound 471** (2.2 g, 53%) as a viscous gum. LCMS APCI *m/z* 655/660 $[M+H]^+$.

Step 7:

To an ice-cooled solution of **compound 471** (500 mg, 0.762 mmol) in DMF (15 mL) was added NBS (137 mg, 0.762 mmol). After 10 minutes, the reaction was diluted with EtOAc and saturated aqueous $NaHCO_3$. The organic was separated, washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography over silica gel (0-100% EtOAc/heptane) to afford **compound 472** (498 mg, 89%) as a light yellow solid. LCMS APCI *m/z* 737/740 $[M+H]^+$.

Step 8:

To a solution of **compound 472** (400 mg, 0.544 mmol), bis(pinacalato)diboron (414 mg, 1.63 mmol) in THF (5.5 mL) was added anhydrous K_2CO_3 (376 mg, 2.72 mmol). The system was flushed with nitrogen, and cataCXium A (50.3 mg, 0.136 mmol) was then added followed by $Pd(OAc)_2$ (15.3 mg, 0.068 mmol). The reaction was purged again, and stirred at 80 °C for 7 hours. The reaction was 50% complete, and an additional portion of $Pd(OAc)_2$ (15.3 mg, 0.068 mmol) was added followed by purging with nitrogen. The reaction was heated at 80 °C for another 5 hours. After cooling, the reaction was filtered, concentrated, and the residue subjected to column chromatography over silica gel (0-100% EtOAc/heptane) to afford **compound 473** (120 mg, 38%, 80% pure) as a yellow gum. This material was used directly in the next step. LCMS APCI *m/z* 575/578 $[M+H]^+$.

Step 9:

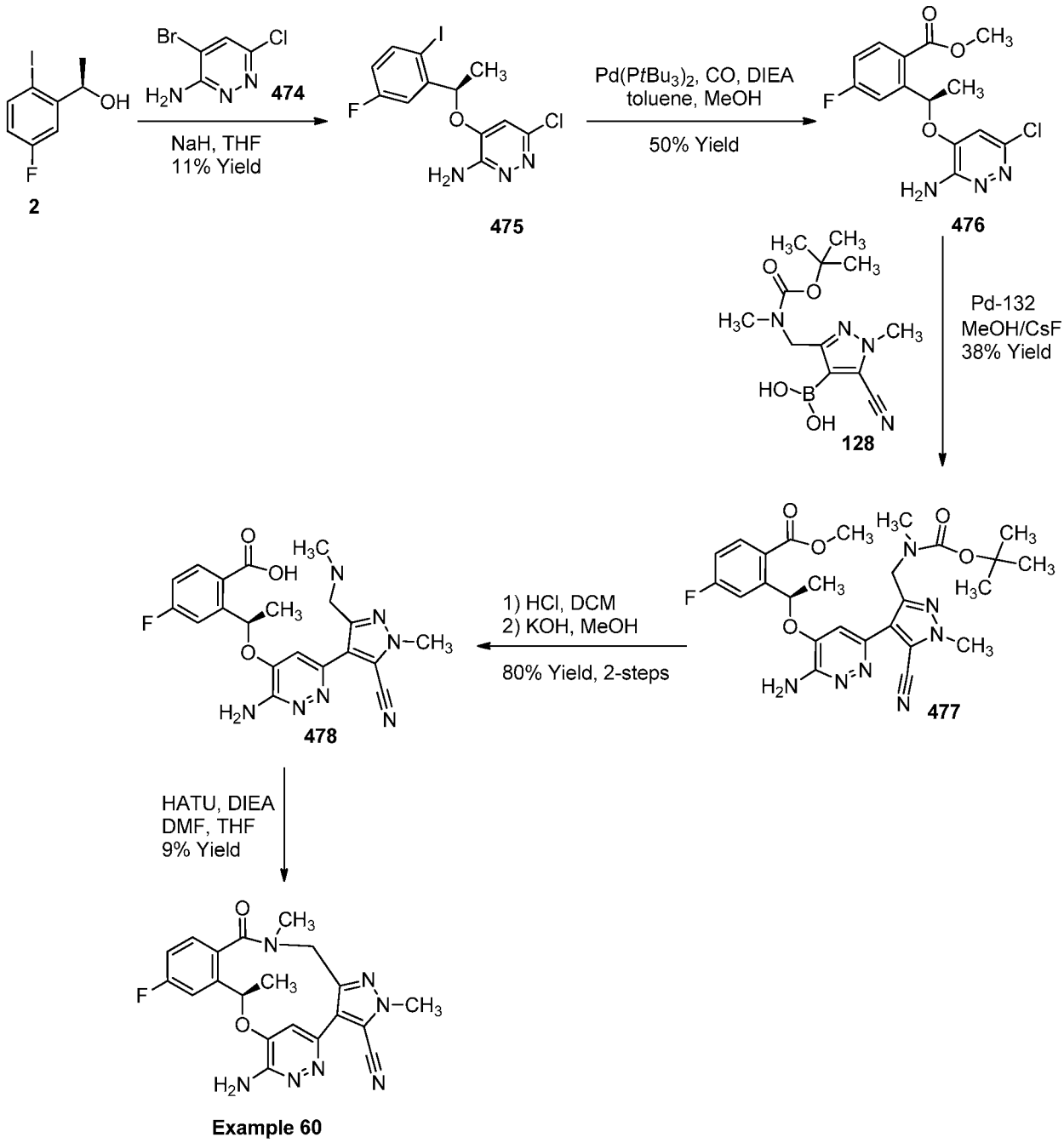
To a solution of **compound 473** (120 mg, 0.209 mmol) in THF (5 mL) was added TBAF (0.209 mL, 1M in THF, 0.209 mmol). The reaction was stirred for 2 hours and concentrated. The

residue was diluted with DCM, washed with water, dried (Na_2SO_4), and concentrated to afford 155 mg of 80% pure material as a mixture, which was followed by chiral separation by SFC to afford both enantiomers of the title **compound**. The analytical chiral separation by SFC was performed using a Regis Whelk-01 (*R, R*) column (4.6 mm x 100 mm column, 5 micron particle size), which was eluted with 40% MeOH in CO_2 held at 25 ºC at 140 bar. A flow rate of 3 mL/min gave $Rt_{(Peak\ 1)}$ = 2.62 minutes and $Rt_{(Peak\ 2)}$ = 3.61 minutes.

Example 58 (Peak 1): 13.7 mg, >99% ee (-), 13% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (s, 1H), 7.35-7.48 (m, 2H), 6.20 (s, 2H), 6.08-6.16 (m, *J* = 7.00 Hz, 1H), 4.78-4.89 (m, 1H), 4.60 (d, *J* = 14.43 Hz, 1H), 4.14-4.40 (m, 3H), 3.74-3.81 (m, 1H), 3.65-3.73 (m, 1H), 2.85 (s, 3H), 2.30 (s, 3H), 1.81 (d, *J* = 6.97 Hz, 3H). LCMS APCI *m/z* 461/464 $[M+H]^+$.

Example 59 (Peak 2): 13.9 mg, 97% ee (+), 13% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (s, 1H), 7.35-7.49 (m, 2H), 6.20 (s, 2H), 6.12 (q, *J* = 6.72 Hz, 1H), 4.78-4.91 (m, 1H), 4.60 (d, J = 14.43 Hz, 1H), 4.15-4.38 (m, 3H), 3.73-3.82 (m, 1H), 3.71 (dd, *J* = 4.03, 7.46 Hz, 1H), 2.84 (s, 3H), 2.30 (s, 3H), 1.81 (d, *J* = 6.85 Hz, 3H). LCMS APCI *m/z* 461/464 $[M+H]^+$.

Preparation of (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,6,11]benzoxatriazacyclotetradecine-3-carbonitrile (Example 60)



Step 1:

To a solution of **compound 2** (2.55 g, 9.6 mmol) in THF (50 mL) at 0 °C was added NaH (384mg, 9.6mmol, 60% dispersion). After being stirred at 0 °C for 30 minutes and being allowed to warm to room temperature, the pyridazine **474** (2 g, 9.6 mmol) was added. The dark brown mixture was then stirred at 75 °C for 18 hours. The reaction mixture was concentrated, and the residue taken up in DCM. The organics were filtered, concentrated, and the residue purified by two column chromatographies over silica gel (10-100% EtOAc/heptanes, followed by 10-75% EtOAc/heptanes) to afford **compound 475** (451 mg, 11%) as a white solid. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 7.92 (dd, 1 H) 7.44 (dd, *J*=10.11, 3.03 Hz, 1 H) 7.02 (td, *J*=8.46, 3.03 Hz, 1 H) 6.62 (s, 2 H) 6.52 (s, 1 H) 5.40 - 5.72 (m, 1 H) 1.57 (d, *J*=6.32 Hz, 3 H).

Step 2:

To a solution of **compound 475** (756 mg, 1.92 mmol) and DIEA (1.27 mL, 7.3 mmol) in toluene (18 mL) and methanol (4 mL) in a stainless steel vessel was added $Pd(P^tBu_3)_2$ (47 mg, 0.09 mmol). The reaction was heated to 85 °C under 4 bar CO pressure for 16 hours. The residue was concentrated, and subjected to column chromatography over silica gel (10-75% EtOAc/heptane). The product containing fractions were triturated with MTBE, and filtered. The solids were washed with warm MTBE. Evaporation of the filtrate afforded **compound 476** (314 mg, 50%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (dd, 1 H) 7.59 (dd, *J*=10.36, 2.78 Hz, 1 H) 7.30 (td, *J*=8.46, 2.78 Hz, 1 H) 6.69 (s, 1 H) 6.63 (s, 2 H) 6.35 (q, *J*=5.98 Hz, 1 H) 3.90 (s, 3 H) 1.62 (d, *J*=6.32 Hz, 3 H).

Step 3:

To the methanolic solution of **compound 476** (9 mL, 1.3 mmol) was added the **compound 128** (204 mg, 0.626 mmol) and CsF (400 mg, 2.6 mmol). The mixture was then degassed, and Pd-132 (22 mg, 0.031 mmol) added. The mixture was heated at 120 °C in the microwave for 30 minutes. LCMS indicates consumption of the boronic acid, but the reaction was not completed. Additional quantities of the boronic acid solution (2 mL, 0.288 mmol), cesium fluoride (400 mg, 2.6 mmol) and Pd-132 (22 mg, 0.031mmol) were added and the reaction heated to 120 °C in the microwave for a further 30 minutes. The reaction was partitioned between EtOAc/brine, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography over silica gel (10-100% EA/heptane followed by 5% MeOH/EtOAc) to afford **compound 477** (128 mg, 38%) as a foam-like solid after trituration with MTBE. ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 7.97 (dd, *J*=8.69, 5.92 Hz, 1 H) 7.53 (dd, *J*=10.32, 2.77 Hz, 1 H) 7.23 (td, 1 H) 6.75 (s, 1 H) 6.39 - 6.54 (m, 1 H) 6.30 (s, 2 H) 4.48 - 4.62 (m, 1 H) 4.36 (d, *J*=15.86 Hz, 1 H) 3.98 (s, 3 H) 3.90 (s, 3 H) 2.73 (s, 3 H) 1.69 (d, *J*=6.29 Hz, 3 H) 1.26 (s, 9 H).

Step 4:

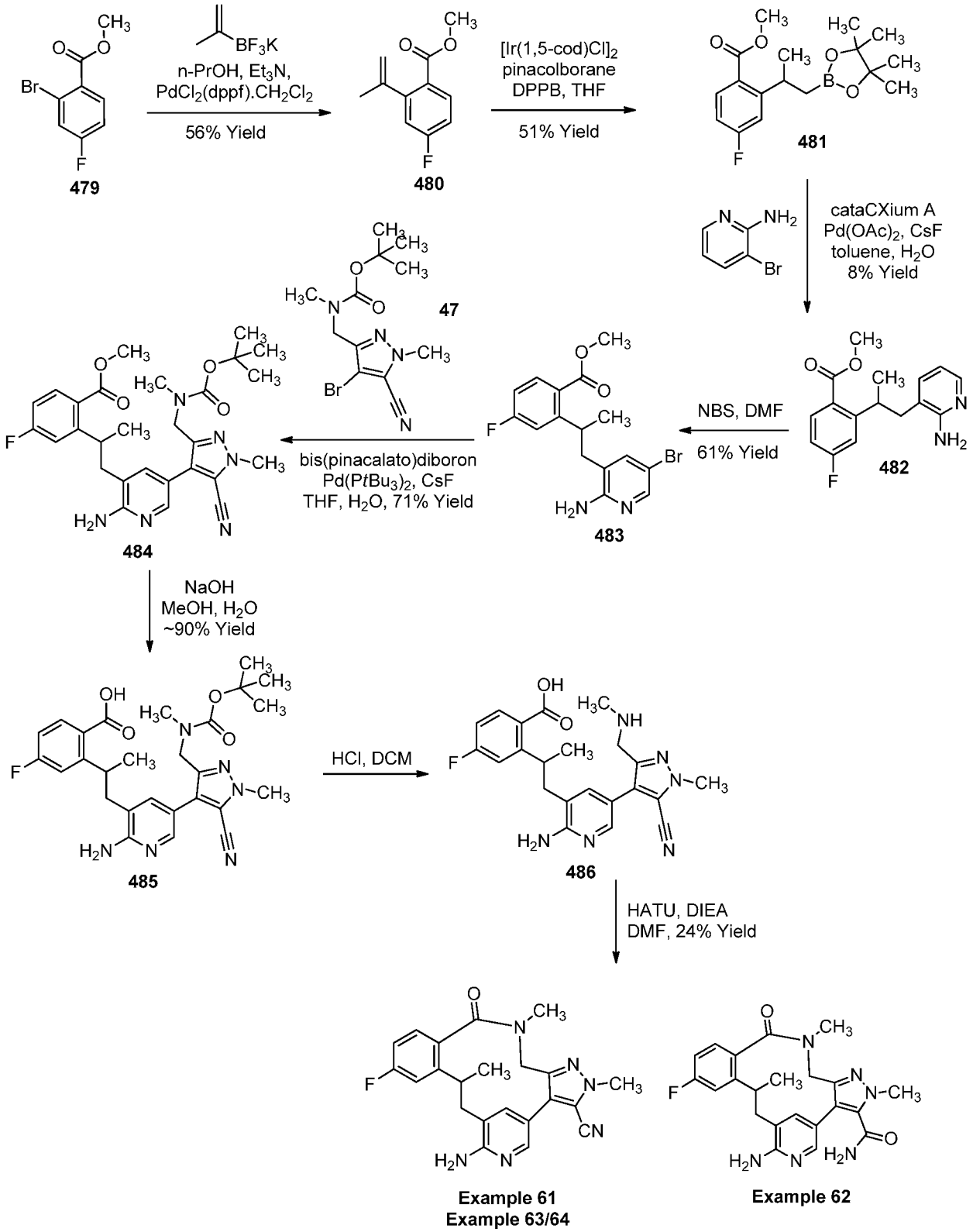
To a solution of **compound 477** (155 mg, 0.287 mmol) in DCM (1.5 mL) was added HCl (1.5 mL, 4M in dioxane, 6 mmol). The reaction mixture was stirred for 1 hour, and concentrated. The residue was azeotroped with MTBE, concentrated, and dried at 50 °C in the vacuum oven for 1 hour. The residue was dissolved in MeOH (3 mL), and KOH (136 mg, 2.41 mmol) added. The reaction was heated to 50 °C for 8 hours. The suspension was allowed to cool, and neutralized with 6N HCl. The solids were removed by filtration, and the filtrate concentrated. The residue was azeotroped with toluene, concentrated and dried at 50 °C in the vacuum oven to afford

compound 478 (122 mg, 70-80% purity by LCMS) as a brown solid, which was used directly in the next step.

Step 5:

To a solution of HATU (158 mg, 0.402 mmol) in DMF (7 mL) at 0 °C was added dropwise a solution of **compound 478** (122 mg, 0.287 mmol) and DIEA (0.3 mL, 1 mmol) in DMF/THF (7 mL/1.4 mL). The addition took 50 minutes. After addition, the resulting mixture was stirred at 0 °C for 10 minutes. The mixture was then poured into saturated aqueous NaHCO3 (400 mL), and filtered. The filtrate was extracted with EtOAc (3x), and the organics washed with water (2x), and brine. The combined organics were dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography over silica gel (0-10% MeOH/DCM:EtOAc 1:1) to afford **Example 60** (10 mg, 9%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 - 7.68 (m, 2 H) 7.15 - 7.31 (m, 1 H) 6.71 (s, 1 H) 6.49 (br. s., 2 H) 5.61 - 5.88 (m, 1 H) 4.50 (d, *J* = 14.43 Hz, 1 H) 4.29 (d, *J* = 14.55 Hz, 1 H) 4.07 (s, 3 H) 3.00 (s, 3 H) 1.71 (d, *J* = 5.75 Hz, 3 H). LCMS APCI m/z 408 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-2,9,10,15,16,17-hexahydro-8,4-(metheno)pyrazolo[3,4-*d*][2,8]benzodiazacyclotetradecine-3-carbonitrile/ 7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-2,9,10,15,16,17-hexahydro-8,4-(metheno)pyrazolo[3,4-*d*][2,8]benzodiazacyclotetradecine-3-carboxamide (Example 61 and 62)



Step 1:

Triethylamine (13 mL, 9.44 g, 93.3 mmol), potassium isopropenyltrifluoroborate (18.0 g, 121.6 mmol) and $PdCl_2(dppf).CH_2Cl_2$ (1.38 g, 1.70 mmol) were added to a solution of **compound 479**

(21.8 g, 93.6 mmol) in *n*-propanol (640 mL) and the mixture was heated at reflux for 17 hours. TLC analysis (10% 2-butanone in heptane) showed starting material remaining and $PdCl_2(dppf).CH_2Cl_2$ (0.69 g, 0.84 mmol) was added and heating continued for a further 4 hours. After cooling to room temperature the mixture was concentrated to ~100 mL *in vacuo* and diluted with EtOAc (400 mL) before being washed with 1M HCl (250 mL) and brine (250 mL). The combined aqueous washings were extracted with EtOAc (100 mL) and this was washed with brine (75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a dark brown oil. Purification by column chromatography (1500 mL silica, 4% EtOAc in heptane) gave the desired product (8.63 g, 47%) as a colorless liquid, contaminated with methyl 4-fluorobenzoate (<10%), and a mixture of the desired product and starting material (5.05 g) also contaminated with methyl 4-fluorobenzoate. Further purification by column chromatography (500 mL silica, 4% EtOAc in heptane) gave a further 1.60 g (9%) of the desired product contaminated with methyl 4-fluorobenzoate (<10%). The product was further purified by Kugelrohr distillation, discarding the forerun (70°C, 4 mmHg), and then increasing the temperature to 95°C to collect the **compound 480** (95% recovery) containing <5% methyl 4-fluorobenzoate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.7, 5.9 Hz, 1H) 6.99 (ddd, *J* = 8.6, 8.0, 2.6 Hz, 1H) 6.93 (dd, *J* = 9.4, 2.6 Hz, 1H) 5.12 (p, *J* = 1.6 Hz, 1H) 4.85 (dq, *J* = 1.8, 0.9 Hz, 1H) 3.85 (s, 3H) 2.07 (t, *J* = 1.2 Hz, 3H). LCMS *m/z* 195 $[M+H]^+$.

Step 2:

$[Ir(1,5\text{-cod})Cl]_2$ (751 mg 1.11 mmol) and DPPB (944 mg 2.21 mmol) were stirred in THF (100 mL) under nitrogen at room temperature for 5 minutes to give a clear yellow solution. **Compound 480** (8.6 g, 44.28 mmol) in THF (10 mL) was added, and the solution stirred for 10 minute. Pinacolborane (7.95 mL, 53.1 mmol) in THF (20 mL) was added in a dropwise fashion, and the cloudy yellow solution stirred for 48 hours. The reaction was concentrated, and purified by column chromatography on silica gel (0-100% DCM/heptane) to give **compound 481** as a colorless oil (7.2 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.68, 6.11 Hz,1H) 7.10 (dd, *J* = 10.70, 2.63 Hz,1H) 6.87 (dt, *J*= 1.00 Hz,1H) 3.84 - 3.99 (m, 4H)1.29 (d, *J* = 1.00 Hz,3H), 1.13 (d, *J*=1.00 Hz,14H). LCMS APCI *m/z* 323 $[M+H]^+$.

Step 3:

To **compound 481** (5.7 g, 17.69 mmol) and 2-amino-3-brompyridine (6.12 g, 35.40 mmol) in toluene (300 mL) and water (60 mL) was added $Pd(OAc)_2$ (248 mg, 1.11 mmol) and cataCXium A (793 mg, 2.21 mmol) followed by CsF (6.72 g ,44.20 mmol). The biphasic reaction mixture was stirred at 120 °C for 48 hrs. LCMS indicated only 20% conversion to the desired product. The reaction was cooled, and the organic layer extracted. The aqueous was further extracted with DCM, and the combined organics dried (Na_2SO_4), filtered and concentrated. The residue

was purified by column chromatography over silica gel (0-75% DCM/heptanes) to give **compound 482** as a brown oil (401 mg, 8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 5.01,1.71 Hz,1H) 7.91 (dd, *J* = 8.80, 6.11 Hz,1H) 7.15 - 7.23 (m,2H) 6.97 (ddd, *J* = 8.68, 7.70, 2.57 Hz,1H) 6.58 (dd, *J* = 7.21,5.01 Hz, 1H) 5.21 (brs.,2H) 4.04-4.17 (m,1H) 3.90 (s, 3H) 3.01 (dd, *J* = 13.88, 4.34 Hz,1H) 2.33 (dd, *J*= 13.88, 11.07 Hz,1H) 1.16 (d, *J* = 6.85 Hz, 3H). LCMS APCI *m/z* 323 $[M+H]^+$. LCMS APCI *m/z* 289 $[M+H]^+$.

Step 4:

Compound 482 (720 mg, 2.50 mmol) was stirred in DMF (20 mL) under nitrogen at room temperature. NBS (494 mg, 2.75 mmol) was added, and the reaction stirred for 14 hours. The reaction was concentrated, and partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography over silica gel (0-75% EtOAc/heptane) to give **compound 483** as a brown oil (558 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 2.32 Hz,1H) 7.93 (dd, *J* = 8.80, 6.11 Hz,1H) 7.33 (d, *J* = 2.32 Hz,1H) 7.17 (dd, *J* =10.39, 2.57 Hz,1H) 6.98 (ddd, *J* = 8.68, 7.70, 2.57 Hz,1H) 5.34 (brs.,2H) 4.08 (m, *J* = 1.50 Hz,1H) 3.91(s, 3H) 3.00 (dd, *J* =13.94, 4.16 Hz, 1H) 2.27 (dd, *J* = 13.82, 11.37 Hz,1H) 1.17 (d, *J* = 6.85 Hz,3H). LCMS APCI *m/z* 366/368 $[M+H]^+$.

Step 5:

Compound 483 (478 mg, 1.30 mmol), **compound 47** (857 mg, 2.60 mmol), bis(pinacalato)diboron (1 g, 3.91 mmol) cesium fluoride (989 mg, 6.51 mmol) and $Pd(P^tBu_3)_2$ (33.9 mg, 0.065 mmol) were combined in THF/water (70 mL/7 mL) and the mixture degassed with nitrogen. The reaction was heated at 100 °C for 14 hours. The reaction was concentrated, and the residue dissolved in EtOAc. The organics were washed with water, dried (Na_2SO_4), and concentrated to give a yellow oil. The residue was purified by column chromatography over silica gel (0-100% EtOAc/heptane) to afford **compound 484** as a golden oil (495 mg, 71%). LCMS APCI *m/z* 537 $[M+H]^+$.

Step 6:

Compound 484 (495 mg, 0.922 mmol) and sodium hydroxide (192 mg, 4.80 mmol) were stirred in water (4.0 mL) and methanol (20 mL) for 10 hours at 40 °C. The reaction was concentrated and acidified to pH-5 with 1M AcOH. The reaction was extracted in EtOAc, dried (Na_2SO_4), and concentrated to give **compound 485** as a brown solid (430 mg 90% - observe ca. 10-15% of amide resulting from cyano hydrolysis). LCMS APCI *m/z* 523 $[M+H]^+$.

Step 7:

Compound 485 (430 mg, 0.823 mmol) was stirred in 4M HCl in dioxane (2.06 mL) and DCM (10 mL) at room temperature for 2 hours. The brown solution was concentrated and azeotroped

with toluene to give **compound 486** as a brown solid which was used directly in the next step. LCMS APCI *m/z* 423 $[M+H]^+$.

Step 8:

A solution of **compound 486** (assumed 0.823 mmol) as the HCl salt and DIEA (2.30 mL, 13.20 mmol) in DMF (10 mL) was added dropwise to a solution of HATU (438 mg, 1.15 mmol) in DMF (15 mL) at 0 °C over 1 hour using a syringe pump. After the addition, the clear yellow solution was allowed to warm to room temperature, and stirred for 14 hours. The reaction was concentrated, and water added. The mixture was extracted into EtOAc (3x), and the combined organics washed with 1M aqueous Na_2CO_3 (5x), 10% aqueous NH_4OH, water and brine, dried (Na_2SO_4) and evaporated to give brown foam. Purification by reverse HPLC gave **Example 61** (81 mg, 24%) as a cream solid, and Example 62 (15 mg, 4%) resulting from amide hydrolysis, also as a cream solid.

Example 61 (81 mg, 24%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (brs, 1H) 7.39 (dt, *J* = 1.00 Hz, 1H) 7.28 (dd, *J* =1.00 Hz, 1H) 7.12 (s,1H) 7.02 (dt, *J* = 1.00 Hz,1H) 6.11 (b s, 2H) 4.42 (d, *J* = 14.31 Hz,1H) 4.24 (d, *J* = 1.00 Hz,1H) 4.0 (s, 3H) 3.61 (bs,1H) 2.97 (s,3H) 2.89 - 2.96 (m, 1H) 2.64 (bd, *J* = 1.00 Hz,1H) 1.35 (d, *J* = 6.48 Hz, 3H). LCMS APCI *m/z* 405 $[M+H]^+$.

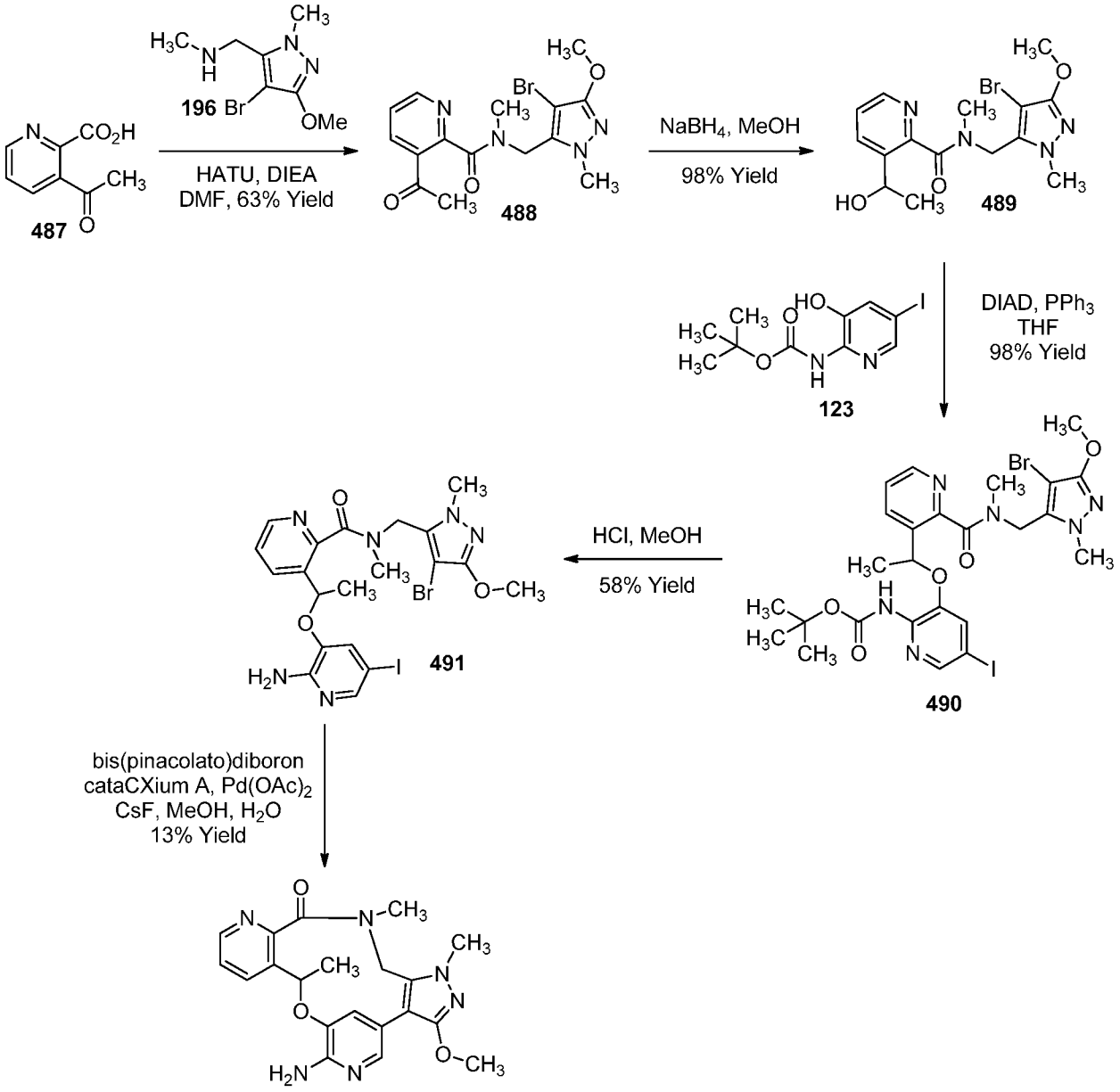
Example 62 (15 mg, 4%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.90 (m,3H) 7.24 - 7.40 (m, 2H) 7.08 (s, 1H) 6.94 - 7.04 (m, 1H) 5.81 (bs, 2H) 4.29 (d, *J* = 13.82 Hz,1H) 4.11 (d, *J* = 13.82 Hz, 1H) 3.89 (s, 3H) 3.61 (bs, 1H) 2.87 - 3.07 (m, 4H) 2.56 - 2.75 (m, 2H) 1.35 (d, *J* = 6.36 Hz, 3H). LCMS APCI *m/z* 423 $[M+H]^+$.

68 mg of **Example 61** was subjected to chiral separation by SFC to afford both enantiomers of the title **compound**. The analytical chiral separation by SFC was performed using a Regis Whelk-01 (*R, R*) column (4.6 mm x 100 mm column, 5 micron particle size), which was eluted with 30% MeOH in CO_2 held at 140 bar. A flow rate of 3 mL/min gave $Rt_{(Peak\ 1)}$ = 3.46 minutes and $Rt_{(Peak\ 2)}$ = 4.76 minutes.

Example 63 (Peak 1): 25.0 mg, >99% ee (-). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (brs, 1H) 7.39 (dt, *J* = 1.00 Hz, 1H) 7.28 (dd, *J* =1.00 Hz, 1H) 7.12 (s,1H) 7.02 (dt, *J* = 1.00 Hz,1H) 6.11 (b s, 2H) 4.42 (d, *J* = 14.31 Hz,1H) 4.24 (d, *J* = 1.00 Hz,1H) 4.0 (s, 3H) 3.61 (bs,1H) 2.97 (s,3H) 2.89 - 2.96 (m, 1H) 2.64 (bd, *J* = 1.00 Hz,1H) 1.35 (d, *J* = 6.48 Hz, 3H). LCMS APCI *m/z* 405 $[M+H]^+$.

Example 64 (Peak 2): 24.8 mg, 98% ee (+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (brs, 1H) 7.39 (dt, *J* = 1.00 Hz, 1H) 7.28 (dd, *J* =1.00 Hz, 1H) 7.12 (s,1H) 7.02 (dt, *J* = 1.00 Hz,1H) 6.11 (b s, 2H) 4.42 (d, *J* = 14.31 Hz,1H) 4.24 (d, *J* = 1.00 Hz,1H) 4.0 (s, 3H) 3.61 (bs,1H) 2.97 (s,3H) 2.89 - 2.96 (m, 1H) 2.64 (bd, *J* = 1.00 Hz,1H) 1.35 (d, *J* = 6.48 Hz, 3H). LCMS APCI *m/z* 405 $[M+H]^+$.

Preparation of 7-amino-3-methoxy-1,10,16-trimethyl-16,17-dihydro-1*H*-8,4-(metheno)-pyrazolo[4,3-*g*]pyrido[2,3-*l*][1,4,10]oxadiazacyclotetradecin-15(10*H*)-one (Example 65 and 66)



Step 1:

A suspension of **compound 487** (965 mg, 5.84 mmol) and **compound 196** (580 mg, 5.84 mmol) in DMF (40 mL) was stirred under nitrogen. DIEA (3.05 mL, 17.5 mmol) was added, and the suspension turned into a thick gel. HATU (2890 mg, 7.60 mmol) was added, and the reaction was stirred for 14 hours. During this time, the solid slowly dissolved to give a clear

brown solution. The reaction was concentrated, and the residue dissolved in EtOAc. The organic extract was washed with saturated aqueous $NaHCO_3$, and dried (Na_2SO_4). The organics were filtered, concentrated, and the residue purified by column chromatography over silica gel (0-4% MeOH/DCM) to give **compound 488** as a cream solid (1400 mg, 63%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 4.93, 1.39 Hz,1H) 8.11 (dd, *J* = 8.08, 1.52 Hz,1H) 7.43 (dd, *J* = 7.83, 4.80 Hz,1H) 4.87 (m, 2H) 4.80-3.95 (s, 3H) 3.90 (s, 3H) 2.72 (s, 3H) 2.59 (s, 3H). LCMS APCI *m/z* 381/383 $[M+H]^+$.

Step 2

A suspension of **compound 488** (1324 mg, 3.473 mmol) in MeOH (60 mL) was stirred at room temperature under nitrogen. $NaBH_4$ (144 mg, 3.82 mmol) was added leading to a vigorous gas evolution and a clear colorless solution. The reaction was stirred for a further 2 hours, concentrated and the residue dissolved in DCM. The organic was washed with water, dried (Na_2SO_4), and concentrated to give **compound 489** as a white solid (1300 mg, 98%). LCMS APCI *m/z* 382/385 $[M+H]^+$.

Step 3

To **compound 489** (650 mg, 1.70 mmol) and **compound 123** (570 mg, 1.70 mmol) in THF (40 mL) under nitrogen at room temperature was added triphenylphosphine (489 mg, 1.87 mmol) followed by dropwise addition of a solution of DIAD (0.37 ml, 1.87 mmol) in THF (4 mL) to give a yellow solution. The reaction was then stirred for 14 hours, concentrated and purified by column chromatography over silica gel (50% DCM/EtOAc) to give **compound 490** as a white solid (1800 mg, 151%). NMR (CDCl3) indicated that the solid is approximately a 1:2 mixture of required product and PPh3=O. Thus 1800 mg of the mixture is equivalent to 1008 mg of product, yield 85%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 4.71, 1.53 Hz, 1H) 8.18 (d, *J* = 1.83 Hz, 1H) 7.86 (dd, *J* = 7.95, 1.47 Hz, 1H) 7.37 (dd, *J* = 8.07, 4.77 Hz, 1H) 7.34 (d, *J* = 1.71 Hz, 1H) 5.63 (q, *J* = 6.40 Hz, 1H) 4.80 - 5.02 (m, 2H) 3.97 (s, 3H) 3.87 (s, 3H) 2.86 (s, 3H) 1.74 (d, *J* = 6.36 Hz, 3H) 1.57 (s, 9H). LCMS APCI *m/z* 700/703 $[M+H]^+$.

Step 4

To a solution of **compound 490** (1800 mg, theory 1.40 mmol) in MeOH (30 mL) was added 4M HCl in dioxane (3.6 mL) giving a solution, which was stirred at room temperature for 15 hours. The reaction was concentrated to give a sticky cream solid. This was slurried in DCM, and washed with saturated aqueous $NaHCO_3$ to form the free base. The organics were dried (Na_2SO_4), concentrated, and purified by column chromatography over silica gel (0-100% EtOAc/DCM) to afford **compound 491** as a cream foam (500 mg, 58%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 4.77, 1.59 Hz, 1H) 7.86 (dd, *J*= 8.07, 1.47 Hz, 1H) 7.81 (d, *J* = 1.71 Hz, 1H) 7.37 (dd, *J* = 7.95, 4.77 Hz, 1H) 7.05 (d, *J* = 1.59 Hz, 1H) 5.56 (q, *J* = 6.40 Hz, 1H) 4.80 -

5.00 (m, 2H) 4.76 (bs, 1H) 3.97 (s, 3H) 3.84 - 3.90 (m, 3H) 2.84 (s, 3H) 1.71 (d, *J* = 6.36 Hz, 3H). LCMS APCI *m/z* 601/602 $[M+H]^+$.

Step 5

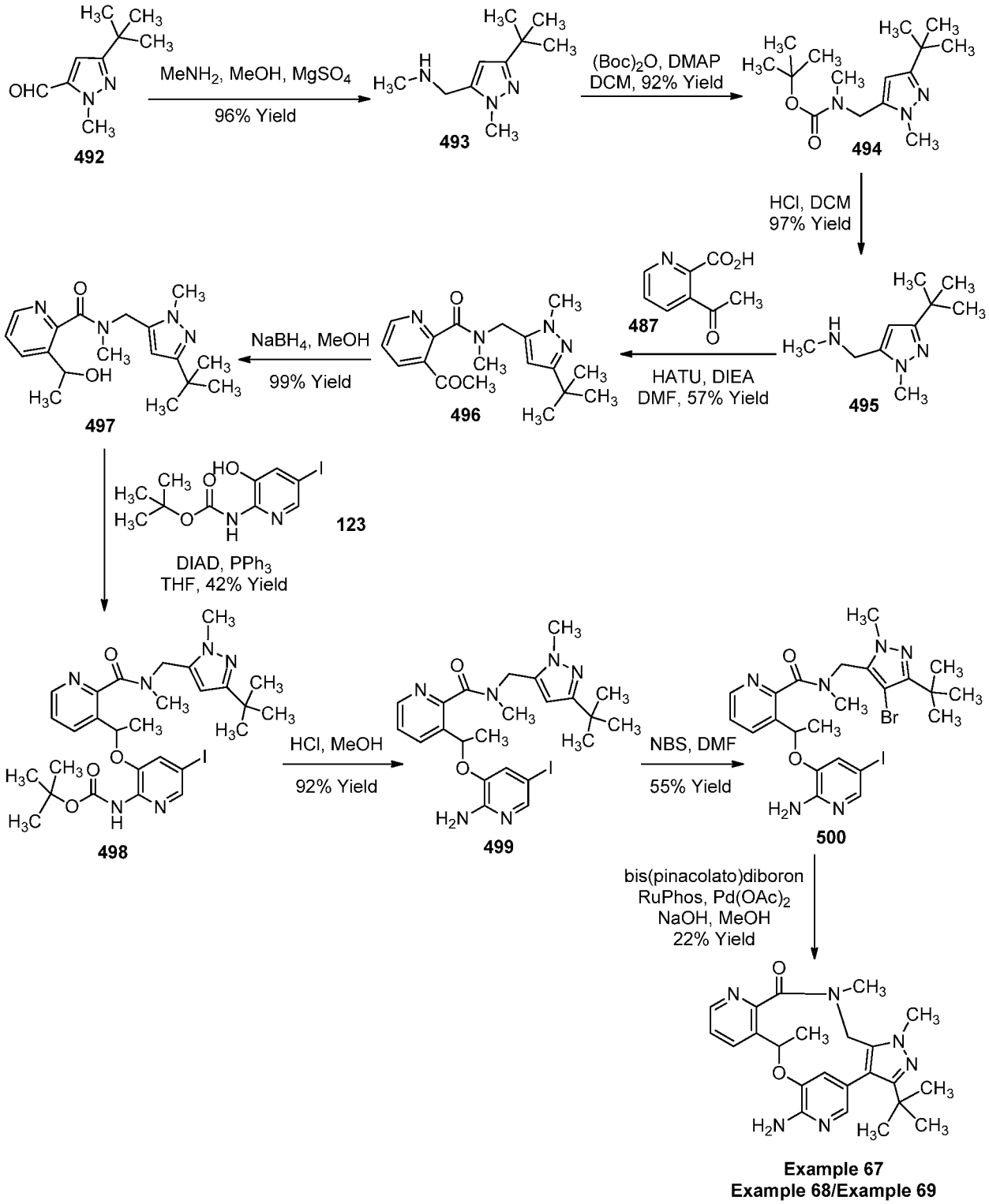
Compound 491 (500 mg, 0.832 mmol), bis(pinacolato)diboron (1070 mg, 4.16 mmol), cataCXium A (60 mg, 0.166 mmol), cesium fluoride (638 mg, 4.16mmol) and palladium acetate (19 mg, 0.830mmol) in water (20 mL) methanol (200 mL) were heated at 100 °C overnight. The reaction was concentrated, and partitioned between water and EtOAc. The organics were dried (Na_2SO_4), concentrated to a yellow oil, which was purified by preparative reverse phase HPLC to give **Example 65 and Example 66** as a white powder (43 mg, 13%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.67, 1.39 Hz, 1H) 8.15 (dd, *J* = 8.08, 1.26 Hz, 1H) 7.43 - 7.54 (m,2H) 6.75 (d, *J* = 1.26 Hz,1H) 5.73 (s, 2H) 5.56 (d, *J* = 6.32 Hz, 1H) 4.59 (d, *J* = 15.66Hz, 1H) 4.01 (d, *J* = 15.41 Hz, 1H) 3.83 (d, *J* = 7.58 Hz, 5H) 3.0 (s, 3H) 1.69 (d, *J* = 6.32 Hz, 3H). LCMS APCI *m/z* 395 $[M+H]^+$.

A sample of 43 mg was subjected to chiral separation by SFC to afford both enantiomers of the title **compound**. The analytical chiral separation by SFC was performed using a Regis Whelk-01 (*R, R*) column (4.6 mm x 100 mm column, 5 micron particle size), which was eluted with 30% MeOH in CO_2 held at 140 bar. A flow rate of 3 mL/min gave $Rt_{(Peak\ 1)}$ = 5.77 minutes and $Rt_{(Peak\ 2)}$ = 7.01 minutes.

Example 65 (Peak 1): 12 mg, 99% ee (-).^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.67, 1.39 Hz, 1H) 8.15 (dd, *J* = 8.08, 1.26 Hz, 1H) 7.43 - 7.54 (m,2H) 6.75 (d, *J* = 1.26 Hz,1H) 5.73 (s, 2H) 5.56 (d, *J* = 6.32 Hz, 1H) 4.59 (d, *J* = 15.66Hz, 1H) 4.01 (d, *J* = 15.41 Hz, 1H) 3.83 (d, *J* = 7.58 Hz, 5H) 3.0 (s, 3H) 1.69 (d, *J* = 6.32 Hz, 3H). LCMS APCI *m/z* 395 $[M+H]^+$.

Example 66 (Peak 2): 15 mg, 97% ee (+).^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.67, 1.39 Hz, 1H) 8.15 (dd, *J* = 8.08, 1.26 Hz, 1H) 7.43 - 7.54 (m,2H) 6.75 (d, *J* = 1.26 Hz,1H) 5.73 (s, 2H) 5.56 (d, *J* = 6.32 Hz, 1H) 4.59 (d, *J* = 15.66Hz, 1H) 4.01 (d, *J* = 15.41 Hz, 1H) 3.83 (d, *J* = 7.58 Hz, 5H) 3.0 (s, 3H) 1.69 (d, *J* = 6.32 Hz, 3H). LCMS APCI *m/z* 395 $[M+H]^+$.

Preparation of 7-amino-3-*tert*-butyl-1,10,16-trimethyl-16,17-dihydro-1*H*-8,4-(metheno)pyrazolo[4,3-*g*]pyrido[2,3-*l*][1,4,10]oxadiazacyclotetradecin-15(10*H*)-one (Example 67, 68 and 69)



Example 67
Example 68/Example 69

Step 1:

Compound 492 (2000 mg, 12.03 mmol) in MeOH (50 mL) was stirred under nitrogen with 33% methylamine in EtOH (1.80 mL. 5.09 mmol). Anhydrous $MgSO_4$ (3000 mg) was added, and the reaction stirred for a further 1.5 hours. The reaction flask was cooled in an ice-bath and $NaBH_4$ (546 mg, 14.40 mmol) added. The reaction was stirred for 14 hours, concentrated and

partitioned between water and DCM. The organic was separated, and the aqueous further extracted with DCM (2 x). The combined organics were dried (Na_2SO_4), and concentrated to give **compound 493** as a colorless oil (2100 mg, 96%). LCMS APCI *m/z* 182 $[M+H]^+$.

Step 2:

To a solution of **compound 493** (2100 mg, 11.58 mmol) in dichloromethane (60 mL) was added DMAP (283 mg, 2.32 mmol), followed by $(Boc)_2O$ (4040 mg, 18.50 mmol) to give a yellow solution. The reaction was stirred at room temperature for 2 hours, and then the solvent was removed under reduced pressure to give a yellow oil. The reaction was purified by column chromatography over silica gel (0-100% EtOAc/heptane) to give **compound 494** as a colorless oil (3000 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 1H) 4.40 (s, 2H) 3.77 (s, 3H) 2.77 (s, 3H) 1.46 (s, 9H), 1.27 (s, 9H). LCMS APCI *m/z* 282 $[M+H]^+$.

Step 3:

To a solution of **compound 494** (3800 mg, 13.50 mmol) in DCM (50 mL) was added 4M HCl in dioxane (34 mL, 135 mmol), and the reaction stirred for 2 hours. At this time, the reaction had turned cloudy, and MeOH was added to give a clear yellow solution, which was stirred for a further 2 hours. The reaction was concentrated to give a cream solid, which was slurried in heptanes, filtered and dried to give **compound 495** as a solid (3318 mg, 97%). ^1H NMR (400 MHz, DMSO-d_6) δ 9.32 - 9.49 (m, 1H) 6.29 - 6.39 (m, 1H) 4.15 (t, 2H) 3.79-3.83 (m, 3H) 2.54 (t, 3H) 1.17 - 1.23 (m, 9H). LCMS APCI *m/z* 182 $[M+H]^+$.

Step 4:

To a suspension of **compound 495** (965 mg, 5.84 mmol) and **compound 487** (1490 mg, 5.84 mmol) in DMF (40 mL) under nitrogen was added DIEA (3.05 mL, 17.5 mmol) to give a clear brown solution. HATU (2890 mg, 7.60 mmol) was added, and the reaction stirred for 16 hours. The reaction was concentrated and the residue dissolved in EtOAc. The organics were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to afford a residue, which was purified by column chromatography over silica gel (0-4% MeOH/DCM) to give **compound 496** as a brown solid (1100 mg, 57%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 4.83, 1.53 Hz, 1H) 8.11 (dd, *J* = 7.95, 1.59 Hz,1H) 7.44 (dd, *J* = 7.89, 4.83 Hz, 1H) 6.17 (s, 1H) 4.81 (s, 2H) 3.93 (s, 3H) 2.75 (s, 3H) 2.61 (s, 3H) 1.32 (s, 9H).LCMS APCI *m/z* 329 $[M+H]^+$.

Step 5:

To a stirred solution of **compound 496** (1100 mg, 3.349 mmol) in MeOH (20 mL) under nitrogen was added sodium borohydride (152 mg, 4.02 mmol) in a portionwise manner. A vigorous gas evolution was observed, and the reaction rapidly turned to a yellow solution. The reaction was stirred for one hour, concentrated and the residue dissolved in DCM. The organic solution was washed with water, dried (Na_2SO_4), and concentrated to give **compound 497** (1100 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 4.71, 1.65 Hz, 1H) 7.90 (dd, *J* = 7.83, 1.47 Hz, 1H) 7.37 (m, *J* = 7.90, 4.70 Hz,1H) 4.88 -4.99 (m,1H) 4.82 (q, *J* = 1.00 Hz, 2H) 3.92 (s, 3H) 2.86 (s, 3H) 1.55 (d, *J* = 6.60 Hz, 3H) 1.30 (s, 9H).LCMS APCI *m/z* 331 $[M+H]^+$.

Step 6:

To a solution of **compound 497** (1100 mg, 3.329 mmol) and **compound 123** (1120 mg, 3.33 mmol) in THF (40 mL) under nitrogen at room temperature was added triphenylphosphine (960 mg, 3.66 mmol) followed by dropwise addition of a solution of DIAD (0.72 mL. 3.66 mmol) in THF (5 mL) to give a yellow solution. The reaction was stirred at room temperature for 20 hours, concentrated, and purified by column chromatography over silica gel (50:50 DCM/EtOAc) to give **compound 498** as a yellow solid (900 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 4.65, 1.47 Hz, 1H) 8.18 (d, *J* = 1.83Hz, 1H) 7.85 (dd, *J* = 8.01, 1.41 Hz,1H) 7.37 (dd, *J* = 7.95, 4.77 Hz, 1H) 7.27-7.33 (m, 3 H) 6.14 (s, 1H) 5.62 (q, *J* = 6.50 Hz, 1H) 4.67-5.01 (m, 2H) 3.92 (s, 3H) 2.82-2.89 (m, 3H) 1.75 (d, *J* = 6.36 Hz, 3H) 1.57 (s, 9H) 1.29 (s, 9H).LCMS APCI *m/z* 649 $[M+H]^+$.

Step 7:

To a stirred solution of **compound 498** (900 mg, 1.39 mmol) in MeOH (30 mL) was added 4M HCl in dioxane (3.6 mL) to give a yellow solution, which was stirred at room temperature for 16 hours. The reaction was concentrated to give an oil, which was partitioned between DCM and saturated aqueous $NaHCO_3$. The organic was separated, and the aqueous further extracted with DCM (3x). The combined organics were dried (Na_2SO_4), and concentrated to give **compound 499** as a golden foam (700 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.71,1.53 Hz, 1H) 7.85 (dd, *J* = 8.07,1.47 Hz, 1H) 7.80 (d, *J* = 1.59 Hz, 1H) 7.64 - 7.72 (m, 2H) 7.03 (d, *J* = 1.59 Hz, 1H) 6.14 (s, 1H) 5.55 (q, *J* = 6.40 Hz, 1H) 4.94 (d, *J* = 15.16 Hz, 1H) 4.69-4.82 (m, 3H) 3.92 (s, 3H) 2.85 (s, 3H) 1.71 (d, *J* = 6.36 Hz, 3H) 1.29 (s, 9H). LCMS APCI *m/z* 549 $[M+H]^+$.

Step 8:

Compound 499 (650 mg, 1.18 mmol) and NBS (234 mg, 1.30 mmol) in DMF (20 mL) were stirred under nitrogen for 1 hour. The reaction was concentrated, and partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organics were dried (Na_2SO_4), concentrated to give a brown oil, which was purified by column chromatography over silica gel (0-4% MeOH/DCM) to give **compound 500** as a brown foam (411 mg, 55% - LCMS indicates dibromo impurity is present). LCMS APCI *m/z* 581/583. $[M+H]^+$.

Step 9:

Compound 500 (370 mg, 0.590 mmol), bis(pinacolato)diboron (454 mg, 1.77mmol), RuPhos (36 mg, 0.074 mmol) and palladium acetate (8.3 mg, 0.037 mmol) in 1M NaOH (3 mL) and methanol (35 mL) were heated at 100 °C for 14 hours. The reaction was concentrated, and

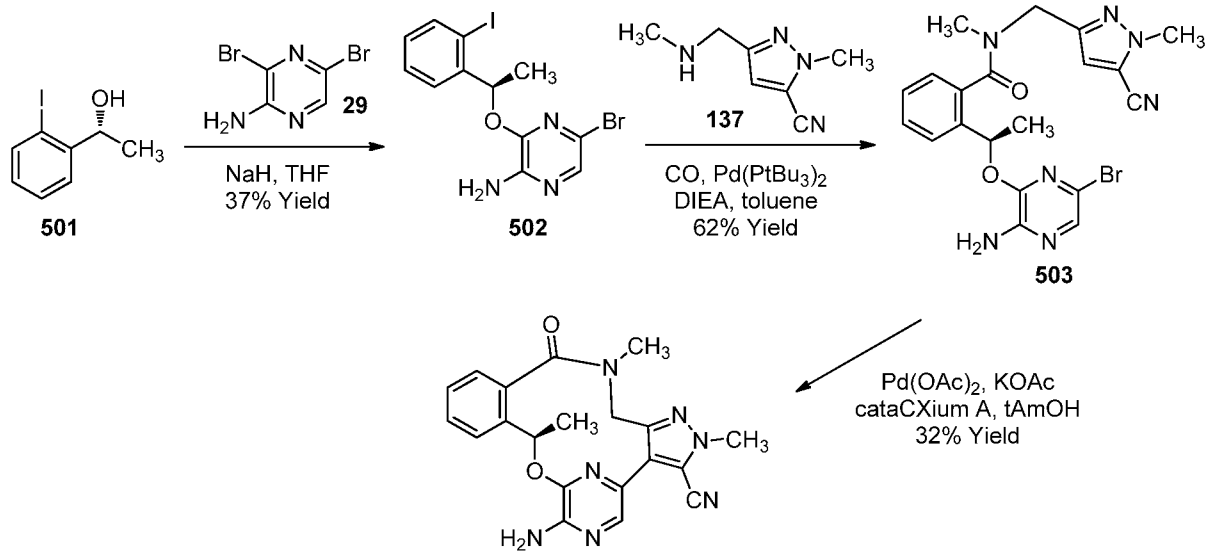
partitioned between water and EtOAc. The organics were dried (Na_2SO_4), and concentrated to give a yellow oil, which was purified by preparative HPLC to give **Example 67** as a white solid (55 mg, 22%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (dd, *J* = 4.66,1.64 Hz, 1H) 8.21 (dd, *J* = 8.06,1.51 Hz, 1H) 7.40 (dd, *J* = 8.06, 4.53 Hz, 1H) 7.33 (d, *J* = 2.01 Hz, 1H) 6.85 (d, *J* = 1.76 Hz, 1H) 5.72 (q, *J* = 6.30 Hz, H) 5.49 (s, 2H) 4.43 (d, *J* = 15.36 Hz, 1H) 3.97 (d, *J* = 15.11 Hz, 1H) 3.91 (s, 3H) 2.98 (s, 3H) 1.73 (d, *J* = 1.00 Hz,3H) 1.23 (s, 9H). LCMS APCI *m/z* 421 $[M+H]^+$.

50 mg of **Example 67** was subjected to chiral separation by SFC to afford both enantiomers of the title **compound**. The analytical chiral separation by SFC was performed using a Regis Whelk-01 (*R, R*) column (4.6 mm x 100 mm column, 5 micron particle size), which was eluted with 30% MeOH in CO_2 held at 140 bar. A flow rate of 3 mL/min gave $Rt_{(Peak\ 1)}$ = 4.87 minutes and $Rt_{(Peak\ 2)}$ = 6.99 minutes. Each peak rapidly equilibrated to a 90 : 10 mixture of atropisomers.

Example 68 (Peak 1): 12 mg, 95% ee (-).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (dd, *J* = 4.66,1.64 Hz, 1H) 8.21 (dd, *J* = 8.06,1.51 Hz, 1H) 7.40 (dd, *J* = 8.06, 4.53 Hz, 1H) 7.33 (d, *J* = 2.01 Hz, 1H) 6.85 (d, *J* = 1.76 Hz, 1H) 5.72 (q, *J* = 6.30 Hz, H) 5.49 (s, 2H) 4.43 (d, *J* = 15.36 Hz, 1H) 3.97 (d, *J* = 15.11 Hz, 1H) 3.91 (s, 3H) 2.98 (s, 3H) 1.73 (d, *J* = 1.00 Hz,3H) 1.23 (s, 9H). LCMS APCI *m/z* 421 $[M+H]^+$.

Example 69 (Peak 2): 13 mg, 95% ee (+).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (dd, *J* = 4.66,1.64 Hz, 1H) 8.21 (dd, *J* = 8.06,1.51 Hz, 1H) 7.40 (dd, *J* = 8.06, 4.53 Hz, 1H) 7.33 (d, *J* = 2.01 Hz, 1H) 6.85 (d, *J* = 1.76 Hz, 1H) 5.72 (q, *J* = 6.30 Hz, H) 5.49 (s, 2H) 4.43 (d, *J* = 15.36 Hz, 1H) 3.97 (d, *J* = 15.11 Hz, 1H) 3.91 (s, 3H) 2.98 (s, 3H) 1.73 (d, *J* = 1.00 Hz,3H) 1.23 (s, 9H). LCMS APCI *m/z* 421 $[M+H]^+$.

Preparation of (10*R*)-7-amino-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(azeno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 70)



Example 70

Step 1:

To an ice-cooled solution of **compound 501** (1593 mg, 6.422 mmol) in THF (30 mL) under nitrogen was added NaH (282 mg, 7.06 mmol, 60% dispersion) leading to a white suspension with very slow gas evolution. The suspension was stirred for 30 minutes, and then a solution of **compound 29** (1620 mg, 6.42 mmol) in THF (8 mL) was added in a dropwise fashion. The bright orange solution was heated to 50 °C for 48 hours. The reaction was concentrated, and partitioned between EtOAc and brine. The insolubles were filtered, and the organic separated, and the aqueous further extracted with EtOAc. The combined organics were dried (Na_2SO_4), concentrated, and the residue purified by column chromatography over silica gel (DCM to give **compound 502**, (R)-5-bromo-3-(1-(2-iodophenyl)ethoxy)pyrazin-2-amine, as a pale yellow oil (1000 mg, 37%). LCMS APCI *m/z* 419/421 $[M+H]^+$.

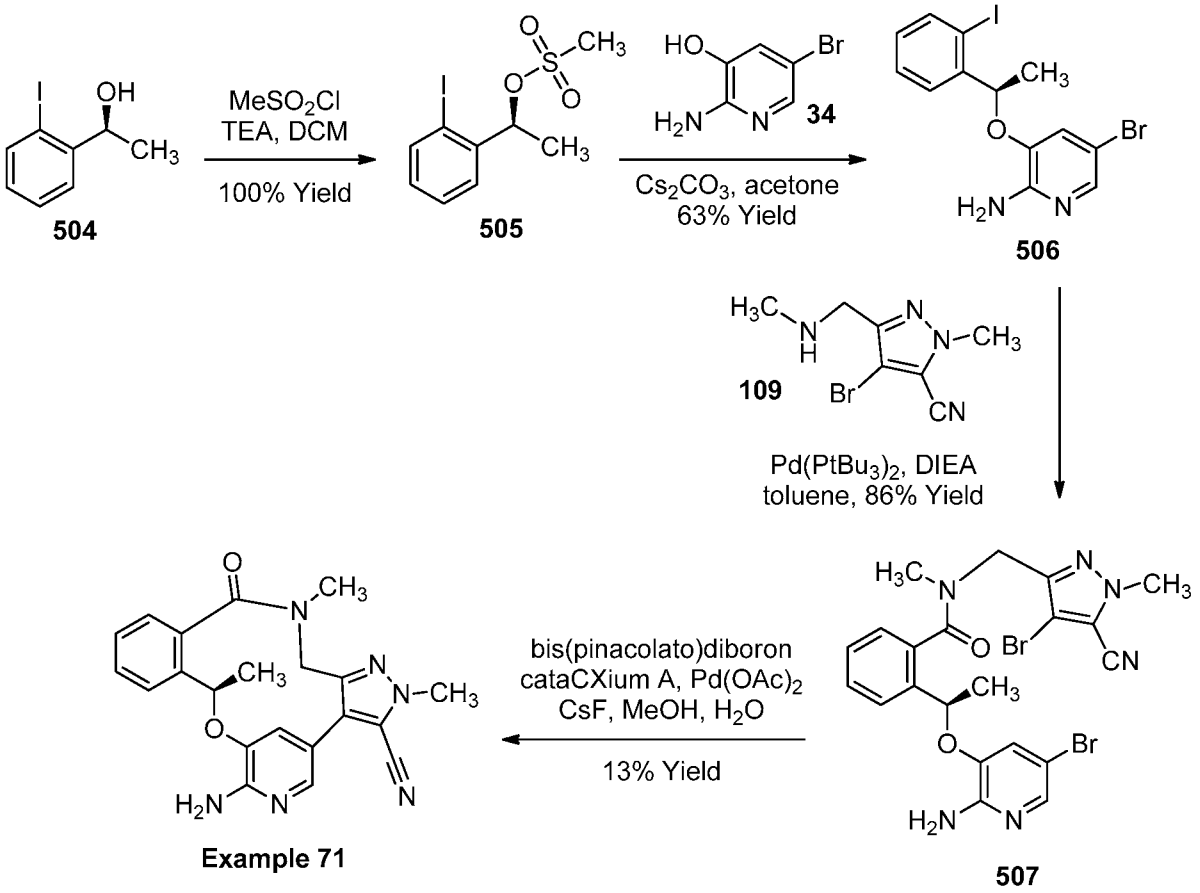
Step 2:

A mixture of **compound 502** (1000 mg, 2.381 mmol), **compound 137** (692 mg, 3.10mmol), DIEA (1.66 mL 9.52 mmol) and Pd ($P^tBu_3)_2$ (124 mg, 0.238mmol) in toluene (25 mL) was stirred at 85 °C under 4 bar CO for 2 hours. The reaction was concentrated to give a red oil, which was purified by column chromatography over silica gel (0-25% EtOAc/heptane) to give **compound 503**,(R)-2-(1-(3-amino-6-bromopyrazin-2-yloxy)ethyl)-N-((5-cyano-1-methyl-1H-pyrazol-3-yl)-methyl)-N-methylbenzamide, as a pale yellow oil (689 mg, 62%). ^1H NMR (400 MHz, DMSO) δ 7.67 (d, *J* = 1.00 Hz,1H) 7.55 (s, 1H) 7.43 (dt, *J* = 1.00 Hz, 1H) 7.35 (m, 1H) 7.21-7.29 (m, 1H) 6.92-7.09 (m, 1H) 6.28 (bs, 2H) 6.10 (q, *J* = 1.00Hz, 1H) 4.70 (bs, 2H) 3.97 (s, 3H) 2.86 (bs, 3H) 1.61 (d, *J* = 6.55 Hz,3H). LCMS APCI *m/z* 470/472 $[M+H]^+$.

Step 3:

Compound 503 (689 mg, 1.46 mmol), KOAc (733 mg, 7.47 mmol) and cataCXium A (163 mg, 0.440mmol) were combined in *tert*-amylalcohol (30 ml) and nitrogen bubbled through the solution prior to $Pd(OAc)_2$ (49 mg, 0.220 mmol) being added. The reaction was heated to 120 °C for 3 hours in the microwave. The reaction was concentrated, and partitioned between water and EtOAc. The insolubles were filtered, and the organics dried (Na_2SO_4) to give the crude product as a yellow oil, which was purified by preparative HPLC to give the macrocycle as a yellow foam. This was slurried in water for 30 minutes then filtered, further washed with water, and dried under vacuum overnight to give **Example 70** (185 mg, 32%) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (s, 1H) 7.65 (d, *J* = 7.83Hz, 1H) 7.39-7.46 (m, 1H) 7.28-7.34 (m, 2H) 6.73 (bs, 2H) 5.91 (q, *J* = 6.50 Hz, 1H) 4.38 (d, *J* = 1.00 Hz, 1H) 4.28 (d, *J* = 1.00 Hz, 1H) 4.03 (s, 3H) 2.90 (s, 3H) 1.65 (d, *J*=6.60 Hz, 3H). LCMS APCI *m/z* 390 $[M+H]^+$.

Preparation of (10*R*)-7-amino-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(metheno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 71)



Step 1:

To a cooled solution of **compound 504** (1283 mg, 5.172 mmol) and triethylamine (1.44 mL, 10.30 mmol) in DCM (15 mL) under nitrogen was slowly added in a dropwise fashion methanesulfonyl chloride (0.60 mL, 7.76 mmol) to give a cream suspension. The reaction was allowed to warm to room temperature and stirred for 15 hours. The reaction was washed with 1M aqueous HCl and saturated aqueous $NaHCO_3$. The organics were dried (Na_2SO_4), and concentrated to give **compound 505** as an orange oil (1704 mg, 100%), which was used directly in the next step without further purification.

Step 2:

Compound 34 (815 mg, 4.31 mmol) and **compound 505** (1687 mg, 5.172 mmol) were stirred at 50 °C in acetone (50 mL) with cesium carbonate (2810 mg, 8.62 mmol) for 6 hours. The reaction was filtered, and the solids rinsed with acetone. The filtrate was concentrated to give a dark residue, which was purified by column chromatography over silica gel (0-25% EtOAc/heptanes) to give **compound 506** as a orange oil (1144 mg, 63%). LCMS APCI *m/z* 418/420 $[M+H]^+$.

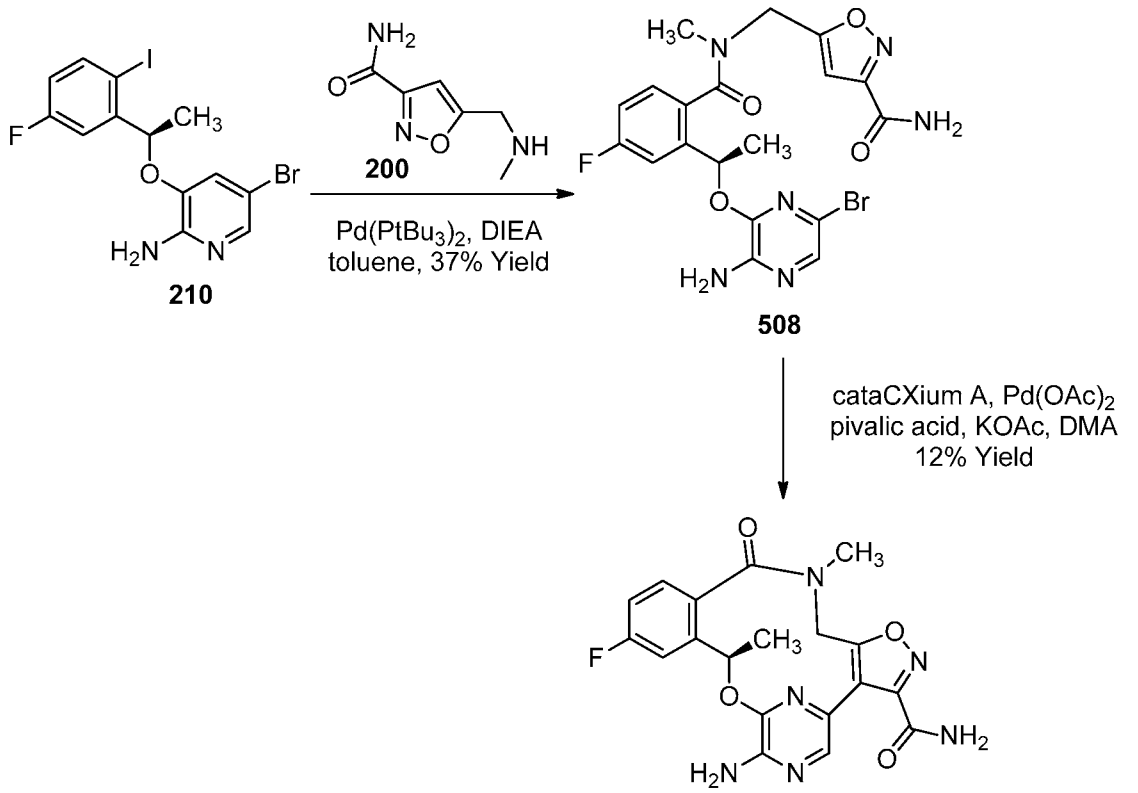
Step 3:

A mixture of **compound 506** (1144 mg, 1.60 mmol), **compound 109** (447 mg, 1.68 mmol),DIEA (1.14 mL, 6.55 mmol) and $Pd(P^tBu_3)_2$ (86 mg, 0.164 mmol) in toluene (20 mL) was heated to 85°C under an atmosphere of 4 bar CO for 14 hours. The reaction was concentrated to give a red oil, which was purified by column chromatography over silica gel (0-100% EtOAc/heptane) to give **compound 507** as a yellow solid (770 mg, 86%). HNMR($CDCl_3$) indicates the presence of rotamers. LCMS APCI *m/z* 548/550 $[M+H]^+$.

Step 4:

Compound 507 (770 mg, 1.40 mmol), bis(pinacolato)diboron (1800 mg, 7.02 mmol), cataCXium A (101 mg, 0.281 mmol), cesium fluoride (1070 mg 7.02 mmol) and palladium acetate (32 mg, 0.14 mmol) in water (10 mL) methanol (100 mL) were heated at 100 °C overnight. The reaction was then concentrated, and partitioned between water and EtOAc. The organics were dried (Na_2SO_4), and concentrated to give a yellow oil, which was subjected to column chromatography over silica gel (0-5% MeOH/DCM) and reverse phase preparative HPLC. The material obtained was slurried in heptane, filtered, and dried under vacuum to give **Example 71** (43 mg, 13%) as a white powder. ^1H NMR (400 MHz, DMSO-d_6) δ 7.72 (d, *J* = 7.81 Hz, 1H) 7.57 (d, *J* = 2.01 Hz, 1H) 7.44 (dt, *J* = 1.00 Hz,1H) 7.29 - 7.39 (m, 2H) 6.83 (d, *J* = 1.76 Hz, 1H) 6.11 (bs, 2H) 5.59 (q, *J* = 6.30 Hz, 1H) 4.45 (d, *J* = 14.35 Hz, 1H) 4.24 (d, *J* = 14.10 Hz, 1H) 4.03 (s, 3H) 3.00 (s, 3H) 1.69 (d, *J* = 6.29 Hz, 3H). LCMS APCI *m/z* 389 $[M+H]^+$.

Preparation of (10*R*)-7-amino-12-fluoro-10,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-8,4-(azeno)[1,2]oxazolo[4,5-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carboxamide (Example 72)



Example 72

Step 1:

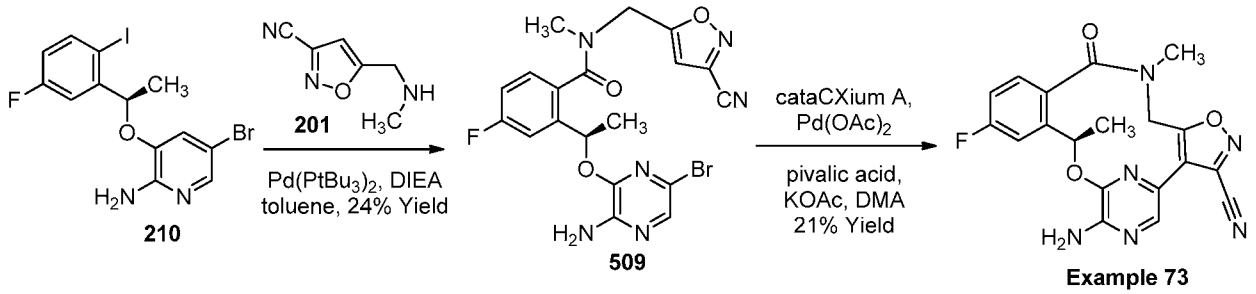
To **compound 210** (150 mg, 0.342 mmol) in toluene (10mL) was added **compound 200** (55.7 mg, 0.359 mmol), DIEA (0.238 mL, 1.37 mmol), and $Pd(P^tBu_3)_2$ (17.7 mg, 0.034 mmol). The mixture was heated in a sealed vessel at 85 °C under 4 bar CO for 16 hours. The reaction was concentrated and purified by column chromatography over silica gel (0-40% EtOAc/heptane – two columns) to give **compound 508** (62 mg, 37%) as a yellow gum. LCMS APCI *m/z* 493 $[M+H]^+$.

Step 2:

To **compound 508** (62.0 mg, 0.13 mmol) in DMA (2.5 mL) was added KOAc (61.8 mg, 0.63 mmol), pivalic acid (3.9 mg, 0.038 mmoL), cataCXium A (14.0 mg, 0.038 mmol) and $Pd(OAc)_2$ (4.3 mg, 0.019 mmol). The mixture was flushed with nitrogen, and was then heated in a microwave at 120 °C for 1hour. Water was added to the reaction, which was extracted with EtOAc (3x), dried (Na_2SO_4), concentrated, and purified by reverse phase HPLC to give **Example 72** (6.48 mg, 12%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1 H) 8.03 (s, 1 H)

7.73 (s, 1 H) 7.52 (dd, *J* = 10.03, 2.57 Hz, 1 H) 7.41 (dd, *J* = 8.50, 5.69 Hz, 1 H) 7.20 (td, *J* = 8.53, 2.63 Hz, 1 H) 6.67 (s, 2 H) 5.89 (dd, *J* = 6.54, 1.77 Hz, 1 H) 4.44 - 4.57 (m, 2 H) 2.96 (s, 3 H)1.65 (d, *J* = 6.48 Hz, 3 H). LCMS APCI *m/z* 413 $[M+H]^+$.

Preparation of (10*R*)-7-amino-12-fluoro-10,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-8,4-(azeno)[1,2]oxazolo[4,5-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 73)



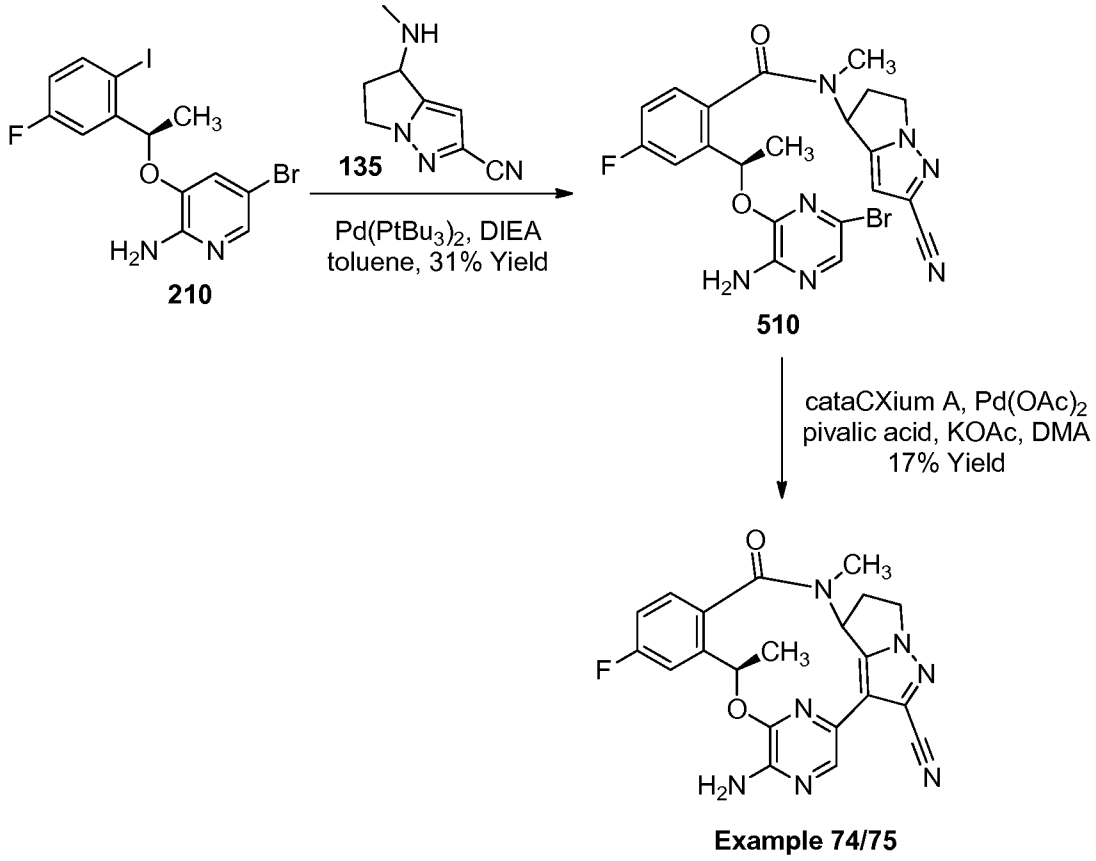
Step 1:

To a solution of **compound 210** (800 mg, 1.83 mmol) in toluene (50 mL) was added **compound 360** (686 mg, 2.73 mmol), DIEA (1.27 mL, 7.30 mmol), and $Pd(P^tBu_3)_2$ (95.4 mg, 0.183 mmol). The mixture was heated in a sealed vessel at 85°C under 4 bar CO for 16 hours. The reaction was concentrated, and purified by column chromatography over silica gel (0-40% EtOAc/heptane) to give **compound 509** (212 mg, 24%) as a yellowish solid. LCMS APCI *m/z* 476 $[M+H]^+$.

Step 2:

To a solution of **compound 509** (188 mg, 0.395 mmol) in DMA (7.92 mL) was added KOAc (194 mg, 1.98 mmol), pivalic acid (12.3 mg, 0.119 mmoL), cataCXium A (44.0 mg,0.30 mmol) and $Pd(OAc)_2$ (13.2 mg, 0.059 mmol). After being flushed with nitrogen, the mixture was heated in a microwave at 120 °C for 1hour. Water was added, and the reaction extracted with EtOAc (3x). The combined organics were dried (Na2SO4), concentrated and purified by reverse phase HPLC to give **Example 73** (32.12 mg, 21%) as a white solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1 H) 7.48 (dd, *J* = 10.03, 2.57 Hz, 1 H) 7.43 (dd, *J* = 8.50, 5.69 Hz, 1 H) 7.18 - 7.25 (m, 1 H) 6.93 (bs., 2 H) 5.85 (dd, *J* = 6.60, 1.59 Hz, 1 H) 4.54 - 4.69 (m, 2 H) 2.94 (s, 3 H) 1.65 (d, *J* = 6.48 Hz, 3 H). LCMS ES *m/z* 395 $[M+H]^+$.

Preparation of (9*R*)-6-amino-11-fluoro-9,15-dimethyl-14-oxo-9,14,15,15a,16,17-hexahydro-7,3-(azeno)-8-oxa-1,5,15,17a-tetraazabenzo[11,12]cyclotetradeca[1,2,3-*cd*]pentalene-2-carbonitrile (Example 74 and 75)



Example 74/75

Step 1:

To **compound 210** (250 mg, 0.571 mmol) in toluene (20 mL) was added **compound 135** (140 mg, 0.685 mmol), DIEA (0.398 mL, 2.28 mmol), and $Pd(P^tBu_3)_2$ (29.7 mg, 0.057 mmol). The mixture was heated in a sealed vessel at 85 °C under 4 bar CO pressure for 16 hours. It was concentrated and purified by column chromatography over silica gel (0-70% EtOAc/heptane) to give **compound 510** (88 mg, 31%) as a colorless gum. LCMS ES *m/z* 500 $[M+H]^+$.

Step 2:

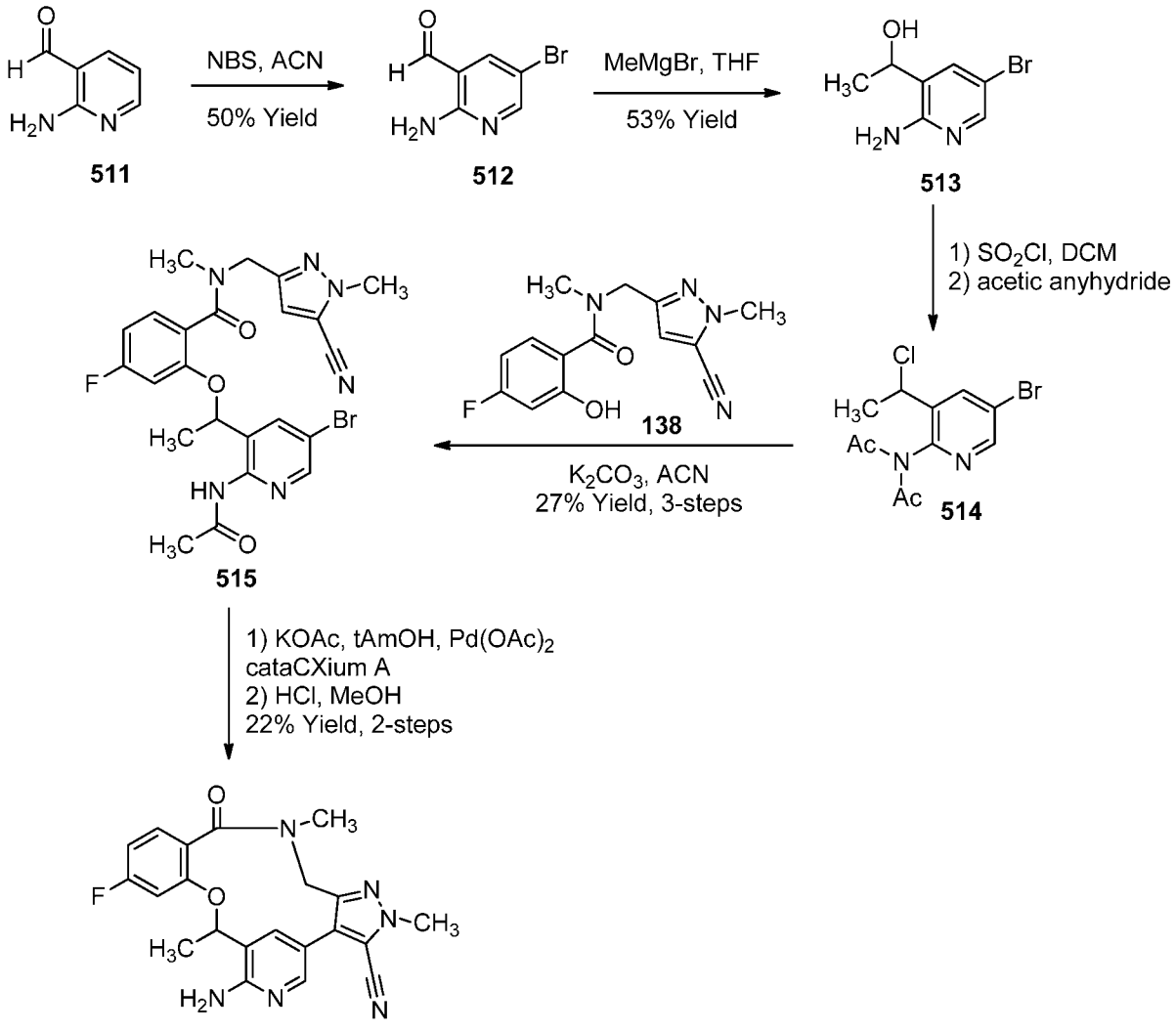
To a solution of **compound 510** (88 mg, 0.18 mmol) in *t*-amyl alcohol (6ml) was added KOAc (86.4 mg, 0.88 mmol), cataCXium A (8.10 mg, 0.022 mmol) and $Pd(OAc)_2$ (8.1 mg, 0.022 mmol). After being flushed with nitrogen, the mixture was heated in a microwave at 140 °C for 1hour. The reaction was filtered and was subjected to chiral separation by SFC to afford both **Example 74** and **Example 75**. The chiral separation by SFC was performed using a Chiralcel OD-H column (21.2 mm x 250 mm column, 5 micron particle size), which was eluted with 34% MeOH in CO_2 held at 100 bar. A flow rate of 62 mL/min gave $Rt_{(Peak\ 1)}$ = 3.11 minutes and $Rt_{(Peak\ 2)}$ = 4.80 minutes.

Example 74 (Peak 1): 4.97 mg, > 99% ee.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1 H) 7.42 (dd, *J* = 9.60, 2.53 Hz, 1 H) 7.21 - 7.25 (m, 1 H) 7.06 (td, *J* = 8.21, 2.53 Hz, 1 H) 6.83 (t, *J* = 8.72 Hz, 1

H) 6.59 - 6.67 (m, 1 H) 5.02 (s, 2 H) 4.39 - 4.48 (m, 1 H) 4.25 (td, *J* = 10.80, 7.20 Hz, 1 H) 3.06 - 3.21 (m, 1 H) 2.55 - 2.68 (m, 1 H) 2.43 (s, 3 H) 1.69 (d, *J* = 6.57 Hz, 3 H). LCMS ES *m/z* 420 $[M+H]^+$.

Example 75 (Peak 2): 7.44 mg, > 99% ee.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1 H) 7.33 (dd, *J* = 9.60, 2.27 Hz, 1 H) 7.17 (dd, *J* = 8.46, 5.43 Hz, 1 H) 7.03 (td, *J* = 8.21, 2.27 Hz, 1 H) 5.80 (d, *J* = 5.56 Hz, 1 H) 5.35 (d, *J* = 8.84 Hz, 1 H) 5.07 (s, 2 H) 4.44 - 4.56 (m, 1 H) 4.23 (t, *J* = 10.61 Hz, 1 H) 3.08 (dd, *J* = 14.02, 9.47 Hz, 1 H) 2.94 (s, 3 H) 2.69 (dd, *J* = 14.15, 7.58 Hz, 1 H) 1.72 (d, *J* = 6.57 Hz, 3 H). LCMS ES *m/z* 420 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-2,9,16-trimethyl-15-oxo-2,15,16,17-tetrahydro-9*H*-8,4-(metheno)pyrazolo[4,3-*h*][1,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 76 and 77)



Example 76/77

Step 1:

A mixture of **compound 511** (1.0 g, 8.2 mmol) and NBS (1.5 g, 8.6 mmol) in acetonitrile (16 mL) was heated to reflux for 1 hour. The reaction was reduced to half the volume and the solids were collected by filtration to give **compound 512**, 2-amino-5-bromopyridine-3-carbaldehyde (820 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1 H) 8.31 (d, *J* = 2.5 Hz, 1 H) 8.24 (d, *J* = 2.5 Hz, 1 H) 7.68 (d, *J* = 2.0 Hz, 2 H).

Step 2:

To a cooled (-50 °C) mixture of **compound 512** (1.1 g, 5.4 mmol) in THF (36 mL) was added dropwise MeMgBr (3 M in Et_2O, 18 mL, 54 mmol) keeping T < - 40 °C. The reaction was stirred at 50 °C for 1 hour then 0 °C for 1 hour before quenching with saturated aqueous ammonium chloride. The aqueous was extracted with Et_2O (3x), and the combined organics dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography over silica gel eluting with DCM/MeOH (0-5%) to give **compound 513**, 1-(2-amino-5-bromopyridin-3-yl)ethanol (630 mg, 53%). ^{1}H NMR (400 MHz ,DMSO-d_6) δ 7.87 (d, *J* = 2.5 Hz, 1 H) 7.52 (d, *J* = 2.3 Hz, 1 H) 5.95 (s, 2 H) 5.33 (d, *J* = 4.3 Hz, 1 H) 4.75 - 4.63 (m, 1 H) 1.27 (d, *J* = 6.5 Hz, 3 H).

Step 3:

To a cooled (-0 °C) solution of **compound 513** (260 mg, 1.2 mmol) in dichloromethane (12 mL) was added thionyl chloride (180 µL, 2.4 mmol). The ice bath was removed, and after stirring for ~4 hours, the solution was concentrated using high vacuum. The residue was dissolved in acetic anhydride and heated to 100 °C overnight. The solution was concentrated and azeotroped with toluene (2x) to give **compound 514**, *N*-acetyl-*N*-[5-bromo-3-(1-chloroethyl)pyridin-2-yl]acetamide which was used directly in the next step.

Step 4:

A mixture of **compound 514** (~1.2 mmol), **compound 138** (350 mg, 1.2 mmol), and potassium carbonate (830 mg, 6.0 mmol) in acetonitrile (8.0 mL) was heated to 60 °C. After ~5 hours, the reaction mixture was cooled and diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography over silica gel eluting with heptane/ethyl acetate (0-100%) to afford **compound 515**, 2-{1-[2-(acetylamino)-5-bromopyridin-3-yl]ethoxy}-*N*-[(5-cyano-1-methyl-1*H*-pyrazol-3-yl)methyl]-4-fluoro-*N*-methylbenzamide (170 mg, 27% over 3 steps). ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 10.00 (br. s., 1 H) 8.47 (d, *J* = 2.5 Hz, 1 H) 7.90 (br. s., 1 H) 7.25 (dd, *J* = 6.8, 8.3 Hz, 1 H) 7.07 - 6.84 (m, 2 H) 6.83 - 6.69 (m, 1 H) 5.56 (q, *J* = 6.3 Hz, 1 H) 4.84 - 4.55 (m, 1 H) 4.31 (br. s., 1H) 3.98 (br. s., 3 H) 2.79 (br. s., 3 H) 2.14 (s, 3 H) 1.50 (d, *J* = 6.3 Hz, 3 H). LCMS APCI m/z 529/531 $[M+H]^+$.

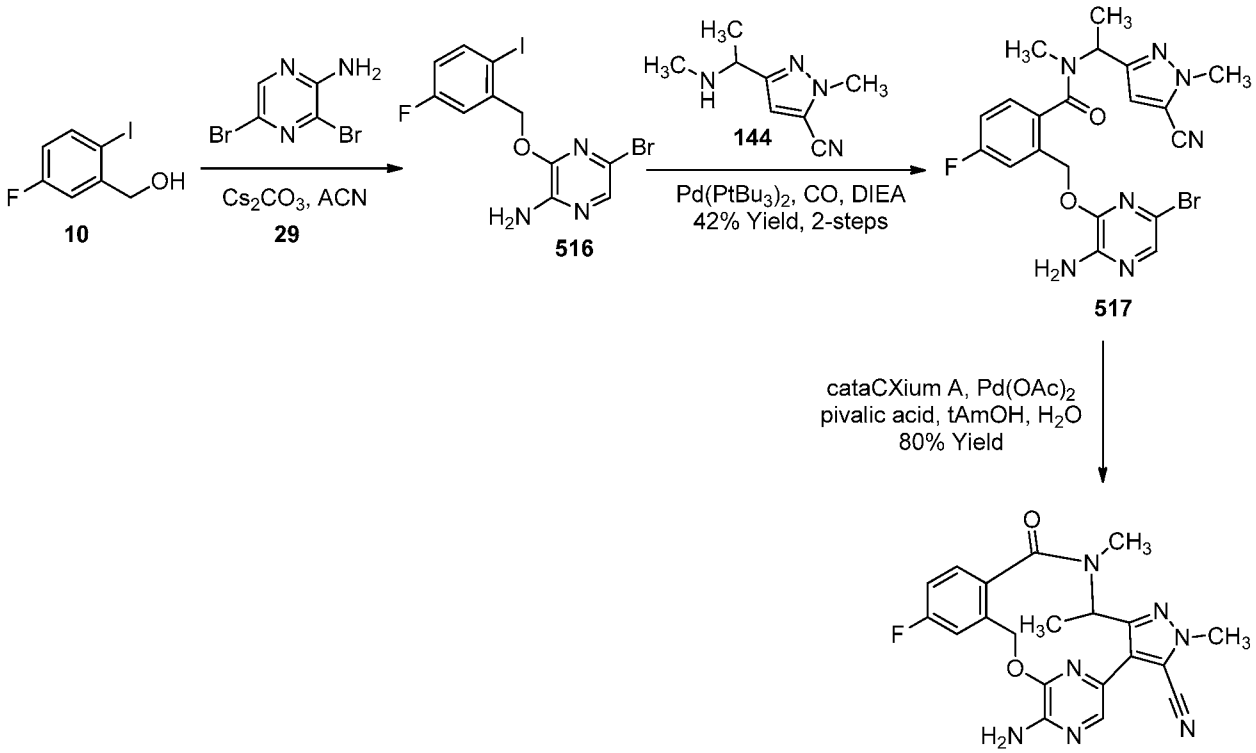
Step 5:

Into a microwave vial was charged **compound 515** (120 mg, 0.23 mmol), KOAc (110 mg, 1.10 mmol) and ^{t}AmOH (2.3 mL). The mixture was bubbled with nitrogen then palladium (II) acetate (5.2 mg, 0.023 mmol) and cataCXium A (17 mg, 0.045 mmol) were added. The vial was sealed and the reaction was irradiated in the microwave for 30 min at 150 °C. The reaction was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography over silica gel eluting with DCM/MeOH (0-10%) to give the protected intermediate. The residue was dissolved in MeOH (1.0 mL) then HCl (4 N in dioxane, 1.0 mL) was added and the solution was heated to 50 °C overnight. The reaction was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ (2x) and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography eluting with DCM/MeOH (0-6%) to give a mixture of **Example 76** and **Example 77**. The chiral separation by SFC was performed using a Regis Whelk-01 (*R, R*) column (4.6 mm x 100 mm column, 5 micron particle size), which was eluted with 30% MeOH in CO_2 held at 140 bar. A flow rate of 3 mL/min gave $Rt_{(Peak\ 1)}$ = 2.68 minutes and $Rt_{(Peak\ 2)}$ = 4.65 minutes.

Example 76 (Peak 1): 10 mg (11%), > 99% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, *J*=2.5 Hz, 1H) 7.45 (d, *J*=2.3 Hz, 1H) 7.33 (dd, *J*=6.9, 8.4 Hz, 1H) 7.21 (dd, *J*=2.3, 11.3 Hz, 1H) 6.85 (dt, *J*=2.0, 8.3 Hz, 1H) 6.26 (s, 2H) 5.88 (q, *J*=6.5 Hz, 1H) 4.30 (d, *J*=14.4 Hz, 1H) 4.13 (d, *J*=14.4 Hz, 1H) 4.04 (s, 3H) 2.95 (s, 3H) 1.48 (d, *J*=6.0 Hz, 3H).LCMS APCI *m/z* 407 $[M+H]^+$.

Example 77 (Peak 2): 11 mg (11%), ~ 98% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, *J* = 2.3 Hz, 1 H) 7.45 (d, *J* = 2.3 Hz, 1 H) 7.33 (dd, *J* = 6.9, 8.4 Hz, 1 H) 7.21 (dd, *J* = 2.3, 11.3 Hz, 1 H) 6.85 (dt, *J* = 2.3, 8.3 Hz, 1 H) 6.26 (s, 2 H) 5.88 (q, *J* = 6.0 Hz, 1 H) 4.30 (d, *J* = 14.4 Hz, 1 H) 4.13 (d, *J* = 14.4 Hz, 1 H) 4.04 (s, 3 H) 2.95 (s, 3 H) 1.48 (d, *J* = 6.0 Hz, 3 H). LCMS APCI *m/z* 407 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-2,16,17-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-8,4-(azeno)pyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 78, 79 and 80)



Example 78
Example 79/Example 80

Step 1:

A mixture of **compound 10** [1.89g, ~7.5 mmol, (containing ~25% (5-fluoro-2-bromo-phenyl)methanol)], **compound 29** (2.28g, 9 mmol) and cesium carbonate (6.11g, 18.7 mmol) in acetonitrile (7 mL) was heated at 80 °C for 18 hours. The crude suspension was added to brine (~400mL) and the resulting rust colored solids were collected by filtration and rinsed with water. The partially dried solids were taken up in hot acetonitrile (~200 mL) and filtered to remove fine dark insolubles which were subsequently discarded. The filtrate was allowed to stand at room temperature overnight. Some crystals were evident in the flask after standing overnight. The supernatant was removed and concentrated to dryness to give **compound 516** as a reddish solid (2.822g), which was carried forward without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (dd, 1 H) 7.58 - 7.69 (m, 2 H) 7.05 (td, J = 8.65, 3.24 Hz, 1 H) 6.69 (s, 2 H) 5.27 (s, 2 H).

Step 2:

A mixture of **compound 516** (616 mg, ~1.45 mmol), **compound 144** (228 mg, 1.14 mmol), DIEA (0.792 mL, 4.54 mmol) and Pd(P^tBu_3)$_2$ (59 mg, 0.114 mmol) in toluene was heated to 85 °C under 4 bar CO overnight. The mixture was concentrated and purified by flash chromatography using a gradient of 25-100% EtOAc/heptane as eluent. The desired fractions were concentrated to dryness to give **compound 517** (233 mg, 42%) as a foamy solid. ^{1}H NMR

(400 MHz, 80°C, DMSO-d_6) δ 7.64 (s, 1 H), 7.51 (dd, *J* = 10.20, 2.64 Hz, 1 H), 7.35 - 7.46 (m, 1 H), 7.24 (td, *J* = 8.62, 2.39 Hz, 1 H), 6.99 (s, 1 H), 6.25 (br. s., 2 H), 5.86 (s, 1 H), 5.35 (s, 2 H), 3.94 (s, 3 H), 2.65 (br. s., 3 H), 1.49 (d, *J* = 7.05 Hz, 3 H).

Step 3:

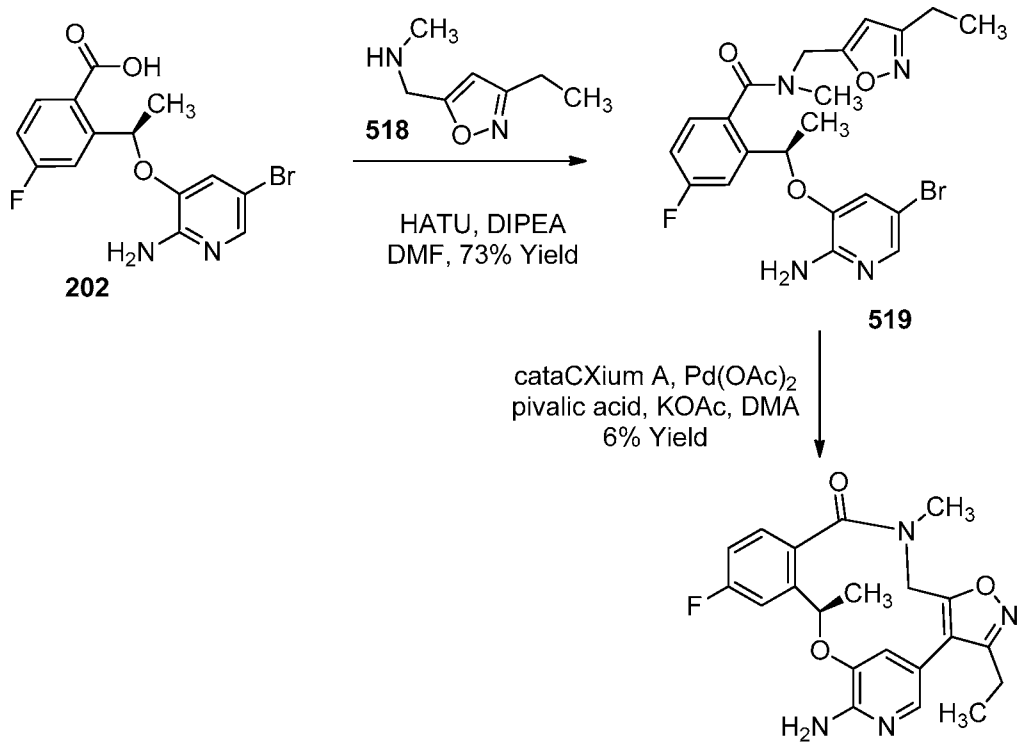
To a solution of **compound 517** (179 mg, 0.367 mmol) in *t*-amyl alcohol (10 mL) was added cataCXium A (40 mg, 0.1 mmol), pivalic acid (11 mg, 0.11 mmol), potassium acetate (180 mg, 1.8 mmol), and water (40 mL). The resulting suspension was sparged with a Nitrogen bubbler for ~5 minutes. Palladium Acetate (12 mg, 0.055 mmol) was then added. The mixture was crimp sealed and heated at 140 °C with microwave irradiation for 1 hour. LCMS indicated desired product as major peak. The mixture was reduced to minimum volume. The residue was suspended in DCM, filtered and the filtrate concentrated, and purified by column chromatography over silica gel using a gradient of 25-100% (EtOAc containing 10% MeOH)/heptanes) as eluent. The desired fractions were reduced to minimum volume to give **Example 78** (120 mg, 0.294 mmol, 80%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (s, 1 H) 7.40 - 7.60 (m, 2 H) 7.18 (td, *J* = 8.44, 3.02 Hz, 1 H) 6.75 (s, 2 H) 5.60 (dd, *J* = 12.46, 1.64 Hz, 1 H) 5.07 (d, *J* = 12.09 Hz, 1 H) 4.59 - 4.77 (m, 1 H) 4.04 (s, 3 H) 2.83 (s, 3 H) 1.61 (d, *J* = 6.80 Hz, 3H).

The chiral separation by SFC was performed using a Chiralcel OJ-H column (4.6 mm x 250 mm column, 5 micron particle size), which was eluted with 30% MeOH in CO_2 held at 140 bar. A flow rate of 3 mL/min gave $Rt_{(Peak\ 1)}$ = 3.67 minutes and $Rt_{(Peak\ 2)}$ = 4.97 minutes.

Example 79 (Peak 1): 44.9 mg > 99% ee (-). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.72 (s, 1 H) 7.41 - 7.58 (m, 2 H) 7.18 (td, *J* = 8.52, 2.54 Hz, 1 H) 6.78 (s, 2 H) 5.55 (d, *J* = 12.46 Hz, 1 H) 5.08 (d, *J* = 12.46 Hz, 1 H) 4.64 (q, *J* = 6.87 Hz, 1 H) 4.02 (s, 3 H) 2.81 (s, 3 H) 1.59 (d, *J* = 6.87 Hz, 3 H). LCMS APCI *m/z* 407 $[M+H]^+$.

Example 80 (Peak 2): 45.2 mg > 99% ee (+). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.72 (s, 1 H) 7.42 - 7.58 (m, 2 H) 7.17 (td, *J* = 8.52, 2.54 Hz, 1 H) 6.78 (s, 2 H) 5.55 (d, *J* = 12.46 Hz, 1 H) 5.08 (d, *J* = 12.46 Hz, 1 H) 4.64 (q, *J* = 7.04 Hz, 1 H) 4.02 (s, 3 H) 2.81 (s, 3 H) 1.59 (d, *J* = 6.87 Hz, 3 H). LCMS APCI *m/z* 407 $[M+H]^+$.

Preparation of (10*R*)-7-amino-3-ethyl-12-fluoro-10,16-dimethyl-16,17-dihydro-8,4-(metheno)[1,2]oxazolo[4,5-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 81)



Example 81

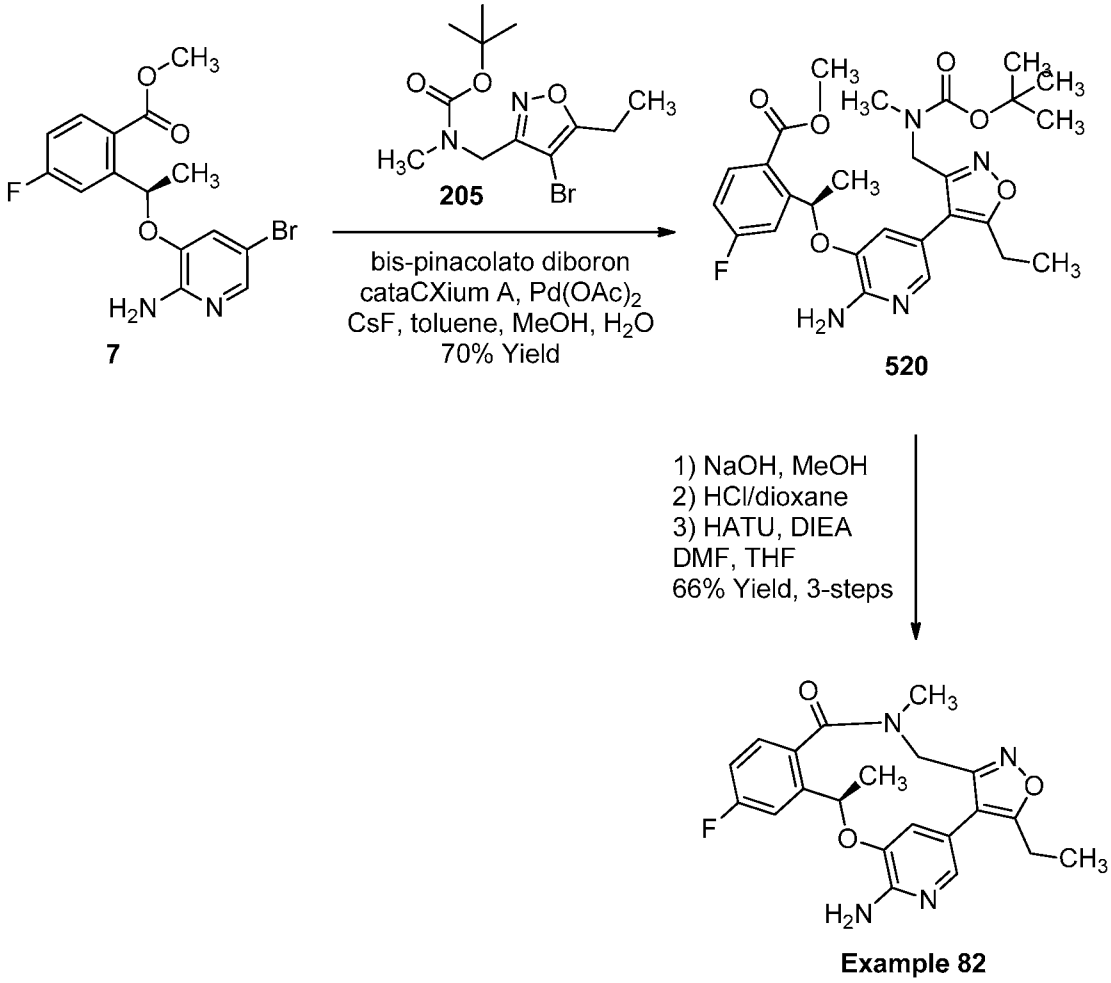
Step 1:

Into a solution of **compound 518** (41 mg, 0.3 mmol), **compound 202** (70 mg, 0.2 mmol), DIPEA (76 mg, 3.0 equiv) in DMF (0.8 mL, 0.25 M) was added HATU (90 mg, 1.2 equiv). The resulting mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed with water, saturated aqueous $NaHCO_3$ solution and brine. Concentration and purification by reverse phase preparative HPLC provided **compound 519** (69 mg, 73%) as white solid. LCMS APCI *m/z* 477 $[M+H]^+$.

Step 2:

To a solution of the **compound 519** (63 mg, 0.13 mmol) and pivalic acid (6 mg, 0.4 equiv) in DMA (2.6 mL) was added KOAc solid (65 mg, 5 equiv), followed by $Pd(OAc)_2$ (6 mg, 0.20 equiv) and cataCXium A (20 mg, 0.4 equiv) under argon. The reaction was heated in the microwave at 160 °C for 65 minutes and purified by reverse phase HPLC to afford **Example 81** (3.3mg, 6%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.63 (dd, *J* = 2.5, 10.4 Hz, 1H) 7.53 (d, *J* = 1.5 Hz, 1H) 7.42 (dd, *J* = 5.8, 8.6 Hz, 1H) 7.18 (dt, *J* = 2.7, 8.4 Hz, 1H) 6.69 (s, 1H) 6.07 (s, 2H) 5.57 - 5.67 (m, 1H) 4.57 (d, *J* = 15.2 Hz, 1H) 4.28 (d, *J* = 14.9 Hz, 1H) 3.02 (s, 3H) 2.69 - 2.85 (m, 2H) 1.66 (d, *J* = 6.3 Hz, 3H) 1.18 (t, *J* = 7.5 Hz, 3H). LCMS APCI *m/z* 397 $[M+H]^+$.

Preparation of (10*R*)-7-amino-3-ethyl-12-fluoro-10,16-dimethyl-16,17-dihydro-8,4-(metheno)[1,2]oxazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecin-15(10*H*)-one (Example 82)



Step 1:

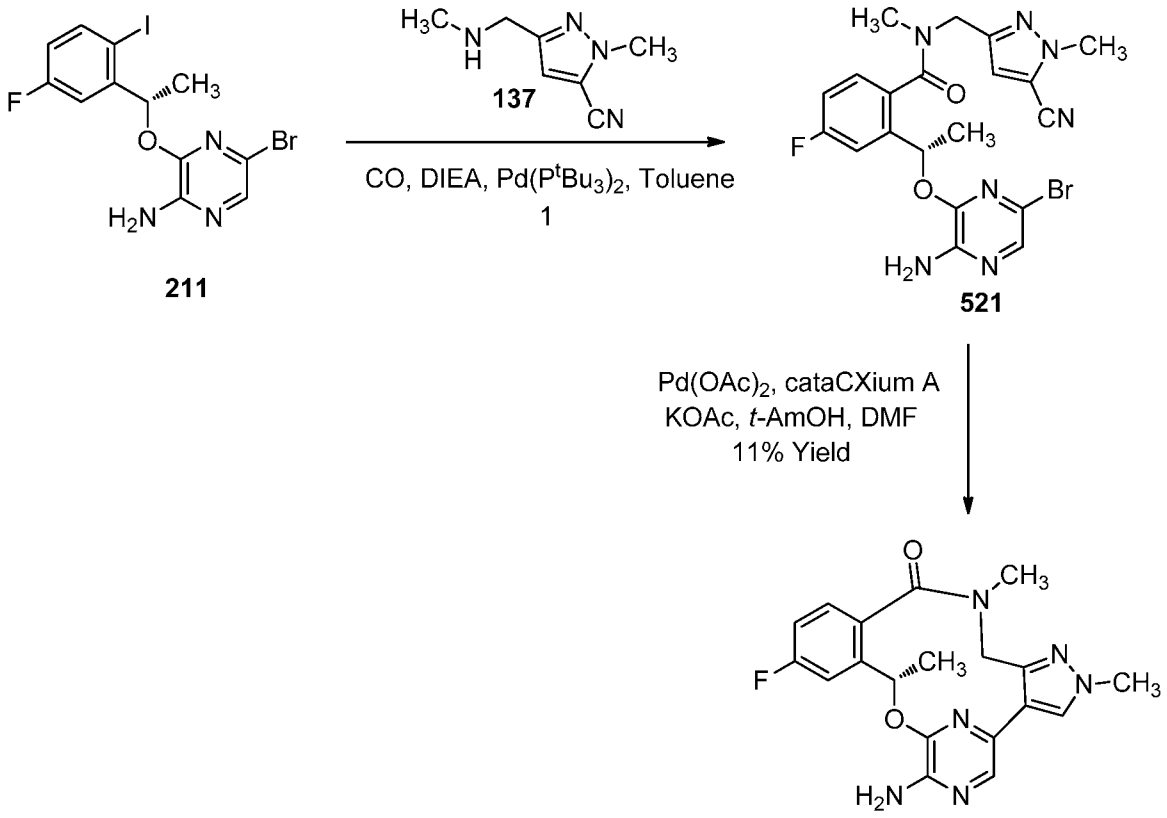
Palladium (II) acetate (82.4 mg, 0.367 mmol) and cataCXium A (271 mg, 0.733 mmol) were mixed together in toluene (3.0 mL, de-gassed) and the resulting solution was added *via* pipette to a stirred solution of **compound 7** (1.35 g, 3.67 mmol), bis-pinacolato diboron (1.86 g, 7.33 mmol) and CsF (2.23 g, 14.7 mmol) in MeOH/H_2O (4:1, 25.5 mL, de-gassed) at 50 °C. After 5 minutes, a solution of **compound 205** (900 mg, 2.82 mmol) in MeOH (5.8 mL, de-gassed) was added. The resulting mixture was stirred at 80 °C. After stirring for 1.5 hours, the reaction was judged to be complete by LCMS analysis. After being cooled to room temperature, the mixture was diluted with EtOAc, washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified by column chromatography over silica gel (0-5% MeOH/DCM) to afford **compound 520** (1.045 g, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 - 7.99 (m, 1 H) 7.50 (dd, *J* = 10.48, 2.65 Hz, 1 H) 7.39 (d, *J* = 1.77 Hz, 1 H) 7.24 (td, *J* = 8.46,

2.53 Hz, 1 H) 6.54 (br. s., 1 H) 6.22 (br. s., 1 H) 6.08 (br. s., 2 H) 3.85 (s, 3 H) 2.64 (s, 3 H) 2.43 - 2.48 (m, 2 H) 1.62 (d, *J* = 6.32 Hz, 3 H) 1.31 (br. s., 3 H) 1.12 - 1.28 (m, 6 H) 1.00 (t, *J* = 7.58 Hz, 3 H). LCMS APCI *m/z* 529 $[M+H]^+$.

Step 2:

NaOH (1.84 g, 46.1 mmol) in 1 mL water was added to a solution of **compound 520** (995 mg, 1.8 mmol) in MeOH (30 mL) and water (3 mL). The reaction mixture was stirred at room temperature. After stirring for 2.5 hours, the reaction was completed, and 4M HCl in dioxane (15 mL) was added slowly. The mixture was stirred at room temperature for 20 hours. The reaction mixture was concentrated under reduced pressure to give crude the deprotected product, which was carried directly to the cyclization step without further purification. To a solution of HATU (1.0 g, 2.56 mmol) in DMF (76 mL) was added dropwise a solution of the crude product and DIEA (5.1 mL, 29.3 mmol) in DMF (76 mL) and THF (7.6 mL) at 0 °C. After addition, the resulting mixture was stirred at 0 °C for 1 hour. The mixture was poured into ice water (400 mL), and the aqueous layer was extracted with EtOAc. The combined EtOAc layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified by column chromatography over silica gel (0-10% MeOH/DCM). After purification, ^{19}F NMR indicated the product was contaminated by $PF6^-$. The glue like product was dissolved in EtOAc and washed with 10% aqueous Na_2CO_3 (3x), and then dried over sodium sulfate and concentrated under reduced pressure to give **Example 82** as a white solid (480 mg, 66%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.63 (dd, *J* = 10.32, 2.77 Hz, 1H) 7.47 (dd, *J* = 8.56, 5.79 Hz, 1 H) 7.40 (d, *J* = 1.76 Hz, 1 H) 7.17 (td, *J* = 8.50, 2.64 Hz, 1 H) 6.78 (d, *J* = 1.76 Hz, 1 H) 6.03 (s, 2 H) 5.65 (dd, *J* = 6.29, 1.76 Hz, 1 H) 4.47 (d, *J* = 14.35 Hz, 1 H) 4.21 (d, *J* = 14.35 Hz, 1 H) 3.01 (s, 3 H) 2.82 - 2.92 (m, 2 H) 1.67 (d, *J* = 6.29 Hz, 3 H) 1.22 (t, *J* = 7.55 Hz, 3 H). LCMS APCI *m/z* 397 $[M+H]^+$.

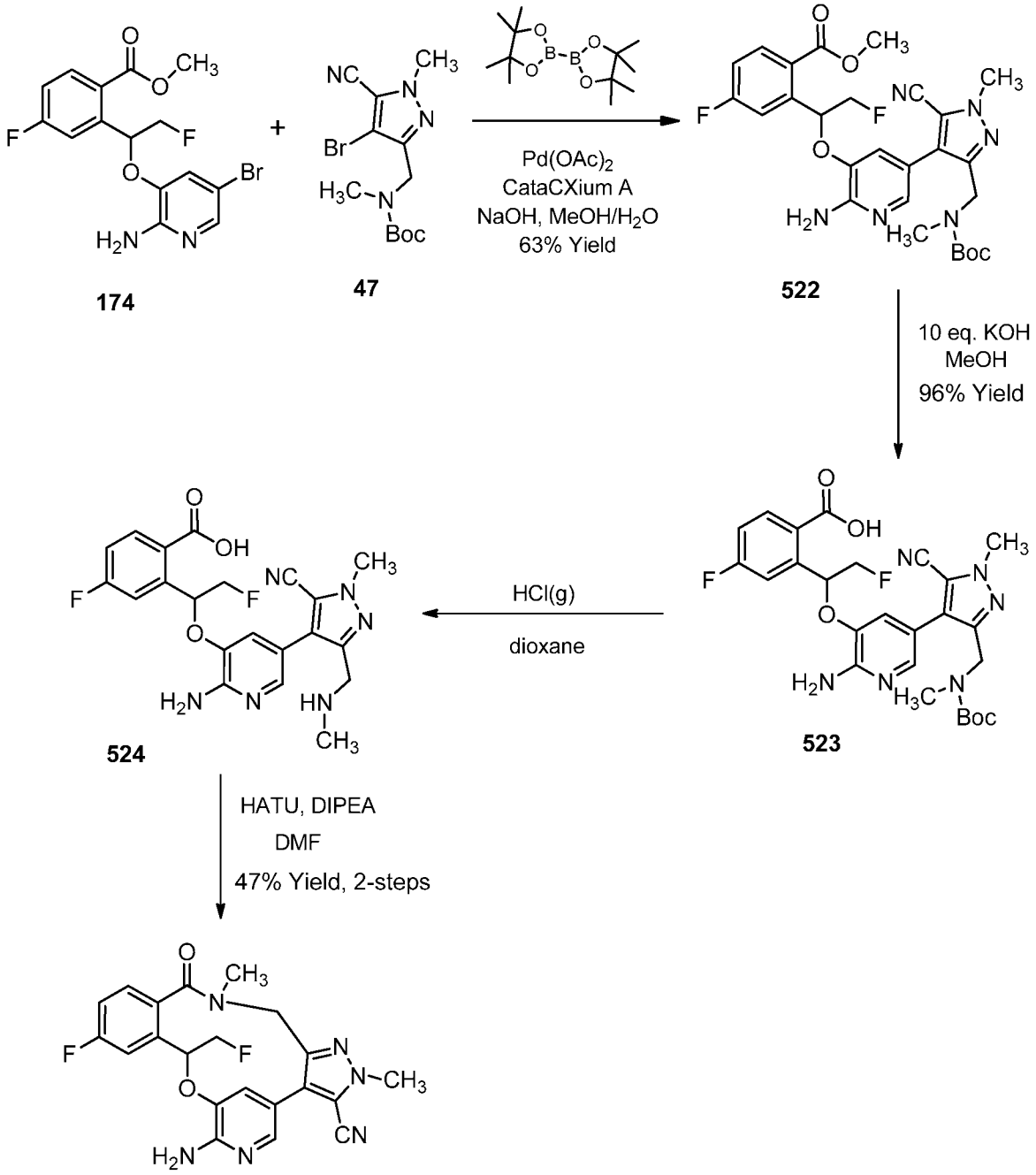
Preparation of (10S)-7-amino-12-fluoro-2,10,16-trimethyl-16,17-dihydro-2H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 83)



Example 83

Using the two step procedure of **Example 56**, **Example 83** (41.4 mg, 11%) was prepared as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.02 (s, 1 H), 7.63 (s, 1 H) 7.44 (dd, *J* = 10.09, 2.63 Hz, 1 H) 7.40 (dd, *J* = 8.57, 5.53 Hz, 1 H) 7.15 (td, *J* = 8.57, 2.76 Hz, 1 H) 6.25 (s, 2 H) 5.74 - 6.04 (m, 1 H) 4.33 (d, *J* = 13.27 Hz, 1 H) 4.18 (d, *J* = 13.27 Hz, 1 H) 3.83 (s, 3 H) 2.87 (s, 3 H) 1.62 (d, *J* = 6.36 Hz, 3 H). LCMS APCI *m/z* 383 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-10-(fluoromethyl)-2,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 84 and 85)



Example 84 and Example 85

Step 1:

To a solution of **compound 174** (0.7 g, 1.81 mmol), **compound 47** (1.22 g, 3.07 mmol) and bis-(pinacalato)diboron (1.38 g, 5.42 mmol) in dry methanol (280 mL) was added NaOH (145 mg, 3.62 mmol) in water (10 mL) under nitrogen gas at room temperature. After the mixture was degassed three times with nitrogen, cataCXium A (68 mg, 0.18 mmol) and $Pd(OAc)_2$ (21 mg, 0.09 mmol) was added. The resulting mixture was degassed with nitrogen three times, and was then refluxed for 16 hours. TLC (petroleum ether/EtOAc 1/1) showed the reaction mixture was completed. The reaction mixture was diluted with EtOAc (300 mL). The mixture was then

washed with brine (2x), dried over Na_2SO_4 and concentrated *in vacuo* to give residue, which was purified via Biotage (petroleum ether/EtOAc = 1:1, Rf =0.1) to give **compound 522** (0.7 g, 62.8 %) as a brown solid. LCMS *m/z* 579 $[M+Na]^+$

Step 2:

A mixture of **compound 522** (0.5 g, 0.90 mmol) and KOH (0.5 g, 8.99 mmol) in methanol (20 mL) was heated to 50 °C for 24 hours. LC-MS showed that the reaction was completed. The reaction mixture was concentrated *in vacuo* to give a residue. The residue was acidified with 1N HCl to pH~5. The mixture was extracted with EtOAc (3x). The combined EtOAc layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the residue, which was purified by flash chromatography over silica gel (DCM/MeOH=25:1, Rf=0.3) to give **compound 523** (320 mg, 95.5% of purity, 62%) as a yellow solid. LCMS *m/z* 543 $[M+H]^+$.

Step 3:

To a stirred solution of **compound 523** (320 mg, 95% pure, 0.56 mmol) in DCM (10 mL) was added dropwise ~ 4M HCl (g) in dioxane (2 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature for 3 hours. LC-MS indicated that the reaction was completed. The reaction mixture was concentrated *in vacuo* to give crude **compound 524**, which was used in the next step without further purification. LCMS *m/z* 443 $[M+H]^+$.

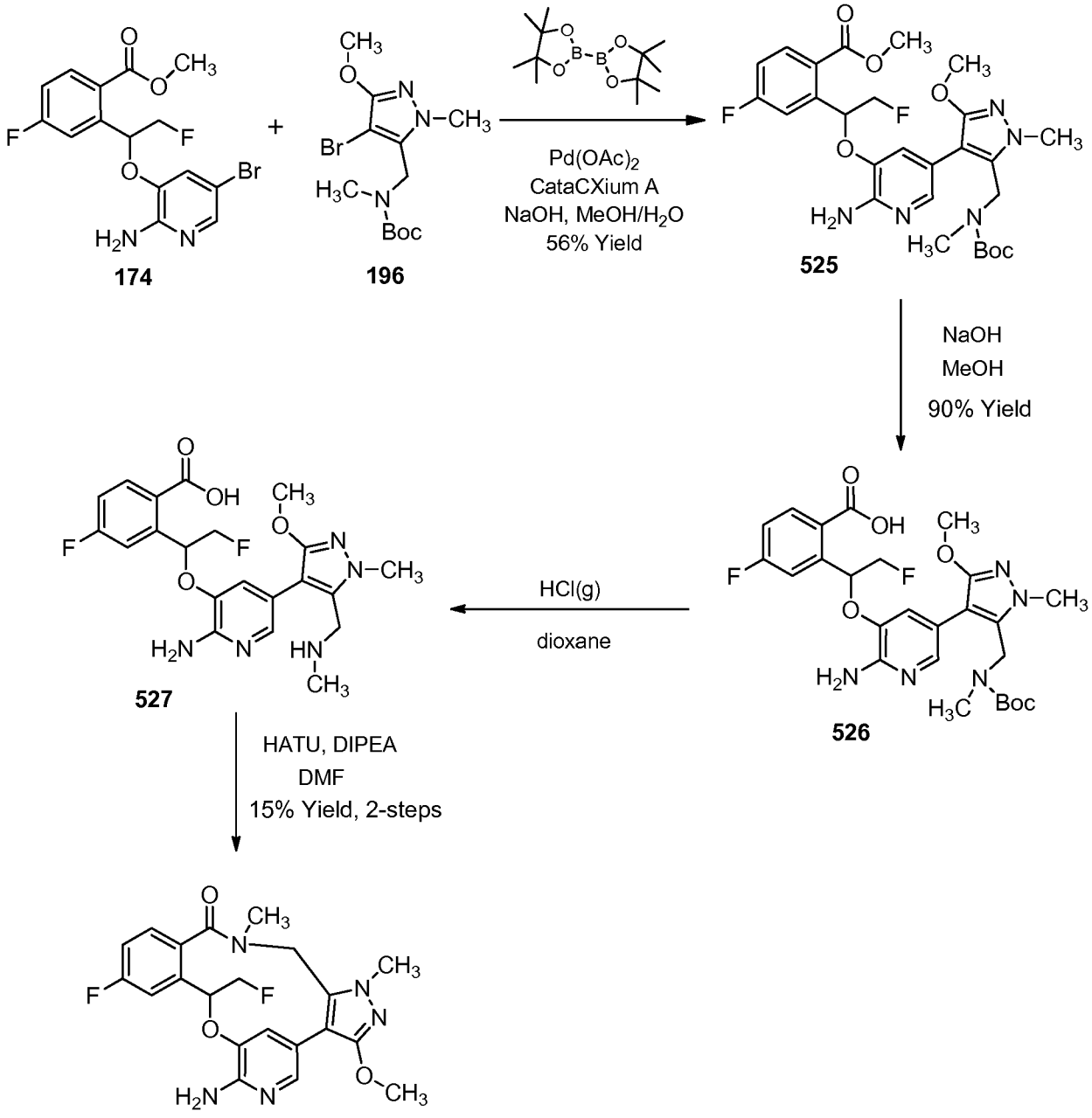
Step: 4

To a solution of HATU (155 mg, 0.4 mmol) in DMF (8 mL) was added dropwise a solution of **compound 424** (~0.29 mmol) and DIEA (0.60 g, 4.64 mmol) in dry DMF (8 mL) and dry THF (1 mL) at 0 °C. After addition, the resulting mixture was stirred at the same temperature for 1 hour. LC-MS showed the reaction was completed. The mixture was poured into ice-water (30 mL). The mixture was extracted with EtOAc (30 mL x 5). The combined EtOAc layers were washed with brine (30 mL x 5), dried over Na_2SO_4 and concentrated *in vacuo* to give residue, which was purified column chromatography over silica gel (DCM/MeOH = 25:1, Rf=0.3) to give a mixture of **Example 84** and **Example 85** (80 mg, 52.6%) as a yellow solid. The chiral separation was performed by preparative SFC on a Chiralcel OJ-H (50 x 4.6 mm I.D., 3 micron particle size) column, which was eluted with 5-40% methanol (0.05% DEA) in @ 140 bar CO_2 with a flow rate of 4 mL/min. $Rt_{(Peak\ 1)}$ = 5.93 minutes and $Rt_{(Peak\ 2)}$ = 9.28 minutes, and gave Peak 1 as a white solid (33 mg, 27%) and Peak 2 as a white solid (30 mg, 20%).

Example 84 (Peak 1): 100% ee. ^1H NMR (400 MHz, Methanol-d_4) δ 7.70 (bs, 1H), 7.54-7.48 (m, 2H), 7.22-7.18 (m, 1H), 6.98 (s, 1H), 5.91-5.90 (m, 1H), 5.16-4.98 (m, 1H), 4.88-4.84 (m, 1H), 4.57-4.53 (d, 1H), 4.49-4.48 (d, 1H), 4.03 (s, 3H), 3.15 (s, 3H). LCMS ES *m/z* 425 $[M+H]^+$.

Example 85 (Peak 2): 100% ee. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (bs, 1H), 7.54-7.48 (m, 2H), 7.232-7.18 (m, 1H), 6.99 (s, 1H), 5.92-5.56 (dd, 1H), 5.12-4.95 (m, 1H), 4.87-4.83 (m, 1H), 4.53-4.50 (d, 1H), 4.43-4.40 (d, 1H), 4.09 (s, 3H), 3.15 (s, 3H). LCMS ES *m/z* 425 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-10-(fluoromethyl)-3-methoxy-1,16-dimethyl-16,17-dihydro-1H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 86/Example 87)



Example 86 and Example 87

Step 1:

To a solution of **compound 174** (0.98 g, 2.5 mmol), **compound 196** (1.01 g, 3.03 mmol) and bis(pinacalato)diboron (1.905 g, 7.5 mmol) in methanol (320 mL) was added NaOH (200 mg, 5 mmol) in water (11 mL) under nitrogen at room temperature. After the mixture was degassed three times with nitrogen, cataCXium A (116 mg, 0.325 mmol) and $Pd(OAc)_2$ (74 mg, 0.325 mmol) were added. The resulting mixture was degassed with nitrogen three times, and was refluxed for 16 hours. TLC (petroleum ether/EtOAc 1/1) showed the reaction was complete. The reaction mixture was diluted with EtOAc (300 mL). The combined EtOAc layers were washed with brine (100 mL x 2), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified via column chromatography (silica gel, petroleum ether/EtOAc from 3/1 to 1/1) to give **compound 525** (800 mg, 94% purity, 56%) as a brown solid. ^{1}H NMR (400 MHz, CDCl3): δ 8.07-8.03 (dd, 1H), 7.53 (s, 1H), 7.31-7.28 (dd, 1H), 7.03-6.99 (m, 1H), 6.55-6.54 (d, 1H), 6.53-6.42 (d, 1H), 6.43-6.37 (dd, 1H), 4.78 (s, 2H), 4.69-4.65 (m, 2H), 4.20-4.08 (m, 2H), 3.89-3.85 (t, 3H), 3.69 (s, 3H), 3.59 (s, 3H),2.30 (s, 3H), 1.39 (s, 9H).

Step 2:

A mixture of **compound 525** (800 mg, 1.42 mmol) and NaOH (1.14 g, 28.5 mmol) in methanol (30 mL) and water (10 mL) was stirred at room temperature for 18 hours. LC-MS showed the reaction was complete. MeOH was removed *in vacuo* to give a residue. The residue was acidified with 6N HCl to pH~5. The mixture was saturated with solid NaCl and then extracted with EtOAc (30 mL x 5). The combined EtOAc layers were dried over Na_2SO_4 and concentrated *in vacuo* to give **compound 526** (700 mg, 89.7%) as a yellow solid. LCMS *m/z* 514 $[M+H]^+$.

Step 3:

To a solution of **compound 526** (700 mg, 1.28 mmol) in dioxane (5 mL) was added dropwise ~ 4M HCl (g) in dioxane (10 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature for 18 hours. TLC (EtOAc) showed the reaction was complete. The reaction mixture was concentrated *in vacuo* to give crude **compound 527**, which was used for next step without any further purification. LCMS *m/z* 448 [M+H]+.

Step 4:

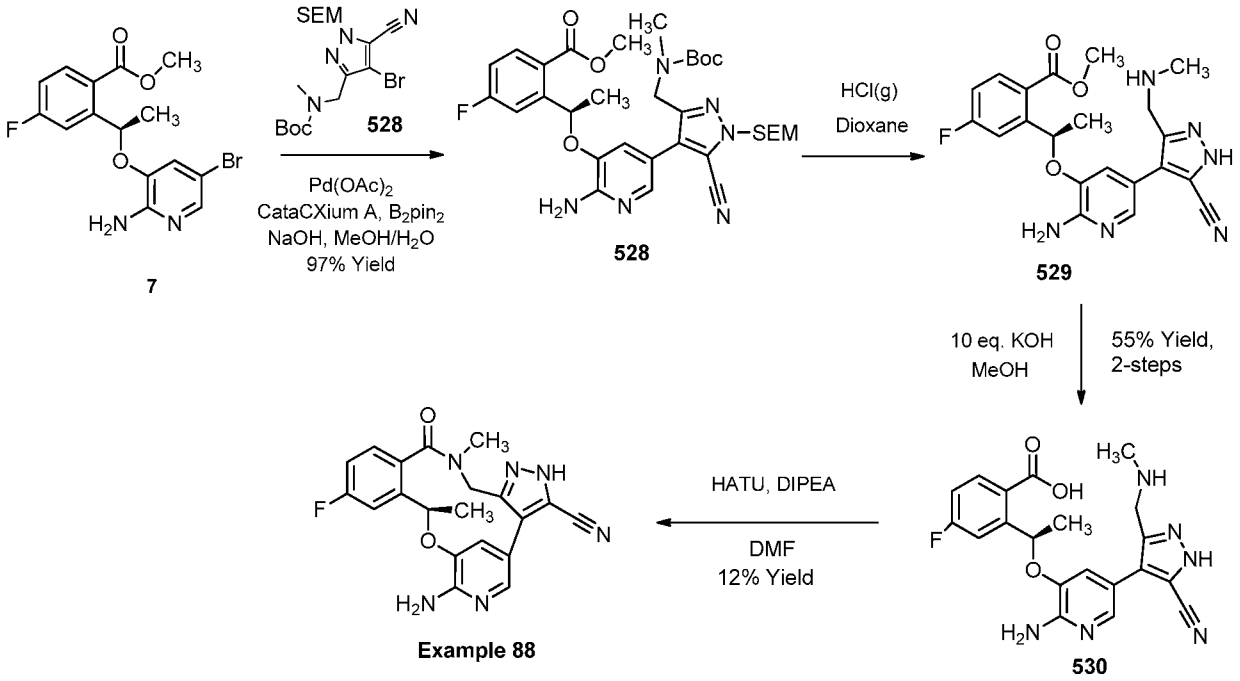
To a solution of HATU (813mg, 2.14 mmol) in DMF (80 mL) was added dropwise the mixture of **compound 527** (~636 mg, 1.13 mmol) and DIPEA (3.69 g, 28.6 mmol) in DMF (20 mL) at 0 °C. After the addition, the resulting mixture was stirred at room temperature for 1 hour. LC-MS showed the reaction was complete. The mixture was poured into ice-water (50 mL). The mixture was extracted with EtOAc (40 mL x 5). The combined EtOAc layers were washed with brine (20 mL x 5), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The residue was purified *via* column chromatography (silica gel, petroleum ether/EtOAc 30-70%) to give a mixture of **Example 86** and **Example 87** (0.2 g, 36.3%) as a pink solid. The chiral separation

was performed by preparative SFC on a Chiralcel OD-3 (50 x 4.6 mm I.D., 3 micron particle size) column, which was eluted with 5-40% ethanol (0.05% DEA) in CO_2 with a flow rate of 4 mL/min. $Rt_{(Peak\ 1)}$ = 1.47 minutes and $Rt_{(Peak\ 2)}$ = 1.71 minutes, and gave Peak 1 as a pink solid (38 mg, 7%) and Peak 2 as a pink solid (42 mg, 8%).

Example 86 (Peak 1): 100% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.86 (d, 1H), 7.34-7.31 (dd, 1H), 7.28-7.25 (m, 1H), 7.09-7.04 (m, 1H), 6.81 (s, 1H), 5.78-5.73 (d, 1H), 4.91-4.78 (m, 4H), 4.45-4.41 (d, 1H), 4.33-4.30 (d, 1H), 3.94-3.91 (d, 3H), 3.74 (d, 3H), 3.16 (s, 3H). LCMS ES *m/z* 430 $[M+H]^+$.

Example 87 (Peak 2): 100% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.27-7.24 (dd, 1H), 7.22-7.19 (m, 1H), 7.03-7.0 (m, 1H), 6.76-6.75 (s, 1H), 5.71-5.67 (d, 1H), 4.85-4.72 (m, 4H), 4.38-4.35 (d, 1H), 4.27-4.23 (d, 1H), 3.89 (s, 3H),.3.81 (s, 3H), 3.09 (s, 3H). LCMS ES *m/z* 430 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-10,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 88)



Step 1:

To a solution of **compound 7** (600 mg, 1.62 mmol), **compound 214** (1.08 g, 2.44 mmol) and bis-(pinacalato)diboron (1.23 g, 4.86 mmol) in methanol (120mL) was added cataCXium A (80 mg, 0.2 mmol) and $Pd(OAc)_2$ (50mg, 0.20 mmol). After the mixture was degassed three times with nitrogen, a solution of NaOH (130 mg, 3.2 mmol) in water (10 mL) was added under nitrogen at room temperature. The resulting mixture was degassed with nitrogen three times and

was then refluxed for 16 hours. TLC (petroleum ether/EtOAc 3/1) showed the reaction was complete. The reaction mixture was diluted with EtOAc (100 mL x 3). The combined EtOAc layers were washed with brine (50 mL x 3), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified by column chromatography (silica gel, petroleum ether/EtOAc = 1:1, Rf= 0.3) to give **compound 528** (650 mg, 96.8% of purify, 59%) as a yellow solid. LCMS *m/z* 655 $[M+H]^+$.

Step 2:

To a stirred solution of **compound 529** (350 mg, 96.8% of purify, 0.55 mmol) in DCM (5 mL) was added dropwise ~ 4M HCl (g) in dioxane (5 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature for 2 hours. LC-MS showed the reaction was complete. The reaction mixture was concentrated *in vacuo* to give crude **compound 529**, which was used for next step without any further purification. LCMS *m/z* 424 $[M+H]^+$

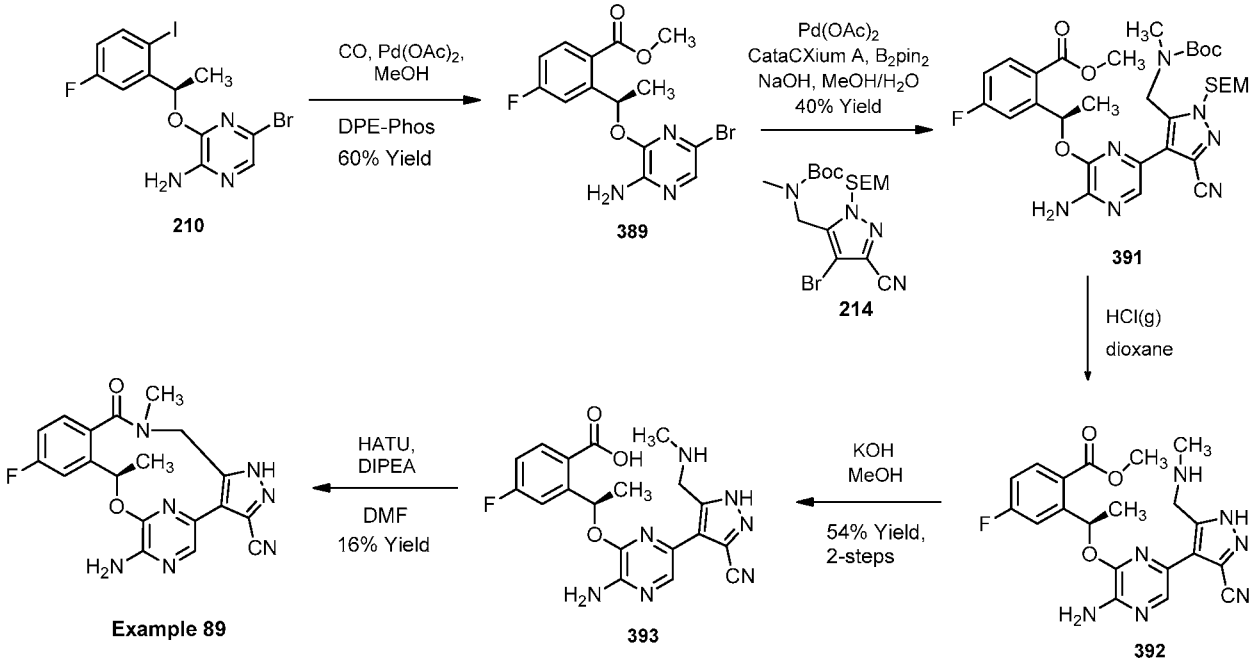
Step 3:

A mixture of **compound 529** (~0.47 mmol) and KOH (0.65 g, 11.7 mmol) in methanol (15 mL) was stirred at 50 °C for 36 hours. LC-MS showed the reaction was complete. MeOH was removed *in vacuo* to give the residue, which was acidified with 1N aq. HCl to pH~6. The mixture was extracted with EtOAc (20 mL x2). The aqueous layer was lyophilized to give crude product, which was diluted with DCM/MeOH (5:1, 20 mL) and filtered. The filtrate was concentrated to give **compound 530** (140 mg, 75% of purity, 54.4%) as a brown solid. LCMS *m/z* 411 $[M+H]^+$.

Step 4:

To a solution of HATU (137 mg, 0.35 mmol) in DMF (20 mL) was added dropwise a solution of **compound 530** (140 mg, 75% of purity, 0.25 mmol) and DIEA (516 mg, 4 mmol) in DMF (10 mL) at 0 °C. After the addition, the resulting mixture was stirred at 0 °C for 1 hour. LC-MS showed the reaction was complete. The mixture was poured into water (50 mL). The mixture was extracted with EtOAc (50 mL x 5). The combined EtOAc layers were washed with brine (40 mL x 5), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography over silica gel (DCM/MeOH =25:1, Rf = 0.3) to give crude material, which was further purified by preparative SFC (Chiralcel OD-3, 150×4.6mm I.D., 3μm. Retention Time 6.93 min Mobile phase: methanol (0.05% DEA) in CO_2 from 5% to 40% Flow rate: 3mL/min) followed by preparative HPLC to afford **Example 88** (12 mg, 12%) as a white solid. ^1H NMR (400 MHz, Methanol-d4) δ 7.70 (s, 1H), 7.54-7.51 (dd, 1H), 7.46-7.42 (m, 1H), 7.15-7.11 (m, 1H), 6.91 (s, 1H), 5.76-5.73 (t, 1H), 4.54 (s, 2H), 3.15 (s, 3H), 1.81-1.80 (d, 3H). LCMS *m/z* 392 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-10,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-1H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 89)



Step 1:

A mixture of **compound 210** (1.5 g, 3.42 mmol), DIPEA (1.76 g, 13.68 mmol), DPE-Phos (0.3 g, 0.58 mmol) and $Pd(OAc)_2$ (77 mg, 0.34 mmol) in MeOH (50 mL) was stirred at 40 °C under 10 bar of CO pressure overnight. TLC (petroleum ether / EtOAc = 3:1) showed the reaction was almost completed. The mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography over silica gel (petroleum ether / EtOAc = 3:1, Rf: 0.5) to give **compound 531** (0.76 g, 60%) as a yellow solid.

Step 2:

To a solution of **compound 531** (300 mg, 0.81 mmol), **compound 214** (541 mg, 1.22 mmol) and bis-(pinacalato)-diboron (617 mg, 2.43 mmol) in methanol (60mL) was added cataCXium A (40 mg, 0.1053 mmol) and Pd(OAc)2 (25mg, 0.1053 mmol). After the mixture was degassed for three times with nitrogen, a solution of NaOH (65 mg, 1.62 mmol) in water (12 mL) was added under nitrogen at room temperature. The resulting mixture was degassed with nitrogen three times, and was then refluxed for 16 hours. TLC (petroleum ether/EtOAc 3/1) showed the reaction was complete. The reaction mixture was diluted with EtOAc (50 mL x 3). The combined EtOAc layers were washed with brine (20 mL x 3), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified *via* column chromatography (silica gel, petroleum

ether/EtOAc from 10/1 to 3/1) to give **compound 532** (400 mg, 53% of purify, 40%) as a brown solid. LCMS *m/z* 655 $[M+H]^+$.

Step 3:

To a stirred solution of **compound 532** (400 mg, 53% of purify, 0.32 mmol) in DCM (2 mL) was added dropwise ~ 4M HCl (g) in dioxane (10 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature for 2 hours. LC-MS showed the reaction mixture was complete. The reaction mixture was concentrated *in vacuo* to give crude **compound 533**, which was used for next step without any further purification. LCMS *m/z* 425 $[M+H]^+$.

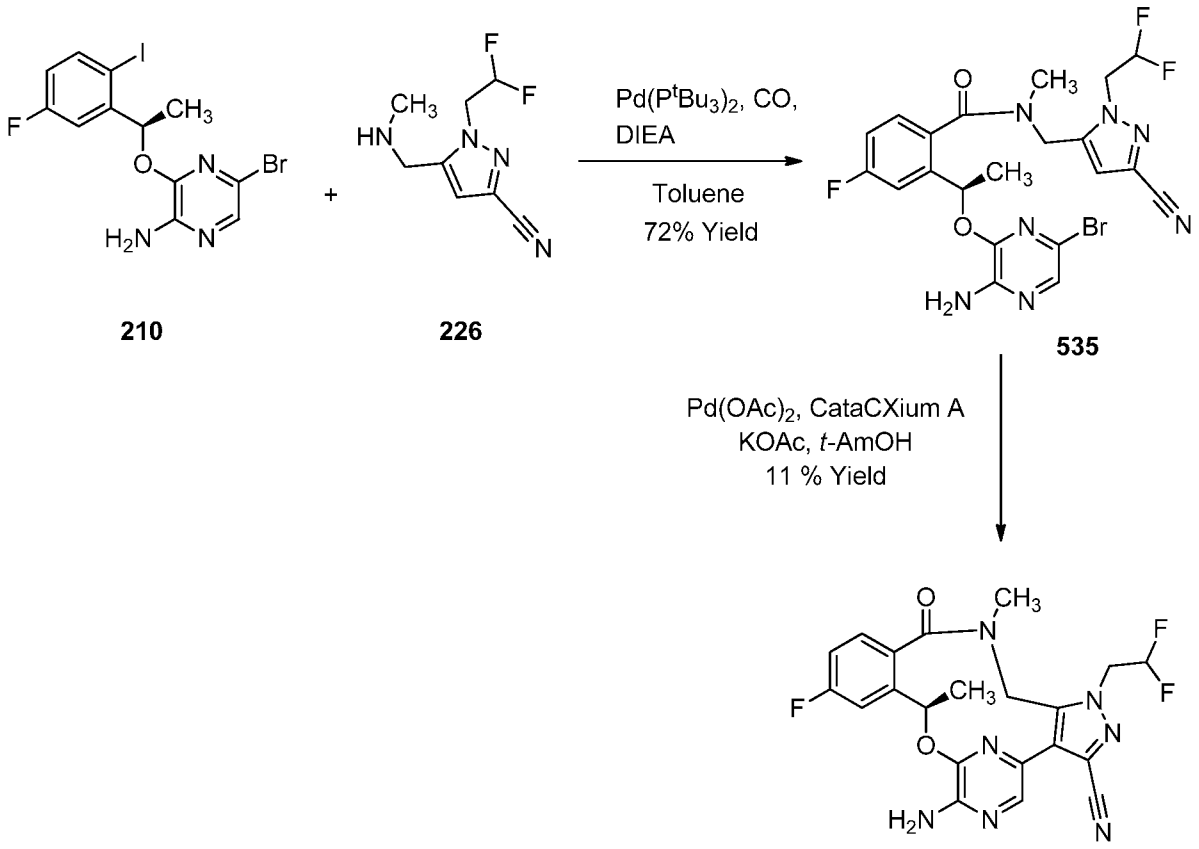
Step 4:

A mixture of **compound 533** (~300 mg) and KOH (0.395 g, 7.0 mmol) in methanol (15 mL) was stirred at 50 °C for 36 hours. LC-MS showed the reaction was complete. MeOH was removed *in vacuo* to give the residue, which was acidified with 1N aq. HCl to pH~5. The mixture was saturated with solid NaCl and then extracted with EtOAc (30 mL x 5). The combined EtOAc layers were dried over Na_2SO_4 and concentrated *in vacuo* to give **compound 534** (180 mg, 39.8% of purity, 53.8%) as a brown solid. LCMS *m/z* 411 $[M+H]^+$.

Step 5:

To a solution of HATU (250 mg, 0.66 mmol) in DMF (25 mL) was added dropwise a solution of **compound 534** (180 mg, 0.44 mmol) and DIEA (908 mg, 7.04 mmol) in DMF (10 mL) at 0 °C. After the addition, the resulting mixture was stirred at room temperature for 1 hour. LC-MS showed the reaction was complete. The mixture was poured into ice-water (50 mL). The mixture was extracted with EtOAc (40 mL x 5). The combined EtOAc layers were washed with brine (20 mL x 5), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The residue was purified *via* column chromatography (silica gel, petroleum ether/EtOAc 2:1~1:2) to give **Example 89** (10.5mg, 15.8%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.30-7.26 (dd, 1H), 7.23-7.20 (m, 1H), 7.01-7.00 (m, 1H), 6.19-6.14 (m, 1H), 5.07 (s, 2H), 4.75-4.72 (d, 1H), 4.28-4.25 (d, 1H), 3.04 (s, 3H), 1.17-1.15 (d, 3H). LCMS ES *m/z* 393 $[M+H]^+$.

Preparation of (10R)-7-amino-1-(2,2-difluoroethyl)-12-fluoro-10,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-1H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 90)



210 **226** **535**

Example 90

Step 1:

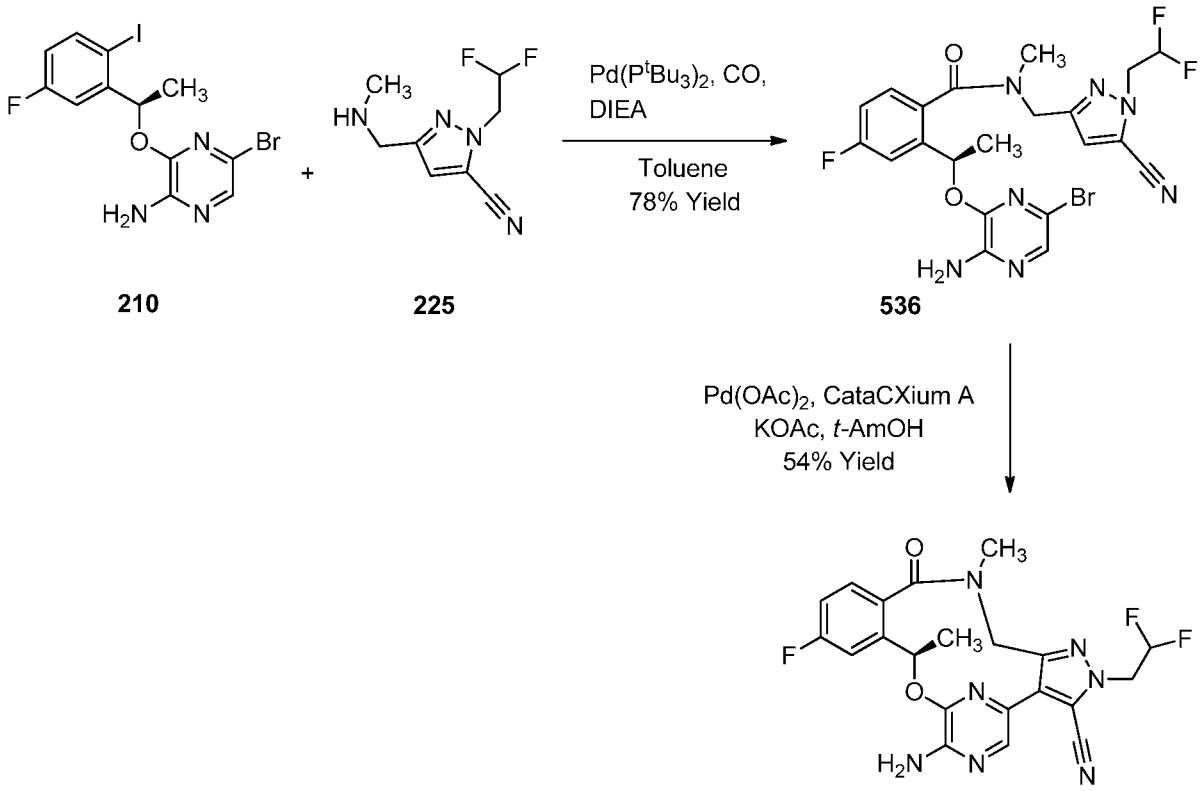
Pd(P^{t}Bu$_3$)$_2$ (97 mg, 0.191 mmol) was added to a mixture of **compound 226** (450 mg, 1.91 mmol), **compound 210**, (R)-5-bromo-3-(1-(5-fluoro-2-iodophenyl)ethoxy)-pyrazin-2-amine (838 mg, 1.91 mmol) and DIEA (1.23 g, 9.55 mmol) in de-gassed toluene (50 mL) and the mixture was stirred under a CO atmosphere (4 bar) at 80 °C for 18 hours. After cooling, the volatiles were removed and the residue purified by flash chromatography on silica gel (1:1 EtOAc/heptane), giving **compound 535** (750 mg, 72%) as a cream colored foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 – 7.08 (m, 5H), 6.75 (s, 2H), 6.51 (tt, *J* = 54.4, 3.5 Hz, 1H), 5.96 (d, J = 6.6 Hz, 1H), 5.01 – 4.35 (m, 4H), 2.95 (d, *J* = 44.5 Hz, 3H), 1.58 (d, *J* = 6.4 Hz, 3H). LCMS *m/z* 538/540 [M+H]$^+$.

Step 2:

Pd(OAc)$_2$ (24.0 mg, 0.11 mmol) and cataCXium A (78.0 mg, 0.22 mmol) were added to a mixture of **compound 535** (300 mg, 0.56 mmol), KOAc (274 mg, 2.8 mmol) and de-gassed *t*-amyl alcohol (12.0 mL) in a 20 mL microwave vial and stirred under microvwave irradiation (130 °C) for 2.5 hours. After cooling, the volatiles were removed and the residue was purified by column chromatography (70% EtOAc in heptanes). Fractions containing the product (Rf = 0.35) were evaporated (product not clean by TLC). The residue was re-purified by column

chromatography (20% acetone in DCM). Fractions containing the product were evaporated (a close running impurity was still present by TLC). The residue was re-purified by column chromatography (70% TBME in heptanes). Fractions containing the product were evaporated and the residue was dissolved in MeOH (1.0 mL). Water (approx. 4 mL) was added slowly while stirring to precipitate the product. The solvent was carefully decanted from the resulting solids were dried under vacuum overnight to give **Example 90** (28.0 mg, 11% yield) as a pale yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.48 (dd, *J* = 10.0, 2.6 Hz, 1H), 7.32 (dd, *J* = 8.5, 5.6 Hz, 1H), 7.23 (td, *J* = 8.5, 2.6 Hz, 1H), 6.76 (s, 2H), 6.66 – 6.32 (m, 1H), 5.93 – 5.78 (m, 1H), 5.19 – 4.87 (m, 2H), 4.72 (d, *J* = 14.9 Hz, 1H), 4.37 (d, *J* = 14.9 Hz, 1H), 2.86 (s, 3H), 1.64 (d, *J* = 6.6 Hz, 3H). LCMS ES *m/z* 458 $[M+H]^+$.

Preparation of (10R)-7-amino-2-(2,2-difluoroethyl)-12-fluoro-10,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclo-tetradecine-3-carbonitrile (Example 91)



210 **225** **536** **Example 91**

Step 1:

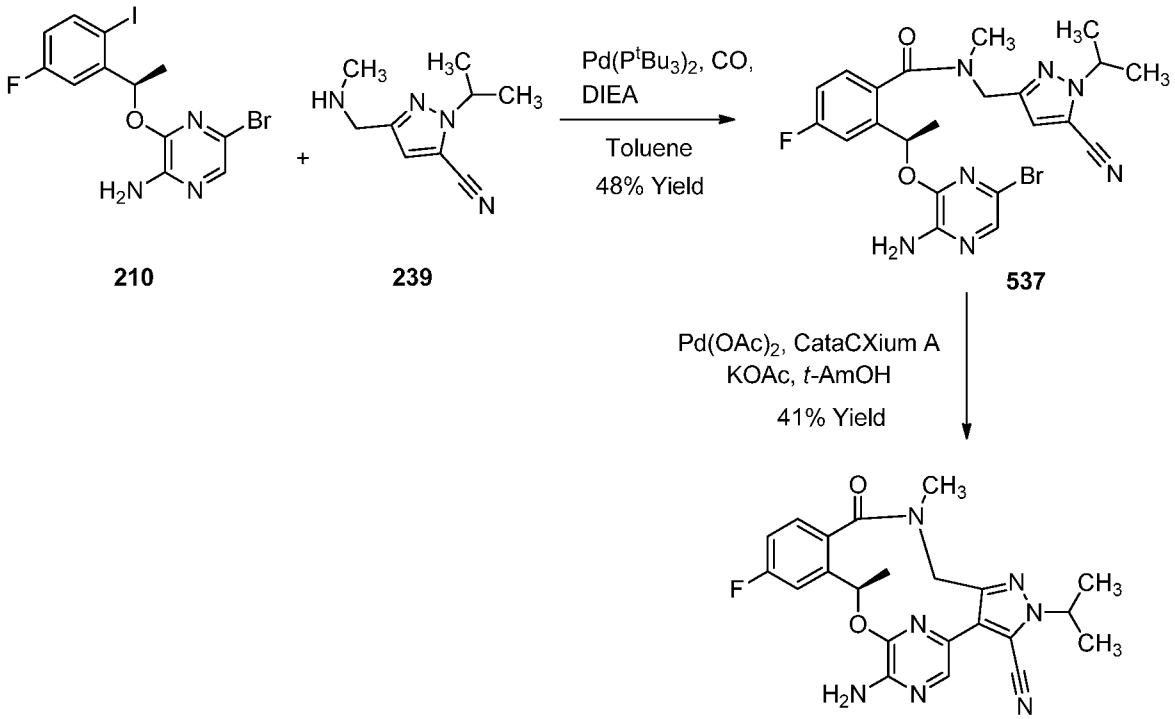
Pd(P^{t}Bu^3)^2 (32 mg, 0.064 mmol) was added to a mixture of **compound 210**, (R)-5-bromo-3-(1-(5-fluoro-2-iodophenyl)ethoxy)pyrazin-2-amine (280 mg, 0.64 mmol), **compound 225** (150 mg,

0.64 mmol) and DIEA (413 mg, 3.2 mmol) in de-gassed toluene (20 mL). The mixture was then stirred under a CO atmosphere (4 bar) at 80 °C for 6 hours. The mixture was concentrated and the residue purified by column chromatography (40% to 75% EtOAc in heptanes), giving **compound 536** (270 mg, 78%) as a pale yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 – 7.06 (m, 5H), 6.73 (s, 2H), 6.43 (tt, *J* = 54.0, 3.0 Hz, 1H), 6.04 (d, *J* = 6.5 Hz, 1H), 4.95 – 4.27 (m, 4H), 2.93 (m, 3H), 1.57 (d, *J* = 6.5 Hz, 3H). LCMS *m/z* 538/540 $[M+H]^+$.

Step 2:

A mixture of **compound 536** (108 mg, 0.20 mmol), $Pd(OAc)_2$ (6.60 mg, 0.03 mmol), cataCXium A (21.4 mg, 0.06 mmol), KOAc (98 mg, 1.0 mmol) in de-gassed *t*-amyl alcohol (7.0 mL) was stirred under microwave irradiation (120 °C) for 2 hours. After cooling, the mixture was concentrated, then purified by column chromatography (1:1 EtOAc/heptanes), giving the **Example 91** (75 mg, 54%) as a cream powder.^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (s, 1H), 7.48 (dd, *J* = 10.1, 2.7 Hz, 1H), 7.42 (dd, *J* = 8.5, 5.7 Hz, 1H), 7.17 (td, *J* = 8.5, 2.7 Hz, 1H), 6.83 (s, 2H), 6.49 (tt, *J* = 53.9, 2.8 Hz, 1H), 5.91 (qd, *J* = 6.5, 1.8 Hz, 1H), 4.88 (td, *J* = 15.8, 2.8 Hz, 2H), 4.35 (q, *J* = 13.7 Hz, 2H), 2.88 (s, 3H), 1.64 (d, *J* = 6.5 Hz, 3H). LCMS *m/z* 458 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-10,16-dimethyl-15-oxo-2-(propan-2-yl)-10,15,16,17-tetrahydro-2H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 92)



210 239 537

Example 92

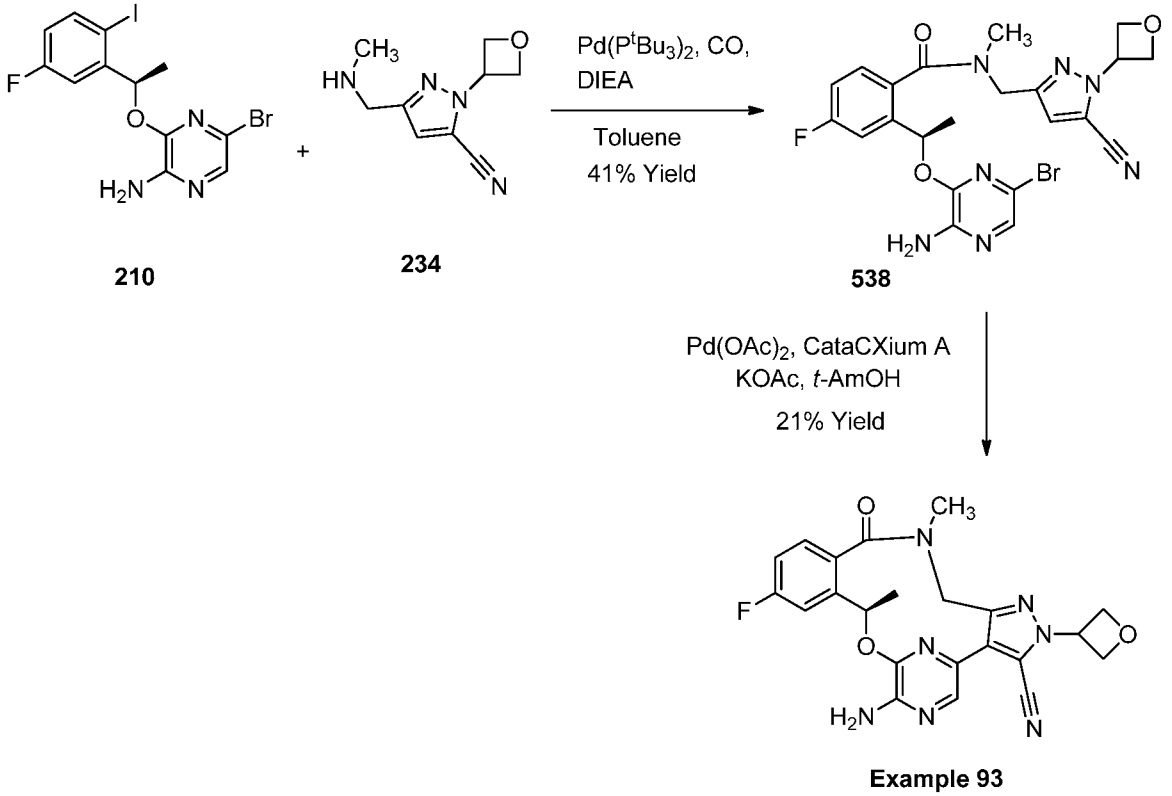
Step 1:

The procedure described in step 1 for **Example 91** was used to prepare **compound 537** (200 mg, 48%) as a pale yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 – 6.98 (m, 5H), 6.74 (s, 2H), 6.17 – 5.90 (m, 1H), 4.95 – 4.22 (m, 3H), 2.93 (m, 3H), 1.57 (d, *J* = 6.4 Hz, 3H), 1.42 (dd, *J* = 8.3, 6.6 Hz, 6H). LCMS ES *m/z* 516/518 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 91** was used to prepare **Example 92** (70 mg, 41%) as a cream powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 7.47 (dd, *J* = 10.1, 2.6 Hz, 1H), 7.40 (dd, J = 8.5, 5.7 Hz, 1H), 7.17 (td, *J* = 8.5, 2.7 Hz, 1H), 6.75 (s, 2H), 5.90 (qd, *J* = 6.4, 1.9 Hz, 1H), 4.77 (hept, *J* = 6.7 Hz, 1H), 4.41 – 4.24 (m, 2H), 2.88 (s, 3H), 1.64 (d, *J* = 6.5 Hz, 3H), 1.50 (dd, *J* = 6.6, 1.1 Hz, 6H). LCMS ES *m/z* 436 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-10,16-dimethyl-2-(oxetan-3-yl)-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 93)



210 **234** **538** **Example 93**

Step 1:

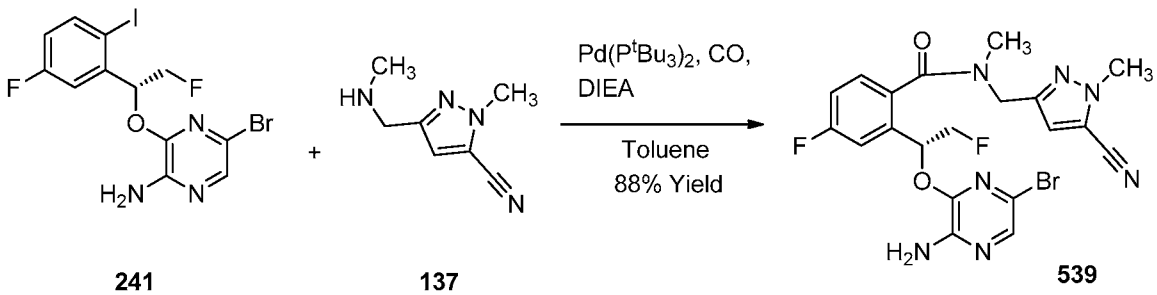
The procedure described in step 1 for **Example 91** was used to prepare **compound 538** (376 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.23 (dd, *J* = 8.5, 5.5 Hz, 1H), 7.15 (dd, *J* = 9.7, 2.6 Hz, 1H), 7.01 (td, J = 8.3, 2.6 Hz, 1H), 6.92 (s, 1H), 6.10 (q, *J* = 6.4 Hz, 1H), 5.66 (tt, *J* =

7.7, 6.2 Hz, 1H), 5.17 – 4.98 (m, 7H), 4.65 (d, *J* = 15.0 Hz, 1H), 3.04 (s, 3H), 1.74 (d, *J* = 6.5 Hz, 3H). LCMS ES *m/z* 530/532 $[M+H]^+$.

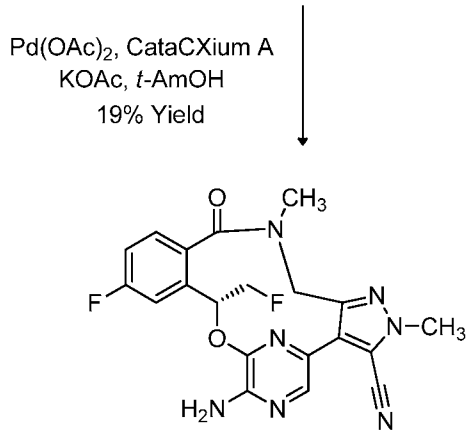
Step 2:

The procedure described in step 2 for **Example 91** was used to prepare **Example 93** as a yellow solid (63 mg, 21% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (s, 1H), 7.48 (dd, J = 10.1, 2.7 Hz, 1H), 7.43 (dd, J = 8.5, 5.7 Hz, 1H), 7.18 (td, *J* = 8.5, 2.7 Hz, 1H), 6.79 (s, 2H), 5.96 – 5.87 (m, 1H), 5.76 (tt, *J* = 7.5, 6.0 Hz, 1H), 5.04 – 4.91 (m, 4H), 4.39 (s, 2H), 2.94 (s, 3H), 1.65 (d, *J* = 6.6 Hz, 3H). LCMS ES *m/z* 450 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-10-(fluoromethyl)-2,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclo-tetradecine-3-carbonitrile (Example 94)



241 **137** **539**



Example 94

Step 1:

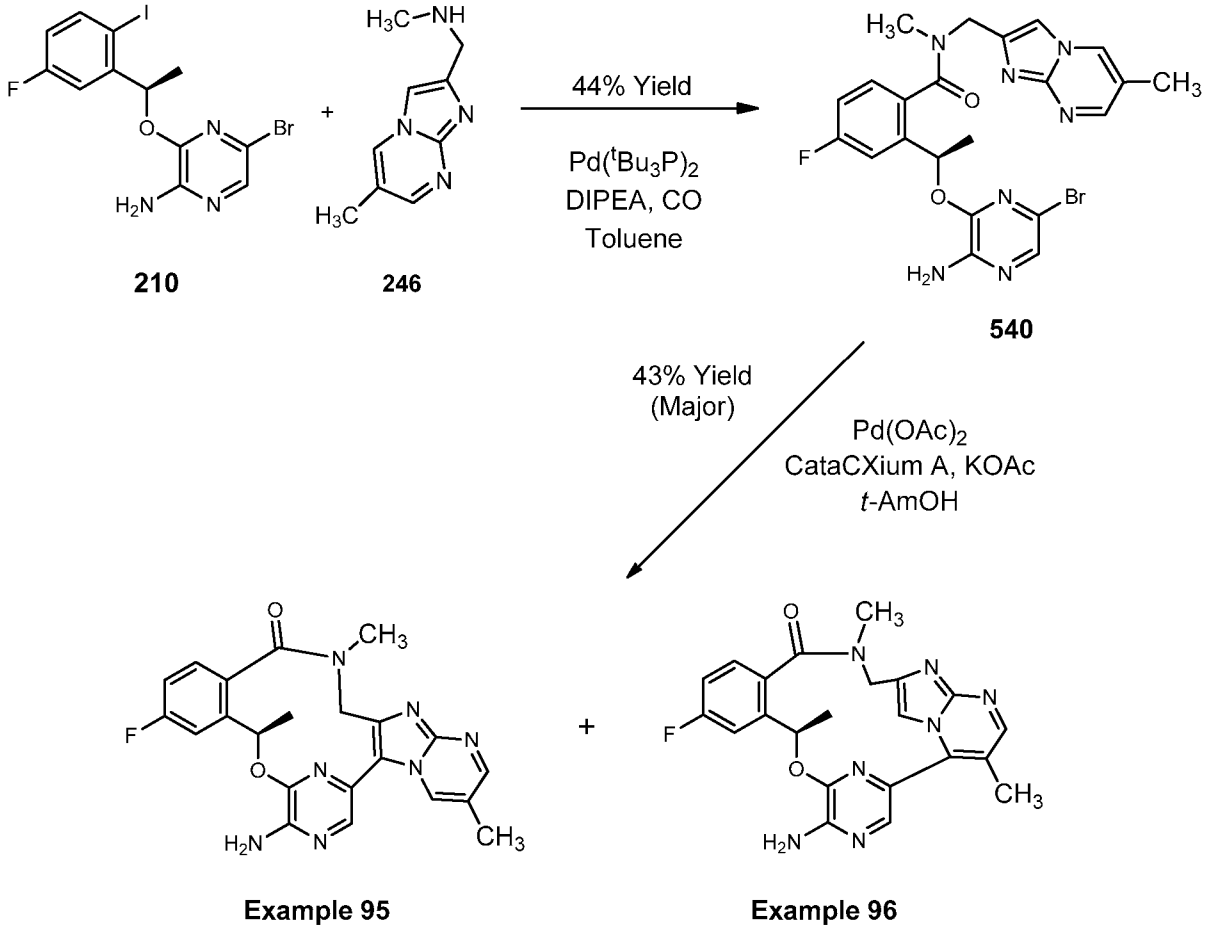
The procedure described in step 1 for **Example 91** was used to prepare **compound 539** (0.08 g, 88%) as a yellow solid.

Step 2:

The procedure described in step 2 for **Example 91** was used to prepare **Example 94** (16 mg, 19%) as a white solid (63 mg, 21% yield). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 (s, 1H), 7.50-

7.43 (m, 2H), 7.21-7.17 (m, 1H), 6.17-6.11 (m, 1H), 5.06-5.01 (m, 1H), 4.74-4.71 (m, 1H), 4.56-4.53 (d, 1H), 4.40-4.37 (d, 1H), 4.14 (s, 3H), 3.05 (s, 3H). LCMS ES *m/z* 426 $[M+H]^+$.

Preparation of 12-fluoro-1,14-dimethyl-1,4,5,6,7,8-hexahydro-14H-16,20-(metheno)-pyrazolo[4,3-g][1,14,11]benzodioxazacycloheptadecin-17-amine (Example 95) and (11R)-8-amino-13-fluoro-4,11,17-trimethyl-17,18-dihydro-9,5:19,1-di(azeno)pyrimido[6,1-h][2,5,9,13]benzoxatriazacyclohexadecin-16(11H)-one (Example 96)



210 **246** **540**

Example 95 **Example 96**

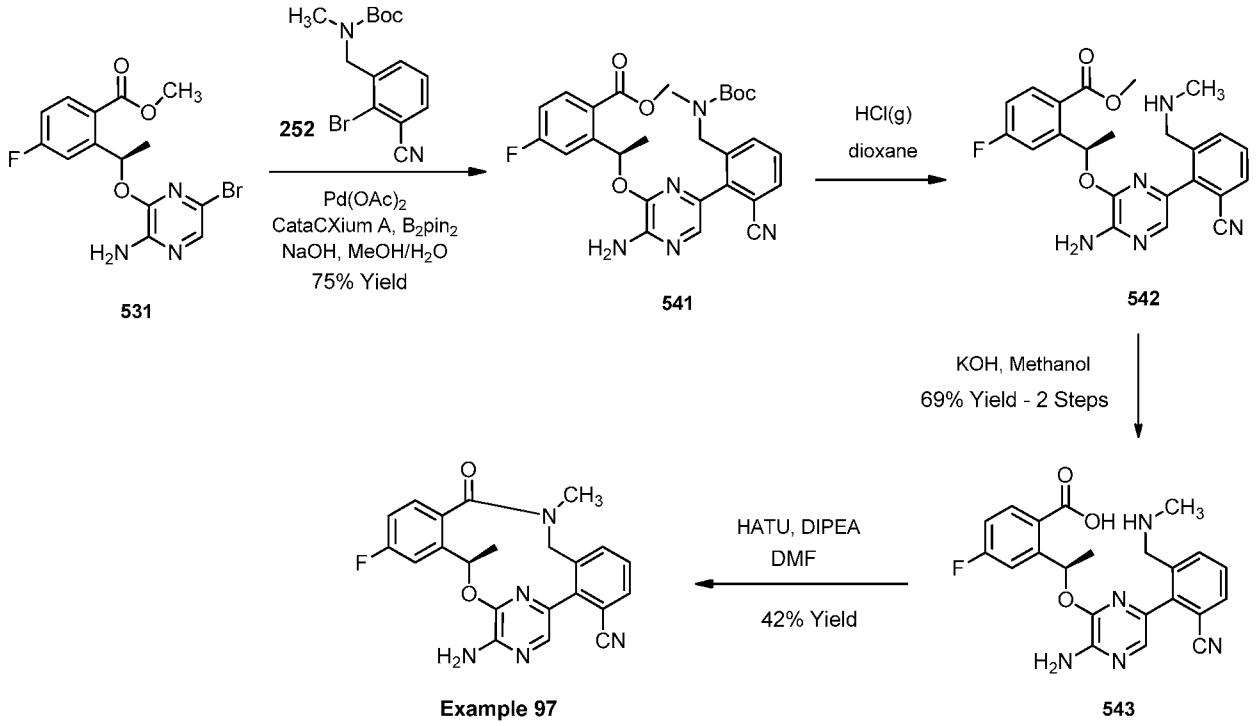
Step 1:

The procedure described in step 1 for **Example 91** was used to prepare **compound 540** (245 mg, 44%) as a pale yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (dt, *J* = 2.6, 1.3 Hz, 1H), 8.63 (s, 1H), 8.49 – 8.25 (m, 1H), 7.83 (s, 1H), 7.69 (s, 1H), 7.63 – 7.46 (m, 2H), 7.37 (dd, *J* = 8.3, 5.8 Hz, 0H), 7.27 – 7.05 (m, 1H), 6.72 (d, *J* = 7.1 Hz, 2H), 6.09 (t, *J* = 6.5 Hz, 0H), 6.00 (d, *J* = 16.3 Hz, 0H), 4.97 – 4.67 (m, 1H), 4.45 (t, *J* = 18.3 Hz, 1H), 3.06 (s, 2H), 2.93 (s, 1H), 2.28 (d, *J* = 7.4 Hz, 4H), 1.59 (dt, *J* = 5.8, 2.4 Hz, 4H). LCMS ES *m/z* 511/513 $[M+H]^+$.

Step 2:

Compound 540 (230 mg, 0.45 mmol) and KOAc (219 mg, 2.23 mmol) were mixed in *tert*-amyl alcohol (15 mL). The mixture was degassed (bubbling nitrogen through for 30 minutes) then $Pd(OAc)_2$ (20 mg, 0.09 mmol) and cataCXium A (64 mg, 0.18 mmol) were added. The mixture was degassed again then heated in the microwave for 2 hours at 120 °C. LC-MS of the crude mixture showed completion of the reaction. The mixture was filtered through a pad of celite and rinsed with EtOAc (50 mL). The filtrate was washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The oil obtained was purified by column chromatography (eluents EtOAc/MeOH from 100:0 to 90:10). The yellow glass obtained (pure macrocycle still containing EtOAc) was dissolved in MeOH (20 mL) and water was added (20 mL). The mixture was concentrated under vacuum then freeze-dried to give **Example 95** as a pale yellow solid (82 mg, 43% yield, 97% purity by LC-MS). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (dd, *J* = 2.5, 1.3 Hz, 1H), 8.45 (d, *J* = 2.2 Hz, 1H), 7.92 (s, 1H), 7.54 (dd, *J* = 10.1, 2.7 Hz, 1H), 7.42 (dd, *J* = 8.5, 5.7 Hz, 1H), 7.17 (td, *J* = 8.5, 2.7 Hz, 1H), 6.75 (s, 2H), 6.18 – 5.92 (m, 1H), 4.62 – 4.19 (m, 2H), 2.96 (s, 3H), 2.32 (d, *J* = 1.1 Hz, 3H), 1.66 (d, J = 6.5 Hz, 3H). LCMS ES *m/z* 434 $[M+H]^+$. Mixed fractions from the column were purified by reverse phase HPLC to give **Example 96** (15 mg, 7% yield, 92% purity by LC-MS) as a mixture of two conformers by ^{1}H NMR (about 1:1 mixture). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.32 (d, *J* = 8.4 Hz, 1H), 7.84 (s, 1H), 7.81 – 7.72 (m, 1H), 7.61 (dd, *J* = 8.5, 5.7 Hz, 0.5H), 7.48 (dd, *J* = 10.4, 2.7 Hz, 0.5H), 7.38 (dd, *J* = 8.5, 5.5 Hz, 0.5H), 7.34 (s, 0.5H), 7.04 (td, *J* = 8.3, 2.7 Hz, 1H), 6.86 (d, *J* = 6.4 Hz, 0.5H), 6.14 (d, *J* = 6.3 Hz, 0.5H), 5.24 (dd, *J* = 15.9, 8.5 Hz, 1H), 4.08 (dd, *J* = 38.3, 15.9 Hz, 1H), 2.97 (s, 1.5H), 2.93 (d, *J* = 1.9 Hz, 1.5H), 2.39 (s, 1.5H), 2.32 (s, 1.5H), 1.63 (dd, *J* = 9.0, 6.5 Hz, 1.5H), 1.40 (d, *J* = 6.4 Hz, 1.5H). LCMS ES *m/z* 434 $[M+H]^+$.

Preparation of (5R)-8-amino-3-fluoro-5,17-dimethyl-18-oxo-5,16,17,18-tetrahydro-7,11-(azeno)dibenzo[g,l][1,4,10]oxadiazacyclotetradecine-12-carbonitrile (Example 97)



Step 1:

To a solution of **compound 531** (300 mg, 0.81 mmol), **compound 252** (393 mg, 1.21 mmol) and bis-(pinacalato)diboron (610 mg, 2.43 mmol) in methanol (60 mL) was added catacxium A (38 mg, 0.1053 mmol) and $Pd(OAc)_2$ (24 mg, 0.1053 mmol) was added. After the mixture was degassed for three times with nitrogen, a solution of NaOH (65 mg, 1.62 mmol) in water (12 mL) was added to the above mixture under nitrogen at room temperature. The resulting mixture was degassed with nitrogen three times and was then refluxed for 16 hours. TLC (petroleum ether/EtOAc 3/1) showed the reaction was complete. The reaction mixture was diluted with EtOAc (50 mL x 3). The combined EtOAc layers were washed with brine (20 mL x 2), dried over Na_2SO_4 and concentrated in vacuo to give a residue, which was purified via column chromatography (silica gel, petroleum ether/EtOAc from 10/1 to 5/1) to give **compound 541** (400 mg, 80% of purity, 75%) as a brown solid. LCMS *m/z* 535 $[M+H]^+$.

Step 2:

To a stirred solution of **compound 541** (400 mg, 80% of purity, 0.61 mmol) in DCM (2 mL) was added dropwise ~ 4M HCl (g) in dioxane (10 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature for 2 hours. LC-MS showed the reaction mixture was complete. The reaction mixture was concentrated *in vacuo* to give crude **compound 542**, which was used for the next step without any further purification. LCMS *m/z* 435 $[M+H]^+$.

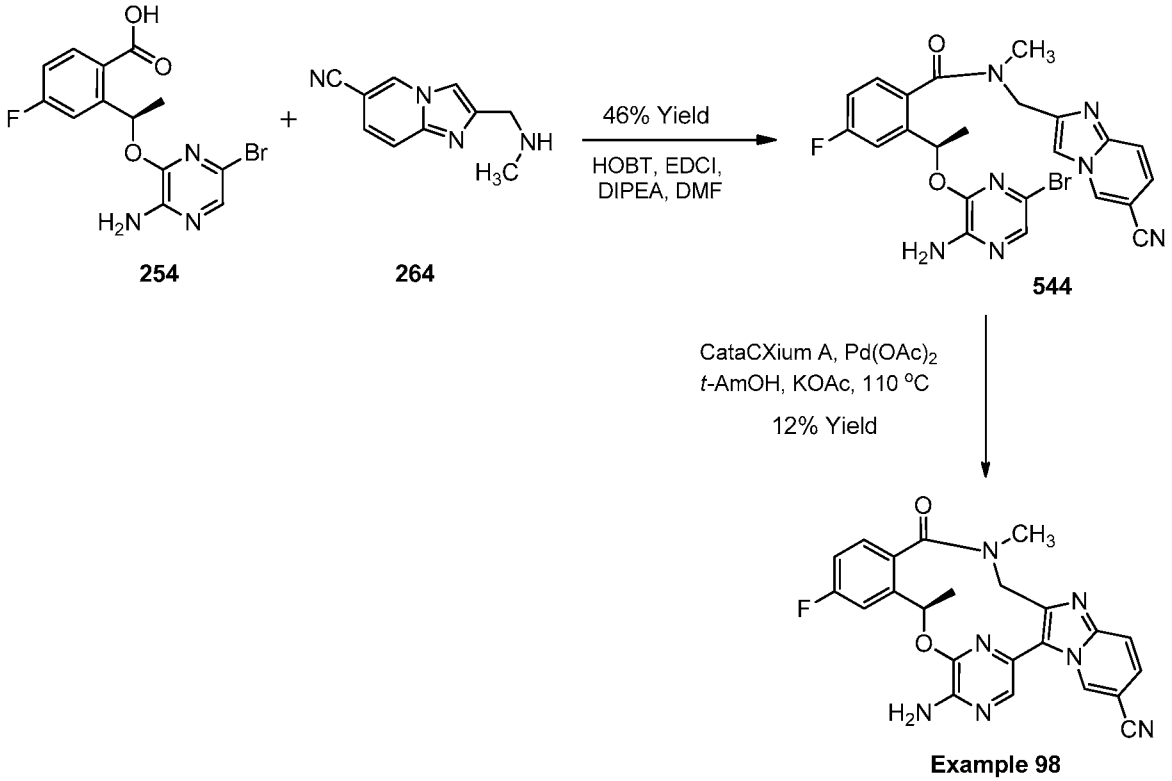
Step 3:

A mixture of **compound 542** (~300 mg) and KOH (316 mg, 5.65 mmol) in methanol (20 mL) was stirred at room temperature for 36 hours. LC-MS showed the reaction was complete. The mixture was concentrated *in vacuo*. The residue was diluted with water, and adjusted to pH ~ 5 with 0.5N.HCl. The aqueous was extracted with EtOAc (30 mL x 5). The combined EtOAc layers were dried over Na_2SO_4 and concentrated *in vacuo* to give **compound 543** (0.2 g, 69%) as a yellow solid. LCMS *m/z* 422 $[M+H]^+$.

Step 4:

To a solution of HATU (271 mg, 0.69) in DMF (60 mL) was added dropwise the mixture solution of **compound 543** (200mg, 0.47 mmol) and DIPEA (980 mg, 7.6 mmol) in DMF (10 mL) at 0 °C. After the addition, the resulting mixture was stirred at room temperature for 1 hour. LC-MS showed the reaction was complete. The mixture was poured into ice-water (20 mL). The mixture was extracted with EtOAc (40 mL x 5). The combined EtOAc layers were washed with brine (20 mL x 5), dried over Na_2SO_4, and concentrated *in vacuo* to give a residue. The residue was purified *via* column chromatography (silica gel, petroleum ether/EtOAc 5:1~1:1) to give **Example 97** (80.8 mg, 42%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.78 (m, 2H), 7.67-7.65 (m, 1H), 7.50-7.47 (m, 1H), 7.29-7.27 (m, 1H), 7.18-7.17 (m, 1H), 6.98-6.94 (m, 1H), 6.34-6.29 (m, 1H), 5.10 (s, 2H), 4.65-4.62 (d, 1H), 4.15-4.12 (d, 1H), 2.94 (s, 3H), 1.79-1.78 (d, 3H). LCMS ES *m/z* 404 $[M+H]^+$.

Preparation of (5R)-8-amino-3-fluoro-5,19-dimethyl-20-oxo-5,18,19,20-tetrahydro-7,11-(azeno)pyrido[2',1':2,3]imidazo[4,5-h][2,5,11]benzoxadiazacyclotetradecine-14-carbonitrile (Example 98)



254 **264** **544**

Example 98

Step 1:

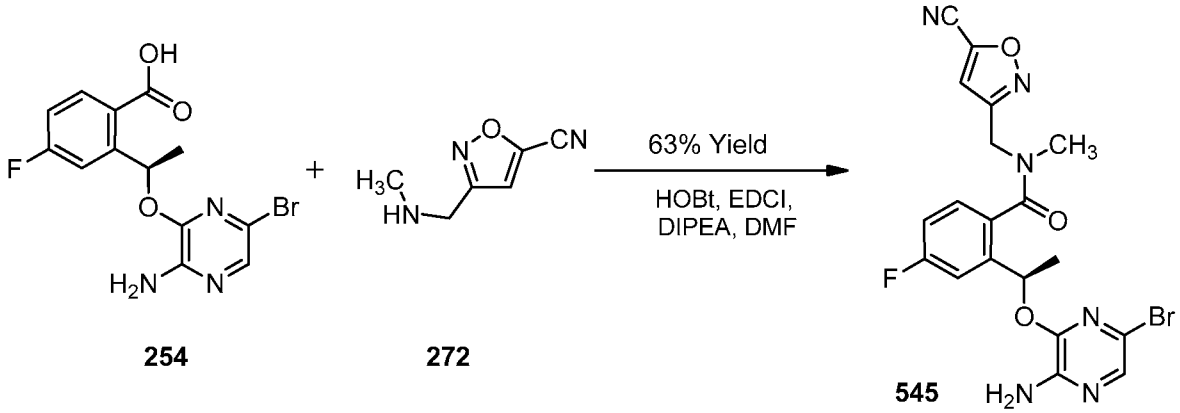
To a mixture of **compound 254** (0.217 g, 0.611 mmol), **compound 264** (0.15 g, 0.673 mmol) in DMF (20 mL) was added EDCI (0.176 g, 0.916 mmol), HOBt (0.124 g, 0.916 mmol) and DIPEA (0.394 g, 3.055 mmol) at -35 °C. The resulting mixture was stirred at -30 °C for 30 min and stirred at room temperature overnight. TLC (Petroleum ether/EtOAc = 1:1) showed that most of **compound 254** was consumed. The mixture was diluted with EtOAc (50 mL) and H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (10 mL x 5), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was purified by prep. TLC to obtain **compound 544** (150 mg, 46%) as a white solid.

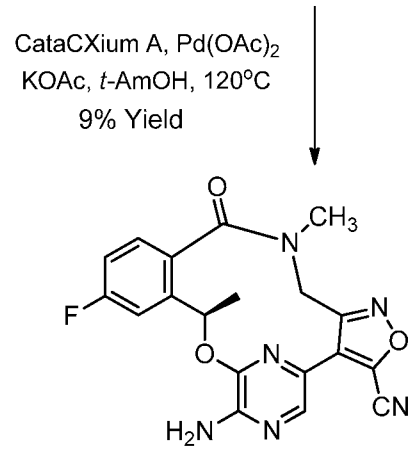
Step 2:

The reaction was run on three 50 mg batches under identical conditions. To a mixture of **compound 544** (0.05 g, 0.095mmol), cataCXium (4.25 mg, 0.0118 mmol), *t*-AmOH (1.94 mg, 0.019 mmol) and KOAc (46.55 mg, 0.475 mmol) in freshly distilled DMAc (8 mL) was added $Pd(OAc)_2$ (2.66 mg, 0.0118 mmol) at room temperature under a nitrogen atmosphere. The resulting mixture was sealed and heated at 110 °C for 12 h. LC-MS showed the reaction was complete. The mixture was diluted with EtOAc (25 mL) and then washed with brine (5 mL x 4). The organic layer was separated and dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was purified by prep. TLC and then re-purified by reverse phase

preparative. HPLC to obtain **Example 98** (15.4 mg, 12%) as a yellow solid. ^{1}H NMR (400 MHz, Methanol d_4 + D_2O): δ 9.38-9.37 (m, 1H), 7.98-7.91 (m, 2H), 7.85-7.80 (m, 1H), 7.55-7.45 (m, 2H), 7.25-7.15 (m, 1H), 6.25-6.15 (m, 1H), 4.80-4.75 (m, 2H), 4.60-4.52 (m, 1H), 3.15 (s, 3H), 1.84-1.82 (dd, 3H). LCMS *m/z* 444 $[M+1]^+$.

Preparation of (10R)-7-amino-12-fluoro-10,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-8,4-(azeno)[1,2]oxazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 99)





Example 99

Step 1:

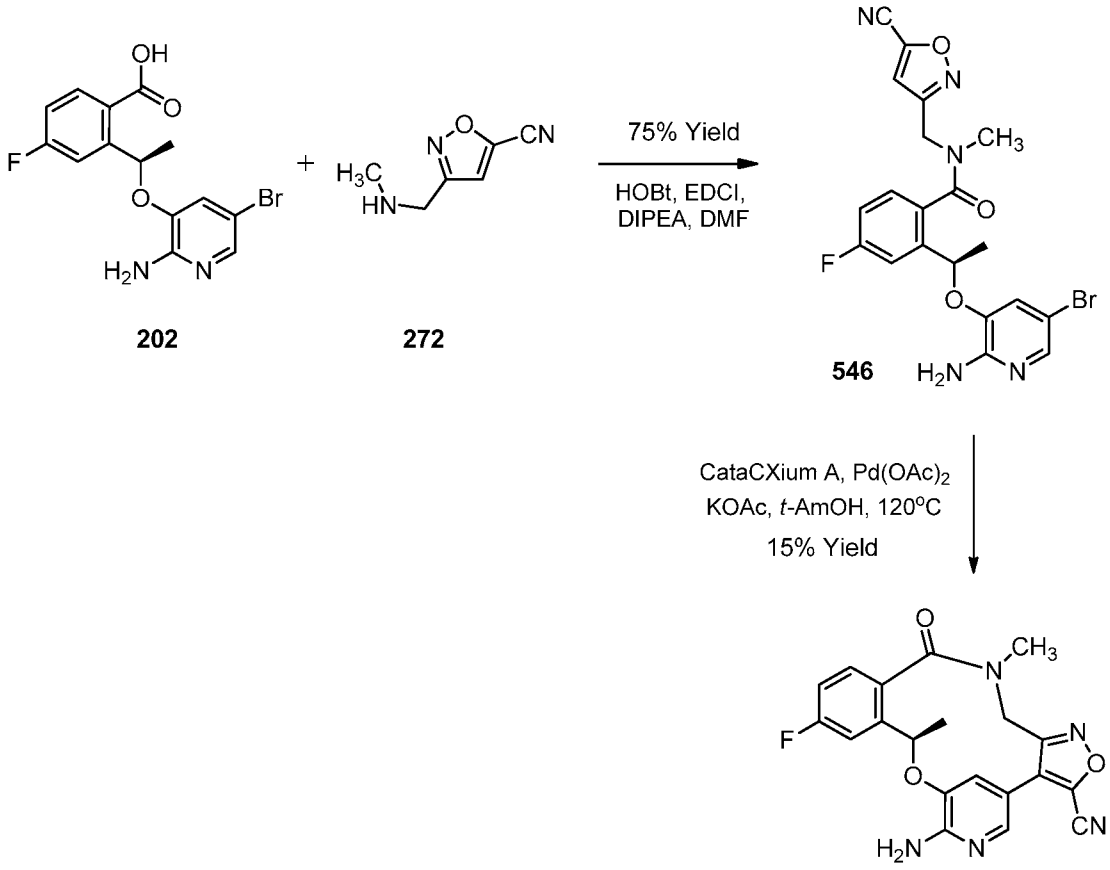
To a stirred solution of **compound 254** (250 mg, 0.7 mmol), **compound 272** (145 mg, 0.7 mmol) and DIPEA (271 mg, 2.1 mmol) in DMF (15 mL) was added HOBt (143 mg, 1.05 mmol) and EDCI (135 mg, 1.05 mmol) at -35 °C under N2. After the addition, the mixture was stirred at room temperature for 24 hours. TLC (petroleum ether/EtOAc = 1:1) indicated the reaction was complete. The mixture was poured into ice-water (20 mL), extracted with EtOAc (20 mL x 5), the combined organic layers were washed with brine (20 mL x 5), dried over Na_2SO_4, concentrated to give a residue, which was purified by column chromatography (silica. gel. Rf = 0.3, petroleum

ether/EtOAc = 2:1-1:1) to give **compound 545** (210 mg, 63%) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.22-7.21 (m, 2H), 7.18 (s, 1H), 7.04-7.02 (m, 1H), 6.12 (m, 1H), 5.02-4.98 (d, 1H), 4.89 (s, 2H), 4.77-4.74 (d, 2H), 3.04 (s, 3H), 1.74-1.72 (d, 3H).

Step 2:

A mixture of **compound 545** (200 mg, 0.42 mmol), KOAc (0.21 g, 2.15 mmol), cataCXium A (18 mg, 0.0504 mmol) and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) in *t*-AmOH (20 mL) was stirred at 120 °C for 18 hours. LC-MS indicted ~30% of desire **compound**. The mixture was poured into ice-water (20 mL), extracted with EtOAc (30 mL x 5), the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated to give a residue, which was purified by reverse phase preparative HPLC to give **Example 99** (14.1 mg, 9 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (S, 1H), 7.29-7.28 (d, 1H), 7.23-7.22 (d, 1H), 7.05-7.00 (m, 1H), 6.08-6.05 (s, 1H), 5.24(s, 2H), 4.7- 4.45 (dd, 2H), 3.08 (s, 3H), 1.78-1.76 (d, 3H). LCMS *m/z* 395 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-10,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-8,4-(metheno)[1,2]oxazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 100)



Example 100

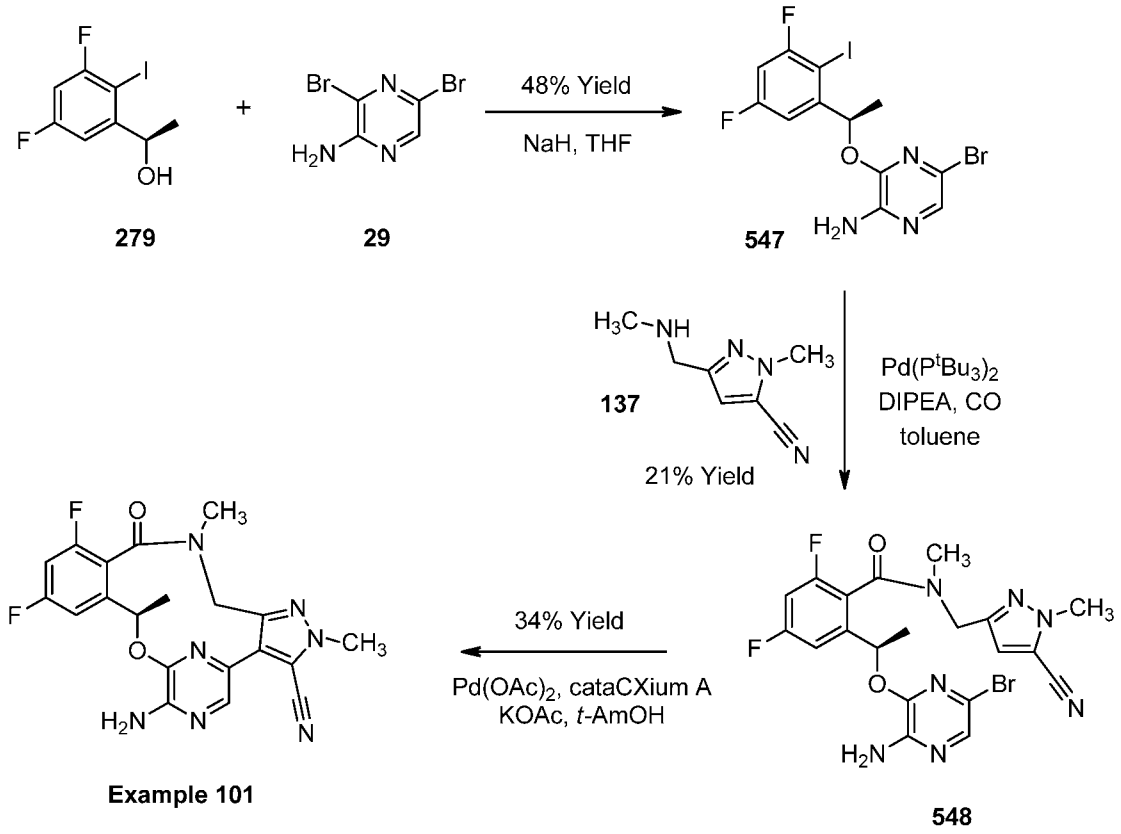
Step 1:

To a stirred solution of **compound 202** (400 mg, 1.13 mmol), **compound 272** (234 mg, 1.13 mmol) and DIPEA (437 mg, 3.4 mmol) in DMF (20 mL) was added HOBt (230 mg, 1.7 mmol) and EDCI (219 mg, 1.7 mmol) at -35 °C under N2. After the addition, the mixture was stirred at room temperature for 24 hours. TLC (petroleum ether/EtOAc =1:1) indicated the reaction was complete. The mixture was poured into ice-water (20 mL), extracted with EtOAc (20 mL x 5), the combined organic layers were washed with brine (20 mL x 5), dried over Na_2SO_4, concentrated to give a residue, which was purified by column chromatography (silica. gel. Rf =0.2, petroleum ether/EtOAc = 2:1-1:1) to give **compound 546** (400 mg, 75%) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.26-7.21 (m, 2H), 7.07 (s, 1H), 7.04-6.98 (m, 1H), 5.50-5.46 (m, 1H), 4.94-4.91 (d, 1H), 4.74 (s, 2H), 4.80-4.76 (d, 1H), 3.14 (s, 3H), 1.66-1.65 (d, 3H)

Step 2:

A mixture of **compound 546** (170 mg, 0.358 mmol), KOAc (0.175 g, 1.8 mmol), cataCXium A (15 mg, 0.043 mmol) and $Pd(OAc)_2$ (5 mg, 0.022 mmol) in *t*-AmOH (20 mL) was stirred at 120 °C for 18 hours. LC-MS indicted ~30% of desire **compound**. The mixture was poured into ice-water (20 mL), extracted with EtOAc (30 mL x 5), the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, concentrated to give a residue, which was purified by column chromatography over silica gel (Rf ~ 0.38, petroleum ether/EtOAc =3 : 1) to give **Example 100** (21 mg, 15 %) as a yellow solid. ^{1}H NMR (400 MHz, CDCl3): δ 7.92-7.91 (S, 1H), 7.32-7.26 (m, 1H), 7.24-7.23 (d, 1H), 7.07-7.02 (m, 1H), 6.84 (s, 1H), 5.72-5.70 (s, 2H), 4.59 (s, 2H), 3.18 (s, 3H), 1.81-1.79 (d, 3H). LCMS *m/z* 394 $[M+H]^+$.

Preparation of (10R)-7-amino-12,14-difluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 101)



Step 1:

A solution of **compound 279** (4.24 g, 14.9 mmol) in dry THF (24 mL) was added dropwise to a cooled (0 °C) suspension of NaH (60% in oil, 746 mg, 18.6 mmol) in dry THF (24 mL). The mixture was stirred 10 min at 0 °C then 30 min at room temperature before adding a solution of **compound 29** (3.14 g, 12.4 mmol) in dry THF (24 mL) in one go. The mixture was stirred at 60 °C for 18 hours then was cooled to RT. Brine (200 mL) was carefully added and the mixture was extracted with EtOAc (3 x 200 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under vacuum. The oil obtained was purified by column chromatography (eluents: heptanes/EtOAc from 98:2 to 75:25). The sticky solid obtained (4.6 g) was slurried in heptanes (~100 mL) for 72 hours. The suspension obtained was filtered and the solid dried under vacuum to give **compound 547** (2.73 g, 48% yield, 99% purity by LC-MS) as a beige powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (s, 1H), 7.55 – 7.42 (m, 1H), 7.31 (td, J = 8.7, 2.8 Hz, 1H), 6.75 (s, 2H), 6.23 (q, J = 6.5 Hz, 1H), 1.53 (d, J = 6.4 Hz, 3H). LCMS *m/z* 455/457 $[M+H]^+$.

Step 2:

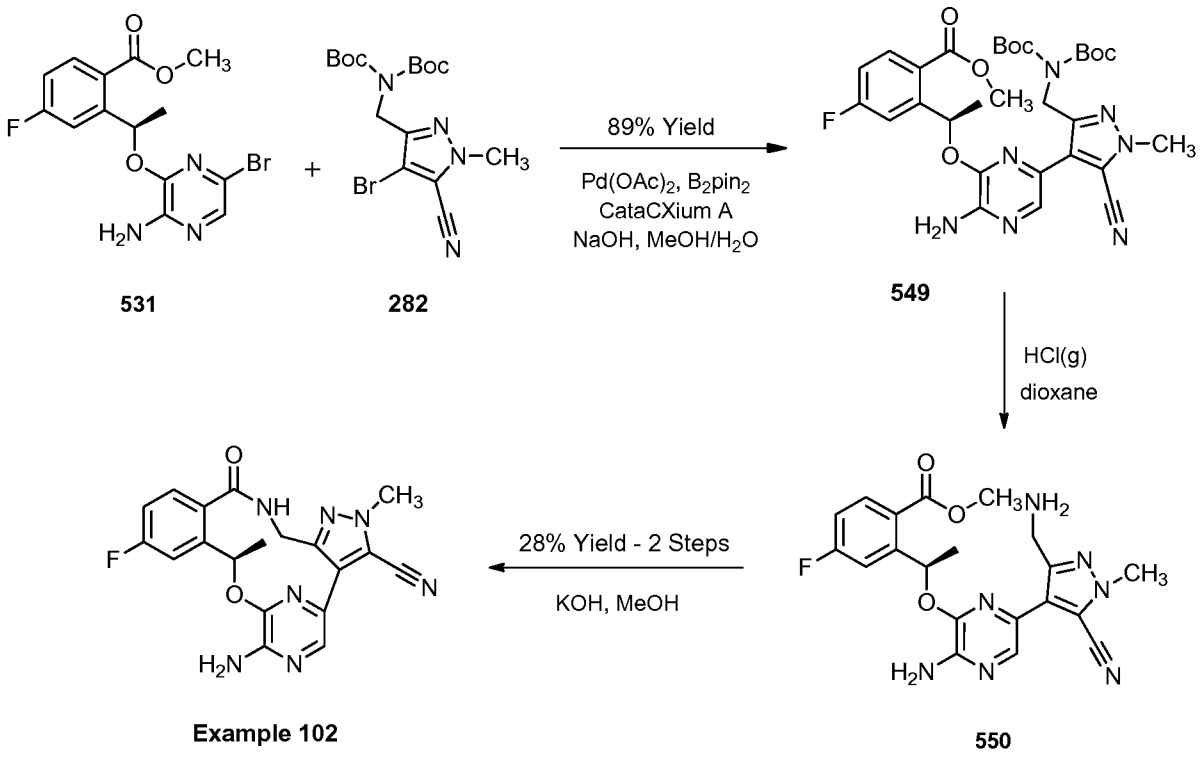
Compound 547 (2.0 g, 4.4 mmol), **compound 137** (HCl salt, 974 mg, 4.4 mmol) and DIEA (3.8 mL, 21.9 mmol) were dissolved in toluene (127 mL). Pd(P^{t}Bu$_3$)$_2$ (224 mg, 0.44 mmol) was added (the reaction becomes black) and the mixture was heated at 85 °C under CO (4 bars) for 18

hours. The mixture was cooled to RT, filtered through a pad of arbocel, rinsed with EtOAc (~100 mL) and the mother liquors concentrated. The oil obtained was purified by column chromatography over silica gel (eluents heptanes/EtOAc from 4:1 to 1:1) to give **compound 548** (460 mg, 21% yield, 89% purity by LC-MS) as a colorless solid foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (d, *J* = 1.1 Hz, 1H), 7.44 (m, 1H), 7.39 – 7.26 (m, 1H), 7.03 (s, 1H), 6.78 (d, *J* = 4.1 Hz, 2H), 5.98 (q, *J* = 6.5 Hz, 1H), 4.83 (d, *J* = 15.0 Hz, 1H), 4.62 (d, *J* = 15.0 Hz, 1H), 3.96 (d, *J* = 1.0 Hz, 3H), 2.90 (s, 3H), 1.59 (d, *J* = 6.5 Hz, 2H). LCMS *m/z* 506/508 $[M+H]^+$.

Step 3:

A solution of **compound 548** (230 mg, 0.45 mmol) in *tert*-amyl alcohol (9 mL) was degassed (3 cycles N_2/vacuum) at 100 °C. $Pd(OAc)_2$ (15 mg, 0.07 mmol), cataCXium A (49 mg, 0.14 mmol) and KOAc (227 mg, 2.3 mmol) were added and the mixture was degassed (3 cycles N_2/vacuum) at 100 °C. The mixture was then heated in a microwave at 120 °C for 2 hours. The reaction was cooled to room temperature, concentrated under vacuum, and DCM (50 mL) was added and the suspension filtered. The mother liquors were concentrated under vacuum and the oil obtained was purified by column chromatography (eluents: heptanes/EtOAc from 3:1 to 1:1) to give the macrocycle as a beige powder (102 mg, 53% yield, 99% purity by LC-MS). This powder was suspended in MeOH (~2 mL) and slurred overnight. The suspension was filtered and the white solids obtained were carefully dried under vacuum (0.3 mBar) at 80 °C for 6 hours. **Example 101** was obtained as a white powder (65 mg, 34% yield, 100% purity by LC-MS). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 1H), 7.38 (dd, *J* = 9.6, 2.5 Hz, 1H), 7.29 (td, *J* = 9.3, 2.4 Hz, 1H), 6.79 (s, 2H), 5.94 – 5.73 (m, 1H), 4.42 (dd, *J* = 13.8, 1.9 Hz, 1H), 4.22 (d, *J* = 13.6 Hz, 1H), 4.04 (s, 3H), 2.90 (s, 3H), 1.63 (d, *J* = 6.5 Hz, 3H). LCMS ES *m/z* 426 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-2,10-dimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 102)



531 **282** **549** **Example 102** **550**

Step 1:

To a solution of **compound 531** (0.2g, 0.54mol), **compound 282** (336 mg, 0.81 mmol) and bis-(pinacalato)diboron (407 g, 1.62 mmol) in methanol (40mL) was added cataCXium A (25 mg, 0.07 mmol) and $Pd(OAc)_2$ (16mg, 0.07 mmol). After the mixture was degassed for three times with nitrogen, a solution of NaOH (65 mg, 1.62 mmol) in water (12 mL) was added to the above mixture under nitrogen gas at room temperature. The resulting mixture was degassed with nitrogen gas three times and was then refluxed for 16 hours. TLC (petroleum ether/EtOAc 3/1) showed the reaction was complete. The reaction mixture was diluted with EtOAc (500 mL x 3). The combined EtOAc layers were washed with brine (100 mL x 2), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified via column chromatography (silica gel, petroleum ether/EtOAc from 10/1 to 5/1) to give **compound 549** (400 mg, 75% of purity, 89%) as a brown solid. LCMS *m/z* 648 $[M+Na]^+$.

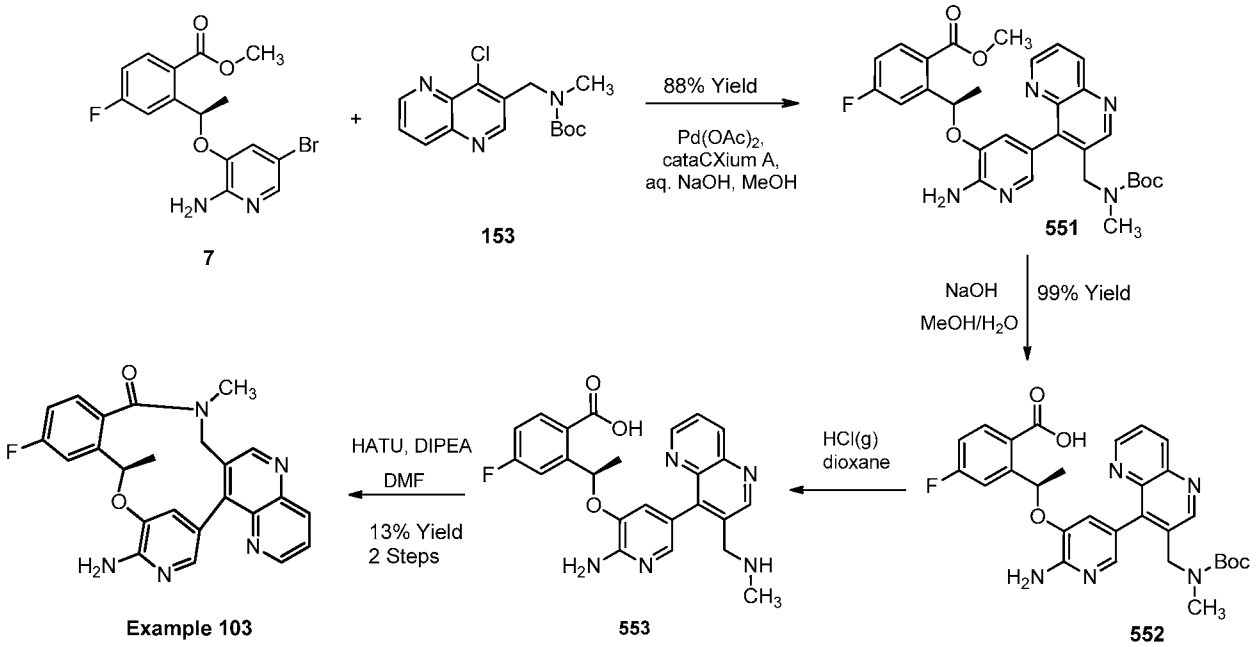
Step 2:

To a stirred solution of **compound 549** (400 mg, 75% of purity, 0.48 mmol) in DCM (2 mL) was added dropwise ~ 4M HCl (g) in dioxane (10 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature for 2 hours. LC-MS showed the reaction mixture was complete. The reaction mixture was concentrated *in vacuo* to give crude **compound 550**, which was used for next step without any further purification. LCMS *m/z* 426 $[M+H]^+$.

Step 3:

A mixture of **compound 550** (~300 mg) and KOH (316 mg, 5.65 mmol) in methanol (20 mL) was stirred at room temperature for 4 hours. LC-MS showed the reaction was complete. The mixture was poured into 0.5N HCl (20 mL), extracted with EtOAc (30 mL x 5). The combined EtOAc layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified *via* column chromatography (silica gel, petroleum ether/EtOAc from 5/1-1/1) to give **Example 102** (53.5 mg, 28%) as a brown solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.32-7.28 (m, 2H), 7.05-7.00 (m, 1H), 6.19-6.14 (m, 1H), 5.08 (s, 2H), 4.30-4.26 (d, 1H), 4.22-4.18 (d, 1H), 3.49 (s, 3H), 2.17 (s, 3H). LCMS m/z 394 $[M+H]^+$.

Preparation of (11R)-8-amino-13-fluoro-11,17-dimethyl-17,18-dihydro-9,5-(metheno)-[1,5]naphthyridino[4,3-h][2,5,11]benzoxadiazacyclotetradecin-16(11H)-one (Example 103)



Step 1:

To a solution of **compound 7** (0.3 g, 0.81 mmol), **compound 153** (400 mg, 1.29 mmol) and bis-(pinacalatodiboron) (618 mg, 2.43 mmol) in methanol (100 mL) was added cataCXium A (37.8 mg, 0.105 mmol) and $Pd(OAc)_2$ (23.7 mg, 0.105 mmol) under nitrogen at room temperature. After the mixture was degassed for three times with nitrogen, NaOH (64.8 mg, 1.62 mmol) in water (12 mL) was added. The resulting mixture was degassed with nitrogen three times and was then refluxed for 3 hours. TLC (EtOAc) showed the reaction mixture was completed. The reaction mixture was diluted with EtOAc (300 mL). The mixture was then washed with brine (100 mL x 2), dried over Na_2SO_4 and concentrated *in vacuo* to give residue, which was purified by

column chromatography over silica gel (DCM/MeOH 20:1, Rf, 0.41) to give **compound 551** (400 mg, 88%) as a brown solid. LCMS *m/z* 308 $[M+Na]^+$.

Step 2:

A mixture of **compound 551** (400 mg, 0.71 mmol) and NaOH (0.57 g, 14.2 mmol) in methanol (15 mL) and water (2 mL) was stirred at 40 °C for 3 hours. LC-MS showed the reaction mixture was completed. The reaction mixture was concentrated *in vacuo* to give a residue. The residue was dissolved with water (20 mL), and was extracted with MTBE (20 mL). The aqueous was then acidified with 6N HCl to pH~5. The mixture was saturated with solid NaCl and then extracted with EtOAc (20 mL x 5). The combined EtOAc layers were dried over Na_2SO_4 and concentrated *in vacuo* to give **compound 552** (388 mg, 99%) as a yellow solid. LCMS *m/z* 548 $[M+H]^+$.

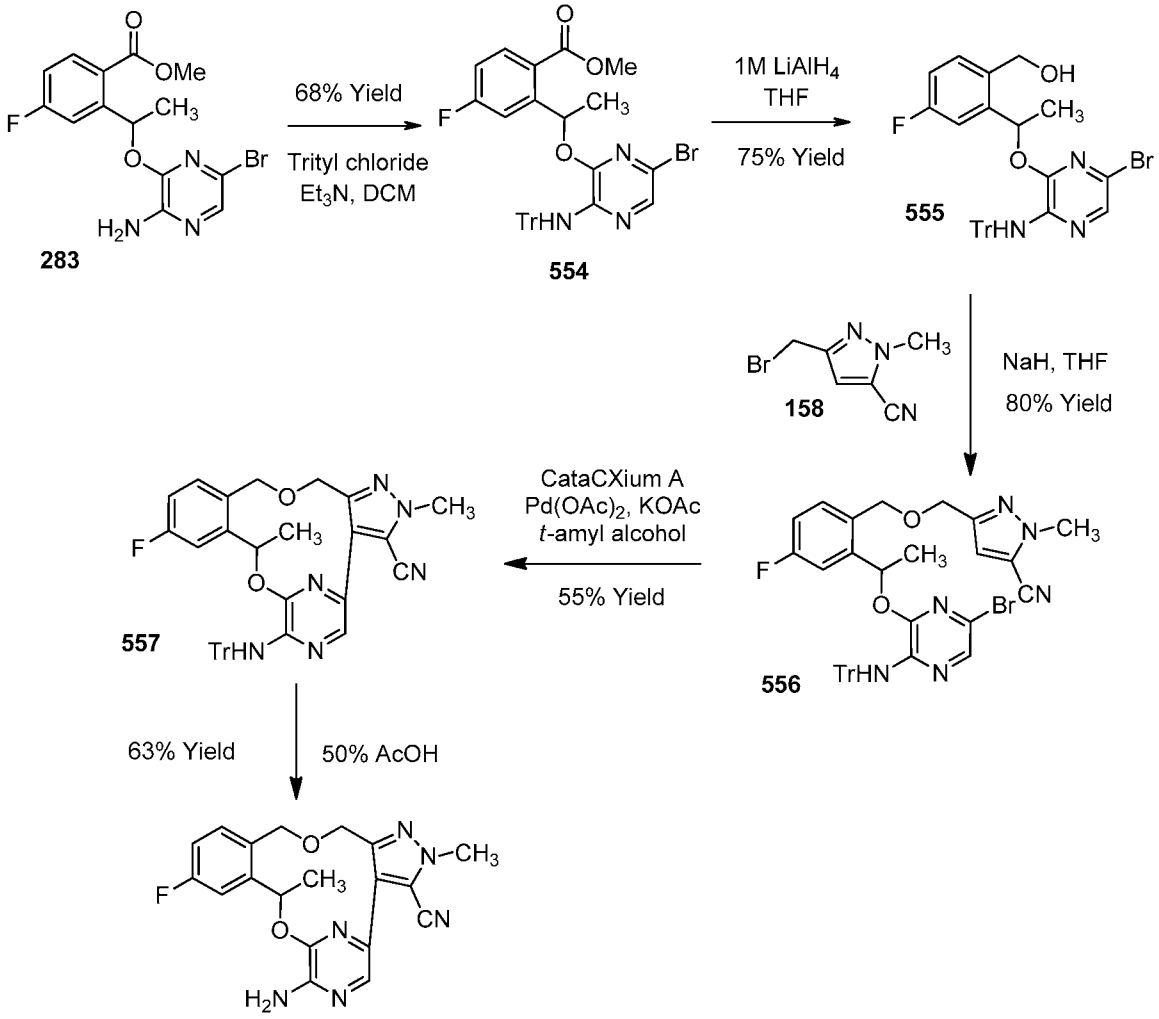
Step 3:

To a solution of **compound 552** (388 mg, 0.7 mmol) in dioxane (5 mL) was added dropwise ~ 4M HCl (g) in dioxane (20 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature for 14 hours. LC-MS showed the reaction mixture was completed. The reaction mixture was concentrated *in vacuo* to give residue, which was azeotroped with toluene three times to give crude **compound 553**, which was used for the next step without any further purification. LCMS *m/z* 448 $[M+H]^+$.

Step 4:

To a solution of HATU (400 mg, 0.313 mmol) in DMF (60 mL) was added dropwise a solution of **compound 553** (~0.7 mmol) and DIEA (1.43 g, 11.2 mmol) in DMF (20 mL) at 0 °C. After addition, the resulting mixture was stirred at this temperature for 1 hour. LC-MS showed the reaction was completed. The mixture was poured into ice-water (50 mL). The mixture was extracted with EtOAc (40 mL x 5). The combined EtOAc layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified by column chromatography over silica gel (DCM/MeOH 20:1 Rf, 0.27) to give **Example 103** (40 mg, 13%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.01-9.00 (m, 2H), 8.44-8.42 (d, 1H), 7.85 (s, 1H), 7.69-7.67 (m, 1H), 7.37-7.34 (m, 1H), 7.24-7.22 (m, 2H), 7.02-6.98 (m, 1H), 5.90-5.88 (m, 1H), 4.94 (br s, 2H), 4.67-4.47 (dd, 2H), 3.18 (s, 3H), 1.83-1.81 (d, 3H). LCMS *m/z* 430 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-2,10-dimethyl-2,10,15,17-tetrahydro-8,4-(azeno)pyrazolo[4,3-h][2,11,5]benzodioxazacyclotetradecine-3-carbonitrile (Example 104, 105 and 106)



Example 104, Example 105 and Example 106

Step 1:

To the solution of **compound 283** (1.48 g, 3.99 mmol) in DCM (25 mL), Et_3N (0.84 mL, 5.98 mmol) and DMAP (20 mg, 0.163 mmol) were added, followed by trityl chloride (1.68 g, 5.98 mmol). The reaction mixture was stirred for 16 hours at room temperature. An additional amount of trityl chloride (0.56g, 1.99 mmol) was added to the reaction mixture and stirred at room temperature for 16 hours. The reaction mixture was diluted with DCM (20 mL) followed by extraction with water (10 ml) and brine (10 ml). The organic layer was removed and evaporated after drying over anhydrous sodium sulfate. The crude obtained as a yellow solid was purified by flash chromatography over silica gel (8% EtOAc in toluene) to give **compound 554** as a colorless solid (1.67 g, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.7, 5.8 Hz, 1H), 7.44 – 7.16 (m, 17H), 7.01 (ddd, J = 8.7, 7.7, 2.7 Hz, 1H), 6.89 (qd, J = 6.4, 1.3 Hz, 1H), 6.36 (s, 1H), 3.93 (s, 3H), 1.72 (d, J = 6.4 Hz, 3H).

Step 2:

Compound 554 (1.6 g, 2.60 mmol) was dissolved in dry THF (15 mL) and cooled to 0 °C under nitrogen. A 1M solution of $LiAlH_4$ in THF (2.0 mL, 2.0 mmol) was added slowly over 15 minutes and the reaction mixture was stirred for 5 minutes at 0 °C. The reaction mixture was quenched by the careful addition of H_2O (1 mL) and stirred for 10 minutes, before EtOAc (40 mL) and MgSO*4* were added. The salts were filtered off, and the filtrate was evaporated to give a pale yellow oil, which was purified by column chromatography over silica gel (heptanes/EtOAc, 5:1) to give **compound 555** as a colorless solid (1.13 g, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 16H), 7.09 (dd, *J* = 9.7, 2.7 Hz, 1H), 6.96 (td, *J* = 8.3, 2.7 Hz, 1H), 6.42 (s, 1H), 6.31 (qd, *J* = 6.5, 1.6 Hz, 1H), 4.92 (d, *J* = 12.1 Hz, 1H), 4.68 (dd, *J* = 12.3, 7.1 Hz, 1H), 3.01 (d, *J* = 8.4 Hz, 1H), 1.70 (d, *J* = 6.5 Hz, 3H). LCMS ES *m/z* 584/586 $[M+H]^+$.

Step 3:

To a solution of **compound 555** (1.1 g, 1.189 mmol) in dry THF (15 mL) was slowly added NaH (60%, 0.15g, 3.78 mmol) in portions at 0 °C for 3 minutes. The reaction was stirred for 30 minutes at 0 °C before adding the solution of **compound 158** (0.452 g, 2.26 mmol) in dry THF (5 mL) slowly. The reaction was allowed to stir at room temperature overnight. The reaction mixture was carefully quenched with water (10 mL) followed by extraction with EtOAc (2 x 20 mL). The organic phase was removed, washed with water (10 mL) and brine (10 mL). The EtOAc extract was evaporated after being dried over anhydrous sodium sulfate. The crude product obtained as a light yellow gum was purified by column chromatography over silica gel using 15% acetone in heptane to provide **compound 556** as a colorless solid (1.06g, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 16H), 7.14 (dd, *J* = 9.8, 2.7 Hz, 1H), 6.94 (td, *J* = 8.3, 2.7 Hz, 1H), 6.82 (s, 1H), 6.32 – 6.22 (m, 1H), 5.05 (d, *J* = 11.5 Hz, 1H), 4.65 – 4.42 (m, 3H), 4.03 (s, 3H), 1.64 (d, *J* = 6.5 Hz, 3H).

Step 4:

The reaction was done in two batches using **compound 556**(0.5 g, 0.71 mmol). In a microwave vial (20 ml capacity) was placed **compound 556** (0.5g, 0.71 mmol), KOAc (0.35g, 3.55 mmol), cataCXium A (0.0763 g, 0.213 mmol) and *t*-amyl alcohol (degassed, 14.5 ml). The reaction mixture was further degassed for 3 minutes before adding $Pd(OAc)_2$. The vial was sealed and irradiated in the microwave for 2 hours at 120 °C. The reaction mixtures were combined, diluted with EtOAc (50 ml), and filtered through celite to remove the inorganics. The clear yellow filtrate were washed with water (2x10 ml), brine (20 ml), dried over anhydrous sodium sulfate and evaporated to give the crude product as yellow solid. The solid was purified by column chromatography over silica gel using 25% acetone in heptane to give **compound 557** as a light yellow solid (0.483 mg, 54.6% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.42 – 7.19 (m, 17H), 6.94 (td, *J* = 8.2, 2.7 Hz, 1H), 6.72 (qd, *J* = 6.7, 1.7 Hz, 1H), 6.52 (s, 1H), 5.35 – 5.23 (m,

1H), 4.48 (d, *J* = 12.6 Hz, 1H), 4.24 (d, *J* = 9.6 Hz, 1H), 4.11 (d, *J* = 9.6 Hz, 1H), 3.97 (s, 3H), 1.65 (d, *J* = 6.7 Hz, 3H). LCMS ES *m/z* 623 $[M+H]^+$.

Step 5:

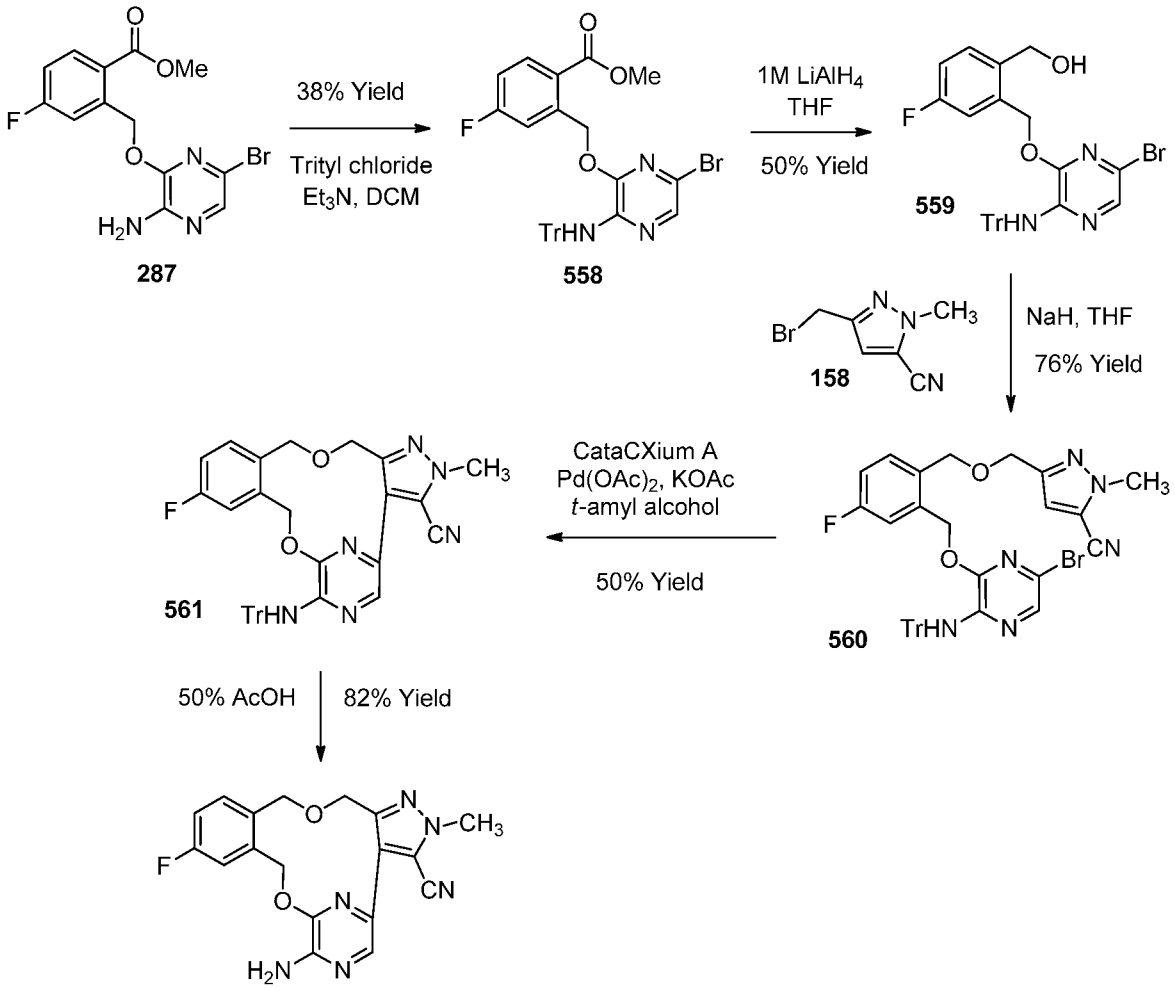
A suspension of **compound 557** (0.476 g, 0.76 mmol) in 50% AcOH in water (20 ml) was heated at 80 °C for 4h. The reaction mixture was cooled to room temperature and was diluted with water (20 ml). The reaction mixture was carefully neutralised to slightly basic pH (pH=8) by slowly adding solid $NaHCO_3$ in a portionwise manner. The resultant reaction mixture was extracted with EtOAc (2x 20ml). The organic phase was removed, washed with water (5 ml), brine (10 ml). The clear yellow EtOAc extract was separated and evaporated after drying over anhydrous sodium sulfate, The crude product obtained as a light yellow solid on purification by column chromatography over silica gel using 25% acetone in heptane to give **Example 104** as a colorless solid (0.183 mg, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.49 (dd, *J* = 10.2, 2.8 Hz, 1H), 7.38 (dd, *J* = 8.4, 5.9 Hz, 1H), 7.07 (td, *J* = 8.4, 2.8 Hz, 1H), 6.78 (s, 2H), 6.61 (qd, *J* = 6.7, 1.8 Hz, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 4.46 (d, *J* = 12.3 Hz, 1H), 4.32 (d, *J* = 9.9 Hz, 1H), 4.02 (d, 1H), 3.98 (s, 3H), 1.60 (d, *J* = 6.6 Hz, 3H). LCMS ES *m/z* 381 $[M+H]^+$.

The chiral separation was performed by preparative SFC on a Whelk-O1 (R,R) (250 x 4.6 mm I.D., 3 micron particle size) column, which was eluted with 20% methanol @ 140 bar CO_2 with a flow rate of 3 mL/min. $Rt_{(Peak\ 1)}$ = 3.77 minutes and $Rt_{(Peak\ 2)}$ = 4.95 minutes, and gave Peak 1 as a white solid (59 mg, 20%) and Peak 2 as a white solid (58 mg, 20%).

Example 105 (Peak 1): > 99% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.49 (dd, *J* = 10.2, 2.8 Hz, 1H), 7.38 (dd, *J* = 8.4, 5.9 Hz, 1H), 7.07 (td, *J* = 8.4, 2.8 Hz, 1H), 6.78 (s, 2H), 6.61 (qd, *J* = 6.7, 1.8 Hz, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 4.46 (d, *J* = 12.3 Hz, 1H), 4.32 (d, *J* = 9.9 Hz, 1H), 4.02 (d, 1H), 3.98 (s, 3H), 1.60 (d, *J* = 6.6 Hz, 3H). LCMS APCI *m/z* 381 $[M+H]^+$.

Example 106 (Peak 2): ~ 99% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.49 (dd, *J* = 10.2, 2.8 Hz, 1H), 7.38 (dd, *J* = 8.4, 5.9 Hz, 1H), 7.07 (td, *J* = 8.4, 2.8 Hz, 1H), 6.78 (s, 2H), 6.61 (qd, *J* = 6.7, 1.8 Hz, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 4.46 (d, *J* = 12.3 Hz, 1H), 4.32 (d, *J* = 9.9 Hz, 1H), 4.02 (d, 1H), 3.98 (s, 3H), 1.60 (d, *J* = 6.6 Hz, 3H). LCMS APCI *m/z* 381 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-2-methyl-2,10,15,17-tetrahydro-8,4-(azeno)pyrazolo[4,3-h][2,11,5]benzodioxazacyclotetradecine-3-carbonitrile (Example 107)



Example 107

Step 1:

The procedure described in step 1 for **Example 104** was used to prepare **compound 558** (1.77 g, 38%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.7, 5.8 Hz, 1H), 7.39 – 7.13 (m, 17H), 7.06 (td, *J* = 8.3, 2.7 Hz, 1H), 6.37 (s, 1H), 5.83 (s, 2H), 3.83 (s, 3H).

Step 2:

The procedure described in step 2 for **Example 104** was used to prepare **compound 559** (0.084 g, 50%) as a colorless solid (835 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.5, 5.7 Hz, 1H), 7.35 (s, 1H), 7.33 – 7.14 (m, 16H), 7.03 (td, *J* = 8.3, 2.7 Hz, 1H), 6.44 (s, 1H), 5.52 (s, 2H), 4.76 (d, *J* = 5.7 Hz, 2H), 2.01 (t, *J* = 5.7 Hz, 1H). LCMS ES *m/z* 570/572 $[M+H]^+$.

Step 3:

The procedure described in step 3 for **Example 104** was used to prepare **compound 560** (0.77 g, 76%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.14 (m, 18H), 7.01 (td, *J* = 8.3, 2.7 Hz, 1H), 6.82 (s, 1H), 6.35 (s, 1H), 5.48 (s, 2H), 4.64 (s, 2H), 4.51 (s, 2H), 4.00 (s, 3H). LCMS ES *m/z* 689/691 $[M+H]^+$.

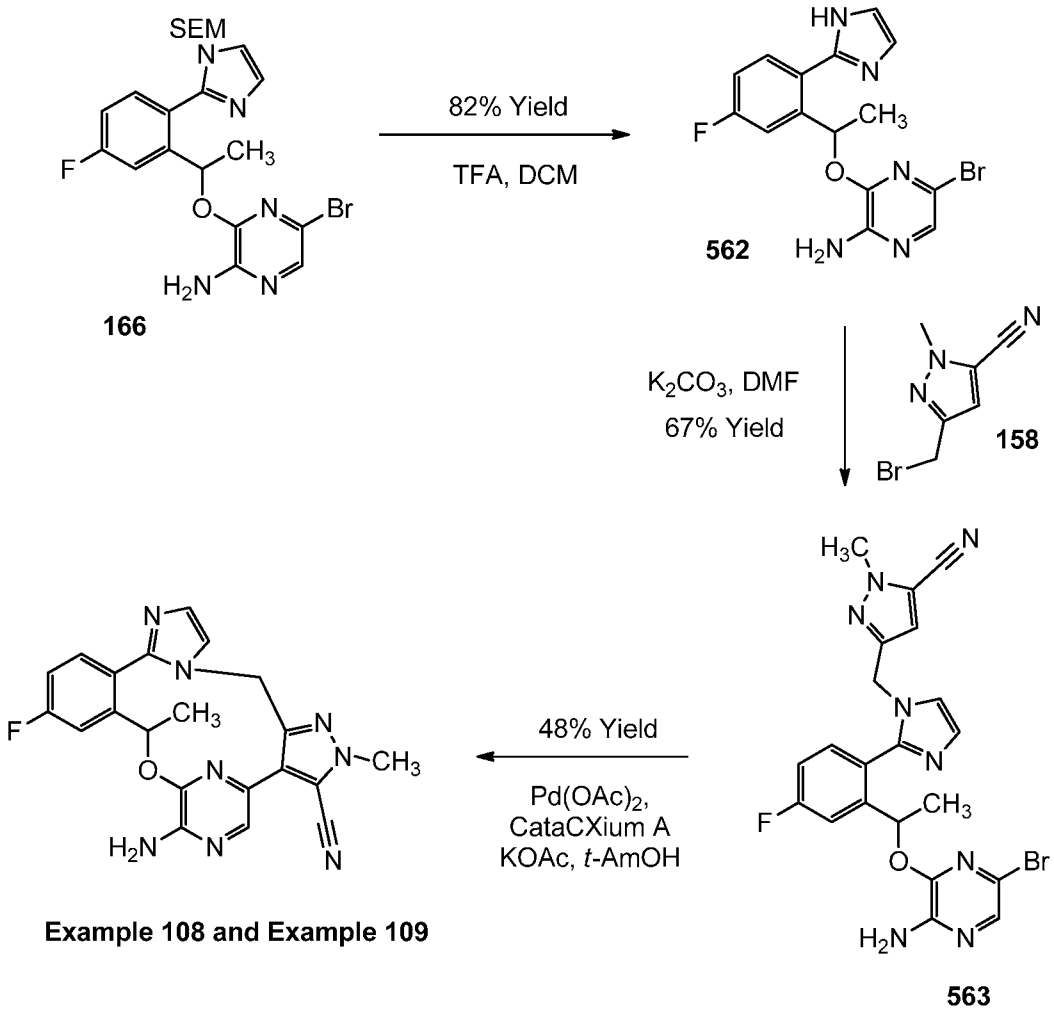
Step 4:

The procedure described in step 4 for **Example 104** was used to prepare **compound 561** (0.31 g, 50%) as a yellow solid. ^{1}NMR (400 MHz, DMSO-d_6) δ 7.67 (dd, *J* = 10.2, 2.8 Hz, 1H), 7.55 (s, 1H), 7.47 – 7.16 (m, 16H), 7.10 (td, *J* = 8.5, 2.8 Hz, 1H), 6.19 – 6.06 (m, 1H), 5.38 – 5.04 (m, 1H), 4.52 – 4.38 (m, 1H), 4.37 – 4.23 (m, 1H), 4.08 – 3.90 (m, 4H). LCMS ES *m/z* 609 $[M+H]^+$.

Step 5:

The procedure described in step 5 for **Example 104** was used to prepare **Example 107** (143 mg, 82%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.48 – 7.39 (m, 2H), 7.13 (td, *J* = 8.5, 2.9 Hz, 1H), 6.82 (s, 2H), 6.23 – 5.95 (m, 1H), 5.44 – 5.17 (m, 1H), 5.16 – 4.90 (m, 1H), 4.61 – 4.21 (m, 2H), 4.00 (s, 3H). LCMS ES *m/z* 367 $[M+H]^+$.

Preparation of 8-amino-3-fluoro-5,13-dimethyl-13,15-dihydro-5H-7,11-(azeno)imidazo[1,2-k]pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-12-carbonitrile (Example 108/109)



Step 1:

Compound 166 (1.5 g, 2.96 mmol), was dissolved in DCM (7 mL) then TFA (15 mL) was added in a dropwise manner to this solution. The mixture was stirred at room temperature for 20 hours (TLC showed full conversion). The reaction was concentrated under vacuum, diluted with EtOAc (100 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (100 mL then 50 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under vacuum. The oil obtained was purified by column chromatography over silica gel (eluents heptanes/EtOAc 1:1 to 1:2) to give **compound 562** as a solid foam (919 mg, 82% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H), 7.70 (dd, *J* = 10.5, 2.8 Hz, 1H), 7.62 (dd, *J* = 8.7, 5.7 Hz, 1H), 7.49 (s, 1H), 7.23 (td, *J* = 8.5, 2.8 Hz, 2H), 7.13 (s, 1H), 7.03 – 6.90 (m, 1H), 6.66 (s, 2H), 1.64 (d, *J* = 6.3 Hz, 3H).

Step 2:

Compound 562 (919 mg, 2.43 mmol), **compound 158** (513 mg, 2.56 mmol) and K_2CO_3 (503 mg, 3.64 mmol) were mixed in DMF (50 mL). The mixture was stirred at room temperature for 20 hours (LC-MS showed full conversion). Water (300 mL) was added and extracted with Et_2O (5 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under vacuum. The oil obtained was purified by column chromatography over silica gel (eluents heptanes/EtOAc 1:1 to 0:1). **Compound 563** was obtained as a white powder (805 mg, 67% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (dd, *J* = 10.2, 2.8 Hz, 1H), 7.53 (s, 1H), 7.42 – 7.30 (m, 2H), 7.22 (td, *J* = 8.4, 2.7 Hz, 1H), 7.07 (d, *J* = 1.3 Hz, 1H), 6.96 (s, 1H), 6.69 (s, 2H), 5.85 (q, *J* = 6.3 Hz, 1H), 5.14 (d, *J* = 15.7 Hz, 1H), 4.98 (d, *J* = 15.7 Hz, 1H), 3.90 (s, 3H), 1.52 (d, *J* = 6.4 Hz, 3H). LCMS *m/z* 497/499 $[M+H]^+$.

Step 3:

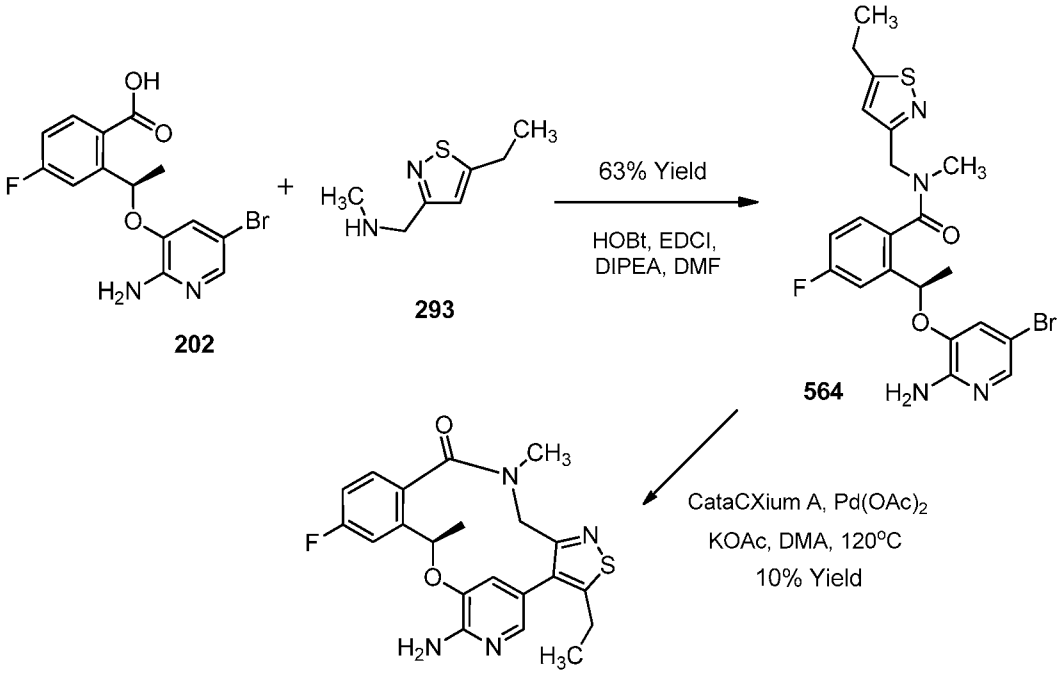
An identical reaction was set-up four times due to the limitation on volume of the microwave vials. **Compound 563** (200 mg, 0.4 mmol) was mixed with KOAc (197 mg, 2.0 mmol) in *tert*-amyl alcohol (10 mL). The reaction was degassed for 30 minutes (by bubbling nitrogen through) then $Pd(OAc)_2$ (18 mg, 0.08 mmol) and cataCXium A (58 mg, 0.16 mmol) were added. The reaction was degassed again for 30 minutes, the microwave vial sealed and heated at 120 °C for 2 hours (LC-MS showed 96% of the expected product). The reaction was cooled to room temperature, filtered through a pad of celite and rinsed with EtOAc (100 mL). The filtrate was washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The oil obtained was combined with the other reactions and purified by column chromatography over silica gel (eluents heptanes/EtOAc from 1:2 to 0:1). A mixture of **Example 108** and **Example 109** was obtained as a beige powder (320 mg, 48% yield, ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (s, 1H), 7.58 (dd, *J* = 10.0, 2.8 Hz, 1H), 7.46 (dd, *J* = 8.5, 5.7 Hz, 1H), 7.24 (td, *J* = 8.5, 2.8 Hz, 1H), 7.01 (s, 2H), 6.75 (s, 2H), 5.71 – 5.46 (m, 1H), 5.00 (d, *J* = 14.1 Hz, 1H),

4.56 (d, *J* = 14.1 Hz, 1H), 4.08 (s, 3H), 1.66 (d, *J* = 6.6 Hz, 3H). LCMS *m/z* 417 $[M+H]^+$. The chiral separation was performed on 32mg of material by preparative SFC on a Whelk-O1 (R,R) (250 x 4.6 mm I.D., 3 micron particle size) column, which was eluted with 30% methanol @ 140 bar CO_2 with a flow rate of 3 mL/min. $Rt_{(Peak\ 1)}$ = 3.00 minutes and $Rt_{(Peak\ 2)}$ = 3.86 minutes, and gave Peak 1 as a white solid (14.4 mg) and Peak 2 as a white solid (14.7 mg).

Example 108 (Peak 1): > 99% ee. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.71 (s, 1H), 7.58 (dd, *J* = 2.6, 9.9 Hz, 1H), 7.46 (dd, *J* = 5.8, 8.6 Hz, 1H), 7.24 (dt, *J* = 2.8, 8.6 Hz, 1H), 7.01 (s, 2H), 6.73 (s, 2H), 5.62 - 5.51 (m, 1H), 5.00 (d, *J* = 14.1 Hz, 1H), 4.56 (d, *J* = 13.8 Hz, 1H), 4.08 (s, 3H), 1.66 (d, *J* = 6.5 Hz, 3H). LCMS APCI *m/z* 417 $[M+H]^+$.

Example 109 (Peak 2): ~ 95% ee. ^{1}H NMR (400MHz, DMSO-d_6) δ 7.71 (s, 1H), 7.58 (dd, *J*=2.6, 9.9 Hz, 1H), 7.46 (dd, *J* = 5.8, 8.6 Hz, 1H), 7.24 (dt, *J* = 2.6, 8.5 Hz, 1H), 7.01 (s, 2H), 6.73 (s, 2H), 5.62 - 5.49 (m, 1H), 5.00 (d, *J* = 14.1 Hz, 1H), 4.56 (d, *J* = 14.1 Hz, 1H), 4.08 (s, 3H), 1.66 (d, *J* = 6.5 Hz, 3H). LCMS APCI *m/z* 417 $[M+H]^+$.

Preparation of (10R)-7-amino-3-ethyl-12-fluoro-10,16-dimethyl-16,17-dihydro-8,4-(metheno)[1,2]thiazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 110)



Example 110

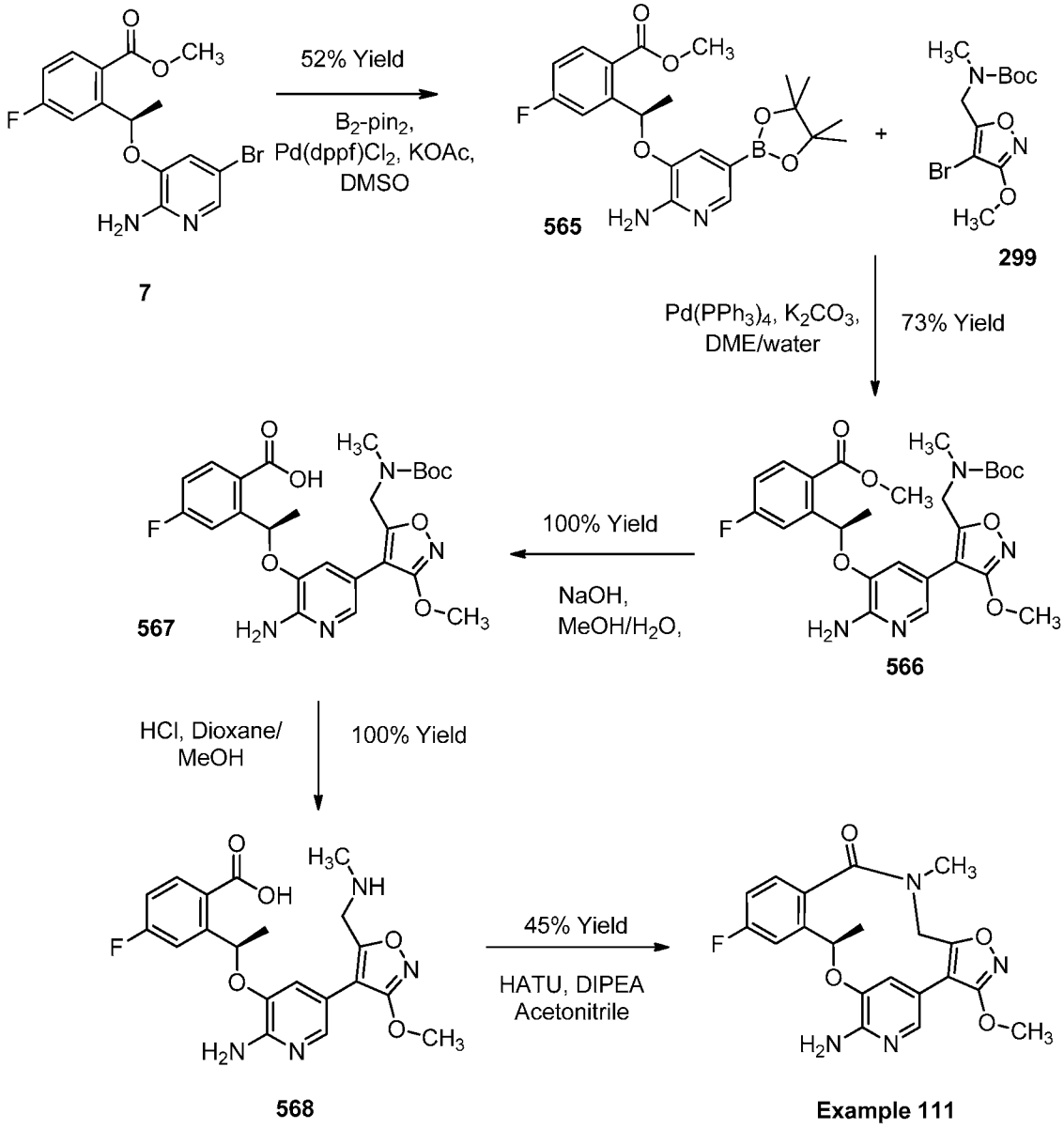
Step 1:

The procedure described in step 1 for **Example 100** was used to prepare **compound 564** as a yellow solid (0.5 g, 63%). LCMS *m/z* 493 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 100** was used to prepare **Example 110** as a yellow solid (16.8 mg, 10%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.59-7.56 (m, 1H), 7.48-7.42 (m, 3H), 7.19-7.14 (m, 1H), 5.99-5.98 (d, 1H), 4.56-4.47 (m, 2H), 3.18 (s, 3H), 3.09-2.99 (m, 2H), 1.88-1.87 (d, 3H), 1.38-1.35 (t, 3H). LCMS *m/z* 413 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-3-methoxy-10,16-dimethyl-16,17-dihydro-8,4-(metheno)[1,2]oxazolo[4,5-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 111)



Step 1:

To a solution of **compound 7** (200 mg, 0.54 mmol) in anhydrous DMSO (2 mL) was added bis-(pinacolato)diboron (635 mg, 2.5 mmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (40 mg, 0.054 mmol) and then KOAc (178 mg, 1.82 mmol) and the mixture was stirred under nitrogen and heated to 80 °C for 1 hour. The mixture was cooled, EtOAc added (40 mL) and filtered through arbocel. The filtrate was washed with water then brine, then the organic layer was extracted into 1M aqueous HCl (2x). The aqueous phase was cooled in ice, neutralised to pH7 by the careful addition of 1M NaOH solution, and the resulting precipitate was extracted into EtOAc (2x). The combined organics were dried over sodium sulphate, filtered and the solvent removed under vacuum. The oily residue was redissolved in EtOAc (1 mL) and heptane (15 mL) was added forming an off white precipitate. The solvent was removed under vacuum to give 115 mg (52%) of **compound 565**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (dd, 1H), 7.74 (d, 1H), 7.67 (dd, 1H), 7.25 (td, 1H), 6.87 (d, Hz, 1H), 6.35 (s, 2H), 6.26 (q, 1H), 3.91 (s, 3H), 1.57 (d, 3H), 1.21 (d, 12H). LCMS *m/z* 335 $[M+H]^+$.

Step 2:

A solution of **compound 299** (1.26g 3.92 mmol), potassium carbonate (811mg, 5.88 mmol) in dimethoxyethane (20 mL) and water (15 mL) was warmed to 40 °C and degassed with bubbling nitrogen through the mixture for 20 minutes. To the mixture was added a solution of **compound 565** (68mg, 0.16 mmol) in degassed dimethoxyethane (1 mL) then $Pd(PPh_3)_4$.The mixture was stirred under nitrogen and warmed further to 100 °C. During this time in 5 minute intervals a further 4 additions of **compound 565** (68 mg, 0.16 mmol) in degassed dimethoxyethane (1 mL) was added to mixture, and after reaction reached 100 °C, in 5 minute intervals a further 7 additions of **compound 565** (68 mg, 0.16 mmol) in degassed dimethoxyethane (1 mL) was added to mixture. (In total 820 mg, 1.96 mmol of **compound 565** was added in 12 mL DME). After the final addition the mixture was stirred at 100 °C under nitrogen for 1.5 hr, then cooled. EtOAc (120 mL) was added, then the mixture was washed with water (2x 50 mL), dried over sodium sulphate, filtered and the solvent removed under vacuum. Purification of the residue by column chromatography over silica gel and eluting with heptane: EtOAc 100:0 – 30:70 yielded the **compound 566** as a colorless solid (750 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 – 7.93 (m, 1H), 7.57 – 7.46 (m, 2H), 7.25 (td, 1H), 6.68 (m, 1H), 6.24 (q, 1H), 6.13 (s, 2H), 4.59 – 4.12 (m, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 2.70 (m, 3H)*, 1.61 (d, J = 6.2 Hz, 3H), 1.42-1.08 (m, 9H). LCMS *m/z* 531 $[M+H]^+$.

Step 3:

To a solution of **compound 566** (1.05 g, 1.98 mmol) in methanol (25 mL) at room temperature was added a solution of sodium hydroxide (1.2 g, 30 mmol) in water (3.5 mL) and mixture stirred for 18 hours at room temperature. To the mixture was added water (100 mL), then the mixture

was washed TBME (10 mL). The aqueous layer was adjusted to pH 4 with the careful addition of 1N HCl and a precipitate formed. The mixture was extracted with EtOAc (80 mL) then sodium chloride (20g) was added to the aqueous layer, which was extracted further with EtOAc (80 mL). The combined organic layers were dried over sodium sulphate, filtered and the solvent removed under vacuum to give **compound 567** as a pale yellow solid (1.02 g, 100%).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (dd, 1H), 7.54 – 7.44 (m, 2H), 7.21 (td, 1H), 6.72 (d, 1H), 6.37 (q, 1H), 6.17 (s, 2H), 4.81 – 3.95 (m, 2H), 3.84 (s, 3H), 2.73-2.66 (m, 3H), 1.60 (d, 3H), 1.36 -1.07 (m, 9H). LCMS *m/z* 517 $[M+H]^+$.

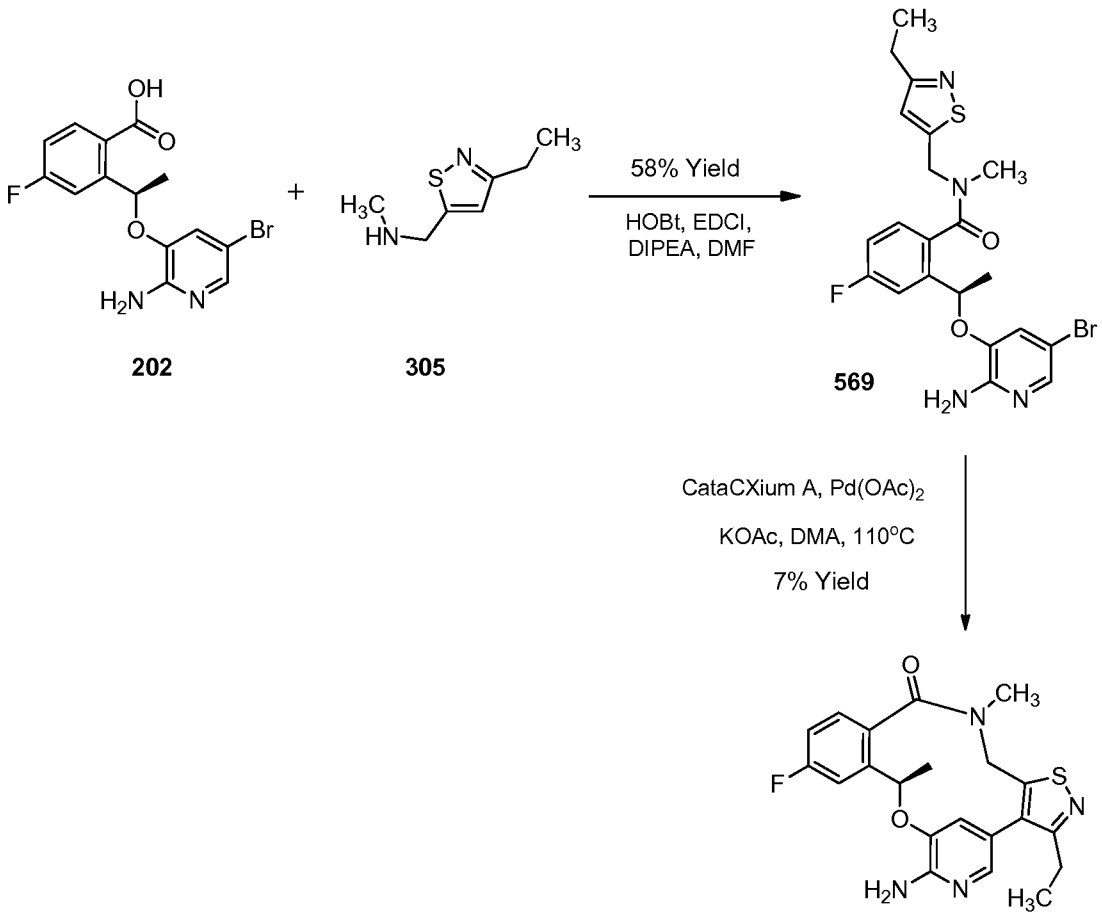
Step 4:

To a solution of **compound 567** (1.02 g, 1.98 mmol) in methanol (10 mL) and dioxane (10 mL) was added a solution of 4N HCl in dioxane (6 mL), and the mixture was stirred at 45 °C under nitrogen for 1.5 hours. The solvent was removed under vacuum, then azeotroped further with dioxane (2 x 25 mL) to give **compound 568** (1.2 g, 100%) as a pale brown solid. The solid was not purified further and was taken onto the next reaction. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 2H), 8.28 – 8.18 (m, 1H), 8.05 (dd, 1H), 7.84 (d, 1H), 7.55 (dd, 1H), 7.29 (td, 1H), 7.10 (d, 1H), 6.56 (q, 1H), 4.28 (s, 2H), 3.87 (s, 3H), 2.55 (s, 3H), 1.66 (d, 3H). LCMS *m/z* 417 $[M+H]^+$.

Step 5:

To a suspension of **compound 568** (1.1g, 1.654 mmol accounting for impurities) in acetonitrile (1.05 L) at room temperature was added DIEA (1.92g, 2.59 mL, 14.88 mmol) and the mixture turned to a solution. To the mixture was added HATU (660 mg, 1.74 mmol) and the mixture was stirred under nitrogen at room temperature for 1 hour. The solvent was removed under vacuum, then the residue re-dissolved in EtOAc (200 mL), washed with water (3 x 40 mL), brine (20 mL), dried over sodium sulphate, filtered and the solvent removed under vacuum. Purification of the residue by column chromatography over silica gel and eluting with EtOAc, then azeotroping the fractions with hexane (30 ml) yielded the desired product as a colourless solid.1H and 19F NMR indicated a trace of PF_6 salt, so the material was re-dissolved in EtOAc (100 mL), washed with 10% aqueous Na_2CO_3 (3x 40 mL), brine (2 x 20 mL), dried over sodium sulphate, filtered and the solvent removed under vacuum. Then the residue was re-dissolved in EtOAc (2 mL), hexane added (30 mL) and white precipitate formed. the solvent was removed under vacuum to give **Example 111** as a colorless solid (323 mg, 45%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (dd, *J* = 10.3, 2.7 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.44 (dd, *J* = 8.6, 5.7 Hz, 1H), 7.21 (td, *J* = 8.4, 2.7 Hz, 1H), 6.67 (d, *J* = 1.8 Hz, 1H), 6.07 (s, 2H), 5.60 – 5.49 (m, 1H), 4.52 (d, *J* = 15.2 Hz, 1H), 4.33 (d, *J* = 15.2 Hz, 1H), 3.98 (s, 3H), 3.03 (s, 3H), 1.66 (d, *J* = 6.2 Hz, 3H). LCMS ES *m/z* 399 $[M+H]^+$.

Preparation of (10R)-7-amino-3-ethyl-12-fluoro-10,16-dimethyl-16,17-dihydro-8,4-(metheno)[1,2]thiazolo[4,5-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 112)



202 305 569

Example 112

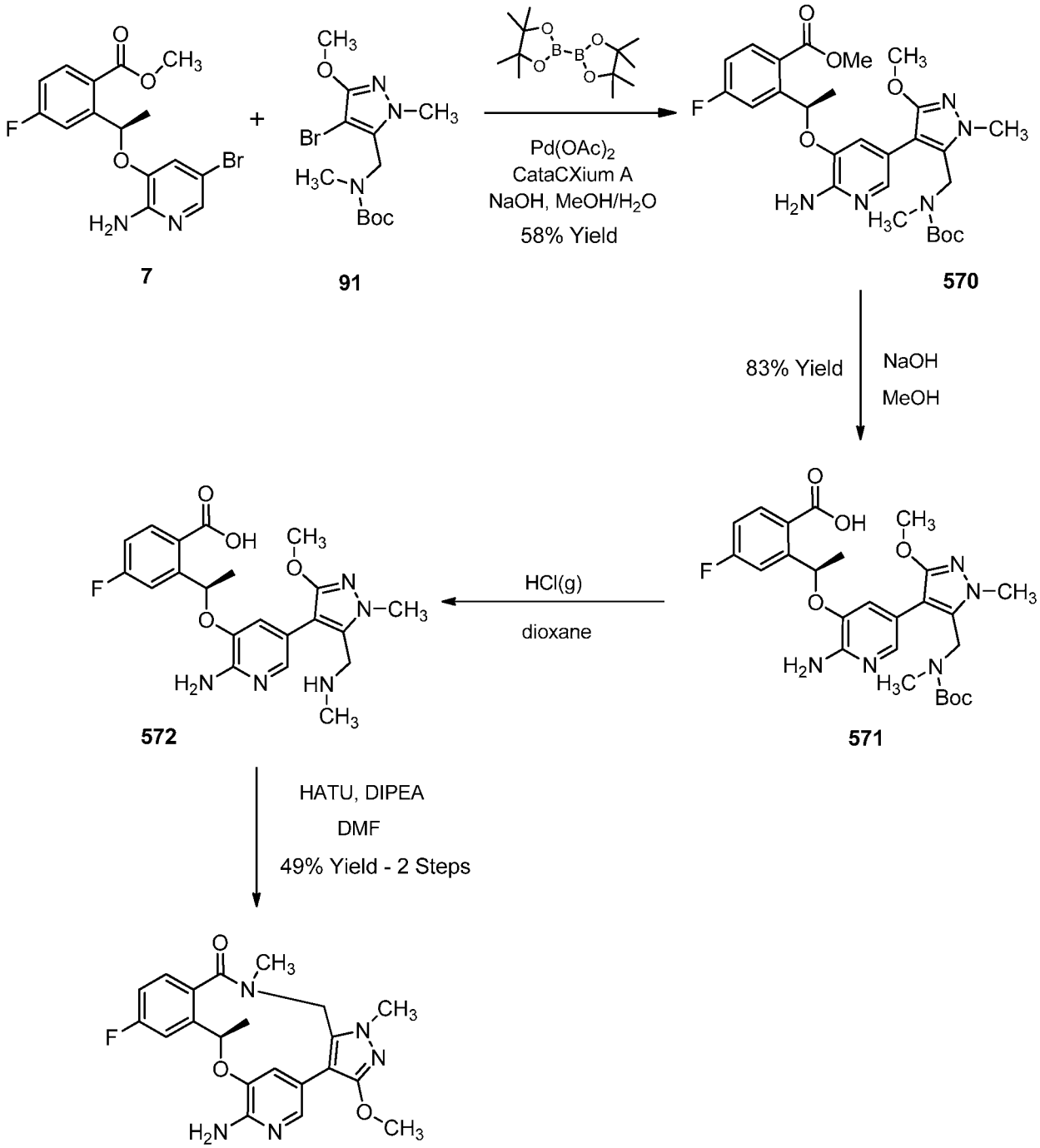
Step 1:

The procedure described in step 1 for **Example 100** was used to prepare **compound 569** (0.4 g, 58%) as a yellow solid. LCMS ES *m/z* 493 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 100** was used to prepare **Example 112** (12.5 mg, 7%) as a white solid. ^{1}NMR (400 MHz, Methanol-d_4) δ 7.60-7.57 (m, 1H), 7.46 (s, 1H), 7.39-7.36 (m, 1H), 7.1-7.09 (d, 1H), 7.02-7.01 (d, 1H), 5.85-5.84 (d, 1H), 4.73-4.52 (m, 2H), 3.22 (s, 3H), 2.91-2.87 (d, 2H), 1.82-1.81 (d, 3H), 1.29-1.26 (t, 3H). LCMS ES *m/z* 413 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-3-methoxy-1,10,16-trimethyl-16,17-dihydro-1H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 113)



Example 113

Step 1:

The procedure described in step 1 for **Example 86** and **Example 87** was used to prepare **compound 570** (1.4 g, 58%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.95 (dd, 1H), 7.48 (s, 1H), 7.21-7.18 (dd, 1H), 6.94-6.89 (m, 1H), 6.53-6.52 (d, 1H), 6.31-6.26 (dd, 1H), 4.73 (s, 2H), 3.87-3.83 (t, 3H), 3.70 (s, 3H), 3.59 (s, 3H), 2.27 (s, 3H), 1.61-1.57 (t, 3H), 1.39 (s, 9H).

Step 2:

The procedure described in step 2 for **Example 86** and **Example 87** was used to prepare **compound 571** (1.0 g, 83%) as a yellow solid. LCMS ES *m/z* 530 $[M+H]^+$.

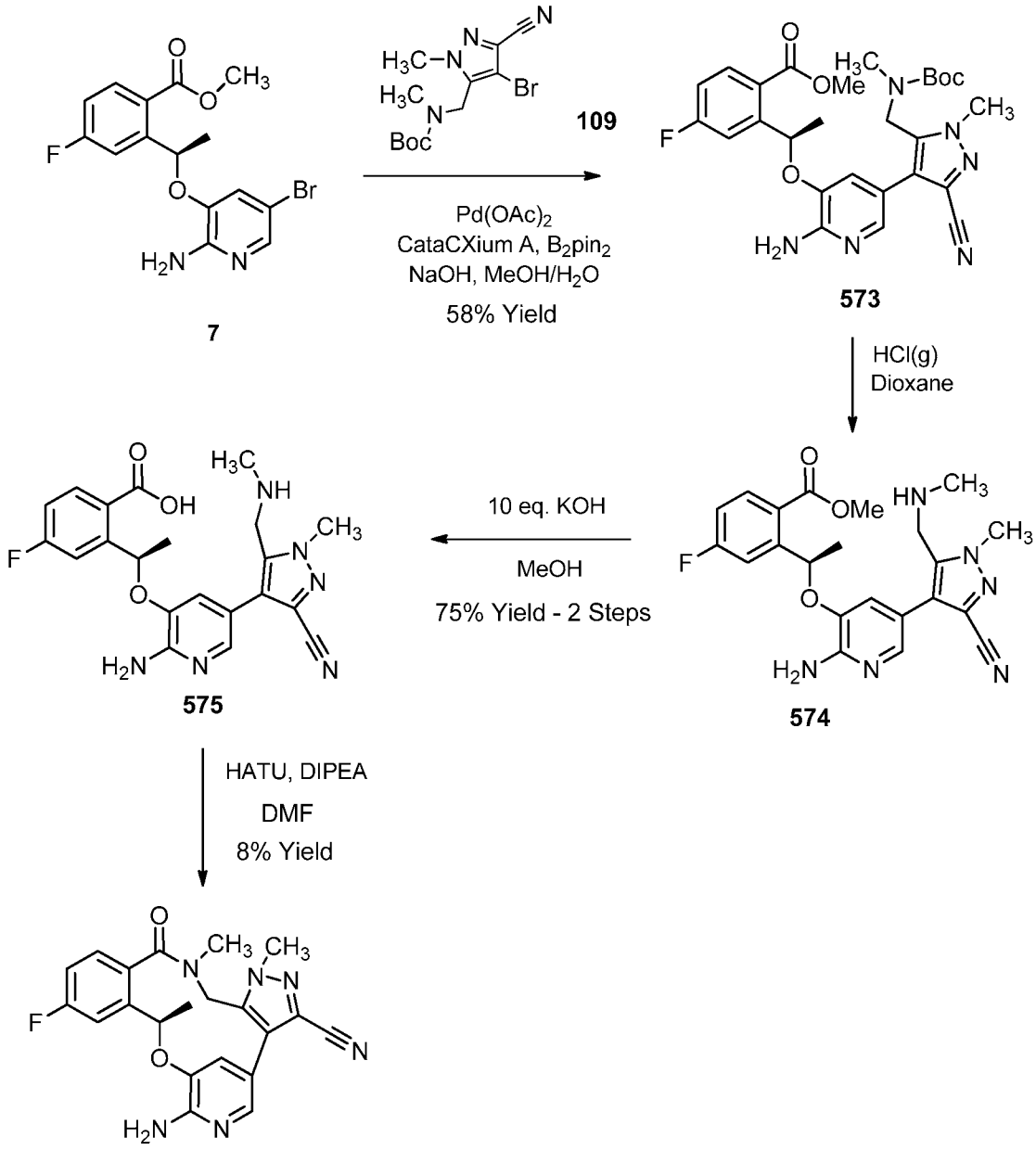
Step 3:

The procedure described in step 3 for **Example 86** and **Example 87** was used to prepare **compound 572**, which was used in the next step directly. LCMS *m/z* 430 $[M+H]^+$.

Step 4:

The procedure described in step 4 for **Example 86** and **Example 87** was used to prepare **Example 113** as an off-white solid (380 mg, 49%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, 1H), 7.25-7.22 (m, 1H), 7.14-7.12 (m, 1H), 6.94-6.92 (d, 1H), 6.74-6.73 (d, 1H), 5.61-5.57 (m, 1H), 4.64 (s, 2H), 4.42-4.21 (dd, 2H), 3.87-3.84 (d, 3H),3.80-3.67 (s, 3H), 3.09 (s, 3H), 1.70-1.69 (d, 3H). LCMS ES *m/z* 412 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-1,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-1H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 114)



Example 114

Step 1:

The procedure described in step 1 for **Example 88** was used to prepare **compound 573** (600 mg, 58%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-7.99 (m, 1H), 7.57-7.56 (d, 1H), 7.24 (s, 1H), 7.03-6.97 (m, 1H), 6.63-6.62 (d, 1H), 6.42-6.40 (m, 1H), 5.01 (s, 2H), 4.54-4.31 (m, 2H), 3.99-3.95 (d, 3H), 3.94-3.86 (m, 3H), 2.307 (s, 3H), 1.69-1.64 (d, 3H), 1.29 (s, 9H)

Step 2:

The procedure described in step 2 for **Example 88** was used to prepare **compound 574**, which was used for next step without any further purification. LCMS *m/z* 439 $[M+H]^+$.

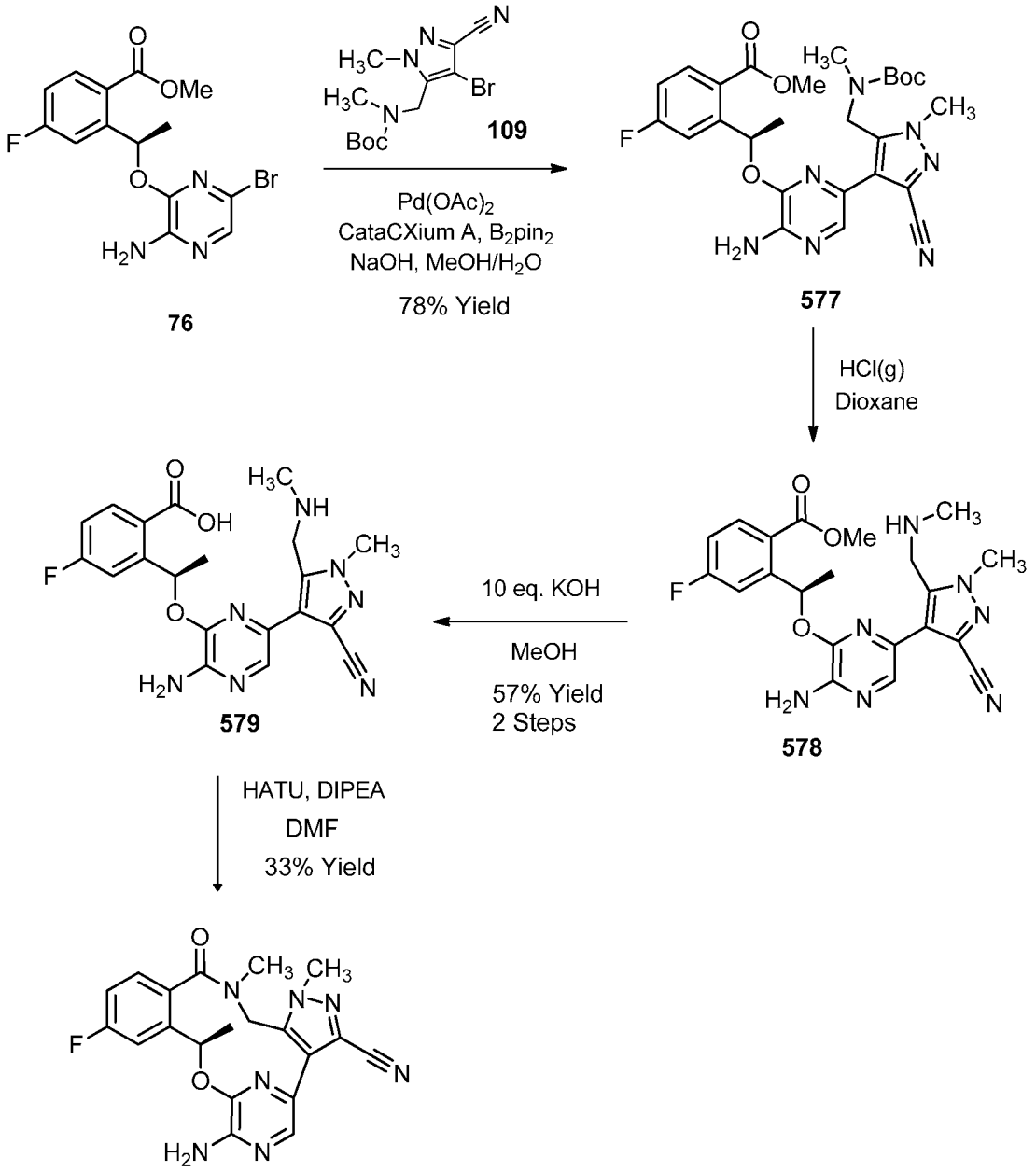
Step 3:

The procedure described in step 3 for **Example 88** was used to prepare **compound 575** (320 mg, 75%) as a brown solid. LCMS *m/z* 425 $[M+H]^+$.

Step 4:

The procedure described in step 4 for **Example 88** was used to prepare **Example 114** (24.1mg, 8%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.33-7.30 (d, 1H), 7.26-7024 (m, 1H), 7.19-7.18 (m, 1H), 7.02-7.00 (m, 1H), 5.71-5.70 (m, 1H), 4.84 (s, 2H), 4.59-4.37 (m, 2H), 4.10 (s, 3H), 3.16 (s, 3H), 1.79-1.64 (d, 3H). LCMS *m/z* 407 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-1,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-1H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 115)



Example 115

Step 1:

The procedure described in step 1 for **Example 88** and was used to prepare **compound 577** (400 mg, 78%) as a brown solid. LCMS *m/z* 562 $[M+Na]^+$.

Step 2:

The procedure described in step 2 for **Example 88** and was used to prepare **compound 578**, which was used for next step without any further purification. LCMS *m/z* 440 $[M+H]^+$.

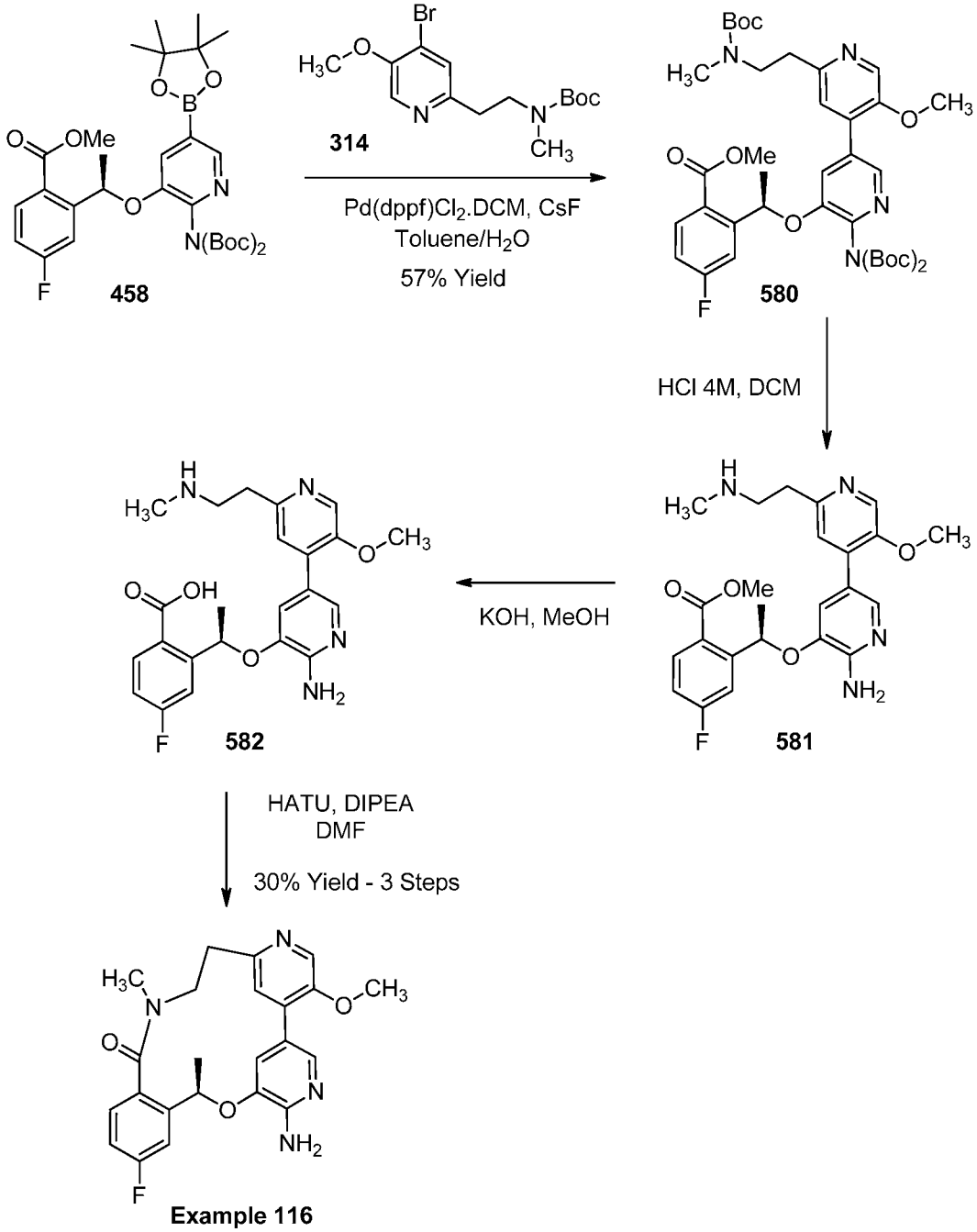
Step 3:

The procedure described in step 3 for **Example 88** and was used to prepare **compound 579** (300 mg, 65% of purity, 57%) as a brown solid. LCMS *m/z* 426 $[M+H]^+$.

Step 4:

The procedure described in step 4 for **Example 88** and was used to prepare **Example 115** (61.5 mg, 33%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.30-7.22 (m, 1H), 7.21-7.19 (m, 1H), 7.02-6.97 (m, 1H), 6.01-5.98 (m, 1H), 5.02 (s, 2H), 4.76-4.24 (dd, 2H), 4.08 (s, 3H), 3.02 (s, 3H), 1.76-1.74 (d, 3H). LCMS ES *m/z* 408 $[M+H]^+$.

Preparation of (1R)-4-amino-19-fluoro-9-methoxy-1,15-dimethyl-14,15-dihydro-1H-3,7:8,12-di(metheno)-2,5,11,15-benzoxatriazacyclooctadecin-16(13H)-one (Example 116)



Step 1:

Compound 458 (475 mg, 0.77 mmol), **compound 314** (280 mg, 0.81 mmol) and CsF (351 mg, 2.3 mmol) were dissolved in a mixture of toluene/H2O (6.6 mL, 10:1). The solution was heated at 60 °C and degassed (3 cycles N_2/vacuum). $Pd(dppf)Cl_2.CH_2Cl_2$ (69 mg, 0.08 mmol) was added, the mixture was degassed (3 cycles N_2/vacuum) and heated at 100 °C for 18 hours. The mixture was cooled to room temperature then filtered through a pad of silica then rinsed with EtOAc (~100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under vacuum to give a brown oil, which was purified by column chromatography over silica gel (eluent heptanes/EtOAc from 1:1 to 0:1). **Compound 580** was obtained as orange solid foam (870 mg, 57% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 1H), 8.17 (d, *J* = 6.8 Hz, 1H), 8.05 (dd, *J* = 8.8, 5.7 Hz, 1H), 7.46 -7.16 (m, 5H), 6.35 (d, *J* = 6.3 Hz, 1H), 3.87 (d, *J* = 1.1 Hz, 3H), 3.69 (s, 3H), 3.47 (q, *J* = 6.4 Hz, 2H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.76 (s, 2H), 1.57 (d, *J* = 6.2 Hz, 3H), 1.43 (s, 16H), 1.34-0.92 (m, 10H). LCMS ES *m/z* 755 $[M+H]^+$.

Step 2:

Compound 580 (876 mg, 1.16 mmol) was dissolved in DCM (6 mL) and the solution was cooled to 0 °C. HCl 4 M in dioxane (5.8 mL) was added drop wise. The mixture was stirred at room temperature for 18 hours then concentrated under vacuum. The HCl salt of **compound 581** was obtained as a white solid (713 mg, 100% purity by LC-MS) and was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48-8.90 (m, 2H), 8.38 (d, *J* = 37.4 Hz, 3H), 7.98-7.76 (m, 2H), 7.60 (s, 1H), 7.48 (dd, *J* = 10.2, 2.6 Hz, 1H), 7.32 (d, *J* = 1.5 Hz, 1H), 7.18 (td, *J* = 8.4, 2.6 Hz, 1H), 6.30 (q, *J* = 6.2 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.17 (d, *J* = 6.3 Hz, 4H), 2.41 (t, *J* = 5.2 Hz, 3H), 1.52 (d, *J* = 6.1 Hz, 3H). LCMS ES *m/z* 455 $[M+H]^+$.

Step 3:

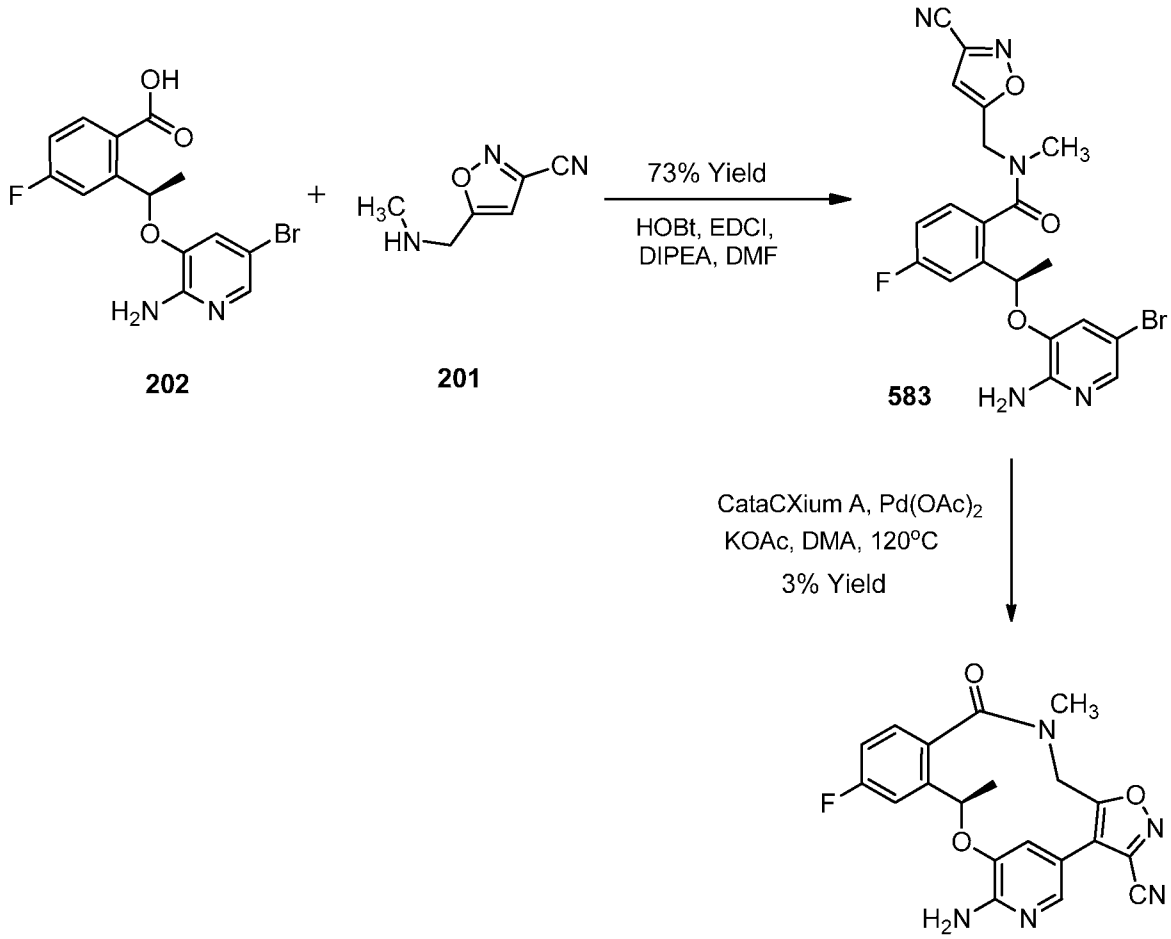
Compound 581 (713 mg, 1.16 mmol) and KOH (520 mg, 9.3 mmol) were dissolved in MeOH (12.3 mL) using ultrasound. The solution was heated at 50 °C for 5 hours, 40 °C for 18 hours then 60 °C for 2 hours. The mixture was cooled at 0 °C then acidified carefully using conc. HCl until pH 4 (formation of white solids). The suspension was filtered. Mother liquors were concentrated under vacuum to give a beige solid which was suspended in MeOH (5 mL). The solids were filtered. The mother liquors were concentrated under vacuum to give the hydrochloride salt of the **compound 582** as pale brown solids (640 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 2H), 8.49 (d, *J* = 22.0 Hz, 4H), 8.05 (dd, *J* = 8.8, 5.9 Hz, 1H), 7.97 (d, *J* = 1.7 Hz, 1H), 7.75-7.50 (m, 2H), 7.45 (d, *J* = 1.7 Hz, 1H), 7.29 (td, *J* = 8.4, 2.7 Hz, 1H), 6.58 (q, *J*

= 6.2 Hz, 1H), 3.79 (s, 3H), 3.36-3.19 (m, 4H), 2.56 (t, *J* = 5.2 Hz, 3H), 1.67 (d, *J* = 6.1 Hz, 3H). LCMS ES *m/z* 441 $[M+H]^+$.

Step 4:

To a cooled solution of HATU (390 mg, 1.0 mmol) in DMF (12 mL) at 0 °C was added dropwise a solution of **compound 582** (450 mg, 0.82 mmol) and DIPEA (0.68 mL, 4.1 mmol) in DMF (21 mL) over 1 hour. 10 min after the end of the addition, H_2O (300 mL) was added and the mixture was extracted with EtOAc (6 x 50 mL). The organic phases were combined, dried over $MgSO_4$ and purified DIRECTLY without being concentrated by SCX-2 column (10 g, eluents: EtOAc (from the work-up) then MeOH the MeOH/NH_3). Fractions obtained by elution with MeOH/NH_3 were combined, concentrated under vacuum and purified by column chromatography over silica gel (eluents DCM/MeOH from 95:5 to 90:10) to give **Example 116** as pale yellow solids (146 mg, 42% yield, 90% purity by ^1H NMR). This sample was slurried in water (2 mL), filtered, slurried with TBME (3 mL) then dried. **Example 116** was obtained as a pale yellow powder (106 mg, 30% yield over final three steps). ^1H NMR (400 MHz, Methanol-d_4) δ 8.63 (s, 1H), 8.53 (s, 1H), 8.33 (d, *J* = 1.6 Hz, 1H), 8.17 (s, 1H), 7.34 (dd, *J* = 9.6, 2.6 Hz, 1H), 6.96 (t, *J* = 6.8 Hz, 1H), 6.81 (dt, *J* = 8.9, 4.5 Hz, 1H), 5.66 (q, *J* = 6.4 Hz, 1H), 4.47 (t, *J* = 10.6 Hz, 1H), 4.09 (s, 3H), 3.93 – 3.65 (m, 2H), 2.84 (s, 3H), 1.65 (d, *J* = 6.4 Hz, 3H). LCMS ES *m/z* 423 $[M+H]^+$.

Preparation of (10R)-7-amino-12-fluoro-10,16-dimethyl-15-oxo-10,15,16,17-tetrahydro-8,4-(metheno)[1,2]oxazolo[4,5-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 117)



Example 117

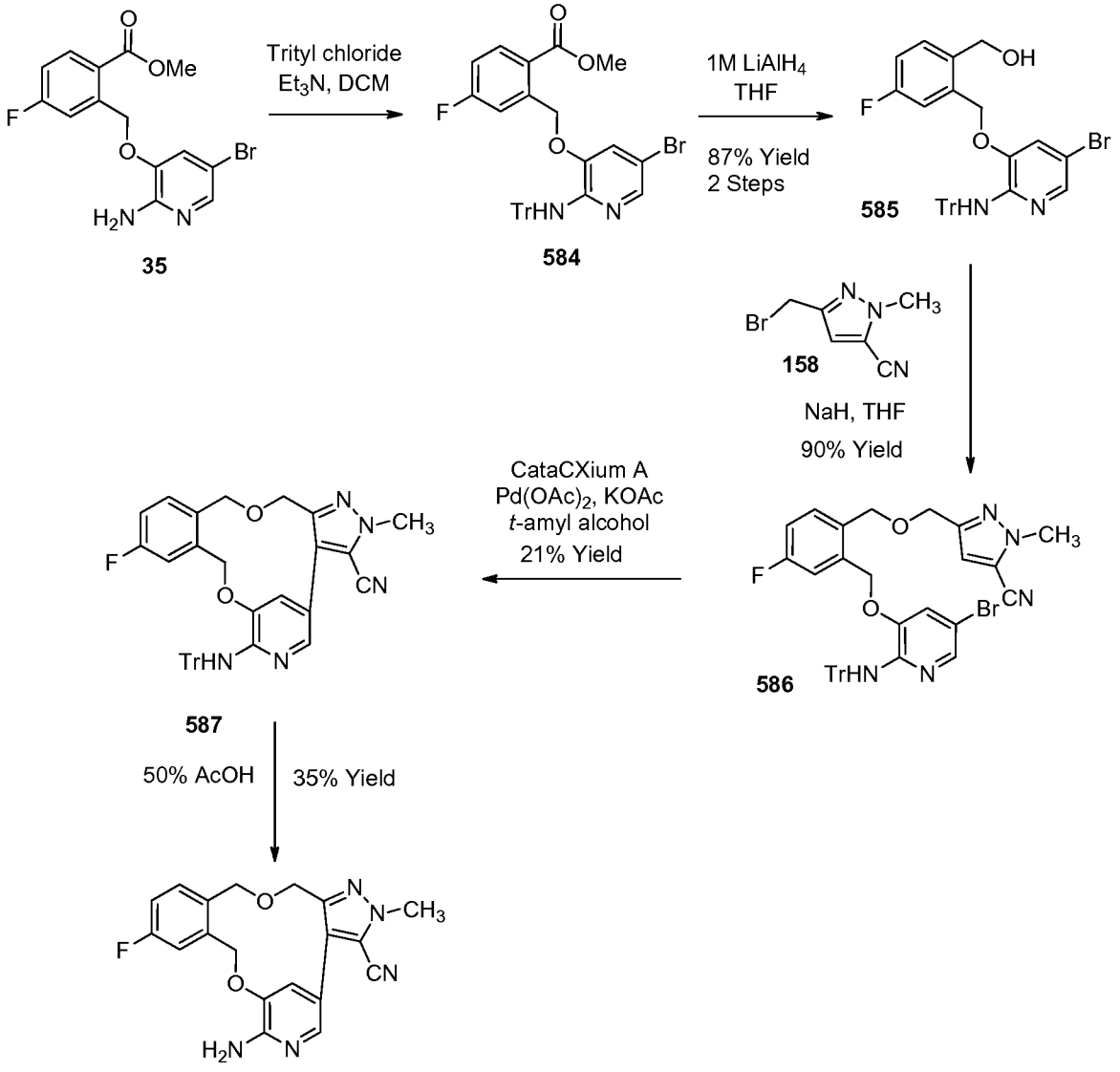
Step 1:

The procedure described in step 3 for **Example 99** was used to prepare **compound 583** (400 mg, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.68 (s, 1H), 7.22-7.20 (m, 2H), 7.08-7.03 (m, 1H), 6.92 (s, 1H), 6.55-6.52 (s, 1H), 5.47-5.42 (m, 1H), 4.98-4.86 (dd, 2H), 4.75 (s, 2H), 2.88 (s, 3H) δ 1.66-1.64 (d, 3H)

Step 2:

The procedure described in step 3 for **Example 99** was used to prepare **Example 117** (4.2 mg, 3%) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.79 (s, 1H), 7.56--7.59 (d, 1H), 7.39-7.49 (d, 1H), 7.12-7.21 (m, 1H), 6.89 (s, 1H), 5.79-5.71 (s, 1H), 4.7-4.65 (dd, 2H), 3.21 (s, 3H), 1.72 (s, 3H). LCMS m/z 394 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-2-methyl-2,10,15,17-tetrahydro-8,4-(metheno)pyrazolo-[4,3-h][2,11,5]benzodioxazacyclotetradecine-3-carbonitrile (Example 118)



Example 118

Step 1:

The procedure described in step 1 for **Example 104** was used to prepare **compound 584** as an off off-white crystalline solid (5.23 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.8, 5.8 Hz, 1H), 7.43 (dd, *J* = 2.0, 0.9 Hz, 1H), 7.39 – 7.17 (m, 16H), 7.08 (ddd, *J* = 8.7, 7.6, 2.7 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.36 (s, 1H), 5.53 (s, 2H), 3.90 (s, 3H). LCMS ES *m/z* 597/599 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 104** was used to prepare **compound 585** as an off-white crystalline solid (3.86 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 2.0 Hz, 1H), 7.36 (dd, *J* = 8.5, 5.6 Hz, 1H), 7.34 – 7.14 (m, 17H), 7.07 – 6.99 (m, 2H), 6.33 (s, 1H), 5.21 (s, 2H), 4.70 (d, *J* = 5.6 Hz, 2H). LCMS ES *m/z* 569/571 $[M+H]^+$.

Step 3:

The procedure described in step 3 for **Example 104** was used to prepare **compound 586** as a colourless foam (1.23 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 2.0, 0.9 Hz, 1H), 7.37 – 7.15 (m, 17H), 7.04 – 6.97 (m, 2H), 6.32 (s, 1H), 5.20 (s, 2H), 4.59 (s, 2H), 4.49 (s, 2H), 3.99 (s, 3H). LCMS ES *m/z* 766/768/770 $[M+H]^+$.

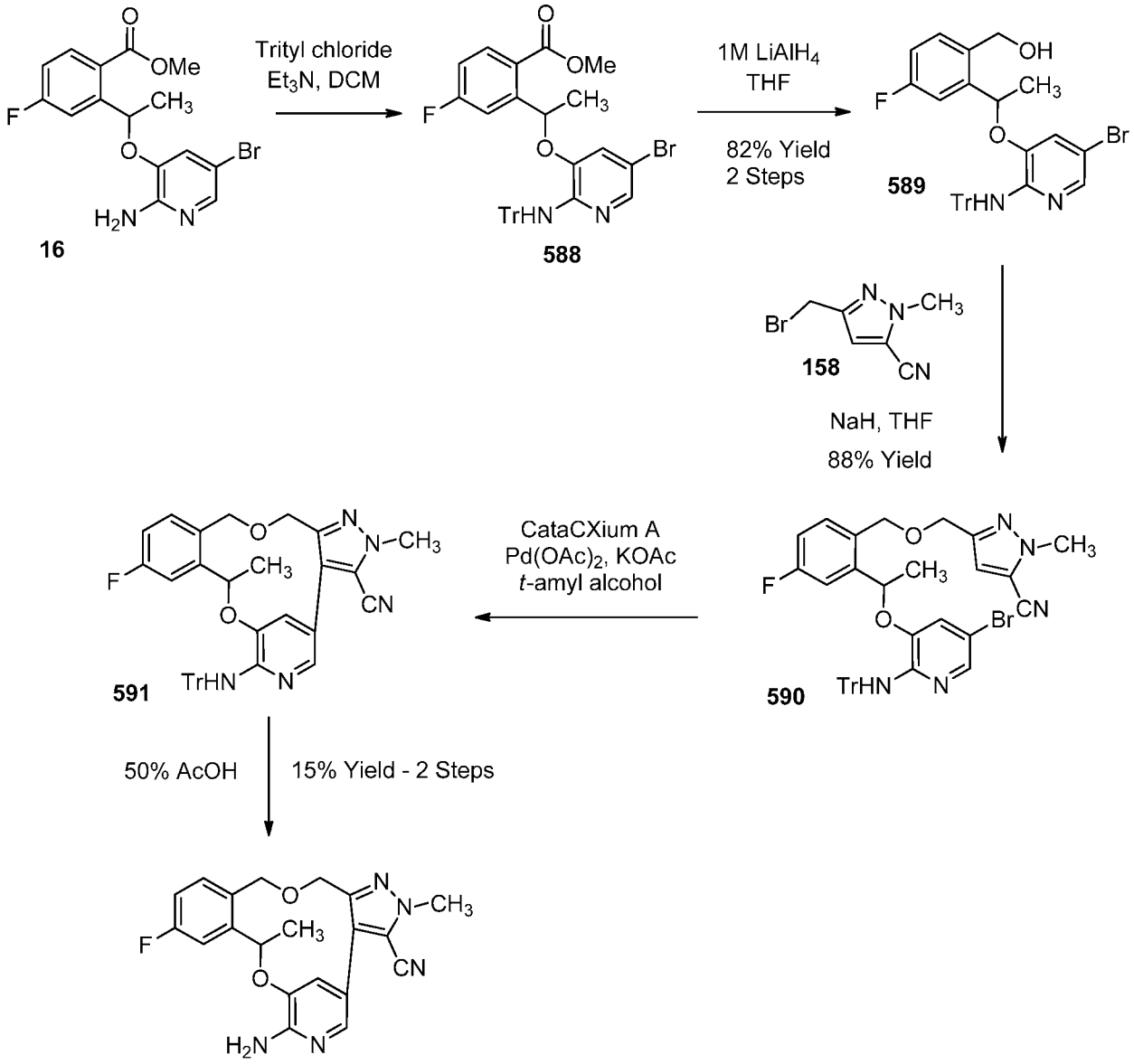
Step 4:

The procedure described in step 4 for **Example 104** was used to prepare **compound 587** (206 mg, 21%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 1.9 Hz, 1H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.42 – 7.12 (m, 17H), 6.97 (td, *J* = 8.1, 2.7 Hz, 1H), 6.32 (s, 1H), 5.60 (d, *J* = 13.2 Hz, 1H), 5.34 – 5.16 (m, 2H), 4.46 (d, *J* = 13.2 Hz, 1H), 4.29 (d, *J* = 10.0 Hz, 1H), 4.03 (dd, *J* = 12.8, 4.0 Hz, 1H), 3.95 (s, 3H). LCMS ES *m/z* 608 $[M+H]^+$

Step 5:

The procedure described in step 5 for **Example 104** was used to prepare **Example 118** as a colorless solid (43 mg, 35%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.60 (d, *J* = 1.8 Hz, 1H), 7.80 (d, *J* = 1.9 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.05 (td, *J* = 8.4, 2.8 Hz, 1H), 5.70 (d, *J* = 13.6 Hz, 1H), 5.61 (s, 2H), 5.37 (d, *J* = 12.1 Hz, 1H), 5.28 (d, *J* = 13.1 Hz, 1H), 4.58 (d, *J* = 12.3 Hz, 1H), 4.46 (d, *J* = 10.6 Hz, 1H), 4.12 (d, *J* = 10.5 Hz, 1H), 4.03 (s, 3H). LCMS ES *m/z* 366 $[M+H]^+$.

Preparation of 7-amino-3-tert-butyl-1,10,16-trimethyl-16,17-dihydro-1H-8,4-(metheno)-pyrazolo[4,3-g]pyrido[2,3-l][1,4,10]oxadiazacyclotetradecin-15(10H)-one (Example 119 and 120)



Example 119 and Example 120

Step 1:

The procedure described in step 1 for **Example 104** was used to prepare **compound 588** as a beige solid (5.82 g, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.8, 5.8 Hz, 1H), 7.39 – 7.18 (m, 17H), 7.03 (ddd, *J* = 8.7, 7.6, 2.7 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.38 (s, 1H), 6.35 (q, *J* = 6.4 Hz, 1H), 3.94 (s, 3H), 1.65 (d, *J* = 6.2 Hz, 3H). LCMS ES *m/z* 611/613 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 104** was used to prepare **compound 589** as a colurless solid, in two batches of slightly different purities (5.43 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.16 (m, 17H), 7.13 (dd, *J* = 9.8, 2.7 Hz, 1H), 6.96 (td, *J* = 8.2, 2.7 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.37 (s, 1H), 5.70 (q, *J* = 6.3 Hz, 1H), 4.79 (dd, *J* = 12.3, 6.1 Hz, 1H), 4.70

(dd, *J* = 12.3, 5.6 Hz, 1H), 1.75 – 1.69 (m, 1H), 1.66 (d, *J* = 6.3 Hz, 3H). LCMS ES *m/z* 583/585 $[M+H]^+$.

Step 3:

The procedure described in step 3 for **Example 104** was used to prepare **compound 590** as a colourless solid (5.88 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.17 (m, 17H), 7.11 (dd, *J* = 9.7, 2.7 Hz, 1H), 6.95 (td, *J* = 8.2, 2.7 Hz, 1H), 6.85 (d, *J* = 2.0 Hz, 1H), 6.37 (s, 1H), 5.67 (q, *J* = 6.3 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.60 (d, *J* = 12.1 Hz, 1H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.01 (s, 3H), 1.62 (d, *J* = 6.3 Hz, 3H). LCMS ES *m/z* 778/780/781 $[M+H]^+$.

Step 4:

The procedure described in step 4 for **Example 104** was used to prepare **compound 591** (1.19 g), which was used without any further purification. LCMS ES *m/z* 622 $[M+H]^+$.

Step 5:

The procedure described in step 5 for **Example 104** was used to prepare a mixture of **Example 119** and **Example 120** as a colorless solid (185 mg, 15% yield over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, *J* = 1.9 Hz, 1H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.55 (dd, *J* = 10.5, 2.8 Hz, 1H), 7.38 (dd, *J* = 8.5, 6.0 Hz, 1H), 7.08 (td, *J* = 8.4, 2.8 Hz, 1H), 6.17 (s, 2H), 6.02 – 5.92 (m, 1H), 5.24 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 10.7 Hz, 1H), 3.97 (s, 3H), 3.92 (d, *J* = 10.7 Hz, 1H), 1.64 (d, *J* = 6.2 Hz, 3H). LCMS ES *m/z* 380 $[M+H]^+$.

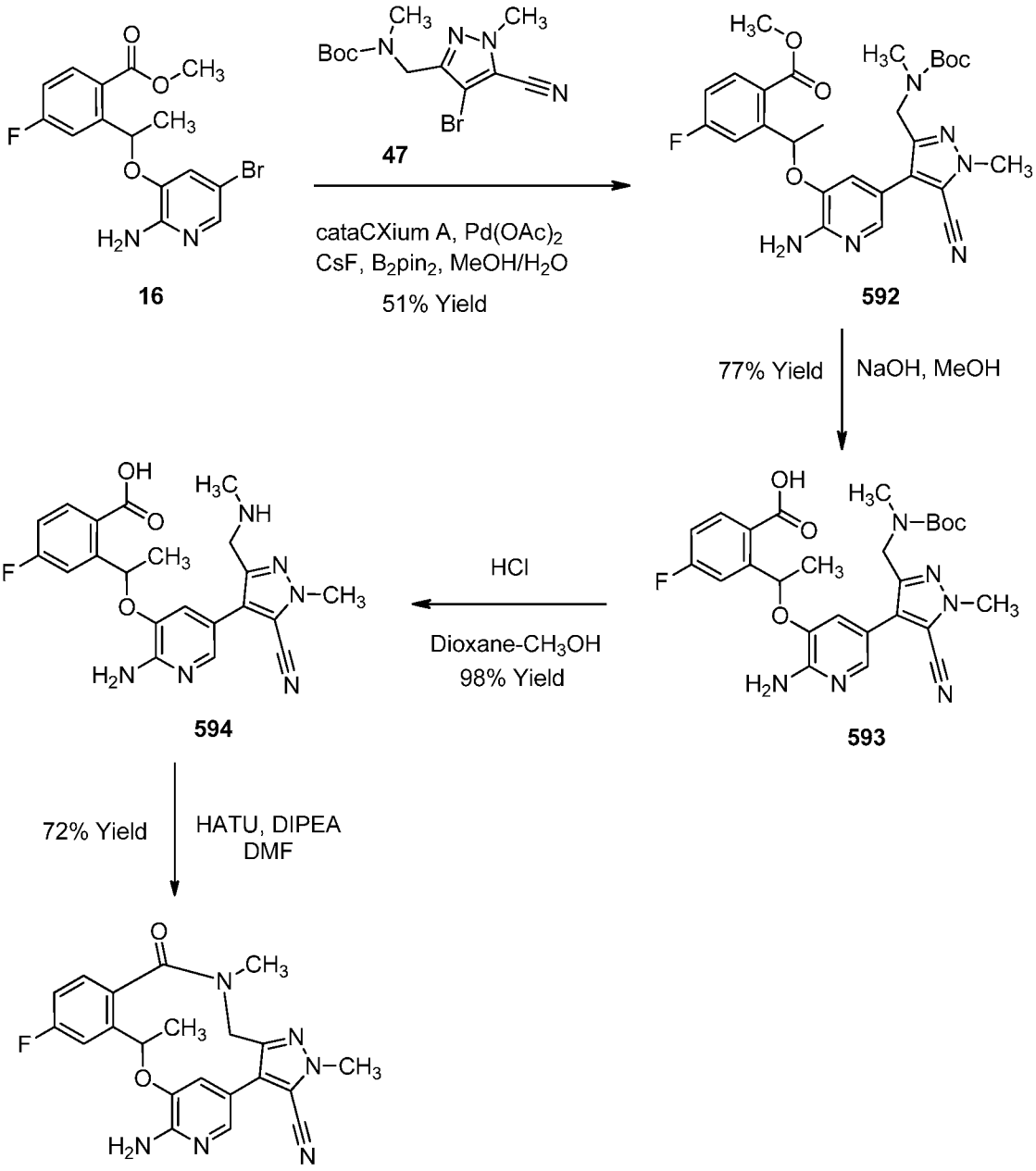
The chiral separation of 146mg of the material was performed by preparative SFC on a Whelk-O1 (R,R) (250 x 4.6 mm I.D., 3 micron particle size) column, which was eluted with 20% methanol @ 140 bar CO_2 with a flow rate of 3 mL/min. $Rt_{(Peak\ 1)}$ = 4.51 minutes and $Rt_{(Peak\ 2)}$ = 6.00 minutes, and gave Peak 1 as a white solid (58 mg) and Peak 2 as a white solid (57 mg). The solids resulting from both peaks were slurried in water, and dried overnight in the vacuum oven.

Example 119 (Peak 1): > 99% ee (47 mg). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.63 (s, 1 H) 8.35 (s, 1 H) 7.55 (dd, *J* = 10.39, 2.57 Hz, 1 H) 7.38 (dt, *J* = 2.20 Hz, 1 H) 7.07 (dt, *J* = 2.60 Hz, 1 H) 6.15 (s, 2 H) 5.91 - 6.01 (m, 1 H) 5.24 (d, *J* = 12.10 Hz, 1 H) 4.47 (dd, *J* = 13.63, 11.68 Hz, 2 H) 3.89 - 4.02 (m, 4 H) 1.65 (d, *J*=6.11 Hz, 3 H).

LCMS APCI *m/z* 380 $[M+H]^+$.

Example 120 (Peak 2): ~ 98% ee (45 mg). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.34 (d, *J* = 1.52 Hz, 1 H) 7.63 (d, *J* = 1.52Hz, 1 H) 7.55 (dd, *J* = 10.48, 2.65 Hz, 1 H) 7.38 (dd, *J* = 8.59, 6.06 Hz, 1 H) 7.07 (dt, *J* = 2.50 Hz, 1 H) 6.15 (s, 2 H) 5.97 (m, *J* = 5.80 Hz, 1 H) 5.24 (d, *J* = 11.87 Hz, 1 H) 4.47 (dd, *J* = 14.02, 11.49 Hz, 2 H) 3.85 - 4.03 (m, 4 H) 1.65 (d, *J* = 6.06 Hz, 3 H). LCMS APCI *m/z* 380 $[M+H]^+$.

Preparation of (10S)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 121)



Example 2 and Example 121

Step 1:

The procedure described in step 1 for **Example 2** was used to prepare **compound 592** (800 mg, 51%) as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (m, 1H), 7.58 (s, 1H), 7.23 (m, 1H), 7.03 (ddd, *J* = 8.7, 7.6, 2.7 Hz, 1H), 6.88 (m, 1H), 6.50 (m, 1H), 6.0 (m, 1H), 5.48 (m, 1H),

4.05-4.65 (m, 2H), 3.98 (s, 3H), 3.94 (s, 3H), 2.60-2.80 (m, 4H), 1.70 (d, *J* = 6.2 Hz, 3H), 1.25-1.45 (m, 9H). LCMS ES m/z 539 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 2** was used to prepare **compound 593** (1060 mg, 77% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.36 (s, 1H), 7.94 (t, *J* = 6.9 Hz, 1H), 7.61 – 7.43 (m, 2H), 7.01-7.25 (m, 2H), 6.75 -7.0(m, 2H), 6.47 (m, 1H), 4.59 – 4.03 (m, 2H), 3.96 (s, 3H), 2.79 – 2.51 (m, 2H), 1.62 (d, *J* = 6.2 Hz, 3H), 1.34 – 1.01 (m, 9H). LCMS ES m/z 525 $[M+H]^+$.

Step 3:

The procedure described in step 3 for **Example 2** was used to prepare **compound 594** (910 mg, 98%) as the hydrochloride salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.38 (s, 1H), 9.36 – 9.16 (m, 2H), 7.98 (dd, *J* = 8.8, 6.0 Hz, 1H), 7.80 (d, *J* = 1.7 Hz, 1H), 7.58 (dd, *J* = 10.3, 2.7 Hz, 1H), 7.26 (ddd, *J* = 12.5, 6.6, 3.3 Hz, 2H), 7.20 – 7.07 (m, 2H), 6.54 (q, *J* = 6.2 Hz, 1H), 4.24 – 4.07 (m, 2H), 4.05 (s, 3H), 2.18 (d, *J* = 90.0 Hz, 2H), 1.64 (d, *J* = 6.2 Hz, 3H). LCMS ES m/z 425 $[M+H]^+$.

Step 4:

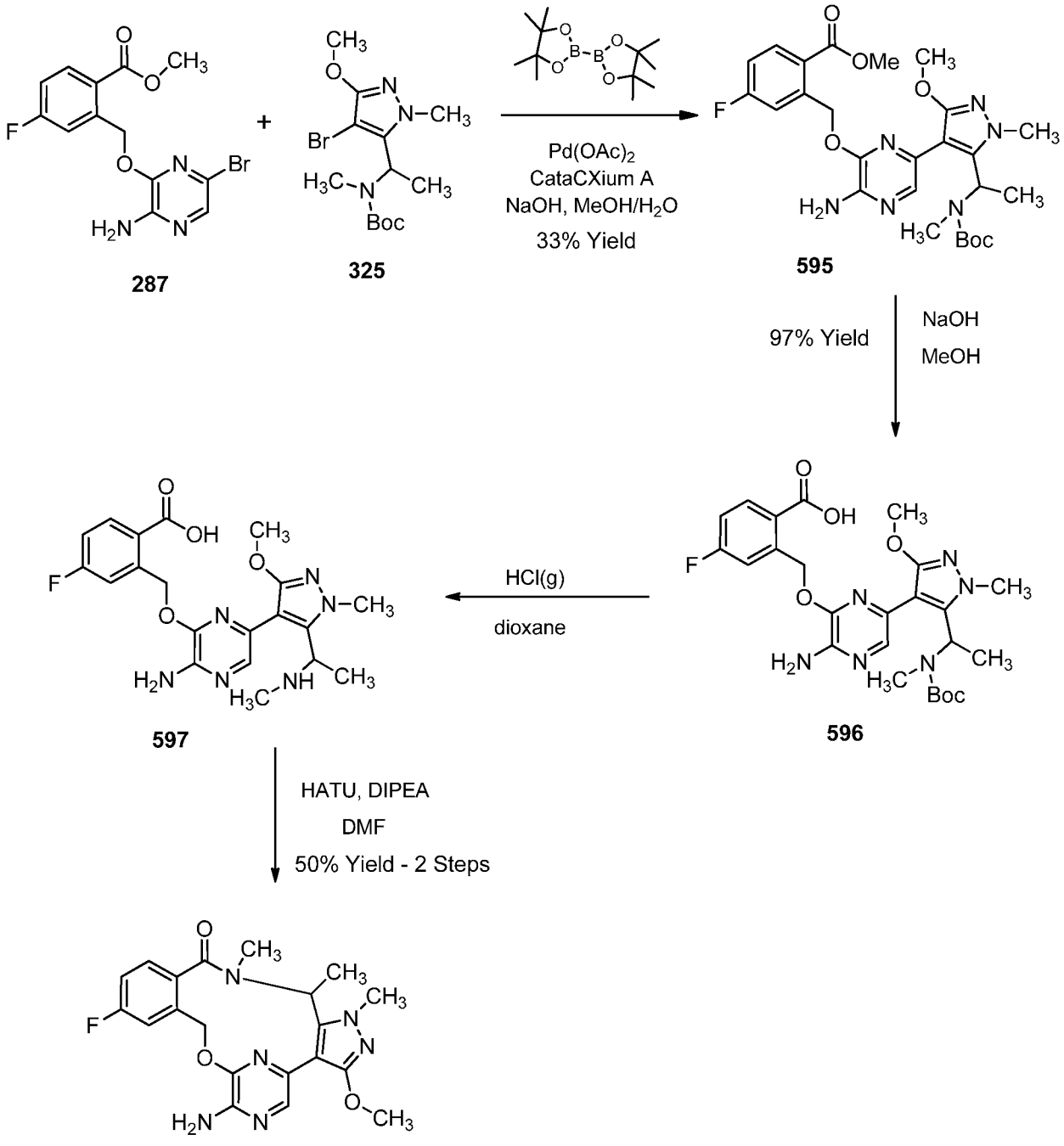
The procedure described in step 4 for **Example 2** was used to prepare a mixture of **Example 2** and **Example 121** as a white solid (570 mg, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 – 7.54 (m, 2H), 7.46 (dd, *J* = 8.6, 5.7 Hz, 1H), 7.18 (td, *J* = 8.5, 2.7 Hz, 1H), 6.81 (d, *J* = 1.9 Hz, 1H), 6.19 (d, *J* = 3.4 Hz, 1H), 5.60 (dt, *J* = 6.7, 3.4 Hz, 1H), 4.44 (d, *J* = 14.4 Hz, 1H), 4.19 (d, *J* = 14.4 Hz, 1H), 4.03 (s, 3H), 2.99 (s, 3H), 1.67 (d, *J* = 6.2 Hz, 3H). LCMS ES m/z 407 $[M+H]^+$.

The chiral separation of 570 mg of the material was performed by preparative SFC on a Whelk-O1 (R,R) (250 x 4.6 mm I.D., 3 micron particle size) column, which was eluted with 30% methanol @ 140 bar CO_2 with a flow rate of 3 mL/min. $Rt_{(Peak\ 1)}$ = 3.06 minutes and $Rt_{(Peak\ 2)}$ = 4.38 minutes, and gave Peak 1 as a white solid (263 mg) and Peak 2 as a white solid (262 mg).

Example 2 (Peak 1): > 99% ee (263 mg).

Example 121 (Peak 2): ~ 98% ee (262 mg). ^{1}H NMR (400MHz, DMSO-d6) δ= 7.63 - 7.55 (m, 2H), 7.46 (dd, *J*=5.8, 8.6 Hz, 1H), 7.17 (dt, *J*=2.8, 8.4 Hz, 1H), 6.81 (d, *J*=1.5 Hz, 1H), 6.17 (s,2H), 5.66 - 5.55 (m, 1H), 4.43 (d, *J*=14.6 Hz, 1H), 4.19 (d, *J*=14.4 Hz, 1H), 4.03 (s, 3H), 2.99 (s, 3H), 1.68 (d, *J*=6.3 Hz, 3H). LCMS APCI *m/z* 407 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-3-methoxy-1,16,17-trimethyl-16,17-dihydro-1H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 122 and 123)



Example 122 and Example 123

Step 1:

The procedure described in step 1 for **Example 86** and **Example 87** was used to prepare **compound 595** (500 mg, 33%, Rf = 0.3) as a brown solid. LCMS *m/z* 567 $[M+Na]^+$.

Step 2:

The procedure described in step 2 for **Example 86** and **Example 87** was used to prepare **compound 596** (470 mg, 97%) as a white solid. LCMS ES *m/z* 531 $[M+H]^+$.

Step 3:

The procedure described in step 3 for **Example 86** and **Example 87** was used to prepare **compound 597**, which was used in the next step directly. LCMS *m/z* 431 $[M+H]^+$.

Step 4:

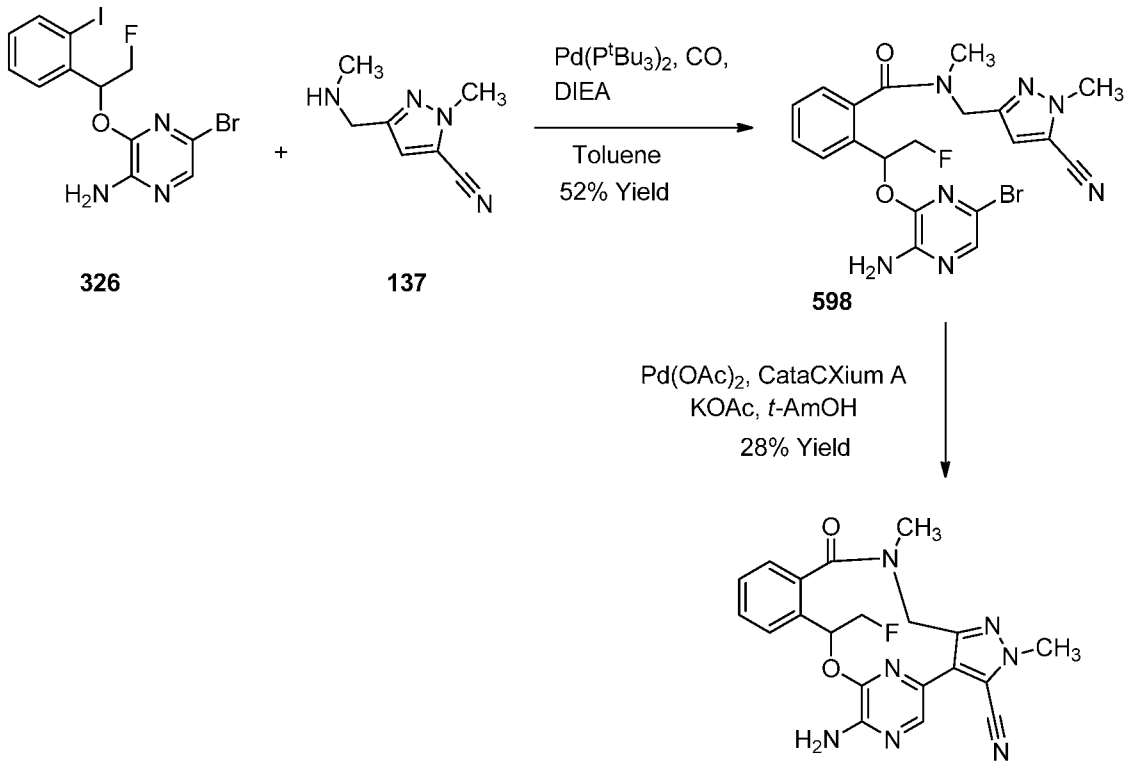
The procedure described in step 4 for **Example 86** and **Example 87** was used to prepare a mixture of **Example 122** and **Example 123** as an off-white solid (190.1 mg, 50% in two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (s, 1H), 7.50-7.44 (m, 2H), 7.20-7.19 (m, 1H), 6.34 (s, 2H), 5.54-5.51 (d, 1H), 5.03-5.00 (d, 1H), 4.81-4.79 (d, 1H), 3.97 (s, 3H), 3.85 (s, 3H), 3.01 (s, 3H), 1.67-1.65 (d, 3H). LCMS *m/z* 413 $[M+H]^+$.

The chiral separation of 70 mg of the material was performed by preparative SFC on a Chiralpak AD-H (250 x 4.6 mm I.D., 5 micron particle size) column, which was eluted with 5-40% ethanol (0.05% DEA) @ 140 bar CO_2 with a flow rate of 4 mL/min. $Rt_{(Peak\ 1)}$ = 6.93 minutes and $Rt_{(Peak\ 2)}$ = 8.52 minutes, and gave Peak 1 as a white solid (9 mg) and Peak 2 as a white solid (6 mg). Separation required two runs. Each peak on isolation equilibrated to a 90 : 10 mixture of atropisomers.

Example 122 (Peak 1): > 99% ee. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.79 (s, 1H), 7.54-7.51 (m, 2H), 7.16-7.11 (m, 1H), 5.68-5.65 (m, 1H), 5.07-5.01 (m, 2H), 4.06 (s, 3H), 3.98 (s, 3H), 3.15 (s, 3H), 1.78-1.76 (d, 3H). LCMS APCI *m/z* 413 $[M+H]^+$.

Example 123 (Peak 2): ~ 98% ee. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.79 (s, 1H), 7.54-7461 (m, 2H), 7.16-7.11 (m, 1H), 5.68-5.65 (m, 1H), 5.07-5.02 (m, 2H), 4.06 (s, 3H), 3.98 (s, 3H), 3.15 (s, 3H), 1.78-1.76 (d, 3H). LCMS APCI *m/z* 413 $[M+H]^+$.

Preparation of 7-amino-12-fluoro-3-methoxy-1,16,17-trimethyl-16,17-dihydro-1H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Examples 124, 125 and 126)



326 137 598

Example 124, Example 125 and Example 126

Step 1:

The procedure described in step 1 for **Example 90** was used to prepare **compound 598** as a white foam (117 mg, 52%). ^{1}H NMR (400 MHz, Methanol-d_4, 2 rotamers) δ 7.63 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.54 and 7.51 (2 x s, 1H), 7.50 – 7.30 (m, 3H), 6.98 and 6.79 (2 x s, 1H), 6.33 (ddd, *J* = 16.1, 7.6, 2.6 Hz) and 6.29 – 6.11 (m) (1H), 5.04 (d, *J* = 15.0 Hz, 1H), 4.94 – 4.65 (m, 2H), 4.57 (d, *J* = 15.0 Hz, 1H), 4.02 and 3.99 (2 x s, 3H), 3.17 and 3.01 (2 x s, 3H). LCMS ES *m/z* 488/490 $[M+H]^+$

Step 2:

The procedure described in step 2 for **Example 90** was used to prepare **Example 124** as a colorless solid (26 mg, 28%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.90 (s, 1H), 7.65 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.48 – 7.34 (m, 3H), 6.21 (ddd, *J* = 17.7, 8.1, 2.3 Hz, 1H), 4.96 (ddd, *J* = 48.6, 10.3, 8.2 Hz, 1H), 4.71 (ddd, *J* = 46.2, 10.3, 2.3 Hz, 1H), 4.53 (d, *J* = 13.6 Hz, 1H), 4.36 (d, J = 13.6 Hz, 1H), 4.11 (s, 3H), 2.97 (s, 3H). LCMS ES *m/z* 408 $[M+H]^+$

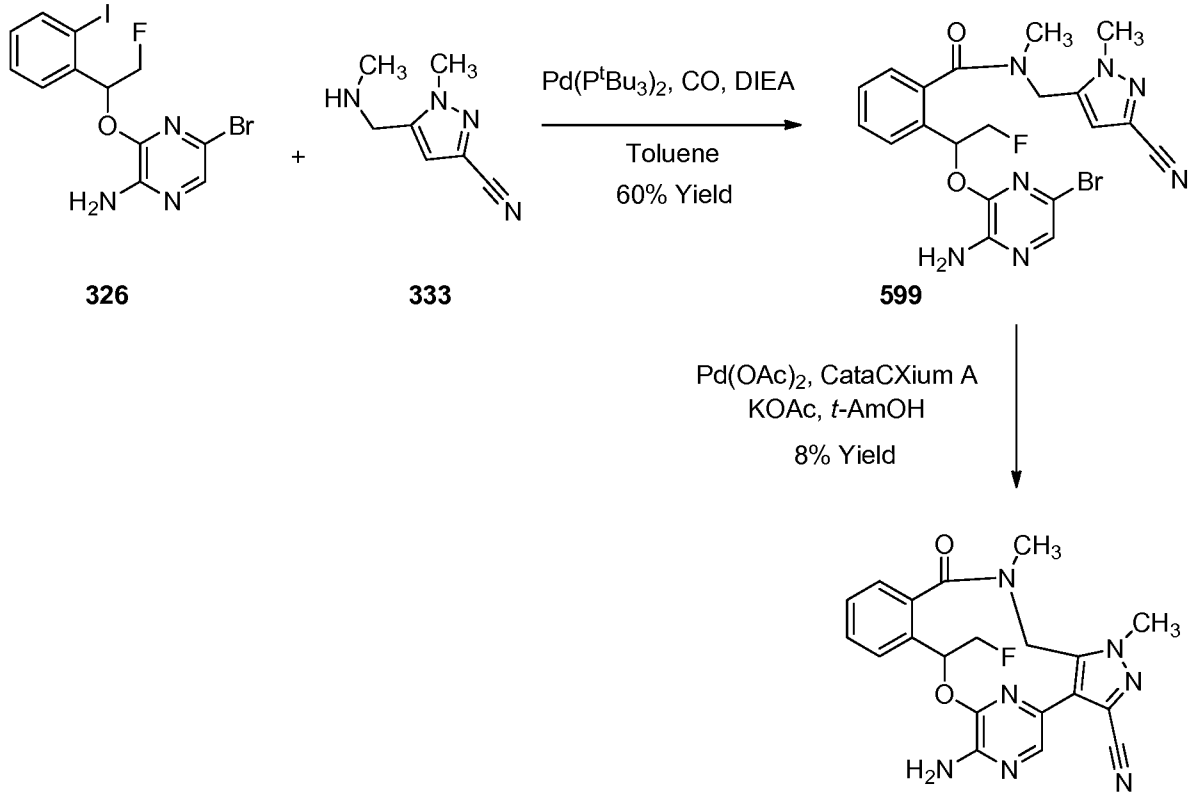
The chiral separation of 23 mg of the material was carried out by preparative SFC on a Whelk-O1 (R,R) (250 x 4.6 mm I.D., 5 micron particle size) column, which was eluted with 35% methanol @ 120 bar CO_2 with a flow rate of 62 mL/min. $Rt_{(Peak\ 1)}$ = 3.06 minutes and $Rt_{(Peak\ 2)}$ = 4.60 minutes, and gave Peak 1 as a white solid (8 mg) and Peak 2 as a white solid (8.23 mg).

Example 125 (Peak 1): > 99% ee (-). ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.90 (s, 1H), 7.65 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.48 – 7.34 (m, 3H), 6.21 (ddd, *J* = 17.7, 8.1, 2.3 Hz, 1H), 4.96 (ddd, *J* =

48.6, 10.3, 8.2 Hz, 1H), 4.71 (ddd, *J* = 46.2, 10.3, 2.3 Hz, 1H), 4.53 (d, *J* = 13.6 Hz, 1H), 4.36 (d, J = 13.6 Hz, 1H), 4.11 (s, 3H), 2.97 (s, 3H). LCMS ES *m/z* 408 $[M+H]^+$

Example 126 (Peak 2): ~ 98% ee (+). ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.90 (s, 1H), 7.65 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.48 – 7.34 (m, 3H), 6.21 (ddd, *J* = 17.7, 8.1, 2.3 Hz, 1H), 4.96 (ddd, *J* = 48.6, 10.3, 8.2 Hz, 1H), 4.71 (ddd, *J* = 46.2, 10.3, 2.3 Hz, 1H), 4.53 (d, *J* = 13.6 Hz, 1H), 4.36 (d, J = 13.6 Hz, 1H), 4.11 (s, 3H), 2.97 (s, 3H). LCMS ES *m/z* 408 $[M+H]^+$

Preparation of 7-amino-12-fluoro-3-methoxy-1,16,17-trimethyl-16,17-dihydro-1H-8,4-(azeno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 127 and Example 128)



326 **333** **599**

Example 127 and Example 128

Step 1:

The procedure described in step 1 for **Example 90** was used to prepare **compound 599** as white solid (723 mg, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 – 7.65 (m, 1H), 7.58 (s, 1H), 7.52 – 7.39 (m, 3H), 7.09 (s, 1H), 6.84 (s, 2H), 6.20 – 6.00 (m, 1H), 5.06 – 4.64 (m, 4H), 3.99 (s, 3H), 2.92 (s, 3H). LCMS *m/z* 488/490 $[M+H]^+$.

Step 2:

The procedure described in step 2 for **Example 90** was used to prepare a mixture of **Example 127 and Example 128** as pale beige solids (33 mg, 8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87

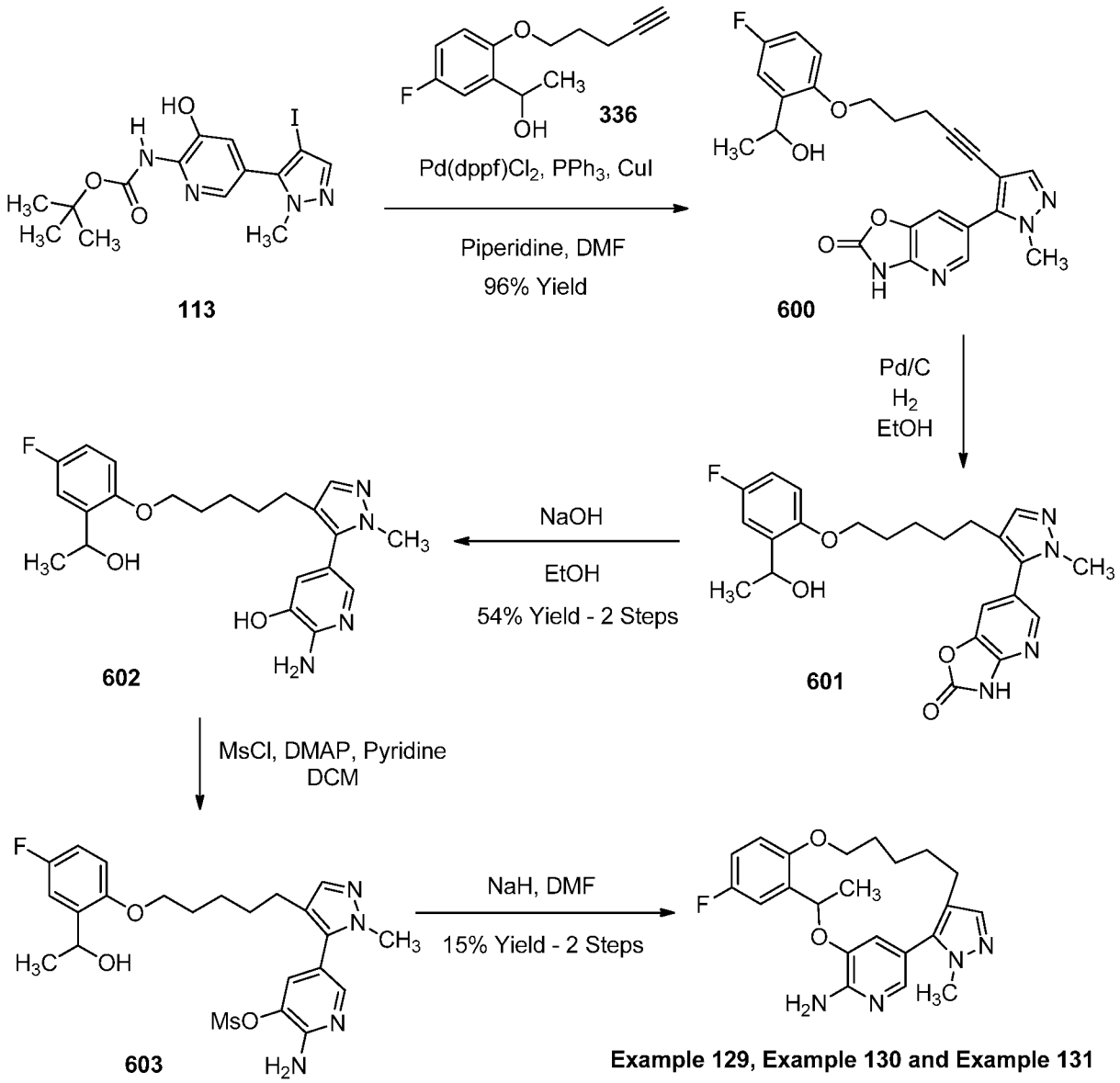
(s, 1H), 7.67 – 7.56 (m, 1H), 7.53 – 7.35 (m, 3H), 6.79 (s, 2H), 6.01 (ddd, *J* = 17.3, 8.3, 2.3 Hz, 1H), 4.98 (ddd, *J* = 48.3, 10.2, 8.3 Hz, 1H), 4.76 – 4.53 (m, 2H), 4.36 (d, *J* = 14.8 Hz, 1H), 4.08 (s, 3H), 2.91 (s, 3H). LCMS *m/z* 408 $[M+H]^+$.

The chiral separation of 27 mg of the material was performed by preparative SFC on a Whelk-O1 (R,R) (250 x 4.6 mm I.D., 5 micron particle size) column, which was eluted with 38% methanol @ 120 bar CO_2 with a flow rate of 62 mL/min. $Rt_{(Peak\ 1)}$ = 4.19 minutes and $Rt_{(Peak\ 2)}$ = 5.50 minutes, and gave Peak 1 as a white solid (11.99 mg) and Peak 2 as a white solid (10.99 mg).

Example 127 (Peak 1): > 99% ee (-). ^{1}H NMR (400MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.60 (d, *J* = 6.8 Hz, 1H), 7.50 - 7.35 (m, 3H), 6.80 (br. s., 2H), 6.01 (dd, *J* = 7.8, 17.4 Hz, 1H), 5.11-4.84 (m, 1H), 4.73 - 4.52 (m, 2H), 4.36 (d, *J* = 15.1 Hz, 1H), 4.08 (s, 3H), 2.91 (s, 3H). LCMS APCI *m/z* 408 $[M+H]^+$

Example 128 (Peak 2): > 99% ee (+). ^{1}H NMR (400MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.60 (d, *J* = 6.8 Hz, 1H), 7.50 - 7.35 (m, 3H), 6.80 (br. s., 2H), 6.01 (dd, *J* = 7.8, 17.4 Hz, 1H), 5.11 -4.84 (m, 1H), 4.73 - 4.52 (m, 2H), 4.36 (d, *J* = 15.1 Hz, 1H), 4.08 (s, 3H), 2.91 (s, 3H). LCMS APCI *m/z* 408 $[M+H]^+$

Preparation of 12-fluoro-1,14-dimethyl-1,4,5,6,7,8-hexahydro-14H-16,20-(metheno)-pyrazolo-[4,3-g][1,14,11]benzodioxazacycloheptadecin-17-amine (Example 129/Example 130/Example 131)



Example 129, Example 130 and Example 131

Step 1:

The procedure described in step 1 for **Example 37** was used to prepare **compound 600** as a yellow oil (709 mg, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 2.0 Hz, 1H), 7.63 (s, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.16 (dd, J = 9.7, 3.3 Hz, 1H), 6.93 (td, J = 8.5, 3.3 Hz, 1H), 6.84 (dd, J = 9.0, 4.6 Hz, 1H), 4.94 (q, J = 6.3 Hz, 1H), 3.98 (q, J = 5.7 Hz, 2H), 3.82 (s, 3H), 1.91 (p, J = 6.6 Hz, 2H), 1.61 (q, J = 6.0, 4.9 Hz,2H), 1.23 (d, J = 6.3 Hz, 3H). LCMS m/z 504 $[M+H]^+$

Step 2:

The procedure described in step 2 for **Example 37** was used to prepare **compound 601** as a yellow oil (603 mg). This was submitted to the next step without further purification. LCMS m/z 439 $[M+H]^+$

Step 3:

The procedure described in step 3 for **Example 37** was used to prepare **compound 602** as a white solid (350 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (d, J = 1.9 Hz, 1H), 7.31 (s, 1H), 7.15 (dd, J = 9.7, 3.2 Hz, 1H), 6.95 (td, J = 8.5, 3.2 Hz, 1H), 6.88 (dd, J = 9.0, 4.6 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 5.76 (s, 2H), 5.11 (d, J =4.4 Hz, 1H), 4.91 (p, J = 6.0 Hz, 1H), 3.95 – 3.83 (m, 2H), 3.63 (s, 3H), 2.31 (t, J = 7.4 Hz, 2H), 1.72 – 1.60 (m, 2H), 1.48 (d, J = 7.5 Hz, 2H), 1.38 (d, J = 7.1 Hz, 2H), 1.21 (d, J = 6.3 Hz, 3H). LCMS m/z 413 $[M+H]^+$

Step 4:

The procedure described in step 4 for **Example 37** was used to prepare **compound 603** as a colorless oil (233 mg, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 1.9 Hz, 1H), 7.38 (s, 1H), 7.12 (dd, J = 9.2, 3.1 Hz, 1H), 6.87 (ddd, J = 8.9, 7.9, 3.1 Hz, 1H), 6.74 (dd, J = 8.9, 4.4 Hz, 1H), 5.25 (s, 2H), 5.05 (q, J = 6.4 Hz, 1H), 4.00 – 3.86 (m, 2H), 3.74 (s, 3H), 3.56 (q, J = 7.3 Hz, 2H), 3.28 (s, 3H), 2.39 (h, J = 7.3 Hz, 2H), 1.77 (dd, J = 14.1, 7.2 Hz, 2H), 1.44 (d, J = 6.5 Hz, 3H). LCMS m/z 493 $[M+H]^+$

Step 5:

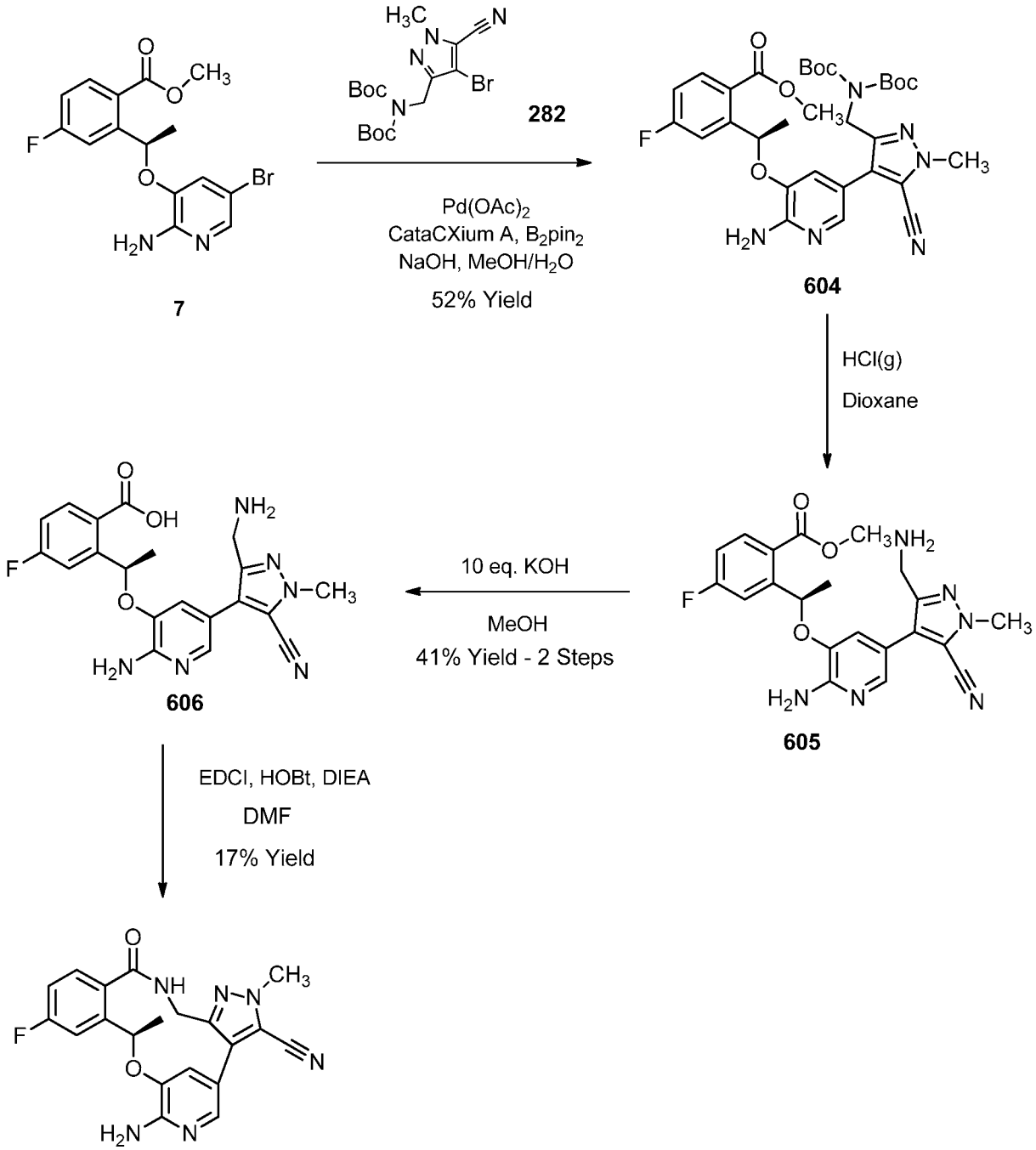
The procedure described in step 5 for **Example 37** was used to prepare **Example 129** as a white solid (29 mg, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 1H), 7.34 (s, 1H), 7.03 (dd, J = 8.9, 3.1 Hz, 1H), 6.91 (ddd, J = 8.9, 7.9, 3.2 Hz, 1H), 6.79 (dd, J = 9.0, 4.3 Hz, 1H), 6.54 (d, J = 1.5 Hz, 1H), 5.73 – 5.65 (m,1H), 4.29 – 4.16 (m, 2H), 3.94 – 3.84 (m, 2H), 3.76 (s, 3H), 2.64 – 2.43 (m, 1H), 2.13 – 1.99 (m, 1H), 1.83 – 1.66 (m, 2H), 1.63 (d, J = 6.4 Hz, 3H), 1.33 (dd, J = 9.7, 5.5 Hz, 2H). LCMS m/z 397 $[M+H]^+$

The chiral separation of 27 mg of the material was performed by preparative SFC on a Chiralpak AD-H (250 x 4.6 mm I.D., 5 micron particle size) column, which was eluted with 38% methanol @ 140 bar CO_2 with a flow rate of 3 mL/min. $Rt_{(Peak\ 1)}$ = 2.37 minutes and $Rt_{(Peak\ 2)}$ = 5.70 minutes, and gave Peak 1 as a white solid (4.9 mg) and Peak 2 as a white solid (4.9 mg).

Example 130 (Peak 1): > 99% ee (+). ^{1}H NMR (400MHz, DMSO-d_6) δ 7.56 (s, 1H), 7.27 (s, 1H), 7.16 (d, J = 8.6 Hz, 1H), 7.08 - 6.95 (m, 2H), 6.42 (s, 1H), 6.12 (s, 2H), 5.65 (d, J = 6.5Hz, 1H), 4.25 (br. s., 1H), 3.86 (t, J = 10.6 Hz, 1H), 3.66 (s, 3H), 2.48 - 2.27 (m, 2H), 2.12 - 1.93 (m, 2H), 1.82 - 1.44 (m, 6H), 1.34 - 1.20 (m, 1H). LCMS APCI m/z 397 $[M+H]^+$

Example 131 (Peak 2): > 99% ee (-). ^{1}H NMR (400MHz, DMSO-d_6) δ 7.56 (s, 1H), 7.27 (s, 1H), 7.16 (d, J = 8.6 Hz, 1H), 7.08 - 6.95 (m, 2H), 6.42 (s, 1H), 6.12 (s, 2H), 5.65 (d, J = 6.5Hz, 1H), 4.25 (br. s., 1H), 3.86 (t, J = 10.6 Hz, 1H), 3.66 (s, 3H), 2.48 - 2.27 (m, 2H), 2.12 - 1.93 (m, 2H), 1.82 - 1.44 (m, 6H), 1.34 - 1.20 (m, 1H). LCMS APCI m/z 397 $[M+H]^+$

Preparation of (10R)-7-amino-12-fluoro-2,10-dimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile (Example 132)



Example 132

Step 1:

The procedure described in step 1 for **Example 88** was used to prepare **compound 604** (340 mg, 52%) as a brown solid. LCMS *m/z* 647 $[M+Na]^+$

Step 2:

The procedure described in step 2 for **Example 88** was used to prepare **compound 605**, which was used for next step without any further purification. LCMS *m/z* 425 $[M+H]^+$

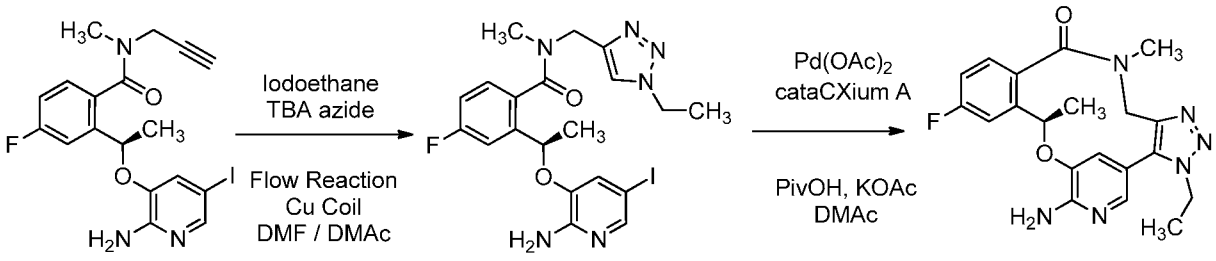
Step 3:

The procedure described in step 3 for **Example 88** was used to prepare **compound 606** (70 mg, 41%) as a white solid. LCMS *m/z* 411 $[M+H]^+$

Step 4:

To a solution of **compound 606** (70 mg, 0.17 mmol) and DIPEA (33 mg, 0.256 mmol) in DMF (25 mL) was HOBt (35 mg, 0.256 mmol) and EDCI (33 mg, 0.256 mmol) in DMF (10 mL) at -35 °C. After the addition, the resulting mixture was stirred at 80 °C for 72 hour. LC-MS showed the reaction was complete. The mixture was poured into ice-water (50 mL). The mixture was extracted with EtOAc (40 mL x 5). The combined EtOAc layers were washed with brine (20 mL x 5), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue. The residue was purified *via* prep. TLC and then further purification by reverse phase preparative HPLC to give **Example 132** (11.5mg, 17%) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4 – sample is a mixture of rotamers) δ 7.8-7.75 (m, 1H), 7.70-7.6 (m, 1H), 7.32-7.20 (m, 2H), 7.01-7.00 (m, 1H), 6.39-6.24 (m, 1H), 5.66-5.64 (d, 1H), 4.45-4.32 (d, 1H), 4.05-4.02 (s, 1H), 1.77-1.75 (d, 3H). LCMS *m/z* 392 $[M+H]^+$

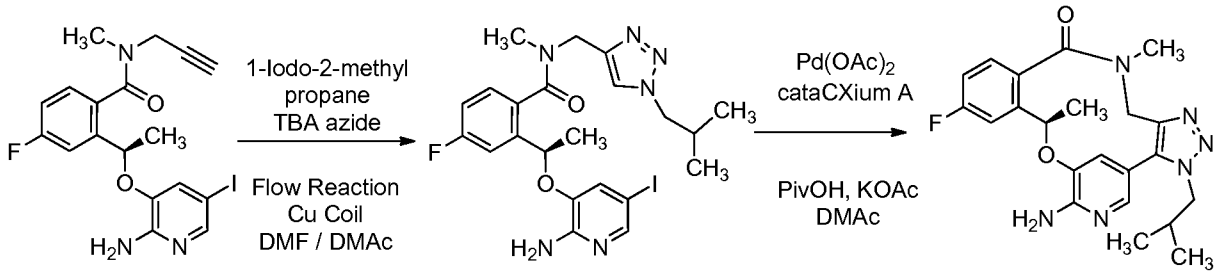
Preparation of (10R)-7-amino-3-ethyl-12-fluoro-10,16-dimethyl-16,17-dihydro-3H-4,8-(metheno)[1,2,3]triazolo[4,5-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 133)



422 **Not isolated** **Example 133**

Combining steps 3 and 4 of **Example 41** in a library protocol gave **Example 133** as a white solid (35.47 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62-7.64 (m, 2 H), 7.44 (dd, *J* = 5.7, 8.5 Hz, 1 H), 7.17 (dt, *J* = 2.8, 8.5 Hz, 1 H), 6.77 (bs, 1 H), 6.35 (bs, 2 H), 5.65 (q, *J* = 7.2, 3.6 Hz, 1 H), 4.51 (d, *J* = 14.4 Hz, 1 H), 4.35 - 4.46 (m, 2 H), 4.13 (d, *J* = 14.7 Hz, 1 H), 2.99 (s, 3 H), 1.67 (d, *J* = 6.1 Hz, 3 H), 1.40 (t, *J* = 7.4 Hz, 3 H). LCMS APCI *m/z* 397 $[M+H]^+$.

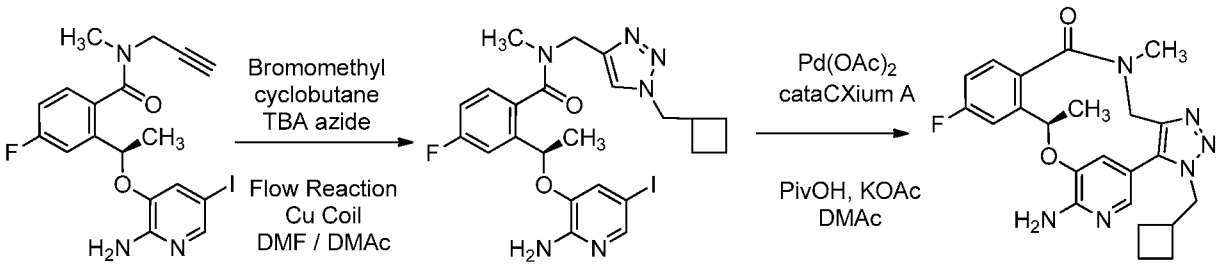
Preparation of (10R)-7-amino-12-fluoro-10,16-dimethyl-3-(2-methylpropyl)-16,17-dihydro-3H-8,4-(metheno)[1,2,3]triazolo[4,5-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 134)



422 **Not isolated** **Example 134**

Combining steps 3 and 4 of **Example 41** in a library protocol gave **Example 134** as a white solid (47.09 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 - 7.64 (m, 2 H), 7.43 (dd, *J* = 5.7, 8.5 Hz, 1 H), 7.16 (dt, *J* = 2.8, 8.5 Hz, 1 H), 6.75 (s, 1 H), 6.33 (s, 2 H), 5.64 (q, *J* = 7.2, 3.6 Hz, 1 H), 4.51 (d, *J* = 14.4 Hz, 1 H), 4.27 - 4.31 (m, 1 H), 4.19 - 4.21 (m, 1 H), 4.13 (d, *J* = 14.7 Hz, 1 H), 2.98 (s, 3 H), 2.03-2.07 (m, 1 H), 1.65 (d, *J* = 6.1 Hz, 3 H), 0.75 (d, *J* = 6.6 Hz, 6 H). LCMS APCI *m/z* 425 $[M+H]^+$.

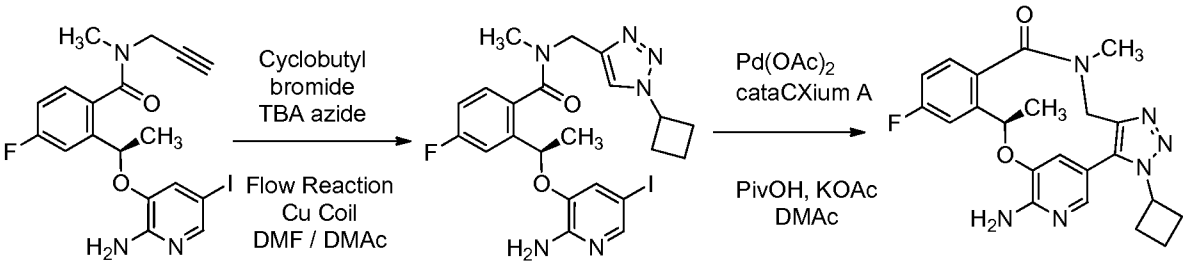
Preparation of (10R)-7-amino-3-(cyclobutylmethyl)-12-fluoro-10,16-dimethyl-16,17-dihydro-3H-8,4-(metheno)[1,2,3]triazolo[4,5-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 135)



422 **Not isolated** **Example 135**

Combining steps 3 and 4 of **Example 41** in a library protocol gave **Example 135** as a white solid (8.3 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62-7.64 (m, 2 H), 7.43 (dd, *J* = 5.7, 8.5 Hz, 1 H), 7.16 (dt, *J* = 2.8, 8.5 Hz, 1 H), 6.77 (s, 1 H), 5.65 (q, *J* = 7.2, 3.6 Hz, 1 H), 4.51 (d, *J* = 14.4 Hz, 1 H), 4.38.4.47 (m, 2 H), 4.14 (d, *J* = 14.7 Hz, 1 H), 2.97 (s, 3 H), 2.71 (m, 1 H), 1.73 - 1.90 (m, 2 H), 1.64-1.73 (m, 7 H). LCMS APCI *m/z* 437 $[M+H]^+$.

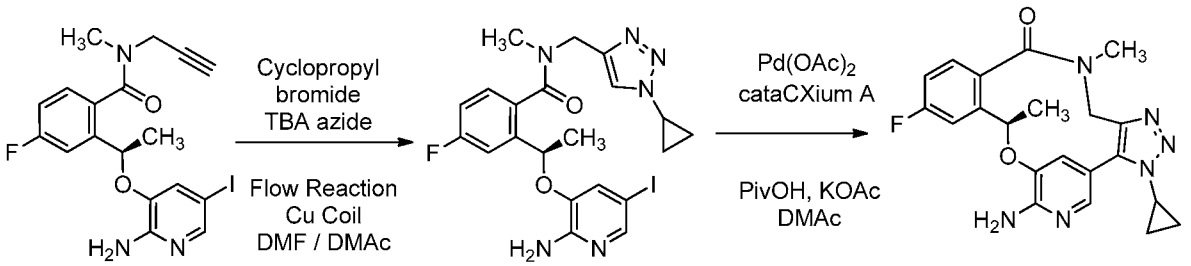
Preparation of (10R)-7-amino-3-cyclobutyl-12-fluoro-10,16-dimethyl-16,17-dihydro-3H-8,4-(metheno)[1,2,3]triazolo[4,5-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 136)



422 Not isolated Example 136

Combining steps 3 and 4 of **Example 41** in a library protocol gave **Example 136** as a white solid (56.97 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 - 7.61 (m, 2 H), 7.44 (s, 1 H), 7.38 – 7.40 (m, 1 H), 7.12 (dt, *J* = 2.8, 8.5 Hz, 1 H), 6.73 (s, 1 H), 6.31 (s, 2 H), 5.60 (q, *J* = 7.2, 3.6 Hz, 1 H), 5.00 (m, 1 H), 4.47 (d, *J* = 14.4 Hz, 1 H), 4.09 (d, *J* = 14.7 Hz, 1 H), 2.95 (s, 3 H), 2.52 (m, 2 H), 2.65 (m, 1 H), 2.26 (m, 1 H), 1.82 (m, 1 H) 1.62 (d, *J* = 6.1 Hz, 3 H), 0.78 (t, *J* = 7.3 Hz, 3 H). LCMS APCI *m/z* 423 $[M+H]^+$.

Preparation of (10R)-7-amino-3-cyclopropyl-12-fluoro-10,16-dimethyl-16,17-dihydro-3H-8,4-(metheno)[1,2,3]triazolo[4,5-h][2,5,11]benzoxadiazacyclotetradecin-15(10H)-one (Example 137)



422 Not isolated Example 137

Combining steps 3 and 4 of **Example 41** in a library protocol gave **Example 137** as a white solid (11.55 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 - 7.62 (m, 2 H), 7.45 (dd, *J* = 5.7, 8.5 Hz, 1 H), 7.16 (dt, *J* = 2.8, 8.5 Hz, 1 H), 6.76 (s, 1 H), 6.35 (s, 2 H), 6.01-6.05 (m, 1 H), 5.62 (q, *J* = 7.2, 3.6 Hz, 1 H), 5.19 (dd, *J* = 1.2, 10.4 Hz, 1 H), 5.13 – 5.16 (m, 1 H), 4.98 – 4.99 (m, 1 H), 4.84 (dd, *J* = 2.2, 18 Hz, 1 H), 4.53 (d, *J* = 14.4 Hz, 1 H), 4.17 (d, *J* = 14.7 Hz, 1 H), 3.00 (s, 3 H), 1.67 (d, *J* = 6.1 Hz, 3 H). LCMS APCI *m/z* 409 $[M+H]^+$.

Biological Examples

Wild-type ALK and L1196M mutant ALK enzyme assays

Wild-type ALK and L1196M mutant ALK enzyme inhibition was measured using a microfluidic mobility shift assay. The reactions were conducted in 50 µL volumes in 96-well plates, and contained preactivated human recombinant wild-type (1.3 nM) or L1196M (0.5 nM) ALK kinase domain (amino acids 1093-1411), 1.5 µM phosphoacceptor peptide, 5'FAM-KKSRGDYMTMQIG-CONH2 (CPC Scientific, Sunnyvale, CA), test compound (11-dose 3-fold serial dilutions, 2% DMSO final) or DMSO only, 1 mM DTT, 0.002% Tween-20 and 5 mM $MgCl_2$ in 25 mM Hepes, pH 7.1, and were initiated by addition of ATP (60 µM final concentration, ~ Km level) following a 20-min preincubation. The reactions were incubated for 1 h at room temperature, stopped by the addition of 0.1 M EDTA, pH 8, and the extent of reactions (~15-20% conversion with no inhibitor) was determined after electrophoretic separation of the fluorescently labeled peptide substrate and phosphorylated product on an LabChip EZ Reader II (Caliper Life Sciences, Hopkinton, MA). The inhibitors were shown to be ATP-competitive from kinetic and crystallographic studies. The Ki values were calculated by fitting the % conversion to the equation for competitive inhibition using non-linear regression method (GraphPad Prism, GraphPad Software, San Diego, CA) and experimentally measured ATP K_m = 58 µM for wild-type and 55 µM for L1196M enzyme. ALK enzymes were produced in-house (baculoviral expression) and preactivated by auto-phosphorylation of 16 µM non-activated enzyme in the presence of 2 mM ATP, 10 mM $MgCl_2$ and 4 mM DTT in 20 mM Hepes, pH 7.5, at room temperature for ~1 h, and the full phosphorylation (~4 phosphates per protein molecule) of ALK kinase domain was verified by Q-TOF mass-spectrometry.

Cellular Phospho-ALK (Tyr1604) ELISA Assay for EML4-ALK:

Cell lines:

NIH-3T3 EML4-ALK wt v1 and NIH-3T3 EML4-ALK v1 L1196M cells are human stable cell lines established at Pfizer - La Jolla, CA. The cells were maintained at 37°C in a 5% CO_2 incubator in DMEM (Invitrogen, Carlsbad, CA) medium supplemented with 1% L-glutamine, 1% penicillin and streptomycin, 1ug/ml puromycin and 10% new born calf serum (NCS) in T-75 flasks.

Assay:

Cells were washed with PBS and re-suspended in DMEM medium supplemented with 0.5% NCS and 1% pen/strep and seeded into 96-well plates at density of 20,000 cells/well/100 µl and incubated in the incubator at 37°C and 5% CO_2. After 20 hours of incubation, 100 µl of assay media (DMEM) in presence of designated PF-compounds concentrations or controls

(DMSO) were added into plates and incubated for 1 hour in the incubator. Media was then removed and lysis buffer, containing phosphatase inhibitors and phenylmethanesulfonyl fluoride (PMSF), was added to wells and shaken at 4 °C for 30 minutes to generate protein lysates. Subsequently, a PathScan phospho-ALK (Tyr1604) chemiluminescent sandwich ELISA kit (Cell Signal Technology Inc., cat # 7020) was used to assess the phosphorylation of ALK as follows:

A phospho-ALK (Tyr1604) rabbit antibody was coated onto the 96-well microplates. 50 µl of cell lysates were added to the antibody coated plate and incubated at room temperature for 2 hours. Following extensive washing with 0.1% Tween 20 in PBS to remove unbound materials, ALK mouse mAb was added to detect captured phospho-ALK (Tyr1604) and phospho-ALK fusion proteins. Anti-mouse IgG, HRP-linked antibody was then used to recognize the bound detection antibody. Finally, the chemiluminescent reagent was added and incubated for 10 minutes for signal development. The assay plates were read in the Envision plate reader in the luminescent mode. IC_{50} values were calculated by a concentration-response curve fitting using a four-parameter analytic method.

Ki and IC_{50} data obtained with the ALK enzymatic assays 1 and 2 and cellular phospho-ALK (Tyr1604) ELISA assay for WT EML4-ALK and L1196M EML4-ALK , disclosed above, are shown in the below table. In the table below, compounds that have no data indicate that those compounds were not tested against the assays listed in **Table 1**.

Table 1

Example	WT ALK enzyme assay (Ki)	L1196M ALK enzyme assay (Ki)	ELISA assay for WT EML4-ALK (IC_{50})	ELISA assay for L1196M EML4-ALK (IC_{50})
1	<0.200 nM	0.26 nM	1.39 nM	22.8 nM
2	<0.200 nM	0.78 nM	1.33 nM	20.7 nM
3	<0.200 nM	0.20 nM	0.99 nM	22.2 nM
4	<0.200 nM	1.20 nM	28.1 nM	184 nM
5	0.340 nM	3.40 nM	12.1 nM	156 nM
6	<0.200 nM	1.93 nM	6.41 nM	97.1 nM
7	NA	14.0 nM	155 nM	2.68 µM
8	0.90 nM	10.0 nM	12.1 nM	0.68 µM
9	0.20 nM	1.06 nM	0.35 nM	9.29 nM
10	13.0 nM	34.0 nM		
11	<0.200 nM	1.10 nM	1.21 nM	27.7 nM
12	10.0 nM	29.0 nM	34.9 nM	0.70 µM
13	<0.200 nM	0.29 nM	0.70 nM	13.9 nM
14	17.0 nM	61.2 nM		

Example	WT ALK enzyme assay (Ki)	L1196M ALK enzyme assay (Ki)	ELISA assay for WT EML4-ALK (IC_{50})	ELISA assay for L1196M EML4-ALK (IC_{50})
15	<0.200 nM	2.50 nM		
16	213 nM	>2.27 μM		
17	<0.200 nM	<0.100 nM	0.30 nM	4.25 nM
18	5.20 nM	24.0 nM		
19	<0.200 nM	0.90 nM	4.89 nM	110 nM
20	34.0 nM	450 nM		
21	<0.200 nM	<0.100 nM	0.18 nM	2.13 nM
22	12.0 nM	17.0 nM	192 nM	305 nM
23	<0.200 nM	0.29 nM	0.77 nM	10.1 nM
24	4.60 nM	14.0 nM		
25	<0.200 nM	0.56 nM	1.35 nM	21.9 nM
26	3.30 nM	15.0 nM	50.5 nM	0.511 μM
27	0.380 nM	5.30 nM	9.15 nM	157 nM
28	<0.200 nM	0.11 nM	<0.205 nM	1.40 nM
29	19.0 nM	31.0 nM		
30	<0.200 nM	0.67 nM	2.64 nM	67.2 nM
31	5.96 nM	15.8 nM	53.2 nM	0.66 μM
32	<0.200 nM	<0.100 nM	0.841 nM	5.36 nM
33	1.01 μM	>2.68 μM		
34	0.56 nM	15.0 nM	36.1 nM	0.89 μM
35	<0.261 nM	1.10 nM	0.98 nM	14.3 nM
36	<0.200 nM	0.560 nM	0.18 nM	2.64 nM
37	3.80 nM	29.0 nM	86.0 nM	0.654 μM
38	0.610 nM	5.70 nM	12.0 nM	201 nM
39	0.220 nM	<0.100 nM	14.9 nM	112 nM
40	0.360 nM	1.60 nM	21.8 nM	101 nM
41	1.50 nM	19.0 nM	33.1 nM	0.68 μM
42	500 nM	2.89 nM		
43	5.23 nM	35.6 nM	0.52 μM	3.66 μM
44	12.0 nM	70.0 nM		
45	> 3.0 μM	500 nM		
46	0.15 nM	1.10 nM	10.42 nM	44.70 nM
47	0.29 nM	3.60 nM	16.41 nM	208.0 nM

Example	WT ALK enzyme assay (Ki)	L1196M ALK enzyme assay (Ki)	ELISA assay for WT EML4-ALK (IC_{50})	ELISA assay for L1196M EML4-ALK (IC_{50})
48	0. 2 nM	1.20 nM	6.75 nM	68.9 nM
49	0.17 nM	1.50 nM	4.08 nM	80.8 nM
50	0.14 nM	1.2 nM	2.37 nM	29.7 nM
51	0.13 nM	0.28 nM	0.95 nM	6.25 nM
52	1.20 nM	10.2 nM	4.78 nM	296.4 nM
53	25.8 nM	164.0 nM		
54	< 0.07 nM	0.06 nM	0.332 nM	3.03 nM
55	< 0.07 nM	0.24 nM	1.03 nM	13.38 nM
56	0.2 nM	0.88 nM	1.83 nM	35.03 nM
57	0.14 nM	2.0 nM	6.79 nM	0.365 µM
58	< 0.1 nM	< 0.1 nM	0.33 nM	2.06 nM
59		14.4 nM	12.98 nM	155.93 nM
60	4.6 nM	21.5 nM		
61	0.15 nM	0.17 nM	4.82 nM	17.07 nM
62	137 nM	253.0 nM	7.605 µM	> 10 µM
63	0.12 nM	0.13 nM	1.95 nM	8.70 nM
64	34.4 nM	33.3 nM	0.407 µM	1.19 µM
65	0.88 nM	9.8 nM	9.36 nM	0.313 µM
66	19.3 nM	122.0 nM		
67	411 nM	> 1.5 µM		
68	207 nM	> 1.5 µM		
69	> 3.0 µM	> 3.0 µM		
70	< 0.16 nM	0.96 nM	6.52 nM	78.54 nM
71	< 0.249 nM	3.73 nM	10.16 nM	169.09 nM
72	5.1 nM	28.0 nM	0.347 µM	4.266 µM
73	0.33 nM	2.4 nM	12.75 nM	0.169 µM
74	0.30 nM	0.86 nM	11.41 nM	51.93 nM
75	0.065 nM	0.095 nM	0.902 nM	7.06 nM
76	3.1 nM	1.9 nM	95.65 nM	108.89 nM
77	75.0 nM	45.8 nM	3.39 µM	3.32 µM
78	2.93 nM	9.61 nM	40.83 nM	0.350 µM
79	1.18 nM	2.9 nM	42.79 nM	179.84 nM
80	> 3.0 µM	> 3.0 µM		

Example	WT ALK enzyme assay (Ki)	L1196M ALK enzyme assay (Ki)	ELISA assay for WT EML4-ALK (IC_{50})	ELISA assay for L1196M EML4-ALK (IC_{50})
81	< 1.88 nM	3.9 nM	2.25 nM	51.98 nM
82	< 0. 2 nM	2.39 nM	11.15 nM	182.59 nM
83	47.6 nM	74 nM		
84	29.3 nM	90.2 nM		
85	0.070 nM	0.13 nM	0.55 nM	6.72 nM
86	< 0.2 nM	0.10 nM	0.45 nM	2.57 nM
87	270.0 nM	51.0 nM		
88	0.2 nM	0.39 nM	15.51 nM	190.94 nM
89	0.339 nM	0.275 nM	6.43 nM	56.05 nM
90	0.079 nM	0.249 nM	1.32 nM	13.00 nM
91	0.177 nM	0.315 nM	0.68 nM	5.88 nM
92	0.23 nM	0.21 nM	0.47 nM	3.66 nM
93	0.048 nM	0.3 nM	3.23 nM	31.67 nM
94	0.93 μM	0.698 μM		
95	0.35 nM	1.9 nM	10.37 nM	169.25 nM
97	3.50 nM	24.7 nM		
98	0.115 nM	0.404 nM	2.21 nM	32.28 nM
99	3.2 nM	11.7 nM	52.38 nM	0.531 μM
100	3.1 nM	24.2 nM	146.29 nM	1.48 μM
101	0.12 nM	0.41 nM	0.92 nM	8.77 nM
102	0.33 nM	1.41 nM	11.62 nM	83.82 nM
103	9.1 nM	131.0 nM		
104	8.4 nM	57.5 nM		
105	3.0 nM	16.7 nM	115.04 nM	0.642 μM
106	> 3 μM	> 3 μM		
107	88.5 nM	179.0 nM		
108	< 0.06 nM	< 0.05 nM	0.068 nM	0.50 nM
109	8.1 nM	4.7 nM	11.029 nM	55.56 nM
110	0.56 nM	7.3 nM	9.99 nM	0.447 μM
111	0.059 nM	0.54 nM	1.42 nM	32.49 nM
112	0.32 nM	3.4 nM	9.67 nM	247.76 nM
113	0.20 nM	0.46 nM	0.68 nM	9.56 nM
114	0.271 nM	1.36 nM	3.29 nM	78.24 nM

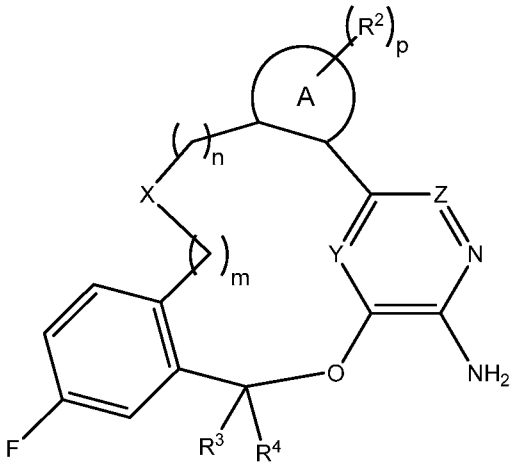
Example	WT ALK enzyme assay (Ki)	L1196M ALK enzyme assay (Ki)	ELISA assay for WT EML4-ALK (IC_{50})	ELISA assay for L1196M EML4-ALK (IC_{50})
115	< 0.08 nM	0.09 nM	0.96 nM	8.18 nM
116	> 1.5 μM	> 3 μM	> 10 μM	> 10 μM
117	2.18 nM	17.8 nM	35.22 nM	393.0 nM
118	17.8 nM	64.7 nM	217.23 nM	1.402 μM
119	1.6 nM	13.4 nM	7.79 nM	264.0 nM
120	146.0 nM	0.821 μM	2.11 μM	> 10 μM
121	132.0 nM	273.0 nM		
122	0.27 nM	0.70 nM	9.27 nM	52.31 nM
123	205.0 nM	333.0 nM	4.79 μM	> 10 μM
124	2.10 nM	7.4 nM	56.17 nM	0.873 μM
125	0.11 nM	0.49 nM	2.30 nM	49.08 nM
126	0.54 μM	1.07 μM		
127	0.099 nM	0.52 nM	2.50 nM	64.97 nM
128	138.0 nM	386.0 nM		
129	353.0 nM	> 1.5 μM		
130	> 3 μM	> 3 μM		
131	78.3 nM	0.794 μM		
132	3.32 nM	16.52 nM	35.27 nM	0.892 μM
133	3.06 nM	32.75 nM	95.77 nM	0.997 μM
134	3.0 nM	20.5 nM		
135	2.1 nM	12.6 nM	45.89 nM	0.814 μM
136	0.6 nM	4.8 nM	28.47 nM	0.419 μM
137	6.1 nM	72.4 nM		2.28 μM

All publications and patent applications cited in the specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

Claims

We Claim:

1. A compound of the formula (I)



(I)

wherein:

X is selected from the group consisting of $-(CR^5R^6)_qO(CR^5R^6)_r-$, $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ and $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$;

Y and Z are each independently N or CH, with the proviso that when Y is N, Z is CH and when Z is N, Y is CH;

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, -

NH_2, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3;

p is 0, 1, 2, 3 or 4;

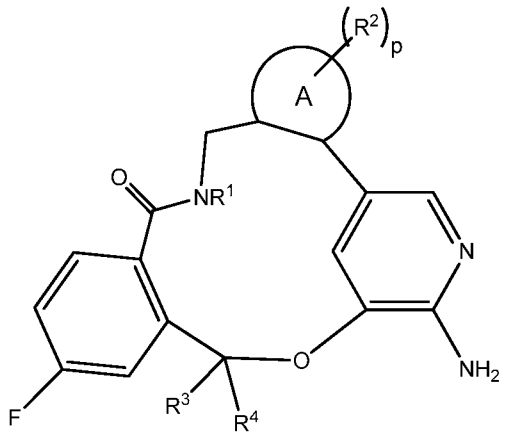
each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

2. A compound of the formula (V)



(V)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $--C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

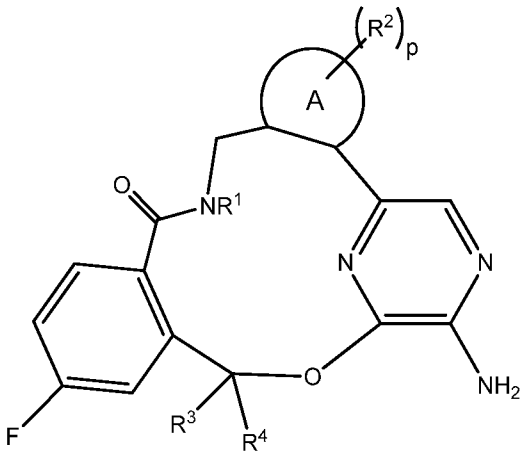
each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

3. A compound of the formula (VI)



(VI)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $--C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl and C_3-C_6 cycloalkyl, wherein each hydrogen on C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

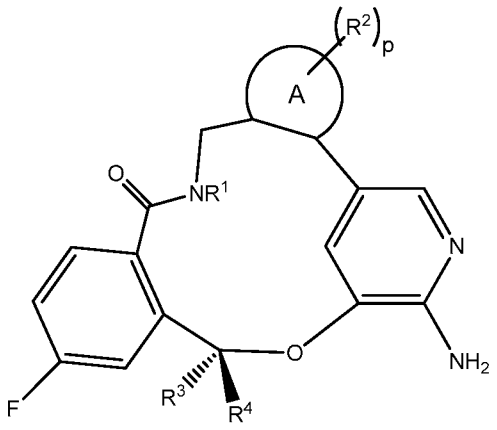
4. The compound of claim 1, 2 or 3, wherein R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1 to 4, wherein each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$, or a pharmaceutically acceptable salt thereof.

6. The compound of any one of claims 1 to 5, wherein A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole, or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1 to 6, wherein R^3 and R^4 are each independently selected from the group consisting of hydrogen and C_1-C_6 alkyl, or a pharmaceutically acceptable salt thereof.

8. A compound of the formula (XV)



(XV)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $--C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on said C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic,

5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

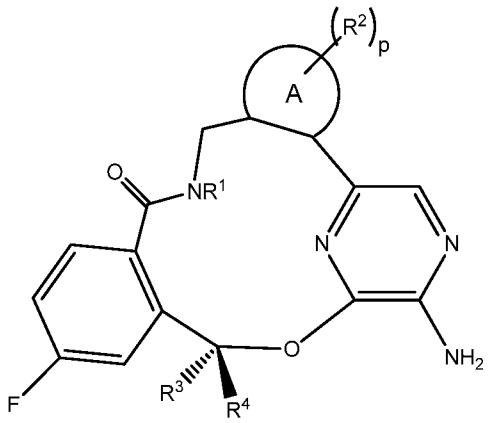
each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

9. A compound of the formula (XVI)



(XVI)

wherein:

A is a ring selected from C_6-C_{12} aryl and 5-6 membered heteroaryl;

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $--C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^2 is independently selected from the group consisting of halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ and $-(CR^5R^6)_qC(O)NR^7R^8$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

R^3 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl and R^4 is hydrogen, wherein each hydrogen on said C_1-C_6 alkyl or C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^5 and R^6 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, 5-6 membered heteroaryl, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$; wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^7 and R^8 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl, wherein each hydrogen on said C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic and 5-6 membered heteroaryl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$,

$-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ or $-C(O)NR^9R^{10}$;

each R^9 and R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, 3-12 membered heteroalicyclic, and 5-6 membered heteroaryl;

p is 0, 1, 2, 3 or 4;

each q is independently 0, 1, 2 or 3;

each r is independently 0, 1, 2 or 3; and

each t is independently 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

10. The compound of claim 7, 8 or 9, wherein R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, or a pharmaceutically acceptable salt thereof.

11. The compound of any one of claims 7 to 10, wherein each R^2 is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ and -CN; wherein each hydrogen on said C_1-C_6 alkyl and C_3-C_6 cycloalkyl may be independently optionally substituted by halogen, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ and $-C(O)NR^9R^{10}$, or a pharmaceutically acceptable salt thereof.

12. The compound of any one of claims 7 to 11, wherein A is a ring selected from the group consisting of phenyl, pyridine, pyrimidine, pyridazine, pyrazine, triazine, pyrazole, imidazole, triazole, tetrazole, thiazole, isothiazole, oxazole and isoxazole, or a pharmaceutically acceptable salt thereof.

13. The compound of any one of claims 7 to 12, wherein R^3 is methyl and R^4 is hydrogen, or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

15. A method of treating abnormal cell proliferation in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof.

16. The method of claim 15, wherein the abnormal cell proliferation is cancer.

17. The method of claim 16, wherein the cancer is mediated by anaplastic lymphoma kinase (ALK).

18. The method of claim 16, wherein the cancer is mediated by an EML4-ALK fusion protein.

19. The method of claim 16, wherein the cancer is mediated by an EML4-ALK fusion protein having at least one mutation.

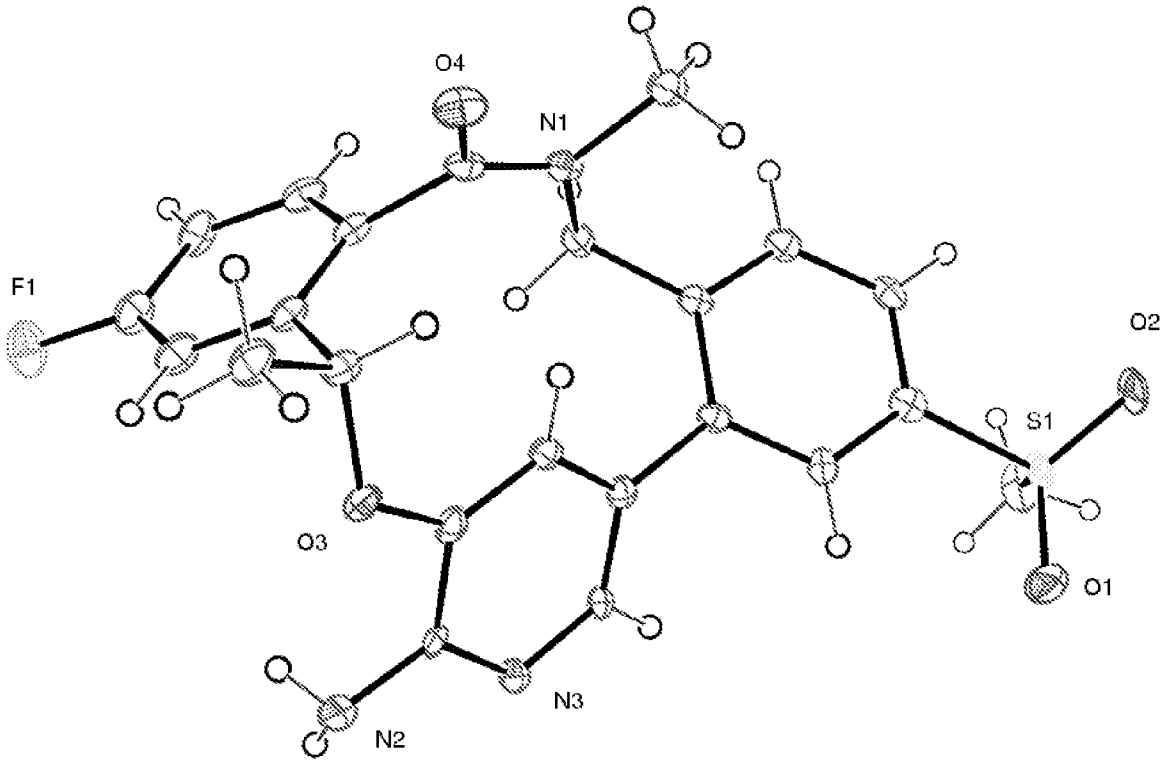
20. The method of claim 19, wherein said mutation is L1196M or C1156Y.

21. The method of any one of claims 16 to 20, wherein the wherein the cancer is selected from the group consisting of non-small cell lung cancer (NSCLC), squamous cell carcinoma, hormone-refractory prostate cancer, papillary renal cell carcinoma, colorectal adenocarcinoma, neuroblastomas, anaplastic large cell lymphoma (ALCL) and gastric cancer.

22. The method of any one of claims 15 to 21, wherein the mammal is a human.

23. The method of any one of claims 15 to 21, wherein the mammal is a dog.

Figure 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/051391

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/08 C07D491/18 C07D498/08 C07D498/18 C07D498/22
C07D513/18 A61K31/4353 A61P35/00
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 practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI 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 2011/138751 A2 (PFIZER [US]; BUNNAGE MARK EDWARD [GB]; COOK ANDREW SIMON [GB]; CUI JIN) 10 November 2011 (2011-11-10) claims 1,20	1-23
A	K.I. Milkiewicz ET AL: "Inhibitors of anaplastic lymphoma kinase: a patent review", Expert Opinion in Therapeutic Patents, vol. 20 1 January 2010 (2010-01-01), pages 1653-1681, XP055064115, DOI: 10.1517/13543776.2010.527332 Retrieved from the Internet: URL:http://informahealthcare.com/doi/pdf/10.1517/13543776.2010.527332 [retrieved on 2013-05-27] the whole document	1-23

☐ 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 application or patent 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 May 2013	03/06/2013

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	Johnson, Claire

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2013/051391

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011138751 A2	10-11-2011	CA 2796967 A1	10-11-2011
		EP 2566858 A2	13-03-2013
		WO 2011138751 A2	10-11-2011

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.
PC71904A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2013/051391	20/02/2013	06/03/2012
Applicant		
PFIZER INC.		

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 4 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. [X] 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:

   MACROCYCLIC DERIVATIVES FOR THE TREATMENT OF PROLIFERATIVE DISEASES

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. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2013/051391

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. (means)

   [ ] on paper

   [X] in electronic form

   b. (time)

   [X] in the international application as filed

   [ ] together with the international application in electronic form

   [ ] subsequently to this Authority for the purpose of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/051391

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/08 C07D491/18 C07D498/08 C07D498/18 C07D498/22
C07D513/18 A61K31/4353 A61P35/00
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 practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	K.I. Milkiewicz ET AL: "Inhibitors of anaplastic lymphoma kinase: a patent review", Expert Opinion in Therapeutic Patents, vol. 20 1 January 2010 (2010-01-01), pages 1653-1681, XP055064115, DOI: 10.1517/13543776.2010.527332 Retrieved from the Internet: URL:http://informahealthcare.com/doi/pdf/10.1517/13543776.2010.527332 [retrieved on 2013-05-27] the whole document	1-23

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"O" document referring to an oral disclosure, use, exhibition or other means

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"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 May 2013	03/06/2013

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	Johnson, Claire

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2013/051391

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011138751 A2	10-11-2011	CA 2796967 A1	10-11-2011
		EP 2566858 A2	13-03-2013
		WO 2011138751 A2	10-11-2011

PC071904-02

DERIVADOS MACROCÍCLICOS PARA EL TRATAMIENTO DE ENFERMEDADES

CAMPO DE LA INVENCIÓN

La presente invención se refiere a los compuestos de las fórmulas (Φ) y (I)-(XXX) y sus sales farmacéuticamente aceptables, a composiciones farmacéuticas que comprenden dichos compuestos y sales, y a sus usos. Los compuestos y las sales de la presente invención inhiben la quinasa del linfoma anaplásico (ALK) y son útiles para tratar o mejorar los trastornos proliferativos celulares anormales, tales como cáncer.

ANTECEDENTES DE LA INVENCIÓN

La quinasa de linfoma anaplásico (ALK) es un miembro de la superfamilia de las tirosina quinasas receptoras y, en un nivel de secuencia de aminoácidos, está más íntimamente relacionada con miembros tales como Ros-1, tirosina quinasa de leucocitos, el receptor insulínico y cMet (receptor del factor de crecimiento hepático) (Kostich M et al, Genome Biology, 2002, 3 ,1-12). Como sucede con todos los miembros de esta familia de genes, posee un dominio de unión de ligandos extracelular, una secuencia de extensión de transmembrana y un dominio de región catalítica/señalización de quinasas intracelular. La identidad del ligando de señalización para ALK no se ha elucidado aún y se han propuesto diferentes mecanismos en la literatura (Stoica G.E. et al., J. Biol. Chem., 2001, 276, 16772-16779; Stoica G.E. et al., J. Biol. Chem., 2002, 277, 35990-35999; Mewng K. et al., PNAS, 2000, 97, 2603-2608; Pérez-Pinera P. et al., J. Biol. Chem., 2007, 282, 28683-28690). La estimulación de ALK produce una cascada de señalización intracelular por medio de la fofolipasa-C, PI3 quinasa y STAT3 (entre otras proteínas de señalización) (Turner S.D. et al., Cell Signal, 2007, 19, 740-747).

ALK se expresa ampliamente en el sistema nervioso en desarrollo (Iwahara T. et al., Oncogene, 1997, 14, 439-449). Su relativa abundancia no tiende a decrecer en el animal adulto, a pesar de que su expresión se mantiene en ciertas regiones del cerebro, la médula espinal y el ojo (Vernersson E. et al., Gene Expression Patterns, 2006, 6, 448-461).

ALK tiene un papel importante en la oncología (Webb T.R. et al., Expert Reviews in Anticancer Therapy, 2009 9 331-355). Se ha demostrado que las mutaciones puntuales en la enzima ALK de longitud total que producen la activación de la enzima y también aumentan su expresión en la enzima de longitud total conducen al neuroblastoma. Además, la fusión de ALK con otras proteínas debido a

eventos de translocación genética también mostró que provoca un dominio de quinasa activado asociado con el cáncer. Una cantidad de tales translocaciones de ALK que producen fusiones génicas se observan en linfomas, siendo la más prevalente la fusión de nucleofosmina NPM-ALK vista en los linfomas anaplásicos de células grandes. La fusión de ALK con EML4 genera una proteína quimérica (EML4-ALK) que se cree es responsable del 3-5% de los adenocarcinomas de pulmón de células no pequeñas (NSCLC) (Soda M. et al., Nature, 2007, 448, 561-567).

Crizotinib es un potente inhibidor dual de tirosina quinasa (TKI) dirigido a c-Met y ALK que halló recientemente aplicación en el tratamiento de pacientes con NSCLC que albergan un evento de fusión de EML4-ALK (Kwak et al., New Eng. J. de Med., 2010, 363, 18, 1693-1703). Crizotinib se describe en la publicación PCT N.º WO 2006/021884 y la patente de los Estados Unidos N.º 7.858.643. Se informó la resistencia adquirida a la terapia con crizotinib y atribuyó a una mutación L1196M y C1156Y en la proteína de fusión EL4-ALK (Choi Y.L. et al., N. Engl. J. Med., 2010, 363, 18, 1734-1739). Como la terapia con crizotinib se volvió más ampliamente disponible para los pacientes que albergaban el evento de fusión génica de EML4-ALK, es más probable que las mutaciones L1196M y C1156Y, y posiblemente otras mutaciones, desempeñen un papel más prevalente en la resistencia adquirida a la terapia con crizotinib. Ver, p. ej., Morris et al., publicación de patente de los Estados Unidos número 2011/0256546 que describe otras mutaciones de resistencia al inhibidor de ALK que se producen en el dominio de quinasa de ALK de la fusión génica relacionada de NPM-ALK.

Conforme a ello, hay una necesidad de hallar inhibidores de ALK e inhibidores de EML4-ALK que tienen un perfil farmacológico apropiado, por ejemplo, en términos de potencia, selectividad, farmacocinética, capacidad para atravesar la barrera hematoencefálica y duración de la acción. Más específicamente, hay una necesidad de hallar inhibidores de ALK que inhiban la proteína de fusión EML4-ALK con una mutación de L1196M y/o C1156Y. En este contexto, la presente invención se refiere a nuevos inhibidores de ALK.

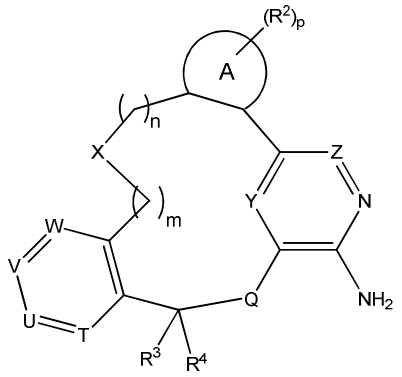
SÍNTESIS DE LA INVENCIÓN

La presente invención provee, en parte, compuestos novedosos y sus sales farmacéuticamente aceptables, que pueden modular la actividad de ALK y/o EML4-ALK, de esta manera efectuando funciones biológicas que incluyen, mas no se limitan a la inhibición de la proliferación celular e invasividad celular, la inhibición de la metástasis, la inducción de apoptosis o la inhibición de la angiogénesis. También se

proveen composiciones farmacéuticas y medicamentos, que comprenden los compuestos o las sales de la invención, en forma individual o en combinación con otros agentes terapéuticos o agentes paliativos. La presente invención también provee, en parte, métodos para preparar los compuestos novedosos, sus sales y composiciones, y métodos de uso de todos éstos.

Se entiende que cada forma de realización que describe los compuestos de la invención en la presente se pueden combinar solos o junto con otra forma de realización que describe los compuestos de la invención, siempre que estas formas de realización no sean inconsistentes entre sí.

En un aspecto, la invención proporciona un compuesto de la fórmula (Φ)



(Φ)

en donde:

X está seleccionado del grupo que consiste en -$(CR^5R^6)_qO(CR^5R^6)_r$-, -$(CR^5R^6)_qN(R^1)(CR^5R^6)_r$-, -$(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r$- y -$(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r$-; o

X es un arileno C_6-C_{12} o un heteroarileno de 5-12 miembros, cada uno de los cuales está opcionalmente sustituido con 0-4 sustituyentes R^{12};

Y y Z son cada uno, de modo independiente, N o CH, siempre que, cuando Y es N, Z sea CH y cuando Z es N, Y sea CH;

T es N o CR^{11a}; U es N o CR^{11b}; V es N o CR^{11c}; y W es N o CR^{11d}; siempre que no más de dos de T, U. V y W sean N;

Q es O o CH_2;

A es un anillo seleccionado del grupo que consiste en arilo C_6-C_{12} y heteroarilo de 5-12 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo

C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^2 y R^{12} está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_q$-cicloalquilo C_3-C_6, $-(CR^5R^6)_q$-arilo C_6-C_{12}, $-(CR^5R^6)_q$-heteroalicíclico de 3-12 miembros, $-(CR^5R^6)_q$ heteroarilo de 5-6 miembros, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6

miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

cada R^{11a}, R^{11b}, R^{11c} y R^{11d} está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, halógeno y alquilo C_1-C_6;

m es 0, 1, 2 o 3;

n es 0, 1, 2 o 3;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

En una forma de realización de este aspecto, T es CR^{11a}; U es CR^{11b}; V es CR^{11c}; y W es CR^{11d}. En otra forma de realización de este aspecto, T es N; U es CR^{11b}; V es CR^{11c}; y W es CR^{11d}. En otra forma de realización de este aspecto, T es CR^{11a}; U es N; V es CR^{11c}; y W es CR^{11d}. En otra forma de realización de este aspecto, T es CR^{11a}; U es CR^{11b}; V es N; y W es CR^{11d}. En una forma de realización adicional de este aspecto, T es CR^{11a}; U es CR^{11b}; V es CR^{11c}; y W es N. En otra forma de realización de este aspecto, T y U son N; V es CR^{11c}; y W es CR^{11d}. En otra forma de realización de este aspecto, T y V son N; U es CR^{11b}; y W es CR^{11d}. En otra forma de realización de este aspecto, T y W son N; U es CR^{11b}; y V es CR^{11c}. En aún otra forma de realización de este aspecto, U y V son N; T es CR^{11a}; y W es CR^{11d}. En otra

forma de realización de este aspecto, U y W son N; T es CR^{11a}; y V es CR^{11c}. En otra forma de realización de este aspecto, V y W son N; T es CR^{11a}; y U es CR^{11b}.

En algunas formas de realización, al menos uno de R^{11a}, R^{11b}, R^{11c}, y R^{11d} es halo, preferentemente flúor o cloro. En otras formas de realización, al menos dos de R^{11a}, R^{11b}, R^{11c}, y R^{11d} son halo, preferentemente flúor o cloro. En algunas de esas formas de realización, R^{11b} es halo, preferentemente flúor. En algunas formas de realización, cada uno de R^{11a}, R^{11c}, y R^{11d} es hidrógeno. En formas de realización específicas, T es CR^{11a}; U es CR^{11b}; V es CR^{11c}; y W es CR^{11d}; R^{11b} es halo, en particular flúor; y cada uno de R^{11a}, R^{11c}, y R^{11d} es hidrógeno.

En otro aspecto de esta forma de realización, Y es CH y Z es CH. En otra forma de realización, Y es CH y Z es N. En otra forma de realización, Y es N y Z es CH.

En una forma de realización de este aspecto, X es $-(CR^5R^6)_qO(CR^5R^6)_r-$. En algunas de esas formas de realización, cuando X es $-(CR^5R^6)_qO(CR^5R^6)_r-$, m es 0 y n es 3. En otras de esas formas de realización, m es 1 y n es 2. En otras de esas formas de realización, m es 2 y n es 1. Aun en otras formas de realización, m es 3 y n es 0. En otras de esas formas de realización, m es 3 y n es 3. En otra de dichas formas de realización, m es 2 y n es 2. En otra de esa forma de realización, m es 1 y n es 1. Aun en otra forma de realización, m es 0, n es 3, q es 0 y r es 0. En otra de esa forma de realización, m es 1, n es 2, q es 0 y r es 0. En otra de esa forma de realización, m es 2, n es 1, q es 0 y r es 0. En otra de esa forma de realización, m es 3, n es 0, q es 0 y r es 0.

En otra forma de realización de este aspecto, X está seleccionado del grupo que consiste en $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ y $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$. En algunas de esas formas de realización, X es $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$. En otras de esas formas de realización, X es $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$. En otras de esas formas de realización de este aspecto, X es $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$.

En otra forma de realización de este aspecto, X es $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$. En algunas de esas formas de realización, cuando X es $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, m es 0 y n es 3. En otras de esas formas de realización, m es 1 y n es 2. En otras de esas formas de realización, m es 2 y n es 1. En otras de esas formas de realización, m es 3 y n es 0. Incluso en otra de esas formas de realización, m es 3 y n es 3. En otras de esas formas de realización, m es 2 y n es 2. Incluso en otra de esas formas de realización, m es 1 y n es 1.

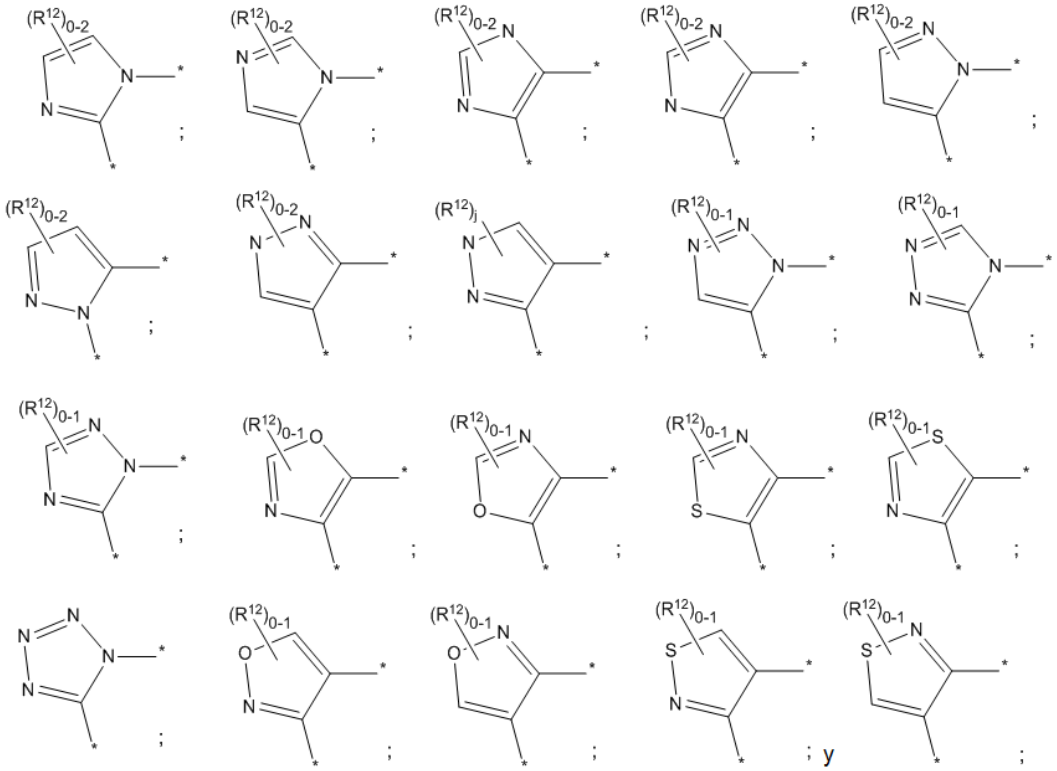
En otra forma de realización de este aspecto, X es $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$. En algunas de esas formas de realización, cuando X es $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$, m es 0 y n es 1. En otras de esas formas de realización, m es 0 y n es 2. En otras de esas formas de realización, m es 0 y n es 3. En otras de esas formas de realización, m es 2 y n es 0. Incluso en otra de esas formas de realización, m es 2 y n es 2. Aun en otra forma de realización, m es 0, n es 1, q es 0 y r es 0. En otra de esa forma de realización, m es 0, n es 2, q es 0 y r es 0. Aun en otra forma de realización, m es 0, n es 3, q es 0 y r es 0. En otra de esa forma de realización, m es 0, n es 0, q es 0 y r es 1. En otra de esa forma de realización, m es 0, n es 0, q es 0 y r es 2. Aun en otra forma de realización, m es 2, n es 0, q es 0 y r es 0.

En otra forma de realización de este aspecto, X es $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$. En algunas de esas formas de realización, cuando X es $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$, m es 0 y n es 1. En otras de esas formas de realización, m es 0 y n es 2. En otras de esas formas de realización, m es 2 y n es 0. En otras de esas formas de realización, m es 0 y n es 3. En otras de esas formas de realización, m es 2 y n es 0. Incluso en otra de esas formas de realización, m es 2 y n es 2. Aun en otra forma de realización, m es 0, n es 1, q es 0 y r es 0. En otra de esa forma de realización, m es 0, n es 2, q es 0 y r es 0. Aun en otra forma de realización, m es 0, n es 3, q es 0 y r es 0. En otra de esa forma de realización, m es 0, n es 0, q es 0 y r es 1. En otra de esa forma de realización, m es 0, n es 0, q es 0 y r es 2. En otra de esa forma de realización, m es 2, n es 0, q es 0 y r es 0. En otra de esa forma de realización, m es 1, n es 1, q es 0 y r es 0. En otra de esa forma de realización, m es 2, n es 1, q es 0 y r es 0.

Aun en otra forma de realización, m es 3, n es 0, q es 0 y r es 0.

En otra forma de realización de este aspecto, X es un arileno C_6-C_{12} o un heteroarileno de 5-12 miembros, cada uno de los cuales está opcionalmente sustituido con 0-4 sustituyentes R^{12}. En algunas de esas formas de realización, m es 0 y n es 1. En otras de esas formas de realización, m es 0 y n es 2. En alguna forma de realización de este aspecto, X es un arileno C_6-C_{12} o un heteroarileno de 5-12 miembros seleccionado del grupo que consiste en un anillo de fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol 1,2-disustituido, cada uno de los cuales está opcionalmente sustituido con 0-4 sustituyentes R^{12}. En algunas de esas formas de realización, m es 0, y n es 1. En otras de esas formas de realización, m es 0, y n es 2.

En formas de realización específicas, X está seleccionado del grupo que consiste en:



en donde los asteriscos (*) representan los puntos de unión al anillo macrocíclico.

En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6, en donde cada hidrógeno en dicho alquilo C_1-C_6, y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$.

En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6. En formas de realización específicas, R^1 es hidrógeno, metilo, etilo o ciclopropilo. En algunas formas de realización, R^1 es hidrógeno. En otras formas de realización, R^1 es metilo. En otras formas de realización, R^1 es etilo. En otras formas de realización, R^1 es ciclopropilo.

En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN;

en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$.

En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, -$S(O)_rR^7$, -$S(O)_2NR^7R^8$, -OR^7, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN.

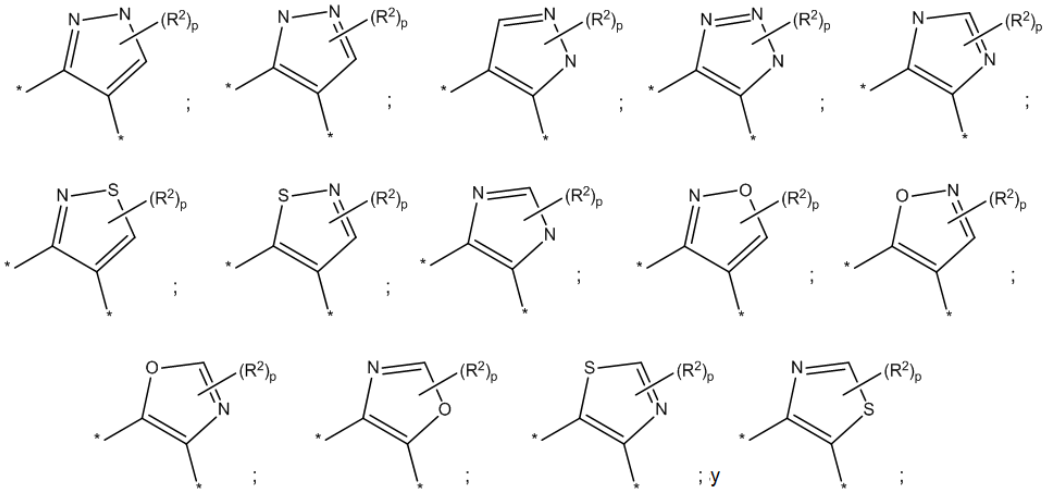
En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En formas de realización frecuentes, R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo. En algunas de esas formas de realización, cada uno de R^3 y R^4 es hidrógeno. En otras de esas formas de realización, uno de R^3 y R^4 es hidrógeno y el otro es metilo.

En algunas formas de realización de este aspecto, Q es O. En otras formas de realización de este aspecto, Q es CH_2.

En una forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en arilo C_6-C_{12} y heteroarilo de 5-12 miembros. En algunas formas de realización de este aspecto, el anillo A está opcionalmente sustituido con 0 a 4 grupos sustituyentes marcados como -$(R^2)_p$, en donde p es 0, 1, 2, 3 o 4. El experto en la técnica comprenderá que la cantidad de sustituyentes R^2 en el anillo A está limitada por la cantidad de posiciones de valencias abiertas en el anillo A, en donde dos de las posiciones de valencia se usan para incorporar el anillo A en el núcleo macrocíclico.

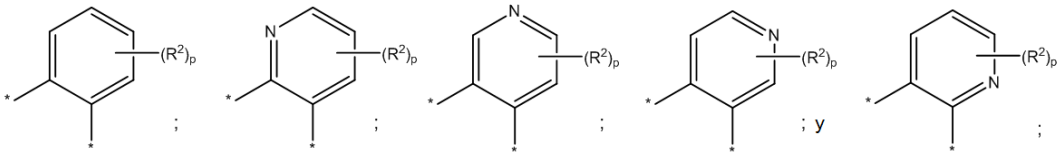
En otra forma de realización de este aspecto, A es un arilo C_6-C_{12} o anillo heteroarilo de 5-12 miembros seleccionado del grupo que consta en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina y triazina. En otras de esas formas de realización, A es un anillo seleccionado del grupo que consiste en pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En ciertas formas de realización, A es un anillo seleccionado del grupo que consiste en pirazol, triazol, tiazol, isotiazol, e isoxazol. En formas de realización específicas, A es un anillo de pirazol. En otras formas de realización, A es un anillo triazol. En otras formas de realización, A es un anillo isotiazol. Aun en otras formas de realización, A es un anillo de isoxazol. En otras formas de realización, A es un anillo fenilo o piridilo.

En algunas formas de realización de este aspecto, A está seleccionado del grupo que consiste en:



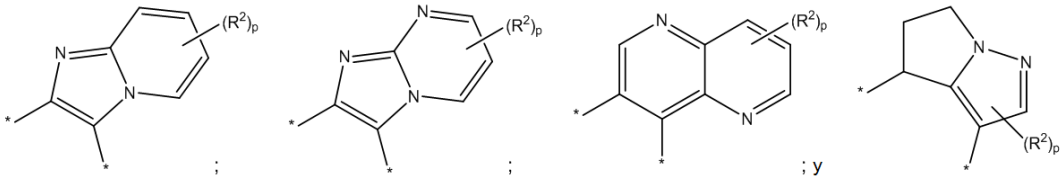
en donde los asteriscos (*) representan los puntos de unión al anillo macrocíclico. En algunas de esas formas de realización, p es 0, 1 o 2, y cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN.

En otras formas de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en:



en donde los asteriscos (*) representan los puntos de unión al anillo macrocíclico. En algunas de esas formas de realización, p es 0, 1 o 2, y cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN.

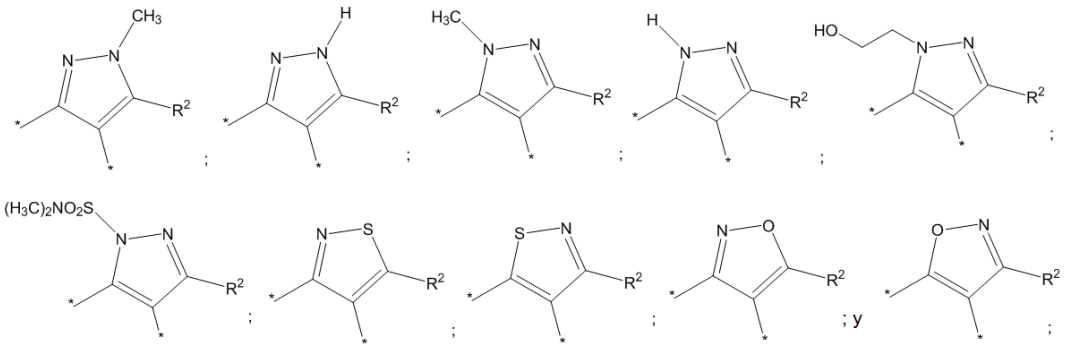
En otras formas de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en:



en donde los asteriscos (*) representan los puntos de unión al anillo macrocíclico. En algunas de esas formas de realización, p es 0, 1 o 2, y cada R^2 está seleccionado, de

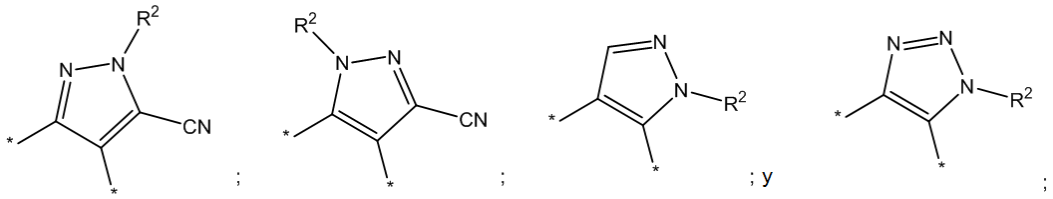
modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, -$S(O)_rR^7$, -$S(O)_2NR^7R^8$, -OR^7, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN.

En formas de realización específicas, A está seleccionado del grupo que consiste en:



en donde los asteriscos (*) representan los puntos de unión al anillo macrocíclico, y en donde R^2 está seleccionado del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, -OR^7, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN. En algunas de esas formas de realización, R^2 está seleccionado del grupo que consiste en metilo, etilo, ciclopropilo, metoxi, etoxi y -CN.

En otras formas de realización específicas, A está seleccionado del grupo que consiste en:



en donde los asteriscos (*) representan los puntos de unión al anillo macrocíclico, y en donde R^2 está seleccionado del grupo que consiste en alquilo C_1-C_6, y cicloalquilo C_3-C_6; y en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno o -OH. En algunas de esas formas de realización, R^2 está seleccionado del grupo que consiste en metilo, etilo, -2-hidroxietilo, propilo, isopropilo, n-butilo, isobutilo, *sec*-butilo, difluoroetilo, trifluoroetilo, ciclopropilo y ciclobutilo.

Ciertas formas de realización preferidas de la fórmula (Φ), o una de sus sales farmacéuticamente aceptables, tienen una, dos o más de las siguientes características preferidas, que se pueden presentar en combinación, en la medida en que no se contradigan entre sí:

T es CR^{11a}; U es CR^{11b}; V es CR^{11c}; y W es CR^{11d}; en donde al menos uno de

R^{11a}, R^{11b}, R^{11c}, y R^{11d} es halo, preferentemente flúor o cloro;

R^{11b} es halo, preferentemente flúor, y cada uno de R^{11a}, R^{11c}, y R^{11d} es hidrógeno;

X es $-(CR^5R^6)_qO(CR^5R^6)_r-$, en donde cada uno de R^5 y R^6 es H; m es 0; y n es 0;

X es $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, en donde cada uno de R^5 y R^6 es H; m es 0; y n es 0;

X es $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$,en donde cada uno de R^5 y R^6 es H, m es 0 y n es 0;

q es 1, y r es 1;

q es 0, y r es 1;

Y y Z son cada uno CH;

Y es N y Z es CH;

Q es O;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6;

R^1 es hidrógeno, metilo, etilo o ciclopropilo;

R^1 es metilo;

A es un arilo C_6-C_{12} o anillo heteroarilo de 5-12 miembros seleccionado del grupo que consta en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol;

A es un arilo C_6-C_{12} o un anillo heteroarilo de 5-12 miembros de fenilo, pirazol, imidazol, triazol, tiazol, isotiazol, oxazol e isoxazol;

A es un arilo C_6-C_{12} o un anillo heteroarilo de 5-12 miembros de fenilo, pirazol, triazol, isotiazol e isoxazol;

A es un pirazol;

p es 0, 1 o 2;

R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y –CN;

R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6;

R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo;

uno de R^3 y R^4 es hidrógeno y el otro es metilo;

R^5 y R^6 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6;

R^5 y R^6 son cada uno, de modo independiente, hidrógeno o metilo;

cada uno de R^5 y R^6 es hidrógeno;

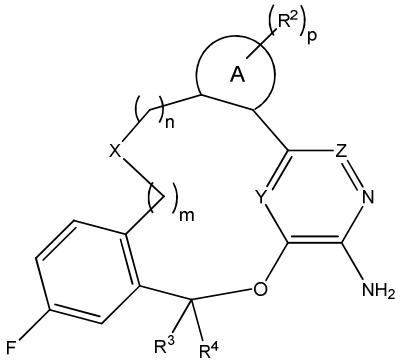
R^7 y R^8 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6; en donde cada hidrógeno en dicho alquilo C_1-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$; y

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6.

Las formas de realización descritas anteriormente como adecuadas para los compuestos de la fórmula (Φ), que incluyen las combinaciones de las formas de realización preferidas, también son adecuadas para los compuestos de las fórmulas (I) a (XXX), en la medida en que no se contradigan entre sí, como también se describió en la presente.

Los grupos aromáticos y heteroaromáticos específicos descritos anteriormente como adecuados para el anillo A en la fórmula Φ también son adecuados para el anillo A en los compuestos de las fórmulas (I) a (XXX), como también se describió en la presente.

En otro aspecto, la invención proporciona un compuesto de la fórmula (I)



(I)

en donde:

X está seleccionado del grupo que consiste en -$(CR^5R^6)_qO(CR^5R^6)_r$-, -$(CR^5R^6)_qN(R^1)(CR^5R^6)_r$-, -$(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r$- y -$(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r$-;

Y y Z son cada uno, de modo independiente, N o CH, siempre que, cuando Y es N, Z sea CH y cuando Z es N, Y sea CH;

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -

NH-
$_2$, -S(O)$_t$R^9, -S(O)$_2$NR^{9}R^{10}, -S(O)$_2$OR^9, -NO$_2$, -CN, -OR^9, -C(O)R^9, -OC(O)R^9, -NR^{9}C(O)R^{10}, -C(O)OR^9, -C(=NR^9)NR^{9}R^{10}, -NR^{9}C(O)NR^{9}R^{10}, -NR^{9}S(O)$_2$R^{10} y -C(O)NR^{9}R^{10}; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH-
$_2$, -S(O)$_t$R^9, -S(O)$_2$NR^{9}R^{10}, -S(O)$_2$OR^9, -NO$_2$, -CN, -OR^9, -C(O)R^9, -OC(O)R^9, -NR^{9}C(O)R^{10}, -C(O)OR^9, -C(=NR^9)NR^{9}R^{10}, -NR^{9}C(O)NR^{9}R^{10}, -NR^{9}S(O)$_2$R^{10} o -C(O)NR^{9}R^{10};

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH$_2$, -S(O)$_t$R^9, -S(O)$_2$NR^{9}R^{10}, -S(O)$_2$OR^9, -NO$_2$, -OR^9, -CN, -C(O)R^9, -OC(O)R^9, -NR^{9}C(O)R^{10}, -C(O)OR^9, -C(=NR^9)NR^{9}R^{10}, -NR^{9}C(O)NR^{9}R^{10}, -NR^{9}S(O)$_2$R^{10} o -C(O)NR^{9}R^{10};

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

m es 0, 1, 2 o 3;

n es 0, 1, 2 o 3;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

En una forma de realización de este aspecto, Y es N. En otra forma de realización de este aspecto, Z es N. En otro aspecto de esta forma de realización, Y es CH y Z es CH.

En otra forma de realización de este aspecto, X es -(CR^{5}R^6)$_q$O(CR^{5}R^6)$_r$-. En algunas de esas formas de realización, cuando X es -(CR^{5}R^6)$_q$O(CR^{5}R^6)$_r$-, m es 0 y n es 3. En otras de esas formas de realización, m es 1 y n es 2. En otras de esas formas de realización, m es 2 y n es 1. En otras de esas formas de realización, m es 3 y n es

0. Incluso en otra de esas formas de realización, m es 3 y n es 3. En otras de esas formas de realización, m es 2 y n es 2. En otras de esas formas de realización, m es 1 y n es 1. En otras de esas formas de realización, m es 0, n es 3, q es 0 y r es 0. Incluso en otra de esas formas de realización, m es 1, n es 2, q es 0 y r es 0. En otras de esas formas de realización, m es 2, n es 1, q es 0 y r es 0. Incluso en otra de esas formas de realización, m es 3, n es 0, q es 0 y r es 0.

En otra forma de realización de este aspecto, X está seleccionado del grupo que consiste en $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ y $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$. En una forma de realización de este aspecto, X es $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$. En otra de esa forma de realización de este aspecto, X es $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$. En otra de esa forma de realización de este aspecto, X es $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$.

En otra forma de realización de este aspecto, X es $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$. En algunas de esas formas de realización, cuando X es $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, m es 0 y n es 3. En otras de esas formas de realización, m es 1 y n es 2. En otras de esas formas de realización, m es 2 y n es 1. En otras de esas formas de realización, m es 3 y n es 0. Incluso en otra de esas formas de realización, m es 3 y n es 3. En otras de esas formas de realización, m es 2 y n es 2. En otras de esas formas de realización, m es 1 y n es 1. En otras de esas formas de realización, m es 0, n es 3, q es 0 y r es 0. Incluso en otra de esas formas de realización, m es 1, n es 2, q es 0 y r es 0. En otras de esas formas de realización, m es 2, n es 1, q es 0 y r es 0. Incluso en otra de esas formas de realización, m es 3, n es 0, q es 0 y r es 0. En otras de esas formas de realización, m es 1, n es 1, q es 0 y r es 0.

En otra forma de realización de este aspecto, X es $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$. En algunas de esas formas de realización, cuando X es $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$, m es 0 y n es 2. En otras de esas formas de realización, m es 0 y n es 1. Incluso en otra de esas formas de realización, m es 2 y n es 0. En otras de esas formas de realización, m es 2 y n es 2. En otras de esas formas de realización, m es 0, n es 2, q es 0 y r es 0. Incluso en otra de esas formas de realización, m es 0, n es 1, q es 0 y r es 0. En otras de esas formas de realización, m es 2, n es 0, q es 0 y r es 0.

En otra forma de realización de este aspecto, X es $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$. En algunas de esas formas de realización, cuando X es $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$, m es 0 y n es 2. En otras de esas formas de realización, m es 0 y n es 1. Incluso en otra de esas formas de realización, m es 2 y n

es 0. En otras de esas formas de realización, m es 0, n es 2, q es 0 y r es 0. Incluso en otra de esas formas de realización, m es 0, n es 1, q es 0 y r es 0. En otras de esas formas de realización, m es 2, n es 0, q es 0 y r es 0.

En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6, en donde cada hidrógeno en dicho alquilo C_1-C_6, y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6.

En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6. En formas de realización específicas, R^1 es hidrógeno, metilo, etilo o ciclopropilo. En algunas formas de realización, R^1 es hidrógeno. En otras formas de realización, R^1 es metilo. En otras formas de realización, R^1 es etilo. En otras formas de realización, R^1 es ciclopropilo.

En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en, alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$.

En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en a fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En formas de realización específicas de este aspecto, A es un anillo seleccionado del grupo que consiste en los anillos específicos indicados como adecuados para los compuestos de fórmula Φ,

anteriores.

En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En formas de realización frecuentes, R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo. En algunas de esas formas de realización, cada uno de R^3 y R^4 es hidrógeno. En otras de esas formas de realización, uno de R^3 y R^4 es hidrógeno y el otro es metilo.

Ciertas formas de realización preferidas de la fórmula (I), o una de sus sales farmacéuticamente aceptables, tienen una, dos o más de las siguientes características preferidas, que se pueden presentar en combinación, en la medida en que no se contradigan entre sí:

X es $-(CR^5R^6)_qO(CR^5R^6)_r-$, en donde cada uno de R^5 y R^6 es H; m es 0; y n es 0;

X es $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, en donde cada uno de R^5 y R^6 es H; m es 0; y n es 0;

X es $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$,en donde cada uno de R^5 y R^6 es H, m es 0 y n es 0;

q es 1, y r es 1;

q es 0, y r es 1;

Y y Z son cada uno CH;

Y es N y Z es CH;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6;

R^1 es hidrógeno, metilo, etilo o ciclopropilo;

R^1 es metilo;

A es un arilo C_6-C_{12} o anillo heteroarilo de 5-12 miembros seleccionado del grupo que consta en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol;

A es un arilo C_6-C_{12} o un anillo heteroarilo de 5-12 miembros de fenilo, pirazol, imidazol, triazol, tiazol, isotiazol, oxazol e isoxazol;

A es un arilo C_6-C_{12} o un anillo heteroarilo de 5-12 miembros de fenilo, pirazol, triazol, isotiazol e isoxazol;

A es un pirazol;

p es 0, 1 o 2;

R^2 está seleccionado, de modo independiente, del grupo que consiste en

alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y –CN;

R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6;

R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo;

uno de R^3 y R^4 es hidrógeno y el otro es metilo;

R^5 y R^6 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6;

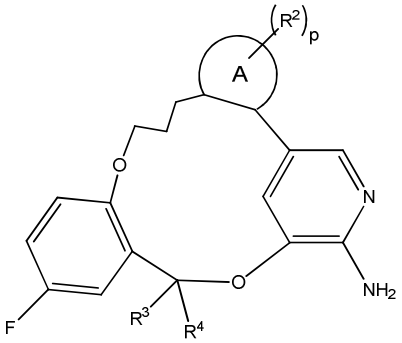
R^5 y R^6 son cada uno, de modo independiente, hidrógeno o metilo;

cada uno de R^5 y R^6 es hidrógeno;

R^7 y R^8 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6; en donde cada hidrógeno en dicho alquilo C_1-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6.

En otro aspecto, la invención proporciona un compuesto de la fórmula (II)



(II)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -

OR^7, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR$

$^{9}R^{10}$, $-NR^{9}S(O)_2R^{10}$ o $-C(O)NR^{9}R^{10}$;

cada R^9 y R^{10} se seleccionan, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

En una forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$.

En otro aspecto de esta forma de realización, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN.

En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En formas de realización frecuentes, R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo. En algunas de esas formas de realización, cada uno de R^3 y R^4 es hidrógeno. En otras de esas formas de realización, uno de R^3 y R^4 es hidrógeno y el otro es metilo.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En formas de realización específicas de este aspecto, A es un anillo seleccionado del grupo que consiste en los anillos específicos indicados como adecuados para los compuestos de fórmula Φ, anteriores.

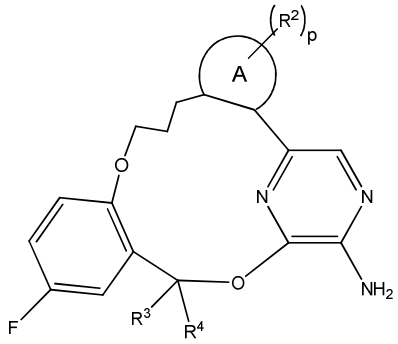
En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol.

En otra forma de realización de este aspecto, A es un anillo seleccionado de

fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol; cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; y R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En otras de esas formas de realización, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; y R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otro aspecto, la invención proporciona un compuesto de la fórmula (III)



(III)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo

C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} se seleccionan, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico

de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

En una forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En formas de realización frecuentes, R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo. En algunas de esas formas de realización, cada uno de R^3 y R^4 es hidrógeno. En otras de esas formas de realización, uno de R^3 y R^4 es hidrógeno y el otro es metilo.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol.

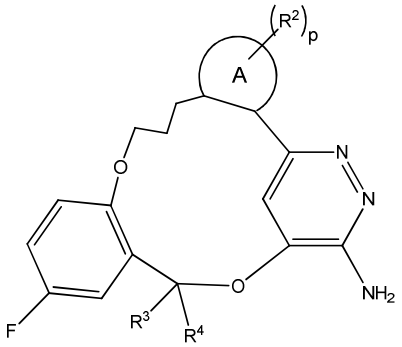
En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En formas de realización específicas de este aspecto, A es un anillo seleccionado del grupo que consiste en los anillos específicos indicados como adecuados para los compuestos de fórmula Φ, anteriores.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En

algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol; cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; y R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otro aspecto, la invención proporciona un compuesto de la fórmula (IV)



(IV)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno,

alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} se seleccionan, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

En una forma de realización de este aspecto, cada R^2 está seleccionado, de

modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, -$S(O)_rR^7$, -$S(O)_2NR^7R^8$, -OR^7, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, -$S(O)_rR^7$, -$S(O)_2NR^7R^8$, -OR^7, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En formas de realización frecuentes, R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo. En algunas de esas formas de realización, cada uno de R^3 y R^4 es hidrógeno. En otras de esas formas de realización, uno de R^3 y R^4 es hidrógeno y el otro es metilo.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En formas de realización específicas de este aspecto, A es un anillo seleccionado del grupo que consiste en los anillos específicos indicados como adecuados para los compuestos de fórmula Φ, anteriores.

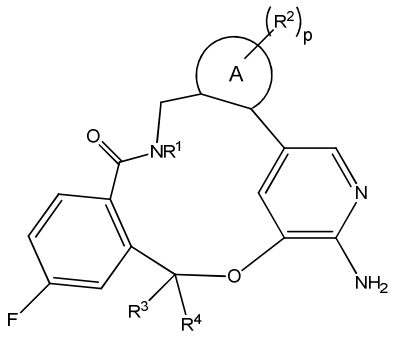
En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol; cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, -$S(O)_rR^7$, -$S(O)_2NR^7R^8$, -OR^7, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; y R^3 y R^4 están

seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol; cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; y R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otro aspecto, la invención proporciona un compuesto de la fórmula (V)



(V)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $--C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -

OR^7, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR$

$^{9}R^{10}$, $-NR^{9}S(O)_2R^{10}$ o $-C(O)NR^{9}R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

En una forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6, en donde cada hidrógeno en dicho alquilo C_1-C_6, y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6.

En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6. En formas de realización específicas, R^1 es hidrógeno, metilo, etilo o ciclopropilo. En algunas formas de realización, R^1 es hidrógeno. En otras formas de realización, R^1 es metilo. En otras formas de realización, R^1 es etilo. En otras formas de realización, R^1 es ciclopropilo.

En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y $-CN$; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y $-CN$. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de

modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En formas de realización frecuentes, R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo. En algunas de esas formas de realización, cada uno de R^3 y R^4 es hidrógeno. En otras de esas formas de realización, uno de R^3 y R^4 es hidrógeno y el otro es metilo.

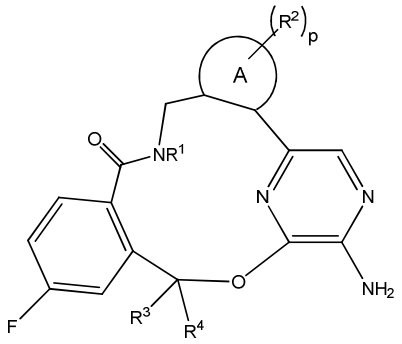
En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En formas de realización específicas de este aspecto, A es un anillo seleccionado del grupo que consiste en los anillos específicos indicados como adecuados para los compuestos de fórmula Φ, anteriores.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol; cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; y R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otro aspecto, la invención proporciona un compuesto de la fórmula (VI)



(VI)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y

cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

En una forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6, en donde cada

hidrógeno en dicho alquilo C_1-C_6, y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6.

En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6. En formas de realización específicas, R^1 es hidrógeno, metilo, etilo o ciclopropilo. En algunas formas de realización, R^1 es hidrógeno. En otras formas de realización, R^1 es metilo. En otras formas de realización, R^1 es etilo. En otras formas de realización, R^1 es ciclopropilo.

En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En formas de realización frecuentes, R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo. En algunas de esas formas de realización, cada uno de R^3 y R^4 es hidrógeno. En otras de esas formas de realización, uno de R^3 y R^4 es hidrógeno y el otro es metilo.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

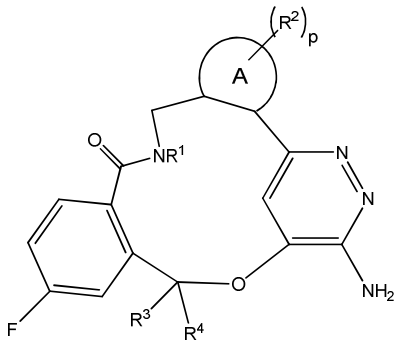
En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En formas de realización específicas de este aspecto, A es un anillo seleccionado del grupo que consiste en los anillos específicos indicados como adecuados para los compuestos de fórmula Φ, anteriores.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol; cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; y R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otro aspecto, la invención proporciona un compuesto de la fórmula (VII)



(VII)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6,

alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6,

cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

En una forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6, en donde cada hidrógeno en dicho alquilo C_1-C_6, y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_rR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6.

En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6. En formas de realización específicas, R^1 es hidrógeno, metilo, etilo o ciclopropilo. En algunas formas de realización, R^1 es hidrógeno. En otras formas de realización, R^1 es metilo. En otras formas de realización, R^1 es etilo. En otras formas de realización, R^1 es

ciclopropilo.

En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En formas de realización frecuentes, R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo. En algunas de esas formas de realización, cada uno de R^3 y R^4 es hidrógeno. En otras de esas formas de realización, uno de R^3 y R^4 es hidrógeno y el otro es metilo.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En formas de realización específicas de este aspecto, A es un anillo seleccionado del grupo que consiste en los anillos específicos indicados como adecuados para los compuestos de fórmula Φ, anteriores.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del

grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol; cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; y R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

Ciertas formas de realización preferidas de las fórmulas (V), (V) y (VI), o una de sus sales farmacéuticamente aceptables, tienen una, dos o más de las siguientes características preferidas, que se pueden presentar en combinación en la medida en que no se contradigan entre sí:

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6;

R^1 es hidrógeno, metilo, etilo o ciclopropilo;

R^1 es metilo;

A es un arilo C_6-C_{12} o anillo heteroarilo de 5-12 miembros seleccionado del grupo que consta en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol;

A es un arilo C_6-C_{12} o un anillo heteroarilo de 5-12 miembros de fenilo, pirazol, imidazol, triazol, tiazol, isotiazol, oxazol e isoxazol;

A es un arilo C_6-C_{12} o un anillo heteroarilo de 5-12 miembros de fenilo, pirazol, triazol, isotiazol e isoxazol;

A es un pirazol;

p es 0, 1 o 2;

R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y –CN;

R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6;

R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo;

uno de R^3 y R^4 es hidrógeno y el otro es metilo;

R^5 y R^6 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6;

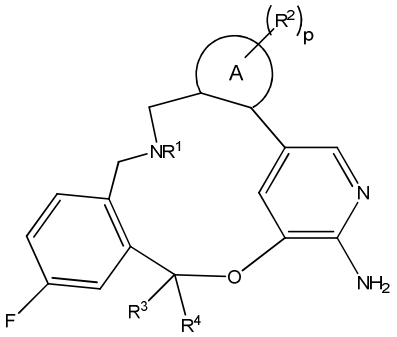
R^5 y R^6 son cada uno, de modo independiente, hidrógeno o metilo;

cada uno de R^5 y R^6 es hidrógeno;

R^7 y R^8 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6; en donde cada hidrógeno en dicho alquilo C_1-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6.

En otro aspecto, la invención proporciona un compuesto de la fórmula (VIII)



(VIII)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en

halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6,

cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

En una forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6, en donde cada hidrógeno en dicho alquilo C_1-C_6, y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_rR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6.

En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6. En formas de realización específicas, R^1 es hidrógeno, metilo, etilo o ciclopropilo. En algunas formas de realización, R^1 es hidrógeno. En otras formas de realización, R^1 es metilo. En otras formas de realización, R^1 es etilo. En otras formas de realización, R^1 es ciclopropilo.

En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, -$S(O)_rR^7$, -$S(O)_2NR^7R^8$, -OR^7, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, cada

R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En formas de realización frecuentes, R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo. En algunas de esas formas de realización, cada uno de R^3 y R^4 es hidrógeno. En otras de esas formas de realización, uno de R^3 y R^4 es hidrógeno y el otro es metilo.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En formas de realización específicas de este aspecto, A es un anillo seleccionado del grupo que consiste en los anillos específicos indicados como adecuados para los compuestos de fórmula Φ, anteriores.

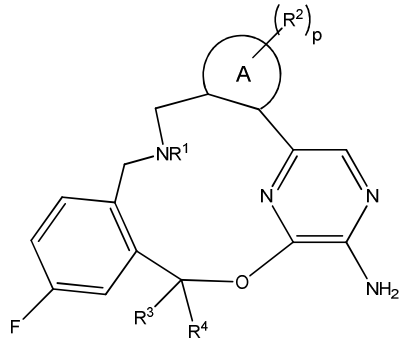
En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol; cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, -

OR^7, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; y R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otro aspecto, la invención proporciona un compuesto de la fórmula (IX)



(IX)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -

OR^9, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6, en donde cada hidrógeno en dicho alquilo C_1-C_6, y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_rR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6.

En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6. En formas de realización específicas, R^1 es hidrógeno, metilo, etilo o ciclopropilo. En algunas formas de realización, R^1 es hidrógeno. En otras formas de realización, R^1 es metilo. En otras formas de realización, R^1 es etilo. En otras formas de realización, R^1 es ciclopropilo.

En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En formas de realización frecuentes, R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo. En algunas de esas formas de realización, cada uno de R^3 y R^4 es hidrógeno. En otras de esas formas de realización, uno de R^3 y R^4 es hidrógeno y el otro es metilo.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

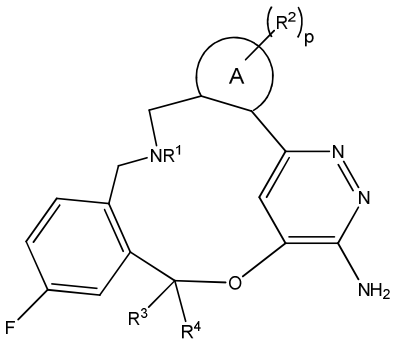
En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En formas de realización específicas de este aspecto, A es un anillo seleccionado del grupo que consiste en los anillos específicos indicados como adecuados para los compuestos de fórmula Φ, anteriores.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol; cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; y R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otro aspecto, la invención proporciona un compuesto de la fórmula (X)



(X)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -

NH-
$_2$, -S(O)$_t$R^9, -S(O)$_2$NR^{9}R^{10}, -S(O)$_2$OR^9, -NO$_2$, -CN, -OR^9, -C(O)R^9, -OC(O)R^9, -NR^{9}C(O)R^{10}, -C(O)OR^9, -C(=NR^9)NR^{9}R^{10}, -NR^{9}C(O)NR^{9}R^{10}, -NR^{9}S(O)$_2$R^{10} y -C(O)NR^{9}R^{10}; en donde cada hidrógeno en dicho alquilo C$_1$-C$_6$, alquenilo C$_2$-C$_6$, alquinilo C$_2$-C$_6$, cicloalquilo C$_3$-C$_6$, arilo C$_6$-C$_{12}$, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH-
$_2$, -S(O)$_t$R^9, -S(O)$_2$NR^{9}R^{10}, -S(O)$_2$OR^9, -NO$_2$, -CN, -OR^9, -C(O)R^9, -OC(O)R^9, -NR^{9}C(O)R^{10}, -C(O)OR^9, -C(=NR^9)NR^{9}R^{10}, -NR^{9}C(O)NR^{9}R^{10}, -NR^{9}S(O)$_2$R^{10} o -C(O)NR^{9}R^{10};

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C$_1$-C$_6$, alquenilo C$_2$-C$_6$, alquinilo C$_2$-C$_6$, cicloalquilo C$_3$-C$_6$, arilo C$_6$-C$_{12}$, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C$_1$-C$_6$, alquenilo C$_2$-C$_6$, alquinilo C$_2$-C$_6$, cicloalquilo C$_3$-C$_6$, arilo C$_6$-C$_{12}$, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH$_2$, -S(O)$_t$R^9, -S(O)$_2$NR^{9}R^{10}, -S(O)$_2$OR^9, -NO$_2$, -OR^9, -CN, -C(O)R^9, -OC(O)R^9, -NR^{9}C(O)R^{10}, -C(O)OR^9, -C(=NR^9)NR^{9}R^{10}, -NR^{9}C(O)NR^{9}R^{10}, -NR^{9}S(O)$_2$R^{10} o -C(O)NR^{9}R^{10};

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C$_1$-C$_6$, alquenilo C$_2$-C$_6$, alquinilo C$_2$-C$_6$, cicloalquilo C$_3$-C$_6$, arilo C$_6$-C$_{12}$, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

En una forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C$_1$-C$_6$, y cicloalquilo C$_3$-C$_6$, en donde cada hidrógeno en dicho alquilo C$_1$-C$_6$, y cicloalquilo C$_3$-C$_6$ puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH$_2$, -S(O)$_r$R^9, -S(O)$_2$NR^{9}R^{10}, -S(O)$_2$OR^9, -NO$_2$, -CN, -OR^9, -C(O)R^9, -OC(O)R^9, -NR^{9}C(O)R^{10}, -C(O)OR^9, -C(=NR^9)NR^{9}R^{10}, -NR^{9}C(O)NR^{9}R^{10}, -NR^{9}S(O)$_2$R^{10} o -C(O)NR^{9}R^{10}. En otra forma de realización de este aspecto, R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C$_1$-C$_6$, y cicloalquilo C$_3$-C$_6$.

En otra forma de realización de este aspecto, cada R^2 está seleccionado, de

modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, -$S(O)_rR^7$, -$S(O)_2NR^7R^8$, -OR^7, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$. En otra forma de realización de este aspecto, cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, -$S(O)_rR^7$, -$S(O)_2NR^7R^8$, -OR^7, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6. En formas de realización frecuentes, R^3 y R^4 son cada uno, de modo independiente, hidrógeno o metilo. En algunas de esas formas de realización, cada uno de R^3 y R^4 es hidrógeno. En otras de esas formas de realización, uno de R^3 y R^4 es hidrógeno y el otro es metilo.

En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En otra forma de realización de este aspecto, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En formas de realización específicas de este aspecto, A es un anillo seleccionado del grupo que consiste en los anillos específicos indicados como adecuados para los compuestos de fórmula Φ, anteriores.

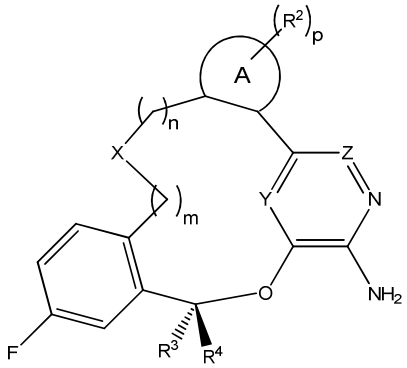
En otra forma de realización de este aspecto, A es un anillo seleccionado de fenilo, piridina, triazina, pirazol, imidazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol. En algunas de esas formas

de realización, R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otra forma de realización de este aspecto, A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol; cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; y R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6.

En otro aspecto, la invención proporciona un compuesto de la fórmula (XI)



(XI)

en donde:

X está seleccionado del grupo que consiste en $-(CR^5R^6)_qO(CR^5R^6)_r-$, $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ y $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$;

Y y Z son cada uno, de modo independiente, N o CH, siempre que, cuando Y es N, Z sea CH y cuando Z es N, Y sea CH;

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$,

$-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en

donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

m es 0, 1, 2 o 3;

n es 0, 1, 2 o 3;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

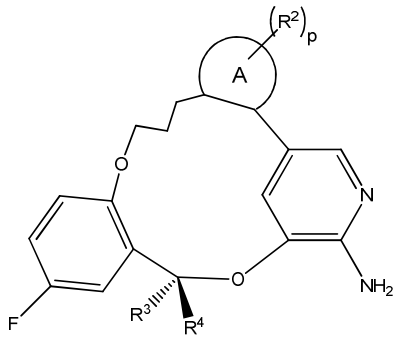
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las mismas formas de realización descritas en la presente como relevantes para los compuestos de la fórmula (I) también son aplicables a los compuestos de la fórmula (XI).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XII)



(XII)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -

OR^7, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^9 y R^{10} se seleccionan, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

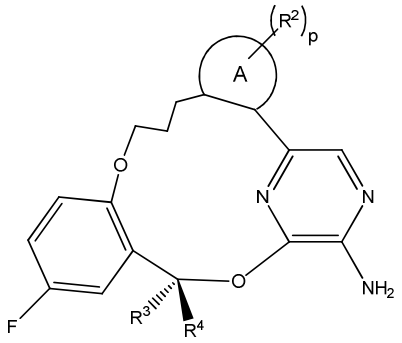
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las mismas formas de realización descritas en la presente como relevantes para los compuestos de la fórmula (II) también son aplicables a los compuestos de la fórmula (XII).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XIII)



(XIII)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR$

$^{9}R^{10}$, $-NR^{9}S(O)_2R^{10}$ o $-C(O)NR^{9}R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^9 y R^{10} se seleccionan, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

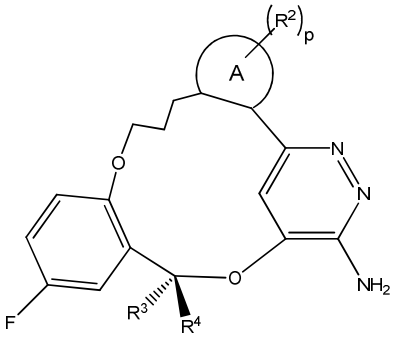
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las mismas formas de realización descritas en la presente como relevantes para los compuestos de la fórmula (III) también son aplicables a los compuestos de la fórmula (XIII).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XIV)



(XIV)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, $-CN$, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, $-CN$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, $-OH$, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-CN$, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-

C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^9 y R^{10} se seleccionan, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

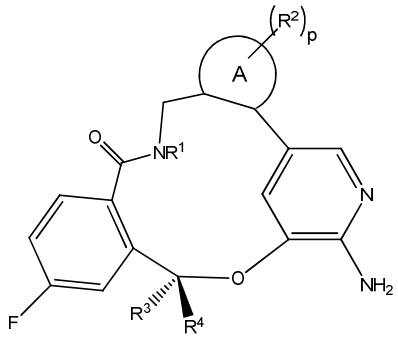
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las mismas formas de realización descritas en la presente como relevantes para los compuestos de la fórmula (IV) también son aplicables a los compuestos de la fórmula (XIV).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XV)



(XV)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido,

de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

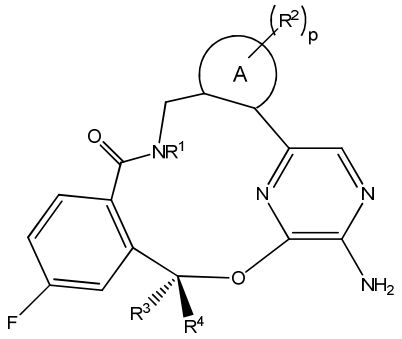
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las mismas formas de realización descritas en la presente como relevantes para los compuestos de la fórmula (V) también son aplicables a los compuestos de la fórmula (XV).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XVI)



(XVI)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada

hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

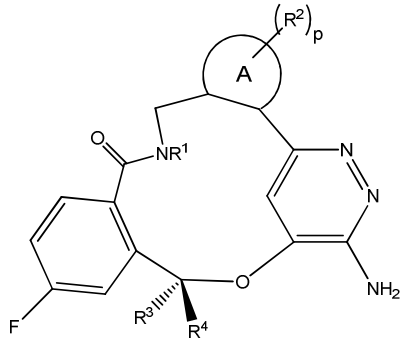
cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las mismas formas de realización descritas en la presente como relevantes para los compuestos de la fórmula (VI) también son aplicables a los compuestos de la

fórmula (XVI).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XVII)



(XVII)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

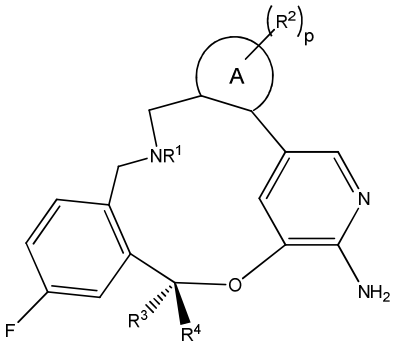
cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las mismas formas de realización descritas en la presente como relevantes

para los compuestos de la fórmula (VII) también son aplicables a los compuestos de la fórmula (XVII).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XVIII)



(XVIII)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR$

$^{9}R^{10}$, $-NR^{9}S(O)_2R^{10}$ o $-C(O)NR^{9}R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

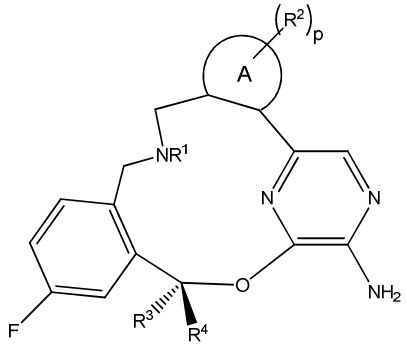
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las mismas formas de realización descritas en la presente como relevantes para los compuestos de la fórmula (VIII) también son aplicables a los compuestos de la fórmula (XVIII).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XIX)



(XIX)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -

OR^9, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

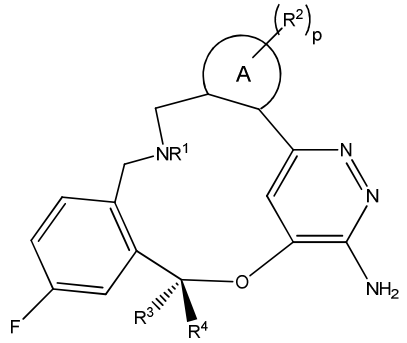
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las mismas formas de realización descritas en la presente como relevantes para los compuestos de la fórmula (IX) también son aplicables a los compuestos de la fórmula (XIX).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XX)



(XX)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2,

$_2$, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

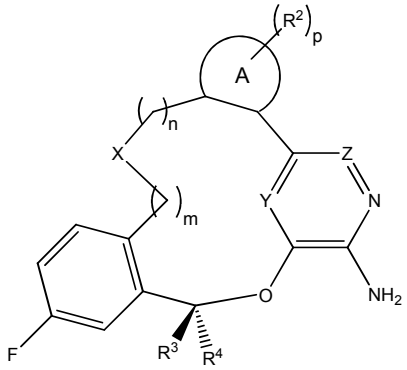
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las mismas formas de realización descritas en la presente como relevantes para los compuestos de la fórmula (X) también son aplicables a los compuestos de la fórmula (XX).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XXI)



(XXI)

en donde:

X está seleccionado del grupo que consiste en $-(CR^5R^6)_qO(CR^5R^6)_r-$, $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ y $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$;

Y y Z son cada uno, de modo independiente, N o CH, siempre que, cuando Y es N, Z sea CH y cuando Z es N, Y sea CH;

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, -

$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR$

$^{9}R^{10}$, $-NR^{9}S(O)_2R^{10}$ o $-C(O)NR^{9}R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

m es 0, 1, 2 o 3;

n es 0, 1, 2 o 3;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

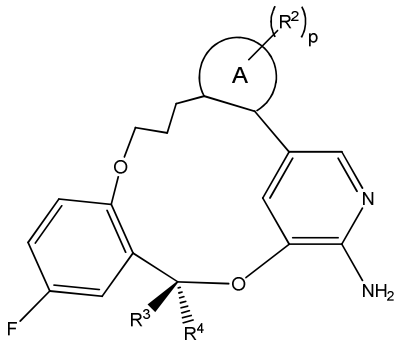
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las formas de realización descritas en la presente como relevantes para los compuestos de las fórmulas (I) y (XI) también son aplicables a los compuestos de la fórmula (XXI), en la medida en que sean compatibles con la definición de R^3 y R^4 en la fórmula (XXI).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XXII)



(XXII)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico

de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} se seleccionan, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

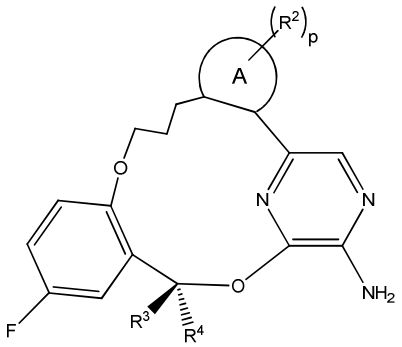
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las formas de realización descritas en la presente como relevantes para los compuestos de la fórmula (II) y (XII), también son aplicables a los compuestos de la fórmula (XXII), en la medida en que sean compatibles con la definición de R^3 y R^4 en la fórmula (XXII).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XXIII)



(XXIII)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido,

de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} se seleccionan, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

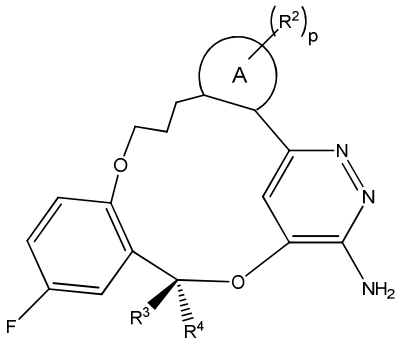
cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las formas de realización descritas en la presente como relevantes para los compuestos de fórmula (III) y (XIII) también son aplicables a los compuestos de la fórmula (XXIII), en la medida en que sean compatibles con la definición de R^3 y R^4 en

la fórmula (XXIII).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XXIV)



(XXIV)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH-

$_2$, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} se seleccionan, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

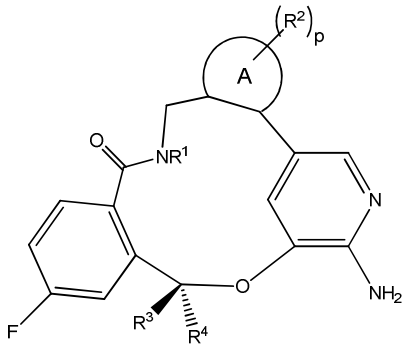
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las formas de realización descritas en la presente como relevantes para los compuestos de fórmula (IV) y (XIV) también son aplicables a los compuestos de la fórmula (XXIV), en la medida en que sean compatibles con la definición de R^3 y R^4 en la fórmula (XXIV).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XXV)



(XXV)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, --$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido,

de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

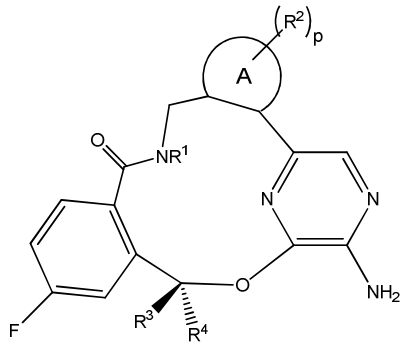
cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las formas de realización descritas en la presente como relevantes para los compuestos de fórmula (V) y (XV) también son aplicables a los compuestos de la fórmula (XV), en la medida en que sean compatibles con la definición de R^3 y R^4 en la

fórmula (XV).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XXVI)



(XXVI)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

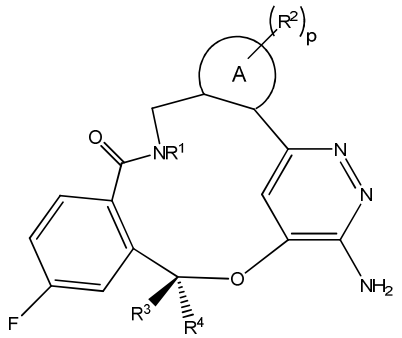
cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las formas de realización descritas en la presente como relevantes para los

compuestos de fórmula (VI) y (XVI) también son aplicables a los compuestos de la fórmula (XVI), en la medida en que sean compatibles con la definición de R^3 y R^4 en la fórmula (XVI).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XXVII)



(XXVII)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -

OR^9, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

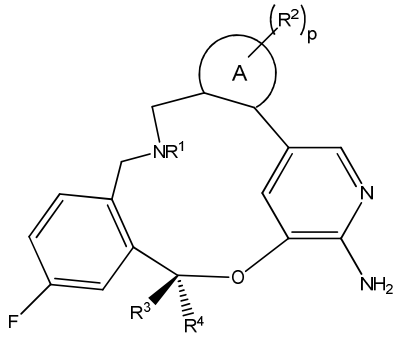
cada r es, de modo independiente, 0, 1, 2 o 3;

cada t es, de modo independiente, 0, 1 o 2; o una de sus sales

farmacéuticamente aceptables.

Las formas de realización descritas en la presente como relevantes para los compuestos de fórmula (VII) y (XVII) también son aplicables a los compuestos de la fórmula (XVII), en la medida en que sean compatibles con la definición de R^3 y R^4 en la fórmula (XVII).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XXVIII)



(XXVIII)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente

sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

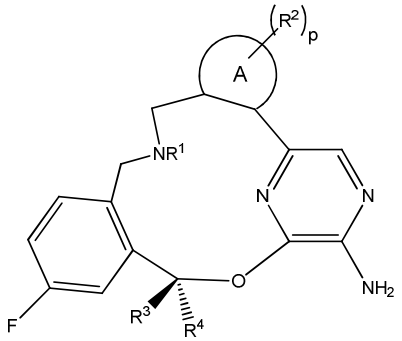
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las formas de realización descritas en la presente como relevantes para los compuestos de fórmula (VIII) y (XVIII) también son aplicables a los compuestos de la fórmula (XVIII), en la medida en que sean compatibles con la definición de R^3 y R^4 en la fórmula (XVIII).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XXIX)



(XXIX)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo

C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

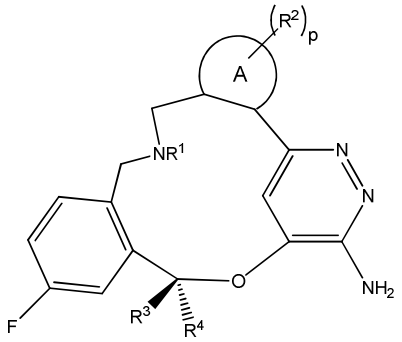
cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las formas de realización descritas en la presente como relevantes para los compuestos de fórmula (IX) y (XIX) también son aplicables a los compuestos de la fórmula (XXIX), en la medida en que sean compatibles con la definición de R^3 y R^4 en la fórmula (XXIX).

En otro aspecto, la invención proporciona un compuesto de la fórmula (XXX)



(XXX)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5$

$R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo

C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

Las formas de realización descritas en la presente como relevantes para los compuestos de fórmula (X) y (XX) también son aplicables a los compuestos de la fórmula (XXX), en la medida en que sean compatibles con la definición de R^3 y R^4 en la fórmula (XXX).

En una forma de realización, la invención proporciona una o más compuestos seleccionados del grupo que consiste en los compuestos de Ejemplo 1 a Ejemplo 137, o una de sus sales farmacéuticamente aceptables.

En otra forma de realización, la invención proporciona un compuesto seleccionado de:

(5*R*)-8-amino-3-fluoro-5,17-dimetil-13-(metilsulfonil)-16,17-dihidro-7,11-(meteno)dibenzo[*g*,*l*][1,4,10]oxadiazaciclotetradecin-18(5*H*)-ona;

(10*R*)-7-amino-12-fluoro-2,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo;

(10*R*)-7-amino-12-fluoro-3-metoxi-10,16-dimetil-16,17-dihidro-8,4-(meteno)isotiazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona;

7-amino-12-fluoro-2,16-dimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo;

8-amino-3-fluoro-17-metil-13-(metilsulfonil)-16,17-dihidro-7,11-(meteno)dibenzo[*g*,*l*][1,4,10]oxadiazaciclotetradecin-18(5*H*)-ona;

7-amino-12-fluoro-1,3,16-trimetil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona;

8-amino-3-fluoro-17-metil-16,17-dihidro-7,11-(meteno)dibenzo[*g*,*l*][1,4,10]oxadiazaciclotetradecin-18(5*H*)-ona;

8-amino-3-fluoro-5,17-dimetil-16,17-dihidro-7,11-(meteno)dibenzo[*g*,*l*][1,4,10]-oxadiazaciclotetradecin-18(5*H*)-ona;

7-amino-16-etil-12-fluoro-1,3,10-trimetil-16,17-dihidro-1H-8,4-(meteno)pirazolo [4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona;

7-amino-16-ciclopropil-12-fluoro-1,3,10-trimetil-16,17-dihidro-1H-8,4-

(meteno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona;

7-amino-12-fluoro-1,3,10,16-tetrametil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona;

7-amino-3-ciclopropil-12-fluoro-2,10,16-trimetil-16,17-dihidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona;

7-amino-3-ciclopropil-12-fluoro-1,10,16-trimetil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona;

7-amino-12-fluoro-3-metoxi-2,10,16-trimetil-16,17-dihidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona;

7-amino-12-fluoro-3-metoxi-1,10,16-trimetil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona;

7-amino-10-etil-12-fluoro-3-metoxi-1,16-dimetil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona;

7-amino-10-ciclopropil-12-fluoro-3-metoxi-1,16-dimetil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona;

(10*R*)-7-amino-3-etil-12-fluoro-10,16-dimetil-16,17-dihidro-3*H*-8,4-(meteno)pirazolo[3,4-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona;

7-amino-12-fluoro-1,3,10,16-tetrametil-16,17-dihidro-1H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona;

8-amino-13-fluoro-4-metoxi-11,17-dimetil-17,18-dihidro-9,5-(azeno)pirido[3,4-h][2,5,11]benzoxadiazaciclotetradecin-16(11H)-ona;

7-amino-12-fluoro-2,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo;

(11*R*)-8-amino-13-fluoro-4-metoxi-11,17-dimetil-17,18-dihidro-9,5-(meteno)pirido[3,4-*h*][2,5,11]benzoxadiazaciclotetradecin-16(11*H*)-ona;

(5*R*)-3-fluoro-5,17-dimetil-13-(metilsulfonil)-5,16,17,18-tetrahidro-7,11-(meteno)dibenzo[*g*,*l*][1,4,10]oxadiazaciclotetradecin-8-amina;

(10*R*)-7-amino-12-fluoro-2,10,16-trimetil-10,15,16,17-tetrahidro-2*H*-4,8-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo;

12-fluoro-3-metil-3,16,17,18-tetrahidro-10H-8,4-(meteno)pirazolo[4,3-e][1,12,9]benzodioxazaciclopentadecin-7-amina;

12-fluoro-3-metil-1,16,17,18-tetrahidro-10H-8,4-(meteno)pirazolo[3,4-e][1,12,9]benzodioxazaciclopentadecin-7-amina;

7-amino-12-fluoro-2,16,17,18-tetrahidro-10H-8,4-(meteno)pirazolo[3,4-e][1,12,9]benzodioxazaciclopentadecin-3-carbonitrilo;

7-amino-12-fluoro-16,17-dihidro-1H,10H-8,4-(meteno)pirazolo[3,4-d][1,11,8]benzodioxazaciclotetradecin-3-carbonitrilo; y

(10*R*)-7-amino-12-fluoro-10,16-dimetil-3-propil-16,17-dihidro-3*H*-8,4-(meteno)[1,2,3]triazolo[4,5-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona;

o una de sus sales farmacéuticamente aceptables.

En otro aspecto, la invención provee una composición farmacéutica que comprende un compuesto de una de las fórmulas descritas en la presente, o una de sus sales farmacéuticamente aceptables, y un portador o excipiente farmacéuticamente aceptable. En algunas formas de realización, la composición farmacéutica comprende dos o más portadores y/o excipientes farmacéuticamente aceptables.

En otro aspecto, la invención provee un compuesto de una de las fórmulas descritas en la presente, o una de sus sales farmacéuticamente aceptables, para uso como un medicamento. En una forma de realización, el medicamento es para usar en el tratamiento del crecimiento celular anormal en un mamífero. En formas de realización frecuentes, el crecimiento celular anormal es cáncer. En una forma de realización, el medicamento es para uso en el tratamiento del crecimiento celular anormal mediado por ALK en un mamífero. En otra forma de realización, el medicamento es para uso en el tratamiento del crecimiento celular anormal mediado por una proteína de fusión EML4-ALK en un mamífero. En algunas de dichas formas de realización, la proteína de fusión EML4-ALK tiene al menos una mutación. En una forma de realización, la mutación es L1196M. En otra forma de realización, la mutación es C_{11}56Y.

En una forma de realización, la invención provee un compuesto de una de las fórmulas descritas en la presente, o una de sus sales farmacéuticamente aceptables, para uso en el tratamiento del crecimiento celular anormal en un mamífero. En formas de realización frecuentes, el crecimiento celular anormal es cáncer. En una forma de realización, el crecimiento celular anormal es mediado por ALK. En otra forma de realización, el crecimiento celular anormal es mediado por una proteína de fusión EML4-ALK. En algunas de dichas formas de realización, la proteína de fusión EML4-ALK tiene al menos una mutación. En una forma de realización, la mutación es L1196M. En otra forma de realización, la mutación es C_{11}56Y.

La invención también provee métodos y usos terapéuticos que comprenden administrar un compuesto de la invención, o una de sus sales farmacéuticamente

aceptables, en forma individual o en combinación con otro agente terapéutico o agente paliativo a un mamífero que necesita dicho tratamiento. En una forma de realización preferida, el mamífero es un ser humano. En otras formas de realización, el mamífero es un perro o un gato.

En un aspecto, la invención provee un método para el tratamiento del crecimiento celular anormal en un mamífero, que comprende administrar a un mamífero una cantidad terapéuticamente efectiva de un compuesto de la invención, o una de sus sales farmacéuticamente aceptables.

En otro aspecto, la invención provee un método para el tratamiento del crecimiento celular anormal en un mamífero, que comprende administrar a un mamífero una cantidad de un compuesto de la invención, o una de sus sales farmacéuticamente aceptables, en combinación con una cantidad de un agente antitumoral, en donde dichas cantidades son, en forma conjunta, efectivas para tratar dicho crecimiento celular anormal. En algunas formas de realización, el agente antitumoral se selecciona entre el grupo que consiste en inhibidores mitóticos, agentes alquilantes, anti-metabolitos, antibióticos intercalantes, inhibidores del factor de crecimiento, radiación, inhibidores del ciclo celular, enzimas, inhibidores de topoisomerasa, modificadores de respuesta biológica, anticuerpos, citotóxicos, anti-hormonas, y anti-andrógenos.

En una forma de realización, la invención provee un método para el tratamiento del crecimiento celular anormal en un mamífero, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva de un compuesto de una de las fórmulas descritas en la presente, o una de sus sales farmacéuticamente aceptables. En formas de realización frecuentes, el crecimiento celular anormal es cáncer. En una forma de realización, el crecimiento celular anormal es mediado por ALK. En otra forma de realización, el crecimiento celular anormal es mediado por una proteína de fusión EML4-ALK. En algunas de dichas formas de realización, la proteína de fusión EML4-ALK tiene al menos una mutación. En una forma de realización, la mutación es L1196M. En otra forma de realización, la mutación es C_{11}56Y.

En otro aspecto, la invención provee un método para el tratamiento de un trastorno mediado por ALK en un mamífero, que comprende administrar al mamífero un compuesto de la invención, o una de sus sales farmacéuticamente aceptables, en una cantidad que es efectiva para tratar dicho trastorno.

Los compuestos y las sales de la presente invención inhiben ALK de tipo silvestre y/o ciertas formas mutantes de ALK, que incluyen las proteínas de fusión

EML4-ALK, con inclusión de las proteínas de fusión EML4-ALK que tienen al menos una mutación. En una forma de realización, la mutación es L1196M. En una forma de realización, la mutación es C_{11}56Y.

En una forma de realización, la invención provee un método para tratar la proliferación celular anormal en un mamífero, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva de un compuesto de la invención o una de sus sales farmacéuticamente aceptables. En algunas de dichas formas de realización, la proliferación celular anormal es cáncer. En una forma de realización, el cáncer es mediado por ALK. En otra forma de realización, el cáncer es mediado por una proteína de fusión EML4-ALK. En otras formas de realización similares, la proteína de fusión EML4-ALK tiene al menos una mutación. En una forma de realización similar, la mutación es L1196M. En otra forma de realización similar, la mutación es C_{11}56Y.

En otro aspecto, la invención provee un compuesto de una de las fórmulas descritas en la presente, o una de sus sales farmacéuticamente aceptables, para usar en el tratamiento del crecimiento celular anormal en un mamífero. En otro aspecto, la invención provee el uso de un compuesto de una de las fórmulas descritas en la presente, o una de sus sales farmacéuticamente aceptables, para el tratamiento del crecimiento celular anormal en un mamífero.

En otro aspecto más, la invención provee el uso de un compuesto de una de las fórmulas descritas en la presente, o una sal farmacéuticamente aceptable del mismo, para la preparación de un medicamento para el tratamiento del crecimiento celular anormal.

En formas de realización frecuentes de los métodos y usos descritos en la presente, el crecimiento celular anormal es cáncer. En algunas formas de realización, el cáncer se selecciona entre cáncer de pulmón, cáncer de huesos, cáncer de páncreas, cáncer de piel, cáncer de cabeza o cuello, melanoma cutáneo o intraocular, cáncer uterino, cáncer ovárico, cáncer rectal, cáncer de la región anal, cáncer de estómago, cáncer de colon, cáncer de mama, carcinoma de las trompas de Falopio, carcinoma del endometrio, carcinoma del cuello uterino, carcinoma de la vagina, carcinoma de la vulva, enfermedad de Hodgkin, cáncer de esófago, cáncer de intestino delgado, cáncer del sistema endocrino, cáncer de la glándula tiroides, cáncer de la glándula paratiroides, cáncer de la glándula suprarrenal, sarcoma de tejidos blandos, cáncer de la uretra, cáncer de pene, cáncer de próstata, leucemia crónica o aguda, linfomas linfocíticos, cáncer de vejiga, cáncer de riñón o uréter, carcinoma de células

renales, carcinoma de la pelvis renal, neoplasias del sistema nervioso central (SNC), linfoma primario del SNC, tumores del eje espinal, glioma del tronco encefálico, adenoma de la pituitaria y sus combinaciones.

En otra forma de realización, el cáncer se selecciona del grupo que consiste en cáncer de pulmonar de células no pequeñas (NSCLC), carcinoma de células escamosas, cáncer de próstata refractario a las hormonas, carcinoma papilar de células renales, adenocarcinoma colorrectal, neuroblastomas, linfoma anaplásico de células grandes (ALCL) y cáncer gástrico.

En algunas formas de realización, los métodos descritos en la presente además comprenden administrar al mamífero una cantidad de un agente terapéutico anticancerígeno o un agente paliativo, en donde dichas cantidades son, en forma conjunta, efectivas para tratar dicho crecimiento celular anormal. En algunas de dichas formas de realización, uno o más agentes terapéuticos anticancerígenos se seleccionan entre agentes antitumorales, agentes anti-angiogénesis, inhibidores de la transducción de señales y agentes antiproliferativos, en donde dichas cantidades son, en forma conjunta, efectivas para tratar dicho crecimiento celular anormal.

En otras formas de realización, los usos descritos en la presente comprenden el uso de un compuesto de una de las fórmulas descritas en la presente, o de sus sales farmacéuticamente aceptables, en combinación con una o más sustancias seleccionadas entre agentes antitumorales, agentes anti-angiogénesis, inhibidores de la transducción de señales y agentes antiproliferativos.

En algunas formas de realización, los medicamentos descritos en la presente se adaptan para uso en combinación con una o más sustancias seleccionadas entre agentes antitumorales, agentes anti-angiogénesis, inhibidores de la transducción de señales y agentes antiproliferativos.

Cada una de las formas de realización de los compuestos de la presente invención descritos en la presente se pueden combinar con una o más formas de realización adicionales de los compuestos de la presente invención descritos en la presente que no sean inconsistentes con la(s) forma(s) de realización con la(s) cual(es) combinan. Asimismo, cada una de las formas de realización que describen la invención abarca dentro de su alcance las sales farmacéuticamente aceptables de los compuestos de la invención. Por consiguiente, la frase “o una de sus sales farmacéuticamente aceptables” está implícita en la descripción de todos los compuestos descritos en la presente.

BREVE DESCRIPCIÓN DE LAS FIGURAS

Figura 1: Estructura de cristales a los rayos X del Ejemplo 1 que muestra una estereoquímica absoluta de una configuración (R) para el compuesto del Ejemplo 1.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención puede comprenderse con mayor facilidad por referencia a la siguiente descripción detallada de las formas de realización preferentes de la invención y los Ejemplos incluidos en la presente. Ha de entenderse que la terminología empleada en la presente es a los efectos de describir solamente formas de realización específicas y no está destinada a ser limitativa. También ha de entenderse que, a menos que se defina específicamente en la presente, la terminología empleada en la presente ha de adquirir su significado tradicional, tal como se conoce en la técnica relevante.

Tal como se usa en la presente, la forma singular "un", "una", "el" y "ella" incluyen referencias plurales a menos que se indique otra cosa. Por ejemplo, "un" sustituyente incluye uno o varios sustituyentes.

"Alquilo" se refiere a un radical hidrocarbonado saturado, monovalente alifático que incluye grupos de cadena lineal y de cadena ramificada que tienen la cantidad especificada de átomos de carbono. Los sustituyentes de alquilo típicamente contienen 1 a 20 átomos de carbono ("alquilo C_1-C_{20}"), con preferencia, 1 a 12 átomos de carbono ("alquilo C_1-C_{12}"), con mayor preferencia, 1 a 8 átomos de carbono ("alquilo C_1-C_8"), 1 a 6 átomos de carbono ("alquilo C_1-C_6") o 1 a 4 átomos de carbono ("alquilo C_1-C_4"). Los ejemplos de grupos alquilo incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, iso-butilo, ter-butilo, n-pentilo, isopentilo, neopentilo, n-hexilo, n-heptilo, n-octilo, y similares. Los grupos alquilo pueden estar sustituidos o no sustituidos**.** En particular, al menos que se especifique otra cosa, los grupos alquilo pueden estar sustituidos con uno o varios grupos halo, hasta la cantidad total de átomos de hidrógeno presentes en la parte alquilo. De esta manera, alquilo C_1-C_4 incluye grupos alquilo halogenados, por ejemplo, trifluorometilo o difluoroetilo (es decir, CF_3 y $-CH_2CHF_2$).

Tal como se usa en la presente, "alquilo C_1-C_6" denota un grupo de cadena lineal o ramificada que contiene 1, 2, 3, 4, 5 o 6 átomos de carbono. Esto también se aplica cuando tienen sustituyentes o se producen como sustituyentes de otros radicales, por ejemplo, en radicales O-(alquilo C_1-C_6). Los ejemplos de radicales alquilo C_1-C_6 apropiados son metilo, etilo, *n*-propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo, *ter*-buti, n-pentilo, *sec*-pentilo, neopentilo, n-hexilo, *sec*-hexilo y similares. Los ejemplos de radicales O-(alquilo C_1-C_6) apropiados son metoxi, etoxi, *n*-propiloxi, *iso*-propiloxi, *n*-butiloxi, *iso*-butiloxi, *sec*-butiloxi y *ter*-butiloxi, n-pentiloxi, neopentiloxi, hexiloxi

y similares.

Los grupos alquilo descritos en la presente como opcionalmente sustituidos, se pueden sustituir con uno o varios grupos sustituyentes, que están seleccionados de modo independiente, a menos que se indique otra cosa. La cantidad total de grupos sustituyentes puede ser igual a la cantidad total de átomos de hidrógeno en la parte alquilo, en la medida en que dicha sustitución tenga un sentido químico. Los grupos alquilo opcionalmente sustituidos típicamente contienen de 1 a 6 sustituyentes opcionales, a veces 1 a 5 sustituyentes opcionales, con preferencia, de 1 a 4 sustituyentes opcionales o con mayor preferencia, de 1 a 3 sustituyentes opcionales.

Los grupos sustituyentes opcionales apropiados para alquilo incluyen, pero sin limitación, cicloalquilo C_3-C_8, heterociclilo de 3-12 miembros, arilo C_6-C_{12} y heteroarilo de 5-12 miembros, halo, =O (oxo), =S (tiono), =N-CN, =N-OR^X, =NR^X, -CN, -C(O)R^x, -CO_2R^x, -C(O)NR^xR^y, -SR^x, -SOR^x, -SO_2R^x, -$SO_2NR^xR^y$, -NO_2, -NR^xR^y, -$NR^xC(O)R^y$, -$NR^xC(O)NR^xR^y$, -$NR^xC(O)OR^x$, -$NR^xSO_2R^y$, -$NR^xSO_2NR^xR^y$, -OR^x, -OC(O)R^x y -OC(O)NR^xR^y; en donde cada R^x y R^y es, de modo independiente, H, alquilo C_1-C_8, acilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, heterociclilo de 3-12 miembros, arilo C_6-C_{12} o heteroarilo de 5-12 miembros, o R^x y R^y se pueden tomar junto con el átomo de N al que están unidos para formar un heterociclilo de 3-12 miembros o heteroarilo de 5-12 miembros, donde cada uno contiene opcionalmente 1, 2 o 3 heteroátomos adicionales seleccionados de O, N y S; cada R^x y R^y está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en halo, =O, =S, =N-CN, =N-OR', =NR', -CN, -C(O)R', -CO_2R', -C(O)NR'_2, -SR', -SOR', -SO_2R', -$SO_2NR'_2$, -NO_2, -NR'_2, -NR'C(O)R', -$NR'C(O)NR'_2$, -NR'C(O)OR', -NR'SO_2R', -$NR'SO_2NR'_2$, -OR', -OC(O)R' y -$OC(O)NR'_2$, en donde cada R' es, de modo independiente, H, alquilo C_1-C_8, acilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, heterociclilo de 3-12 miembros, arilo C_6-C_{12} o heteroarilo C_5-C_{12}; y en donde cada uno de cicloalquilo C_3-C_8, heterociclilo de 3-12 miembros, arilo C_6-C_{12} y heteroarilo de 5-12 miembros está opcionalmente sustituido tal como se define en la presente más adelante.

Los grupos sustituyentes típicos en el alquilo incluyen halo, -OH, alcoxi C_1-C_4, -O-arilo C_6-C_{12}, -CN, =O, -$COOR^x$, -OC(O)R^x, -C(O)NR^xR^y, -$NR^xC(O)R^y$, –NR^xR^y, cicloalquilo C_3-C_8, arilo C_6-C_{12}, heteroarilo de 5-12 miembros y heterociclilo de 3-12 miembros; donde cada R^x y R^y es, de modo independiente, H o alquilo C_1-C_4, o R^x y R^y se pueden tomar junto con el N al que están unidos para formar un anillo heterociclilo de 3-12 miembros o anillo heteroarilo de 5-12 miembros, donde cada uno contiene

opcionalmente 1, 2 o 3 heteroátomos adicionales seleccionados de O, N y S; en donde cada uno de dicho cicloalquilo C_3-C_8, arilo C_6-C_{12}, heteroarilo de 5-12 miembros y heterociclilo de 3-12 miembros está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en halo, -OH, =O, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_6, hidroxialquilo C_1-C_6, alcoxi C_1-C_4-alquilo C_1-C_6, -CN, $-NH_2$, -NH(alquilo C_1-C_4) y -N(alquilo C_1-C_4)$_2$.

En algunas formas de realización, el alquilo está opcionalmente sustituido con uno o varios sustituyentes y con preferencia, con 1 a 3 sustituyentes, que están seleccionados, de modo independiente, del grupo que consiste en halo, -OH, alcoxi C_1-C_4, -O-arilo C_6-C_{12}, -CN, =O, $-COOR^x$, $-OC(O)R^x$, $-C(O)NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xR^y$, cicloalquilo C_3-C_8, arilo C_6-C_{12}, heteroarilo de 5-12 miembros y heterociclilo de 3-12 miembros; donde cada R^x y R^y es, de modo independiente, H o alquilo C_1-C_4, o R^x y R^y se pueden tomar junto con el N al que están unidos para formar un anillo heterociclilo de 3-12 miembros o anillo heteroarilo de 5-12 miembros, donde cada uno contiene opcionalmente 1, 2 o 3 heteroátomos adicionales seleccionados de O, N y S; y cada uno de cicloalquilo C_3-C_8, arilo C_6-C_{12}, heteroarilo de 5-12 miembros y heterociclilo de 3-12 miembros está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en halo, -OH, =O, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_6, hidroxialquilo C_1-C_6, alcoxi C_1-C_4-alquilo C_1-C_6, -CN, $-NH_2$, -NH(alquilo C_1-C_4) y -N(alquilo C_1-C_4)$_2$.

En otras formas de realización, el alquilo está opcionalmente sustituido con uno o varios sustituyentes y con preferencia, con 1 a 3 sustituyentes, seleccionados, de modo independiente, del grupo que consiste en halo, -OH, alcoxi C_1-C_4, -CN, $-NR^xR^y$, cicloalquilo C_3-C_8, heterociclilo de 3-12 miembros, arilo C_6-C_{12} y heteroarilo de 5-12 miembros; donde cada R^x y R^y es, de modo independiente, H o alquilo C_1-C_4, o R^x y R^y se pueden tomar junto con el N al que están unidos para formar un anillo heterociclilo de 3-12 miembros o anillo heteroarilo de 5-12 miembros, donde cada uno contiene opcionalmente 1, 2 o 3 heteroátomos adicionales seleccionados de O, N y S; y donde cada uno de cicloalquilo, heterociclilo, arilo o heteroarilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en halo, -OH, =O, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_6, hidroxialquilo C_1-C_6, alcoxi C_1-C_4-alquilo C_1-C_6, -CN, $-NH_2$, -NH(alquilo C_1-C_4) y -N(alquilo C_1-C_4)$_2$.

En algunas instancias, los grupos alquilo sustituidos se pueden mencionar específicamente con referencia al grupo sustituyente. Por ejemplo, “haloalquilo” se refiere a un grupo alquilo que tiene la cantidad especificada de átomos de carbono que

está sustituido con uno o varios sustituyentes halo, y típicamente contiene 1-6 átomos de carbono y 1, 2 o 3 átomos de halo (es decir, "haloalquilo C_1-C_6"). De esta manera, un grupo haloalquilo C_1-C_6 incluye trifluorometilo (-CF_3) y difluorometilo (-CF_2H).

De modo similar, "hidroxialquilo" se refiere a un grupo alquilo que tiene la cantidad especificada de átomos de carbono que está sustituido con uno o varios sustituyentes hidroxi, y típicamente contiene 1-6 átomos de carbono y 1, 2 o 3 hidroxi (es decir, "hidroxialquilo C_1-C_6"). De esta manera, hidroxialquilo C_1-C_6 incluye hidroximetilo (-CH_2OH) y 2-hidroxietilo (-CH_2CH_2OH).

"Alcoxialquilo" se refiere a un grupo alquilo que tienen la cantidad especificada de átomos de carbono que está sustituido con uno o varios sustituyentes alcoxi. Los grupos alcoxialquilo típicamente contienen 1-6 átomos de carbono en la porción alquilo y están sustituidos con 1, 2 o 3 sustituyentes alquil C_1-C_4-oxi. Estos grupos se describen a veces en la presente como alquil C_1-C_4-oxi-alquilo C_1-C_6.

"Aminoalquilo" se refiere al grupo alquilo que tiene la cantidad especificada de átomos de carbono que está sustituido con uno o varios grupos amino sustituidos o no sustituidos; tales grupos se definen luego en la presente. Los grupos aminoalquilo típicamente contienen 1-6 átomos de carbono en la porción alquilo y están sustituidos con 1, 2 o 3 sustituyentes amino. De esta manera, un grupo aminoalquilo C_1-C_6 incluye, por ejemplo, aminometilo (-CH_2NH_2), *N,N*-dimetilamino-etilo (-$CH_2CH_2N(CH_3)_2$), 3-(*N*-ciclopropilamino)propilo (-$CH_2CH_2CH_2NH$-^{c}Pr) y *N*-pirrolidiniletilo (-CH_2CH_2-N-pirrolidinilo).

"Alquenilo" se refiere a un grupo alquilo, tal como se define en la presente, que consiste en al menos dos átomos de carbono y al menos un enlace doble carbono-carbono. Típicamente, los grupos alquenilo tienen 2 a 20 átomos de carbono ("alquenilo C_2-C_{20}"), con preferencia, 2 a 12 átomos de carbono ("alquenilo C_2-C_{12}"), con mayor preferencia, 2 a 8 átomos de carbono ("alquenilo C_2-C_8"), 2 a 6 átomos de carbono ("alquenilo C_2-C_6") o 2 a 4 átomos de carbono ("alquenilo C_2-C_4"). Los ejemplos representativos incluyen, pero sin limitación, etenilo, 1-propenilo, 2-propenilo, 1-, 2- o 3-butenilo, y similares. Un "alquenilo C_2-C_6" denota un grupo de cadena lineal o ramificada que contiene 1 a 6 átomos de carbono y al menos un enlace doble entre dos átomos de carbono sp^2 hibridados. Esto también se aplica si llevan sustituyentes o se producen como sustituyentes de otros radicales, por ejemplo en radicales O-alquenilo (C_1-C_6). Los ejemplos de radicales alquilo C_1-C_6 apropiados son *n*-propenilo, *iso*-propenilo, *n*-butenilo, *iso*-butenilo, n-pentenilo, *sec*-pentenilo, n-hexenilo, *sec*-hexenilo, y similares. Los grupos alquenilo pueden no estar sustituidos o pueden estar

sustituidos con los mismos grupos que se describen en la presente como apropiados para alquilo.

"Alquinilo" se refiere a un grupo alquilo, tal como se define en la presente, que consiste en al menos dos átomos de carbono y al menos un enlace triple de carbono-carbono. Los grupos alquinilo tienen 2 a 20 átomos de carbono ("alquinilo C_2-C_{20}"), con preferencia, 2 a 12 átomos de carbono ("alquinilo C_2-C_{12}"), con mayor preferencia, 2 a 8 átomos de carbono ("alquinilo C_2-C_8"), 2 a 6 átomos de carbono ("alquinilo C_2-C_6") o 2 a 4 átomos de carbono ("alquinilo C_2-C_4"). Los ejemplos representativos incluyen, pero sin limitación, etinilo, 1-propinilo, 2-propinilo, 1-, 2- o 3-butinilo, y similares. Los grupos alquinilo pueden no estar sustituidos o pueden estar sustituidos con los mismos grupos que se describen en la presente como apropiados para alquilo. Un "alquinilo C_2-C_6" denota un grupo de cadena lineal o ramificada que contiene 1 a 6 átomos de carbono y al menos un enlace triple entre dos átomos de carbono sp hibridados. Esto también se aplica si tienen sustituyentes u ocurren como sustituyentes de otros radicales, por ejemplo en radicales O-alquinilo (C_1-C_6). Los ejemplos de radicales alquinilo C_1-C_6 apropiados son propinilo, butinilo, pentinilo, hexinilo, y similares.

"Alquileno" tal como se usa en la presente se refiere a un grupo hidrocarbilo divalente que tiene la cantidad especificada de átomos de carbono que puede ligar otros dos grupos juntos. A veces se refiere a $–(CH_2)_n–$ donde n es 1-8 y con preferencia, n es 1-4. Cuando se especifica, un alquileno también puede estar sustituido con otros grupos y puede incluir uno o varios grados de insaturación (es decir, una parte alquenileno o alquinileno) o anillos. Las valencias abiertas de un alquileno no necesitan estar en extremos opuestos de la cadena. De esta manera, –CH(Me) – y $–C(Me)_2–$ también están incluidos dentro del alcance del término 'alquilenos', cuando son grupos cíclicos tales como ciclopropan-1,1-diilo y grupos insaturados tales como etileno (-CH=CH-) o propileno ($-CH_2$-CH=CH-). Cuando un grupo alquileno se describe como opcionalmente sustituido, los sustituyentes incluyen aquellos típicamente presentes en grupos alquilo tal como se describe en la presente.

"Heteroalquileno" se refiere a un grupo alquileno tal como se describió con anterioridad, en donde uno o varios átomos de carbono no contiguos de la cadena de alquileno se reemplazan por -N(R)-, -O- o $-S(O)_q$-, donde R es H o alquilo C_1-C_4, y q es 0-2. Por ejemplo, el grupo $–O-(CH_2)_{1-4}$- es un grupo heteroalquileno 'C_2-C_5', donde uno de los átomos de carbono del correspondiente alquileno está reemplazado por O.

"Alcoxi" se refiere a un grupo –O-alquilo monovalente, en donde la porción alquilo tiene la cantidad especificada de átomos de carbono**.** Los grupos alcoxi

típicamente contienen 1 a 8 átomos de carbono ("alcoxi C_1-C_8"), 1 a 6 átomos de carbono ("alcoxi C_1-C_6") o 1 a 4 átomos de carbono ("alcoxi C_1-C_4"). Por ejemplo, alcoxi C_1-C_4 incluye $–OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, y similares. Estos grupos también se pueden mencionar en la presente como metoxi, etoxi, isopropoxi, ter-butiloxi, etc. Los grupos alcoxi pueden no estar sustituidos o pueden estar sustituidos en la porción alquilo con los mismos grupos que se describen en la presente como apropiados para alquilo. En particular, los grupos alcoxi pueden estar sustituidos con uno o varios grupos halo, hasta la cantidad total de átomos de hidrógeno presentes en la porción alquilo. De esta manera, alcoxi C_1-C_4 incluye grupos alcoxi halogenados, por ejemplo, trifluorometoxi y 2,2-difluoroetoxi (es decir, $-OCF_3$ y $-OCH_2CHF_2$).

De modo similar, "tioalcoxi" se refiere a un grupo –S-alquilo monovalente, en donde la porción alquilo tiene la cantidad especificada de átomos de carbono, y puede estar opcionalmente sustituido en la porción alquilo con los mismos grupos que se describen en la presente como apropiados para alquilo. Por ejemplo, un tioalcoxi C_1-C_4 incluye $–SCH_3$ y $-SCH_2CH_3$.

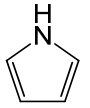
"Halógeno" o "halo" se refiere a flúor, cloro, bromo y yodo (F, Cl, Br, I). Con preferencia, halo se refiere a flúor o cloro (F o Cl).

"Heteroarilo" o "heteroaromático" se refieren a sistemas de anillos bicíclicos o policíclicos monocíclicos o fusionados que tienen las características bien conocidas de aromaticidad que contienen la cantidad especificada de átomos de anillo e incluyen al menos un heteroátomo seleccionado de N, O y S como un miembro del anillo en un anillo aromático. La inclusión de un heteroátomo permite la aromaticidad en anillos de 5 miembros así como en anillos de 6 miembros. Típicamente, los grupos heteroarilo contienen 5 a 20 átomos del anillo ("heteroarilo de 5-20 miembros"), con preferencia, 5 a 14 átomos del anillo ("heteroarilo de 5-14 miembros") y con mayor preferencia, 5 a 12 átomos del anillo ("heteroarilo de 5-12 miembros") o 5 a 6 átomos del anillo ("heteroarilo de 5-6 miembros"). Los anillos heteroarilo se unen a la molécula de base por medio de un átomo del anillo heteroaromático de modo que la aromaticidad se mantiene. De esta manera, los anillos heteroarilo de 6 miembros se pueden unir a la molécula de base por medio de un átomo de C del anillo, mientras que los anillos heteroarilo de 5 miembros pueden estar unidos a la molécula de base por medio de un anillo N o C del anillo. El grupo heteroarilo puede no estar sustituido o puede estar sustituido tal como se describe más adelante en la presente. Tal como se usa en la presente, "heteroarilo de 5-6 miembros" se refiere a un grupo monocíclico de 5 o 6 átomos del anillo, que contiene uno, dos o tres heteroátomos del anillo seleccionados

de N, O y S, siendo los demás átomos del anillo C y, además, con un sistema de electrones pi completamente conjugados. Los sustituyentes en átomos del anillo adyacentes de un heteroarilo de 5 o 6 miembros se pueden combinar para formar un anillo carbocíclico fusionado de 5 o 6 miembros opcionalmente sustituido con uno o más sustituyentes, tales como oxo, alquilo C_1-C_6, hidroxilo, amino y halógeno, o un anillo heterocíclico fusionado de 5 o 6 miembros que contiene uno, dos o tres heteroátomos del anillo seleccionados de N, O y $S(O)_p$ (donde p es 0, 1 o 2) opcionalmente sustituido con uno o más sustituyentes, tales como oxo, alquilo C_1-C_6, hidroxilo, amino y halógeno. Un heteroarilo farmacéuticamente aceptable es uno que es suficientemente estable para estar unido a un compuesto de la invención, formulado en una composición farmacéutica y posteriormente administrado a un paciente que lo necesita.

Los ejemplos de anillos heteroarilo de 5 miembros que contienen 1, 2 o 3 heteroátomos seleccionados, de modo independiente, de O, N y S, incluyen pirrolilo, tienilo, furanilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, triazolilo, tetrazolilo, oxadiazolilo y tiadiazolilo. Los anillos heteroarilo de 6 miembros preferidos contienen 1 o 2 átomos de nitrógeno. Los ejemplos de heteroarilo de 6 miembros son piridilo, piridazinilo, pirimidinilo y pirazinilo. Los ejemplos de anillos heteroarilo fusionados incluyen benzofurano, benzotiofeno, indol, bencimidazol, indazol, quinolina, isoquinolina, purina, triazina, naftriidina y carbazol.

Los ejemplos de grupos heteroarilo monocíclicos típicos incluyen, sin limitación:



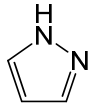
pirrol (pirrolilo)



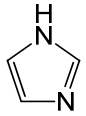
furano (furanilo)



tiofeno (tiofenilo)



pirazol (pirazolilo)



imidazol (imidazolilo)



isoxazol (isoxazolilo)



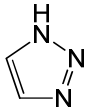
oxazol (oxazolilo)



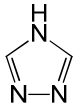
isotiazol (isotiazolilo)



tiazolilo (tiazolilo)



1,2,3-triazol (1,2,3-triazolilo)



1,3,4-triazol (1,3,4-triazolilo)



1-oxa-2,3-diazol (1-oxa-2,3-diazolilo)



1-oxa-2,4-diazol (1-oxa-2,4-diazolilo)



1-oxa-2,5-diazol (1-oxa-2,5-diazolilo)



1-oxa-3,4-diazol
(1-oxa-3,4-diazolilo)



1-tia-2,3-diazol
(1-tia-2,3-diazolilo)



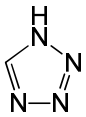
1-tia-2,4-diazol
(1-tia-2,4-diazolilo)



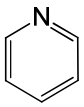
1-tia-2,5-diazol
(1-tia-2,5-diazolilo)



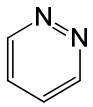
1-tia-3,4-diazol
(1-tia-3,4-diazolilo)



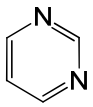
tetrazol
(tetrazolilo)



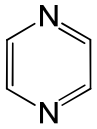
piridina
(piridinilo)



piridazina
(piridazinilo)

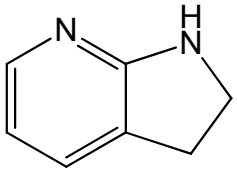


pirimidina
(pirimidinilo)

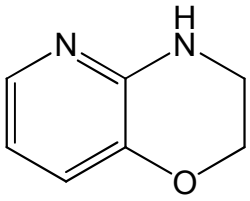


pirazina
(pirazinilo)

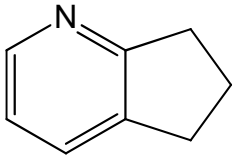
Los ejemplos de grupos heteroarilo de 6 miembros que tienen átomos del anillo adyacentes que forman un anillo heterocíclico fusionado o un anillo carbocíclico incluyen, sin limitación:



2,3-dihidro-1*H*-pirrolo
[2,3-*b*]piridinilo

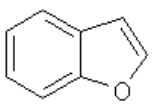


3,4-dihidro-2*H*-pirido
[3,2-*b*][1,4]oxazinilo

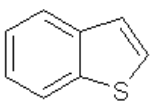


6,7-dihidro-5*H*-ciclopenta
[*b*]piridinilo

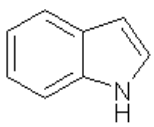
Los ejemplos ilustrativos de los grupos heteroailo fusionados incluyen, sin limitación:



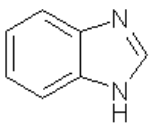
benzofuran
(benzofuranilo)



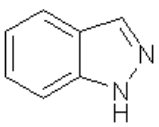
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(benzotiofenilo)



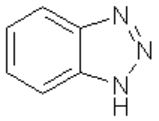
indol
(indolilo)



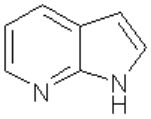
bencimidazol
(bencimidazolilo)



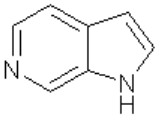
indazol
(indazolilo)



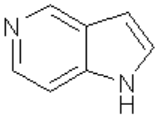
benzotriazol
(benzotriazolilo)



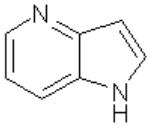
pirrolo[2,3-b]piridina
(pirrolo[2,3-b]piridinilo)



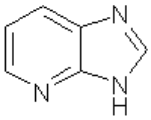
pirrolo[2,3-c]piridina
(pirrolo[2,3-c]piridinilo)



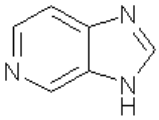
pirrolo[3,2-c]piridina
(pirrolo[3,2-c]piridinilo)



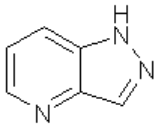
pirrolo[3,2-b]piridina
(pirrolo[3,2-b]piridinilo)



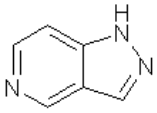
imidazo[4,5-b]piridina
(imidazo[4,5-b]piridinilo)



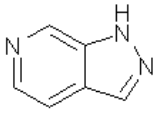
imidazo[4,5-c]piridina
(imidazo[4,5-c]piridinilo)



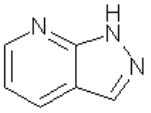
pirazolo[4,3-d]piridina
(pirazolo[4,3-d]piridinilo)



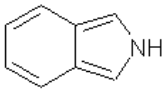
pirazolo[4,3-c]piridina
(pirazolo[4,3-c]piridinilo)



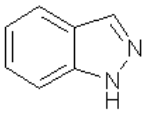
pirazolo[3,4-c]piridina
(pirazolo[3,4-c]piridinilo)



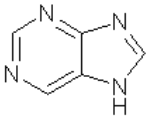
pirazolo[3,4-b]piridina
(pirazolo[3,4-b]piridinilo)



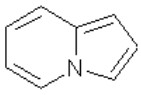
isoindol
(isoindolilo)



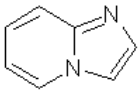
indazol
(indazolilo)



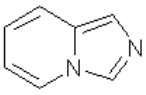
purina
(purinilo)



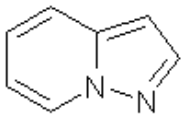
indolizina
(indolizinilo)



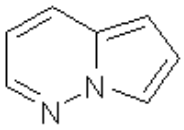
imidazo[1,2-a]piridina
(imidazo[1,2-a]piridinilo)



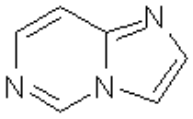
imidazo[1,5-a]piridina
(imidazo[1,5-a]piridinilo)



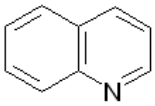
pirazolo[1,5-a]piridina
(pirazolo[1,5-a]piridinilo)



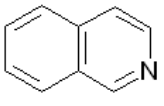
pirrolo[1,2-b]piridazina
(pirrolo[1,2-b]piridazinilo)



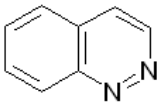
imidazo[1,2-c]pirimidina
(imidazo[1,2-c]pirimidinilo)



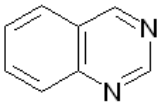
quinolina
(quinolinilo)



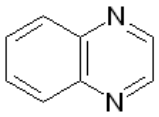
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(isoquinolinilo)



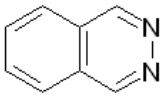
cinnolina
(cinnolinilo)



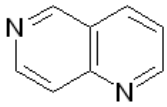
quinzolina
(quinzolinilo)



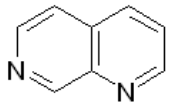
quinoxalina
(quinoxalinilo)



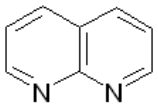
ftalazina
(ftalazinilo)



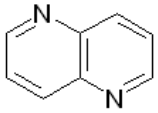
1,6-naftiridina
(1,6-naftiridinilo)



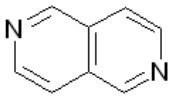
1,7-naftiridina
(1,7-naftiridinilo)



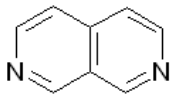
1,8-naftiridina
(1,8-naftiridinilo)



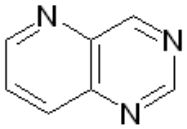
1,5-naftiridina
(1,5-naftiridinilo)



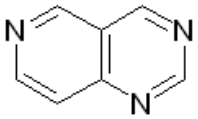
2,6-naftiridina
(2,6-naftiridinilo)



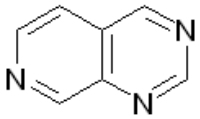
2,7-naftiridina
(2,7-naftiridinilo)



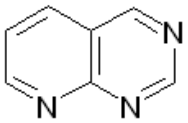
pirido[3,2-d]pirimidina
(pirido[3,2-d]pirimidinilo)



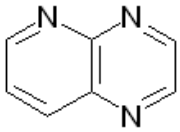
pirido[4,3-d]pirimidina
(pirido[4,3-d]pirimidinilo)



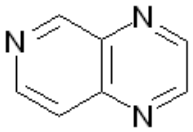
pirido[3,4-d]pirimidina
(pirido[3,4-d]pirimidinilo)



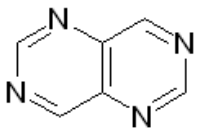
pirido[2,3-d]pirimidina
(pirido[2,3-d]pirimidinilo)



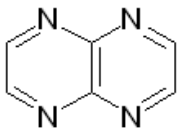
pirido[2,3-b]pirazina
(pirido[2,3-b]pirazinilo)



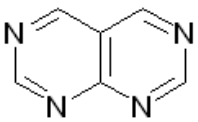
pirido[3,4-b]pirazina
(pirido[3,4-b]pirazinilo)



pirimido[5,4-d]pirimidina
(pirimido[5,4-d]pirimidinilo)



pirazino[2,3-b]pirazina
(pirazino[2,3-b]pirazinilo)

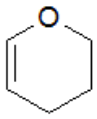


pirimido[4,5-d]pirimidina
(pirimido[4,5-d]pirimidinilo)

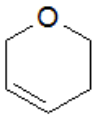
Los términos “heteroalicíclico”, “heterociclilo” o “heterocíclico” se pueden usar indistintamente en la presente para referirse a un sistema de anillos no aromático saturado o parcialmente insaturado que contiene la cantidad especificada de átomos del anillo, que incluye al menos un heteroátomo seleccionado de N, O y S como un miembro del anillo, en donde el anillo heterocíclico se conecta con la molécula de base

por medio de un átomo del anillo, que puede ser C o N. Los anillos heteroalicíclicos se pueden fusionar con uno o varios otros anillos heteroalicíclicos o carbocíclicos, cuyos anillos fusionados pueden ser saturados, parcialmente insaturados o aromáticos. Con preferencia, los anillos heteroalicíclicos contienen 1 a 4 heteroátomos seleccionados de N, O y S como miembros del anillo, y con mayor preferencia, 1 a 2 heteroátomos del anillo, siempre que estos anillos heteroalicíclicos no contengan dos átomos de oxígeno contiguos. Los grupos heteroalicíclicos pueden no estar sustituidos o pueden estar sustituidos con los mismos grupos que se describen en la presente como apropiados para alquilo, arilo o heteroarilo. Además, los átomos de N del anillo pueden estar opcionalmente sustituidos con grupos apropiados para una amina, por ejemplo, sustituyentes alquilo, acilo, carbamoilo, sulfonilo, etc., y los átomos S de anillo pueden estar opcionalmente sustituidos con uno o dos grupos oxo (es decir, $S(O)_p$, donde p es 0, 1 o 2). Los grupos heteroalicíclicos preferidos incluyen grupos heteroalicíclicos de 3-12 miembros de acuerdo con la definición en la presente. Tal como se usa en la presente, "heteroalicíclico de 3-12 miembros" se refiere a un grupo monocíclico o bicíclico que tiene de 3 a 12 átomos del anillo, en donde uno, dos, tres o cuatro átomos del anillo son heteroátomos seleccionados de N, O y $S(O)_p$ (donde p es 0, 1, 2), siendo los demás átomos del anillo C. El anillo también puede tener uno o más enlaces dobles. Sin embargo, el anillo no tiene un sistema de electrones pi completamente conjugados. Los sustituyentes en dos átomos de carbono del anillo se pueden combinar para formar un anillo en puente de 5 o 6 miembros que es carbocíclico o heteroalicíclico que contiene uno, dos o tres heteroátomos del anillo seleccionados de N, O y $S(O)_p$ (donde p es 0, 1 o 2). El grupo heteroalicíclico está opcionalmente sustituido con oxo, hidroxilo, amino, alquilo C_1-C_6 y similares.

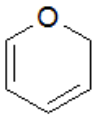
Los ejemplos de grupos heteroalicíclicos parcialmente insaturados apropiados incluyen, sin limitación:



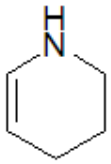
3,4-dihidro-2H-pirano
(3,4-dihidro-2H-piranilo)



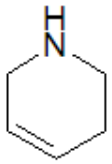
5,6-dihidro-2H-pirano
(5,6-dihidro-2H-piranilo)



2H-pirano
(2H-piranilo)



1,2,3,4-tetrahidropiridina
(1,2,3,4-tetrahidropiridinilo)



1,2,5,6-tetrahidropiridina
(1,2,5,6-tetrahidropiridinilo)

Los ejemplos de grupos heteroalicíclicos saturados apropiados incluyen, sin limitación:



oxirano
(oxiranilo)



tiarano
(tiaranilo)



aziridina
(aziridinilo)



oxetano
(oxetanilo)



tiatano
(tiatanilo)



azetidina
(azetidinilo)



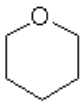
tetrahidrofurano
(tetrahidrofuranilo)



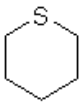
tetrahidrotiofeno
(tetrahidrotiofenilo)



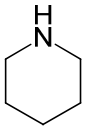
pirrolidina
(pirrolidinilo)



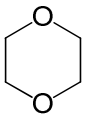
tetrahidropirano
(tetrahidropiranilo)



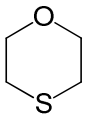
tetrahidrotiopirano
(tetrahidrotiopiranilo)



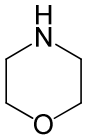
piperidina
(piperidinilo)



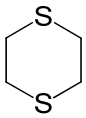
1,4-dioxano
(1,4-dioxanilo)



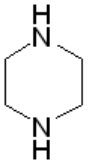
1,4-oxatiano
(1,4-oxatianilo)



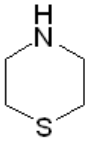
morfolina
(morfolinilo)



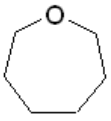
1,4-ditiano
(1,4-ditianilo)



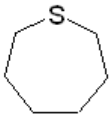
piperazina
(piperazinilo)



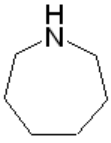
1,4-azatiano
(1,4-azatianilo)



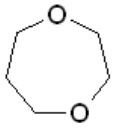
oxepano
(oxepanilo)



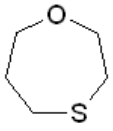
tiepano
(tiepanilo)



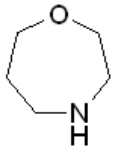
azepano
(azepanilo)



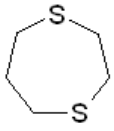
1,4-dioxepano
(1,4-dioxepanilo)



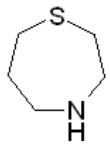
1,4-oxatiepano
(1,4-oxatiepanilo)

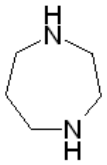


1,4-oxaazepano
(1,4-oxaazepanilo)



1,4-ditiepano
(1,4-ditiepanilo)





1,4-tieazepano (1,4-tieazepanilo)

1,4-diazepano (1,4-diazepanilo)

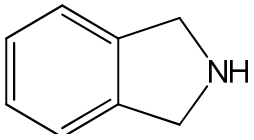
En formas de realización frecuentes, los grupos heteroalicíclicos contienen 3-12 miembros del anillo, que incluyen tanto heteroátomos de carbono como no carbono y con preferencia, 4-6 miembros del anillo. En ciertas formas de realización preferidas, los grupos sustituyentes que comprenden grupos heteroalicíclico de 3-12 miembros están seleccionados de anillos azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo y tiomorfolinilo, cada uno de los cuales puede estar opcionalmente sustituido en la medida en que dicha sustitución tenga un sentido químico.

Se entiende que no más de dos átomos de N, O o S se conectan ordinariamente de forma secuencial, excepto cuando un grupo oxo está unido con N o S para formar un grupo nitro o sulfonilo o en el caso de ciertos anillos heteroaromáticos, tales como triazina, triazol, tetrazol, oxadiazol, tiadiazol, y similares.

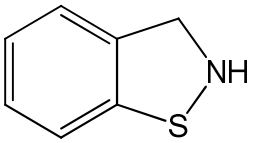
El término “heterociclilalquilo” se puede usar para describir un grupo heterocíclico del tamaño especificado que está conectado con la molécula de base a través de un ligador de alquileno de la longitud especificada. Típicamente, estos grupos contienen un heterociclo de 3-12 miembros opcionalmente sustituido unido a la molécula de base a través de un ligador de alquileno C_1-C_4. Donde se indica, estos grupos pueden estar opcionalmente sustituidos en la porción alquileno con los mismos grupos que se describen en la presente como apropiados para grupos alquilo y en la porción heterocíclica con grupos descritos como apropiados para anillos heterocíclicos**.**

Tal como se usa en la presente, “arilo C_6-C_{12}” se refiere a grupos monocíclicos con todos carbonos o policíclicos de anillos fusionados de 6 a 12 átomos de carbono con un sistema de electrones pi completamente conjugados. Los ejemplos de grupos arilo son fenilo y naftalenilo. El grupo arilo puede estar sustituido o no sustituido. Los sustituyentes en los átomos de carbono del anillo adyacentes de un arilo C_6-C_{12} pueden combinarse para formar un anillo carbocíclico de 5 o 6 miembros

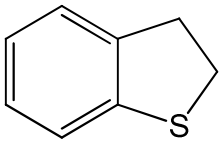
opcionalmente sustituido con uno o más sustituyentes, tales como oxo, alquilo C_1-C_6, hidroxilo, amino y halógeno, o un anillo heterocíclico de 5 o 6 miembros que contiene uno, dos o tres heteroátomos del anillo seleccionados de N, O y $S(O)_p$ (donde p es 0, 1 o 2) opcionalmente sustituido con uno o más sustituyentes, tales como oxo, alquilo C_1-C_6, hidroxilo, amino y halógeno. Los ejemplos de grupos arilo incluyen fenilo, bifenilo, naftilo, antracenilo, fenantrenilo, indanilo, indenilo y tetrahidronaftilo. El grupo arilo puede no estar sustituido o puede estar sustituido tal como se describe más adelante en la presente. Los ejemplos adicionales del arilo C_6-C_{10} que tienen dos átomos de carbono del anillo que forman un anillo heterocíclico o carbocíclico fusionado incluyen pero sin limitación:



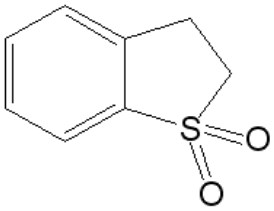
isoindolinilo



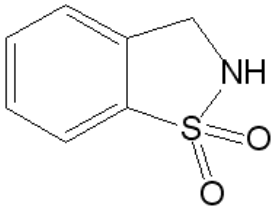
2,3-dihidrobenzo[d]isotiazolilo



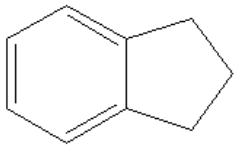
2,3-dihidrobenzo[b]tiofenilo



2,3-dihidrobenzo [b]tiofen-1,1-dióxido



2,3-dihidrobenzo [d]isotiazol-1,1-dióxido



2,3-dihidro-1H-indenilo

Las partes arilo, heteroarilo y heteroalicíclico descritas en la presente como opcionalmente sustituidas pueden estar sustituidas con uno o varios grupos sustituyentes, que están seleccionados de modo independiente, a menos que se indique otra cosa. La cantidad total de grupos sustituyentes puede ser igual a la cantidad total de átomos de hidrógeno en la parte arilo, heteroarilo o heterociclilo, en la medida en que dicha sustitución tenga un sentido químico y se mantenga la aromaticidad en el caso de anillos arilo y heteroarilo. Los grupos arilo, heteroarilo o heterociclilo opcionalmente sustituidos típicamente contienen de 1 a 5 sustituyentes opcionales, a veces 1 a 4 sustituyentes opcionales, con preferencia, 1 a 3 sustituyentes opcionales, o con mayor preferencia, de 1 a 2 sustituyentes opcionales.

Un “arileno” tal como se usa en la presente se refiere a un radical bivalente derivado de un hidrocarburo aromático por eliminación de un átomo de hidrógeno de

cada uno de dos átomos de carbono del núcleo. En formas de realización frecuentes, el anillo arileno es un arileno 1,2-disustituido o a 1,3-disustituido. El anillo arilo de la parte arileno puede estar opcionalmente sustituido en posiciones de valencia abierta con grupos apropiados para un anillo arilo, en la medida en que se indique cada sustitución. Con preferencia, el anillo arileno es un anillo arileno C_6-C_{12}, por ejemplo, una parte 1,2-fenileno o 1,3-fenileno.

De modo similar, un "heteroarileno" tal como se usa en la presente se refiere a un radical bivalente derivado de un anillo heteroaromático por eliminación de un átomo de hidrógeno de cada uno de dos átomos de carbono o de nitrógeno del núcleo. En formas de realización frecuentes, el anillo heteroarileno es un heteroarileno 1,2-disustituido o 1,3-disustituido. El anillo heteroarilo de la parte heteroarileno está opcionalmente sustituido con grupos apropiados para un anillo heteroarilo, en la medida que se indique esta sustitución. Con preferencia, el anillo heteroarileno es un anillo heteroarileno de 5-12 miembros, con mayor preferencia, un anillo heteroarileno de 5-6 miembros, cada uno de los cuales puede estar opcionalmente sustituido.

Los grupos sustituyentes opcionales apropiados para anillos arilo, heteroarilo y heteroalicíclico incluyen, pero sin limitación: alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, heterociclilo de 3-12 miembros, arilo C_6-C_{12} y heteroarilo de 5-12 miembros; y halo, =O, -CN, $-C(O)R^x$, $-CO_2R^x$, $-C(O)NR^xR^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-SO_2NR^xR^y$, $-NO_2$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(O)NR^xR^y$, $-NR^xC(O)OR^x$, $-NR^xSO_2R^y$, $-NR^xSO_2NR^xR^y$, $-OR^x$, $-OC(O)R^x$ y $-OC(O)NR^xR^y$; donde cada R^x y R^y es, de modo independiente, H, alquilo C_1-C_8, acilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, heterociclilo de 3-12 miembros, arilo C_6-C_{12} o heteroarilo de 5-12 miembros, o R^x y R^y se pueden tomar junto con el átomo de N al que están unidos para formar un heterociclilo de 3-12 miembros o heteroarilo de 5-12 miembros, donde cada uno contiene opcionalmente 1, 2 o 3 heteroátomos adicionales seleccionados de O, N y S; cada R^x y R^y está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en halo, =O, =S, =N-CN, =N-OR', =NR', -CN, -C(O)R', $-CO_2R'$, $-C(O)NR'_2$, -SR', -SOR', $-SO_2R'$, $-SO_2NR'_2$, $-NO_2$, $-NR'_2$, -NR'C(O)R', $-NR'C(O)NR'_2$, -NR'C(O)OR', $-NR'SO_2R'$, $-NR'SO_2NR'_2$, -OR', -OC(O)R' y $-OC(O)NR'_2$, en donde cada R' es, de modo independiente, H, alquilo C_1-C_8, acilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, heterociclilo de 3-12 miembros, arilo C_6-C_{12} o heteroarilo de 5-12 miembros; y cada uno de alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, heterociclilo de 3-12 miembros, arilo

C_6-C_{12} y heteroarilo de 5-12 miembros está opcionalmente sustituido tal como se define en la presente más adelante.

En formas de realización típicas, la sustitución opcional en los anillos arilo, heteroarilo y heteroalicíclico incluye uno o varios sustituyentes y con preferencia, 1 a 3 sustituyentes, seleccionados, de modo independiente, del grupo que consiste en halo, alquilo C_1-C_8, -OH, alcoxi C_1-C_8, -CN, =O, -C(O)R^x, -COOR^x, -OC(O)R^x, -C(O)N$R^x$$R^y$, -N$R^x$C(O)$R^y$, -S$R^x$, -SO$R^x$, -$SO_2R^x$, -$SO_2NR^x$$R^y$, -$NO_2$, –N$R^x$$R^y$, -N$R^x$C(O)$R^y$, -N$R^x$C(O)N$R^x$$R^y$, -N$R^x$C(O)O$R^y$ –N$R^x$$SO_2R^y$, -N$R^x$$SO_2NR^x$$R^y$, -OC(O)$R^x$, -OC(O)N$R^x$$R^y$, cicloalquilo C_3-C_8, heterociclilo de 3-12 miembros, arilo C_6-C_{12}, heteroarilo de 5-12 miembros, -O-(cicloalquilo C_3-C_8), -O-(heterociclilo de 3-12 miembros), -O-(arilo C_6-C_{12}) y –O-(heteroarilo de 5-12 miembros); donde cada R^x y R^y es, de modo independiente, H o alquilo C_1-C_4, o R^x y R^y se pueden tomar junto con el N al que están unidos para formar un anillo heterociclilo de 3-12 miembros o anillo heteroarilo de 5-12 miembros, donde cada uno contiene opcionalmente 1, 2 o 3 heteroátomos adicionales seleccionados de O, N y S; y en donde cada uno de alquilo C_1-C_8, alcoxi C_1-C_8, cicloalquilo C_3-C_8, heterociclilo de 3-12 miembros, arilo C_6-C_{12}, heteroarilo de 5-12 miembros, -O-(cicloalquilo C_3-C_8), -O-(heterociclilo de 3-12 miembros), -O-(arilo C_6-C_{12}) y –O-(heteroarilo de 5-12 miembros) que se describe como un sustituyente opcional o es parte de R^x o R^y está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, de modo independiente, del grupo que consiste en halo, -OH, =O, alquilo C_1-C_4, alcoxi C_1-C_4, haloalquilo C_1-C_6, hidroxialquilo C_1-C_6, alcoxi C_1-C_4-alquilo C_1-C_6, -CN, -NH_2, -NH(alquilo C_1-C_4), -N(alquilo C_1-C_4)$_2$ y N-pirrolidinilo.

“Cicloalquilo” se refiere a un sistema de anillos carbocíclicos no aromáticos, saturados o parcialmente insaturados que contienen la cantidad especificada de átomos de carbono, que puede ser un sistema de anillos bicíclicos o policíclicos monocíclicos, en puente o fusionados que se conecta con la molécula de base a través de un átomo de carbono del anillo cicloalquilo. Típicamente, los grupos cicloalquilo de la invención contienen 3 a 12 átomos de carbono (“cicloalquilo C_3-C_{12}”), con preferencia, 3 a 8 átomos de carbono (“cicloalquilo C_3-C_8”). Los ejemplos representativos incluyen, por ejemplo, ciclopropano, ciclobutano, ciclopentano, ciclopenteno, ciclohexano, ciclohexeno, ciclohexadieno, cicloheptano, cicloheptatrieno, adamantano, y similares. Los grupos cicloalquilo pueden no estar sustituidos o pueden estar sustituidos con los mismos grupos que se describen en la presente como apropiados para alquilo. Tal como se usa en la presente, “cicloalquilo C_3-C_6” se refiere

a un grupo policíclico de anillo fusionado o monocíclico de todos carbonos de 3 a 6 átomos de carbono.

"Cicloalquilalquilo" se puede usar para describir un anillo cicloalquilo, típicamente un cicloalquilo C_3-C_8, que está conectado con la molécula de base a través de un ligador de alquileno, típicamente un alquileno C_1-C_4. Los grupos cicloalquilalquilo se describen por la cantidad total de átomos de carbono en el ligador y anillo carbocíclico, y típicamente contienen de 4-12 átomos de carbono ("cicloalquilalquilo C_4-C_{12}"). De esta manera, un grupo ciclopropilmetilo es un grupo cicloalquilalquilo C_4 y un ciclohexiletilo es un cicloalquilalquilo C_8. Los grupos cicloalquilalquilo pueden no estar sustituidos o pueden estar sustituidos en las porciones de cicloalquilo y/o alquileno con los mismos grupos que se describen en la presente como apropiados para grupos alquilo**.**

Un grupo "arilalquilo" se refiere a un grupo arilo tal como se describe en la presente que está ligado a la molécula de base a través de un alquileno o ligador similar. Los grupos arilalquilo se describen por medio de la cantidad total de átomos de carbono en el ligador y anillo. De esta manera, un grupo bencilo es un grupo arilalquilo C_7, y un feniletilo es un arilalquilo C_8. Típicamente, los grupos arilalquilo contienen 7-16 átomos de carbono ("arilalquilo C_7-C_{16}"), en donde la porción arilo contiene 6-12 átomos de carbono, y la porción alquileno contiene 1-4 átomos de carbono. Estos grupos también pueden estar representados como –alquilen C_1-C_4-arilo C_6-C_{12}.

"Heteroarilalquilo" se refiere a un grupo heteroarilo tal como se describió con anterioridad que está unido a la molécula de base a través de un ligador de alquileno y difiere del "arilalquilo" en que al menos un átomo del anillo de la parte aromática es un heteroátomo seleccionado de N, O y S. Los grupos heteroarilalquilo se describen a veces en la presente de acuerdo con la cantidad total de átomos no hidrógeno (es decir, átomos de C, N, S y O) en el anillo y ligador combinados, excluyendo los grupos sustituyentes. De esta manera, por ejemplo, el piridinilmetilo se puede mencionar como un heteroarilalquilo "C_7". Típicamente, los grupos heteroarilalquilo no sustituidos contienen 6-20 átomos no hidrógeno (incluidos los átomos de C, N, S y O), en donde la porción heteroarilo típicamente contiene 5-12 átomos, y la porción alquileno típicamente contiene 1-4 átomos de carbono. Estos grupos también pueden estar representados como –alquilen C_1-C_4 -heteroarilo de 5-12 miembros.

De modo similar, "arilalcoxi" y "heteroarilalcoxi" se refieren a grupos arilo y heteroarilo, unidos a la molécula de base a través de un ligador de heteroalquileno (es decir, -O-alquileno-), en donde los grupos se describen de acuerdo con la cantidad

total de átomos no hidrógeno (es decir, átomos de C, N, S y O) en el anillo y ligador combinados. De esta manera, los grupos -O-CH_2-fenilo y –O-CH_2-piridinilo se mencionarían como grupos arilalcoxi C_8 y heteroarilalcoxi C_8, respectivamente.

Cuando un grupo arilalquilo, arilalcoxi, heteroarilalquilo o heteroarilalcoxi se describe como opcionalmente sustituido, los sustituyentes pueden estar en la porción ligadora divalente, o en la porción arilo o heteroarilo del grupo. Los sustituyentes opcionalmente presentes en la porción alquileno o heteroalquileno son iguales a aquellos descritos con anterioridad para grupos alquilo o alcoxi en general, mientras que los sustituyentes opcionalmente presentes en la porción arilo o heteroarilo son iguales a los descritos con anterioridad para grupos arilo o heteroarilo en general.

“Hidroxi” se refiere a un grupo -OH.

“Aciloxi” se refiere a un grupo –OC(O)alquilo monovalente, en donde la porción alquilo tiene la cantidad especificada de átomos de carbono (típicamente C_1-C_8, con preferencia, C_1-C_6 o C_1-C_4) y puede estar opcionalmente sustituida con grupos apropiados para alquilo. De esta manera, aciloxi C_1-C_4 incluye un sustituyente de –OC(O)alquilo C_1-C_4, por ejemplo, -OC(O)CH_3.

“Acilamino” se refiere a un grupo monovalente, -NHC(O)alquilo o –NRC(O)alquilo, en donde la porción alquilo tiene la cantidad especificada de átomos de carbono (típicamente C_1-C_8, con preferencia, C_1-C_6 o C_1-C_4), y puede estar opcionalmente sustituido con grupos apropiados para alquilo. De esta manera, acilamino C_1-C_4 incluye un sustituyente de –NHC(O)alquilo C_1-C_4, por ejemplo, -NHC(O)CH_3.

“Ariloxi” o “heteroariloxi” se refieren a –O-arilo u –O-heteroarilo opcionalmente sustituido, en cada caso donde arilo y heteroarilo son como se definen más adelante en la presente.

“Arilamino” o “heteroarilamino” se refieren a –NH-arilo, -NR-arilo, –NH-heteroarilo o –NR-heteroarilo opcionalmente sustituidos, en cada caso donde arilo y heteroarilo son como se definen más adelante en la presente y R representa un sustituyente apropiado para un grupo amina, por ejemplo, un grupo alquilo, acilo, carbamoílo o sulfonilo, o similares.

“Ciano” se refiere a un grupo -C≡N.

“Amino no sustituido” se refiere a un grupo –NH_2. Cuando el amino se describe como sustituido u opcionalmente sustituido, el término incluye grupos de la forma –NR^xR^y, donde cada uno o R^x y R^y son, de modo independiente, H, alquilo, alquenilo, alquinilo, cicloalquilo, heterociclilo, acilo, tioacilo, arilo, heteroarilo, cicloalquilalquilo,

arilalquilo o heteroarilalquilo, en cada caso con la cantidad especificada de átomos y opcionalmente sustituidos tal como se describe en la presente. Por ejemplo, “alquilamino” se refiere a un grupo $–NR^xR^y$, en donde uno de R^x y R^y es una parte alquilo, el otro es H, y “dialquilamino” se refiere a $–NR^xR^y$ en donde los dos R^x y R^y son partes alquilo, donde las partes alquilo tienen la cantidad especificada de átomos de carbono (por ejemplo, –NH-alquilo C_1-C_4 o –N(alquilo C_1-$C_4)_2$). Típicamente, los sustituyentes de alquilo en las aminas contienen 1 a 8 átomos de carbono, con preferencia, 1 a 6 átomos de carbono o con mayor preferencia, 1 a 4 átomos de carbono. El término también incluye formas en las que R^x y R^y se toman junto con el átomo de N al que están unidos para formar un anillo heterociclilo de 3-12 miembros o anillo heteroarilo de 5-12 miembros, cada uno de los cuales puede en sí estar opcionalmente sustituido tal como se describe en la presente para anillos heterociclilo o heteroarilo y que pueden contener 1 a 3 heteroátomos adicionales seleccionados de N, O y S como miembros del anillo, siempre que estos anillos no contengan dos átomos de oxígeno contiguos.

"Opcional" u "opcionalmente" significa que es posible, mas no necesario, que el evento o la circunstancia posteriormente descrita ocurra, y la descripción incluye instancias donde el evento o la circunstancia ocurre e instancias en las que no.

Los términos “opcionalmente substituido/a” y “sustituido/a o no sustituido/a” se pueden usar en forma intercambiable para indicar que el grupo particular que está siendo descrito puede no tener sustituyentes no hidrógeno (es decir, no sustituidos), o el grupo puede tener uno o más sustituyentes no hidrógeno (es decir, sustituidos). A menos que se especifique lo contrario, la cantidad total de sustituyentes que puede estar presente es igual al número de átomos de H presentes en la forma no sustituida del grupo que se está describiendo, al punto que dicha sustitución tiene sentido a nivel químico. Cuando un sustituyente opcional se une mediante un enlace doble, tal como un sustituyente oxo (=O), el grupo ocupa dos valencias disponibles, de tal manera que la cantidad total de los otros sustituyentes que pueda incluirse se reduzca a dos. En el caso donde los sustituyentes opcionales se seleccionan independientemente entre una lista de alternativas, los grupos seleccionados pueden ser iguales o diferentes.

Una "composición farmacéutica" se refiere a una mezcla de uno o más de los compuestos descritos en la presente, o una de sus sales, solvatos, hidratos o profármacos farmacéuticamente aceptables como ingrediente activo, y al menos un portador o excipiente farmacéuticamente aceptable. El objetivo de una composición farmacéutica es facilitar la administración de un compuesto a un mamífero.

En un aspecto, la invención provee una composición farmacéutica que comprende un compuesto de una de las fórmulas descritas en la presente, o una de sus sales farmacéuticamente aceptables, y un portador o excipiente farmacéuticamente aceptable. En algunas formas de realización, la composición farmacéutica comprende dos o más portadores y/o excipientes farmacéuticamente aceptables.

En algunas formas de realización, la composición farmacéutica además comprende al menos un agente terapéutico anticancerígeno o un agente paliativo adicionales. En algunas de dichas formas de realización, dicho al menos un agente medicinal o farmacéutico adicional es un agente anticancerígeno tal como se describe a continuación. En algunas de dichas formas de realización, la combinación provee un efecto anticancerígeno aditivo, más que aditivo, o sinérgico. En algunas de dichas formas de realización, uno o más de los agentes terapéuticos anticancerígenos adicionales se selecciona entre el grupo que consiste en agentes antitumorales, agentes anti-angiogénesis, inhibidores de la transducción de señales y agentes antiproliferativos.

En un aspecto, la invención provee un método para el tratamiento del crecimiento celular anormal en un mamífero, que comprende administrar al mamífero una cantidad terapéuticamente efectiva de un compuesto de la invención, o una de sus sales farmacéuticamente aceptables.

En otro aspecto, la invención provee un método para el tratamiento del crecimiento celular anormal en un mamífero, que comprende administrar al mamífero una cantidad de un compuesto de la invención, o una de sus sales farmacéuticamente aceptables, en combinación con una cantidad de un agente antitumoral, en donde dichas cantidades son, en forma conjunta, efectivas para tratar dicho crecimiento celular anormal. En algunas formas de realización, el agente antitumoral se selecciona entre el grupo que consiste en inhibidores mitóticos, agentes alquilantes, anti-metabolitos, antibióticos intercalantes, inhibidores del factor de crecimiento, radiación, inhibidores del ciclo celular, enzimas, inhibidores de topoisomerasa, modificadores de respuesta biológica, anticuerpos, citotóxicos, anti-hormonas, y anti-andrógenos.

En las formas de realización frecuentes de los métodos provistos en la presente, el crecimiento celular anormal es cáncer. En algunas formas de realización, los métodos provistos generan uno o más de los siguientes efectos: (1) inhibición de la proliferación de células cancerosas; (2) inhibición de la invasividad de células

cancerosas; (3) inducción de la apoptosis de células cancerosas; (4) inhibición de la metástasis de células cancerosas; o (5) inhibición de la angiogénesis.

En otro aspecto, la invención provee un método para el tratamiento de un trastorno mediado por ALK o por una proteína de fusión EML4-ALK en un mamífero, que comprende administrar al mamífero un compuesto de la invención, o una de sus sales farmacéuticamente aceptables, en una cantidad que es efectiva para tratar dicho trastorno. En algunas de dichas formas de realización, la proteína de fusión EML4-ALK tiene al menos una mutación.

El término "mamífero", tal como se usa en la presente, se refiere a un animal humano o no humano clasificado como mamífero. Más particularmente, el término "mamífero" incluye seres humanos, animales domésticos y de granja, animales de investigación, zoológico, deporte y de compañía, tales como mascotas domésticas y otros animales domesticados que incluyen, mas no se limitan a: ganado, ovejas, hurones, cerdos, caballos, conejos, cabras, perros, gatos y similares. En las formas de realización frecuentes, el mamífero es un ser humano. En algunas formas de realización, el término "sujeto" se puede usar para hacer referencia a un ser humano. En algunas formas de realización adicionales, el mamífero es un perro o un gato.

Las proteínas de fusión ALK de particular interés para la presente invención son las formas mutadas de EML4-ALK. De particular interés son los compuestos susceptibles de inhibir la proteína de fusión EML4-ALK mutante L1196M y la proteína de fusión EML4-ALK mutante C_{11}56Y.

Los compuestos, las composiciones y los métodos provistos en la presente son útiles para el tratamiento de tipos de cáncer que incluyen, mas no se limitan a tipos de cáncer del sistema circulatorio, tracto respiratorio, sistema gastrointestinal, tracto genitourinario, hígado, óseo, sistema nervioso, sistema reproductivo, sistema hematológico, cavidad oral, piel, glándulas adrenales, y otros tejidos que incluyen el tejido conectivo y blando, retroperitoneo y peritoneo, ocular, melanoma intraocular, y partes anexas, mama, cabeza y/o cuello, región anal, tiroides, paratiroides, glándula adrenal y otras glándulas endocrinas y estructuras relacionadas, neoplasma maligno secundario y no especificado de los nódulos linfáticos, neoplasma maligno secundario de sistemas respiratorios y digestivos, y neoplasma maligno secundario de otros sitios.

Más específicamente, los ejemplos de cáncer, cuando se usan en la presente en relación con la presente invención incluyen tipos de cáncer seleccionados entre cáncer de pulmón, preferentemente carcinoma pulmonar de células no pequeñas

(NSCLC), linfoma, preferentemente linfoma anaplásico de células grandes, neuroblastoma o cáncer de tejido blando, tal como tumor miofibroblástico inflamatorio.

A menos que se indique lo contrario, todas las referencias en la presente a los compuestos inventivos incluyen las referencias a sus sales, solvatos, hidratos y complejos, y a los solvatos, hidratos y complejos de las sales de aquellos, con inclusión sus de polimorfos, estereoisómeros y versiones isotópicamente marcadas.

Los compuestos de la invención pueden existir en la forma de sales farmacéuticamente aceptables, tales como sales de adición de ácido y sales de adición de base de los compuestos de una de las fórmulas provistas en la presente. Tal como se usa en la presente, el término "sal farmacéuticamente aceptable" se refiere a aquellas sales que retienen la efectividad biológica y las propiedades del compuesto madre. La frase "sal(s) farmacéuticamente aceptable(s)", tal como se usa en la presente, a menos que se indique lo contrario, incluye sales de grupos ácidos o básicos, que pueden estar presentes en los compuestos de las fórmulas descritas en la presente.

Por ejemplo, los compuestos de la invención que son básicos por naturaleza son capaces de formar una amplia variedad de sales con varios ácidos inorgánicos u orgánicos. Si bien dichas sales deben ser farmacéuticamente aceptables para la administración a mamíferos, con frecuencia es deseable —en la práctica— aislar inicialmente el compuesto de la presente invención de la mezcla de reacción como sal farmacéuticamente inaceptable y luego simplemente convertir este último nuevamente en el compuesto de base libre mediante tratamiento con un reactivo alcalino y posteriormente convertir esta última base libre en una sal de adición de ácido farmacéuticamente aceptable. Las sales de adición de ácido de los compuestos de base de esta invención se pueden preparar al tratar el compuesto de base con una cantidad sustancialmente equivalente del ácido orgánico o mineral seleccionado en un medio de solvente acuoso o en un solvente orgánico adecuado, tal como metanol o etanol. Ante la evaporación del solvente, se obtiene la sal sólida deseada. La sal de ácido deseada también se puede precipitar a partir de una solución de la base libre en un solvente orgánico al agregar un ácido mineral u orgánico apropiado a la solución.

Los ácidos se pueden usar para preparar las sales de adición de ácido farmacéuticamente aceptables de dichos compuestos básicos son los que forman sales de adición de ácido no tóxicas, es decir, sales que contienen aniones farmacológicamente aceptables, tales como sales clorhidrato, bromhidrato, yodhidrato, nitrato, sulfato, bisulfato, fosfato, fosfato de ácido, isonicotinato, acetato, lactato,

salicilato, citrato, citrato de ácido, tartrato, pantotenato, bitartrato, ascorbato, succinato, maleato, gentisinato, fumarato, gluconato, glucuronato, sacarato, formato, benzoato, glutamato, metansulfonato, etansulfonato, bencensulfonato, p-toluensulfonato y pamoato [es decir, 1,1'-metilen-bis-(2-hidroxi-3-naftoato)].

Los ejemplos de sales incluyen, pero no se limitan a: sales acetato, acrilato, bencensulfonato, benzoato (tal como clorobenzoato, metilbenzoato, dinitrobenzoato, hidroxibenzoato, y metoxibenzoato), bicarbonato, bisulfato, bisulfito, bitartrato, borato, bromuro, butina-1,4-dioato, edetato de calcio, camsilato, carbonato, cloruro, caproato, caprilato, clavulanato, citrato, decanoato, diclorhidrato, dihidrogenfosfato, edetato, edisilato, estolato, esilato, etilsuccinato, formato, fumarato, gluceptato, gluconato, glutamato, glicolato, glicolilarsanilato, heptanoato, hexina-1,6-dioato, hexilresorcinato, hidrabamina, bromhidrato, clorhidrato, γ-hidroxibutirato, yoduro, isobutirato, isotionato, lactato, lactobionato, laurato, malato, maleato, malonato, mandelato, mesilato, metafosfato, metano-sulfonato, metilsulfato, monohidrogenfosfato, mucato, napsilato, naftaleno-1-sulfonato, naftaleno-2-sulfonato, nitrato, oleato, oxalato, pamoato (embonato), palmitato, pantotenato, fenilacetato, fenilbutirato, fenilpropionato, ftalato, fosfato/difosfato, poligalacturonato, propansulfonato, propionato, propiolato, pirofosfato, pirosulfato, salicilato, estearato, subacetato, suberato, succinato, sulfato, sulfonato, sulfito, tanato, tartrato, teoclato, tosilato, trietiyoduro y valerato.

Los ejemplos ilustrativos de sales adecuadas incluyen sales orgánicas derivadas de aminoácidos, tales como glicina y arginina, amoníaco, aminas primarias, secundarias y terciarias, y aminas cíclicas, tales como piperidina, morfolina y piperazina, y sales inorgánicas derivadas de sodio, calcio, potasio, magnesio, manganeso, hierro, cobre, zinc, aluminio y litio.

Los compuestos de la invención que incluyen una parte básica, tal como un grupo amino, pueden formar sales farmacéuticamente aceptables con varios aminoácidos, además de los ácidos mencionados con anterioridad.

Aquellos compuestos de la invención que son ácidos por naturaleza son capaces de formar sales de base con varios cationes farmacológicamente aceptables. Los ejemplos de dichas sales incluyen las sales de metal alcalino o metal alcalino-térreo y, particularmente, las sales de sodio y potasio. Estas sales son preparadas, todas, mediante técnicas convencionales. Las bases químicas que se usan como reactivos para preparar las sales de base farmacéuticamente aceptables de esta invención son las que forman sales de base no tóxicas con los compuestos ácidos en la presente. Estas sales se pueden preparar a través de cualquier método adecuado,

por ejemplo, tratamiento del ácido libre con una base orgánica o inorgánica, tal como una amina (primaria, secundaria o terciaria), un hidróxido de metal alcalino o un hidróxido de metal alcalino-térreo, o similares. Estas sales también se pueden preparar al tratar los correspondientes compuestos ácidos con una solución acuosa que contiene los cationes farmacológicamente aceptables deseados, y luego evaporar la solución resultante hasta secarse, preferentemente bajo presión reducida. En forma alternativa, también se pueden preparar al mezclar soluciones alcanólicas inferiores de los compuestos ácidos y el alcóxido de metal alcalino deseado en forma conjunta, y luego evaporar la solución resultante hasta secarse de la misma manera que antes. En cualquier caso, las cantidades estequiométricas de los reactivos se emplean preferentemente a fin de asegurar la concreción de la reacción y los máximos rendimientos del producto final deseado.

Las bases químicas que se pueden usar como reactivos para preparar las sales de base farmacéuticamente aceptables de los compuestos de la invención que son ácidos por naturaleza son las que forman sales de base no tóxicas con dichos compuestos. Dichas sales de base no tóxicas incluyen, pero no se limitan a las derivadas de cationes farmacológicamente aceptables tales como cationes de metal alcalino (por ejemplo, potasio y sodio) y cationes de metal alcalino-térreo (por ejemplo, calcio y magnesio), amonio o sales de adición de amina solubles en agua tales como N-metilglucamina-(meglumina), y alcanolamonio inferior y otras sales de base de aminas orgánicas farmacéuticamente aceptables.

También pueden formarse hemisales de ácidos y bases; por ejemplo, sales hemisulfato y hemicalcio.

Para una revisión de las sales adecuadas, véase *Handbook of Pharmaceutical Salts: Properties, Selection, and Use,* de Stahl y Wermuth (Wiley-VCH, Weinheim, Alemania, 2002).

Las sales de la presente invención se pueden preparar de acuerdo con los métodos conocidos por los expertos en la técnica. Una sal farmacéuticamente aceptable de los compuestos inventivos se puede preparar con facilidad al mezclar, en forma conjunta, soluciones del compuesto y el ácido o base deseados, según sea apropiado. La sal se puede precipitar de la solución y recolectar mediante filtración, o se puede recuperar mediante evaporación del solvente. El grado de ionización en la sal puede variar de completamente ionizada a casi no ionizada.

Los expertos en la técnica comprenderán que los compuestos de la invención en forma de base libre que tienen una funcionalidad básica pueden convertirse en las

sales de adición de ácido mediante tratamiento con un exceso estequiométrico del ácido apropiado. Las sales de adición de ácido de los compuestos de la invención se pueden reconvertir en la correspondiente base libre mediante tratamiento con un exceso estequiométrico de una base adecuada, tal como carbonato de potasio o hidróxido de sodio, típicamente en presencia de solvente acuoso, y a una temperatura que oscila entre aproximadamente 0 °C y 100 °C. La forma de base libre se puede aislar a través de medios convencionales, tales como extracción con un solvente orgánico. Asimismo, las sales de adición de ácido de los compuestos de la invención se pueden intercambiar al tomar ventaja de las solubilidades diferenciales de las sales, volatilidades o acidez de los ácidos, o mediante tratamiento con la resina de intercambio iónico cargada de manera apropiada. Por ejemplo, el intercambio puede ser afectado por la reacción de una sal de los compuestos de la invención con un ligero exceso estequiométrico de un ácido de menor pK que el componente de ácido de la sal inicial. Esta conversión se lleva a cabo típicamente a una temperatura que oscila entre aproximadamente 0 °C y el punto de ebullición del solvente que se usa como el medio para el procedimiento. Son posibles los intercambios similares con las sales de adición de base; típicamente mediante la mediación de la forma de base libre.

Las sales farmacéuticamente aceptables de los compuestos de la invención se pueden preparar mediante uno o más de los siguientes métodos:

(i) al hacer reaccionar el compuesto de la invención con el ácido o la base deseados;

(ii) al extraer un grupo protector lábil ante ácido o base de un precursor adecuado del compuesto de la invención o al abrir el anillo de un precursor cíclico adecuado, por ejemplo, una lactona o lactama, usando el ácido o la base deseados; o

(iii) al convertir una sal del compuesto de la invención en otra mediante reacción con un ácido o una base apropiados, o mediante una columna de intercambio iónico adecuada.

Todas estas tres reacciones se llevan a cabo típicamente en solución. La sal resultante se puede precipitar y recolectar mediante filtración o se puede recuperar mediante evaporación del solvente. El grado de ionización en la sal resultante puede variar desde completamente ionizada hasta casi no ionizada.

Los compuestos de la invención pueden existir tanto en formas solvatadas como no solvatadas. Cuando el solvente o el agua están unidos en forma ajustada, el complejo tendrá una estequiometría bien definida, independiente de la humedad. Sin

embargo, cuando el solvente o el agua están unidos en forma débil, como en los solvatos en canal y los compuestos higroscópicos, el contenido agua/solvente dependerá de la humedad y las condiciones de secado. En dichos casos, la no estequiometría será la norma. El término "solvato" se usa en la presente para describir un complejo molecular que comprende el compuesto de la invención y una o más moléculas de solvente farmacéuticamente aceptable, por ejemplo, etanol. El término "hidrato" se emplea cuando el solvente es agua. Los solvatos farmacéuticamente aceptables de acuerdo con la invención incluyen hidratos y solvatos en donde el solvente de cristalización puede estar isotópicamente sustituido, por ejemplo D_2O, d_6-acetona, d_6-DMSO.

También se incluyen dentro del alcance de la invención los complejos tales como clatratos, complejos de inclusión fármaco-huésped en donde, al contrario de los solvatos mencionados con anterioridad, el fármaco y el huésped están presentes en cantidades estequiométricas y no estequiométricas. También se incluyen los complejos del fármaco que contiene dos o más componentes orgánicos y/o inorgánicos que pueden estar en cantidades estequiométricas y no estequiométricas. Los complejos resultantes se pueden ionizar, ionizar parcialmente o no ionizar. Para una revisión de dichos complejos, véase Haleblian*, J. Pharm. Sci.*,1975, 64 (8):1269-1288, cuya divulgación de incorpora en la presente por referencia en su totalidad.

En lo sucesivo, todas las referencias a los compuestos de la invención incluyen referencias a sus sales, solvatos y complejos, y a los solvatos y los complejos de las sales de aquellos.

Los compuestos de la invención incluyen compuestos de la invención según se han definido con anterioridad, con inclusión de todos sus polimorfos y cristales, sus profármacos e isómeros (con inclusión de isómeros ópticos, geométricos y tautoméricos) tal como se definen en lo sucesivo y compuestos isotópicamente marcados de la invención.

La invención también se refiere a profármacos de los compuestos de las fórmulas provistas en la presente. Por ende, ciertos derivados de los compuestos de la invención que pueden tener poco o nada de actividad farmacológica en sí mismos pueden, cuando se administran a un paciente, convertirse en los compuestos inventivos, por ejemplo, mediante escisión hidrolítica. Dichos derivados se denominan "profármacos". La información adicional sobre el uso de profármacos se puede encontrar en *Pro-drugs as Novel Delivery Systems*, Vol. 14, ACS Symposium Series (T. Higuchi y W. Stella) y *Bioreversible Carriers in Drug Design*, Pergamon Press, 1987

(ed. E B Roche, American Pharmaceutical Association), cuya divulgación se incorpora en la presente por referencia en su totalidad.

Los profármacos de acuerdo con la invención pueden producirse, por ejemplo, al reemplazar las funcionalidades apropiadas presentes en los compuestos inventivos con ciertas partes conocidas para los expertos en la técnica como "pro-partes" tal como se describen, por ejemplo, en *Design of Prodrugs*, de H Bundgaard (Elsevier, 1985), cuya divulgación se incorpora en la presente por referencia en su totalidad.

Algunos ejemplos no limitativos de profármacos de acuerdo con la invención incluyen:

(i) cuando el compuesto contiene una funcionalidad de ácido carboxílico (-COOH), uno de sus ésteres, por ejemplo, reemplazo del hidrógeno con alquilo (C_1-C_8);

(ii) cuando el compuesto contiene una funcionalidad de alcohol (-OH), uno de sus éteres, por ejemplo, reemplazo del hidrógeno con alcanoiloximetilo (C_1-C_6); y

(iii) cuando el compuesto contiene una funcionalidad de amino primaria o secundaria (-NH_2 o -NHR cuando R ≠ H), una de sus amidas, por ejemplo, reemplazo de uno o ambos hidrógenos con un grupo lábil metabólicamente adecuado, tal como una amida, carbamato, urea, fosfonato, sulfonato, etc..

Otros ejemplos de grupos de reemplazo de acuerdo con los ejemplos anteriores y ejemplos de otros tipos de profármacos se pueden encontrar en las referencias mencionadas con anterioridad.

Finalmente, ciertos compuestos inventivos pueden actuar, en sí mismos, como profármacos de los otros compuestos inventivos.

También se incluyen dentro del alcance de la invención los metabolitos de los compuestos de la invención, es decir, compuestos formados *in vivo* ante la administración del fármaco. Algunos ejemplos de metabolitos de acuerdo con la invención incluyen:

(i) cuando el compuesto de la invención contiene un grupo metilo, uno de sus derivados hidroximetilo (-CH_3 → -CH_2OH);

(ii) cuando el compuesto de la invención contiene un grupo alcoxi, uno de sus derivados hidroxi (-OR → -OH);

(iii) cuando el compuesto de la invención contiene un grupo amino terciario, uno de sus derivados amino secundarios (-NR^1R^2 → -NHR^1 o -NHR^2);

(iv) cuando el compuesto de la invención contiene un grupo amino secundario, uno de sus derivados primarios (-NHR^1 → -NH_2);

(v) cuando el compuesto de la invención contiene una parte fenilo, uno de sus derivados de fenol (-Ph → -PhOH); y

(vi) cuando el compuesto de la invención contiene un grupo amida, uno de sus derivados de ácido carboxílico (-$CONH_2$ → COOH).

Los compuestos de las fórmulas provistas en la presente pueden tener átomos de carbono asimétricos. Los enlaces carbono-carbono de los compuestos de la invención se pueden ilustrar en la presente usando una línea sólida (———), una cuña sólida (◣), o una cuña punteada (⁞⁞⁞⁞⁞). El uso de una línea sólida para ilustrar enlaces a átomos de carbono asimétricos indica que están incluidos todos los posibles estereoisómeros (por ejemplo enantiómeros específicos, mezclas racémicas, etc.) en ese átomo de carbono. El uso de una cuña sólida o de una cuña punteada para ilustrar enlaces a átomos de carbono asimétricos indica que solamente se pretende incluir el estereoisómero ilustrado. Es posible que los compuestos de la invención contengan más de un átomo de carbono asimétrico. En esos compuestos, el uso de una línea sólida para ilustrar enlaces a átomos de carbono asimétricos indica que se pretende incluir todos los posibles estereoisómeros. Por ejemplo, a menos que se establezca lo contrario, los compuestos de la invención pueden existir como enantiómeros y diastereómeros, o como racematos y mezclas de aquellos. El uso de una línea sólida para ilustrar enlaces a uno o más átomos de carbono asimétricos en un compuesto de la invención y el uso de una cuña sólida o de una cuña punteada para ilustrar enlaces a otros átomos de carbono asimétricos en el mismo compuesto indica se encuentra presente que una mezcla de diastereómeros.

Los compuestos de la invención que contienen uno o más átomos de carbono asimétricos pueden existir como dos o más estereoisómeros, tales como racematos, enantiómeros o diastereómeros. Los estereoisómeros de los compuestos de las fórmulas en la presente pueden incluir isómeros cis y trans, isómeros ópticos tales como enantiómeros (R) y (S), diastereómeros, isómeros geométricos, isómeros de rotación, atropisómeros, isómeros de conformación, y tautómeros de los compuestos de la invención, que incluyen compuestos que exhiben más de un tipo de isomerismo; y sus mezclas (tales como racematos y pares diastereoméricos). También se incluyen las sales de adición de ácido o de adición de base en las cuales el contraión es ópticamente activo, por ejemplo, d-lactato o l-lisina, o racémico, por ejemplo, dl-tartrato o dl-arginina.

Cuando cualquier racemato se cristaliza, los cristales de dos tipos diferentes son posibles. El primer tipo es el compuesto racémico (racemato verdadero) aludido

con anterioridad, en donde se produce una forma homogénea de cristal que contiene ambos enantiómeros en cantidades equimolares. El segundo tipo es la mezcla racémica o conglomerado en donde se producen dos formas de cristal en cantidades equimolares, cada una de las cuales comprende un único enantiómero.

Los compuestos de la invención pueden exhibir el fenómeno de tautomerismo e isomerismo estructural. Por ejemplo, los compuestos pueden existir en varias formas tautoméricas, con inclusión de la forma enol e imina, y la forma ceto y enamina, e isómeros geométricos y sus mezclas. Todas dichas formas tautoméricas están incluidas dentro del alcance de los compuestos de la invención. Los tautómeros existen como mezclas de un conjunto tautomérico en solución. En forma sólida, usualmente predomina un tautómero. Si bien se puede describir un tautómero, la presente invención incluye todos los tautómeros de los compuestos de las fórmulas provistas.

Asimismo, algunos de los compuestos de la invención pueden formar atropisómeros (por ejemplo, biarilos sustituidos). Los atropisómeros son estereoisómeros de conformación que aparecen cuando se previene la rotación alrededor de un enlace simple en la molécula, o se enlentece en gran medida, como resultado de interacciones estéricas con otras partes de la molécula y los sustituyentes a ambos extremos del enlace simple son asimétricos. La interconversión atropisómeros es lo suficientemente lenta para permitir la separación y el aislamiento bajo condiciones predeterminadas. La barrera de energía a la racemización térmica se puede determinar mediante bloqueo estérico a la libre rotación de uno o más enlaces que forman un eje quiral.

Cuando un compuesto de la invención contiene un grupo alquenilo o alquenileno, los isómeros *cis*/*trans* (o Z/E) geométricos son posibles. Los isómeros cis/trans se pueden separar mediante técnicas convencionales ampliamente conocidas por los expertos en la técnica, por ejemplo, cromatografía y cristalización fraccional.

Las técnicas convencionales para la preparación/el aislamiento de los enantiómeros individuales incluyen la síntesis quiral de un precursor ópticamente puro adecuado o resolución del racemato (o el racemato de una sal o un derivado) usando, por ejemplo, cromatografía líquida de alta presión (HPLC) quiral.

En forma alternativa, el racemato (o un precursor racémico) puede someterse a una reacción con un compuesto ópticamente activo adecuado, por ejemplo, un alcohol, o en el caso que el compuesto contiene una fracción ácida o básica, un ácido o una base tal como ácido tartárico o 1-feniletilamina. La mezcla diastereomérica resultante

se puede separar mediante cromatografía y/o cristalización fraccional y uno o ambos de los diaestereoisómeros se pueden convertir en los correspondientes enantiómeros puros a través de medios ampliamente conocidos por el experto en la técnica.

Los compuestos quirales de la invención (y sus precursores quirales) se pueden obtener en una forma enriquecida a nivel enantiomérico usando cromatografía, típicamente HPLC, o una resina asimétrica con una fase móvil que consiste en un hidrocarburo, típicamente heptano o hexano, que contiene desde 0 hasta 50% de isopropanol, típicamente desde 2 hasta 20%, y desde 0 hasta 5% de una alquilamina, típicamente 0,1% de dietilamina. La concentración del eluato forma la mezcla enriquecida.

Los conglomerados estereoisoméricos 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, Nueva York, 1994), cuya divulgación se incorpora en la presente por referencia en su totalidad.

"Enantioméricamente puro" tal como se usa en la presente, describe un compuesto que está presente como un único enantiómero y que se describe en términos de exceso enantiomérico (e.e.). Preferentemente, cuando el compuesto está presente como un enantiómero, el enantiómero está presente como un exceso enantiomérico igual o superior a aproximadamente 80%, más preferentemente, a un exceso enantiomérico igual o superior a aproximadamente 90%, incluso más preferentemente, a un exceso enantiomérico igual o superior a aproximadamente 95%, incluso más preferentemente, a un exceso enantiomérico igual o superior a aproximadamente 98%, con mayor preferencia, a un exceso enantiomérico igual o superior a aproximadamente 99%. En forma similar, "diastereoméricamente puro" tal como se usa en la presente, describe un compuesto que está presente como un diastereómero y que se describe en términos de exceso diastereomérico (e. d.). Preferentemente, cuando el compuesto está presente como diastereómero, el diastereómero está presente a un exceso diastereomérico igual o superior a aproximadamente 80%, más preferentemente, a un exceso diastereomérico igual o superior a aproximadamente 90%, incluso más preferentemente, a un exceso diastereomérico igual o superior a aproximadamente 95%, incluso más preferentemente, a un exceso diastereomérico igual o superior a aproximadamente 98%, con mayor preferencia, a un exceso diastereomérico igual o superior a aproximadamente 99%.

La presente invención también incluye compuestos isotópicamente marcados, que son idénticos a los citados en una de las fórmulas provistas, salvo por el hecho de que uno o más átomos son reemplazados por un átomo que tiene una masa atómica o número de masa diferente de la masa atómica o número de masa usualmente encontrados en la naturaleza.

Los compuestos isotópicamente marcados de la invención por lo general se pueden preparar mediante técnicas convencionales conocidas por los expertos en la técnica o mediante procesos análogos a los descritos en la presente, usando un reactivo isotópicamente marcado apropiado en lugar del reactivo no marcado empleado en su defecto.

Los ejemplos de isótopos que se pueden incorporar en los compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, azufre, flúor y cloro, tales como, mas sin limitarse a, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, y ^{36}Cl. Ciertos compuestos isotópicamente marcados de la invención, por ejemplo, aquellos en los cuales los isótopos radioactivos tales como ^{3}H y ^{14}C se incorporan, son útiles en los ensayos de distribución en tejido de sustrato y/o fármaco. Los isótopos tipificados, es decir, ^{3}H, y carbono-14, es decir, ^{14}C, son particularmente preferidos por su facilidad de preparación y detectabilidad. Además, la sustitución con isótopos más pesados tales como deuterio, es decir, ^{2}H, pueden ofrecer ciertas ventajas terapéuticas generadas de una estabilidad metabólica superior, por ejemplo vida media *in vivo* incrementada o requisitos de dosificación reducidos y, por ende, pueden ser preferentes en algunas circunstancias. Los compuestos isotópicamente marcados de la invención por lo general se pueden preparar al llevar a cabo los procedimientos divulgados en los Esquemas y/o en los Ejemplos y las Preparaciones que siguen, al sustituir un reactivo isotópicamente marcado por un reactivo no isotópicamente marcado. Los solvatos farmacéuticamente aceptables de acuerdo con la invención incluyen aquellos en donde el solvente de cristalización se puede sustituir isotópicamente, por ejemplo D_2O, d_6-acetona, d_6-DMSO.

Los compuestos de la invención destinados a uso farmacéutico se pueden administrar como productos cristalinos o amorfos, o sus mezclas. Se pueden obtener, por ejemplo, como tapones sólidos, polvos o películas mediante métodos tales como precipitación, cristalización, secado por congelación, secado por pulverización o secado por evaporación. El secado con radio frecuencia o microondas se puede usar con este propósito.

Métodos y usos terapéuticos

La invención además provee métodos y usos terapéuticos que comprenden administrar los compuestos de la invención, o sus sales farmacéuticamente aceptables, en forma individual o en combinación con otros agentes terapéuticos o agentes paliativos.

En un aspecto, la invención provee un método para el tratamiento del crecimiento celular anormal en un mamífero, que comprende administrar al mamífero una cantidad terapéuticamente efectiva de un compuesto de la invención, o una de sus sales farmacéuticamente aceptables.

En otro aspecto, la invención provee un método para el tratamiento del crecimiento celular anormal en un mamífero, que comprende administrar al mamífero una cantidad de un compuesto de la invención, o una de sus sales farmacéuticamente aceptables, en combinación con una cantidad de un agente antitumoral, en donde dichas cantidades son, en forma conjunta, efectivas para tratar dicho crecimiento celular anormal. En algunas de dichas formas de realización, el agente antitumoral se selecciona entre el grupo que consiste en inhibidores mitóticos, agentes alquilantes, anti-metabolitos, antibióticos intercalantes, inhibidores del factor de crecimiento, radiación, inhibidores del ciclo celular, enzimas, inhibidores de topoisomerasa, modificadores de respuesta biológica, anticuerpos, citotóxicos, antihormonas, y anti-andrógenos.

Los compuestos de la invención incluyen los compuestos de cualquiera de las fórmulas descritas en la presente, con inclusión de las fórmulas (Φ) y (I)-(XXX), o una de sus sales farmacéuticamente aceptables.

En otro aspecto, la invención provee un método para el tratamiento del crecimiento celular anormal en un mamífero, que comprende administrar al mamífero una cantidad de un compuesto de la invención, o una de sus sales farmacéuticamente aceptables, que es efectiva para tratar el crecimiento celular anormal.

Incluso en otro aspecto, la invención provee un método para inhibir la proliferación de células cancerosas en un mamífero, que comprende administrar al mamífero un compuesto de la invención, o una de sus sales farmacéuticamente aceptables, en una cantidad efectiva para inhibir la proliferación celular.

En otro aspecto, la invención provee un método para inhibir la invasividad de células cancerosas en un mamífero, que comprende administrar al mamífero un compuesto de la invención, o una de sus sales farmacéuticamente aceptables, en una cantidad efectiva para inhibir la invasividad celular.

En otro aspecto, la invención provee un método para inducir apoptosis en células cancerosas en un mamífero, que comprende administrar al mamífero un compuesto de la invención, o una de sus sales farmacéuticamente aceptables, en una cantidad efectiva para inducir apoptosis.

En otro aspecto, la invención provee un método para inducir apoptosis en un mamífero, que comprende administrar al mamífero una cantidad terapéuticamente efectiva de un compuesto de una de las fórmulas descritas en la presente, o una de sus sales farmacéuticamente aceptables.

En formas de realización frecuentes de los métodos provistos en la presente, el crecimiento celular anormal es cáncer, en donde dicho cáncer se selecciona entre el grupo que consiste en cáncer de células basales, meduloblastoma, cáncer de hígado, rabdomiosarcoma, cáncer pulmonar, cáncer óseo, cáncer pancreático, cáncer de piel, cáncer de cabeza o cuello, melanoma cutáneo o intraocular, cáncer uterino, cáncer ovárico, cáncer rectal, cáncer de la región anal, cáncer de estómago, cáncer de colon, cáncer de mama, cáncer uterino, carcinoma de las trompas de Falopio, carcinoma del endometrio, carcinoma cervicouterino, carcinoma de la vagina, carcinoma de la vulva, enfermedad de Hodgkin, cáncer del esófago, cáncer del intestino delgado, cáncer del sistema endocrino, cáncer de la glándula tiroides, cáncer de la glándula paratiroides, cáncer de la glándula adrenal, sarcoma del tejido blando, cáncer de la uretra, cáncer del pene, cáncer de próstata, leucemia aguda o crónica, linfomas linfocíticos, cáncer de vejiga, cáncer de riñón o uretra, carcinoma de células renales, carcinoma de la pelvis renal, neoplasmas del sistema nervioso central (SNC), linfoma de SNC primario, tumores del eje espinal, glioma del tronco encefálico, adenoma pituitario, o una combinación de uno o más de los tipos de cáncer anteriormente citados.

Los compuestos de la invención, sus sales farmacéuticamente aceptables y/o sus composiciones o formas derivadas, son compuestos farmacéuticamente activos valiosos, que son adecuados para la terapia de numerosos trastornos, en particular, el cáncer, en los cuales participa el receptor de ALK y/o una proteína de fusión ALK, por ejemplo EML4-ALK, o en los cuales la inhibición de la actividad de ALK puede inducir beneficios.

Otro aspecto de la invención se refiere a un compuesto de la invención, o a sus sales farmacéuticamente aceptables, formas derivadas o composiciones, para uso como medicamento, y en particular para uso en el tratamiento de enfermedades, tales como el cáncer, en las cuales la inhibición de la actividad de ALK y/o una proteína de fusión ALK, por ejemplo, EML4-ALK, puede inducir beneficio.

Otro aspecto más de la presente invención también se refiere al uso de los compuestos de la invención, o sus sales farmacéuticamente aceptables, formas derivadas o composiciones, para la fabricación de un fármaco que tiene actividad inhibitoria de ALK para el tratamiento de enfermedades y/o afecciones mediadas por ALK, en particular las enfermedades y/o afecciones citadas con anterioridad.

Otro aspecto de la presente invención también se refiere al uso de los compuestos de la invención, o sus sales farmacéuticamente aceptables, formas derivadas o composiciones, para la fabricación de un fármaco que tiene actividad inhibitoria de EML4-ALK para el tratamiento de enfermedades y/o afecciones mediadas por EML4-ALK, en particular las enfermedades y/o afecciones citadas con anterioridad.

Los compuestos de la invención, sus sales farmacéuticamente aceptables y/o formas derivadas o composiciones, son compuestos farmacéuticamente activos valiosos, adecuados para el tratamiento del dolor, con inclusión de: dolor agudo; dolor crónico; dolor neuropático; dolor inflamatorio (inclusive, por ejemplo, dolor por osteoartritis, dolor por artritis reumatoide); dolor visceral; dolor nociceptivo que incluye dolor post-quirúrgico; y tipos de dolores mixtos que implican las vísceras, el tracto gastrointestinal, las estructuras craneanas, el sistema musculoesquelético, la columna vertebral, el sistema urogenital, el sistema cardiovascular y el SNC, con inclusión de dolor por cáncer, dolor de espalda y dolor orofacial.

Otro aspecto de la invención se refiere a un compuesto de la invención, o sus sales farmacéuticamente aceptables, formas derivadas o composiciones, para uso como medicamento, y en particular para uso en el tratamiento de dolor, con inclusión de dolor agudo; dolor crónico; dolor neuropático; dolor inflamatorio (inclusive, por ejemplo, dolor por osteoartritis, dolor por artritis reumatoide); dolor visceral; dolor nociceptivo que incluye dolor post-quirúrgico; y tipos de dolores mixtos que implican las vísceras, el tracto gastrointestinal, las estructuras craneanas, el sistema musculoesquelético, la columna vertebral, el sistema urogenital, el sistema cardiovascular y el SNC, con inclusión de dolor por cáncer, dolor de espalda y dolor orofacial.

Otro aspecto más de la presente invención también se refiere al uso de los compuestos de la invención, o sus sales farmacéuticamente aceptables, formas derivadas o composiciones, para la fabricación de un fármaco para el tratamiento de las enfermedades y/o afecciones enunciadas con anterioridad.

Como consecuencia, la presente invención provee un método para tratar un mamífero, inclusive un ser humano, con una cantidad terapéuticamente efectiva de un compuesto de la invención, o una de sus sales farmacéuticamente aceptables, formas derivadas o composiciones farmacéuticas. Más precisamente, la presente invención provee un método para el tratamiento de tipos de cáncer mediados por ALK en un mamífero, inclusive un ser humano, en particular los tipos de cáncer enunciados con anterioridad, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva de un compuesto de la invención, sus sales farmacéuticamente aceptables y/o formas derivadas, o una composición farmacéutica del mismo.

Otra forma de realización de la presente invención de particular interés se refiere a un método para el tratamiento de cáncer pulmonar en un ser humano que necesita dicho tratamiento, que comprende administrar a dicho ser humano una cantidad de un compuesto de la invención, en combinación con uno o más (preferentemente uno a tres) agentes anticancerígenos seleccionados entre el grupo que consiste en capecitabina, bevacizumab, gemcitabina, docetaxel, paclitaxel, premetrexed disódico, erlotinib, gefitinib, vinorelbina, irinotecán, etopósido, vinblastina, y carboplatino, en donde las cantidades del agente activo junto con las cantidades de los agentes anticancerígenos en combinación es efectiva para tratar el cáncer pulmonar.

Preferentemente, los compuestos de la invención son inhibidores selectivos de ALK. Preferentemente, los compuestos de la invención son inhibidores selectivos del mutante L1196M de EML4-ALK. Preferentemente, los compuestos de la invención son inhibidores selectivos del mutante C_{11}56Y de EML4-ALK.

El término "cantidad terapéuticamente efectiva" tal como se usa en la presente se refiere a la cantidad de un compuesto administrado, que aliviará hasta cierto punto uno o más de los síntomas del trastorno que está siendo tratado. Con referencia al tratamiento del cáncer, una cantidad terapéuticamente efectiva se refiere a esa cantidad que tiene el efecto de: (1) reducir el tamaño del tumor, (2) inhibir (es decir, enlentecer hasta cierto punto, preferentemente detener) la metástasis tumoral, (3) inhibir hasta cierto punto (es decir, enlentecer hasta cierto punto, preferentemente detener) el crecimiento del tumor o la invasividad del tumor, y/o (4) aliviar hasta cierto punto (o, preferentemente, eliminar) uno o más signos o síntomas asociados con el cáncer.

El término "tratar", tal como se usa en la presente, a menos que se indique lo contrario, significa revertir, aliviar, inhibir el avance, o prevenir el trastorno o la afección a los cuales dicho término se aplica, o uno o más síntomas de dicho trastorno o afección. El término "tratamiento", tal como se usa en la presente, a menos que se indique lo contrario, se refiere al acto de tratar de acuerdo con la forma en que el término “tratar” se define inmediatamente arriba. El término “tratar” también incluye tratamiento adyuvante y neo-adyuvante de un mamífero.

Los términos “crecimiento celular anormal” y “trastorno hiperproliferativo” se usan en forma intercambiable en esta solicitud.

“Crecimiento celular anormal”, tal como se usa en la presente, a menos que se indique lo contrario, se refiere al crecimiento celular que es independiente de los mecanismos reguladores normales (por ejemplo, pérdida de inhibición por contacto). El crecimiento celular anormal puede ser benigno (no canceroso) o maligno (canceroso). Esto incluye el crecimiento anormal de: (1) células tumorales (tumores) que proliferan al expresar ALK o una proteína de fusión ALK, por ejemplo, EML4-ALK; (2) células benignas y malignas de otras enfermedades proliferativas en las cuales ALK o una proteína de fusión ALK aparece; (3) cualquier tumor que prolifere mediante la activación aberrante de ALK o proteína de fusión ALK; y (4) células benignas y malignas de otras enfermedades proliferativas en las cuales ocurre la activación aberrante de ALK o proteína de fusión ALK.

Tal como se usa en la presente “cáncer” se refiere a cualquier crecimiento o tumor maligno y/o invasivo causado por el crecimiento celular anormal, que incluye tumores sólidos que llevan el nombre del tipo de células que los conforman, cáncer de la sangre, médula ósea o el sistema linfático. Los ejemplos de tumores sólidos incluyen, mas no se limitan a, sarcomas y carcinomas. Los ejemplos de tipos de cáncer de la sangre incluyen, mas no se limitan a, leucemias, linfomas y mieloma. El término “cáncer” incluye, mas no se limita a, cáncer primario que se origina en un sitio específico del cuerpo, un cáncer metastásico que se ha diseminado desde el lugar en el que comenzó a otras partes del cuerpo, una recurrencia del cáncer primario original después de la remisión, y un segundo cáncer primario que es un cáncer primario nuevo en una persona con antecedentes de cáncer anterior de diferente tipo.

Los compuestos de la invención inhiben ALK y, por ende, se adaptan –todos– al uso terapéutico como agentes antiproliferativos (por ejemplo, cáncer) o agentes antitumorales (por ejemplo, efecto contra tumores sólidos) en mamíferos, particularmente en seres humanos. En particular, los compuestos de la invención son

útiles en la prevención y el tratamiento de una variedad de trastornos hiperproliferativos en seres humanos que incluyen el crecimiento celular anormal tanto maligno como benigno.

Los compuestos, las composiciones y los métodos provistos en la presente son útiles para el tratamiento de tipos de cáncer, que incluyen mas no se limitan a los tipos de cáncer que se enumeran a continuación:

sistema circulatorio, por ejemplo, corazón (sarcoma [angiosarcoma, fibrosarcoma, rabdomiosarcoma, liposarcoma], mixoma, rabdomioma, fibroma, lipoma y teratoma), mediastino y pleura, y otros órganos intratoráxicos, tumores vasculares y tejido vascular asociado con tumor;

tracto respiratorio, por ejemplo, cavidad nasal y oído medio, senos accesorios, laringe, tráquea, bronquios y pulmones, tales como cáncer pulmonar de células pequeñas (SCLC), cáncer pulmonar de células no pequeñas (NSCLC), carcinoma broncogénico (célula escamosa, célula pequeña no diferenciada, célula grande no diferenciada, adenocarcinoma), carcinoma alveolar (bronquiolar), adenoma bronquial, sarcoma, linfoma, hamartoma condromatoso, mesotelioma;

sistema gastrointestinal, por ejemplo, esófago (carcinoma de célula escamosa, adenocarcinoma, leiomiosarcoma, linfoma), estómago (carcinoma, linfoma, leiomiosarcoma), gástrico, páncreas (adenocarcinoma ductal, insulinoma, glucagonoma, gastrinoma, tumores carcinoides, vipoma), intestino delgado (adenocarcinoma, linfoma, tumores carcinoides, sarcoma de Karposi, leiomioma, hemangioma, lipoma, neurofibroma, fibroma), intestino grueso (adenocarcinoma, adenoma tubular, adenoma velloso, hamartoma, leiomioma);

tracto genitourinario, por ejemplo, riñón (adenocarcinoma, tumor de Wilm [nefroblastoma], linfoma, leucemia), vejiga y/o uretra (carcinoma de célula escamosa, carcinoma de células transicionales, adenocarcinoma), próstata (adenocarcinoma, sarcoma), testículos (seminoma, teratoma, carcinoma embrionario, teratocarcinoma, coriocarcinoma, sarcoma, carcinoma de células intersticiales, fibroma, fibroadenoma, tumores adenomatoides, lipoma);

hígado, por ejemplo, hepatoma (carcinoma hepatocelular), colangiocarcinoma, hepatoblastoma, angiosarcoma, adenoma hepatocelular, hemangioma, tumores endocrinos pancreáticos (tales como feocromocitoma, insulinoma, tumor productor de péptido intestinal vasoactivo, insulinoma y glucagonoma);

huesos, por ejemplo, sarcoma osteogénico (osteosarcoma), fibrosarcoma, histiocitoma fibroso maligno, condrosarcoma, sarcoma de Ewing, linfoma maligno

(sarcoma de células reticulares), mieloma múltiple, cordoma, tumor de células gigantes maligno, osteocronfroma (exostosis osteocartilaginosa), condroma benigno, condroblastoma, condromixofibroma, osteoma osteoide y tumores de células gigantes;

sistema nervioso, por ejemplo, neoplasmas del sistema nervioso central (SNC), linfoma primario del SNC, cáncer en el cráneo (osteoma, hemangioma, granuloma, xantoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), cáncer cerebral (astrocitoma, meduloblastoma, glioma, ependimoma, germinoma [pinealoma], glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, tumores congénitos), neurofibroma de la médula espinal, meningioma, glioma, sarcoma);

sistema reproductivo, por ejemplo, ginecológico, útero (carcinoma endometrial), cuello uterino (carcinoma cervicouterino, displasia cervical pre-tumoral), ovarios (carcinoma ovárico [cistadenocarcinoma seroso, cistadenocarcinoma mucinoso, carcinoma no clasificado], tumores de células de la granulosa-teca, tumores de células de Sertoli-Leydig, disgerminoma, teratoma maligno), vulva (carcinoma de células escamosas, carcinoma intraepitelial, adenocarcinoma, fibrosarcoma, melanoma), vagina (carcinoma de células claras, carcinoma de células escamosas, sarcoma botrioide (rabdomiosarcoma embrionario), trompas de Falopio (carcinoma) y otros sitios asociados con los órganos genitales femeninos; placenta, pene, próstata, testículos, y otros sitios asociados con los órganos genitales masculinos;

sistema hematológico, por ejemplo, sangre (leucemia mieloide [aguda y crónica], leucemia linfoblástica aguda, leucemia linfoblástica crónica, enfermedades mieloproliferativas, mieloma múltiple, síndrome mielodisplásico), enfermedad de Hodgkin, linfoma no Hodgkin [linfoma maligno];

cavidad oral, por ejemplo, labio, lengua, encía, base de la boca, paladar y otras partes de la boca, glándula parótida, y otras partes de las glándulas salivales, amígdala, orofaringe, nasofaringe, senos piriformes, hipofaringe, y otros sitios en labio, cavidad oral y faringe;

piel, por ejemplo, melanoma maligno, melanoma cutáneo, carcinoma de células basales, carcinoma de células escamosas, sarcoma de Karposi, lunares, nevos displásicos, lipoma, angioma, dermatofibroma, y queloides;

glándulas adrenales: neuroblastoma; y

otros tejidos con inclusión de tejido conectivo y tejido blando, retroperitoneo y peritoneo, ojo, melanoma intraocular y partes anexas, mama, cabeza y/o cuello, región anal, tiroides, paratiroides, glándula adrenal y otras glándulas endocrinas y estructuras

relacionadas, neoplasma maligno secundario y no especificado de los nódulos linfáticos, neoplasma maligno secundario del sistema respiratorio y digestivo, y neoplasma maligno secundario de otros sitios.

Más específicamente, los ejemplos de cáncer, cuando se usan en la presente con relación a la presente invención incluyen cáncer seleccionado entre cáncer pulmonar (NSCLC y SCLC), cáncer de cabeza o cuello, cáncer ovárico, cáncer de colon, cáncer rectal, cáncer de la región anal, cáncer de estómago, cáncer de mama, cáncer de riñón o uretra, carcinoma de células renales, carcinoma de la pelvis renal, neoplasmas del sistema nervioso central (SNC), linfoma del SNC primario, linfoma no Hodgkin, tumores del eje espinal, o una combinación de uno o más de los tipos de cáncer citados.

Incluso más específicamente, los ejemplos de cáncer cuando se usan en la presente en relación con la presente invención incluyen cáncer seleccionado entre cáncer pulmonar (NSCLC y SCLC), cáncer de mama, cáncer ovárico, cáncer de colon, cáncer rectal, cáncer de la región anal, o una combinación de uno o más de los tipos de cáncer citados.

En una forma de realización de la presente invención, las afecciones no cancerosas incluyen afecciones hiperplásicas, tales como la hiperplasia benigna de la piel (por ejemplo, psoriasis) y la hiperplasia benigna de la próstata (BPH).

En otro aspecto, la invención provee un método para inhibir la proliferación celular, que comprende poner en contacto las células con un compuesto de la invención o una de sus sales farmacéuticamente aceptables en una cantidad efectiva para inhibir la proliferación de las células.

En otro aspecto, la invención provee métodos para inducir la apoptosis celular, que comprenden poner en contacto las células con un compuesto descrito en la presente en una cantidad efectiva para inducir apoptosis de las células.

"Poner en contacto" se refiere a formar un puente entre un compuesto o sal farmacéuticamente aceptable de la invención, y una célula que expresa ALK en forma conjunta de tal manera que el compuesto pueda afectar la actividad de ALK, ya sea de manera directa o indirecta. El contacto se puede lograr *in vitro* (es decir, en un medio artificial tal como, por ejemplo, en un tubo de ensayo o medio de cultivo) o *in vivo* (es decir, dentro de un organismo vivo tal como, un ratón, una rata o un conejo).

En algunas formas de realización, las células están en una línea celular, tal como una línea celular cancerosa. En otras formas de realización, las células están en

un tejido o tumor, y el tejido o tumor puede estar en un mamífero, inclusive un ser humano.

Formas y regímenes de dosificación

La administración de los compuestos de la invención se puede efectuar mediante cualquier método que permita el suministro de los compuestos al sitio de acción. Estos métodos incluyen vías orales, vías intraduodenales, inyección parenteral (inclusive intravenosa, subcutánea, intramuscular, intravascular o infusión), administración tópica y administración rectal.

Los regímenes de dosificación se pueden ajustar para proveer la respuesta óptima deseada. Por ejemplo, es posible administrar un único bolo, administrar varias dosis divididas en el tiempo, o reducir o incrementar de manera proporcional la dosis según lo indiquen las exigencias de la situación terapéutica. Es especialmente ventajoso formular composiciones parenterales en forma de dosis unitaria para facilitar la administración y la uniformidad de la dosis. La “forma de dosis unitaria”, tal como se usa en la presente, se refiere a las unidades físicamente discretas adecuadas como dosis unitarias para los mamíferos a ser tratados; cada unidad contiene una cantidad predeterminada de compuesto activo calculada para producir el efecto terapéutico deseado en asociación con el portador farmacéutico requerido. La especificación para las formas de dosis unitarias de la invención son dictadas y dependen directamente de lo siguiente: (a) las características únicas del agente quimioterapéutico y el efecto terapéutico o profiláctico particular a ser alcanzado, y (b) las limitaciones inherentes en la técnica de la formación de compuestos, tal como en el caso de un compuesto activo para el tratamiento de la sensibilidad en los individuos.

Por ende, el experto en la técnica apreciaría, sobre la base de la divulgación provista en la presente, que la dosis y el régimen de dosificación se ajusta de acuerdo con métodos ampliamente conocidos en la técnica terapéutica. Es decir, la dosis tolerable máxima se puede establecer con facilidad, y la cantidad efectiva que provee un beneficio terapéutico detectable a un paciente también se puede determinar, de la misma manera que los requisitos temporales para administrar cada agente con el objeto de brindar un beneficio terapéutico detectable al paciente. Por consiguiente, si bien ciertas dosis y regímenes de administración están ejemplificados en la presente, estos ejemplos no limitan de manera alguna la dosis ni el régimen de dosificación que se pueden proveer a un paciente al llevar a la práctica la presente invención.

Ha de destacarse que los valores de dosis pueden variar con el tipo y la severidad de la afección a ser aliviada, y pueden incluir dosis únicas o múltiples. Ha de entenderse, además, que para cualquier mamífero particular, los regímenes de dosificación específicos deberían ajustarse con el tiempo de acuerdo con la necesidad individual y el juicio profesional de la persona que administra o supervisa la administración de las composiciones, y que los rangos de dosis establecidos en la presente se incluyen solo a modo de ejemplo y no están destinados a limitar el alcance ni la práctica de la composición reivindicada. Por ejemplo, es posible ajustar las dosis sobre la base de parámetros farmacodinámicos o farmacocinéticos, que pueden incluir efectos clínicos tales como efectos tóxicos y/o valores de laboratorio. Por ende, la presente invención abarca la escala de dosis intrapaciente según lo determina el experto en la técnica. Determinar las dosis y los regímenes apropiados para la administración del agente quimioterapéutico es una acción ampliamente conocida en la técnica relevante, y el experto en la técnica entendería que aquella está abarcada una vez provistas las enseñanzas reveladas en la presente.

La cantidad del compuesto de la invención administrada será dependiente del mamífero que es tratado, la severidad del trastorno o la afección, la tasa de administración, la disposición del compuesto y el criterio del médico a cargo. No obstante, una dosificación efectiva se encuentra en el rango de aproximadamente 0,001 a aproximadamente 100 mg por kg de peso corporal al día, preferentemente de aproximadamente 1 a aproximadamente 35 mg/kg/día, en dosis únicas o divididas. Para un ser humano de 70 kg, esto equivaldría a aproximadamente 0,05 a aproximadamente 7 g/día, preferentemente aproximadamente 0,1 a aproximadamente 2,5 g/día. En algunos casos, los niveles de dosificación por debajo del límite inferior del rango anteriormente citado pueden ser más de lo adecuado, si bien en otros casos se pueden emplear dosis incluso mayores sin causar un efecto colateral dañino, siempre que dichas dosis mayores se dividan primero en varias dosis pequeñas para su administración a lo largo del día.

Formulaciones y vías de administración

Tal como se usa en la presente, un "portador farmacéuticamente aceptable" se refiere a un portador o diluyente que no causa irritación significativa a un organismo y no abroga la actividad biológica ni las propiedades del compuesto administrado.

El portador farmacéutico aceptable puede comprender cualquier excipiente o portador farmacéutico convencional. La elección del portador y/o excipiente dependerá

en gran medida de factores tales como el modo de administración particular, el efecto del excipiente sobre la solubilidad y estabilidad, y la naturaleza de la forma de dosificación.

Los portadores farmacéuticos adecuados incluyen diluyentes o agentes de relleno inertes, agua y varios solventes orgánicos (tales como hidratos y solvatos). Las composiciones farmacéuticas pueden contener, si se desea, ingredientes adicionales tales como saborizantes, aglutinantes, excipientes y similares. Por ende, para la administración oral, es posible emplear comprimidos que contengan varios excipientes, tales 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. Los ejemplos, sin limitación, de excipientes incluyen carbonato de calcio, fosfato de calcio, varios azúcares y tipos de almidones, derivados de celulosa, gelatina, aceites vegetales y polietilenglicoles. Asimismo, con frecuencia los agentes lubricantes, tales como estearato de magnesio, lauril sulfato de sodio y talco son útiles a los fines de la formación de comprimidos. Las composiciones sólidas de tipo similar también se pueden emplear en cápsulas blandas y duras llenas de gelatina. Los ejemplos no limitativos de materiales incluyen, por ende, lactosa o azúcar de leche y polietilenglicoles de alto peso molecular. Cuando se desean elíxires o suspensiones acuosas para la administración oral, el compuesto activo en ellos se puede combinar con varios agentes edulcorantes o saborizantes, sustancias colorantes o tintes y, si se desea, agentes emulsionantes o agentes de suspensión, junto con diluyentes tales como agua, etanol, propilenglicol, glicerina, o combinaciones de aquellos.

La composición farmacéutica puede estar, por ejemplo, en una forma adecuada para la administración oral, como comprimido, cápsula, píldora, polvo, formulaciones de liberación prolongada, suspensión de solución; para inyección parenteral, como solución estéril, suspensión o emulsión; para administración tópica, como ungüento o crema; o para administración rectal, como un supositorio.

Las formas de administración parenteral de ejemplo incluyen soluciones o suspensiones de compuestos activos en soluciones acuosas estériles, por ejemplo, soluciones acuosas de propilenglicol o dextrosa. Dichas formas de dosificación pueden estar tamponadas de manera adecuada, si se desea.

La composición farmacéutica puede estar en formas de dosis unitarias adecuadas para la administración individual de dosis precisas.

Las composiciones farmacéuticas adecuadas para el suministro de los compuestos de la invención y los métodos para su preparación serán fácilmente vislumbrados por los expertos en la técnica. Dichas composiciones y dichos métodos para su preparación se pueden encontrar, por ejemplo, en *Remington's Pharmaceutical Sciences*, 19.ª Edición (Mack Publishing Company, 1995), cuya divulgación se incorpora en la presente por referencia en su totalidad.

Los compuestos de la invención se pueden administrar en forma oral. La administración oral puede implicar la deglución, de tal manera que el compuesto ingresa en el tracto gastrointestinal, o se puede emplear la administración bucal o sublingual mediante la cual el compuesto ingresa en el torrente sanguíneo directamente desde la boca.

Las formulaciones adecuadas para administración oral incluyen formulaciones sólidas tales como comprimidos, cápsulas que contienen particulados, líquidos o polvos, pastillas (inclusive las rellenas con líquidos), gomas, multi- y nanoparticulados, geles, solución sólida, liposoma, películas (inclusive muco-adhesivas), óvulos, aerosoles y formulaciones líquidas.

Las formulaciones líquidas incluyen suspensiones, soluciones, jarabes y elíxires. Dichas formulaciones se pueden usar como agentes de relleno en cápsulas blandas o duras, y típicamente incluyen un portador, por ejemplo, agua, etanol, polietilenglcol, propilenglicol, metilcelulosa, o un aceite adecuado, y uno o más agentes emulsionantes y/o agentes de suspensión. Las formulaciones líquidas también se pueden preparar mediante la reconstitución de un sólido, por ejemplo, de un sachet.

Los compuestos de la invención también se pueden utilizar en formas de dosis de rápida disolución y rápida desintegración, tales como las descritas en *Expert Opinion in Therapeutic Patents*, 11 (6), 981-986 de Liang y Chen (2001), cuya divulgación se incorpora en la presente por referencia en su totalidad.

Para las formas de dosis en comprimidos, según la dosis, el fármaco puede conformar desde el 1% en peso hasta el 80% en peso de la forma de dosis, más típicamente desde el 5% en peso hasta el 60% en peso de la forma de dosis. Además del fármaco, los comprimidos por lo general contienen un desintegrante. Los ejemplos de desintegrantes incluyen glicolato de almidón sódico, carboximetilcelulosa sódica, carboximetilcelulosa de calcio, croscarmelosa sódica, crospovidona, polivinilpirrolidona, metilcelulosa, celulosa microcristalina, hidroxipropilcelulosa sustituida con alquilo inferior, almidón, almidón pregelatinizado y alginato de sodio. Por

lo general, el desintegrante comprenderá desde 1% en peso hasta 25% en peso, preferentemente desde 5% en peso hasta 20% en peso de la forma de dosis.

Los aglutinantes por lo general se usan para impartir cualidades cohesivas a una formulación en comprimidos. Los aglutinantes adecuados incluyen celulosa microcristalina, gelatina, azúcares, polietilenglicol, gomas naturales y sintéticas, polivinilpirrolidona, almidón pregelatinizado, hidroxipropilcelulosa e hidroxipropilmetilcelulosa. Los comprimidos también pueden contener diluyentes, tales como lactosa (monohidrato, monohidrato secado por aspersión, anhidro y similares), manitol, xilitol, dextrosa, sacarosa, sorbitol, celulosa microcristalina, almidón y fosfato de calcio dibásico dihidratado.

Los comprimidos también pueden incluir, opcionalmente, agentes activos de superficie, tales como lauril sulfato de sodio y polisorbato 80, y glidantes tales como dióxido de silicio y talco. Cuando están presentes, los agentes activos de superficie se encuentran típicamente en cantidades que abarcan desde el 0,2% en peso hasta el 5% en peso del comprimido, y deslizantes que abarcan típicamente desde el 0,2% en peso hasta el 1% en peso del comprimido.

Los comprimidos también contienen, por lo general, lubricantes tales como estearato de magnesio, estearato de calcio, estearato de zinc, estearilfumarato sódico, y mezclas de estearato de magnesio con lauril sulfato de sodio. Los lubricantes por lo general están presentes en cantidades que abarcan desde 0,25% en peso hasta 10% en peso, preferentemente desde 0,5% en peso hasta 3% en peso del comprimido.

Otros ingredientes convencionales incluyen antioxidantes, colorantes, agentes saborizantes, conservantes y agentes enmascaradores del sabor.

Los comprimidos de ejemplo contienen hasta aproximadamente 80% en peso de 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.

Las mezclas de los comprimidos se pueden comprimir directamente o mediante rodillo para formar los comprimidos. Las mezclas de los comprimidos o las porciones de las mezclas pueden someterse, en forma alternativa, a granulación en húmedo, en seco, o por fundición, gelatinización, o extrusión antes de la formación en comprimidos. La formulación final puede incluir una o más capas y se puede revestir o no; o puede estar encapsulada.

La formulación de comprimidos se analiza en detalle en *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, de H. Lieberman y L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X), cuya divulgación se incorpora en la presente por referencia en su totalidad.

Las formulaciones sólidas para administración oral se pueden formular de tal manera que ofrezcan liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retardada, prolongada, pulsada, controlada, dirigida y programada.

Las formulaciones de liberación modificada adecuadas se describen en la patente estadounidense N.° 6.106.864. Los detalles de otras tecnologías de liberación adecuadas, tales como dispersiones de alta energía y partículas osmóticas y revestidas se pueden encontrar en Verma et al, *Pharmaceutical Technology On-line*, 25(2), 1-14 (2001). El uso de goma de mascar para alcanzar la liberación controlada se describe en el documento WO 00/35298. La divulgación de estas referencias se incorpora en la presente por referencia en su totalidad.

Administración parenteral

Los compuestos de la invención también se pueden administrar directamente en el torrente sanguíneo, en el músculo, o en un órgano interno. Los medios adecuados para la administración parenteral incluyen medio intravenoso, intraarterial, intraperitoneal, intratecal, intraventricular, intrauretral, intraesternal, intracranial, intramuscular y subcutáneo. Los dispositivos adecuados para administración parenteral incluyen inyectores de aguja (con inclusión de microaguja), inyectores libres de aguja y técnicas de infusión.

Las formulaciones parenterales son, típicamente, soluciones acuosas que pueden contener excipientes tales como sales, carbohidratos y agentes de tamponamiento (preferentemente a un pH de 3 a 9), pero, para algunas aplicaciones, pueden formularse, de manera más adecuada, como una solución no acuosa estéril o como una forma secada a ser usada junto con un vehículo adecuado tal como agua libre de pirógeno estéril.

La preparación de formulaciones parenterales bajo condiciones estériles, por ejemplo, por liofilización, se pueden lograr con facilidad usando técnicas farmacéuticas estándares ampliamente conocidas por los expertos en la técnica.

La solubilidad de los compuestos de la invención usados en la preparación de soluciones parenterales se puede incrementar mediante el uso de técnicas de

formulación apropiadas, tales como la incorporación de agentes de refuerzo de la solubilidad.

Las formulaciones para administración parenteral se pueden formular de manera tal que ofrezcan liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retardada, prolongada, pulsada, controlada, dirigida y programada. Por ende, los compuestos de la invención se pueden formular como un líquido sólido, semisólido o tixotrópico para la administración como depósito implantado que provee liberación modificada del compuesto activo. Los ejemplos de dichas formulaciones incluyen stents revestidos con fármacos y microesferas de PGLA.

Los compuestos de la invención también se pueden administrar en forma tópica a la piel o mucosa, es decir, en forma dérmica o transdérmica. Las formulaciones típicas para este propósito incluyen geles, hidrogeles, lociones, soluciones, cremas, ungüentos, polvos para espolvorear, vendajes, espumas, películas, parches para la piel, obleas, implantes, esponjas, fibras, vendajes y microemulsiones. También se pueden usar liposomas. Los portadores típicos incluyen alcohol, agua, aceite mineral, petrolato líquido, petrolato blanco, glicerina, polietilenglicol y propilenglicol. Es posible incorporar reforzadores de penetración; véase, por ejemplo, *J Pharm Sci*, 88 (10), 955-958 de Finnin y Morgan (octubre de 1999). Otros medios de administración tópica incluyen el suministro mediante electroporación, iontoforesis, fonoforesis, sonoforesis e inyección con microaguja o libre de aguja (por ejemplo, Powderject™, Bioject™, etc.). La divulgación de estas referencias se incorpora en la presente por referencia en su totalidad.

Las formulaciones para administración tópica se pueden formular de tal manera que ofrezcan liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retardada, prolongada, pulsada, controlada, dirigida y programada.

Los compuestos de la invención también se pueden administrar por vía intranasal o mediante inhalación, típicamente en forma de polvo seco (ya sea solo, como una mezcla, por ejemplo, en una combinación seca con lactosa, o como una partícula de componentes mixtos, por ejemplo, mezclada con fosfolípidos, tal como fosfatidilcolina) de un inhalador de polvo seco o como un pulverizador en aerosol de un recipiente presurizado, bomba, pulverizador, atomizador (preferentemente un atomizador que usa electrohidrodinámica para producir una fina bruma), o nebulizador, con o sin el uso de un propelente adecuado, tal como 1,1,1,2-tetrafluoroetano o

1,1,1,2,3,3,3-heptafluoropropano. Para uso intranasal, el polvo puede incluir un agente bioadhesivo, por ejemplo, quitosano o ciclodextrina.

El recipiente presurizado, bomba, pulverizador, atomizador o nebulizador contiene una solución o suspensión de los compuestos de la invención que comprende, por ejemplo, etanol, etanol acuoso, o un agente alternativo adecuado para dispersar, solubilizar o prolongar la liberación del activo, uno o más propelentes como solvente y un agente tensoactivo opcional, tal como trioleato de sorbitán, ácido oleico o un ácido oligoláctico.

Antes del uso de una formulación en suspensión o polvo seco, el producto de fármaco es micronizado a un tamaño adecuado para el suministro mediante inhalación (típicamente menos de 5 micrones). Esto se puede alcanzar mediante cualquier método de trituración adecuado, tal como molienda de chorro en espiral, molienda de chorro en lecho fluidizado, procesamiento de fluido supercrítico para formar nanopartículas, homogenización a alta presión o secado por pulverización.

Las cápsulas (hechas, por ejemplo, de gelatina o HPMC), los blísteres y los cartuchos para uso en un inhalador o insuflador se pueden formular de tal manera que contengan una mezcla en polvo del compuesto de la invención, una base en polvo adecuada tal como lactosa o almidón y un modificador del rendimiento tal como l-leucina, manitol, o estearato de magnesio. La lactosa puede ser anhidra o puede estar en la forma del monohidrato, preferentemente este último. Otros excipientes adecuados incluyen dextrano, glucosa, maltosa, sorbitol, xilitol, fructosa, sacarosa y trehalosa.

Una formulación en solución adecuada para uso en un atomizador que usa electrohidrodinámica para producir una fina bruma puede contener desde 1µg hasta 20 mg del compuesto de la invención por accionamiento y el volumen de accionamiento puede variar desde 1 µL hasta 100 µL. Una formulación típica incluye un compuesto de la invención, propilenglicol, agua estéril, etanol y cloruro de sodio. Los solventes alternativos que se pueden usar en lugar de propilenglicol incluyen glicerol y polietilenglicol.

Es posible agregar saborizantes adecuados, tales como mentol y levomentol, o edulcorantes, tales como sacarina o sacarina sódica, a aquellas formulaciones de la invención destinadas para administración inhalada/intranasal.

Las formulaciones para administración inhalada/intranasal se pueden formular de tal manera que provean liberación inmediata y/o modificada usando, por ejemplo,

ácido poli(DL-láctico-coglicílico) (PGLA). Las formulaciones de liberación modificada incluyen liberación retardada, prolongada, pulsada, controlada, dirigida y programada.

En el caso de los inhaladores de polvo y aerosoles, la unidad de dosis se determina por medio de una válvula que suministra una cantidad medida. Las unidades de acuerdo con la invención típicamente se disponen para administrar una dosis medida o "puff" (disparo) que contiene una cantidad deseada del compuesto de la invención. La dosis diaria total se puede administrar en una única dosis o, más usualmente, en dosis divididas a lo largo del día.

Los compuestos de la invención se pueden administrar por vía rectal o vaginal, por ejemplo, en forma de un supositorio, pesario o enema. La manteca de cacao es una base de supositorio tradicional, pero existen varias alternativas apropiadas que se pueden utilizar.

Las formulaciones para administración rectal/vaginal se pueden formular de tal manera que provean liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retardada, prolongada, pulsada, controlada, dirigida y programada.

Los compuestos de la invención también se pueden administrar directamente en el ojo o el oído, típicamente en forma de gotas de una solución o suspensión micronizada en solución salina estéril isotónica, con pH ajustado. Otras formulaciones adecuadas para administración ocular y auditiva incluyen ungüentos, implantes biodegradables (por ejemplo esponjas de gel absorbibles, colágeno) y no biodegradables (por ejemplo silicona), obleas, lentes y sistemas particulados o vesiculares, tales como niosomas o liposomas. Es posible incorporar un polímero tal como ácido poliacrílico reticulado, alcohol polivinílico, ácido hialurónico, 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. Dichas formulaciones también se pueden administrar mediante iontoforesis.

Las formulaciones para la administración ocular/auditiva se pueden formular de tal manera que provean liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retardada, prolongada, pulsada, controlada, dirigida y programada.

Otras tecnologías

Los compuestos de la invención se pueden combinar con entidades macromoleculares solubles, tales como ciclodextrina y derivados adecuados de las mismas, o polímeros que contienen polietilenglicol, a fin de mejorar su solubilidad, velocidad de disolución, enmascaramiento del sabor, biodisponibilidad y/o estabilidad para uso en cualquiera de los modos de administración mencionados con anterioridad.

Por lo general, se encuentra que los complejos fármaco-ciclodextrina, por ejemplo, son útiles para la mayoría de las formas de dosis y vías de administración. Es posible usar tanto los complejos de inclusión como los complejos de no inclusión. Como alternativa a la formación de complejos directa con el fármaco, la ciclodextrina se puede usar como aditivo auxiliar, es decir, como portador, diluyente o solubilizador. Las más comúnmente utilizadas a estos efectos son las alfa, beta y gamma-ciclodextrinas, cuyos ejemplos se pueden encontrar en las Publicaciones PCT N.os WO 91/11172, WO 94/02518 y WO 98/55148, cuya divulgación se incorpora en la presente por referencia en su totalidad.

Dosificación

La cantidad del compuesto activo administrada dependerá del mamífero que es tratado, la severidad del trastorno o la afección, la tasa de administración, la disposición del compuesto y la discreción del médico a cargo. No obstante, una dosis efectiva se encuentra típicamente en el rango de aproximadamente 0,001 a aproximadamente 100 mg por kg de peso corporal por día, preferentemente de aproximadamente 0,01 a aproximadamente 35 mg/kg/día, en dosis únicas o divididas. Para un humano de 70 kg, esto representaría de aproximadamente 0,07 a aproximadamente 7000 mg/día, preferentemente de aproximadamente 0,7 a aproximadamente 2500 mg/día. En algunos casos, los niveles de dosis debajo del límite inferior del rango mencionado con anterioridad pueden ser más que lo adecuado, mientras que en otros casos, es posible usar dosis incluso mayores sin causar ningún efecto colateral dañino, en donde dichas dosis mayores se dividen típicamente en varias dosis más pequeñas para su administración durante todo el día. La dosis diaria total se puede administrar en dosis individuales o divididas y puede, a criterio del médico, caer fuera del rango típico dado en la presente. Estas dosis se basan en el sujeto humano promedio que tiene un peso de aproximadamente 65 kg a 70 kg. El médico podrá fácilmente determinar las dosis para los sujetos cuyo peso cae fuera de este rango, tal como infantes y ancianos.

Siempre que sea deseable administrar una combinación de compuestos activos, por ejemplo, a los efectos de tratar una enfermedad o afección particular, se

contempla dentro del alcance de la presente invención que dos o más composiciones farmacéuticas, al menos una de las cuales contiene un compuesto de acuerdo con la invención, puedan ser combinadas de manera conveniente en forma de un kit adecuado para la coadministración de las composiciones. Por ende, del kit de la invención incluye dos o más composiciones farmacéuticas separadas, al menos una de las cuales contiene un compuesto de la invención, y medios para retener dichas composiciones de manera separada, tal como un recipiente, botella dividida o paquete dividido con láminas metálicas. Un ejemplo de dicho kit es el envase blíster familiar usado para el envasado de comprimidos, cápsulas y similares.

El kit de la invención es particularmente adecuado para administrar diferentes formas de dosis, por ejemplo, orales y parenterales, para administrar las composiciones separadas en diferentes intervalos de dosificación, o para titular las composiciones separadas una contra la otra. Para ayudar con el cumplimiento, el kit típicamente incluye instrucciones de administración y puede contener una ayuda memoria.

Terapia de combinación

Tal como se usa en la presente, el término “terapia de combinación” se refiere a la administración de un compuesto de la invención junto con al menos un agente farmacéutico o medicinal adicional (por ejemplo, un agente anticancerígeno), ya sea en forma secuencial o simultánea.

Tal como se destacó con anterioridad, los compuestos de la invención se pueden usar en combinación con uno o más agentes anticancerígenos adicionales que se describen a continuación. Cuando se usa una terapia de combinación, dichos uno o más agentes anticancerígenos adicionales se pueden administrar en forma secuencial o simultánea con el compuesto de la invención. En una forma de realización, el agente anticancerígeno adicional se administra a un mamífero (por ejemplo, un ser humano) antes de la administración del compuesto de la invención. En otra forma de realización, el agente anticancerígeno adicional se administra al mamífero después de la administración del compuesto de la invención. En otra forma de realización, el agente anticancerígeno adicional se administra al mamífero (por ejemplo, un ser humano) en forma simultánea con la administración del compuesto de la invención.

La invención también se refiere a una composición farmacéutica para el tratamiento del crecimiento celular anormal en un mamífero, inclusive un ser humano, que comprende una cantidad de un compuesto de la invención, tal como se definió con

anterioridad (inclusive hidratos, solvatos y polimorfos de dicho compuesto, o sus sales farmacéuticamente aceptables), en combinación con uno o más (preferentemente uno a tres) agentes anticancerígenos seleccionados entre el grupo que consiste en agentes antiangiogénesis e inhibidores de la transducción de señales, y un portador farmacéuticamente aceptable, en donde las cantidades del agente activo y los agentes anticancerígenos de combinación cuando se toman como un todo son terapéuticamente efectivas para tratar dicho crecimiento celular anormal.

En una forma de realización de la presente invención, el agente anticancerígeno usado junto con un compuesto de la invención y las composiciones farmacéuticas descritas en la presente es un agente antiangiogénesis (por ejemplo, un agente que evita que los tumores desarrollen nuevos vasos sanguíneos). Los ejemplos de agentes angiogénesis incluyen, por ejemplo inhibidores de VEGF, inhibidores de VEGFR, inhibidores de TIE-2, inhibidores de PDGFR, inhibidores de angiopoyetina, inhibidores de PKCβ, inhibidores de COX-2 (ciclooxigenasa II), integrinas (alfa-v/beta-3), inhibidores de MMP-2 (metaloprotienasa de matriz 2), e inhibidores de MMP-9 (metaloprotienasa de matriz 9).

Los agentes antiangiogénesis preferidos incluyen sunitinib (Sutent™), bevacizumab (Avastin™), axitinib (AG 13736), SU 14813 (*Pfizer*), y AG 13958 (Pfizer).

Los agentes anti-angiogénesis adicionales incluyen vatalanib (CGP 79787), Sorafenib (Nexavar™), pegaptanib octasódico (Macugen™), vandetanib (Zactima™), PF-0337210 (Pfizer), SU 14843 (Pfizer), AZD 2171 (AstraZeneca), ranibizumab (Lucentis™), Neovastat™ (AE 941), tetratiomolibdata (Coprexa™), AMG 706 (Amgen), VEGF Trap (AVE 0005), CEP 7055 (Sanofi-Aventis), XL 880 (Exelixis), telatinib (BAY 57-9352), y CP-868,596 (Pfizer).

Otros agentes antiangiogénesis incluyen enzastaurina (LY 317615), midostaurina (CGP 41251), perifosina (KRX 0401), teprenona (Selbex™) y UCN 01 (Kyowa Hakko).

Otros ejemplos de agentes antiangiogénesis que se pueden usar junto con un compuesto de la invención y las composiciones farmacéuticas descritas en la presente incluyen celecoxib (Celebrex™), parecoxib (Dynastat™), deracoxib (SC 59046), lumiracoxib (Preige™), valdecoxib (Bextra™), rofecoxib (Vioxx™), iguratimod (*Careram*™), IP 751 (Invedus), SC-58125 (Pharmacia) y etoricoxib (Arcoxia™).

Otros agentes anti-angiogénesis incluyen exisulind (Aptosyn™), salsalato (Amigesic™), diflunisal (Dolobid™), ibuprofeno (Motrin™), ketoprofeno (Orudis™), nabumetona (Relafen™), piroxicam (Feldene™), naproxeno (Aleve™, Naprosyn™),

diclofenac (Voltaren™), indometacina (Indocin™), sulindac (Clinoril™), tolmetin (Tolectin™), etodolac (Lodine™), ketorolac (Toradol™) y oxaprozina (Daypro™).

Otros agentes anti-angiogénesis incluyen ABT 510 (Abbott), apratastat (TMI 005), AZD 8955 (AstraZeneca), inciclinida (Metastat™) y PCK 3145 (Procyon).

Otros agentes antiangiogénesis incluyen acitretina (Neotigason™), plitidepsina (aplidine™), cilengtida (EMD 121974), combretastatina A4 (CA4P), fenretinida (*4 HPR)*, halofuginona (Tempostatin™), Panzem™ (2-metoxiestradiol), PF-03446962 (Pfizer), rebimastat *(BMS 275291),* catumaxomab (Removab™), lenalidomida (Revlimid™), escualamina (EVIZON™), talidomida (Thalomid™), Ukrain™ (NSC 631570), Vitaxin™ (MEDI 522) y ácido zoledrónico (Zometa™).

En otra forma de realización, el agente anticancerígeno es el denominado "inhibidor de la transducción de señales" (por ejemplo, que inhibe los medios mediante los cuales las moléculas reguladoras que gobiernan los procesos fundamentales del crecimiento, diferenciación y supervivencia celular, comunicados dentro de la célula). Los inhibidores de la transducción de señales incluyen moléculas pequeñas, anticuerpos y moléculas antisentido. Los inhibidores de la transducción de señales incluyen, por ejemplo, inhibidores de quinasa (por ejemplo, inhibidores de tirosina quinasa o inhibidores de serina/treonina quinasa) e inhibidores del ciclo celular. Más específicamente, los inhibidores de la transducción de señales incluyen, por ejemplo, inhibidores de la proteína farnesil transferasa, inhibidor de EGF, ErbB-1 (EGFR), ErbB-2, pan erb, inhibidores de IGF1R, MEK, inhibidores de c-Kit, inhibidores de FLT-3, inhibidores de K-Ras, inhibidores de PI3 quinasa, inhibidores de JAK, inhibidores de STAT, inhibidores de Raf quinasa, inhibidores de Akt, inhibidor de mTOR, inhibidores de P70S6 quinasa, inhibidores de la vía WNT y los denominados "inhibidores de quinasa multi-dirigidos".

Los inhibidores de la transducción de señales preferentes incluyen gefitinib (Iressa™), cetuximab (Erbitux™), erlotinib (Tarceva™), trastuzumab (Herceptin™), sunitinib (Sutent™), imatinib (Gleevec™) y PD325901 (Pfizer).

Los ejemplos adicionales de inhibidores de la transducción de señales que se pueden usar junto con un compuesto de la invención y las composiciones farmacéuticas descritas en la presente incluyen BMS 214662 (Bristol-Myers Squibb), lonafarnib (Sarasar™), pelitrexol (AG 2037), matuzumab (EMD 7200), nimotuzumab (TheraCIM h-R3™), panitumumab (Vectibix™), Vandetanib (Zactima™), pazopanib (SB 786034), ALT 110 (Alteris Therapeutics), BIBW 2992 (Boehringer Ingelheim) y Cervene™ (TP 38).

Otros ejemplos de inhibidores de la transducción de señales incluyen PF-2341066 (Pfizer), PF-299804 (Pfizer), canertinib (CI 1033), pertuzumab (Omnitarg™), Lapatinib (Tycerb™), pelitinib (EKB 569), miltefosina (Miltefosin™), BMS 599626 (Bristol-Myers Squibb), Lapuleucel-T (Neuvenge™), NeuVax™ (vacuna contra el cáncer E75), Osidem™ (IDM 1), mubritinib (TAK-165), CP-724,714 (Pfizer), panitumumab (Vectibix™), lapatinib (Tycerb™), PF-299804 (Pfizer), pelitinib (EKB 569) y pertuzumab (Omnitarg™).

Otros ejemplos de inhibidores de la transducción de señales incluyen ARRY 142886 (Array Biopharm), everolimus (Certican™), zotarolimus (Endeavor™), temsirolimus (Torisel™), AP 23573 (ARIAD), y VX 680 (Vertex).

Asimismo, otros inhibidores de la transducción de señales incluyen XL 647 (Exelixis), sorafenib (Nexavar™), LE-AON (Georgetown University) y GI-4000 (GlobeImmune).

Otros inhibidores de la transducción de señales incluyen ABT 751 (Abbott), alvocidib (flavopiridol), BMS 387032 (Bristol Myers), EM 1421 (Erimos), indisulam (E 7070), seliciclib (CYC 200), BIO 112 (Onc Bio), BMS 387032 (Bristol-Myers Squibb), PD 0332991 (Pfizer) y AG 024322 (Pfizer).

Esta invención contempla el uso de compuestos de la invención junto con agentes antineoplásicos clásicos. Los agentes antineoplásicos clásicos incluyen, mas no se limitan a moduladores hormonales tales como agentes terapéuticos anti-estrógeno, antagonistas de andrógenos y agonistas de andrógenos hormonales, anti-hormonales, inhibidores de histona deacetilasa (HDAC), agentes de silenciamiento de genes o agentes de activación de genes, ribonucleasas, proteosómicos, inhibidores de topoisomerasa I, derivados de Camptotecina, inhibidores de topoisomerasa II, agentes alquilantes, antimetabolitos, inhibidor de poli(ADP-ribosa) polimerasa-1 (PARP-1), inhibidores de microtubulina, antibióticos, inhibidores de huso derivados de plantas, compuestos coordinados por platino, agentes terapéuticos génicos, oligonucleótidos antisentido, agentes de direccionamiento vascular (VTA) y estatinas.

Los ejemplos de agentes antineoplásicos clásicos usados en terapia de combinación con un compuesto de la invención, opcionalmente con uno o más agentes adicionales incluyen, pero no se limitan a glucocorticoides, tales como dexametasona, prednisona, prednisolona, metilprednisolona, hidrocortisona y progestinas, tales como medroxiprogesterona, acetato de megestrol (Megace), mifepristona (RU-486), moduladores de receptores de estrógenos selectivos (SERM; tales como tamoxifeno, raloxifeno, lasofoxifeno, afimoxifeno, arzoxifeno, bazedoxifeno, fispemifeno,

ormeloxifeno, ospemifeno, tesmilifeno, toremifeno, trilostano y CHF 4227 (Cheisi)), reguladores descendientes de los receptores de estrógeno selectivos (SERD; tales como fulvestrant), exemestano (Aromasin), anastrozol (Arimidex), atamestano, fadrozol, letrozol (Femara), hormona de liberación de gonadotropina (GnRH*;* también denominada comúnmente "hormona de liberación de la hormona luteinizante" [LHRH]), agonistas tales como buserelina (Suprefact), goserelina (Zoladex), leuprorelina (Lupron) y triptorelina (Trelstar), abarelix (Plenaxis), bicalutamida (Casodex), ciproterona, flutamida (Eulexin), megestrol, nilutamida (Nilandron), y osaterona, dutasterida, epristerida, finasterida, Serenoa repens, PHL 00801, abarelix, goserelina, leuprorelina, triptorelina, bicalutamida, tamoxifeno, exemestano, anastrozol, fadrozol, formestano, letrozol y sus combinaciones.

Otros ejemplos de agentes antineoplásicos clásicos usados en combinación con los compuestos de la invención incluyen, mas no se limitan a ácido hidroxámico suberoilanilida (SAHA*,* Merck Inc./Aton Pharmaceuticals), depsipéptido (FR901228 o FK228), G2M-777, MS-275, pivaloiloximetil butirato y PXD-101; Onconasa (ranpirnasa), PS-341 (MLN-341), Velcade (bortezomib), 9-aminocamptotecina, belotecán, BN-80915 (Roche), camptotecina, diflomotecán, edotecarina, exatecán (Daiichi), gimatecán, 10-hidroxicamptotecina, irinotecán HCl (Camptosar), lurtotecán, Oratecina (rubitecán, Supergen), SN-38, topotecán, camptotecina, 10-hidroxicamptotecina, 9-aminocamptotecina, irinotecán, SN-38, edotecarina, topotecán, aclarubicina, adriamicina, amonafida, amrubicina, anamicina, daunorubicina, doxorubicina, elsamitrucina, epirubicina, etopósido, idarubicina, galarubicina, hidroxicarbamida, nemorubicina, novantrona (mitoxantrona), pirarubicina, pixantrona, procarbazina, rebecamicina, sobuzoxano, taflupósido, valrubicina, Zinecard (dexrazoxano), N-óxido de mostaza de nitrógeno, ciclofosfamida, AMD-473, altretamina, AP-5280, apazicuona, brostalicina, bendamustina, busulfán, carbocuona, carmustina, clorambucil, dacarbazina, estramustina, fotemustina, glufosfamida, ifosfamida, KW-2170, lomustina, mafosfamida, mecloretamina, melfalán, mitobronitol, mitolactol, mitomicina C, mitoxatrona, nimustina, ranimustina, temozolomida, tiotepa, y compuestos alquilantes coordinados por platino tales como cisplatino, Paraplatino (carboplatino), eptaplatino, lobaplatino, nedaplatino, Eloxatino (oxaliplatino, Sanofi), estreptozocina, satrplatino, y combinaciones del mismo.

La invención también contempla el uso de los compuestos de la invención junto con inhibidores de dihidrofolato reductasa (tales como metotrexato y NeuTrexin (trimetresato glucuronato)), antagonistas de purina (tales como 6-mercaptopurina

ribosida, mercaptopurina, 6-tioguanina, cladribina, clofarabina (Clolar), fludarabina, nelarabina y raltitrexed), antagonistas de pirimidina (tales como 5-fluorouracil (5-FU), Alimta (premetrexed disódico, LY231514, MTA), capecitabina (Xeloda™), citosina arabinosida, Gemzar™ (gemcitabina, Eli Lilly), Tegafur (UFT Orzel o Uforal y con inclusión de combinación TS-1 de tegafur, gimestat y otostat), doxifluridina, carmofur, citarabina (con inclusión de formas liposomales y de liberación prolongada de ocfosfato, fosfato, estearato), enocitabina, 5-azacitidina (Vidaza), decitabina, y etinilcitidina) y otros antimetabolitos tales como eflornitina, hidroxiurea, leucovorina, nolatrexed (Thymitaq), triapina, trimetrexato, ácido N-(5-[N-(3,4-dihidro-2-metil-4-oxoquinazolin-6-ilmetil)-N-metilamino]-2-tenoil)-L-glutámico, AG-014699 (Pfizer Inc.), ABT-472 (Abbott Laboratories), INO-1001 (Inotek Farmaceuticals), KU-0687 (KuDOS Farmaceuticals) y GPI 18180 (Guilford Farm Inc) y sus combinaciones.

Otros ejemplos de agentes citotóxicos antineoplásicos clásicos usados en terapia de combinación con un compuesto de la invención, opcionalmente con uno o más agentes adicionales incluyen, pero no se limitan a: Abraxane (Abraxis BioScience, Inc.), Batabulin (Amgen), EPO 906 (Novartis), Vinflunina (Bristol- Myers Squibb Company), actinomicina D, bleomicina, mitomicina C, neocarzinostatina (Zinostatin), vinblastina, vincristina, vindesina, vinorelbina (Navelbine), docetaxel (Taxotere), Ortataxel, paclitaxel (con inclusión de Taxoprexina, un conjugado de DHA/paciltaxel), cisplatino, carboplatino, Nedaplatino, oxaliplatino (Eloxatin), Satraplatino, Camptosar, capecitabina (Xeloda), oxaliplatino (Eloxatin), Taxotere alitretinoina, Canfosfamida (Telcyta™), DMXAA (Antisoma), ácido ibandrónico, L-asparaginasa, pegaspargasa (Oncaspar™), Efaproxiral (Efaproxyn™ - terapia de radiación)), bexaroteno (Targretin™), Tesmilifeno (DPPE – potencia la eficacia de los citotóxicos)), Theratope™ (Biomira), Tretinoina (Vesanoid™), tirapazamina (Trizaone™), motexafina gadolinio (Xcytrin™) Cotara™ (mAb), y NBI-3001 (Protox Therapeutics), poliglutamato-paclitaxel (Xyotax™) y sus combinaciones.

Otros ejemplos de agentes antineoplásicos clásicos usados en terapia de combinación con un compuesto de la invención, opcionalmente con uno o más agentes adicionales incluyen, pero no se limitan a: Advexin (ING 201), TNFerade (GeneVec, un compuesto que expresa TNFalfa en respuesta a la radioterapia), RB94 (Baylor College of Medicine), Genasense (Oblimersen, Genta), Combretastatina A4P (CA4P), Oxi-4503, AVE-8062, ZD-6126, TZT-1027, Atorvastatina (Lipitor, Pfizer Inc.), Provastatina (Pravachol, Bristol-Myers Squibb), Lovastatina (Mevacor, Merck Inc.), Simvastatina (Zocor, Merck Inc.), Fluvastatina (Lescol, Novartis), Cerivastatina (Baycol, Bayer),

Rosuvastatina (Crestor, AstraZeneca), Lovostatina, Niacina (Advicor, Kos Farmaceuticals), Caduet, Lipitor, torcetrapib y sus combinaciones.

Otra forma de realización de la presente invención de particular interés se refiere a un método para el tratamiento de cáncer de mama en un ser humano que necesita dicho tratamiento, que comprende administrar a dicho ser humano una cantidad de un compuesto de la invención, en combinación con uno o más (preferentemente uno a tres) agentes anticancerígenos seleccionados entre el grupo que consiste en trastuzumab, tamoxifeno, docetaxel, paclitaxel, capecitabina, gemcitabina, vinorelbina, exemestano, letrozol y anastrozol.

En una forma de realización, la invención provee un método para tratar cáncer colorrectal en un mamífero, tal como un ser humano, que necesita dicho tratamiento, al administrar una cantidad de un compuesto de la invención, en combinación con uno o más (preferentemente uno a tres) agentes anticancerígenos. Los ejemplos de agentes anticancerígenos particulares incluyen los típicamente usados en quimioterapia coadyuvante, tal como FOLFOX, una combinación de 5-fluorouracilo (5-FU) o capecitabina (Xeloda), leucovorina y oxaliplatino (Eloxatin). Otros ejemplos de agentes anticancerígenos particulares incluyen los típicamente usados en quimioterapia para enfermedad metastásica, tales como FOLFOX o FOLFOX en combinación con bevacizumab (Avastin); y FOLFIRI, una combinación de 5-FU o capecitabina, leucovorina e irinotecán (Camptosar). Otros ejemplos incluyen 17-DMAG, ABX-EFR, AMG-706, AMT-2003, ANX-510 (CoFactor), aplidina (plitidepsina, Aplidina), Aroplatino, axitinib (AG-13736), AZD-0530, AZD-2171, bacillus Calmette-Guerin (BCG), bevacizumab (Avastin), BIO-117, BIO-145, BMS-184476, BMS-275183, BMS-528664, bortezomib (Velcade), C-1311 (Symadex), cantuzumab mertansina, capecitabina (Xeloda), cetuximab (Erbitux), clofarabina (Clofarex), CMD-193, combretastatina, Cotara, CT-2106, CV-247, decitabina (Dacogen), E-7070, E-7820, edotecarina, EMD-273066, enzastaurina (LY-317615)epotilona B (EPO-906), erlotinib (Tarceva), flavopiridol, GCAN-101, gefitinib (Iressa), huA33, huC$_{24}$2-DM4, imatinib (Gleevec), indisulam, ING-1, irinotecán (CPT-11, Camptosar) ISIS 2503, ixabepilona, lapatinib (Tykerb), mapatumumab (HGS-ETR1), MBT-0206, MEDI-522 (Abregrin), Mitomicina, MK-0457 (VX-680), MLN-8054, NB-1011, NGR-TNF, NV-1020, oblimersén (Genasense, G3139), OncoVex, ONYX 015 (CI-1042), oxaliplatino (Eloxatin), panitumumab (ABX-EGF, Vectibix), pelitinib (EKB-569), pemetrexed (Alimta), PD-325901, PF-0337210, PF-2341066, RAD-001 (Everolimus), RAV-12, Resveratrol, Rexin-G, S-1 (TS-1), seliciclib, SN-38 liposoma, estiboglucinato de sodio (SSG, del

inglés *Sodium Stibogluconate*), sorafenib (Nexavar), SU-14813, sunitinib (Sutent), temsirolimus (CCI 779), tetratiomolibdato, talomida, TLK-286 (Telcyta), topotecán (Hycamtin), trabectedina (Yondelis), vatalanib (PTK-787), vorinostat (SAHA, Zolinza), WX-UK1, y $ZYC_3$00, en donde las cantidades del agente activo junto con las cantidades de los agentes anticancerígenos en combinación son efectivas para tratar el cáncer colorrectal.

Otra forma de realización de la presente invención de particular interés se refiere a un método para el tratamiento de carcinoma de células renales en un ser humano que necesita dicho tratamiento, que comprende administrar a dicho ser humano una cantidad de un compuesto de la invención, en combinación con uno o más (preferentemente uno a tres) agentes anticancerígenos seleccionados entre el grupo que consiste en axitinib (AG 13736), capecitabina (Xeloda), interferón alfa, interleuquina-2, bevacizumab (Avastin), gemcitabina (Gemzar), talidomida, cetuximab (Erbitux), vatalanib (PTK-787), sunitinib (Sutent™), AG-13736, SU-11248, Tarceva, Iressa, Lapatinib y Gleevec, en donde las cantidades del agente activo junto con las cantidades de los agentes anticancerígenos en combinación es efectiva para tratar el carcinoma de células renales.

Otra forma de realización de la presente invención de particular interés se refiere a un método para el tratamiento de melanoma en un ser humano que necesita dicho tratamiento, que comprende administrar a dicho ser humano una cantidad de un compuesto de la invención, en combinación con uno o más (preferentemente uno a tres) agentes anticancerígenos seleccionados entre el grupo que consiste en interferón alfa, interleuquina-2, temozolomida (Temodar), docetaxel (Taxotere), paclitaxel, Dacarbazine (DTIC), carmustina (también conocido como BCNU), Cisplatino, vinblastina, tamoxifeno, PD-325,901, axitinib (AG 13736), bevacizumab (Avastin), talidomida, sorafanib, vatalanib (PTK-787), sunitinib (Sutent™), CpG-7909, AG-13736, Iressa, Lapatinib y Gleevec, en donde las cantidades del agente activo junto con las cantidades de los agentes anticancerígenos en combinación es efectiva para tratar melanoma.

Otra forma de realización de la presente invención de particular interés se refiere a un método para el tratamiento de cáncer pulmonar en un ser humano que necesita dicho tratamiento, que comprende administrar a dicho ser humano una cantidad de un compuesto de la invención, en combinación con uno o más (preferentemente uno a tres) agentes anticancerígenos seleccionados entre el grupo que consiste en capecitabina (Xeloda), axitinib (AG 13736), bevacizumab (Avastin),

gemcitabina (Gemzar), docetaxel (Taxotere), paclitaxel, premetrexed disódico (Alimta), Tarceva, Iressa, Vinorelbina, Irinotecán, Etopósido, Vinblastina, sunitinib (Sutent™) y Paraplatin (carboplatino), en donde las cantidades del agente activo junto con las cantidades de los agentes anticancerígenos en combinación es efectiva para tratar el cáncer pulmonar.

De acuerdo con otra forma de realización de la presente invención, los compuestos de la invención, o sus sales farmacéuticamente aceptables, formas derivadas o composiciones, también se pueden utilizar como una combinación con uno o más agentes terapéuticos adicionales a ser co-administrados a un paciente para obtener cierto resultado final terapéutico particularmente deseado tal como el tratamiento de enfermedades del sistema nervioso central y cáncer. El segundo y los agentes terapéuticos adicionales también pueden ser un compuesto de la fórmula (1), o una de sus sales farmacéuticamente aceptables, formas derivadas o composiciones, o se pueden seleccionar entre una clase diferente de agentes terapéuticos.

Tal como se usa en la presente, los términos “co-administración”, “co-administrado/a” y “en combinación con”, con referencia a los compuestos de la invención y uno o más agentes terapéuticos adicionales, están destinados a incluir y hacer referencia a lo siguiente:

i. administración simultánea de dicha combinación de compuesto(s) de la invención y agente(s) terapéutico(s) a un paciente que necesita dicho tratamiento, cuando dichos componentes se formulan juntos en una única forma de dosis que libera dichos componentes sustancialmente al mismo tiempo a dicho paciente,

ii. administración sustancialmente simultánea de dicha combinación de compuesto(s) de la invención y agente(s) terapéutico(s) a un paciente que necesita dicho tratamiento, cuando dichos componentes se formulan separados entre sí en formas de dosis separadas que son tomadas sustancialmente al mismo tiempo por dicho paciente, con lo cual dichos componentes son liberados sustancialmente al mismo tiempo a dicho paciente,

iii. administración secuencial de dichos compuesto(s) de combinación de la invención y agente(s) terapéutico(s) a un paciente que necesita dicho tratamiento, cuando dichos componentes se formulan separados entre sí en formas de dosis separadas que son tomadas en momentos consecutivos por dicho paciente con un intervalo de tiempo significativo entre cada

administración, con lo cual dichos componentes son liberados en momentos sustancialmente diferentes a dicho paciente; y

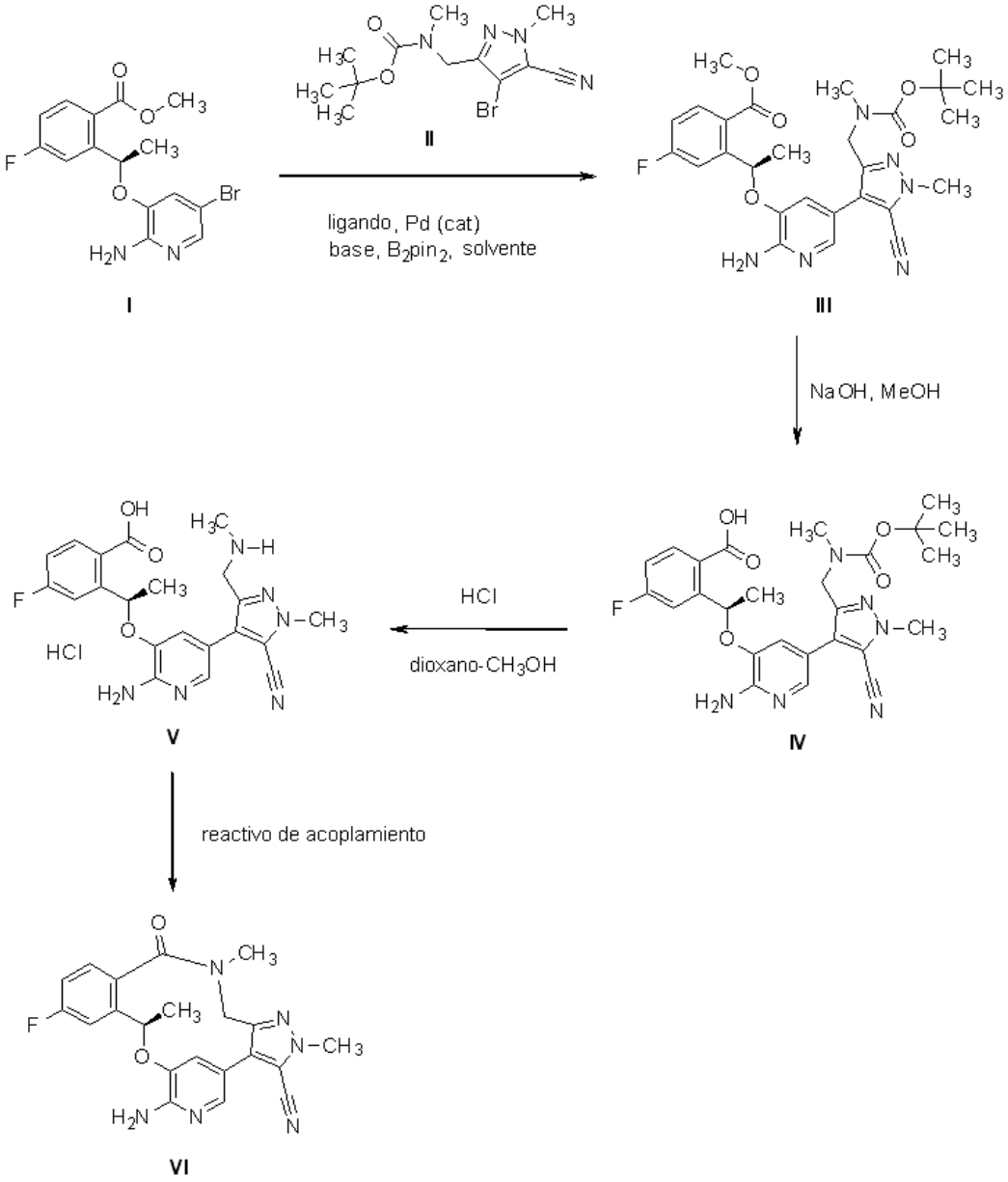
iv. administración secuencial de dichos compuesto(s) de combinación de la invención y agente(s) terapéutico(s) a un paciente que necesita dicho tratamiento, cuando dichos componentes se formulan juntos en una única forma de dosis que libera dichos componentes de manera controlada, con lo cual son administradas de manera concurrente, consecutiva y/o superpuesta al mismo tiempo y/o en diferentes tiempos a dicho paciente,
donde cada parte se puede administrar ya sea mediante la misma vía o mediante una vía distinta de administración.

Métodos de síntesis

Los compuestos de la invención se pueden preparar por medio de una variedad de métodos de síntesis, tal como se describe luego y se ilustra en la presente. Los expertos en la técnica entenderán que los siguientes métodos de síntesis generales son representativos y no pretenden ser limitativos.

Método A

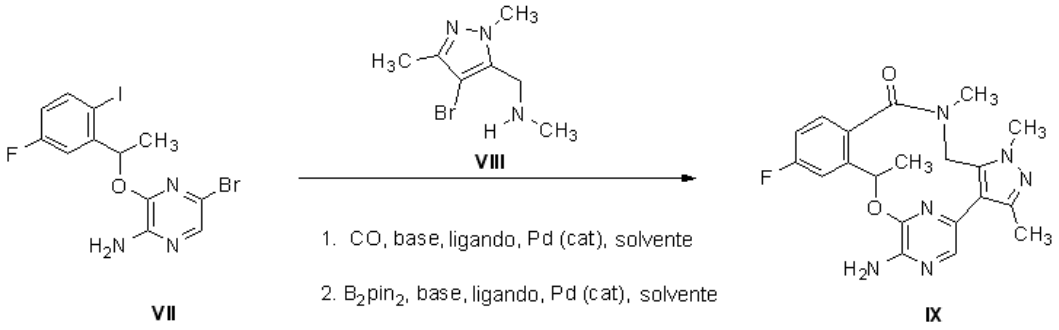
En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto **VI** se preparan de acuerdo con el **método A**.



El haluro de arilo (**I)** se puede acoplar con haluro de arilo (**II**) usando las condiciones de acoplamiento de Suzuki, donde el ácido borónico generado *in situ* reacciona con el haluro de arilo para obtener el compuesto (**III**). El grupo éster del compuesto (**III**) se puede hidrolizar usando una base apropiada, tal como hidróxido de sodio, para proporcionar el compuesto (**IV**), y el grupo protector BOC se puede eliminar usando HCl o TFA para obtener el compuesto (**V**). Finalmente, la formación de la lactama se puede lograr usando el reactivo de acoplamiento apropiado, tal como HATU, para obtener el compuesto **(VI)**.

Método B

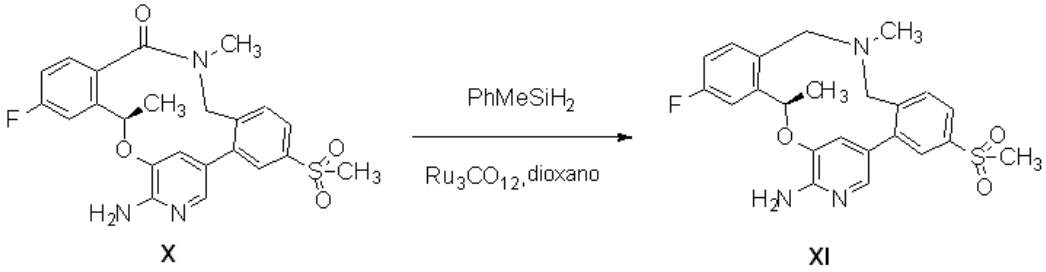
En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**IX**) se preparan de acuerdo con el **método B**.



En la primera etapa de una secuencia de dos etapas, la carboamidación regioselectiva de dihaluro de arilo (**VII**) se puede llevar a cabo con la amina (**VIII)** en presencia de monóxido de carbono y un catalizador de paladio apropiado y una base. En la segunda etapa, el acoplamiento de Suzuki de la amida cruda se puede llevar a cabo usando éster pinacólico de diboro y el catalizador de paladio apropiado y la base para proporcionar el macrociclo (**IX**).

Método C

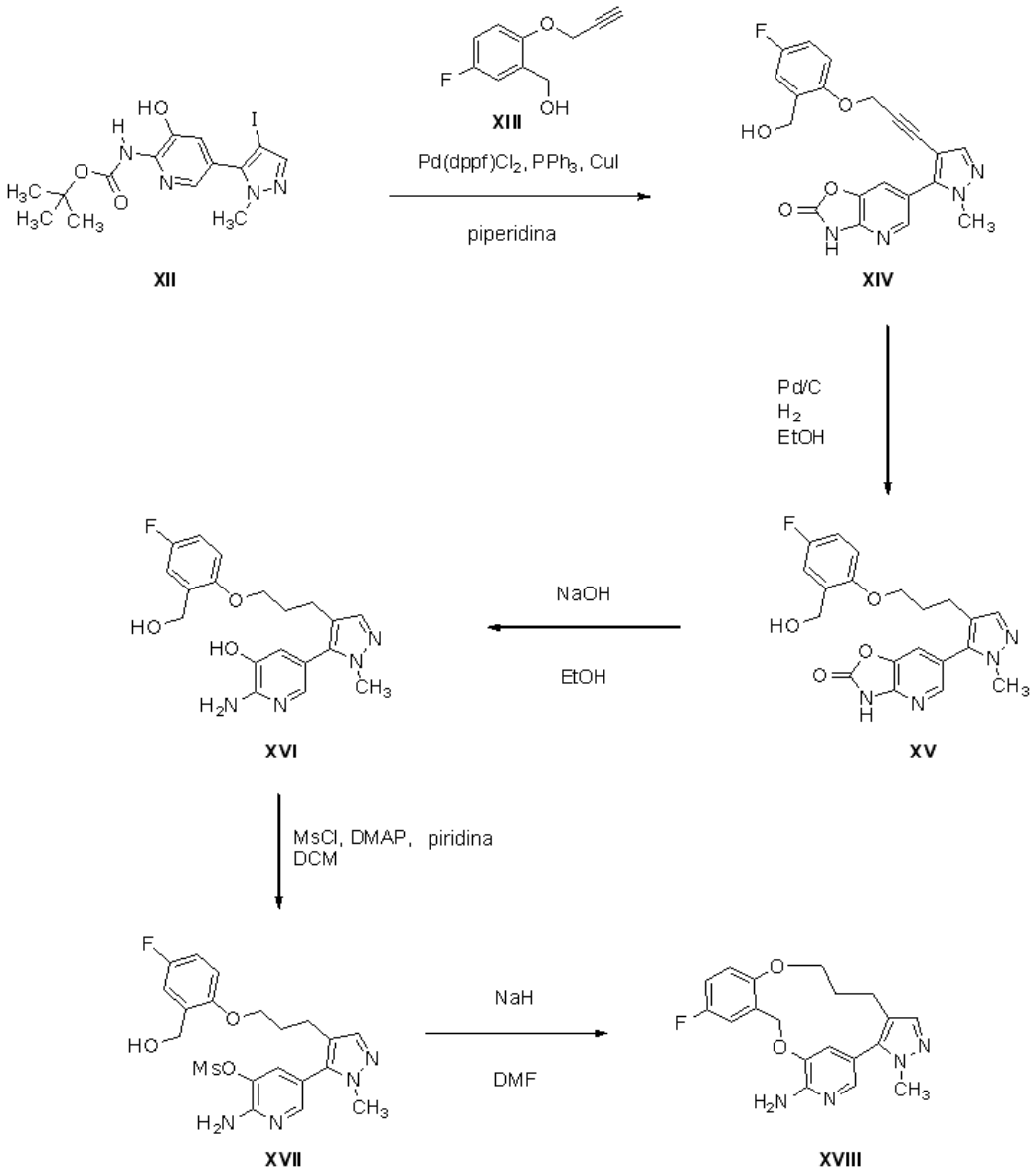
En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**XI**) se preparan de acuerdo con el **método C**.



La amida (**X**) se reduce por medio del reactivo de reducción apropiado, tal como un $PhMeSiH_2$, en presencia de un catalizador de rutenio para obtener el compuesto (**XI**).

Método D

En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto **(XII)** se preparan de acuerdo con el **método D**.

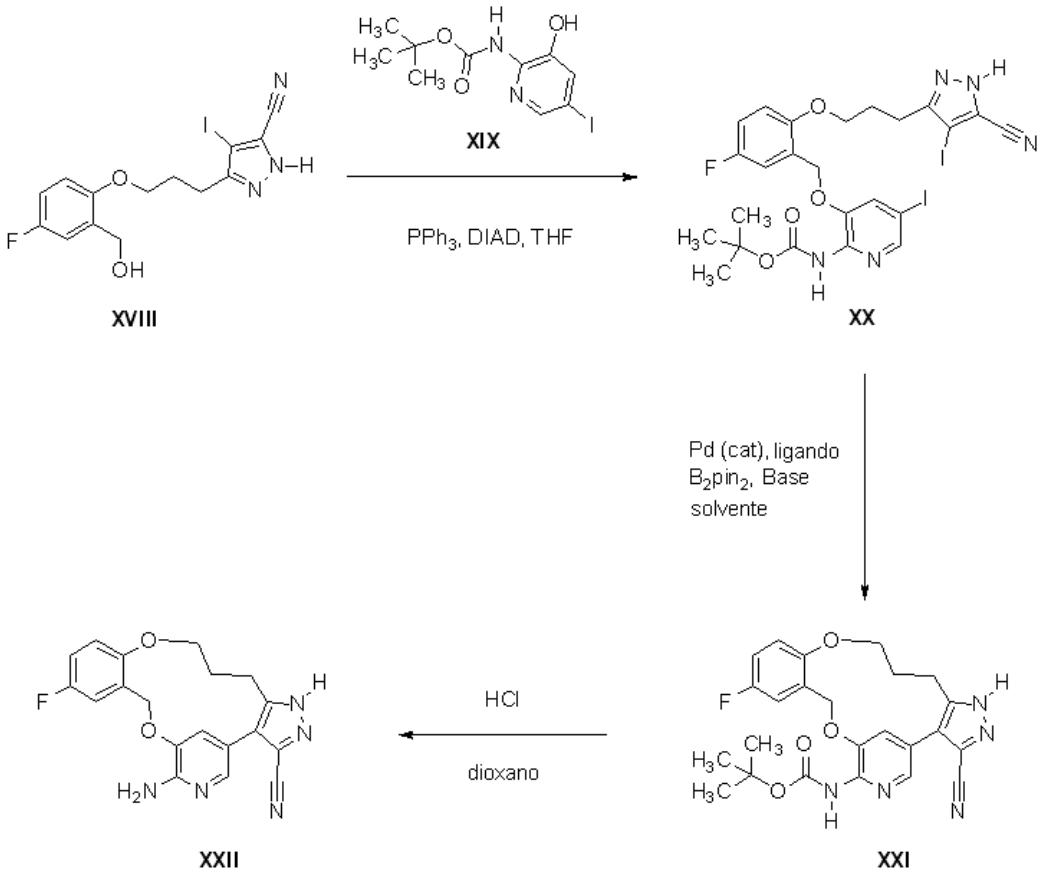


El acoplamiento cruzado de Sonagashira entre haluro de arilo **(XII)** y alquino (**XIII**) se llevó a cabo en presencia de los catalizadores de paladio y cobre apropiados y la base para proporcionar el compuesto **(XIV)**. El alquino (**XIV**) se puede reducir en una atmósfera de hidrógeno en presencia del catalizador de paladio apropiado para proporcionar el compuesto (**XV**). El compuesto (**XV**) se puede desproteger usando una base apropiada, tal como hidróxido de sodio, para proporcionar el compuesto (**XVI**). El grupo hidroxilo del compuesto **(XVI)** se puede convertir en un agente reactivo, seguido de un desplazamiento intramolecular por el fenóxido al **macrociclo (XVIII)** generado. Así, el **compuesto (XVI)** se puede tratar con cloruro de mesilo en presencia de una

base para proporcionar el **compuesto (XVII)**. La adición de una base apropiada, tal como hidruro de sodio, al **compuesto (XV11)** proporciona el macrociclo (**XVIII**).

Método E

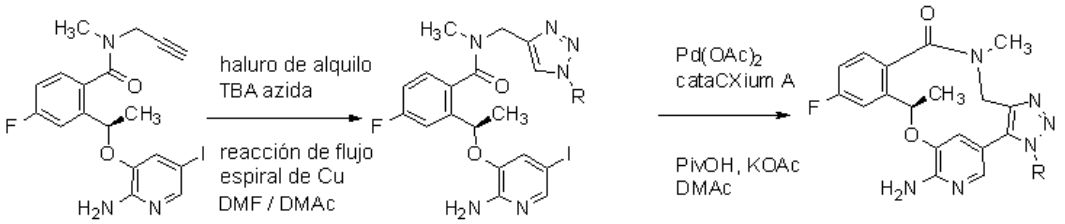
En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**XXI**) se preparan de acuerdo con el **método E**.



El **fenol (XIX)** se puede acoplar con el **compuesto (XVIII)** usando las condiciones de Mitsunobu para proporcionar el **compuesto (XX)**. En la segunda etapa, el acoplamiento intramolecular de Suzuki del **compuesto (XX)** se puede llevar a cabo usando éster pinacólico de diboro y el catalizador de paladio apropiado y la base para proporcionar el **macrociclo (XXI)**. El grupo protector BOC del **compuesto (XXI)** se puede eliminar usando HCl para proporcionar el **compuesto (XXII)**.

Método F

En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**XXV**) se preparan de acuerdo con el **método F**.

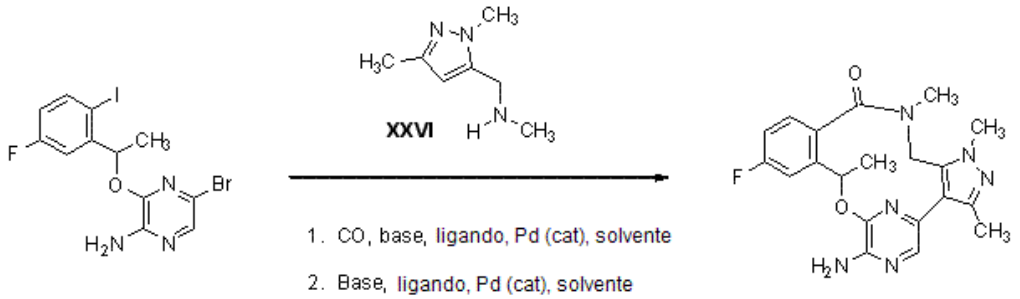


XXIII **XXIV** **XXV**

Un haluro de alquilo se puede convertir en una azida de alquilo, seguido de la adición del alquino **(XXIII)** y cobre para proporcionar el **compuesto (XXIV)**. El triazol 1,4-disustituido **(XXIV)** se puede tratar con un catalizador de paladio para proporcionar el **macrociclo (XXV)**.

Método G

En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**IX**) se preparan de acuerdo con el **Método G**.

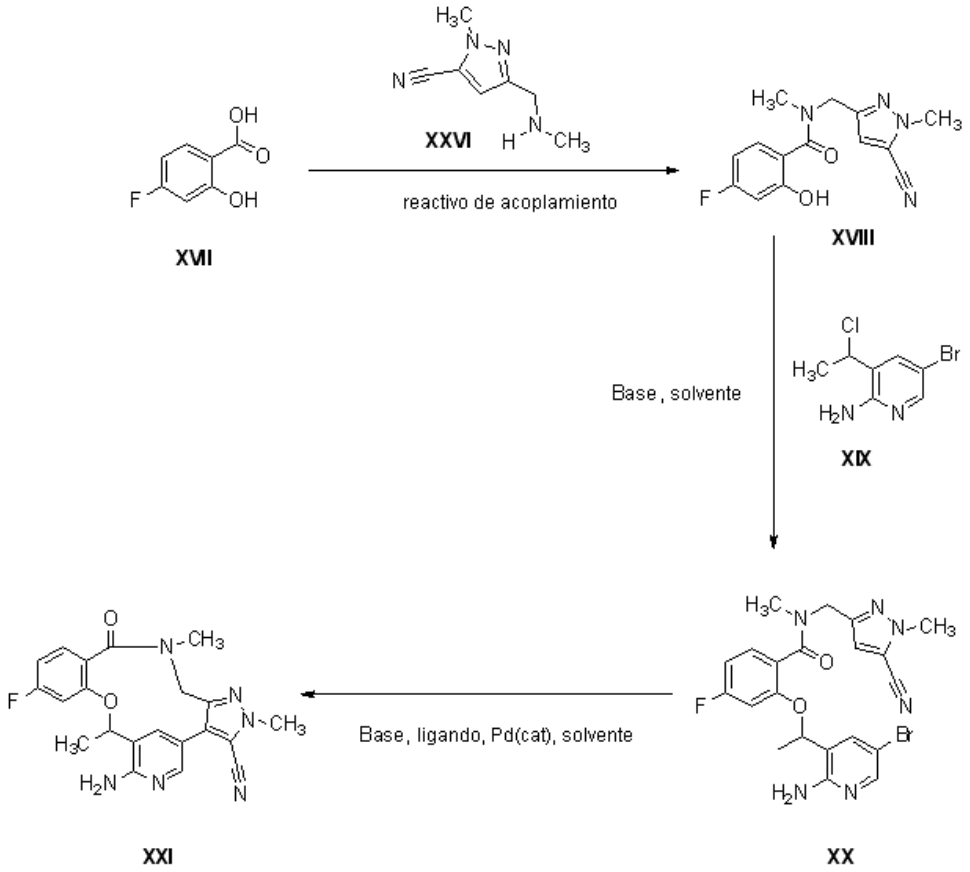


VII **XXVI** **IX**

En la primera etapa de una secuencia de dos etapas, la carboamidación regioselectiva de dihaluro de arilo (**VII**) se puede llevar a cabo con amina (**XXVI**) en presencia de monóxido de carbono y un catalizador de paladio apropiado y una base. En la segunda etapa, una reacción de activación C-H sobre la amida (ya sea cruda o purificada) se puede llevar a cabo usando el catalizador de paladio apropiado y una base para proporcionar el macrociclo (**IX**).

Método H

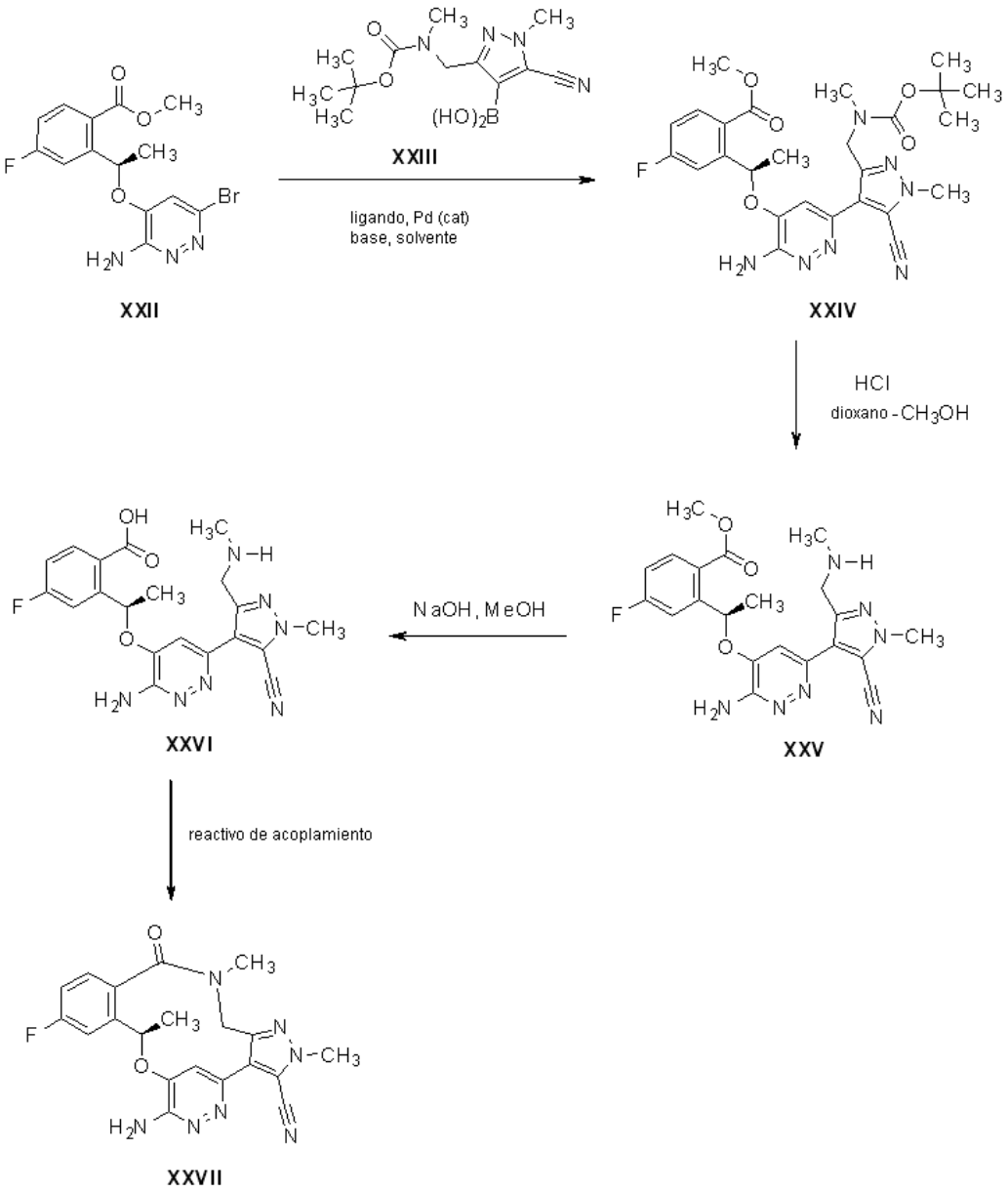
En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**XXI**) se preparan de acuerdo con el **Método H**.



En la primera de una secuencia de tres etapas, la formación de enlaces amida del ácido (**XVII**) y amina (**XVI**) se puede llevar a cabo usando un agente de acoplamiento apropiado, tal como HATU, para proporcionar el compuesto (**XVIII**). El desplazamiento nucleofílico de (**XVIII**) con el compuesto (**XIX**) para obtener el compuesto (**XX**) se puede producir en presencia de una base apropiada, tal como carbonato de potasio. En la etapa final, una reacción de activación C-H sobre la amida (**XX**) se puede llevar a cabo usando el catalizador de paladio apropiado y una base para proporcionar el macrociclo (**XXI**).

Método I

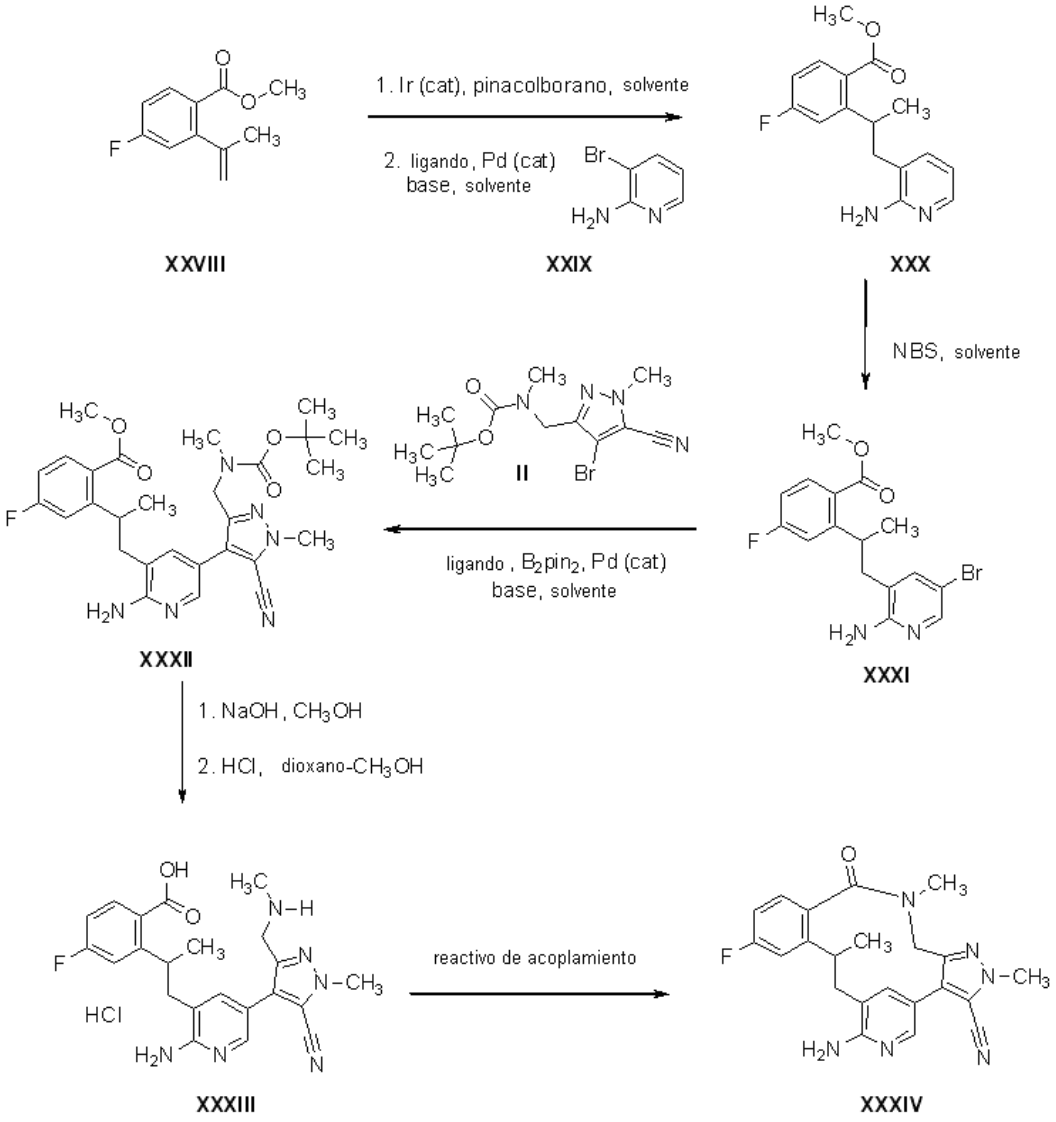
En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**XXVII**) se preparan de acuerdo con el **Método I**.



El haluro de arilo (**XXII**) se puede acoplar con ácido borónico (**XXIII**) usando las condiciones de acoplamiento de Suzuki para obtener el compuesto (**XXIV**). El grupo protector BOC se puede remover usando HCl o TFA para obtener el compuesto (**XXV**) y el grupo éster del compuesto (**XXV**) se puede hidrolizar usando una base apropiada, tal como hidróxido de sodio, para proporcionar el compuesto (**XXVI**). Finalmente, la formación de la lactama se puede lograr usando el reactivo de acoplamiento apropiado, tal como HATU para obtener el compuesto **(XXVII)**.

Método J

En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**XXXIV**) se preparan de acuerdo con el **Método J**.

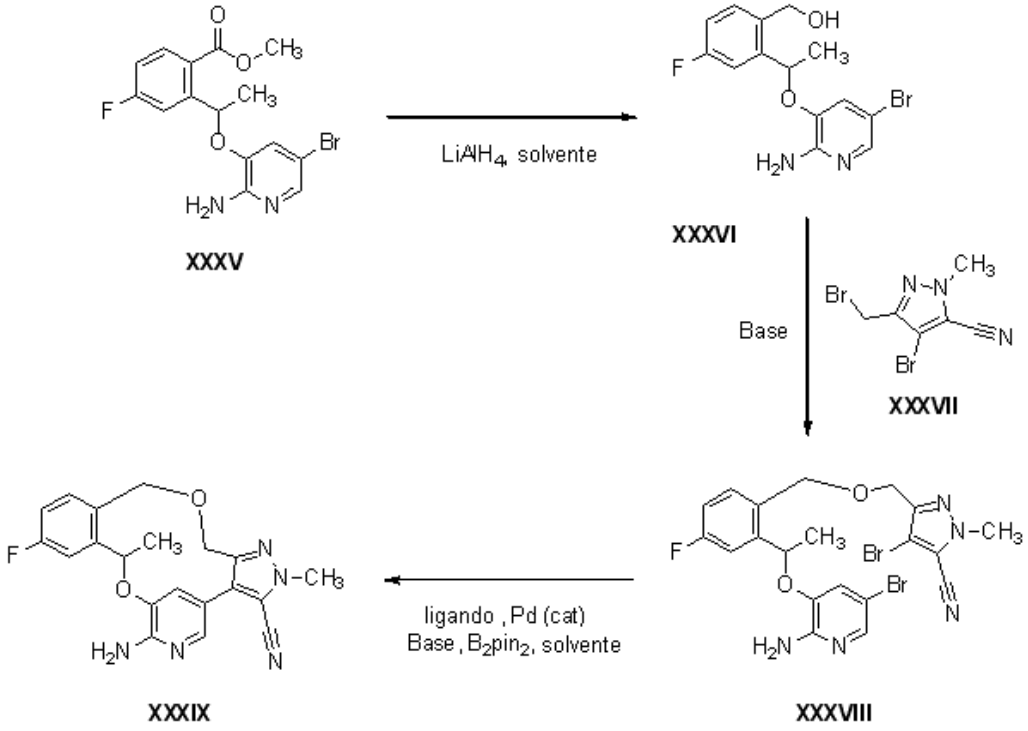


La hidroboración regioselectiva del alqueno (**XXVIII**) se puede lograr usando pinacolborano y un catalizador apropiado. Las especies de boronato formadas se pueden acoplar directamente con un haluro de arilo (**XXIX**) usando las condiciones de acoplamiento de Suzuki para obtener el compuesto (**XXX**). La halogenación regioselectiva del compuesto (**XXX**) se puede llevar a cabo usando un reactivo, tal como NBS, para obtener el compuesto (**XXXI**). El haluro de arilo (**XXXI**) se puede acoplar con haluro de arilo (**II**) usando las condiciones de acoplamiento de Suzuki, donde el ácido borónico generado *in situ* reacciona con el haluro de arilo para obtener el compuesto (**XXXII**). El grupo éster del compuesto (**XXXII**) se puede hidrolizar

usando una base apropiada, tal como hidróxido de sodio, y luego sin purificación, el grupo protector BOC se puede eliminar usando HCl o TFA para obtener el compuesto (**XXXIII**). Finalmente, la formación de la lactama se puede lograr usando el reactivo de acoplamiento apropiado, tal como HATU, para obtener el compuesto **(XXXIV)**.

Método K

En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**XXXIX**) se preparan de acuerdo con el **Método K**.

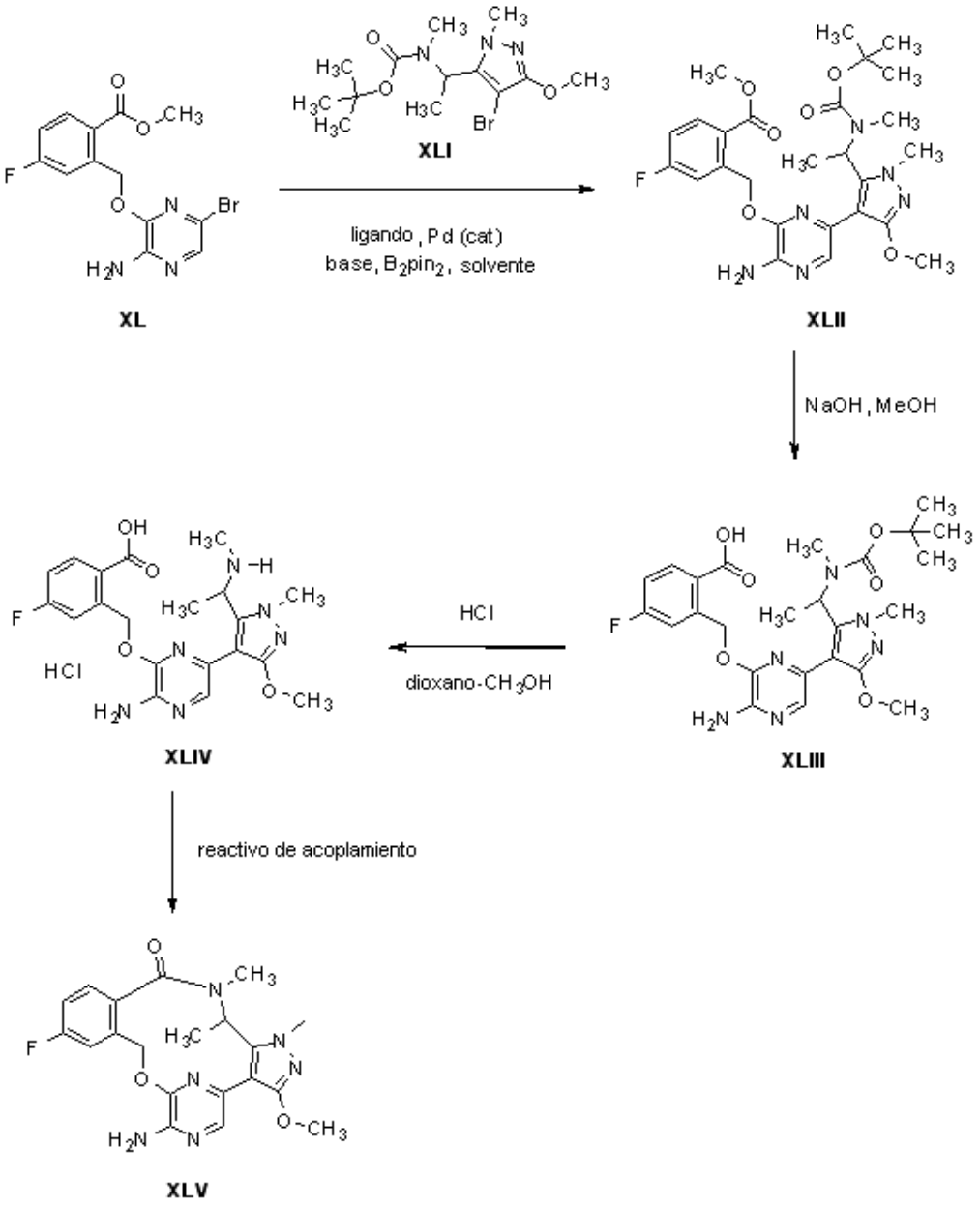


XXXV **XXXVI** **XXXVII** **XXXVIII** **XXXIX**

La reducción del éster (**XXXV**) en el alcohol (**XXXVI**) se puede llevar a cabo con un agente de reducción, tal como LAH. La formación del enlace éter entre alcohol (**XXXVI**) y haluro de arilo (**XXXVII**) se puede producir mediada por una base, tal como NaH. El dihaluro de arilo (**XXXVIII**) se puede acoplar de manera intramolecular usando las condiciones de acoplamiento de Suzuki, donde el ácido borónico generado *in situ* en un haluro reacciona con el otro haluro en la molécula para obtener el compuesto (**XXXIX**).

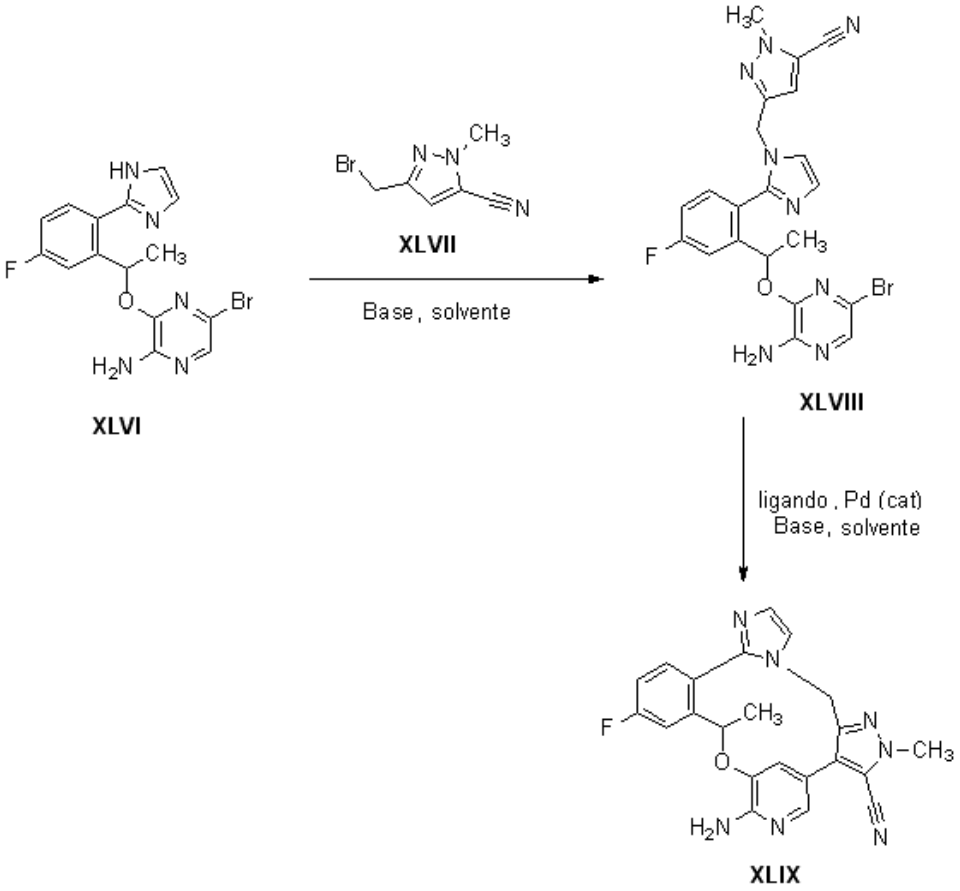
Método L

En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**XLV**) se preparan de acuerdo con el **Método L**.



Método M

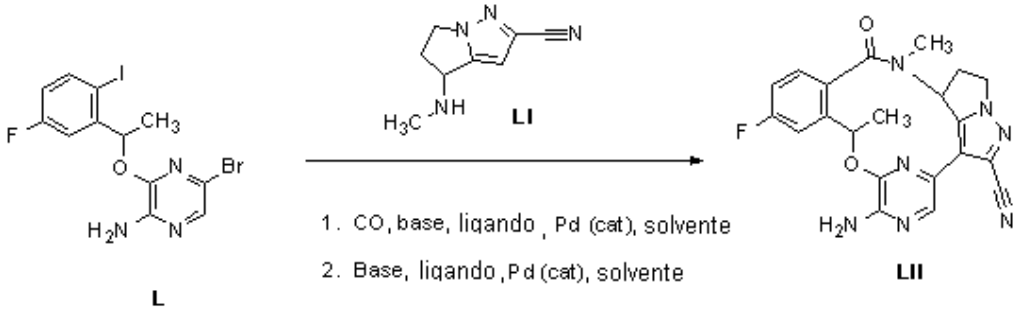
En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**XLIX**) se preparan de acuerdo con el **Método M**.



El imidazol simétrico (**XLVI**) se puede alquilar con el haluro bencílico (**XLVII**) en presencia de una base apropiada, tal como K_2CO_3. En la etapa final, una reacción de activación C-H sobre la amida (**XLVIII**) se puede llevar a cabo usando el catalizador de paladio apropiado y una base para proporcionar el macrociclo (**XLIX**).

Método N

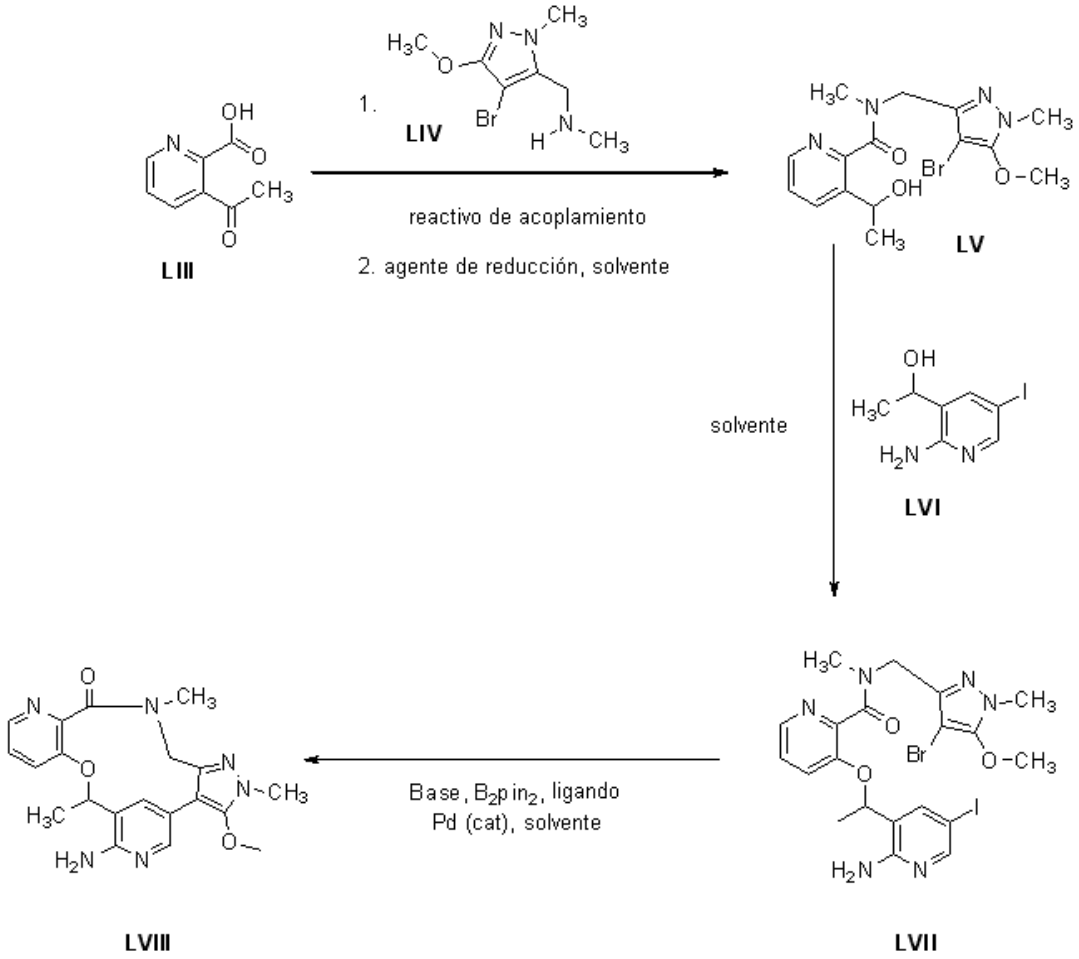
En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**LII**) se preparan de acuerdo con el **Método N**.



En la primera etapa de una secuencia de dos etapas, la carboamidación regioselectiva de dihaluro de arilo (**L**) se puede llevar a cabo con una amina bicíclica (**LII)** en presencia de monóxido de carbono y un catalizador de paladio apropiado y una base. En la segunda etapa, una reacción de activación C-H sobre la amida (ya sea cruda o purificada) se puede llevar a cabo usando el catalizador de paladio apropiado y una base para proporcionar el macrociclo (**LII**).

Método O

En un proceso de síntesis general, los compuestos de la estructura general representados por el compuesto (**LVIII**) se preparan de acuerdo con el **Método N**.



La formación de enlaces amida entre el ácido (**LIII**) y la amina (**LIV**) se puede llevar a cabo usando un agente de acoplamiento apropiado, tal como HATU. La posterior reducción de la funcionalidad de acetofenona en el alcohol (**LV**) se puede llevar a cabo usando un reactivo, tal como $NaBH_4$. La formación de enlaces éter entre

(**LV**) y el alcohol (**LVI**) se puede llevar a cabo usando la metodología, tal como una reacción de Mitsunobu para obtener el compuesto (**LVII**). El dihaluro de arilo (**LVII**) se puede acoplar de manera intramolecular usando las condiciones de acoplamiento de Suzuki, donde el ácido borónico generado *in situ* en un haluro reacciona con el otro haluro en la molécula para obtener el compuesto (**LVIII**).

Para algunas de las etapas del proceso descrito anteriormente en la presente de preparación de los compuestos de la invención, puede ser necesario proteger las funciones reactivas potenciales de los que no se desea su reacción y, por lo tanto, escindir dichos grupos protectores. En tal caso, puede utilizarse cualquier radical protector compatible. En particular, pueden utilizarse métodos de protección y desprotección, tales como los descritos por TW GREENE (*Protective Groups in Organic Synthesis*, A. Wiley-Interscience Publication, 1981) o por PJ Kocienski (*Protecting Groups*, Georg Thieme Verlag, 1994).

Todas las reacciones anteriores y las preparaciones de nuevos materiales de partida usados en los métodos precedentes son reactivos convencionales y apropiados, y las condiciones de reacción para su rendimiento o preparación, así como los procedimientos para aislar los productos deseados, son bien conocidos por los expertos en la técnica con respecto a los precedentes de la literatura y a los ejemplos y las preparaciones de la presente. Los compuestos de la invención, así como los intermediarios para la preparación de ellos, pueden purificarse de acuerdo con diversos métodos conocidos, tales como cristalización o cromatografía.

EJEMPLOS

Las preparaciones y ejemplos que siguen ilustran la invención pero no limitan la invención. Todos los materiales de partida están disponibles comercialmente o se describen en la bibliografía del caso. Todas las temperaturas están en ºC. La cromatografía de columna flash se realizó usando gel de sílice Merck 60 (9385). La cromatografía en capa fina (TLC) se llevó a cabo sobre placas de gel de sílice Merck 60 (5729). "Rf" representa la distancia recorrida por un compuesto dividida por la distancia recorrida por el frente del solvente sobre una placa de TLC. Los puntos de fusión se determinaron usando un aparato Gallenkamp MPD350 y están sin corregir. La RMN se llevó a cabo utilizando un espectrómetro Varian Unity Inova-400 MHz NMR o un espectrómetro Varian Mercury 400 MHz RMN. La espectroscopía de masas se realizó usando un espectrómetro de masas de electropulverización cuadrupolo simple Finnigan Navigator o un espectrómetro de masas Finnigan aQa APCI.

Cuando se indique que los compuestos fueron preparados en la forma descrita

para una preparación o ejemplo anterior, la persona experta comprenderá que los tiempos de reacción, el número de equivalentes de los reactivos y las temperaturas de reacción, pueden ser modificados para cada reacción específica, y que sin embargo puede ser necesario o deseable emplear diferentes condiciones de purificación o preparación.

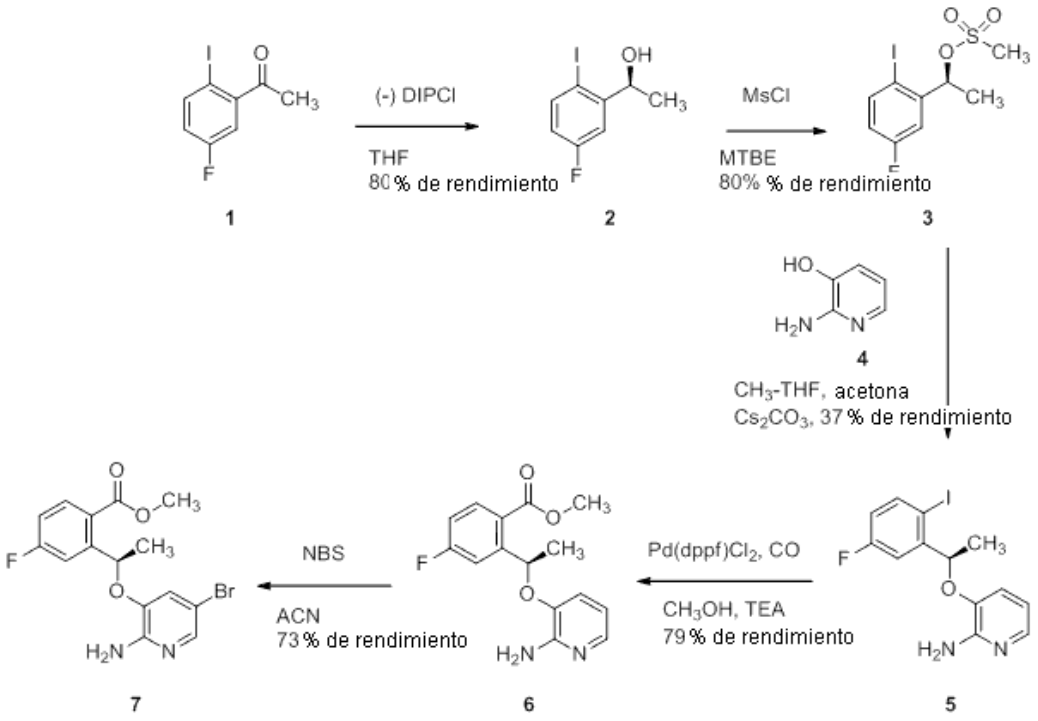
La invención se ilustra mediante los siguientes ejemplos, no limitantes, en los que se utilizan las siguientes abreviaturas y definiciones:

"Et" significa etilo, "Ac" significa acetilo, "Me" significa metilo, "Ph" significa fenilo, "Boc", "BOC", "t-Boc", o "t-BOC" significa ter-butoxicarbonilo, "EtOAc" significa etil acetato, "TEA", "NEt_3" o "Et_3N" significa trietilamina, "THF" significa tetrahidrofurano, "MeTHF" significa metiltetrahidrofurano, "MeOH" significa metanol, "DMSO" significa dimetilsulfóxido, "$CDCl_3$" significa cloroformo deuterado, "TBME" o "MTBE" significa metil t-butil éter, "DMF" significa dimetilformamida, "DMAP" significa 4-dimetilaminopiridina, "dppf" significa difenilfosfinoferroceno, "DME" significa etilenglicoldimetiléter, "TLC" significa cromatografía de capa delgada, "SFC" significa cromatografía de fluido supercrítico, "h", "hr" o "hrs" significan horas, "min." o "mins." significa minutos, "DCM" o "CH_2Cl_2" significan cloruro de metileno, "Et_2O" significa dietiléter, "LC-MS" o "LCMS" significan cromatografía liquida- espectroscopía de masa, "MS" significa espectrometría de masa, "ta" o "TA" significa temperatura ambiente, "NBS" significa N-bromosuccinimida, "MeCN" o "CH_3CN" significa acetonitrilo, "salmuera" significa cloruro de sodio acuoso saturado, "HATU" significa hexafluorofosfato de 2-(7-aza-1H-benzotriazol-1-IL)-1,1,3,3-tetrametiluronio, "APCI" significa ionización química bajo presión atmosférica; "CD_3OD" significa metanol deuterado, "$(CD_3)_2SO$" significa dimetilsullfóxido deuterado, "δ" significa corrimiento químico, "d" significa doblete, "Dad" significa detector de conjunto ordenado de diodos, g significa gramos, "ESCI" significa ionización química por electrospray; "HPLC" significa cromatografía de líquidos de alta resolución, "LRMS" significa espectro de masa de baja resolución, "M" significa molar, "m" significa multiplete, "mg" o "mgs" significan miligramos, "MHz" significa mega herzio, "mL" significa mililitros, "µL" significa microlitros, "mmol" significa millimoles, "mol" significa moles, "RMN" significa resonancia magnética nuclear, "q" significa cuarteto, "Rt" significa tiempo de retención, "s" significa singulete, "t" significa triplete, "TFA" significa ácido fluoroacético, "SFC" significa cromatografía de fluido supercrítico, "MeMgBr" significa bromuro de metilmagnesio, "DMSO-d_6" significa dimetilsulfóxido deuterado, "DiBAL" o "DIBAL-H" significa hidruro de diisobutilaluminio, "CH_3I" significa ioduro de metilo, "ppm" significa

partes por millón, “mCPBA” significa ácido meta-cloroperoxibenzoico, “DIPCl” significa β-clorodiisopinocam fenilborano (DIP-Chloride®), “N_2” significa gas nitrógeno, “MeI” significa ioduro de metilo, “NBS” significa N-bromosuccinimida, “NIS” significa N-iodosuccinimida, “DIAD” significa diisopropilazodicarboxilato, “DCE” significa 1,2-dicloroetano, “HOBt” significa hidroxibenzotriazol, “EDCl” significa 1-etil-3-(3-dimetilaminopropil)carbodiimida, “CDI” significa 1,1'-carbonildiimidazol, “DMS” significa sulfuro de dimetilo, “DIEA”, “DIPEA” o “base de Hünig” significan *N,N*-diisopropiletilamina, “MsCl” significa cloruro de metansulfonilo, “AIBN” significa azobisisobutironitrilo, “cataCXium” significa di(1-adamantil)-*n*-butilfosfina, “HATU” significa 2-(7-aza-1H-benzotriazol-1-il)-1,1,3,3-tetrametil uronio hexafluorofosfato, “AgOTf” significa sal de plata de ácido trifluorometansulfónico**, “**TFAA” significa ácido trifluoroacético, “cartucho SCX” significa cartucho de columna de intercambio catiónico fuerte, y “DMAc” significa dimetilacetamida.

Preparación de intermediarios sintéticos

Preparación de 2-(1-((2-amino-5-bromopiridin-3-il)oxi)etil)-4-fluorobenzoato de (*R*)-metilo (7).



Etapa 1:

Una solución de (-)-DIPCl (57,1 g, 178 mmol) en THF (100 ml) se enfrió de -20 a -30 ºC. Una solución del compuesto **1** (31,3 g, 119 mmol) en THF (100 ml) luego se añadió gota a gota, por medio de un embudo de adición (30 min de adición). La reacción se dejó calentar hasta temperatura ambiente. Después de 2 h, la reacción se enfrió hasta -30 ºC y se añadió otra porción de (-)-DIPCl (38,0 g, 119 mmol). Después de 30 min, la reacción se dejó calentar hasta temperatura ambiente y después de 1 h, los solventes se eliminaron al vacío y el residuo se redisolvió en MTBE (200 ml). Una solución de dietanolamina (31 g, 296 mmol) en etanol/THF (15 ml/30 ml) se añadió por medio de un embudo de adición a la mezcla de reacción bajo un baño de hielo. Se observó la formación de un precipitado blanco. La suspensión se calentó a reflujo durante 2 horas, luego se enfrió hasta temperatura ambiente, se filtró y los líquidos madre se concentraron al vacío. El residuo se suspendió en heptano/EtOAc (7:3, 200 ml) y se volvió a filtrar. Este procedimiento se repitió hasta no poder observar más sólidos después de concentrar los líquidos. El aceite amarillo final se purificó por cromatografía en columna (eluyente: ciclohexano/EtOAc- 99:1 a 96:4). El aceite incoloro resultante también se purificó por recristalización en heptanos, para dar el compuesto **2** de alcohol (25 g, 80% de rendimiento, 99% de pureza y 96% ee) en forma de cristales blancos. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,73 (dd, 1 H), 7,32 (dd, 1 H), 6,74 (ddd, 1 H), 4,99 - 5,04 (m, 1 H), 2,01 (d, 1 H), 1,44 (d, 3 H). LCMS-ES: sin ionización, pureza del 99%. GC quiral (columna CP-Chirasil-DexnCB): 96% ee; Rt (menor) 17,7 minutos y Rt (mayor) 19,4 minutos.

Etapa 2:

Una solución del compuesto **2** (22 g, 83 mmol) en MTBE (350 mL) se enfrió bajo un baño de hielo y se añadieron gota a gota trietilamina (23 mL, 166 mmol) y luego cloruro de mesilo (9,6 mL, 124 mmol). La reacción luego se calentó hasta temperatura ambiente y se agitó durante 3 h. La mezcla de reacción se filtró y los sólidos se lavaron con EtOAc. Los líquidos madre se concentraron al vacío para dar el compuesto **3** (35 g, 80% de rendimiento) en forma de un aceite amarillo pálido. Este material se usó en la siguiente etapa sin ulterior purificación. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,78 (dd, 1 H), 7,24 (dd, 1 H), 6,82 (ddd, 1 H), 2,92 (s, 3 H), 1,64 (d, 3 H). LCMS-ES sin ionización.

Etapa 3:

Una suspensión de Cs_2CO_3 (65 g, 201 mmol) y el compuesto **4** (13,3 g, 121 mmol) en CH_3-THF (600 mL) y acetona (300 mL) se agitó a temperatura ambiente

durante 30 minutos, luego se calentó hasta 40 ºC antes de la adición gota a gota de una solución del compuesto **3** (34,4 g, 80 mmol) en CH_3-THF (300 mL) por medio de un embudo de adición. La mezcla resultante se dejó bajo agitación a 75 - 80 ºC durante 24 h. La reacción luego se filtró a través de Celite con MTBE, los solventes se eliminaron al vacío y el residuo se purificó por cromatografía en columna en gel de sílice que se eluyó con ciclohexano/EtOAc (9:1 a 1:1) para dar el compuesto **5** (14,3 g, 39 % de rendimiento, 90% ee) en forma de un sólido blanco. Los sólidos luego se recristalizaron en heptano/EtOAc para dar el compuesto **5** (10,8 g, 37% de rendimiento, 95% ee). ^{1}H RMN (400 MHz, $CDCl_3$) δ□7,38 (dd, 1 H), 7,62 (dd, 1 H), 7,10 (dd, 1 H), 6,75 (ddd, 1 H), 6,44 - 6,51 (m, 2 H), 5,34 - 5,39 (m, 1 H), 4,73 (br s, 2 H), 1,61 (d, 3 H). LCMS-ES *m/z* 359 $[M+H]^+$. HPLC (Chiralpak IC 4,6 x 250 mm): 95% ee; Rt (menor) 10,4 minutos; Rt (mayor) 14,7 minutos; eluyente: Heptano 80%/IPA 20% con 0,2% de DEA, 0,7 mL/min.

Etapa 4:

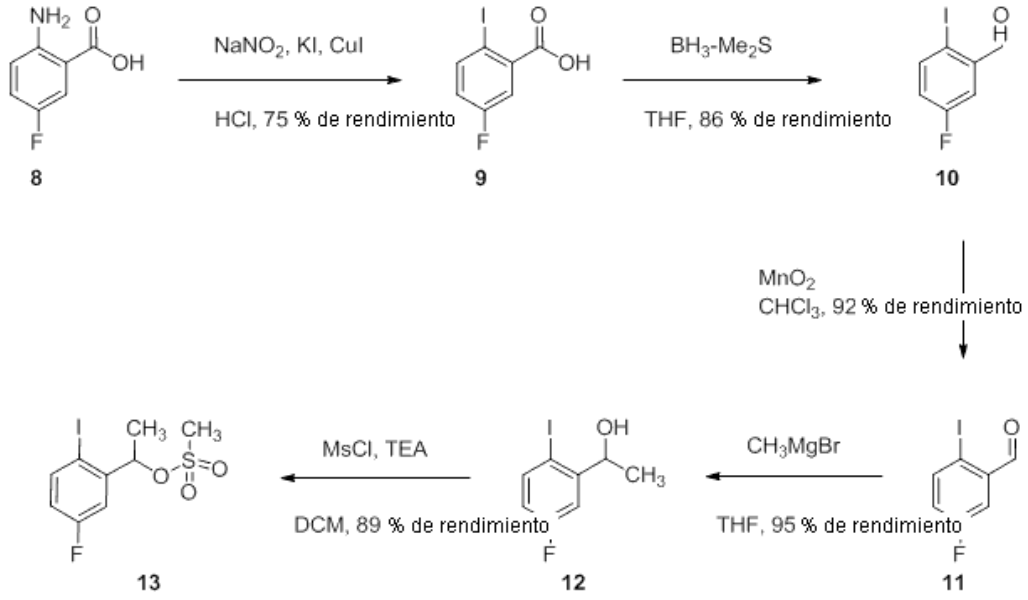
El compuesto **5** (20 g, 57 mmol) se disolvió en metanol (300 mL) y se trató secuencialmente con trietilamina (15,4 mL, 113 mmol) y $PdCl_2$(dppf) (4,1 g, 5,7 mmol). Esta mezcla se calentó a 100 ºC durante 16 horas, bajo una atmósfera de monóxido de carbono de 100 psi. LCMS indicó el consumo del material de partida. La mezcla de reacción se filtró a través de un taco de Celite y el filtrado se evaporó en un aceite marrón. El producto crudo se purificó por cromatografía flash sobre gel de sílice que se eluyó con 50% al 75% de acetato de etilo en ciclohexano, dando como resultado el producto puro **6** en forma de un sólido de color rojo ladrillo (13,0 g, 79% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,65 (d, 3 H), 3,94 (s, 3 H), 4,75 (br s, 2 H), 6,32 (q, 1 H), 6,42 (dd, 1 H), 6,61 (dd, 1 H), 7,00 (ddd, 1 H), 7,28 (dd, 1 H), 7,60 (dd, 1 H), 8,03 (dd, 1 H). LCMS ES *m/z* 291 para $[M+H]^+$.

Etapa 5:

El compuesto **6** (13,0 g, 45 mmol) se disolvió en acetonitrilo (195 mL) y se enfrió hasta <10 ºC en un baño de agua helada. NBS (7,9 g, 45 mmol) se añadió gota a gota a la mezcla de reacción enfriada como una solución en acetonitrilo (195 mL), controlando la temperatura interna para asegurar que no suba a más de 10 ºC. Una vez completa la adición, la mezcla se agitó durante 15 minutos. La TLC (1:1 ciclohexano/acetato de etilo) mostró el consumo del material de partida. La mezcla de reacción se evaporó y el residuo se redisolvió en acetato de etilo (400 mL) y se lavó con NaOH acuoso 2 M (2 x 300 mL) y solución acuosa al 10% de tiosulfato de sodio (300 mL). Los extractos orgánicos se secaron sobre $MgSO_4$ y se evaporaron en un

aceite rojo (17,6 g). El producto crudo se purificó por gel de sílice, que se eluyó con 10% al 50% de acetato de etilo en ciclohexano, que produjo el compuesto **7** (12,0 g, 73% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,65 (d, 3 H), 3,96 (s, 3 H), 4,74 - 4,81 (br s, 2 H), 6,33 (q, 1 H), 6,75 (d, 1 H), 7,03 (ddd, 1 H), 7,25 (dd, 1 H), 7,66 (d, 1 H), 8,06 (dd, 1 H). LCMS ES *m/z* 369/371 $[M+H]^+$. Una columna Chiralpak AD-H (4,6 x 100 mm, 5 micrones) se eluyó con 10% de MeOH (0,1% de DEA) en CO_2 a 120 bar. Una tasa de flujo de 5,0 mL/min produjo el isómero menor Rt 0,6 minutos y el isómero mayor Rt 0,8 minutos (99% ee). Rotación óptica: $[\alpha]_d^{20}$ = -92,4 deg (c=1,5, MeOH).

Preparación de metansulfonato de 1-(5-fluoro-2-yodofenil)etilo (11).



Etapa 1:

A una solución del compuesto **8** (25 g, 0,162 mol) en solución de HCl 2 N (350 mL) se añadió una solución de nitrito de sodio (11,2 g, 0,16 mol) en H_2O (150 mL) gota a gota mientras se mantenía la temperatura entre 0 - 5 °C. Una vez completa la adición, la mezcla se agitó a 0~5 °C durante 90 minutos. A continuación, la mezcla se añadió a una solución de yoduro de potasio (53 g, 0,32 mol) y yoduro de cobre (I) (15,2 g, 0,081 mol) en H_2O (150 mL) gota a gota con la temperatura mantenida a ~5 °C. Una vez completa la adición, la mezcla se agitó a temperatura ambiente durante 18 horas tras lo cual la TLC (EtOAc) indicó que la reacción estaba completa. La mezcla se filtró y la torta se secó. El residuo se diluyó con MTBE (500 mL), se calentó a reflujo durante 20 minutos y se filtró. El filtrado se concentró para obtener el

compuesto **9** en forma de un sólido amarillo (30 g, 75% de rendimiento). ^{1}H RMN (400 MHz, Metanol-d_4) δ 8,04 - 8,00 (m, 1 H), 7,59 - 7,56 (m, 1 H), 7,08 - 7,03 (m, 1 H).

Etapa 2:

A una solución del compuesto **9** (67 g, 0,26 mol) en THF anhidro (500 mL) se añadió una solución de BH_3•SMe_2 (50,9 mL, 0,51 mol, 1,0 M) en THF seco (150 mL) gota a gota a 0 °C bajo N_2. Una vez completa la adición, la mezcla se agitó a 0 °C durante 30 min y luego se calentó a reflujo durante 2 horas. La TLC (éter de petróleo/EtOAc 1/1) indicó que la reacción estaba completa. La mezcla se neutralizó con solución saturada acuosa de NH_4Cl (300 mL). Las sustancias volátiles se eliminaron al vacío y el residuo se extrajo con EtOAc (200 mL × 3). Las capas orgánicas combinadas se lavaron con salmuera (200 mL), se secaron Na_2SO_4 y se concentraron para obtener un residuo, que se purificó por cromatografía en gel de sílice eluyendo con éter de petróleo : EtOAc (50/1 a 25/1) y produjo el **compuesto 10** en forma de un sólido blanco (55 g, 86% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,69 - 7,66 (m, 1 H), 7,20 - 7,17 (m, 1 H), 6,72 - 6,67 (m, 1 H), 4,57 (d, 2 H), 1,98 (t, 1 H).

Etapa 3:

A una mezcla del compuesto **10** (55 g, 221 mmol) en $CHCl_3$ (500 mL) se añadió MnO_2 (115 g, 1,33 mol) y la mezcla se calentó a reflujo durante 18 horas. La TLC (éter de petróleo : EtOAc = 10 : 1) indicó que la reacción estaba completa. La mezcla se filtró y el filtrado se concentró para obtener el compuesto **11** en forma de un sólido amarillo (50 g, 97% de rendimiento).

Etapa 4:

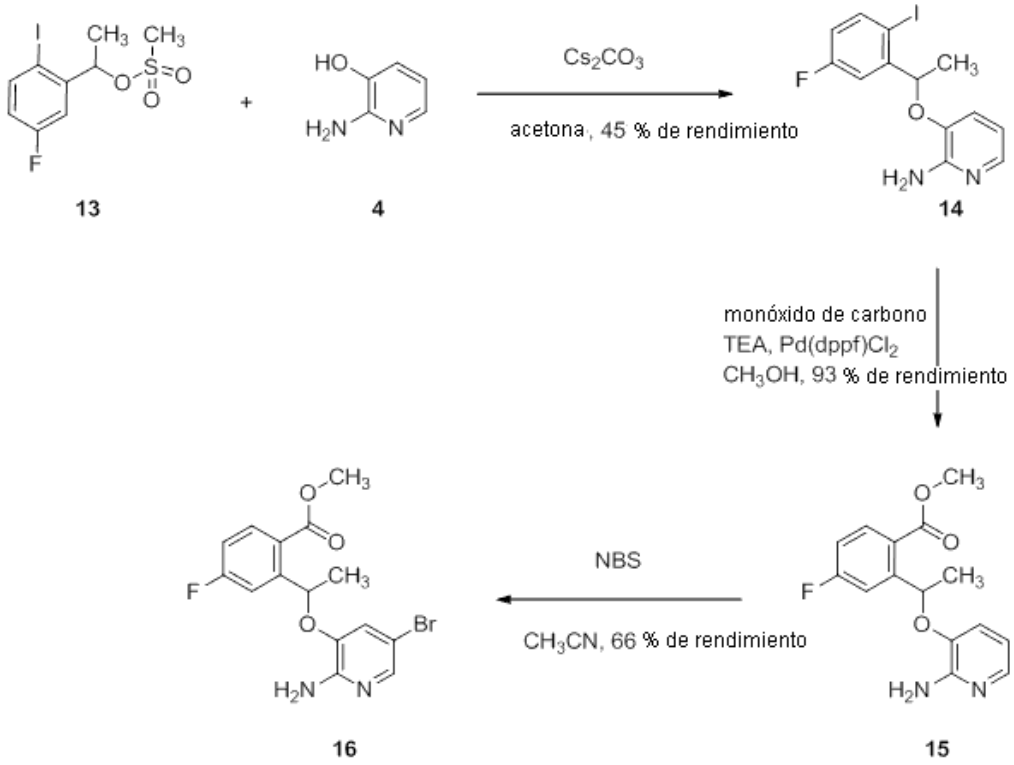
A una solución del compuesto **11** (50 g, 200 mmol) en THF anhidro (500 mL) se añadió CH_3MgBr (200 mL, 600 mmol, 3 M en dietiléter) gota a gota a -60 °C bajo N_2. Una vez completa la adición, la mezcla se calentó hasta temperatura ambiente y se agitó durante otras 2 horas. La TLC (éter de petróleo: EtOAc 10:1) indicó que la reacción estaba completa. La mezcla se neutralizó con solución saturada acuosa de NH_4Cl (300 mL) y se extrajo con EtOAc (200 mL × 3). Los extractos orgánicos combinados se lavaron con salmuera (200 mL), se secaron Na_2SO_4 y se concentraron al vacío para obtener el compuesto **12** en forma de un sólido amarillo (50 g, 95% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,69 - 7,64 (m, 1 H), 7,27 - 7,24 (m, 1 H), 6,71 - 6,65 (m, 1 H), 4,96 - 4,94 (m, 1 H), 1,38 (d, 3 H).

Etapa 5:

A una solución agitada del compuesto **12** (57 g, 0,213 mol) y TEA (38,5 mL,

0,277 mol) en DCM seco (1 L) se añadió gota a gota MsCl (35,7 g, 0,213 mol) con la temperatura mantenida a 0 °C. Una vez completa la adición, la mezcla de reacción se agitó a esta temperatura durante 30 minutos y luego la mezcla se dejó calentar y se agitó a temperatura ambiente durante 3 horas. La TLC (éter de petróleo/EtOAc 10: 1) indicó que la reacción estaba completa. La mezcla de reacción se lavó secuencialmente con HCl 1 N (200 mL × 3), solución saturada acuosa de $NaHCO_3$ (200 mL × 3) y salmuera (100 mL × 3), se secó sobre Na_2SO_4 y se concentró al vacío para obtener el compuesto **13** en forma de un aceite amarillo (65 g, 89% de rendimiento). ^{1}H-RMN (400 MHz, $CDCl_3$) δ 7,79 (1 H, dd), 7,24 (1 H, dd), 6,82 (1 H, td), 5,88 (1 H, q), 2,92 (3 H, s), 1,64 (3 H, d).

Preparación de 2-(1-((2-amino-5-bromopiridin-3-il)oxi)etil)-4-fluorobenzoato de metilo (16).



Etapa 1:

A una suspensión agitada del compuesto **13** (57 g, 0,16 mol) y compuesto **4** (18,1 g, 0,16 mol) en acetona (1 L) se añadió Cs_2CO_3 (70 g, 0,21 mol) en porciones a temperatura ambiente. Una vez completa la adición, la mezcla de reacción se agitó a temperatura ambiente durante 15 minutos y luego se agitó a 45 °C durante 18 horas. La TLC (éter de petróleo/EtOAc=3:1) indicó que la reacción estaba completa. La

mezcla de reacción se filtró y el filtrado se concentró al vacío para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice eluyendo con éter de petróleo/EtOAc (10:1 a 3:1) y se produjo el compuesto **14** en forma de un sólido marrón (47 g, 65% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,73 - 7,69 (m, 1 H), 7,54 (d, 1 H), 7,03 (dd, 1 H), 6,71 - 6,68 (m, 1 H), 6,44 - 6,37 (m, 2 H), 5,32 - 5,27 (m, 1 H), 4,68 (br s, 2 H), 1,54 (d, 3 H).

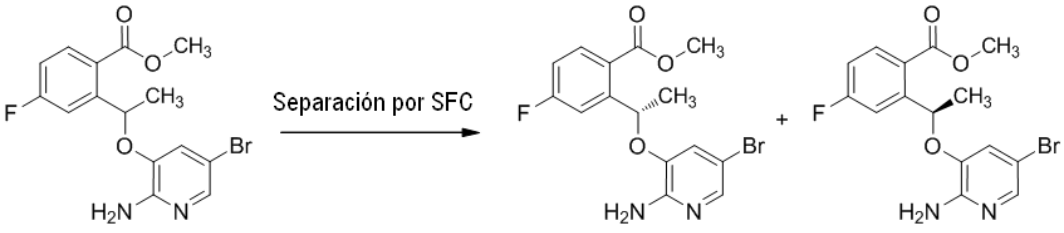
Etapa 2:

El procedimiento descrito en la etapa 4 para el compuesto **6** se usó para preparar el compuesto **15** (35,5 g, 93% de rendimiento). ^{1}H-RMN (400 MHz, $CDCl_3$) δ 7,77 (1 H, dd), 7,61 (1 H, d), 7,10 (1 H, dd), 6,75 (1 H, td), 6,51 - 6,44 (2 H, m), 5,36 (1 H, q), 4,75 (2 H, br s), 1,61 (3 H, d).

Etapa 3:

El procedimiento descrito en la etapa 5 para el compuesto **7** se usó para preparar el compuesto **16** (29 g, 66% de rendimiento). ^{1}H-RMN (400 MHz, $CDCl_3$) δ□8,06 (1 H, dd), 7,67 (1 H, d), 7,25 (1 H, dd), 7,03 (1 H, td), 6,75 (1 H, d), 6,33 (1 H, q), 4,76 (2 H, br s), 3,96 (3 H, s), 1,65 (3 H, d). LCMS *m/z* 181 (fragmento de estireno de escisión en el enlace éter).

Preparación de 2-(1-((2-amino-5-bromopiridin-3-il)oxi)etil)-4-fluorobenzoato de (*S*)-metilo (17) y 2-(1-((2-amino-5-bromopiridin-3-il)oxi)etil)-4-fluorobenzoato de (*R*)-metilo (7).



16 17 7

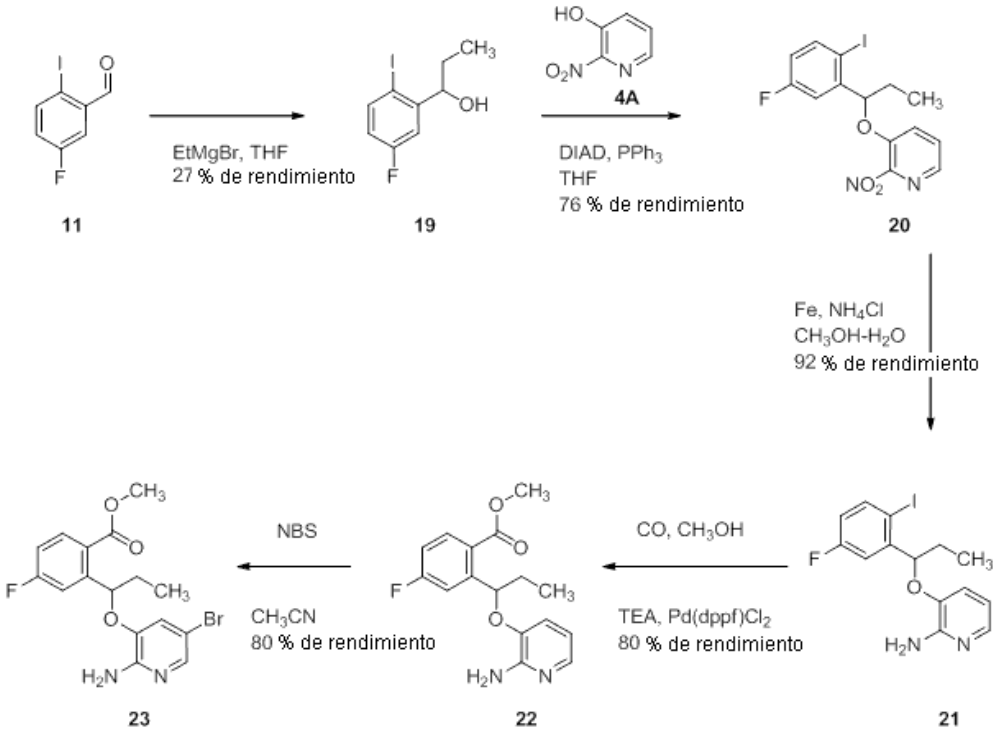
El compuesto **16** (24 g) se resolvió por SFC y produjo el compuesto **17** (pico 1) (10,6 g, 88% de rendimiento) y el compuesto **7** (pico 2) (10,2 g, 85% de rendimiento) en forma de sólidos amarillos. Una columna Chiralpak AD-H (250 × 4,6 mm I.D., 5 micrones de tamaño de partícula) se eluyó con 5% al 40% de etanol (0,05% de DEA) en CO_2 a una tasa de flujo de 2,3 mL/min y produjo el pico 1, tiempo de retención de 4,1 minutos y el pico 2, tiempo de retención de 5,8 minutos.

Compuesto 17 (pico 1): 99 % ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,99 (dd, 1 H), 7,60 (d, 1 H), 7,18 (t, 1 H), 6,99 - 6,94 (m, 1 H), 6,68 (d, 1 H), 6,28 - 6,24 (dd, 1 H), 4,69 (s, 2

H), 3,89 (s, 3 H), 1,58 (d, 3 H). LCMS *m/z* 369/371 $[M+H]^+$. $[\alpha]_d$= +108,0 deg (c=0,5, MeOH).

Compuesto 7 (pico 2): 100% ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,99 (dd, 1 H), 7,60 (d, 1 H), 7,18 (t, 1 H), 6,99 - 6,95 (m, 1 H), 6,68 (d, 1 H), 6,24 (dd, 1 H), 4,69 (s, 2 H), 3,89 (s, 3 H), 1,58 (d, 3 H). LCMS *m/z* 369/371 $[M+H]^+$. $[\alpha]_d$= -100,0 deg (c=0,5, MeOH).

Preparación de 2-(1-((2-amino-5-bromopiridin-3-il)oxi)propil)-4-fluorobenzoato de metilo (23).



Etapa 1:

A una solución del compuesto **11** (40 g, 0,16 mol) en THF seco (400 mL) se añadió gota a gota EtMgBr (320 mL, 1 M en THF) a 0 ºC. Después de la adición, la mezcla resultante se agitó a esta temperatura durante 2 horas. La TLC (éter de petróleo/EtOAc= 10: 1) indicó la reacción estaba completa. La mezcla de reacción se neutralizó con NH_4Cl saturado (200 mL) a 0 ºC y la mezcla se extrajo con EtOAc (300 mL × 2). Las capas orgánicas combinadas se lavaron con salmuera (500 mL × 2), se secaron sobre Na_2SO_4 y se concentraron. El residuo se purificó por Biotage (éter de petróleo/EtOAc 20:1 a 10:1) para obtener el compuesto **19** en forma de un aceite amarillo claro (12 g, 27% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,67 - 7,64 (m, 1 H), 7,20 - 7,17 (m, 1 H), 6,66 (t, 1 H), 4,72 - 4,70 (m, 1 H), 2,20 (s, 1 H), 1,77 - 1,69

(m, 1 H), 1,61 - 1,52 (m, 1 H), 0,98 (t, 3 H).

Etapa 2:

A una solución agitada del compuesto **19** (11g, 0,039 mol), se agregaron el compuesto **4A** (5,5 g, 0,039 mol) y PPh_3 (14 g, 0,055 mol) en THF anhidro (200 mL) gota a gota DIAD (11 g, 0,055 mol) a 0 ºC. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La TLC (éter de petróleo/EtOAc 10: 1) indicó que la reacción estaba completa. La mezcla de reacción se concentró al vacío *y* el residuo se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc 10:1 a 3:1) para obtener el compuesto **20** en forma de un sólido amarillo (12 g, 76% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,11 (d, 1 H), 7,83 - 7,81 (m, 1 H), 7,47 - 7,42 (m, 1 H), 7,22 - 7,19 (m, 1 H), 7,09 - 7,07 (m, 1 H), 6,85 - 6,82 (m, 1 H), 5,36 - 5,32 (m, 1 H), 1,88 - 1,85 (m, 1 H), 1,09 (t, 3 H).

Etapa 3:

Una suspensión del compuesto **20** (12 g, 0,029 mol), Fe (10 g, 0,18 mol) en metanol (100 mL) y NH_4Cl saturado acuoso (100 mL) se agitó a 80 ºC durante 2 horas. La TLC (éter de petróleo/EtOAc=1:1) mostró que la reacción estaba completa. La mezcla de reacción se filtró y el filtrado se concentró al vacío para dar una solución acuosa, que se extrajo con EtOAc (150 mL x 2). Las capas orgánicas combinadas se lavaron con salmuera (100 mL), se secaron sobre Na_2SO_4 y se concentraron al vacío para dar el compuesto **21** en forma de un sólido marrón pálido (10 g, 92% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,96 - 7,93 (m, 1 H), 7,50 (d, 1 H), 7,34 (d, 1 H), 7,02 (t, 1 H), 6,59 - 6,57 (m, 1 H), 6,41 - 6,40 (m, 1 H), 5,94 (s, 2 H), 5,24 (t, 1 H), 1,96 - 1,85 (m, 2 H), 1,08 (t, 3 H).

Etapa 4:

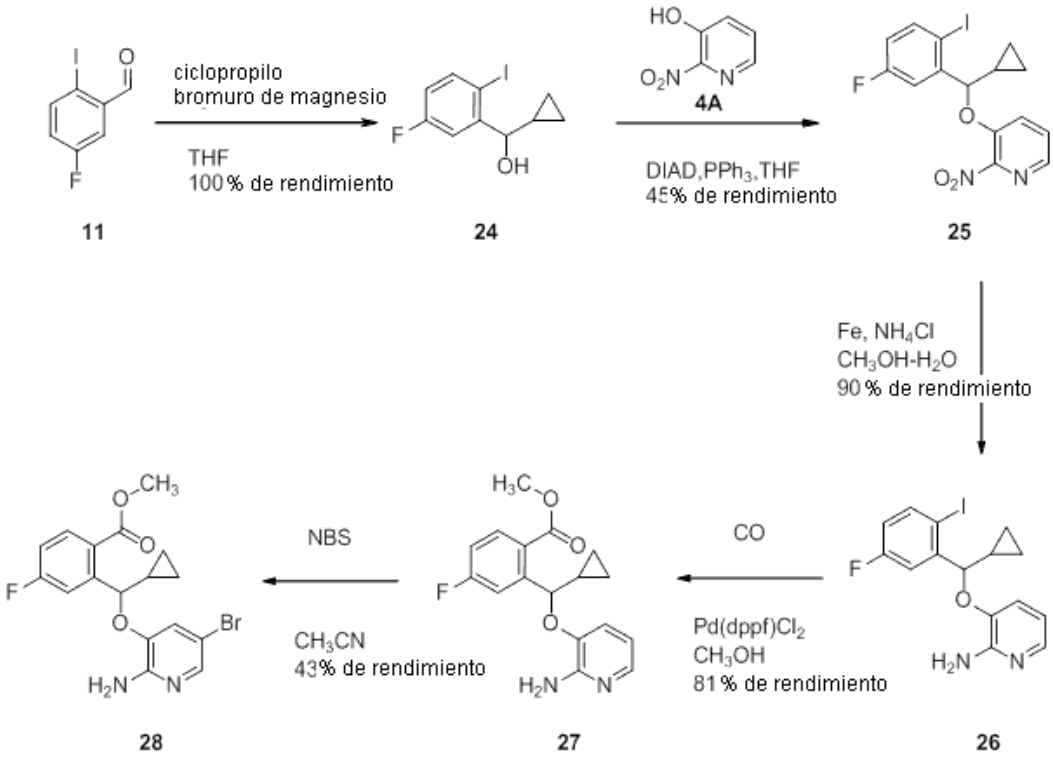
Una mezcla del compuesto **21** (10 g, 0,027 mol), $Pd(dppf)Cl_2$ (2,6 g, 0,0027 mol) y TEA (10 mL, 0,08 mol) en metanol (250 mL) se selló bajo CO (2 MPa) a 100 ºC durante 16 horas. La TLC (éter de petróleo/EtOAc = 1:1) indicó que la reacción estaba completa. La mezcla de reacción se filtró y el filtrado se concentró al vacío para producir el residuo, que se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc de 5:1 a 2:1) para obtener el compuesto **22** en forma de un sólido amarillo pálido (6,5 g, 80% de rendimiento).

Etapa 5:

A una solución agitada del compuesto **22** (6,5 g, 0,02 mol) en CH_3CN (50 mL) se añadió gota a gota una solución de NBS (3,8 g, 0,02 mol) en CH_3CN (40 mL) a 0 ºC durante un período de 30 minutos. Después de la adición, la mezcla de reacción se

agitó a esta temperatura durante 30 minutos. La TLC (éter de petróleo/EtOAc =1:1) indicó que la reacción estaba completa. La mezcla se diluyó con EtOAc (200 mL), se lavó con $NaHCO_3$ saturado (100 mL), salmuera (100 mL), se secó sobre Na_2SO_4 y se concentró. El residuo se purificó por cromatografía en columna en gel de sílice, que se eluyó con éter de petróleo/EtOAc (10:1 a 3:1) para obtener el compuesto **23** en forma de un sólido amarillo pálido (5,8 g, 76% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,01 - 7,98 (m, 1 H), 7,59 (s, 1 H), 7,12 (d, 1 H), 6,96 - 6,94 (m, 1 H), 6,69 (s, 1 H), 6,09 - 6,06 (m, 1 H), 4,74 (s, 2 H), 3,89 (s, 3 H), 1,88 - 1,82 (m, 2 H), 1,02 - 096 (m, 3 H). LCMS *m/z* 383/385 $[M+H]^+$.

Preparación de 2-(((2-amino-5-bromopiridin-3-il)oxi)(ciclopropil)metil)-4-fluorobenzoato de metilo (28).



Etapa 1:

El procedimiento descrito en la etapa 1 para el compuesto **23** se usó para preparar el compuesto **24** en forma de un aceite amarillo claro (29 g, 100% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,68 (dt, 1 H), 7,21 (dd, 1 H), 6,68 (dt, 1 H), 4,45 (d, 1 H), 4,10 - 4,00 (m, 1 H), 1,97 (s, 1 H), 1,20 - 1,11 (m, 1 H), 0,56 - 0,36 (m, 4 H).

Etapa 2:

El procedimiento descrito en la etapa 2 para el compuesto **23** se usó para preparar el compuesto **25** en forma de un sólido amarillo (18 g, 44% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,96 (d, 1 H), 7,74 (dd, 1 H), 7,32 - 7,29 (m, 1 H), 7,16 - 7,07 (m, 2 H), 6,76 - 6,68 (m, 1 H), 5,22 (d, 1 H), 1,38 - 1,19 (m, 1 H), 0,71 - 0,56 (m, 4 H).

Etapa 3:

El procedimiento descrito en la etapa 3 para el compuesto **23** se usó para preparar el compuesto **26** en forma de un sólido marrón pálido (15 g, 90% de rendimiento).

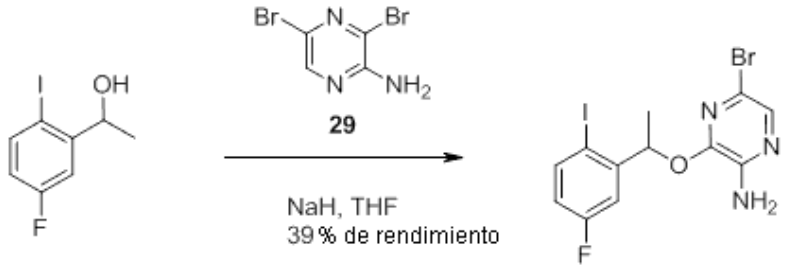
Etapa 4:

El procedimiento descrito en la etapa 4 para el compuesto **23** se usó para preparar el compuesto **27** en forma de un sólido amarillo (10 g, 81% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,98 (q, 1 H), 7,59 (d, 1 H), 7,32 - 7,26 (m, 1 H), 7,03 - 6,99 (m, 1 H), 6,74 - 6,72 (m, 1 H), 6,44 - 6,40 (m, 1 H), 6,04 (d, 1 H), 4,73 (s, 2 H), 3,94 (s, 3 H), 1,35 - 1,28 (m, 1 H), 0,62 - 0,52 (m, 4 H).

Etapa 5:

El procedimiento descrito en la etapa 5 para el compuesto **23** se usó para preparar el compuesto **28** en forma de un sólido amarillo pálido (5,3 g, 43% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,01 - 7,98 (m, 1 H), 7,49 - 7,45 (m, 2 H), 7,16 - 7,11 (m, 1 H), 6,99 (d, 1 H), 5,90 (q, 1 H), 3,96 (s, 3 H), 1,42 - 1,41 (m, 1 H), 0,69 - 0,68 (m, 1 H), 0,56 - 0,49 (m, 3 H). LCMS *m/z* 395/397 $[M+H]^+$.

Preparación de 5-bromo-3-(1-(5-fluoro-2-yodofenil)etoxi)pirazin-2-amina (30).

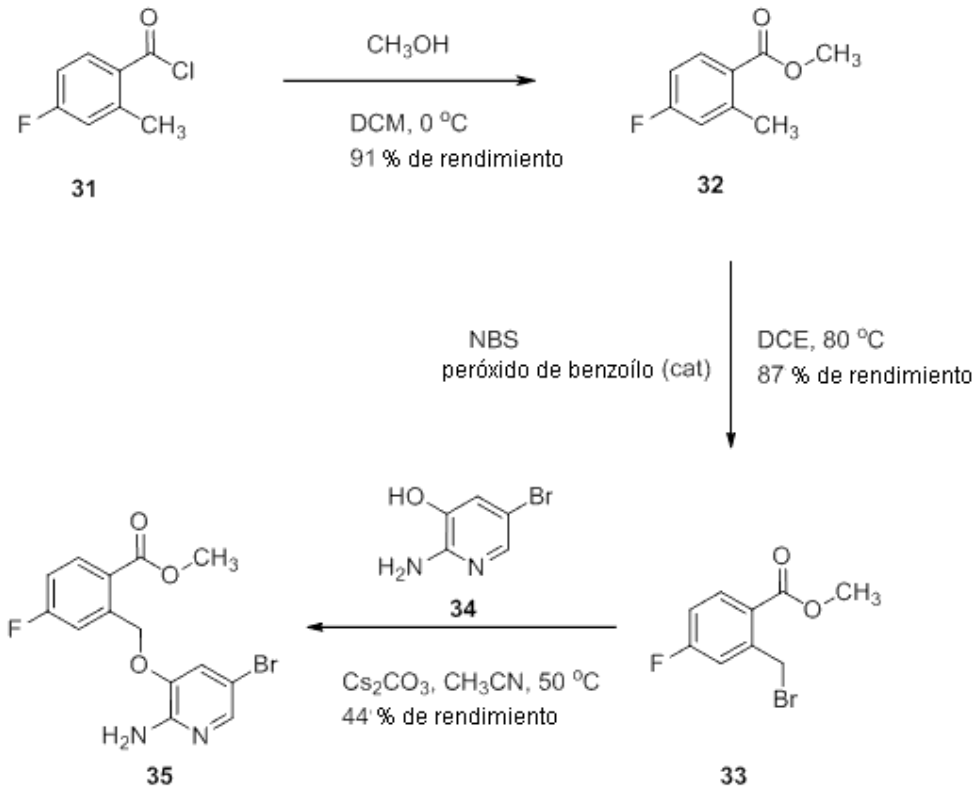


12 30

A una solución del compuesto **12** (17,8 g, 67,9 mmol) en THF anhidro (350 mL) se añadió NaH (2,7 g, 67,9 mmol, 60% en aceite) a 0 °C bajo nitrógeno. La mezcla se agitó durante otros 30 minutos. Una solución del compuesto **29** (17,1 g, 67,9 mmol) en

THF anhidro (150 mL) se añadió a la mezcla anterior a 0 ℃ y la mezcla se calentó a reflujo durante 18 horas. La LCMS indicó que el 90% del alcohol de partida se había consumido. Las sustancias volátiles se eliminaron a presión reducida y el residuo se diluyó con una mezcla de H_2O (100 mL) y EtOAc (100 mL). La mezcla se filtró, la capa orgánica se retiró y la capa acuosa se extrajo luego con EtOAc (100 mL × 3). Las capas orgánicas combinadas se lavaron con salmuera (100 mL), se secaron sobre Na_2SO_4 y se concentraron para dar un residuo, que se purificó por columna en gel de sílice eluyendo con éter de petróleo : EtOAc (30/1 a 20/1) para obtener el compuesto **30** en forma de un sólido amarillo (11,5 g, 39% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,69 - 7,73 (m, 1 H), 7,55 (s, 1 H), 7,04 (d, *J* = 6,8 Hz, 1 H), 6,65 - 6,71 (m, 1 H), 6,10 (q, *J* = 6,4 Hz, 1 H), 4,81 (br s, 2 H), 1,55 (d, *J* = 6,4 Hz, 3 H). LCMS *m/z* 438/440 $[M+H]^+$.

Preparación de 2-(((2-amino-5-bromopiridin-3-il)oxi)metil)-4-fluorobenzoato de metilo (35).



Etapa 1:

A una solución helada del compuesto **31** (24,3 g, 141 mmol) en DCM (300 mL)

se añadió metanol (100 mL) gota a gota durante 20 minutos. La mezcla de reacción luego se dejó calentar hasta temperatura ambiente y se agitó a temperatura ambiente durante 2 horas. La reacción luego se concentró al vacío y el residuo se disolvió en DCM (200 mL) y luego se lavó con bicarbonato de sodio saturado acuoso (150 mL). Las capas orgánicas se secaron luego sobre $MgSO_4$, se filtraron y se concentraron al vacío para obtener el compuesto **32** en forma de un aceite incoloro (19,5 g, 91% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,95 (1 H, m), 6,95 - 6,85 (2 H, m), 3,90 (3 H, s), 2,60 (3 H, s). LCMS ES sin ionización.

Etapa 2:

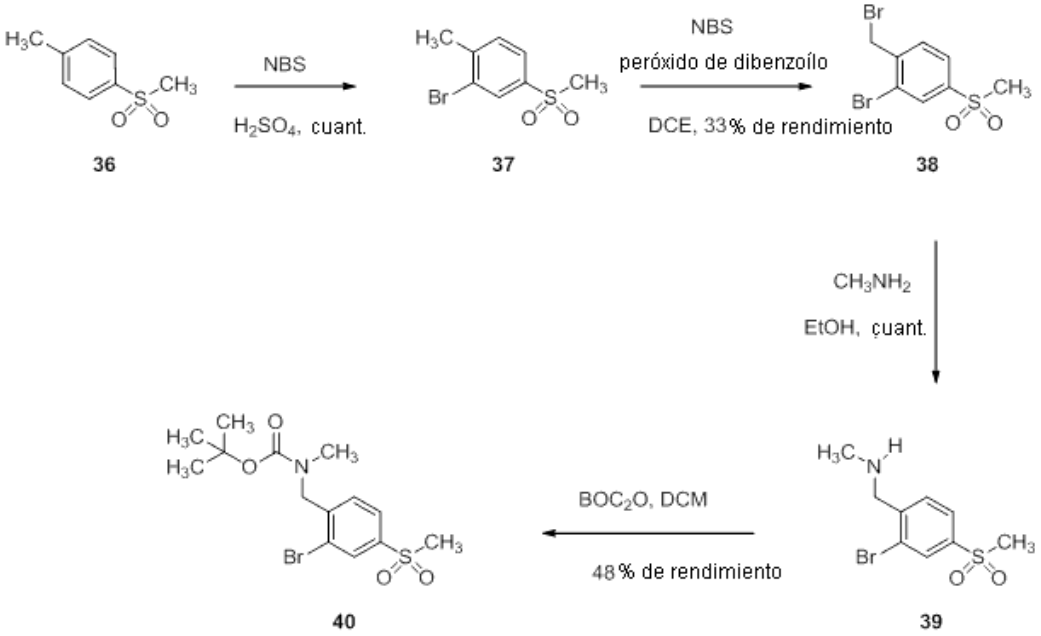
A una solución del compuesto **32** (6,3 g, 41,4 mmol) en DCE (100 mL) se añadió NBS (8,1 g, 46 mmol) seguido de una cantidad catalítica de peróxido de benzoílo (200 mg, 0,82 mmol). La reacción luego se calentó a 80 ºC durante 8 hrs. La reacción se enfrió hasta temperatura ambiente y el sólido precipitado se eliminó por filtración y se lavó con MTBE. El filtrado se concentró al vacío y el residuo se dividió en NaOH 2 N (150 mL) y MTBE (150 mL). La capa orgánica se separó, se secó sobre $MgSO_4$, se filtró y se concentró para dar el compuesto **33** (8,9 g, 87% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,05 (1 H, m), 7,20 (1 H, m), 7,10 (1 H, m), 4,90 (2 H, s), 3,95 (3 H, s).

Etapa 3:

Al compuesto **33** (15,0 g, 61 mmol) en acetonitrilo (150 mL) a temperatura ambiente se añadió el compuesto **34** (10,9 g, 58 mmol) seguido de carbonato de cesio (23 g, 69 mmol). La mezcla luego se calentó a 50 ºC durante 5 horas antes de enfriar hasta temperatura ambiente. La mezcla luego se concentró al vacío para eliminar ~ 80% del acetonitrilo antes de dividir el residuo en agua (400 mL) y acetato de etilo (400 mL). Las dos capas se separaron y la capa acuosa se reextrajo con acetato de etilo (400 mL). Las capas orgánicas combinadas se concentraron luego al vacío para obtener un sólido marrón oscuro. (Nótese que la capa acuosa aún era muy oscura y contenía sólidos insolubles– rendimiento probablemente comprometido por falta de solubilidad del producto en solventes orgánicos). El residuo sólido luego se suspendió en MTBE (300 mL) durante 20 minutos y el **compuesto 35** se recolectó en forma de un sólido gris oscuro (11,5 g, 52% de rendimiento). Este producto luego se purificó por cromatografía en columna en gel de sílice eluyendo con acetato de etilo y ciclohexano (33% de EtOAc a EtOAc puro) para obtener el compuesto **35** (9,5 g, 44% de rendimiento) en forma de un sólido blanquecino. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,10 (1 H, m), 7,75 (1 H, s), 7,35 (1 H, m), 7,10 (1 H, m), 7,05 (1 H, s), 5,50 (2 H, s), 4,75 (1 H,

br s), 3,90 (3 H, s). LCMS ES *m/z* 355/357 $[M+H]^+$.

Preparación de 2-bromo-4-(metilsulfonil)bencil(metil)carbamato de *ter*-butilo (40).



Etapa 1:

A una mezcla agitada de NBS (12,0 g, 68 mmol) y el compuesto **36** (10,0 g, 58 mmol) se añadió ácido sulfúrico concentrado (50 mL). La solución inicialmente se volvió verde, tras lo cual persistió un color amarillo pálido. La solución se agitó durante 16 horas a temperatura ambiente. La mezcla se vertió cuidadosamente en hielo (400 mL) y luego se extrajo con acetato de etilo (500 mL). La capa orgánica se lavó con hidróxido de sodio acuoso 2 M (2x 300 mL), luego se secó sobre sulfato de magnesio y se evaporó para obtener el compuesto **37** en forma de un sólido blanco (14,7 g, rendimiento cuantitativo). ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,48 (s, 3 H), 3,05 (s, 3 H), 7,43 (d, 1 H), 7,77 (dd, 1 H), 8,10 (d, 1 H).

Etapa 2:

El compuesto **37** (10,0 g, 40 mmol) se disolvió en 1,2-dicloroetano (250 mL), seguido de la adición de NBS (7,1 g, 40 mmol) y peróxido de dibenzoílo (970 mg, 4,0 mmol), en pequeñas porciones. Después de agitar a 85 °C durante 2 horas, la TLC (8:2 ciclohexano/acetato de etilo) indicó un consumo casi total del material de partida y la emergencia de una mancha menor de material dibromado. La mezcla se dejó enfriar, se diluyó en 500 mL con diclorometano y se lavó con agua (2 x 250 mL). La capa orgánica se secó sobre $MgSO_4$ y se evaporó en un aceite amarillo. El aceite

viscoso se enfrió en un baño de hielo que produjo un sólido. La trituración del sólido con dietiléter produjo el compuesto **38** (4,4 g, 33% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 3,05 (s, 3 H), 4,60 (s, 2 H), 7,66 (d, 1 H), 7,87 (dd, 1 H), 8,15 (d, 1 H). LCMS ES sin ionización del compuesto **11** evidente.

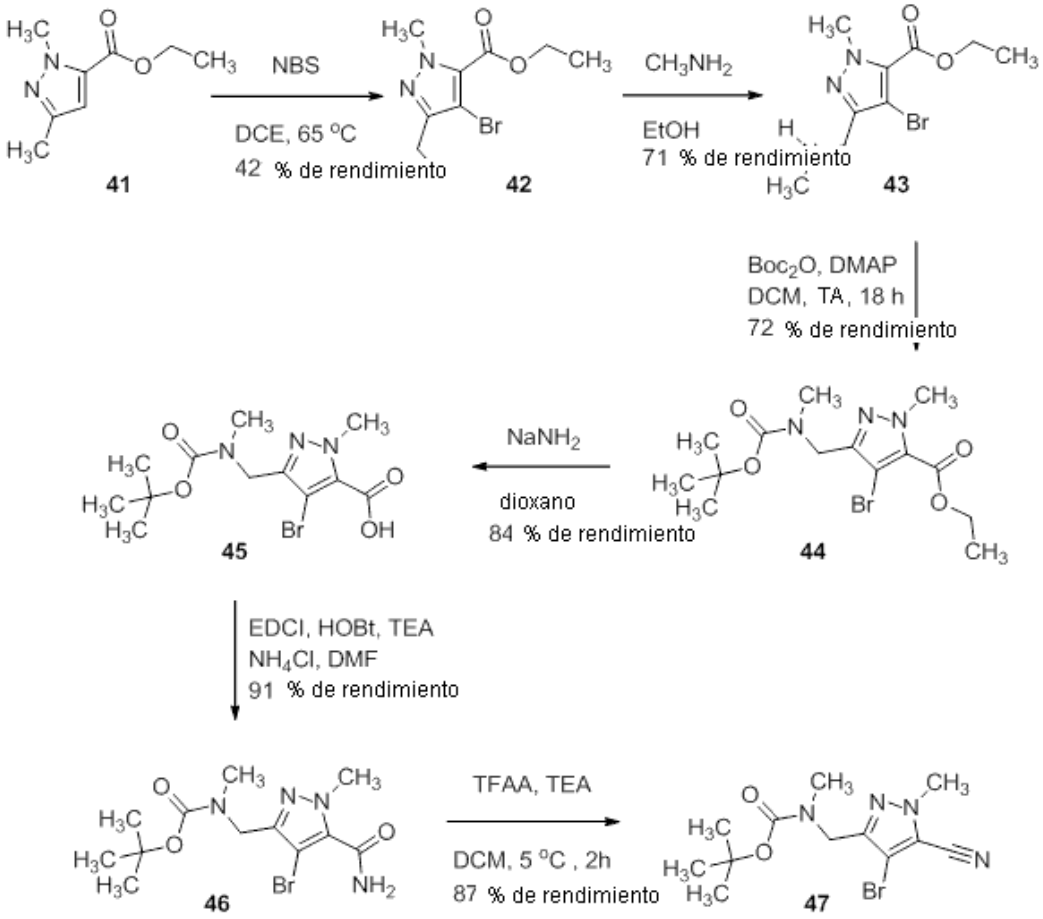
Etapa 3:

El compuesto **38** (4,3 g, 13 mmol) se disolvió en solución de metilamina (solución al 33% en etanol, 100 mL) y se agitó a temperatura ambiente durante 16 horas. La TLC (acetato de etilo) y la LCMS indicaron el consumo del material de partida y el mayor pico para el producto. La mezcla se evaporó en el compuesto **39** en forma de un sólido blanco (3,7 g, rendimiento cuantitativo). ^{1}H RMN (400 MHz, metanol-d_4) δ 2,49 (s, 3 H), 3,15 (s, 3 H), 3,97 (s, 2 H), 7,71 (d, 1 H), 7,94 (dd, 1 H), 8,16 (d, 1 H). LCMS *m/z* 278/280 $[M+H]^+$.

Etapa 4:

El compuesto **39** (3,7 g, 13 mmol) se disolvió en diclorometano (40 mL) y la mezcla se enfrió hasta 0 °C. Una solución de dicarbonato de di(ter-butilo) (3,5 g, 16 mmol) en diclorometano (35 mL) se añadió gota a gota. El baño de hielo se retiró y la mezcla se agitó durante 18 horas a temperatura ambiente. LCMS y TLC (1:1 ciclohexano/acetato de etilo) mostraron el consumo del compuesto **12**, así que la reacción se diluyó en 150 mL con diclorometano y se lavó con agua (2 x 100 mL). Los extractos orgánicos se secaron sobre sulfato de magnesio y se evaporaron en un aceite amarillo pálido. El producto crudo se purificó por gel de sílice, que se eluyó con un gradiente de 10% a 20% de acetato de etilo en ciclohexano, y produjo el compuesto **40** (2,4 g, 48% de rendimiento). ^{1}H RMN (400 MHz, metanol-d_4) δ 1,36 - 1,52 (br, 9 H, t-Bu rotámeros), 2,95 (s, 3 H), 3,15 (s, 3 H), 4,58 (s, 2 H), 7,40 (d, 1 H), 7,95 (d, 1 H), 8,15 (d, 1 H). LCMS ES *m/z* 378/380 $[M+H]^+$.

Preparación de ((4-bromo-5-ciano-1-metil-1H-pirazol-3-il)metil)(metil)carbamato de *ter*-butilo (47).



Etapa 1:

El procedimiento descrito en la etapa 2 para el compuesto **40** se usó para preparar el compuesto **42** (4,1 g, 42% de rendimiento). TLC (EtOAc/Ciclohexano; 1:10; $KMnO_4$): Rf~0,3. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,47 (s, 2 H), 4,41 (q, 2 H), 4,15 (s, 3 H), 1,42 (t, 3 H). LCMS ES *m/z* 324/326/328 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 3 para el compuesto **40** se usó para preparar el compuesto **43** (1,8 g, 71% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,39 (q, 2 H), 4,14 (s, 3 H), 4,05 (s, 2 H), 2,62 (d, 3 H), 1,41 (t, 3 H). LCMS ES *m/z* 276/278 $[M+H]^+$.

Etapa 3:

El procedimiento descrito en la etapa 4 para el compuesto **40** se usó para preparar el compuesto **44** (1,8 g, 72% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,48 - 4,44 (m, 2 H), 4,41 (q, 2 H), 4,12 (s, 3 H), 2,82 - 2,79 (m, 3 H), 1,47 (s, 9 H), 1,41

(t, 3 H). LCMS ES *m/z* 376/378 $[M+H]^+$ y 276/278 $[M\text{-}BOC]^+$.

Etapa 4:

El compuesto **44** (4 g, 11 mmol) se disolvió en dioxano (43 mL). Se añadió amida de sodio (1 g, 27 mmol) en una porción. La mezcla de reacción se agitó a 100 ºC durante 24 h. Después de este tiempo, el solvente se eliminó a presión reducida para obtener un sólido blanco. El material se suspendió en EtOAc (100 mL) y se lavó con solución al 5% de ácido cítrico (100 mL). La fase orgánica se separó y se lavó con agua (100 mL), se secó sobre $MgSO_4$, se filtró y el solvente se eliminó al vacío para obtener el compuesto **45** en forma de una goma amarilla (3,1 g, 84% de rendimiento). ^1H RMN (400 MHz, DMSO-d_6) δ 4,27 (s, 2 H), 3,92 (s, 3 H), 2,70 (s, 3 H), 1,40 (s, 9 H). LCMS ES *m/z* 348/350 $[M+H]^+$ y 248/250 [M-BOC]+.

Etapa 5:

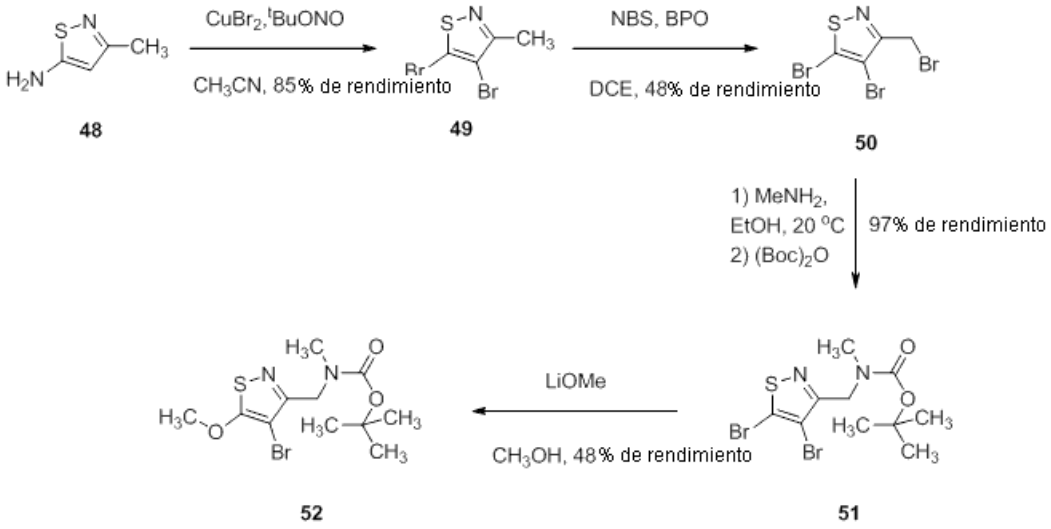
El compuesto **45** (3 g, 8,6 mmol) se disolvió en DMF (43 mL, 0,2 M). Se añadió HOBt (1,2 g, 8,6 mmol), seguido de cloruro de amonio (0,9 g, 17,2 mmol). Luego se añadió EDCI (2,5 g, 13 mmol), seguido de TEA (2,4 mL, 17 mmol). La mezcla de reacción se agitó a temperatura ambiente. Después de 18 h, el solvente se eliminó a presión reducida para obtener un aceite amarillo (8,0 g). El residuo se disolvió en EtOAc (7 5 mL). La fase orgánica se lavó con $NaHCO_3$ (solución saturada, 70 mL) y luego salmuera (100 mL). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y el solvente se eliminó al vacío para obtener el compuesto **46** en forma de un aceite amarillo oscuro (2,7 g, 91% de rendimiento). Este material se usó directamente en la siguiente etapa sin ulterior purificación. ^1H RMN (400 MHz, $CDCl_3$) δ 6,74 (br s, 1 H), 5,95 (br s, 1 H), 4,49 (br s, 2 H), 4,16 (s, 3 H), 2,81 (br s, 3 H), 1,47 (s, 9 H). LCMS ES *m/z* 347/349 $[M+H]^+$ y 247/249 $[M\text{-}BOC]^+$.

Etapa 6:

El compuesto **46** (2,7 g, 7,9 mmol) se disolvió en DCM (80 mL, 0,1 M). Luego se añadió TEA (3,3 mL, 23,8 mmol) y la mezcla de reacción se enfrió hasta -5 ºC. Se añadió anhídrido trifluoroacético (2,2 mL, 15,8 mmol) en DCM (15 mL) gota a gota durante 30 min. Después de la adición, la mezcla de reacción se agitó a 0 ºC durante 1 h. Después de este tiempo, los solventes se eliminaron a presión reducida para obtener un aceite amarillo oscuro. Este residuo se diluyó en DCM (100 mL), se lavó con ácido cítrico al 5%, $NaHCO_3$ sat. y salmuera, se secó sobre $MgSO_4$, se filtró y los solventes se eliminaron al vacío para obtener un aceite amarillo oscuro (2,6 g). El producto crudo se purificó por cromatografía en fase inversa para obtener el compuesto **47** en forma de un aceite amarillo (2,3 g, 87% de rendimiento). ^1H RMN

(400 MHz, $CDCl_3$) δ 4,46 (br s, 2 H), 4,01 (s, 3 H), 2,83 (br s, 3 H), 1,47 (s, 9 H). LCMS ES *m/z* 331/329 $[M+H]^+$ y 229/231 $[M\text{-}BOC]^+$ en forma de base iónica.

Preparación de ((4-bromo-5-metoxiisotiazol-3-il)metil)(metil)carbamato de *ter*-butilo (52).



Etapa 1:

Se añadió nitrito de *ter*-butilo (47,4 g, 0,46 mol) lentamente a una mezcla agitada de $CuBr_2$ (103 g, 0,46 mol) y CH_3CN (900 mL) a 0 °C durante 2 minutos. Después de agitar durante 5 minutos, la sal de HCl del compuesto **48** (35 g, 0,23 mol) se añadió en porciones en forma de un sólido durante 20 minutos. Durante la adición, se observó una ligera exotermia de 10 °C pero rápidamente desapareció con la adición completa del compuesto **48**. Después de la adición completa del compuesto **48**, la reacción se agitó mientras se calentaba lentamente hasta temperatura ambiente durante 20 minutos. Se añadió HCl (ac, 1 M, 2,5 L) lentamente con agitación (cierta frotación y escape de gas NO_2). La mezcla se extrajo en dietiléter (2 x 800 mL). Las capas orgánicas combinadas se lavaron con HCl (ac. 1 M, 2 x 1 L), luego salmuera (1 L), se secaron sobre Na_2SO_4 y el solvente se eliminó a presión reducida, para obtener el compuesto **49** en forma de un sólido amarillo/anaranjado (45 g, 76% de rendimiento). TLC: R_f = 0,75 (10% de EtOAc en heptanos). ^1H RMN (400 MHz, $CDCl_3$) δ 2,46 (s, 3 H). LCMS ES sin ionización detectada.

Etapa 2:

Una mezcla del compuesto **49** (45 g, 175 mmol), NBS (47 g, 265 mmol) y peróxido de dibenzoílo (70% en H_2O, 9,7 g, 40 mmol) en DCE (400 mL) se agitó a

reflujo durante 12 horas. La TLC (10% de DCM en heptanos) mostró aproximadamente el 50% de material de partida (R_f = 0,50) y 50% de producto (R_f = 0,55). Se añadió una porción adicional de NBS (10 g, 56 mmol) y la reacción se agitó a reflujo durante 6 horas. Después de enfriarla, la mezcla se filtró para eliminar succinimida y el filtrado se concentró. El residuo se purificó por cromatografía en columna en gel de sílice, que se eluyó con 5% de EtOAc en heptanos, para obtener 50 g de una mezcla inseparable que consiste en el material de partida **49**, el producto **50** y el subproducto de dibromometilo en una relación aproximada de 1:2,7:1, respectivamente. El compuesto **50** se obtuvo en 48% de rendimiento. ^{1}H RMN ($CDCl_3$, 400 MHz) δ 6,77 (s, 1 H, corresponde a subproducto de dibromometilo); 4,59 (s, 2 H, corresponde al compuesto **31**); 2,55 (s, 3 H, corresponde al material de partida **30**). LCMS ES sin ionización.

Etapa 3:

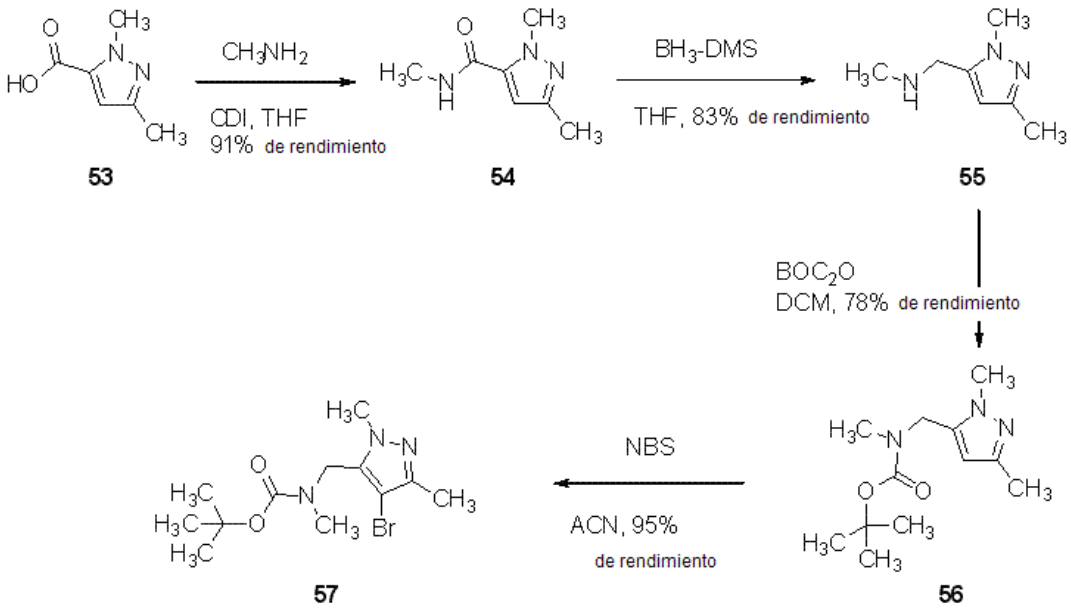
Una solución de la mezcla obtenida de la etapa 2 (50 g, calculada para contener 28 g, 83 mmol del compuesto puro **31**) en THF (20 mL) se añadió lentamente a una solución de CH_3NH_2 (33% en EtOH, 200 mL, 2,1 mol) diluida con EtOH adicional (200 mL) a 0 ºC durante 10 minutos. Después de completar la adición, la reacción se agitó a 0 ºC durante 25 minutos. La reacción luego se concentró al vacío hasta aproximadamente 300 mL de volumen. Se añadió etanol (150 mL) y la mezcla se concentró nuevamente hasta aproximadamente 300 mL en volumen. La solución resultante luego se enfrió hasta 0 ºC y se añadió $(BOC)_2O$ (33 g, 150 mmol) en porciones durante 5 minutos (evolución de CO_2). Después de completar la adición, la mezcla se dejó agitar a 20 ºC durante la noche. La mezcla de reacción se concentró al vacío y el residuo se purificó por cromatografía en columna en gel de sílice, que se eluyó con 10% de EtOAc en heptanos, para obtener el compuesto **51** en forma de un sólido de color crema (32 g, 97% de rendimiento). TLC (R_f = 0,30, 10% de EtOAc en heptanos). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,50 - 4,60 (m, 2 H), 2,90 - 2,99 (m, 3 H), 1,35 - 1,55 (m, 9 H). LCMS ES *m/z* 287 ES $[M\text{-}Boc]^+$.

Etapa 4:

Se añadió cuidadosamente litio (40 mg, 5,7 mmol) al metanol (6 mL), con agitación, en un recipiente de reacción equipado con un condensador de reflujo. Después de disolver el litio, se añadió el compuesto **51** (350 mg, 0,91 mmol), disuelto en metanol (2 mL), en una porción y la solución resultante se agitó a 60 ºC durante 20 horas. La TLC (10% de EtOAc en heptanos) mostró una nueva mancha mayor (R_f = 0,20), junto con aproximadamente 20% del compuesto **51** (Rf = 0,30) y trazas de otros

dos productos (R_f's = 0,25 y línea de base). Después de enfriarla, se añadió la reacción (que ahora contiene una suspensión) en agua (30 mL) y la mezcla se extrajo en EtOAc (20 mL). La capa orgánica se separó, se lavó con salmuera (20 mL), se secó sobre Na_2SO_4 y se evaporó. El residuo se purificó por cromatografía en columna en gel de sílice, que se eluyó con 10% de EtOAc en heptanos, para dar el compuesto **52** en forma de un aceite amarillo pálido (150 mg, 48% de rendimiento). TLC: R_f = 0,20 (10% de EtOAc en heptanos. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,40 - 4,55 (m, 2 H), 4,04 (s, 3 H), 2,85 - 2,95 (m, 3 H), 1,40 - 1,50 (m, 9 H). LCMS ES *m/z* 237/239 $[M – Boc]^+$.

Preparación de ((4-bromo-1,3-dimetil-1H-pirazol-5-il)metil)(metil)carbamato de *ter*-butilo (57).



Etapa 1:

Se añadió CDI (2,8 g, 17 mmol) a una suspensión del compuesto **53** (2,0 g, 14 mmol) en THF (25 mL) a 20 ºC. La mezcla luego se calentó hasta 50 ºC con agitación durante 30 min (evolución de gas). La mezcla luego se enfrió hasta -10 ºC y se añadió $MeNH_2$ (2 M en THF, 20 mL, 40,0 mmol) en una porción. El baño de hielo se eliminó y la reacción se agitó a temperatura ambiente durante 60 minutos. La mezcla luego se concentró y se purificó por cromatografía en columna en gel de sílice, que se eluyó con 100% de EtOAc, para obtener el compuesto **54** (2,0 g, 91% de rendimiento) en forma de un aceite claro. TLC: R_f = 0,60 (100% de EtOAc). ^{1}H RMN (400 MHz, $CDCl_3$) δ□2,23 (s, 3 H), 2,93 (d, 3 H), 4,09 (s, 3 H), 6,00 (br s, 1 H), 6,12 (s, 1 H). LCMS ES

m/z 154 $[M+H]^+$.

Etapa 2:

Se añadió BH_3·DMS (8,0 g, 105 mmol) lentamente a una solución del compuesto **54** (2,0 g, 13,0 mmol) en THF a -5 ºC. Después de completar la adición, la mezcla se agitó a 50 ºC durante 3 hrs, antes de enfriar y agitar a temperatura ambiente durante la noche. La reacción luego se enfrió hasta 0 ºC y se añadió HCl 6 M (30 mL) lentamente (se produjo frotación). Después de completar la adición, la mezcla se agitó a 70 ºC durante 30 mins, antes de enfriarla hasta 0 ºC y se alcalinizó con NaOH (solución acuosa al 30%) hasta pH 13 (papel de pH). La mezcla se concentró a presión reducida para eliminar THF y luego se extrajo en DCM (5 x 40 mL). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se evaporaron, lo que produjo el compuesto **55** (1,5 g, 83% de rendimiento). TLC: R_f = 0,20 (98% de EtOAc y 2% NH_3 7 M en MeOH). ^{1}H RMN (400 MHz, $CDCl_3$) δ 2,20 (s, 3 H), 2,40 (s, 3 H), 3,68 (s, 2 H), 3,78 (s, 3 H), 5,91 (s, 1 H).

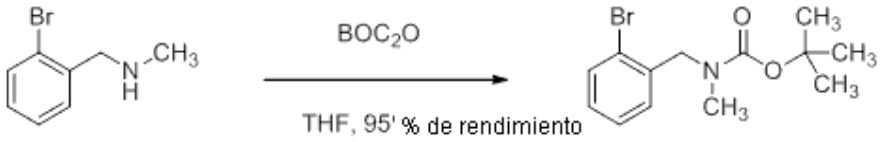
Etapa 3:

A una solución del compuesto **55** (1,5 g, 10,7 mmol) en DCM (30 mL) se añadió $(BOC)_2O$ (3,27 g, 15 mmol). La mezcla se agitó durante la noche, se concentró a presión reducida y el residuo se purificó por cromatografía flash en gel de sílice, que se eluyó con 30-50% de EtOAc en ciclohexano y produjo el compuesto **56** (2,0 g, 78% de rendimiento) en forma de un aceite incoloro. TLC: Rf = 0,50 (1:1 EtOAc/ciclohexano). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,48 (s, 9 H), 2,20 (s, 3 H), 2,78 (s, 3 H), 3,78 (s, 3 H), 4,61 (s, 2 H), 5,94 (s, 1 H).

Etapa 4:

El compuesto **56** (2,1 g, 8,8 mmol) se disolvió en acetonitrilo (31 mL), se añadió bicarbonato de sodio (0,88 g, 10 mmol) y la mezcla se enfrió hasta 0 ºC. Se añadió NBS (1,6 g, 9,2 mmol) y la mezcla de reacción se agitó durante 1 hora a ~5 ºC. La LCMS mostró el consumo del compuesto **56**. La mezcla de reacción se calentó hasta temperatura ambiente, se filtró y se concentró al vacío para producir un aceite amarillo. Se añadió MTBE y se observó un sólido blanco, que se filtró. Los licores madre se concentraron y se volvió a añadir MTBE. El sólido blanco formado se filtró y los licores madre se lavaron con una solución acuosa diluida de tiosulfato de sodio, agua, luego salmuera. La solución se secó sobre $MgSO_4$, se filtró y se concentró al vacío para dar el compuesto **57** en forma de un sólido blanco (2,7 g, 95% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,50 (s, 2 H), 3,79 (s, 3 H), 2,70 (s, 3 H), 2,20 (s, 3 H), 1,45 (s, 9 H). LCMS ES *m/z* 318/320 $[M+H]^+$.

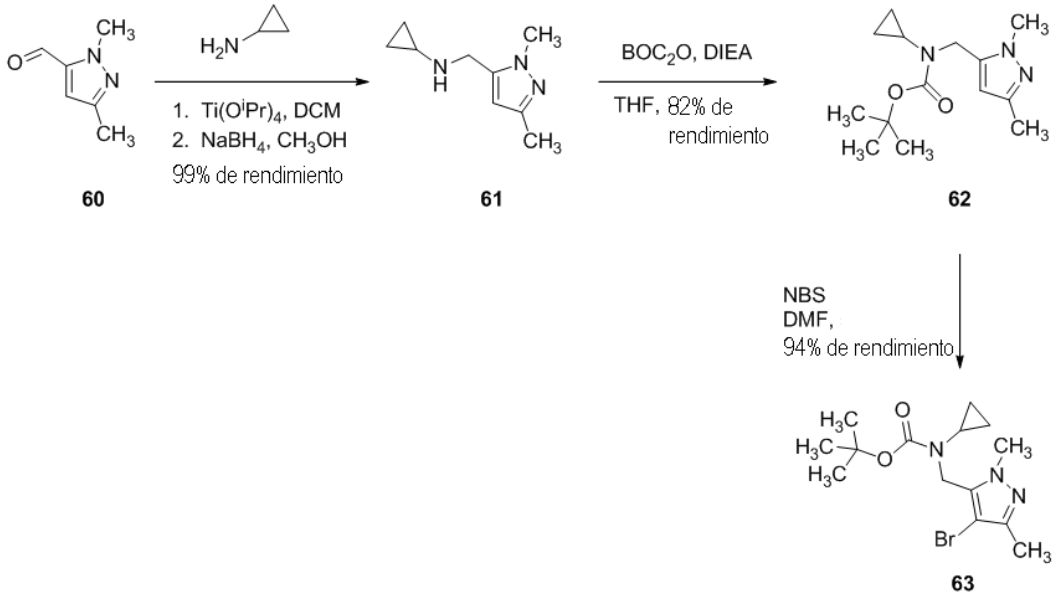
Preparación de 2-bromobencil(metil)carbamato de *ter*-butilo (59).



58 59

Una solución del compuesto **58** (2,0 g, 10,0 mmol) y Boc_2O (2,29 g, 10,5 mmol) en THF (40 mL) se agitó a temperatura ambiente durante 16 horas. La mezcla luego se concentró al vacío. El producto crudo se purificó por cromatografía flash en columna en gel de sílice, que se eluyó con 10% de EtOAc en heptanos y produjo el compuesto **59** en forma de un aceite incoloro (2,8 g, 95% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,54 (d, 1 H), 7,30 (t, 1 H), 7,13 (m, 2 H), 4,53 (br d, 2 H), 2,87 (br s, 3 H), 1,46 (br d, 9 H).

Preparación de ((4-bromo-1,3-dimetil-1H-pirazol-5-il)metil)(ciclopropil)carbamato de *ter*-butilo (63).



60 61 62 63

Etapa 1:

A una solución del compuesto **60** (1,00 g, 8,06 mmol) en DCM (80 mL) se añadió ciclopropilamina (0,850 mL, 12 mmol) ten Ti(O*i*-Pr)$_4$ (4,7 mL, 16 mmol). La solución se agitó a temperatura ambiente durante la noche, luego se añadió MeOH (20

mL) seguido de $NaBH_4$ (610 mg, 16 mmol) en porciones (producción de gas). La reacción se neutralizó con $NaHCO_3$ saturado, formando sólidos blancos. La mezcla se filtró a través de Celite, luego se extrajo el licor madre con EtOAc (2x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron para producir el compuesto **61** (1,38 g). ^{1}H RMN (400 MHz, DMSO-d_6) δ□5,88 (s, 1 H), 3,68 - 3,66 (m, 2 H), 3,65 (s, 3 H), 2,57 (br. s., 1 H), 2,07 (s, 3 H), 2,06 - 2,01 (m, 1 H), 0,40 - 0,30 (m, 2 H), 0,25 - 0,18 (m, 2 H).

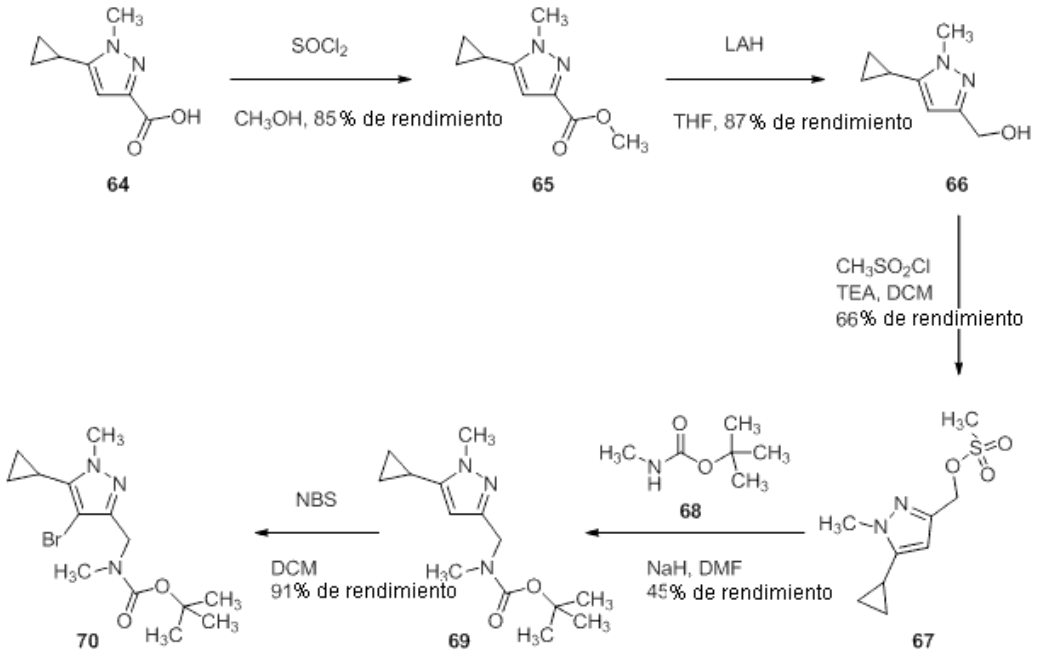
Etapa 2:

Una solución del compuesto **61** (1,33 g, 8,06 mmol), DIEA (2,81 mL, 16,1 mmol) y Boc_2O (2,64 g, 12,1 mL) en THF (27 mL) se agitó a temperatura ambiente durante 2 días. La solución se concentró y se purificó por cromatografía flash eluyendo con heptanos/EtOAc (0-50%) para obtener el compuesto **62** (1,75 g, 82% de rendimiento durante 2 etapas). ^{1}H RMN (400 MHz, DMSO-d_6) δ 5,85 (s, 1 H), 4,34 (s, 2 H), 3,68 (s, 3 H), 2,36 (br s, 1 H), 2,08 (s, 3 H), 1,40 (s, 9 H), 0,68 (d, J = 6,0 Hz, 2 H), 0,61 (br s, 2 H).

Etapa 3:

A una solución del compuesto **62** (1,75 g, 6,60 mmol) en DMF (44 mL) se añadió NBS (1,2 g, 6,6 mmol). Después de 1 hora, la solución se diluyó con EtOAc, se lavó con 50% de Na_2CO_3 saturado (2x) y salmuera, se secó ($MgSO_4$), se filtró y se concentró para dar el compuesto **63** en forma de una goma amarilla (2,14 g, 94% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 4,45 (s, 2 H), 3,73 (s, 3 H), 2,23 - 2,14 (m, 1 H), 2,09 (s, 3 H), 1,41 (s, 9 H), 0,70 - 0,52 (m, 4 H).

Preparación de ((4-bromo-5-ciclopropil-1-metil-1H-pirazol-3-il)metil)-(metil)carbamato de *ter*-butilo (70).



Etapa 1:

A una solución del compuesto **64** (2,9 g, 17,4 mmol) en metanol seco (100 mL) se vertió gota a gota $SOCl_2$ (20 mL) a 0 ºC. Después de la adición, la solución de reacción se agitó a temperatura ambiente durante 48 horas. La TLC (diclorometano/metanol 10/1) mostró que la reacción estaba completa. La mezcla de reacción se concentró al vacío y produjo un residuo que se disolvió con EtOAc (200 mL). La capa orgánica se lavó con $NaHCO_3$ saturada (100 mL x 3), salmuera (100 mL), se secó sobre Na_2SO_4, se concentró al vacío y produjo el compuesto **65** en forma de un aceite amarillo pálido (2,7 g, 85% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,63 (s, 1 H), 4,19 (s, 3 H), 4,12 (s, 3 H), 1,99 - 1,92 (m, 1 H), 1,27 - 1,23 (m, 2 H), 0,94 - 0,91 (m, 2 H).

Etapa 2:

A una mezcla de $LiAlH_4$ (0,85 g, 22,5 mmol) en THF seco (40 mL) se añadió gota a gota el compuesto **65** (2,7 g, 15 mmol) en THF (10 mL) a -10 ~ 0 ºC. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La TLC (éter de petróleo/EtOAc 1/1) mostró que la mezcla de reacción estaba completa. La reacción se neutralizó con 20% de NaOH acuoso (4 mL). La mezcla se filtró y el filtrado se concentró a presión reducida. El producto crudo se purificó por cromatografía flash sobre gel de sílice que se eluyó con éter de petróleo/EtOAc (3/1) y produjo el compuesto **66** en forma de un sólido blanco (2,3 g, 87% de rendimiento).

Etapa 3:

A una solución del compuesto **66** (2,5 g, 16,4 mmol) y Et_3N (2,48 g, 24,6 mmol) en DCM seco (100 mL) se añadió gota a gota MsCl (2,13 g, 18,1 mmol) a 0 ºC. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La TLC (éter de petróleo/EtOAc 3/1) mostró que la reacción estaba completa. La mezcla de reacción se lavó con agua (100 mL x 3), $NaHCO_3$ saturado (100 mL x 3), salmuera (100 mL), se secó sobre Na_2SO_4, se concentró al vacío y produjo el compuesto **67** en forma de un aceite rojo (2,5 g, 66% de rendimiento).

Etapa 4:

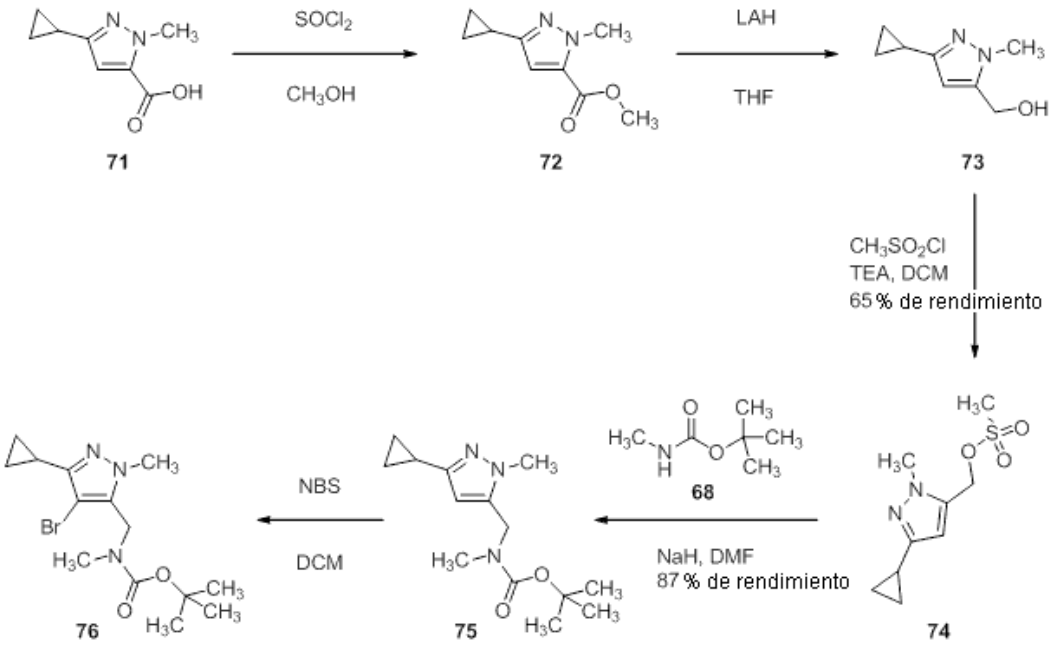
A una solución del compuesto **68** (2,8 g, 21,3 mmol) en DMF seca (40 mL) se añadió NaH (60% en aceite, 0,96 g, 121 mmol) a 0 ºC en pequeñas porciones. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 1 hora. Luego se añadió el compuesto **67** (2,5 g, 10,8 mmol) en DMF (10 mL) gota a gota al anión a 0 ºC. La mezcla resultante se agitó luego a temperatura ambiente durante la noche. Ninguno de los compuestos **67** fue detectado por TLC (éter de petróleo/EtOAc 3/1). La mezcla de reacción se vertió en agua helada (100 mL). La mezcla luego se extrajo con EtOAc (50 mL x 3). Los extractos orgánicos combinados se lavaron con salmuera (100 mL), se secaron sobre Na_2SO_4 y se concentraron a presión reducida. El producto crudo se purificó por flash cromatografía en columna en gel de sílice, que se eluyó con éter de petróleo/EtOAc (3/1) y produjo el compuesto **69** en forma de un sólido blanquecino (1,3 g, 45% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,32 (d, 1 H), 4,30 (s, 2 H), 3,84 (s, 3 H), 2,82 (s, 3 H), 1,62 - 1,54 (m, 1 H), 1,48 (s, 9 H), 0,96-0,94 (m, 2 H), 0,64 - 0,63 (m, 2 H).

Etapa 5:

A una solución del compuesto **69** (1,2 g, 4,14 mmol) en DCM (50 mL) se añadió incrementalmente NBS (0,77 g, 4,35 mmol) a 0 ºC. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. No se detectó el compuesto **69** por TLC (éter de petróleo/EtOAc 3/1). La mezcla de reacción se lavó con $NaHCO_3$ saturado (50 mL x 3), salmuera (100 mL), se secó sobre Na_2SO_4 y se concentró a presión reducida. El producto crudo se purificó por cromatografía en columna en gel de sílice que se eluyó con éter de petróleo/EtOAc (4/1) y produjo el compuesto **70** en forma de un aceite amarillo pálido (1,3 g, 91% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,35 - 4,33 (s, 2 H), 3,79 (s, 3 H), 2,71 (s, 3 H), 1,62 - 1,54 (m, 1 H), 1,41 (s, 9 H), 0,96 - 0,94 (m, 2 H), 0,80 - 0,78 (m, 2 H).

Preparación de ((4-bromo-3-ciclopropil-1-metil-1H-pirazol-5-

il)metil)(metil)carbamato de *ter*-butilo (76).



Etapa 1:

El procedimiento descrito en la etapa 1 para el compuesto **70** se usó para preparar el compuesto **72**. ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,43 (s, 1 H), 4,05 (s, 3 H), 3,78 (s, 3 H), 1,83 - 1,81 (m, 1 H), 0,87 - 0,83 (m, 2 H), 0,65 - 0,62 (m, 2 H).

Etapa 2:

El procedimiento descrito en la etapa 2 para el compuesto **70** se usó para preparar el compuesto **73**. ^{1}H RMN (400 MHz, $CDCl_3$) δ 5,87 - 5,77 (d, 1 H), 4,53 (s, 3 H), 3,74 - 3,71 (t, 3 H), 1,83 - 1,77 (m, 3 H), 1,60 (s, 1 H), 0,84 - 0,80 (m, 2 H), 0,61 - 0,57 (m, 2 H).

Etapa 3:

El procedimiento descrito en la etapa 2 para el compuesto **70** se usó para preparar el compuesto **74** (1,7 g, 65% de rendimiento).

Etapa 4:

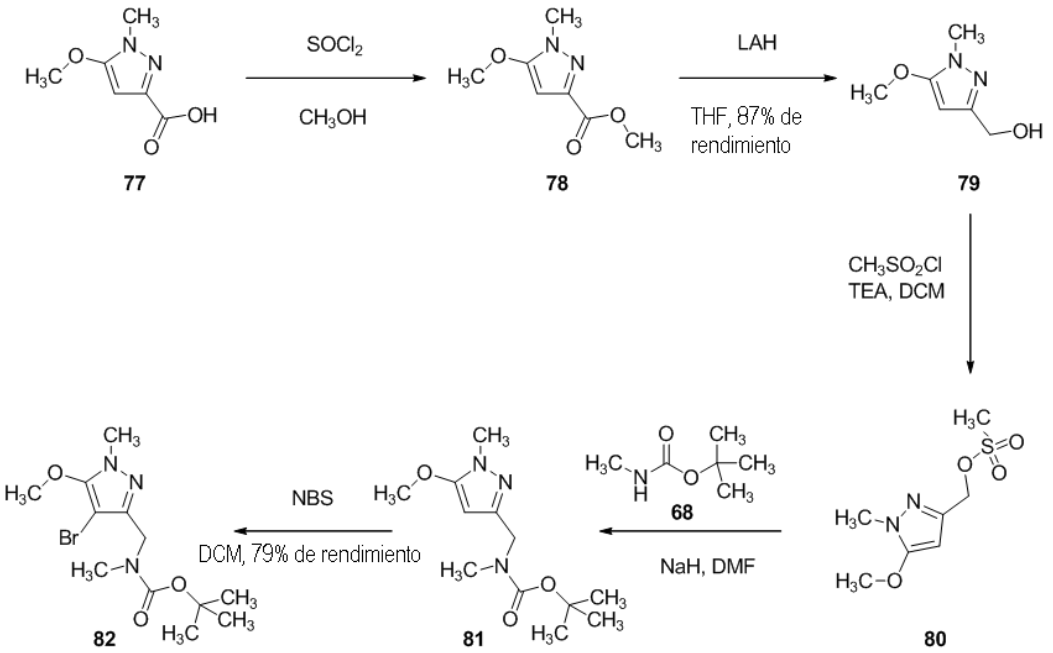
El procedimiento descrito en la etapa 4 para el compuesto **70** se usó para preparar el compuesto **75** (1,6 g, 87% de rendimiento).

Etapa 5:

El procedimiento descrito en la etapa 5 para el compuesto **70** se usó para preparar el compuesto **76**. ^{1}H RMN (400 MHz, $CDCl_3$) δ□4,43 (s, 2 H), 4,06 - 4,04 (s, 3

H), 2,66 (s, 3 H), 1,77 - 1,76 (m, 1 H), 1,41 (s, 9 H), 0,83 - 0,79 (m, 4 H).

Preparación de ((4-bromo-5-metoxi-1-metil-1H-pirazol-3-il)metil)(metil)carbamato de *ter*-butilo (82).



Etapa 1:

El procedimiento descrito en la etapa 1 para el compuesto **70** se usó para preparar el compuesto **78**. ^{1}H RMN (400 MHz, $CDCl_3$) δ□6,08 (s, 1 H), 3,94 - 3,92 (m, 6 H), 3,75 - 3,72 (m, 3 H).

Etapa 2:

El procedimiento descrito en la etapa 2 para el compuesto **70** se usó para preparar el compuesto **79** (0,6 g, 87% de rendimiento).

Etapa 3:

El procedimiento descrito en la etapa 3 para el compuesto **70** se usó para preparar el compuesto **80**.

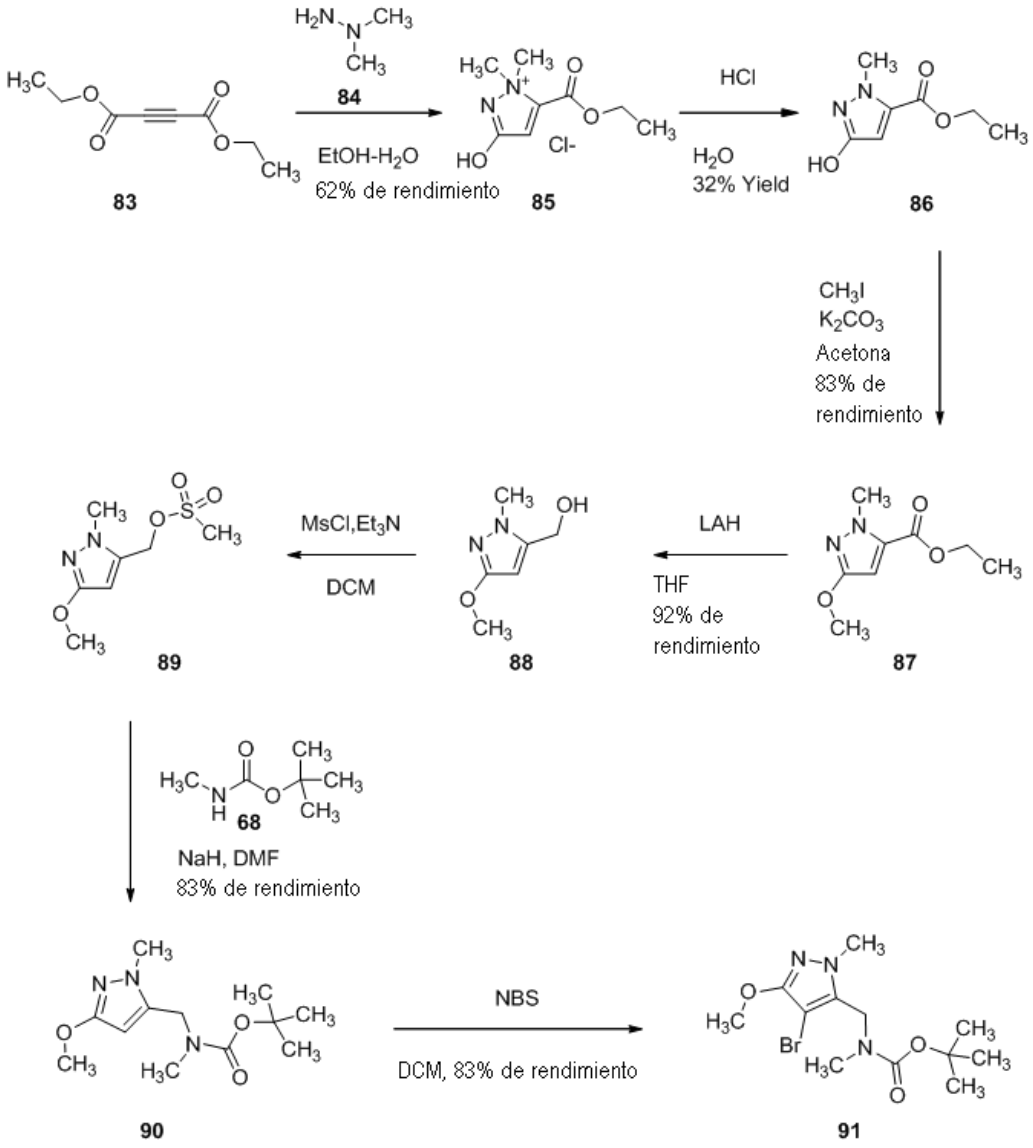
Etapa 4:

El procedimiento descrito en la etapa 4 para el compuesto **70** se usó para preparar el compuesto **81.** ^{1}H RMN (400 MHz, $CDCl_3$) δ 5,47 (s, 1 H), 4,27 (s, 2 H), 3,83 (s, 3 H), 3,57 (s, 3 H), 2,82 (s, 3 H), 1,48 (s, 9 H).

Etapa 5:

El procedimiento descrito en la etapa 5 para el compuesto **70** se usó para preparar el compuesto **82** (3,9 g, 79% de rendimiento). LCMS *m/z* 333 $[M+H]^+$.

Preparación de ((4-bromo-3-metoxi-1-metil-1H-pirazol-5-il)metil)(metil)-carbamato de *ter*-butilo (91).



Etapa 1:

A una mezcla del compuesto **83** (10,7 mL, 0,067 mol) en 1:1 EtOH/ H_2O (120 mL) se añadió lentamente a 0 ºC una solución del compuesto **84** (7,72 g, 0,08 mol) y NaOH (3,2 g, 0,08 mol) en 1:1 EtOH/ H_2O (40 mL). La solución se agitó a 0 ºC durante 30 min y se calentó hasta temperatura ambiente durante 1 hora. La mezcla se concentró y el residuo se dividió en agua (100 mL) y EtOAc (100 mL). La capa acuosa se concentró y produjo el compuesto **85** en forma de un aceite marrón (7,6 g, 62% de

rendimiento).

Etapa 2:

Una mezcla del compuesto **85** (7,6 g, 41 mmol) en HCl 1 N (75 mL) se agitó a temperatura ambiente durante 1,5 horas. La mezcla se extrajo con DCM (50 mL), la capa acuosa se concentró y produjo un residuo. El producto crudo se purificó por cromatografía flash en gel de sílice, que se eluyó con éter de petróleo / EtOAc 6:1) y produjo el compuesto **86** en forma de un sólido blanco (2,2 g, 32% de rendimiento).

Etapa 3:

Una mezcla del compuesto **86** (1,6 g, 9,1 mmol), K_2CO_3 (3,7 g, 27,5 mmol) y yoduro de metilo (6,5 g, 46 mmol) se calentó a reflujo durante 3 horas. La TLC (éter de petróleo / EtOAc = 6:1) mostró que la reacción estaba completa. La mezcla se filtró y el filtrado se concentró para obtener un residuo. El producto crudo se purificó por cromatografía flash en gel de sílice, que se eluyó con éter de petróleo / EtOAc (20:1) y produjo el compuesto **87** en forma de un aceite amarillo (1,4 g, 83% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,18 (s, 1 H), 4,30 (q, 2 H), 4,05 (s, 3 H), 3,83 (s, 3 H), 1,36 (t, 3 H).

Etapa 4:

El procedimiento descrito en la etapa 2 para el compuesto **70** se usó para preparar el compuesto **88** (1,0 g, 92% de rendimiento).

Etapa 5:

El procedimiento descrito en la etapa 3 para el compuesto **70** se usó para preparar el compuesto **89**.

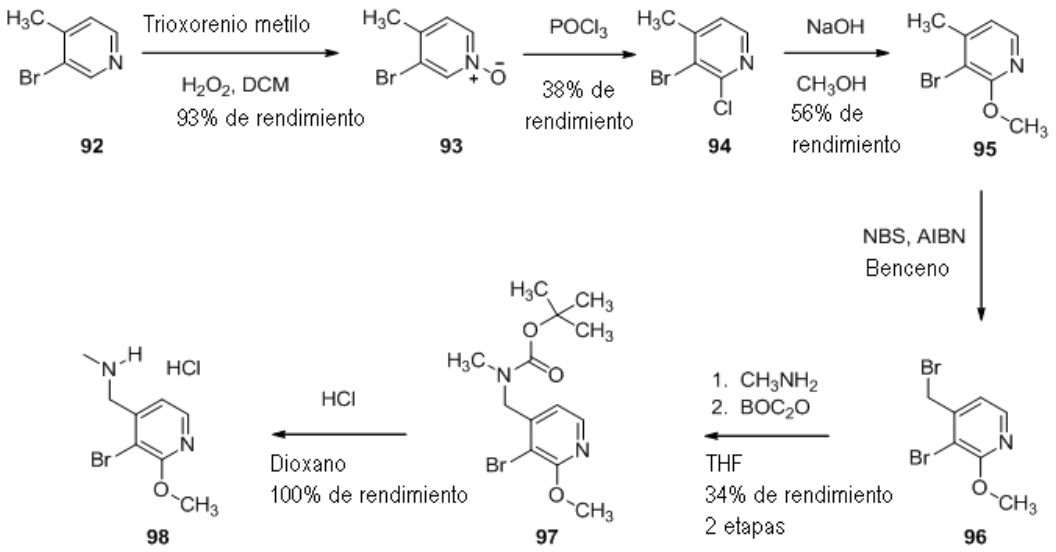
Etapa 6:

El procedimiento descrito en la etapa 4 para el compuesto **70** se usó para preparar el compuesto **90** (1,5 g, 83% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 5,57 (s, 1 H), 4,36 (s, 2 H), 3,84 (s, 3 H), 3,67 (s, 3 H), 2,77 (s, 3 H), 1,47 (s, 9 H).

Etapa 7:

El procedimiento descrito en la etapa 5 para el compuesto **70** se usó para preparar el compuesto **91** (1,3 g, 83% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,47 (s, 2 H), 3,93 (s, 3 H), 3,75 (s, 3 H), 2,73 (s, 3 H), 1,32 (s, 9 H). LCMS *m/z* 335 $[M+H]^+$.

Preparación de 1-(3-bromo-2-metoxipiridin-4-il)-N-metilmetanamina (98)



Etapa 1:

A una solución del compuesto **92** (5,0 g, 29 mmol) en DCM (15 mL) se añadió trioxorenio de metilo (73 mg, 0,29 mmol) seguido de H_2O_2 (50% en agua, 3,6 mL, 58 mmol). La mezcla bifásica amarilla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con agua y se extrajo con DCM (2x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron para producir el compuesto **93** en forma de un sólido blanco (5,1 g, 93% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,53 (s, 1 H), 8,15 (d, J = 6,5 Hz, 1 H), 7,40 (d, J = 6,5 Hz, 1 H), 2,35 - 2,27 (m, 3 H).

Etapa 2:

El compuesto **93** (4,0 g, 21 mmol) se añadió en porciones al $POCl_3$ puro (14 mL) a 0 ºC dando como resultado una suspensión. El baño de hielo se retiró y la mezcla de reacción se calentó hasta 70 ºC durante la noche. La mayor parte del $POCl_3$ se eliminó al vacío. Se añadió hielo lentamente al residuo seguido de la adición cuidadosa de Na_2CO_3 1 N. Una vez completa la liberación de CO_2, la solución se extrajo con EtOAc (3x). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron. El producto crudo se purificó por cromatografía flash sobre gel de sílice que se eluyó con heptanos/EtOAc (0-20%) para obtener el compuesto **94** en forma de un sólido blanco (1,65 g, 38% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,27 (d, J = 4,8 Hz, 1 H), 7,42 (d, J = 4,8 Hz, 1 H), 2,48 - 2,38 (m, 3 H).

Etapa 3:

En un tubo sellado, se añadió NaOMe (25% en MeOH, 3,1 mL, 13 mmol) a una

solución del compuesto **94** (1,8 g, 8,7 mmol) en MeOH (17 mL). La reacción se calentó hasta 75 ºC durante 3 días. La mezcla de reacción se enfrió hasta temperatura ambiente, se diluyó con EtOAc, se lavó con NH_4Cl saturado y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El producto crudo se purificó por cromatografía flash en gel de sílice, que se eluyó con heptanos/EtOAc (0-15%) para obtener el compuesto **95** en forma de un aceite claro (991 mg, 56% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,00 (d, J = 5,0 Hz, 1 H), 6,98 (d, J = 4,8 Hz, 1 H), 3,90 (s, 3 H), 2,35 (s, 3 H).

Etapa 4:

A una solución del compuesto **95** (990 mg, 4,9 mmol) en benceno (33 mL) se añadió NBS (870 mg, 4,9 mmol) y luego AIBN (40 mg, 0,25 mmol). La mezcla se colocó en un baño de aceite de 80 ºC. Después de seis horas, la reacción se diluyó con EtOAc, se lavó con Na_2CO_3 1 M y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El producto crudo se purificó por cromatografía flash eluyendo con heptanos/EtOAc (0-10%) para obtener el compuesto **96** en forma de un aceite (669 mg, 70% puro por RMN). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,14 (d, J = 5,0 Hz, 1 H), 7,22 (d, J = 5,0 Hz, 1 H), 4,68 (s, 2 H), 3,93 (s, 3 H).

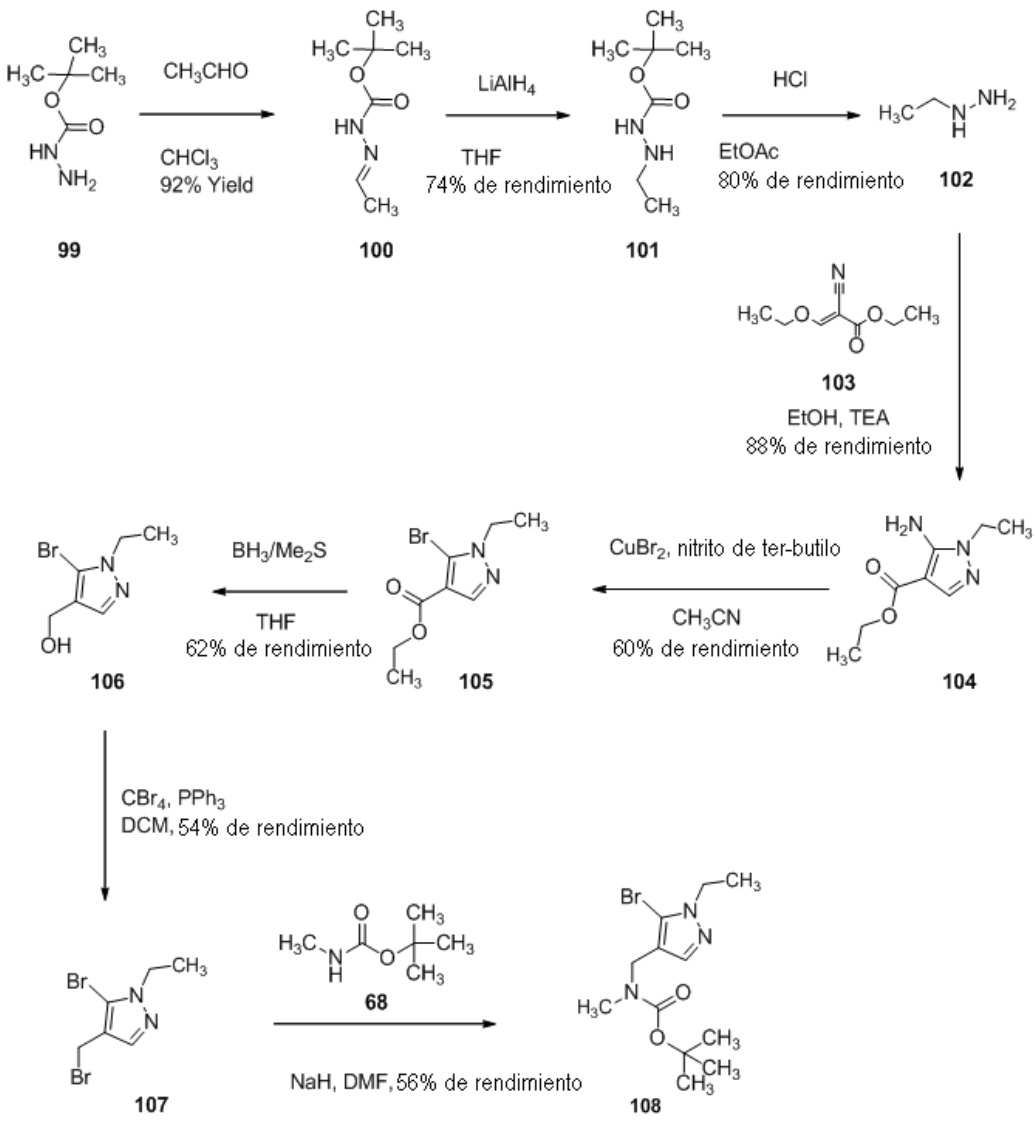
Etapa 5:

A una solución del compuesto **96** (665 mg, 70% puro) en THF (12 mL) se añadió metilamina (2 M en THF, 3,5 mL, 6,9 mmol). Después de 2 horas, se añadió Boc_2O (1,5 g, 6,9 mmol). Después de otras 2 horas, la reacción se diluyó con EtOAc, se lavó con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El producto crudo se purificó por cromatografía flash eluyendo con heptanos/EtOAc (0-20%) para obtener el compuesto **97** en forma de una goma clara (552 mg, 34% durante 2 etapas). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,13 (d, J = 5,0 Hz, 1 H), 6,71 (br s, 1 H), 4,42 (s, 2 H), 3,93 (s, 3 H), 2,87 (s, 3 H), 1,56 - 1,16 (m, 9 H).

Etapa 6:

A una solución enfriada (0 ºC) del compuesto **97** (530 mg, 1,6 mmol) en DCM (8,0 mL) se añadió HCl (4 N en dioxano, 8 mL). El baño de hielo se eliminó y se formó un precipitado blanco. Una vez completa por LCMS, la mezcla se concentró para obtener el compuesto **98** en forma de un sólido blanco (cuantitativo).

Preparación de ((5-bromo-1-etil-1H-pirazol-4-il)metil)(metil)carbamato de *ter*-butilo (108).



Etapa 1:

A una solución agitada del compuesto **99** (145 g, 1,1 mol) en $CHCl_3$ (1,4 L) se añadió gota a gota MeCHO (40% en agua, 500 g, 4,5 mol) a temperatura ambiente. Después de la adición, la reacción se agitó a temperatura ambiente durante 24 horas. La TLC (éter de petróleo/EtOAc = 1/1) mostró que la reacción estaba completa. La mezcla de reacción se filtró y el filtrado se concentró al vacío para obtener el compuesto **100** en forma de un aceite amarillo claro (160 g, 92% de rendimiento).

Etapa 2:

A una suspensión agitada de $LiAH_4$ (22,5 g, 0,505 mol) en THF seco (1 L) se añadió gota a gota una solución del compuesto **100** (80 g, 0,505 mol) a -10 ºC.

Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La TLC (éter de petróleo/EtOAc = 3/1) mostró que la mezcla de reacción estaba completa. La mezcla de reacción se neutralizó con NH_4Cl saturado (100 mL) a menos de 0 ºC, se vertió EtOAc (500 mL) en la reacción anterior y se agitó durante 10 minutos. La mezcla de reacción se filtró y el filtrado se lavó con salmuera (100 mL x 3), se secó sobre Na_2SO_4, se concentró al vacío y produjo un residuo, que se purificó por cromatografía en columna (en gel de sílice éter de petróleo/EtOAc 20/1~10/1) para obtener el compuesto **101** en forma de un aceite incoloro (60 g, 74% de rendimiento).

Etapa 3:

A una solución agitada del compuesto **101** (60 g, 0,375 mol) en EtOAc (100 mL) se añadió gota a gota HCl 4 N en EtOAc (200 mL) a 0 ºC. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 10 horas. La TLC (éter de petróleo/EtOAc = 3/1) mostró que la reacción estaba completa. La mezcla de reacción se filtró, la torta se recolectó y se secó a presión reducida para obtener el compuesto **102** en forma de un sólido blanco (40 g, 80% de rendimiento).

Etapa 4:

Una mezcla del compuesto **102** (40 g, 0,3 mol) y compuesto **103** (56 g, 0,33 mol) y TEA (105 mL, 0,76 mol) en EtOH (500 mL) se calentó a reflujo durante 24 horas. La TLC (éter de petróleo/EtOAc = 3/1) mostró que la reacción estaba completa. La mezcla de reacción se concentró al vacío para obtener un residuo, que se diluyó con EtOAc (500 mL). La solución se lavó con salmuera (100 mL x 3), se secó sobre Na_2SO_4 y se concentró al vacío para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice, que se eluyó con éter de petróleo/EtOAc (10/1~3/1) para obtener el compuesto **104** en forma de un sólido blanco (48 g, 88% de rendimiento).

Etapa 5:

A una solución agitada de nitrito de *ter*-butilo (35 mL, 0,31 mol) y $CuBr_2$ (56,3 g, 0,252 mol) en CH_3CN (1 L) se añadió gota a gota una solución del compuesto **104** (38 g, 0,21 mol) a 0 ºC. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La TLC (éter de petróleo/EtOAc = 3/1) mostró que la reacción estaba completa. La mezcla de reacción se vertió en HCl acuoso 6 N (400 mL) y se extrajo con DCM (200 mL x 3). Las capas orgánicas combinadas se lavaron con salmuera (100 mL x 3), se secaron sobre Na_2SO_4 y se concentraron al vacío para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice, que se eluyó con éter de petróleo/EtOAc (20/1~1/1) para obtener el compuesto

105 en forma de un aceite amarillo claro (35 g, 60% de rendimiento).

Etapa 6:

A una solución agitada del compuesto **105** (20 g, 81 mmol) en THF seco (200 mL) se añadió gota a gota BH_3/Me_2S (1 N, 81 mL, 0,81 mol) a 0 °C. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 1 hora y luego se calentó a reflujo durante 4 horas. La TLC (éter de petróleo/EtOAc = 3/1) mostró que la reacción estaba completa. La mezcla de reacción se neutralizó con NH_4Cl (100 mL) saturado acuoso a 0 °C. La mezcla se filtró y el filtrado se extrajo con EtOAc (100 mL x 3). Las capas orgánicas combinadas se lavaron con salmuera (50 mL x 3), se secaron sobre Na_2SO_4 y se concentraron al vacío para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice, que se eluyó con éter de petróleo/EtOAc (6/1~3/1) para obtener el compuesto **106** en forma de un aceite amarillo claro (10 g, 62% de rendimiento).

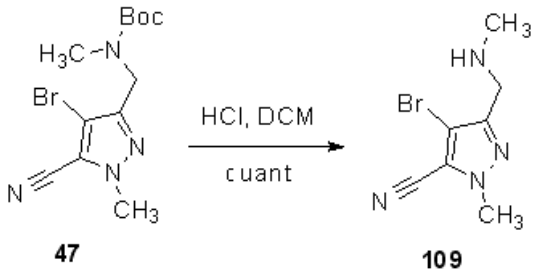
Etapa 7:

A una solución agitada del compuesto **106** (10 g, 48,8 mmol) y PPh_3 (15,4 g, 58,5 mmol) en DCM seco (200 mL) se añadió gota a gota una solución de CBr_4 (19,3 g, 58,8 mmol) en DCM a 0 °C. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 24 horas. La TLC (éter de petróleo/EtOAc = 3/1) mostró que la reacción estaba completa. La mezcla de reacción se concentró al vacío para dar un residuo, que se purificó por cromatografía en columna en gel de sílice, que se eluyó con éter de petróleo/EtOAc (50/1~10/1) para dar el compuesto **107** en forma de un sólido blanco (7,0 g, 54% de rendimiento).

Etapa 8:

El procedimiento descrito en la etapa 4 para el compuesto **70** se usó para preparar el compuesto **108** en forma de un aceite incoloro (4,8 g, 56% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ 7,53 (s, 1 H), 4,28 - 4,25 (m, 2 H), 4,23 (d, 2 H), 2,83 (s, 3 H), 1,50 (s, 9 H), 1,44 - 1,38 (m, 3 H). LCMS *m/z* 318/320 $[M+H]^+$.

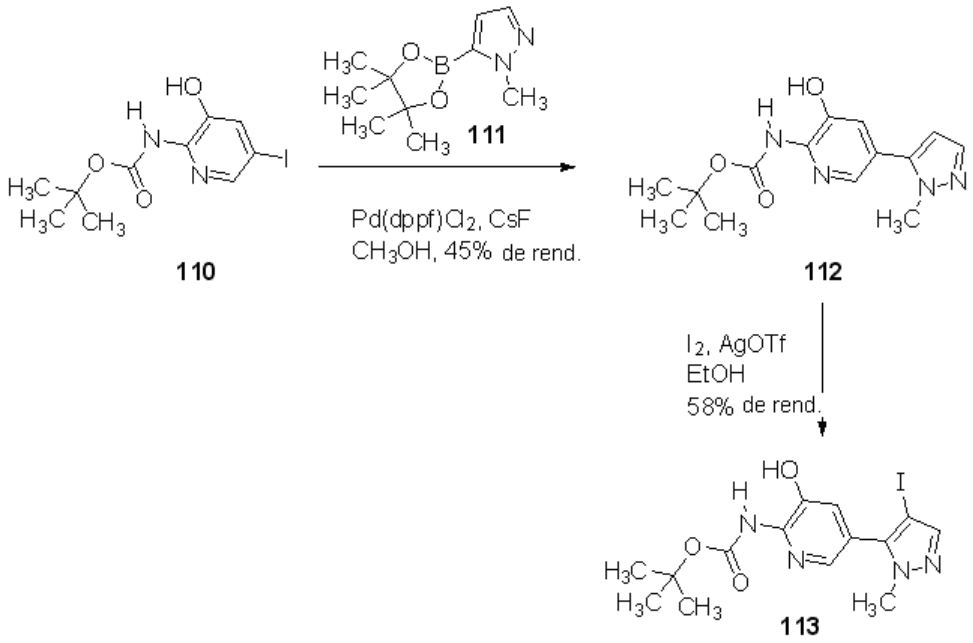
Preparación de 4-bromo-1-metil-3-[(metilamino)metil]-1*H*-pirazol-5-carbonitrilo (109)



47 109

A una solución a 0 ºC del **compuesto 47** (1,0 g, 3,0 mmol) en DCM (15 mL) se añadió HCl 4 N en dioxano (3,8 mL, 15 mmol). Se agitó a temperatura ambiente durante 3 horas y luego se concentró al vacío para obtener el **compuesto 109** (810 mg, cuantitativo) en forma de un sólido blanco.

Preparación de (3-hidroxi-5-(4-yodo-1-metil-1H-pirazol-5-il)piridin-2-il)carbamato de ter-butilo (113).



110 111 112 113

Etapa 1:

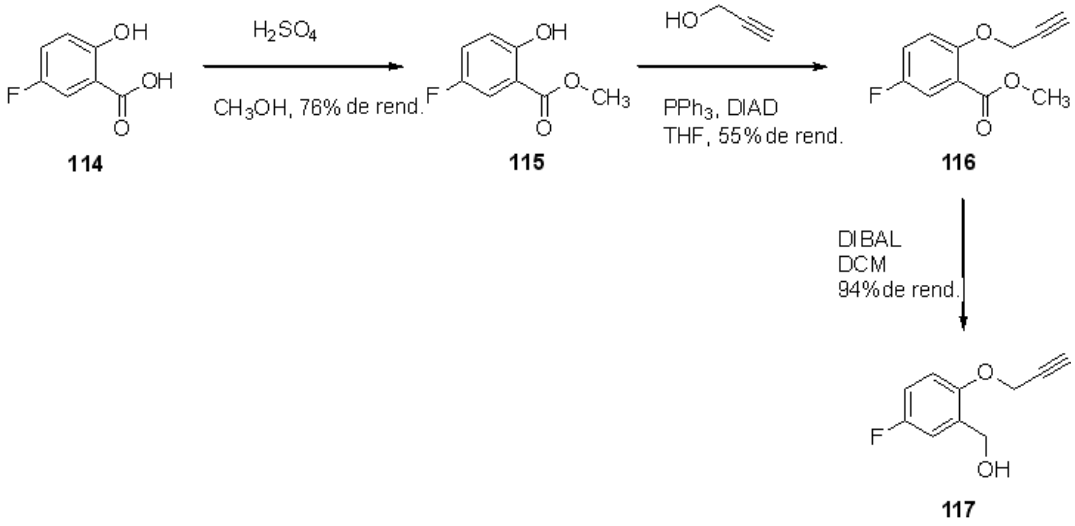
A una mezcla de **compuesto 110** y **compuesto 111** en MeOH se añadió CsF 2 M en agua. La mezcla se burbujeó con nitrógeno durante 5 minutos, y luego se añadió $PdCl_2$dppf 1:1 con CH_2Cl_2. La reacción se calentó a 60 ºC durante la noche, luego se diluyó con EtOAc, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró. El producto crudo se purificó por cromatografía flash eluyendo con heptanos/EtOAc (0-75%). Las fracciones que contenían el producto deseado se concentraron y el producto se fracturó usando DCM/Et_2O para obtener el **compuesto**

112 (960 mg, 45% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ □1,46 (s, 9 H) 3,85 (s, 3 H) 6,44 (s, 1 H) 7,31 (s, 1 H) 7,48 (s, 1 H) 7,99 (s, 1 H) 9,02 (s, 1 H) 10,12 (s, 1 H).

Etapa 2:

A una mezcla de **compuesto 112** (960 mg, 3,3 mmol) y AgOTf (850 mg, 3,3 mmol) en EtOH (30 mL) se añadió una solución de I_2 (0,25 M en EtOH, 13 mL, 3,31 mmol). Después de 1 hora, se añadieron más AgOTf (425 mg, 1,66 mmol) e I_2 (0,25 M en EtOH, 6,6 mL, 1,66 mmol). Una vez que la LCMS mostró que la reacción estaba completa, la mezcla se filtró y el licor madre se diluyó con EtOAc, se lavó con $Na_2CO_3$1 N, $Na_2S_2O_3$ saturado/agua y salmuera. Las capas acuosas combinadas se neutralizaron con HCl 4 N y se extrajeron con DCM (2x). Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron. El producto crudo se purificó por cromatografía flash en gel de sílice, que se eluyó con heptanos/EtOAc (0-100%) y produjo el **compuesto 113** en forma de un sólido crema (800 mg, 58% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,47 (s, 9 H), 3,80 (s, 3 H), 7,25 (d, J = 2,0 Hz, 1 H), 7,63 (s, 1 H), 7,89 (d, J = 2,0 Hz, 1 H), 9,02 (s, 1 H), 10,28 (br s, 1 H).

Preparación de (5-fluoro-2-(prop-2-in-1-iloxi)fenil)metanol (117).



Etapa 1:

A una solución de **compuesto 114** (2,5 g, 16 mmol) en metanol (32 mL) se añadió ácido sulfúrico (2,0 mL, 21 mmol). La solución se calentó a reflujo durante la noche, se enfrió hasta temperatura ambiente y se concentró. El residuo se disolvió en EtOAc, se lavó con $NaHCO_3$ saturado (3x) y salmuera, se secó ($MgSO_4$), se filtró y se concentró para obtener el **compuesto 115** en forma de un sólido crema (2,1 g, 76%

de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,89 (s, 3 H), 7,01 (dd, *J* = 9,1, 4,5 Hz, 1 H), 7,40 (td, *J* = 8,6, 3,2 Hz, 1 H), 7,45 - 7,54 (m, 1 H), 10,28 (s, 1H).

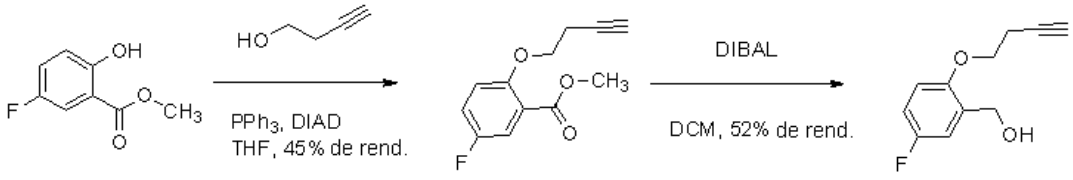
Etapa 2:

A una solución de **compuesto 115** (2,1 g, 12 mmol), alcohol propargílico (830 µL, 14 mmol) y trifenilfosfina (4,8 g, 18 mmol) en THF (31 mL) se añadió TEA (1,7 mL, 12 mmol) seguido de DIAD (3,7 mL, 18 mmol). La solución se agitó a temperatura ambiente durante la noche y se concentró. El residuo se purificó por cromatografía flash eluyendo con heptanos/EtOAc (0-30%) para obtener el **compuesto 116** en forma de un sólido tipo aguja (1,4 g, 55% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,51 - 3,64 (m, 1 H), 3,80 (s, 3 H), 4,86 (d, *J* = 2,3 Hz, 2 H), 7,25 (dd, *J* = 9,1, 4,3 Hz, 1 H), 7,38 - 7,55 (m, 2 H).

Etapa 3:

A una solución enfriada (-78 ºC) del **compuesto 116** (1,4 g, 6,7 mmol) en DCM (34 mL) se añadió DiBAL (1 M en hexanos, 18,5 mL, 18,5 mmol) gota a gota por medio de una bomba de jeringa a ~1 mL/min. La reacción se neutralizó con MeOH (10 mL) a -78 ºC. El baño de hielo seco se retiró, luego se añadió tartrato de sodio y potasio saturado (40 mL) y la mezcla de reacción se diluyó con EtOAc (50 mL). La mezcla se agitó a temperatura ambiente durante 2 horas, luego se diluyó con EtOAc, se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró para obtener el **compuesto 117** en forma de un aceite claro (1,1 g, 94% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,55 (t, *J* = 2,4 Hz, 1 H), 4,48 (d, *J* = 5,8 Hz, 2 H), 4,79 (d, *J* = 2,3 Hz, 2 H), 5,20 (t, *J* = 5,7 Hz, 1 H), 7,03 (dd, *J* = 6,2, 1,6 Hz, 2 H), 7,13 - 7,21 (m, 1 H).

Preparación de (2-(but-3-in-1-iloxi)-5-fluorofenil)metanol (120).



118 **119** **120**

Etapa 1:

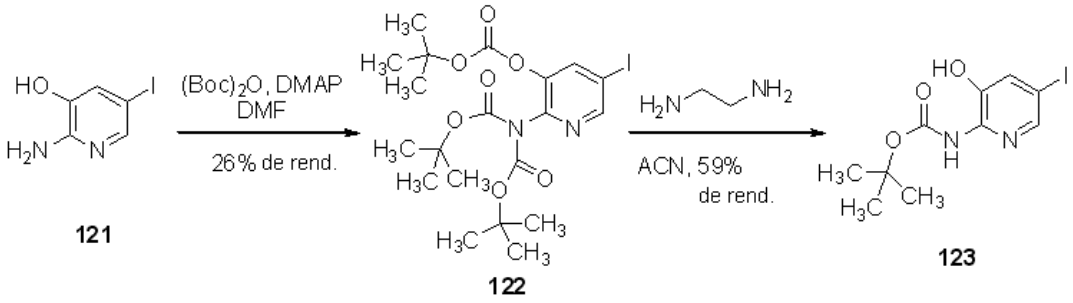
El procedimiento descrito en la etapa 2 para el **compuesto 117** se usó para preparar el **compuesto 119** (13 g, 45% de rendimiento).

Etapa 2:

El procedimiento descrito en la etapa 3 para el **compuesto 117** se usó para preparar el **compuesto 120** (13 g, 52% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6)

δ 7,20 - 7,17 (m, 1 H), 7,05 - 6,96 (m, 2 H), 5,20 (t, 1 H), 4,54 (t, 2 H), 4,08 (t, 2 H), 2,90 (t, 1 H), 2,66 - 2,62 (m, 2 H). LCMS *m/z* 176 $[M - OH]^+$.

Preparación de éster ter-butílico del ácido (3-Hidroxi-5-yodo-piridin-2-il)-carbámico (123)



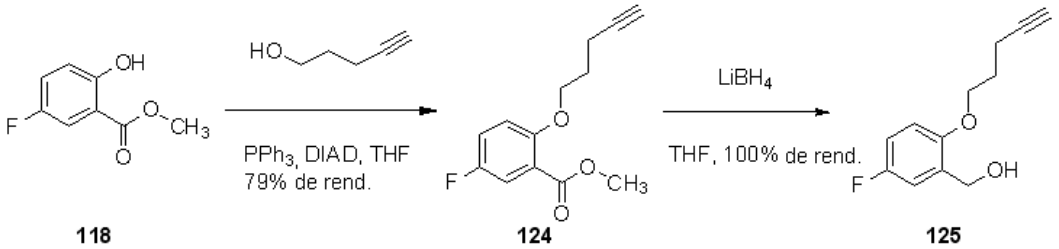
Etapa 1:

Una mezcla de 2-amino-5-yodopiridin-3-ol **compuesto 121** (623 mg, 2,64 mmol), 4-dimetaminopiridina (64,5 mg, 0,528 mmol) y bicarbonato de di-ter-butilo (1,73g, 7,92 mmol) en DMF (7,5 mL) se agitó a temperatura ambiente durante la noche. La mezcla se diluyó con EtOAc, se lavó con bicarbonato acuoso saturado (2x) y salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró hasta sequedad. El residuo se purificó por cromatografía flash (cartucho ISCO 40 g) usando un gradiente de 0-35% de EtOAC/heptano como eluyente para obtener el **compuesto 122** (372 mg, 26,3%) en forma de una goma. ^{1}H RMN (400 MHz, DMSO-*d*6) δ ppm 8,62 (d, *J*=1,77 Hz, 1 H) 8,36 (d, *J*=1,77 Hz, 1 H), 1,48 (2, 9H), 1,39 (s, 18 H).

Etapa 2:

Una mezcla de **compuesto 122** (106 mg, 0,98 mmol) y N,N-dietilendiamina (30,6 µL, 0,218 mmol)) en acetonitrilo (1 mL) se agitó a temperatura ambiente durante 5 h. El material de partida aún era evidente por LCMS. Se añadió más N,N-dietilendiamina (28 µL, 0,198 mmol). Después de agitar a temperatura ambiente durante 1 h más, la LCMS indicó que la reacción estaba completa. La mezcla se concentró hasta sequedad y el residuo se purificó por cromatografía flash usando un gradiente de 0-50% de diclorometano/heptano como eluyente para obtener el **compuesto 123** en forma de un sólido blanco en 59% de rendimiento. ^{1}H RMN (400 MHz, DMSO-*d*6) δ ppm 10,29 (br. s., 1 H), 8,83 (s, 1 H), 8,00 (d, *J*=1,52 Hz, 1 H), 7,48 (d, *J*=1,77 Hz, 1 H), 1,43 (s, 9 H).

Preparación de (5-fluoro-2-(pent-4-in-1-iloxi)fenil)metanol (125).



118 **124** **125**

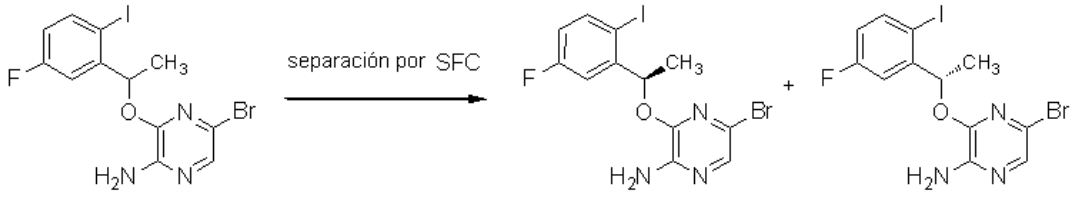
Etapa 1:

El procedimiento descrito en la etapa 2 para el **compuesto 117** se usó para preparar el **compuesto 124** (10,0 g, 79% de rendimiento).

Etapa 2:

A una solución agitada de **compuesto 124** (9,0 g, 38,1 mmol) en THF seco (180 mL) se añadió en porciones $LiBH_4$ (2,1 g, 95,2 mmol) a 0 °C bajo nitrógeno. Después de la adición, la mezcla se agitó a 50 °C durante 5 horas. La TLC (éter de petróleo/EtOAc = 6: 1) indicó que la reacción estaba completa. La mezcla se enfrió hasta 0 °C y se añadió agua (50 mL) gota a gota. La capa acuosa se extrajo con EtOAc (150 mL × 2). Los extractos orgánicos combinados se lavaron con salmuera (150 mL × 2), se secaron sobre Na_2SO_4 y se concentraron para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice (éter de petróleo / EtOAc = 15:1) para obtener el **compuesto 125** en forma de un aceite amarillo (9,0 g, 100% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,22 - 7,19 (m, 1 H), 7,08 - 6,98 (m, 2 H), 5,23 (t, 1 H), 4,55 (t, 2 H), 4,08 (t, 2 H), 2,88 (t, 1 H), 2,40 - 2,38 (m, 2 H), 1,97 - 1,91 (m, 2 H). LCMS *m/z* 191 $[M - OH]^+$.

Separación SFC de 5-bromo-3-[1-(5-fluoro-2-yodofenil)etoxi]pirazin-2-amina (30) en 5-bromo-3-[(1*R*)-1-(5-fluoro-2-yodofenil)etoxi]pirazin-2-amina (126) y 5-bromo-3-[(1*S*)-1-(5-fluoro-2-yodofenil)etoxi]pirazin-2-amina (127)



30 **126** **127**

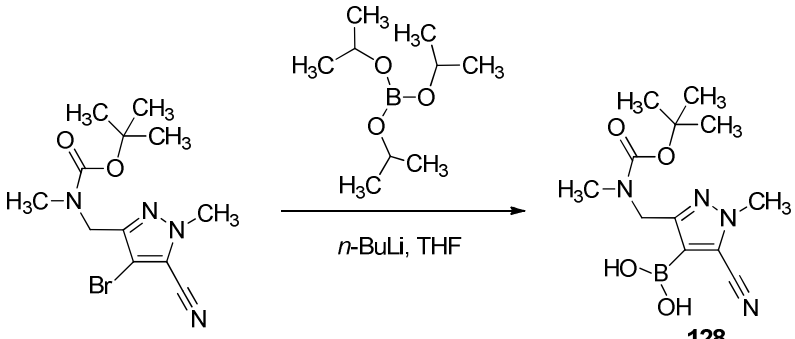
El **compuesto 30** (18 g) se resolvió por SFC y produjo el **compuesto 126** (pico 1) (7,75 g, 86%) y el **compuesto 127** (pico 2) (7,72 g, 85%) en forma de sólidos

amarillos. Una columna Chiralpak AD-H (250 × 4,6 mm I.D., tamaño de partícula de 5 micrones) se eluyó con 15% de metanol en CO_2 a 140 bar a una tasa de flujo de 3 mL/min y produjo el pico 1 con un tiempo de retención de 3,76 minutos y el pico 2 con un tiempo de retención de 4,51 minutos.

Compuesto 126 (pico 1): 99 % ee. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,87 (dd, J = 5,8, 8,8 Hz, 1 H), 7,61 - 7,54 (m, 2 H), 6,98 (dt, J = 3,0, 8,6 Hz, 1 H), 6,71 (s, 2 H), 6,18 - 6,04 (m,1 H), 1,53 (d, J = 6,3 Hz, 1 H). LCMS *m/z* 437/439 $[M+H]^+$.

Compuesto 127 (pico 2): > 98% ee. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,86 (dd, J = 5,8, 8,8 Hz, 1 H), 7,62 - 7,54 (m, 2 H), 6,97 (dt, J = 3,1, 8,5 Hz, 1 H), 6,71 (s, 2 H), 6,17 - 6,04 (m,1 H), 1,52 (d, J = 6,5 Hz, 3 H). LCMS *m/z* 437/439 $[M+H]^+$.

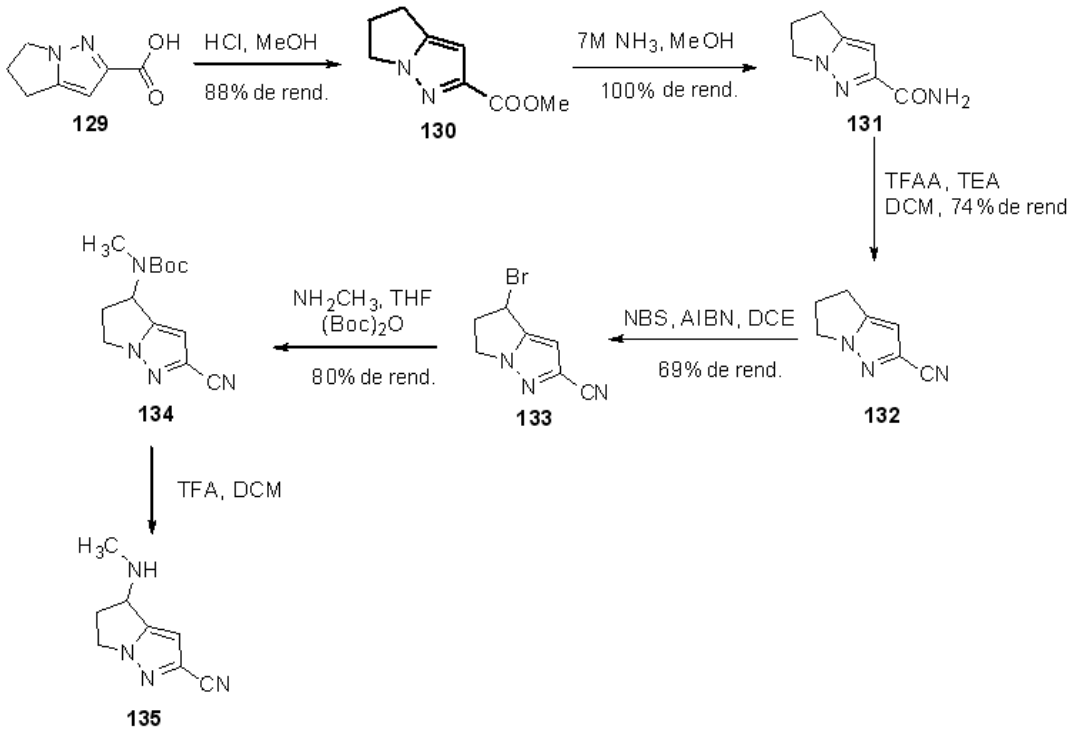
Preparación de ácido (3-{[(ter-butoxicarbonil)(metil)amino]metil}-5-ciano-1-metil-1H-pirazol-4-il)borónico (128)



47 **128**

A una solución de compuesto **47** (800 mg, 2,43 mmol) en THF anhidro (30 mL) a -78 °C se añadió *n*-BuLi (1,2 mL, 2,5 M en hexanos, 3,2 mmol) gota a gota por medio de una jeringa. La mezcla se volvió de color anaranjado y se agitó a -78 °C durante 30 minutos. Se añadió una solución de borato de triisopropilo (0,85 mL, 3,64 mmol) en THF (5 mL) gota a gota por medio de un embudo de adición. La mezcla resultante se agitó a -78 °C durante 30 minutos. Se añadió HCl 1 N (6 mL) gota a gota y el baño de enfriamiento se retiró. La mezcla se calentó hasta temperatura ambiente. La mezcla se dividió entre EtOAc/salmuera y se extrajo con EtOAc. Las capas orgánicas combinadas se secaron ($MgSO_4$) y se redujeron a un volumen mínimo para obtener 738 mg de un residuo, que se extrajo en MeOH (17,2 mL) para proporcionar una solución 0,14 M de compuesto **128**, que se usó sin otra purificación.

Preparación de 4-(metilamino)-5,6-dihidro-4*H*-pirrolo[1,2-*b*]pirazol-2-carbonitrilo (135)



Etapa 1:

Una solución de **compuesto 129** (284 mg, 1,87 mmol) en MeOH (10 mL) se trató con 4 gotas de HCl concentrado. La reacción se calentó a 50 °C durante 24 horas. La reacción se concentró y se dividió entre EtOAc y $NaHCO_3$ acuoso saturado. La reacción se extrajo con EtOAc y las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron para obtener el compuesto **130** (273 mg, 88%) en forma de un sólido blanquecino. LCMS ES *m/z* 167 $[M+H]^+$.

Etapa 2:

Una mezcla de **compuesto 130** (273 mg, 1,64 mmol) en NH3 7 M en MeOH (5 mL) se calentó a 80 °C en un tubo sellado durante 20 horas. La reacción se concentró hasta lograr un sólido blanquecino que se redisolvió en NH3 7 M en MeOH (5 mL) y se calentó durante otras 60 horas. La reacción se concentró para obtener el **compuesto 131** (276 mg, 100%) en forma de un sólido amarronado, que se usó en la siguiente etapa sin otra purificación. LCMS ES *m/z* 152 $[M+H]^+$.

Etapa 3:

A una suspensión de **compuesto 131** (248 mg, 1,64 mmol) en DCM (10 mL) se añadió TEA (0,686 mL, 4,92 mmol). La mezcla resultante se enfrió hasta 0 °C y se añadió TFAA (0,456 mL, 3,28 mmol). Después de 1,5 horas, la LCMS mostró que la reacción estaba completa. La reacción se concentró y se purificó por cromatografía en

columna en gel de sílice (0-50% de EtOAc/heptano) para obtener 5,6-dihidro-4H-pirrolo[1,2-b]pirazol-2-carbonitrilo, **compuesto 132** (168 mg, 74%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,70 (s, 1 H) 4,13 - 4,21 (m, 2 H) 2,89 (t, *J* = 7,33 Hz, 2 H), 2,53 - 2,62 (m, 2 H).

Etapa 4:

El **compuesto 132** (165 mg, 1,24 mmol), NBS (451 mg, 2,51 mmol) y AIBN (10,2 mg, 0,062 mmol) se combinaron en DCE (8 mL) y la reacción se calentó a 85 °C durante 60 horas. La reacción se concentró para obtener un sólido crema. Se añadió agua (10 mL) y la capa acuosa se extrajo con EtOAc (2x). Las capas orgánicas se secaron (Na2SO4), se concentraron y se purificaron por cromatografía en columna en gel de sílice (0-30% de EtOAc/heptanos) para obtener el **compuesto 133** (182 mg, 69%) en forma de un aceite anaranjado espeso. ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,59 (s, 1 H) 5,35 (dd, *J* = 6,82, 1,77 Hz, 1 H) 4,35 - 4,46 (m, 1 H) 4,21 - 4,29 (m, 1 H) 3,28 (ddt, *J* = 14,81, 8,32, 8,32 Hz, 1 H) 2,95 (ddt, *J* = 14,59, 6,76, 1,96 Hz, 1 H).

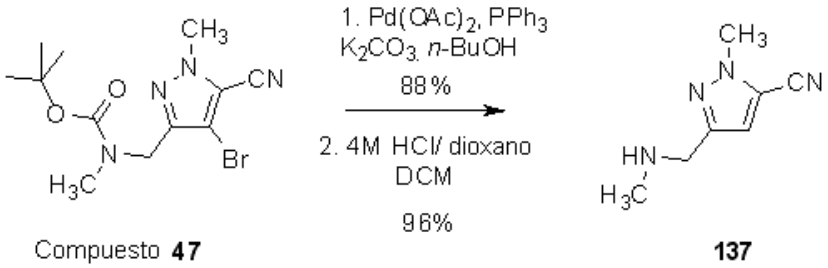
Etapa 5:

A una solución enfriada de **compuesto 133** (182 mg, 0,858 mmol) en THF (8 mL) se añadió NH_2CH_3 2 M en THF (1,27 mL). La mezcla se agitó a 50 °C durante 14 horas. La LCMS mostró ~50% de terminación. Se añadieron otros 4 mL de NH_2CH_3 2 M en THF y la mezcla resultante se calentó a 50 °C durante 16 horas. La reacción se dejó enfriar, se añadió $(Boc)_2O$ (281 mg, 1,29 mmol) y la reacción se agitó a temperatura ambiente durante 18 horas. La reacción se concentró y se dividió entre agua y EtOAc. La fase orgánica se separó, se secó (Na_2SO_4) y se concentró para obtener un residuo marrón, que se purificó por cromatografía en columna en gel de sílice (0-50% de EtOAc/heptano) para obtener el **compuesto 134** (180 mg, 80%) en forma de un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,44 (d, *J* = 0,76 Hz, 1 H) 5,53 - 5,82 (m, 1 H) 4,33 (ddd, *J* = 11,68, 9,28, 4,55 Hz, 1 H) 4,13 (ddd, *J* = 11,75, 8,72, 6,82 Hz, 1 H) 2,98 (dtd, *J* = 13,58, 8,94, , 4,67 Hz, 1 H) 2,64 (br. s., 3 H) 2,49 (d, *J* = 5,56 Hz, 1 H) 1,43 (s, 9 H). LCMS ES *m/z* 263 $[M+H]^+$.

Etapa 6:

A una solución de **compuesto 134** (180 mg, 0,686 mmol) en DCM (2 mL) se añadió TFA (2 mL). La reacción estaba completa después de 1 hora. Se concentró para obtener el **compuesto 135** (237 mg) en forma de un aceite amarillo espeso, que se usó sin otra purificación. LCMS ES *m/z* 163 $[M+H]^+$.

Preparación de 1-metil-3-((metilamino)metil)-1*H*-pirazol-5-carbonitrilo (137)



Compuesto **47** **137**

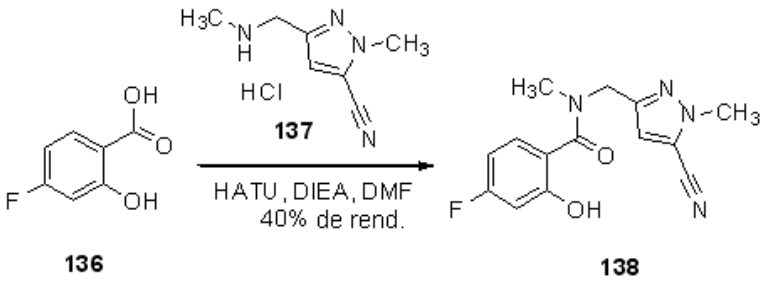
Etapa 1:

Una suspensión de **compuesto 47** (118 g, 358 mmol) en *n*-butanol (1,20 L) se desgasificó y se colocó bajo nitrógeno. Luego se añadieron K_2CO_3 (99,0 g, 716 mmol), trifenilfosfina (18,7 g, 71,3 mmol) y acetato de paladio (II) (4,00 g, 17,8 mmol) y la mezcla se calentó durante 4 horas, llegando a 80 °C después de 1 hora y logrando reflujo después de 3 horas. La mezcla se dejó enfriar hasta temperatura ambiente, luego se diluyó con EtOAc (1 L) y se lavó con agua (1 L) y salmuera (1 L). La capa orgánica se secó ($MgSO_4$) y se filtró. Al reposar durante la noche, se formó una pequeña cantidad de precipitado, por lo que la mezcla se filtró y luego se concentró al vacío para obtener 117,4 g de aceite marrón. La purificación por cromatografía en columna en gel de sílice (10-30% de EtOAc/heptano) produjo el **compuesto** intermediario **137A** protegido con Boc en forma de un aceite amarillo (74,8 g, 83,5%). Las fracciones impuras se combinaron para obtener 5,98 g de aceite amarillo que se purificó luego por cromatografía en columna en gel de sílice eluyendo con 10% de EtOAc en heptano, por lo que se aumentó la polaridad a EtOAc puro. Esto produjo otros 3,92 g de **compuesto 137A** en forma de un aceite amarillo (4,4%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,68 (s, 1H), 4,38 (s, 2H), 4,01 (s, 3H), 2,84 (s, 3H), 1,47 (s, 9H). LCMS ES *m/z* 251 [M+H]+.

Etapa 2:

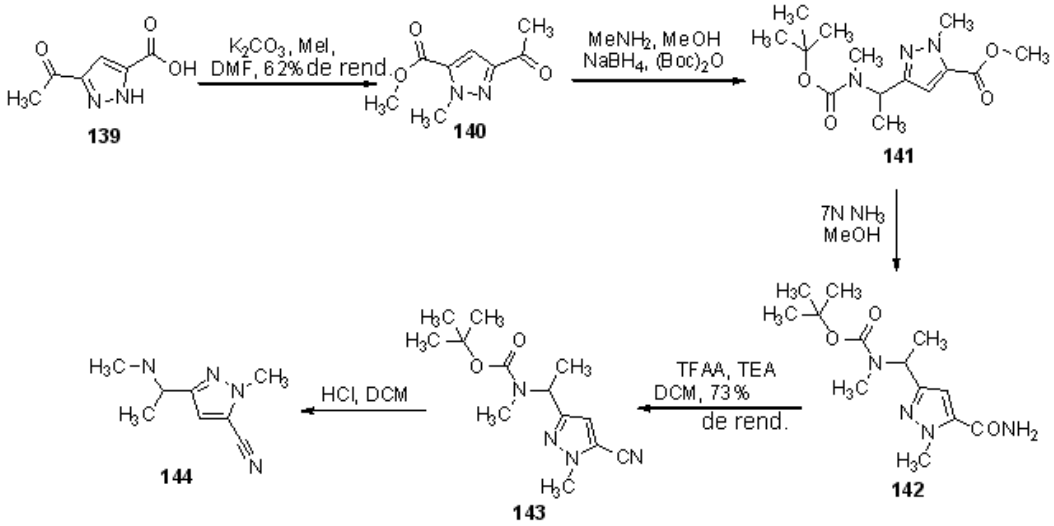
Una solución de **compuesto 137** (78,7 g, 314 mmol) en diclorometano (400 mL) se enfrió hasta 0 °C bajo nitrógeno y se añadió una solución 4 M de HCl en dioxano (400 mL, 1,6 mol) durante 5 minutos. Después de agitar a 0 °C durante 30 minutos, la mezcla se calentó hasta temperatura ambiente y se agitó durante otras 3 horas. La mezcla de reacción se concentró hasta aproximadamente 150 mL, se enfrió y se filtró, lavando con TBME 100 mL). El residuo se secó al aire para obtener el **compuesto 137** en forma de un sólido cristalino incoloro (56,12 g, 96%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,50 (s, 2H), 7,31 (s, 1H), 4,13 (s, 2H), 4,03 (s, 3H), 2,52 (s, 3H). LCMS ES *m/z* 151$[M+H]^+$.

Preparación de *N*-[(5-ciano-1-metil-1*H*-pirazol-3-il)metil]-4-fluoro-2-hidroxi-*N*-metilbenzamida (138)



A una solución de ácido 4-fluoro-2-hidroxibenzoico **136** (500 mg, 3,2 mmol), cloruro de (5-ciano-1-metil-1*H*-pirazol-3-il)-*N*-metilmetanaminio **137** (600 mg, 3,2 mmol) y HATU (1,4 g, 3,5 mmol) en DMF (21 mL) se añadió DIEA (2,8 mL, 16 mmol). Después de agitar a temperatura ambiente durante 14 horas, la solución se concentró y se purificó por cromatografía en columna en gel de sílice eluyendo con heptano/acetato de etilo (0-75%) para obtener el **compuesto 138** (370 mg, 40%) en forma de un semisólido. ^{1}H RMN (400 MHz, 80 ˚C, DMSO-d_6) δ 10,08 (s, 1 H) 7,19 (m, 1 H) 6,94 (s, 1 H) 6,70 - 6,59 (m, 2 H) 4,52 (s, 2 H) 3,98 (d, *J* = 0,8 Hz, 3 H) 2,86 (s, 3 H). LCMS APCI *m/z* 298 $[M+H]^+$.

Preparación de 1-metil-3-[1-(metilamino)etil]-1H-pirazol-5-carbonitrilo (144)



Etapa 1:

A una suspensión agitada de **compuesto 139** (200 mg, 1,3 mmol) y carbonato de potasio (450 mg, 3,26 mmol) en DMF (5 mL) se añadió yoduro de metilo (456 mg,

3,21 mmol) gota a gota a temperatura ambiente. El recipiente se selló y la mezcla se calentó a 50 ˚C durante 1 hora. La LCMS indicó el consumo completo del material de partida y 2 productos en una relación ~ 3 : 1. La mezcla se dividió entre EtOAc/salmuera. La capa acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con agua (2x) y salmuera (1x), se secaron sobre $MgSO_4$ y se redujeron hasta un volumen mínimo. El residuo se purificó por cromatografía en columna en gel de sílice usando un gradiente de 10-75% de EtOAc/heptano como eluyente. Se aislaron dos isómeros, siendo el mayor isómero el **compuesto 140** (146 mg de sólido blanco, 62 %) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,32 (s, 1 H) 4,25 (s, 3 H) 3,91 (s, 3 H) 2,59 (s, 3 H). Menor regioisómero (49 mg, 21%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,38 (s, 1 H) 4,24 (s, 3 H) 3,96 (s, 3 H) 2,56 (s, 3 H).

Etapa 2:

A una solución de **compuesto 140** (1,13 g, 6,2 mmol) en metanol (50 mL) se añadió una solución de metilamina (3,8 mL, 2 M en THF, 7,6 mmol) y se agitó a temperatura ambiente durante 20 horas. A la mezcla de reacción se añadió $NaBH_4$ (235 mg, 6,21 mmol). Inicialmente se observó una evolución de gas vigorosa, que cesó después de ~30 minutos. La LCMS indicó la conversión completa en la amina. A la mezcla resultante se añadió $(Boc)_2O$ (2 g, 9,1 mmol) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró hasta sequedad. El residuo se purificó por cromatografía en columna en gel de sílice usando un gradiente de 10-75% de EtOAc/heptano como eluyente. Las fracciones deseadas se combinaron y se concentraron para obtener el **compuesto 141** (1,6 g, ~85% puro) en forma de un aceite. Este material se usó directamente en la siguiente etapa sin otra purificación. ^{1}H RMN (400 MHz, 80 ˚C, DMSO-d_6) δ 6,67 (s, 1 H) 5,26 (q, J = 7,05 Hz, 1 H) 4,05 (s, 3 H) 3,84 (s, 3 H) 2,60 (s, 3 H) 1,43 (d, J = 7,30 Hz, 12 H).

Etapa 3:

El **compuesto 141** (1,6 g, 5,4 mmol) se disolvió en amoníaco 7 M en metanol (20 mL). El recipiente se selló y la mezcla se calentó a 50 ºC durante 5 días. La LCMS indicó la conversión completa en el producto deseado. La mezcla se concentró para obtener el **compuesto 142** (1,496 g ~85% puro) en forma de una goma. Este material se usó directamente en la siguiente etapa sin otra purificación. ^{1}H RMN (400 MHz, 80 ˚C, DMSO-d_6) δ 7,38 (br. s., 2 H) 6,69 (s, 1 H) 5,26 (q, J=6,97 Hz, 1 H) 4,01 (s, 3 H) 2,60 (s, 3 H) 1,44 (s, 9 H) 1,41 (d, J=7,05 Hz, 3 H).

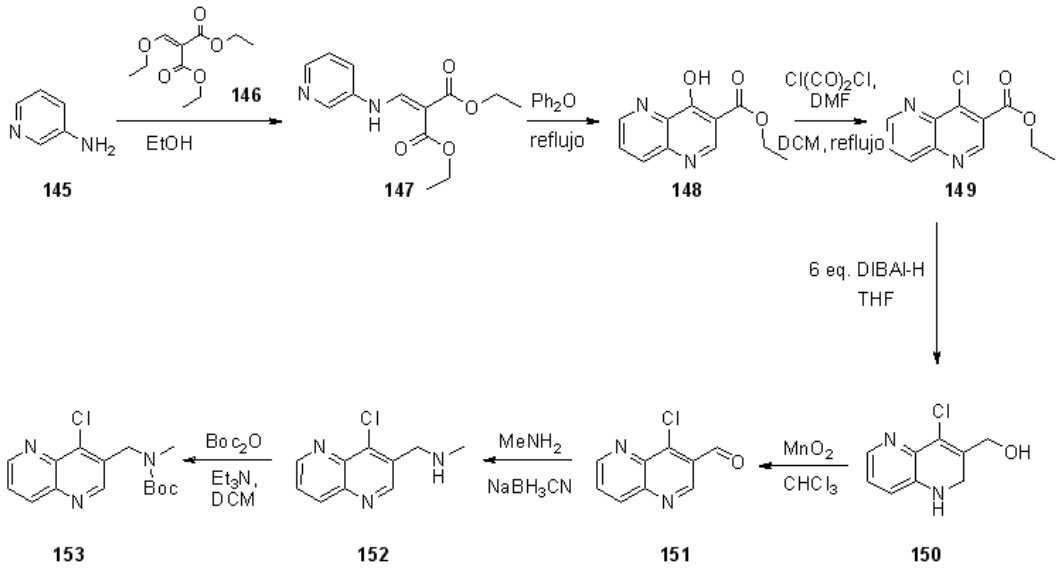
Etapa 4:

A una suspensión de **compuesto 142** (1,496 g, 5,3 mmol) en diclorometano (20 mL) se añadió trietilamina (2,2 mL, 15,9 mmol). La suspensión resultante se enfrió hasta -10 ˚C y se añadió gota a gota una solución de anhídrido trifluoroacético (1,5 mL, 10,6 mmol) en diclorometano (10 mL) durante 20 minutos. Una vez completa la adición, la mezcla de reacción se agitó a 0 ˚C durante 1 hora. La mezcla se dividió entre diclorometano y $NaHCO_3$ acuoso. La capa acuosa se extrajo con diclorometano (2x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ y se concentraron para obtener un aceite amarillo oscuro. El residuo se purificó por cromatografía en columna en gel de sílice usando un gradiente de 10-75% de EtOAc/heptano como eluyente. Las fracciones deseadas se concentraron para obtener el **compuesto 143** (1,026 g, 73%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, 80 ˚C, DMSO-d_6) δ 6,90 (s, 1 H) 5,27 (q, *J*=7,13 Hz, 1 H) 3,97 (s, 3 H) 2,61 (s, 3 H) 1,37 - 1,51 (m, 12 H).

Etapa 5:

A una solución de **compuesto 143** (300 mg, 1,14 mmol) en diclorometano (4,5 mL) se añadió una solución de HCl en dioxano (4M, 4,5 mL). Después de agitar a temperatura ambiente durante 1 hora, la solución resultante se redujo hasta un volumen mínimo. El residuo se concentró en tolueno y se secó a 50 ºC en un horno de vacío durante 1,5 horas para obtener el **compuesto 144** (228 mg, cuant) en forma de un sólido blanco. El material se usó directamente en la siguiente etapa sin purificación. ^{1}H RMN (400 MHz, 80 ˚C, DMSO-d_6) δ 9,39 (br. s., 2 H) 7,30 (s, 1 H) 4,42 (q, *J*=6,88 Hz, 1 H) 4,03 (s, 3 H) 2,46 (s, 3 H) 1,59 (d, *J*=6,80 Hz, 3 H).

Preparación de [(4-cloro-1,5-naftiridin-3-il)metil]metilcarbamato de ter-butilo (153)



Etapa 1:

Una mezcla de **compuesto 145** (35 g, 0,372 mol) y **compuesto 146** (96,5 g, 0,447 mol) en EtOH (300 mL) se calentó a reflujo durante la noche. La TLC (PE/EtOAc 1/1) mostró que la reacción estaba completa. La mezcla de reacción se concentró al vacío para obtener un residuo. Se añadió éter de petróleo (200 mL) y luego se agitó a temperatura ambiente durante 30 minutos. La mezcla se filtró para obtener el **compuesto 147** (95 g, 97%) en forma de un sólido blanquecino. ^{1}H RMN (400 MHz, $CDCl_3$) δ 11,03-11,00 (d, 1H), 8,50-8,41 (m, 3H), 7,49-7,47 (d, 1H), 7,34-7,30 (m, 1H), 4,35-4,20 (m, 4H), 1,62-1,18 (m, 6H).

Etapa 2:

A un solvente en reflujo de Ph_2O (200 mL) se añadió en porciones el **compuesto 147** (30 g, 0,113 mol). Después de la adición, la mezcla resultante se agitó entre 250~260 °C durante 30 minutos. La TLC (PE/EtOAc 1/1) mostró que el material de partida se había consumido por completo. La mezcla de reacción se enfrió hasta temperatura ambiente y luego se vertió en EtOAc (200 mL). La mezcla se filtró y la torta húmeda se lavó con EtOH (50 mL), EtOAc (50 mL) y éter de petróleo (50 mL) para obtener el **compuesto 148** (11 g, 45%) en forma de un sólido marrón.

Etapa 3:

A una suspensión de **compuesto 148** (12 g, 55 mmol) y DMF (5 mL) en DCM (200 mL) se añadió gota a gota cloruro de oxalilo (20 mL) a menos de 0 °C. Después de la adición, la mezcla resultante se calentó a reflujo durante tres horas. La TLC (PE/EtOAc 3/1) mostró que la reacción estaba completa. La mezcla de reacción se

vertió en agua helada con cuidado. La mezcla se concentró al vacío para eliminar DCM. La mezcla se extrajo con MTBE (500 mL x 3). Las capas orgánicas combinadas se lavaron con salmuera (100 mL x 2), se secaron sobre Na_2SO_4 y se concentraron al vacío para obtener un residuo, que se purificó por cromatografía en columna (gel de sílice, PE/EtOAc 5/1) para obtener el **compuesto 149** (6 g, 46%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,26 (s, 1H), 9,17-9,16 (d, 1H), 8,49-8,16 (d, 1H), 7,81-7,78 (t, 1H), 4,56-4,51 (q, 2H), 1,50-1,47 (m, 3H).

Etapa 4:

A una solución de **compuesto 149** (4 g, 16,9 mmol) en THF seco (100 mL) se añadió gota a gota DIBAL-H (101,4 mL, 101,4 mmol, 1 M en tolueno) a menos de 0 °C. Después de la adición, la mezcla resultante se agitó a esta temperatura durante 3 horas. La TLC (PE/EtOAc 1/1) mostró que la reacción estaba completa. La mezcla de reacción se neutralizó con Na_2SO_4 acuoso saturado (100 mL) a menos de 0 °C y se agitó a esta temperatura durante 30 minutos y luego a temperatura ambiente durante 30 minutos. La mezcla se filtró. La torta húmeda se lavó con EtOAc (100 mL x 5). Los filtrados combinados se lavaron con salmuera (100 mL), se secaron sobre Na_2SO_4 y se concentraron al vacío para obtener un residuo, que se purificó por cristalización en DCM (10 mL) para obtener el **compuesto 150** (2,5 g, 75,1%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,96-7,95 (d, 1H), 6,94-6,91 (m, 1H), 6,75-6,68 (t, 1H), 4,51 (s, 2H), 4,42 (s, 2H), 3,79-3,71 (brs, 1H), 1,70-1,63 (brs, 1H).

Etapa 5:

Una mezcla de **compuesto 150** (2,5 g, 12,7 mmol) y MnO_2 (10 g, 115 mmol) en $CHCl_3$ (100 mL) se calentó a reflujo durante la noche. La TLC (PE/EtOAc 1/1) mostró que la reacción estaba completa. La mezcla de reacción se filtró y la torta húmeda se lavó con DCM (20 mL x 5). Los filtrados combinados se secaron sobre Na_2SO_4 y se concentraron al vacío para obtener el **compuesto 151** (2,1 g, 86%) en forma de un sólido blanquecino. ^{1}H RMN (400 MHz, $CDCl_3$) δ 10,80 (s, 1H), 9,45 (s, 1H), 9,19-9,11 (m, 1H), 8,51-8,44 (m, 1H), 7,86-7,79 (m, 1H).

Etapa 6:

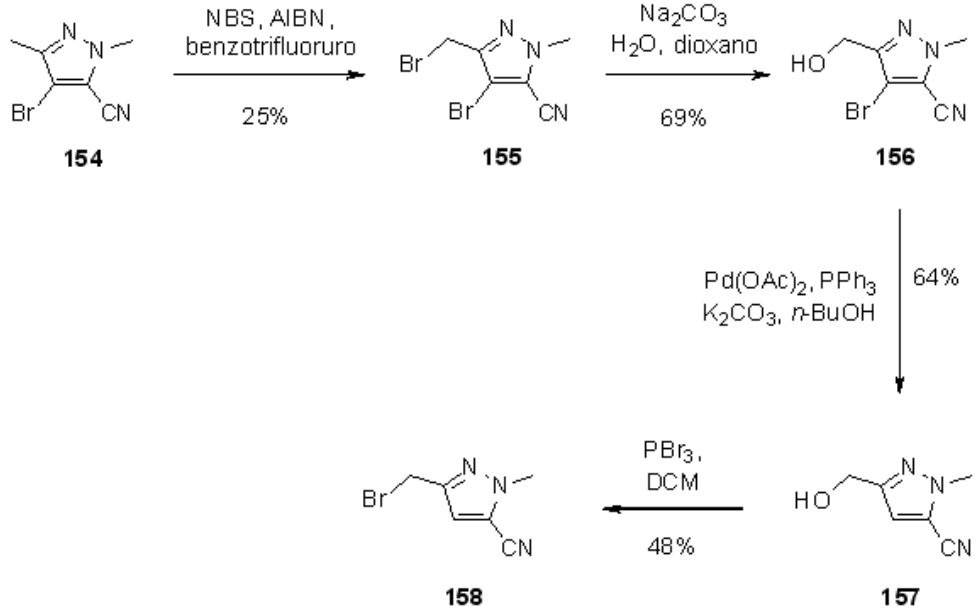
Una mezcla de **compuesto 151** (2,7 g, 14,02 mmol), $MeNH_2$.HCl (1,9 g, 28,04 mmol), $MgSO_4$ (5 g) y Et_3N (2,83 g, 158,04 mmol) en metanol (50 mL) se agitó a temperatura ambiente durante la noche. Luego se añadió $NaBH_3CN$ (2,5 g, 42,06 mmol) a la mezcla anterior y se agitó a temperatura ambiente durante 4 horas. La TLC (PE/EtOAc 1/1) mostró que la reacción estaba completa. La mezcla de reacción se concentró al vacío para obtener el **compuesto 152** crudo, que se usó en la siguiente

etapa sin otra purificación. ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,11-9,10 (d, 1H), 9,02 (s, 1H), 8,46-8,44 (d, 1H), 7,73-7,70 (m, 1H), 4,19 (s, 2H), 2,55 (s, 3H).

Etapa 7:

A una solución de **compuesto 152** crudo (~ 14,02 mmol) y $(Boc)_2O$ (6,1 g, 28,06 mmol) en DCM (100 mL) se añadió gota a gota Et_3N (2,86 g, 28,04 mmol) a temperatura ambiente durante la noche. Después de la adición, la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La TLC (PE/EtOAc 3/1) mostró que la reacción estaba completa. La mezcla de reacción se concentró al vacío para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice (PE/EtOAc 3/1, Rf, 0,15) para obtener el **compuesto 153** (1,7 g, 36% en dos etapas) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,10-9,09 (d, 1H), 8,88-8,86 (d, 1H), 8,45-8,43 (d, 1H), 7,72-7,71 (m, 1H), 4,87-4,83 (d, 2H), 2,99-2,93 (d, 3H), 1,51-1,47 (d, 9H). LCMS *m/z* 308 $[M+H]^+$.

Preparación de 3-(bromometil)-1-metil-1*H*-pirazol-5-carbonitrilo (158)



Etapa 1:

El **compuesto 154** (25,0 g, 124,9 mmol) se disolvió en benzotrifluoruro (300 mL) y se añadieron NBS (31,1 g, 174,9 mmol) y AIBN (0,25 g, 1,53 mmol) a 45 °C. La temperatura luego se incrementó a 80 °C y se calentó durante una hora. Se añadió más AIBN (0,25 g, 1,53 mmol) y el calentamiento continuó durante la noche. La reacción se enfrió hasta temperatura ambiente y el solvente se eliminó al vacío para

obtener una goma amarilla. La goma se extrajo en DCM (300 mL) y los demás sólidos se eliminaron por filtración. El filtrado se concentró y se añadió MeOH frío al aceite amarillo. Después de reposar a 0 ºC durante dos horas, el sólido incoloro resultante se recogió por filtración y se lavó con MeOH frío (2 x 20 mL). El sólido luego se recristalizó en metilciclohexano para obtener el **compuesto 155** en forma de un sólido incoloro (9,4 g, 25% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,42 (s, 2H), 4,05 (s, 3H).

Etapa 2:

El **compuesto 155** (16,0 g, 57,36 mmol) se disolvió en dioxano (200 mL) y se añadió una solución de Na_2CO_3 (30,4 g, 286,8 mmol) en H_2O (200 mL) y la mezcla bifásica se calentó a 60 ºC durante 16 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y el dioxano se eliminó al vacío. El residuo se dividió entre DCM (150 mL) y salmuera (100 mL) y las fases se separaron. La fase acuosa se extrajo con DCM (3 x 50 mL) y los extractos orgánicos combinados se secaron sobre $MgSO_4$ y se concentraron para obtener un aceite amarillo. El aceite crudo se purificó por cromatografía en columna en gel de sílice (1:3 EtOAc:heptano a 1:1 EtOAc:heptano) para obtener el **compuesto 156** en forma de un sólido incoloro (8,60 g, 69% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,68 (d, *J* = 6,1 Hz, 2H), 4,04 (s, 3H), 1,99 (t, *J* = 6,1 Hz, 1H).

Etapa 3:

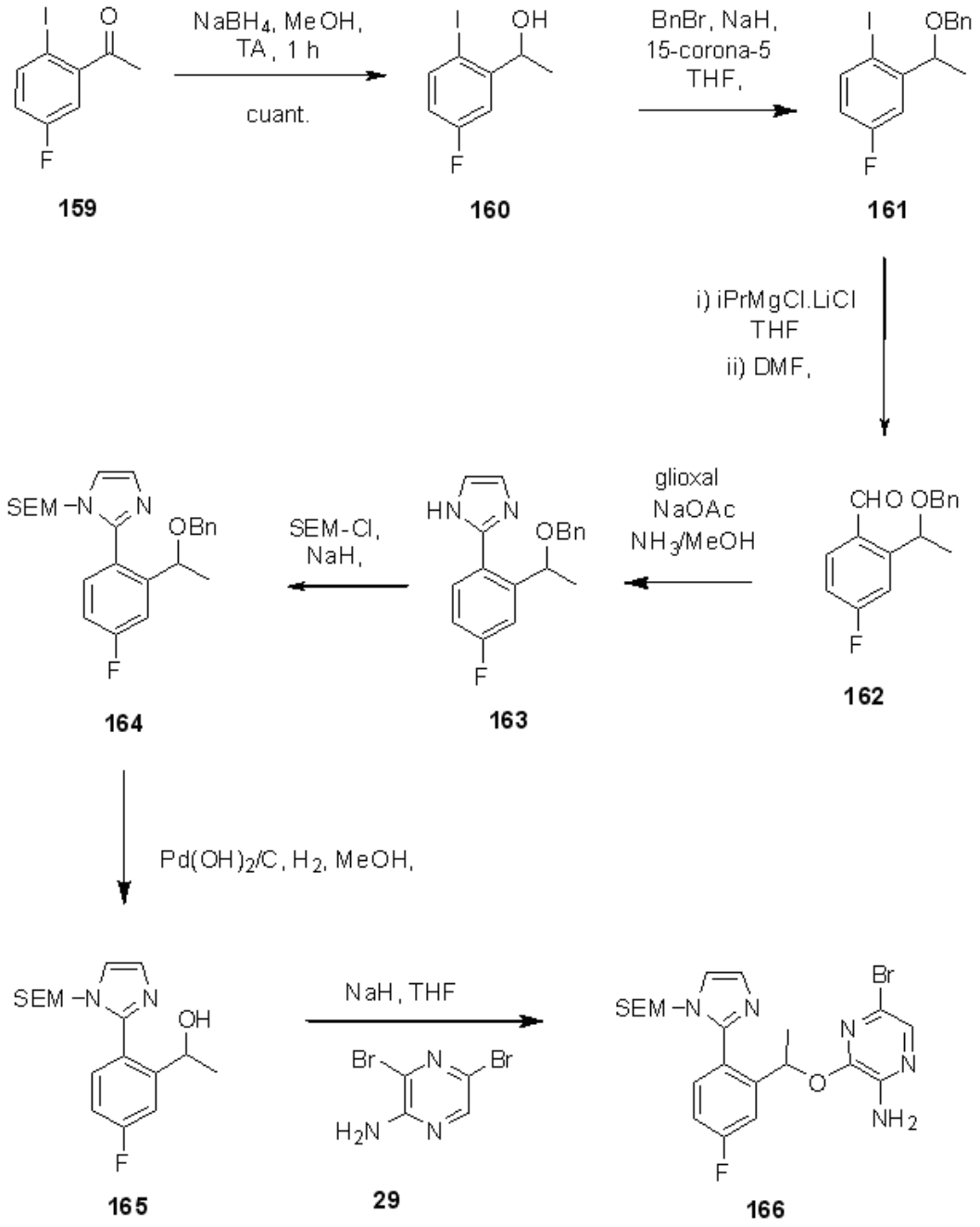
El **compuesto 156** (8,60 g, 39,81 mmol) se disolvió en *n*-butanol (90 mL) y se añadieron PPh_3 (2,09 g, 7,97 mmol), $Pd(OAc)_2$ (440 mg, 1,96 mol) y K_2CO_3 (11,0 g, 79,6 mmol) y la mezcla de reacción se calentó a reflujo durante 4 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con EtOAc (150 mL) y se lavó con solución saturada de $NaHCO_3$ (100 mL) y salmuera (100 mL). La fase orgánica se secó sobre $MgSO_4$ y se concentró para obtener un aceite amarillo. El aceite crudo se purificó por cromatografía en columna en gel de sílice (1:1 EtOAc : heptano) para obtener el **compuesto 157** en forma de un sólido incoloro (3,49 g, 64%).^{1}H RMN (400 MHz, $CDCl_3$) δ 4,68 (d, *J* = 6,1 Hz, 2H), 4,04 (s, 3H), 1,99 (t, *J* = 6,1 Hz, 1H).

Etapa 4:

El **compuesto 157** (3,47 g, 25,30 mmol) se disolvió en DCM (50 mL) y se enfrió hasta 0 ºC. Se añadió PBr_3 (3,12 mL, 32,89 mmol) gota a gota para obtener una suspensión blanca que se agitó a temperatura ambiente durante la noche. La solución resultante que contenía una goma amarilla pálida se diluyó con DCM (30 mL) y se

neutralizó por la adición cuidadosa de H_2O (20 mL) y se neutralizó con solución saturada de $NaHCO_3$. Las fases se separaron y la fase acuosa se extrajo con DCM (2 x 60 mL). Los extractos de DCM combinados se secaron sobre $MgSO_4$ y se concentraron para obtener un aceite amarillo. El aceite crudo se purificó por cromatografía en columna en gel de sílice (1:1 DCM : heptano) para obtener el **compuesto 158** en forma de un aceite incoloro (2,43 g, 48% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,82 (s, 1H), 4,43 (s, 2H), 4,03 (s, 3H).

Preparación de 5-bromo-3-{1-[5-fluoro-2-(1-{[2-(trimetilsilil)etoxi]metil}-1*H*-imidazol-2-il)fenil]etoxi}pirazin-2-amina (166)



Etapa 1:

La reacción se llevó a cabo en 2 lotes de 50 g cada uno para la adición en porciones de $NaBH_4$. A la solución enfriada (baño de hielo) de **compuesto 159** (100 g, 379 mmol) en THF (800 ml) y MeOH (400 mL), se añadió $NaBH_4$ (28,7 g, 757 mmol) en porciones (2 g cada una) durante 2 horas (se observó fuerte evolución de gas). La reacción se agitó a temperatura ambiente durante 3 horas. El análisis de TLC indicó que la reacción estaba completa. La reacción se neutralizó con NH_4Cl acuoso (300

mL). La mezcla se extrajo con EtOAc (500 mL), las capas orgánicas se separaron y se volvieron a lavar con NH_4Cl (300 mL), agua (1x 300 mL) y luego salmuera (1x 400 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$) y los solventes se eliminaron al vacío para obtener el **compuesto 160** (104,1 g, cuant) en forma de un aceite amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,80 (dd, *J* = 8,6, 5,7 Hz, 1H), 7,31 (dd, *J* = 10,4, 3,2 Hz, 1H), 6,92 (td, *J* = 8,4, 3,2 Hz, 1H), 5,55 (d, *J* = 4,1 Hz, 1H), 4,71-4,76 (m, 1H), 1,26 (d, *J* = 6,3 Hz, 3H).

Etapa 2:

Se añadió una solución de **compuesto 160** (119,7 g, 450 mmol) en THF (300 mL) por medio de un embudo de adición a una suspensión helada de NaH (60% en peso, 19,8 g, 495 mmol) en THF (500 mL) (tiempo de adición - ~1 hora). Se añadió 15-corona-5 r (13,3 ml, 67,5 mmol) y la reacción se calentó hasta temperatura ambiente. Después de 2 horas, se añadió una solución de BnBr (51 mL, 427 mmol) en THF (300 mL) (~20 min, pequeña exotermia observada hasta ~40 °C). La mezcla de reacción se dejó en agitación a temperatura ambiente durante la noche y luego se neutralizó con NH_4Cl (200 mL). La mezcla se diluyó con EtOAc (200 mL), las capas orgánicas se separaron y se volvieron a lavar con NH_4Cl (200 mL), agua (300 mL) y luego salmuera (2x 300 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$), y los solventes se eliminaron al vacío para obtener un aceite anaranjado que se purificó por cromatografía en columna (eluyente: Heptano/EtOAc – 99:1 a 8:2) para obtener el **compuesto 161** (144,3 g, 90%) en forma de un líquido incoloro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,87 (dd, *J* = 8,7, 5,7 Hz, 1H), 7,53 – 7,24 (m, 6H), 7,00 (td, *J* = 8,5, 3,1 Hz, 1H), 4,63 (qd, *J* = 6,4, 1,5 Hz, 1H), 4,40 (d, *J* = 12,0 Hz, 1H), 4,32 (d, *J* = 11,9 Hz, 1H), 1,34 (d, *J* = 6,4 Hz, 3H).

Etapa 3:

Una solución de **compuesto 161** (50 g, 140 mmol) en THF (500 mL) se enfrió hasta -45 °C (temperatura interna). Se añadió una solución de *i*-PrMgCl.LiCl (1,3 M en THF, 121 mL, 160 mmol) por medio de un embudo de adición (~20 min de período de adición) manteniendo la temperatura de reacción interna entre -40 y -50 °C. Después de agitar durante 1 hora, se había formado una suspensión blanca. Después de otra hora, se añadió una solución de DMF (15,5 mL, 201 mmol) en THF (100 mL) (~30 min de adición). La mezcla de reacción clara resultante se calentó lentamente hasta temperatura ambiente. Después de 16 horas, la reacción se diluyó con EtOAc (200 mL) y se lavó con NH_4Cl (3x 300 mL) y luego salmuera (2x 400 mL). Las capas orgánicas combinadas se secaron con $MgSO_4$ y los solventes se eliminaron al vacío

para obtener 2-(1-(benciloxi)etil)-4-fluorobenzaldehído **compuesto 162** (37,9 g, cuant) en forma de un aceite amarillo pálido que se usó en la siguiente etapa sin otra purificación. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,19 (s, 1H), 8,02 (dd, J = 8,6, 5,9 Hz, 1H), 7,62 – 7,16 (m, 8H), 5,61 – 5,38 (m, 1H), 4,41 (s, 2H), 1,42 (d, J = 6,4 Hz, 3H).

Etapa 4:

Se añadieron glioxal (88,2 mL, 771,6 ml) seguido de NaOAc (95,5 g, 701,5 mmol) a un solución enfriada (baño de hielo) de **compuesto 162** (38,22 g, 140,3 mmol) en MeOH (100 mL). Después de agitar durante 5 min, se añadió una solución 7 N de NH_3 en MeOH (425 mL) y la mezcla resultante se agitó a 0 °C durante otros 10 min antes de sellarla en un autoclave y se calentó a 120 °C durante 5 horas. La reacción luego se enfrió hasta temperatura ambiente, los solventes se eliminaron al vacío para obtener una pasta negra que se redisolvió en DCM (600 mL) y luego se lavó con una solución acuosa 1:1 de NH_4Cl/HCl 1 M (2x 500 mL) y luego salmuera (1x 500 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$), los solventes se eliminaron al vacío y el residuo (adsorbido en Celite) se purificó por cromatografía en columna (eluyente: Heptano/EtOAc – 9:1 a 1:1). Los sólidos marrones aislados luego se purificaron por suspensión en una cantidad mínima de EtOAc seguido de filtración. Después de secar al vacío, el **compuesto 163** (16,2 g, 39%) se aisló en forma de sólidos blanquecinos. ^{1}H RMN (400 MHz, DMSO-d_6) δ 12,47 (s, 1H), 7,62 (s, 1H), 7,40 (dd, J = 10,4, 2,7 Hz, 1H), 7,35 – 7,19 (m, 8H), 5,47 (s, 1H), 4,43 – 4,12 (m, 2H), 1,40 (d, J = 5,1 Hz, 3H). LCMS ES m/z 297 $[M+H]^+$.

Etapa 5:

Se añadió NaH (60% en peso, 2,23 g, 55,7 mmol) en porciones a una solución enfriada (baño de hielo) de **compuesto 163** (14 g, 47,2 mmol) en THF (250 mL). La mezcla se agitó durante 30 minutos antes de añadir SEM-Cl (9,28 mL, 55,7 mmol) gota a gota. La mezcla resultante se calentó hasta temperatura ambiente. Después de 6 horas, la reacción se colocó en un baño de hielo, se neutralizó por la adición lenta de agua (150 mL) y luego se diluyó con EtOAc. Las fases se separaron y la capa acuosa se extrajo otra vez con EtOAc (2x 100 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$) y los solventes se eliminaron al vacío para obtener un residuo que se purificó por cromatografía en columna (eluyente: Heptano/EtOAc – 7:3 a 1:1) para obtener el **compuesto 164** (32 g, 70%) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,36-7,49 (m, 2H), 7,34 – 7,18 (m, 7H), 7,04 (d, J = 1,3 Hz, 1H), 5,22 – 5,05 (m, 2H), 4,57 (qd, J = 6,4, 1,6 Hz, 1H), 4,37 – 4,12 (m, 2H), 3,54 – 3,38 (m,

2H), 1,33 (d, *J* = 6,4 Hz, 3H), 0,85 – 0,63 (m, 2H), -0,08 (s, 9H). LCMS APCI *m/z* 427 $[M+H]^+$.

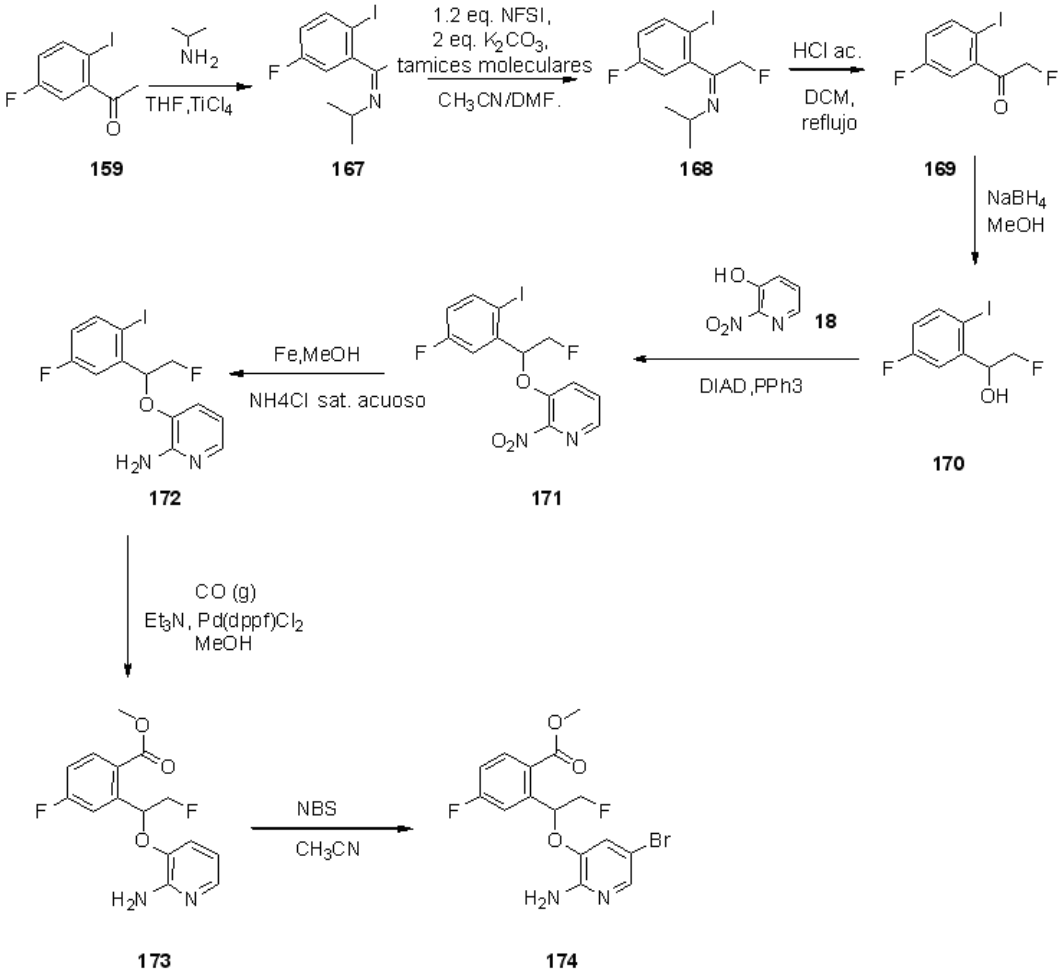
Etapa 6:

A una solución agitada de **compuesto 164** (24 g, 56,3 mmol) en MeOH (375 mL) se añadió 20% en peso de $Pd(OH)_2/C$ (5 g) y la mezcla resultante se calentó a 50 °C bajo una atmósfera de H_2 (30 psi) durante 6 horas y luego a temperatura ambiente durante 16 horas. La mezcla de reacción se filtró a través de un taco de Celite lavando los filtrados con MeOH. Los líquidos madre se concentraron al vacío y el residuo resultante se purificó por cromatografía en columna (eluyente: Heptano/EtOAc – 3:1 a 1:1) para obtener el **compuesto 165** (18,19 g, 96%) en forma de un aceite amarillo pálido. Este material se usó en la siguiente etapa sin otra purificación. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,45 (d, *J* = 1,4 Hz, 1H), 7,44 – 7,37 (m, 2H), 7,16 (td, *J* = 8,4, 2,8 Hz, 1H), 7,05 (d, *J* = 1,3 Hz, 1H), 5,40 (d, *J* = 4,5 Hz, 1H), 4,68-4,74 (m, 1H), 3,41 (dd, *J* = 9,0, 7,3 Hz, 2H), 1,15 (d, *J* = 6,4 Hz, 3H), 0,83 – 0,73 (m, 2H), -0,06 (s, 9H). LCMS APCI *m/z* 337 $[M+H]^+$.

Etapa 7:

Una solución de **compuesto 165** (18,19 g, 54,06) en THF (200 mL) se enfrió en un baño de hielo antes de añadir NaH (60% en peso, 2,59 g, 64,87 mmol) (en 3 porciones). Después de agitar durante 30 minutos, la reacción se calentó hasta temperatura ambiente. Se añadió una solución de **compuesto 29** (16,4 g, 64,87 mmol) en THF (50 mL) por medio de un embudo de adición. La mezcla de reacción se calentó a 60 °C durante 16 horas y luego se enfrió hasta temperatura ambiente. La mezcla se diluyó con EtOAc (300 mL) y luego se lavó con agua (2x 300 mL). Las capas orgánicas se secaron ($MgSO_4$) y los solventes se eliminaron al vacío para obtener sólidos oscuros crudos. Ests se purificaron por cromatografía en columna en gel de sílice (eluyente: Heptano/EtOAc – 9:1 a 1:1) para obtener el **compuesto 166** (19,36 g, 70%) en forma de un sólido blanquecino. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,71 (dd, *J* = 10,3, 2,8 Hz, 1H), 7,63 – 7,49 (m, 3H), 7,29 (td, *J* = 8,5, 2,8 Hz, 1H), 7,15 (d, *J* = 1,3 Hz, 1H), 6,71 (s, 2H), 6,08 – 5,89 (m, 1H), 5,32 (d, *J* = 10,9 Hz, 1H), 5,16 (d, *J* = 10,9 Hz, 1H), 3,66 – 3,48 (m, 2H), 1,65 (d, *J* = 6,4 Hz, 3H), 0,85 (ddd, *J* = 10,1, 6,2, 2,5 Hz, 2H), -0,00 (s, 9H). LCMS APCI *m/z* 508/509 $[M+H]^+$.

Preparación de 2-{1-[(2-amino-5-bromopiridin-3-il)oxi]-2-fluoroetil}-4-fluorobenzoato de metilo (174)



Etapa 1:

A una solución de **compuesto 159** (40 g, 0,153 mol) e isopropilamina (36,2 g, 0,613 mol) en THF seco (500 mL) se añadió $TiCl_4$ (10 mL) gota a gota a 0 °C. Después de la adición, la mezcla se agitó a temperatura ambiente durante 2 horas. La TLC (éter de petróleo/EtOAc 10/1) mostró que la reacción estaba completa. La mezcla se filtró. El filtrado se vertió en una solución 0,5 M de NaOH (500 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (200 mL × 3). Las capas orgánicas combinadas se lavaron con salmuera (200 mL), se secaron sobre Na_2SO_4 y se concentraron para obtener el **compuesto 167** (43 g, 93,5%) en forma de un aceite amarillo.

Etapa 2:

Una mezcla de NFSI (25 g, 79,4 mmol), K_2CO_3 (18,4 g, 132,4 mmol) y tamices moleculares 4Å (25 g) en CH_3CN/DMF seco (250 mL/50 mL) se agitó a 0 °C bajo nitrógeno durante 15 minutos. El **compuesto 167** (20 g, 66,2 mmol) se añadió a la

mezcla. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante dos días. La TLC (éter de petróleo/EtOAc = 10: 1) indicó que el 90% de **compuesto 167** se había consumido. Se añadió Et_3N (5 mL) a la mezcla de reacción a 0 ℃ y la mezcla se agitó durante otros 15 minutos. La mezcla se filtró. El filtrado se vertió en solución 0,5 M de NaOH (300 mL). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (100 mL × 3). Las capas orgánicas combinadas se lavaron con salmuera (100 mL × 3), se secaron sobre Na_2SO_4 y se concentraron para obtener el **compuesto 168** (20 g, 95%) en forma de un aceite marrón que se usó directamente sin otra purificación.

Etapa 3:

A una solución de **compuesto 168** (27,8 g, 86,3 mmol) en CH_2Cl_2/H_2O (250 mL/200 mL) se añadió HCl concentrado (50 mL). Después de la adición, la mezcla se calentó a reflujo durante 1 hora. La TLC (éter de petróleo: EtOAc = 50:1) mostró que la reacción estaba completa. La mezcla se enfrió hasta temperatura ambiente. La capa orgánica se separó y la capa acuosa se extrajo con CH_2Cl_2 (200 mL × 3). Las capas orgánicas combinadas se lavaron con salmuera (100 mL), se secaron sobre Na_2SO_4 y se concentraron. El residuo se purificó por HPLC preparativa en fase inversa para obtener el **compuesto 169** (13 g, 54%) en forma de un sólido amarillo.

Etapa 4:

A una solución de **compuesto 169** (13 g, 45,9 mmol) en MeOH (100 mL) se añadió $NaBH_4$ (3,4 g, 91,9 mol) en porciones a 0 ℃. Después de la adición, la mezcla se agitó a temperatura ambiente durante 2 horas. La TLC (éter de petróleo: EtOAc = 10:1) mostró que la reacción estaba completa. La mezcla se concentró. El residuo se diluyó con H_2O (100 mL) y se extrajo con EtOAc (100 mL × 3). Las capas orgánicas combinadas se lavaron con salmuera (100 mL × 3), se secaron sobre Na_2SO_4 y se concentraron para obtener el **compuesto 170** (13 g, 100%) en forma de un aceite amarillo.

Etapa 5:

A una solución agitada de **compuesto 170** (4,5 g, 15,8 mmol), **compuesto 18** (2,23 g, 15,8 mmol) y PPh_3 (5,59 g, 22 mmol) en THF anhidro (80 mL) se añadió gota a gota DIAD (4,4 g, 0,22 mmol) a 0 ℃. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La TLC (éter de petróleo/EtOAc 3: 1) indicó que la reacción estaba completa. La mezcla de reacción se concentró al vacío y el residuo se purificó por cromatografía en columna en gel de sílice (éter de

petróleo/EtOAc 20:1 a 10:1) para obtener el **compuesto 171** (5 g, 78 %) en forma de un sólido amarillo.

Etapa 6:

Una suspensión de **compuesto 171** (6 g, 14,7 mmol) y Fe (3,3 g, 59 mmol) en MeOH (80 mL) y NH_4Cl acuoso saturado (80 mL) se calentó a reflujo durante 2 horas. La TLC (éter de petróleo/EtOAc = 2:1) mostró que la reacción estaba completa. La mezcla de reacción se filtró y el filtrado se concentró para obtener una solución acuosa, que se extrajo con EtOAc (100 mL x 3). Las capas orgánicas combinadas se lavaron con salmuera (50 mL), se secaron sobre Na_2SO_4 y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice eluyendo con éter de petróleo/EtOAc 6/1 ~ 3/1 para obtener el **compuesto 172** (5 g, 91%) en forma de un sólido amarillo.

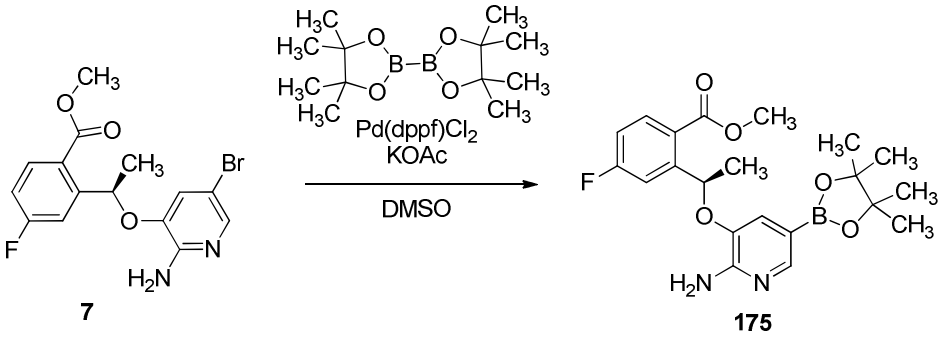
Etapa 7:

Una mezcla de **compuesto 172** (5 g, 13,3 mmol), $Pd(dppf)Cl_2$ (1,15 g, 1,33 mmol) y TEA (2,65g, 26,5 mmol) en metanol (100 mL) se selló bajo CO (4 bar) a 100 ℃ durante 16 horas. La TLC (éter de petróleo/EtOAc=1:1) indicó que la reacción estaba completa. La mezcla de reacción se filtró y el filtrado se concentró para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice, (éter de petróleo/EtOAc de 8:1 a 6:1) para obtener el **compuesto 173** (3,5 g, 84%) en forma de un sólido marrón pálido.

Etapa 8:

A una solución agitada de **compuesto 173** (3,5 g, 11,3 mmol) en CH_3CN (50 mL) se añadió gota a gota una solución de NBS (2 g, 11,3 mmol) en CH_3CN (30 mL) a 0 ℃. Después de la adición, la mezcla de reacción se agitó a esta temperatura durante 30 minutos. La TLC (éter de petróleo/EtOAc =1:1) indicó que la reacción estaba completa. La mezcla se diluyó con EtOAc (200 mL) y se lavó con $NaHCO_3$ acuoso saturado (50 mL). La capa acuosa se extrajo con EtOAc (50 mL). Las capas orgánicas combinadas se lavaron con salmuera (50 mL), se secaron sobre Na_2SO_4 y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc 3:1) para obtener el **compuesto 174** (3,5 g, 79 %) en forma de un sólido marrón pálido. ^1H RMN (400 MHz, $CDCl_3$) δ 8,17-8,22 (m, 1H), 7,77 (s, 1H), 7,37-7,40 (d, 1H), 7,14-7,19 (m, 1H), 6,78 (s, 1H), 6,45-6,51 (m, 1H), 4,85-4,9 (s, 2H), 4,59-4,76 (m, 2H), 4,01(s, 3H). LCMS *m/z* 388 $[M+H]^+$.

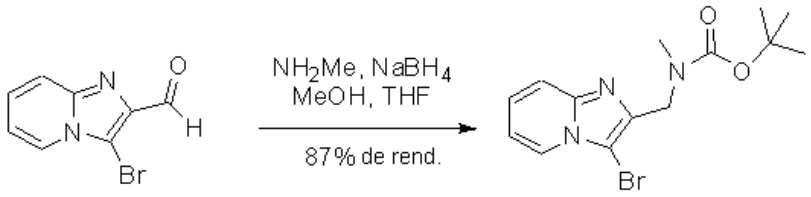
Preparación de 2-[(1*R*)-1-{[2-amino-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-3-il]oxi}etil]-4-fluorobenzoato de metilo (175)



7 175

El procedimiento descrito en la etapa 1 para el **Ejemplo 45** se usó para preparar el **compuesto 175,** ^{1}H RMN (600 MHz, DMSO-d_6) δ 7,94 (dd, *J* = 8,80, 5,87 Hz, 1 H), 7,74 (s, 1 H), 7,68 (dd, *J* = 10,56, 2,35 Hz, 1 H), 7,25 (td, *J* = 8,36, 2,64 Hz, 1 H), 6,87 (s, 1 H), 6,36 (s, 2 H), 6,26 (q, *J* = 6,46 Hz, 1 H), 3,91 (s, 3 H), 1,57 (d, *J* = 5,87 Hz, 3 H), 1,21 (d, J = 5,87 Hz, 12 H).

Preparación de [(3-bromoimidazo[1,2-*a*]piridin-2-il)metil]metilcarbamato de ter-butilo (177)

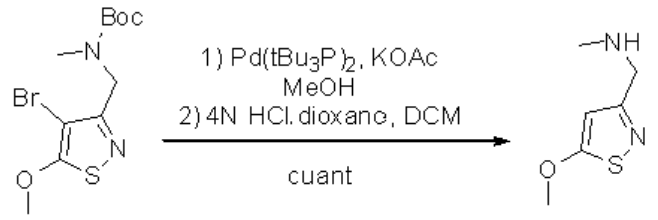


176 177

A una solución de **compuesto 176** (0,5 g, 2,22 mmol) en MeOH (20 mL) se añadió una solución de metilamina (2 M en THF, 1,33 mL, 2,67 mmol). La mezcla resultante se agitó a temperatura ambiente durante 1 h. A la mezcla de reacción se añadió $NaBH_4$ (84 mg, 2,22 mmol). Se observó una evolución de gas vigorosa. La evolución de gas cesó después de 30 minutos. La LCMS indicó la conversión completa en la amina. Se añadió bicarbonato de di-ter-butilo (735 mg, 3,33 mmol) y la mezcla se agitó a temperatura ambiente durante 18 h. La LCMS mostró la conversión completa en el producto deseado. La solución se concentró y el residuo se purificó por Biotage (cartucho 40+S) usando un gradiente de 10-75% de EtOAc/heptano como eluyente para obtener el **compuesto 177** (654 mg, 86,5 %) en forma de un aceite. H RMN realizada a 80 ºC. ^{1}H RMN (400 MHz. **80ºC**, DMSO-d_6) δ ppm 8,21 - 8,44 (m, 1 H),

7,50 - 7,64 (m, 1 H), 7,27 - 7,43 (m, 1 H), 6,96 - 7,14 (m, 1 H), 4,54 (s, 2 H), 2,86 (s, 3 H), 1,42 (s, 8 H).

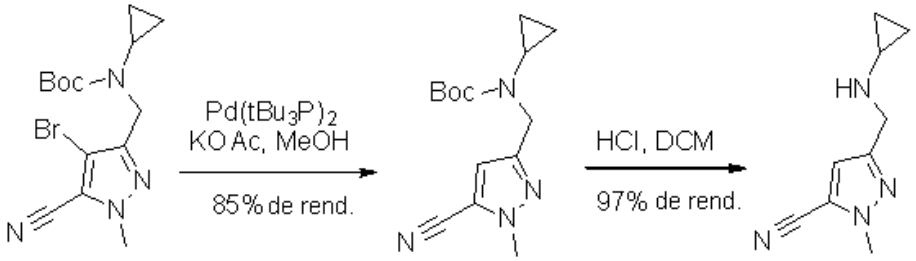
Preparación de 1-(5-metoxi-1,2-tiazol-3-il)-*N*-metilmetanamina (178)



52 **178**

En un vial de microondas sellado de 20 ml, se calentó una solución de **compuesto 52** (340 mg, 1,01 mmol), KOAc (297 mg, 3,02 mmol) y $Pd(P^tBu_3)_2$ (52,7 mg, 0,101 mmol) en MeOH (5 mL) en el microondas durante 45 min a 100 ºC. Se diluyó con EtOAc, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró al vacío. El residuo se disolvió en DCM (2,50 mL) y luego se añadió HCl 4 N en dioxano (2,52 mL, 10,1 mmol). La reacción se agitó a temperatura ambiente y se concentró al vacío para obtener el **compuesto 178** (196 mg, cuantitivo) en forma de un sólido. ^{1}H RMN (400MHz ,DMSO-d6) δ 9,46 (br. s., 2 H), 6,92 (s, 1 H), 4,15 (s, 2 H), 4,00 (s, 3 H), 2,58 (s, 3 H).

Preparación de 3-[(ciclopropilamino)metil]-1-metil-1*H*-pirazol-5-carbonitrilo (181).



179 **180** **181**

Etapa 1:

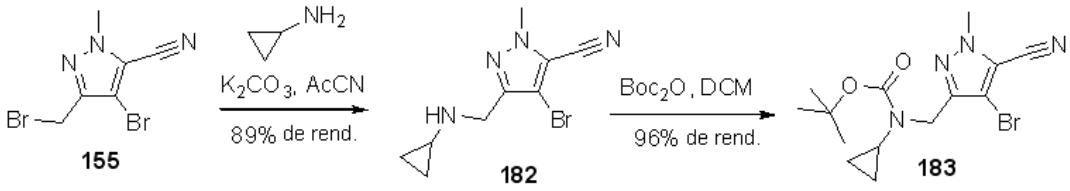
A una solución de **compuesto 179** (1,50 g, 4,22 mmol) en MeOH desgasificado se añadieron KOAc (1,24 g, 3,00 mmol) y $Pd(tBu_3P)_2$ (220 mg, 0,10 mmol). Se calentó hasta 120 ºC en el microondas durante 1 hora. La mezcla de reacción se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (0-40% de EtOAc/heptanos) para obtener el **compuesto 180** (990 mg, 85%) en forma de un

aceite claro. ^{1}H RMN (400MHz ,DMSO-d6) δ 6,91 (s, 1 H), 4,31 (s, 2 H), 3,96 (s, 3 H), 2,49 - 2,43 (m, 1 H), 1,39 (s, 9 H), 0,72 - 0,53 (m, 4 H).

Etapa 2:

A una solución de **compuesto 180** (990 mg, 3,58 mmol) en DCM (9 mL) se añadió HCl 4 N en dioxano (8,96 mL, 35,8 mmol). La suspensión se agitó durante 2 horas a temperatura ambiente y luego la mezcla de reacción se concentró al vacío para obtener el **compuesto 181** (739 mg, 97%) en forma de un sólido blanco. ^{1}H RMN (400MHz ,DMSO-d6) δ 9,72 (br. s., 2 H), 7,33 (s, 1 H), 4,22 (s, 2 H), 4,03 (s, 3 H), 2,66 (tt, *J* = 3,8, 7,4 Hz, 1 H), 0,95 - 0,83 (m, 2 H),0,77 - 0,66 (m, 2 H).

Preparación de [(4-bromo-5-ciano-1-metil-1*H*-pirazol-3-il)metil]ciclopropil-carbamato de ter-butilo (183).



Etapa 1:

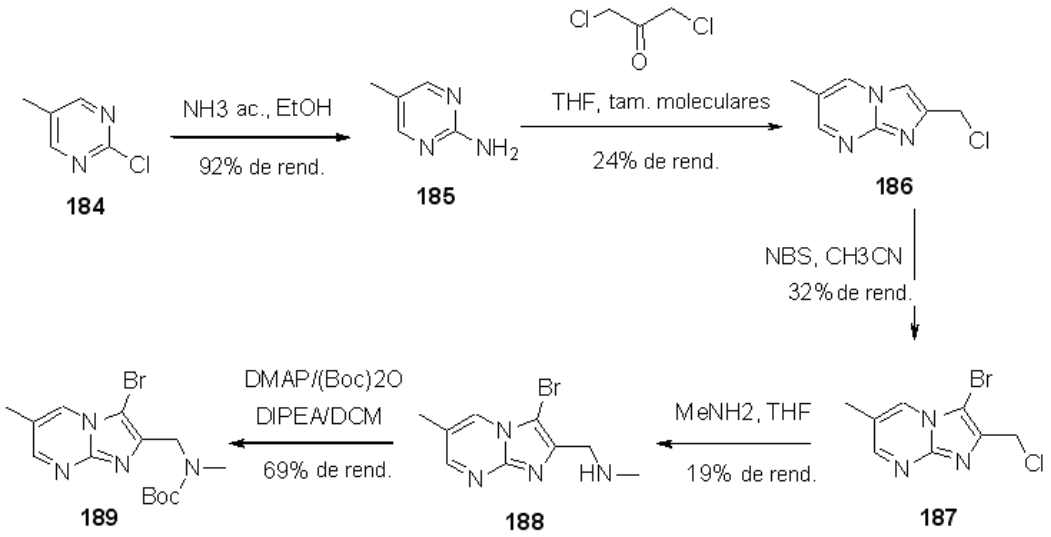
La ciclopropilamina (31,07 g, 544 mmol) se diluyó en acetonitrilo (30 ml), y luego se añadió carbonato de potasio (8,4 g, 61 mmol), seguido del **compuesto 155** (8,5 g, 279 mmol) disuelto en acetonitrilo (30 ml). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. A la mezcla de reacción se añadieron EtOAc (400 ml) y agua (80 ml). Las fases se separaron, y luego la fase orgánica se evaporó para eliminar el exceso de ciclopropilamina. Al compuesto crudo se añadieron EtOAc (400 ml) y una solución acuosa de HCl 1 M (80 ml). La fase acuosa se llevó a pH 7 con una solución acuosa de NaOH 1 M y se extrajo con EtOAc (3*400 ml). Las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y los solventes se eliminaron a presión reducida para obtener el **compuesto 182** en forma de un sólido amarillo pálido (6,95 g, 89% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d6) δ 3,99 (s, 3H), 3,68 (s, 2H), 2,05 (tt, 1H, J = 6,65, 3,53 Hz), 0,34 (td, 2H, J = 4,06, 6,43 Hz), 0,23 - 0,19 (m, 2H), [M+H]+= 257,06 – 258,14 (1/1)

Etapa 2:

El compuesto 182 (6,95 g, 27,2 mmol, 1 eq.) se disolvió en diclorometano (90 ml, 0,3 M), y luego se añadió anhídrido de Boc (5,94 g, 27,2 mmol, 1 eq.) en una porción pequeña. La mezcla de reacción se agitó a temperatura ambiente durante 60 horas. Los solventes se eliminaron al vacío. El material crudo se combinó con la

reacción en menor escala (792 mg) y se purificó por cromatografía flash para obtener el **compuesto 183** en forma de un sólido blanco (10,29 g, 96% de rendimiento, 97% de pureza por LC-MS). ^{1}H RMN (400 MHz, DMSO-d6) δ 4,35 (s, 2H), 3,99 (s, 3H), 2,42 (tt, J = 6,6, 4,0 Hz, 1H), 1,37 (s, 8H), 0,63 (ddt, J = 5,1, 3,4, 2,1 Hz, 4H). [M+H-Boc]= 255,01 – 256,99 (1/1).

Preparación de ((3-bromo-6-metilimidazo[1,2-a]pirimidin-2-il)metil)(metil)-carbamato de ter-butilo (189).



Etapa 1:

A una solución de **compuesto 184** (10,0 g, 77,79 mmol) en IMS (100 mL) se añadió amoníaco acuoso (35%, 100 ml). La mezcla de reacción se transfirió a una bomba sellada y se calentó a 200 °C durante 4 h. La mezcla de reacción se dejó enfriar hasta temperatura ambiente y se concentró para eliminar la mayor parte del solvente y se añadió agua (25 mL). El sólido obtenido se filtró y se secó al vacío para obtener el **compuesto 185** deseado en forma de un sólido blanquecino (7,85 g, 92% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d6) δ 8,06 (s, 2H), 6,30 (s, 2H), 2,03 (s, 3H). LCMS *m/z* 110 $[M+H]^+$.

Etapa 2:

La reacción se realizó en dos lotes usando 1 g y 9,36 g de **compuesto 185 y** el material crudo obtenido de ambos lotes se combinó para purificación. A una suspensión de **compuesto 185** (9,36 g, 85,82 mmol) en THF seco (250 mL) se añadieron dicloroacetona (21,80 g, 171,64 mmol) y tamices moleculares 4A° (25 g). La mezcla de reacción se calentó a 90 °C durante 3 días, luego la mezcla de reacción se concentró y el residuo resultante se disolvió en agua (200 mL). La solución se trató

con K_2CO_3 sólido (10 g) y se agitó durante 10 min antes de la extracción con acetato de etilo (3 x 400 mL). Los extractos combinados de acetato de etilo se lavaron con salmuera (100 mL) y se concentraron para obtener el producto crudo en forma de un aceite marrón espeso. La fase acuosa se sometió a extracción de líquido-líquido con DCM (500 mL) y el producto resultante obtenido se combinó con el aceite crudo obtenido de las extracciones de acetato de etilo para la purificación. La purificación por cromatografía en columna de gel de sílice usando 0,5% - 1% de MeOH en DCM produjo el **compuesto 186** en forma de un sólido blanquecino (4,2 g, 24% de rendimiento). ^{1}H RMN (400 MHz, Cloroformo-d) δ 8,44 (d, *J* = 2,4 Hz, 1H), 8,23 (dd, *J* = 2,4, 1,2 Hz, 1H), 7,56 (d, *J* = 0,8 Hz, 1H), 4,79 (d, *J* = 0,8 Hz, 2H), 2,37 (d, *J* = 1,1 Hz, 3H). LCMS *m/z* 182 $[M+H]^+$.

Etapa 3:

La reacción se realizó en dos lotes usando 2,0 g y 2,2 g de **compuesto 186 y** el material crudo obtenido de ambos lotes se combinó para la purificación. A una solución de **compuesto 186** (2,0 g, 11,01 mmol) en acetonitrilo (30 mL) se añadió NBS (2,14 g, 12,0 mmol) y la reacción se agitó a temperatura ambiente durante la noche. El solvente se eliminó al vacío y el producto crudo combinado se disolvió en EtOAc (100 mL). El sólido que se precipitó se eliminó por filtración y el filtrado se evaporó para obtener el producto crudo en forma de una goma amarilla clara. La purificación del crudo por cromatografía en columna de gel de sílice usando 0,5% de MeOH en DCM produjo el **compuesto 187** puro en forma de un sólido blanquecino (1,9 g, 32% de rendimiento). ^{1}H RMN (400 MHz, Cloroformo-d) δ 8,47 (d, *J* = 2,4 Hz, 1H), 8,14 (dd, *J* = 2,4, 1,2 Hz, 1H), 4,78 (s, 2H), 2,44 (s, 3H). LCMS *m/z* 260/262 $[M+H]^+$.

Etapa 4:

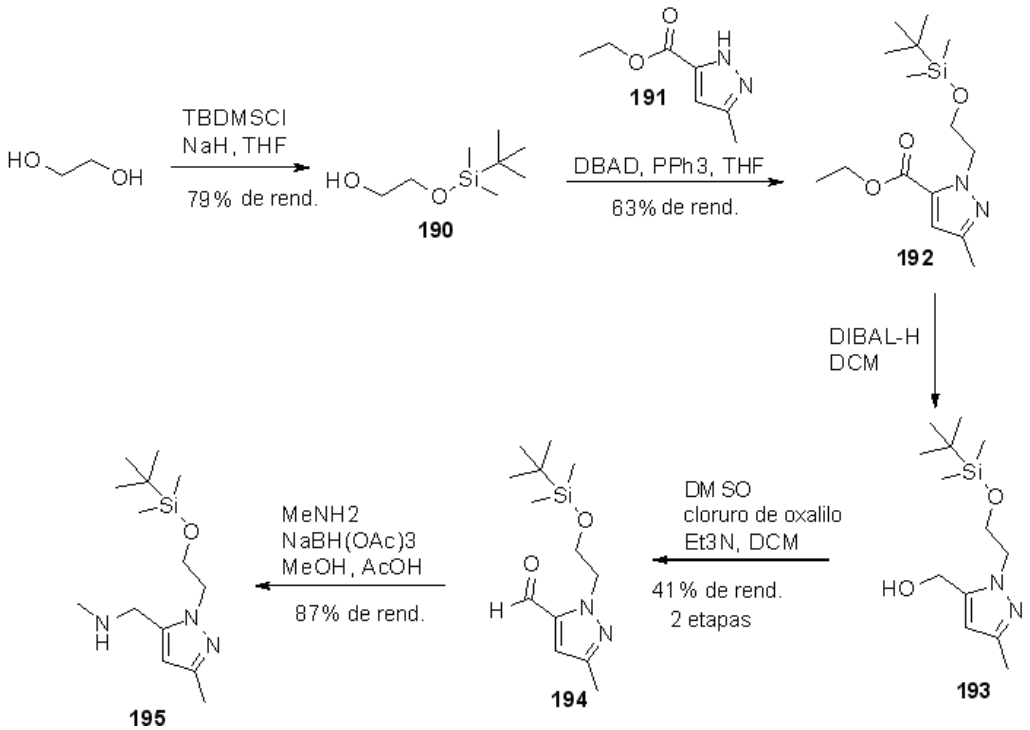
A una suspensión de **compuesto 187** (1,68 g, 6,45 mmol) en THF (20 mL) calentada a 60 °C, se añadió lentamente una solución de metilamina en THF (2 M, 53,2 mL, 96,75 mmol) durante un período de 30 min usando una bomba de jeringa. Una vez completa la adición, la reacción se calentó a 60 °C durante 4 h. El producto crudo obtenido después de la concentración de la mezcla de reacción se purificó por cromatografía flash en columna de gel de sílice usando 10% de MeOH en DCM junto con 0,1% de 35% de amoníaco acuoso. Se halló que el producto obtenido contenía una pequeña cantidad de dímero no deseado, por lo que se purificó luego por fase inversa usando un gradiente de solvente CH_3CN/H_2O. El producto así obtenido se contaminó con una traza de impureza y se purificó otra vez por cromatografía flash en

columna de gel de sílice usando 4% de MeOH en DCM (con amoníaco 7 N) para obtener el **compuesto 188** en forma de un sólido amarillo (254 mg, 15% de rendimiento). ^{1}H RMN (400 MHz, Metanol-d4) δ 8,89 – 8,22 (m, 2H), 3,88 (s, 2H), 2,45 (d, *J* = 1,1 Hz, 3H), 2,42 (s, 3H). LCMS *m/z* 255/257 $[M+H]^+$.

Etapa 5:

A una solución de **compuesto 188** (250 mg, 0,980 mmol), DIEA (0,512 mL, 2,94 mmol) y DMAP (23,9 mg, 0,196 mmol) en DCM (4 mL) se añadió $(Boc)_2O$ (856 mg, 3,92 mmol) a 0 ºC. La mezcla se agitó a temperatura ambiente durante la noche. Se concentró y se purificó por ISCO (24 g) usando 0% - 75% de EtOAc/Heptanos para obtener el **compuesto 189** en forma de una goma (241 mg, 69% de rendimiento). ^{1}H RMN (400MHz, DMSO-d6) δ 8,59 (s, 1H), 8,48 (d, *J*=2,3 Hz, 1H), 4,52 (s, 2H), 2,85 (br. s., 3H), 2,37 (s, 3H), 1,39 (d, *J*=15,9 Hz, 9H). LCMS *m/z* 355/357 $[M+H]^+$.

Preparación de 1-[1-(2-{[ter-butil(dimetil)silil]oxi}etil)-3-metil-1*H*-pirazol-5-il]-*N*-metilmetanamina (195).



Etapa 1:

En una atmósfera inerte a 0 ºC (baño de hielo/agua), a una suspensión de NaH (60% en aceite mineral, 6,44 g, 0,161 mol) (temperatura interna = 4 ºC) se añadió etilenglicol (10,0 g, 0,161 mol). La temperatura interna después de la adición era de 6 ºC. La reacción se agitó durante 45 minutos en el baño de hielo/agua (temperatura

interna = 4 °C). Se añadió en porciones ter-butilclorodimetilsilano (29,121 g, 0,161 mol) durante 15 minutos manteniendo la temperatura a menos de 10 °C. Después de la adición de ter-butilclorodimetilsilano la mezcla de reacción se calentó hasta temperatura ambiente y se agitó durante 2,5 horas. La reacción luego se neutralizó por adición de solución de NaHCO3 saturada (250 mL) y agua (100 mL). La mezcla se extrajo con TBME (250 mLX2), y las capas orgánicas combinadas se lavaron con salmuera (250 mL), se secaron sobre Na_2SO_4, se filtraron y se redujeron hasta sequedad para obtener un aceite amarillo. El crudo se purificó por filtración en un taco de sílice usando heptanos/EtOAc (elución en gradiente 95/5 luego 9/1, 8/2, 7/3). Las fracciones correctas se combinaron y se redujeron hasta sequedad para obtener el **compuesto 190** en forma de aceite incoloro (22,5 g, 79%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,00 (s, 6H), 0,82 (s, 9H), 2,00 (t, 1H), 3,54-3,58 (m, 2H), 3,62-3,64 (m, 2H).

Etapa 2:

En una atmósfera inerte, a una solución de **compuesto 191** (20,00 g, 129,7 mmol), 2-((ter-butildimetilsilil)oxi)etanol **190** (27,45 g, 155,7 mmol) y trifenilfosfina (40,83 g, 155,7 mmol) en THF (400 mL) enfriada hasta 0 °C se añadió gota a gota una solución de DBAD (35,85 g, 155,7 mmol) en THF (200 mL) durante 1 hora. Después de agitar durante 3 horas a temperatura ambiente, se añadieron 0,1 equiv de 2-((ter-butildimetilsilil)oxi)etanol (2,2 g, 12,48 mmol). La mezcla de reacción se agitó durante otras 18 horas y luego se concentró. El aceite amarillo resultante se trituró con heptano (1 L) formando un sólido blanco que se eliminó por filtración. El filtrado se concentró y el residuo oleoso se purificó por cromatografía en columna (sílice, 2% al 6% de EtOAc en heptano) para obtener el **compuesto 192** en forma de un aceite amarillo pálido (25,47 g, 63%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,11 (s, 6H), 0,78 (s, 9H), 1,33 (t, 3H), 2,25 (s, 3H), 3,89 (t, 2H), 4,29 (q, 2H), 4,63 (t, 2H), 6,57 (s, 1H), [MH]+ 313.

Etapa 3:

En una atmósfera inerte, a una solución de **compuesto 192** (24,8 g, 79,4 mmol) en DCM (600 mL) enfriada hasta – 78 °C se añadió gota a gota DIBAL-H (solución 1 M en DCM, 250 mL, 250 mmol). Después de agitar durante 1 hora a –78 °C, la mezcla de reacción se neutralizó con metanol (60 mL) y luego se calentó hasta temperatura ambiente. Se añadieron agua y salmuera para formar un precipitado gris. El intento por preparar una extracción no fue exitoso porque las dos fases eran difíciles de visualizar. La mezcla de reacción luego se filtró sobre Celite y se lavó con grandes cantidades de DCM (4 L). La capa de agua se separó y la fase orgánica se secó

(Na_2SO_4) y se concentró para obtener el **compuesto 193** en forma de un aceite (20 g) que se usó como tal en la siguiente etapa. ^{1}H RMN (400 MHz, CDCl3) δ 0,04 (s, 6H), 0,79 (s, 9H), 2,23 (s, 3H), 3,96 (t, 2H), 4,22 (t, 2H), 4,55 (d, 2H), 5,97 (s, 1H), [MH]+ 271.

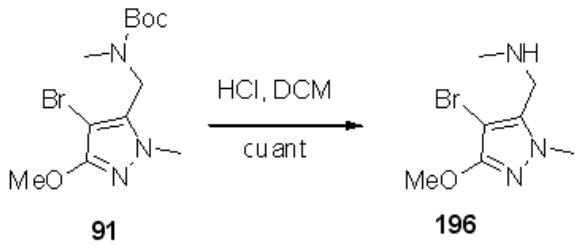
Etapa 4:

En una atmósfera inerte, a una solución de cloruro de oxalilo (8,70 mL, 103 mmol) en DCM (188 mL) enfriada hasta – 78 °C se añadió durante 30 min una solución de DMSO (14,4 mL, 205 mmol) en DCM (75 mL). La mezcla de reacción se agitó durante 30 min a –78 °C, y luego se añadió gota a gota una solución de **compuesto 193** (20 g) en DCM (188 mL). La mezcla de reacción se agitó durante 1,25 horas a –78 °C seguido de la adición gota a gota de trietilamina (66,0 mL, 474 mmol). La reacción se calentó hasta temperatura ambiente y se añadió agua (600 mL). Las fases se separaron y la capa acuosa se extrajo con DCM (3 x 500 mL). Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron. El residuo oleoso resultante se purificó por cromatografía en columna (sílice, 0% al 2% de EtOAc en DCM) para obtener el **compuesto 194** en forma de un aceite amarillo pálido (8,75 g, 41% en dos etapas). ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,11 (s, 6H), 0,78 (s, 9H), 2,29 (s, 3H), 3,90 (t, 2H), 4,56 (t, 2H), 6,63 (s, 1H), 9,80 (s, 1H), [MH]+ 269.

Etapa 5:

En una atmósfera inerte, a una solución de **compuesto 194** (11,15 g, 41,54 mmol) y metilamina (33% p/p en EtOH, 14,77 g, 157,22 mmol) en metanol (280 mL) se añadió ácido acético (2,50 mL, 41,54 mmol) gota a gota. La mezcla de reacción se agitó a temperatura ambiente durante 1,3 horas, se enfrió hasta 0 °C, se trató con $NaBH(OAc)_3$ (13,2 g, 62,31 mmol) y luego se agitó a temperatura ambiente durante 18 horas. Después de este tiempo, se añadió cierta cantidad de amina (3,90 mg, 41,92 mmol) seguido de $NaBH(OAc)_3$ (8,80 g, 41,5 mmol) 30 minutos después. La mezcla de reacción se agitó durante otros 40 minutos, se concentró, se extrajo en EtOAc (375 mL) y se lavó con $NaHCO_3$ sat. ac. (275 mL) y salmuera (200 mL). La capa orgánica se secó (Na_2SO_4) y se concentró. El residuo oleoso resultante se purificó por cromatografía en columna (sílice neutralizada, 0% al 6% de NH_3/MeOH 7 N en DCM) para obtener el **compuesto 195** (10,3 g, 87%). ^{1}H RMN (400 MHz, CDCl3) δ 0,10 (s, 6H), 0,80 (s, 9H), 1,60 (br, 1H), 2,20 (s, 3H), 2,42 (s, 3H), 3,71 (s, 2H), 3,92 (t, 2H), 4,11 (t, 2H), 5,88 (s, 1H), MH]+ 284,

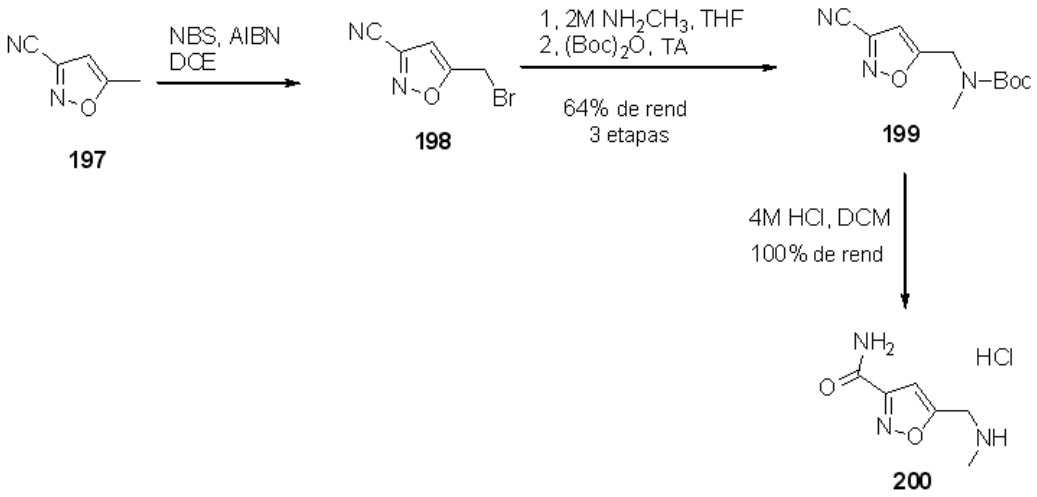
Preparación de 1-(4-bromo-3-metoxi-1-metil-1*H*-pirazol-5-il)-*N*-metilmetanamina (196)



91 **196**

A una solución de **compuesto 91** (1613 mg, 4,826 mmol) en DCM (10 ml) se añadió HCl 4 N en dioxano.(10 ml). La solución se agitó a temperatura ambiente durante 2 horas, y luego la mezcla de reacción se concentró para obtener el **compuesto 196** (1357 mg, 104%) en forma de un sólido amarillo.

Preparación de 5-((metilamino)metil)isoxazol-3-carboxamida (200)



197 **198** **199** **200**

Etapa 1:

A una solución de **compuesto 197** (800 mg, 7,40 mmol) en DCE (30 mL) se añadieron NBS (2,79 g, 15,5 mmol) y AIBN (60,8 mg, 0,375 mmol). La reacción se agitó a 85 ºC durante la noche. Se concentró para obtener un sólido crema. Se añadió agua (20 mL) y se extrajo con EtOAc (30 mL × 2). Las capas orgánicas combinadas se lavaron con salmuera (20 mL), se secaron sobre Na_2SO_4 y se concentraron para obtener el **compuesto 198** (1,44 g, 2,90 mmol) en forma de un semisólido blanquecino, que se usó en la siguiente etapa sin otra purificación.

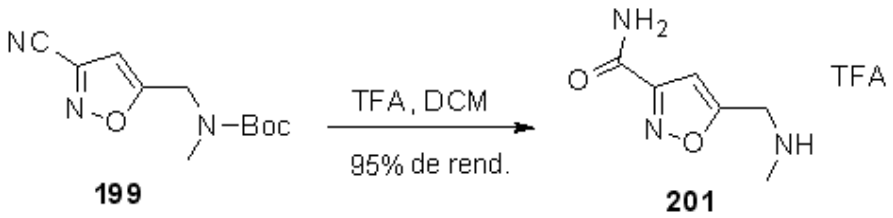
Etapa 2:

Una solución de **compuesto 198** (1,44 g, 2,90 mml) en THF (15 mL) se enfrió hasta 0 ºC, y se añadió NH_2CH_3 2 M en THF (4,36 mL, 8,73 mmol). La mezcla se agitó a 0 ºC durante 2,5 h. Se añadió $(Boc)_2O$ (635 mg, 2,91 mmol). Se dejó reposar durante la noche a temperatura ambiente. La LCMS mostró el nuevo pico y el material de partida. Se añadieron 380 mg de $(Boc)_2O$. La mezcla resultante se agitó a temperatura ambiente durante 3 h. La LCMS mostró que el nuevo pico crecía. Después de otras 2 h, la LCMS no demostró ningún progreso. Se añadieron 283 mg de $(Boc)_2O$. Se agitó a temperatura ambiente durante la noche. El solvente se eliminó al vacío y la reacción se dividió entre agua y EtOAc (50 ml/50 ml). La fase orgánica se separó, se secó sobre Na_2SO_4 y se concentró. Se purificó por ISCO con 0-40% de EtOAc/Heptano para obtener el **compuesto 199** en forma de un aceite incoloro (445 mg, 64% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,47 (br. s., 9 H) 2,98 (s, 3 H) 4,60 (br. s., 2 H) 6,56 (br. s., 1 H).

Etapa 3:

A una solución de **compuesto 199** (445 mg, 1,88 mmol) en DCM (5 mL) se añadió HCl 4 M en dioxano (5 mL) gota a gota. La reacción estaba completa después de 2 horas por LCMS. Se concentró y se secó en un horno de vacío a 60 ºC durante la noche para obtener el **compuesto 200,** sal de HCl en forma de un sólido blanco (333 mg, 100% de rendimiento). ^{1}H RMN (400 MHz, DMSO-*d*6) δ 2,59 (s, 3 H) 4,44 (s, 2 H) 7,00 (s, 1 H) 7,90 (br. s., 1 H) 8,21 (br. s., 1 H) 9,77 (br. s., 2 H). LCMS *m/z* 156 $[M+H]^+$.

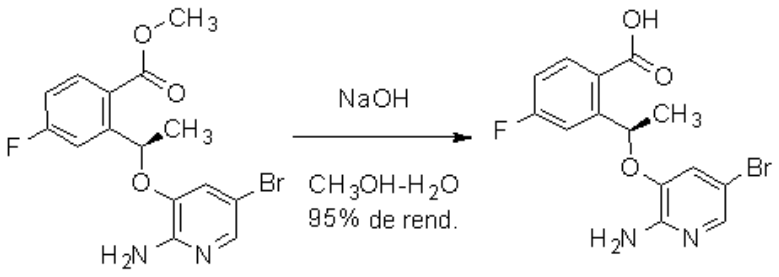
Preparación de 5-[(metilamino)metil]-1,2-oxazol-3-carbonitrilo (201)



199 **201**

A una solución de **compuesto 199** (850 mg, 2,90 mmol) en DCM (3 mL) se añadió TFA (3 mL, 38,9 mmol) gota a gota. La reacción estaba completa después de 1,5 horas por LCMS. Se concentró y se secó en un horno de vacío a 60 ºC durante la noche para obtener el **compuesto 201** en forma de una goma marrón (686 mg, 95% de rendimiento).

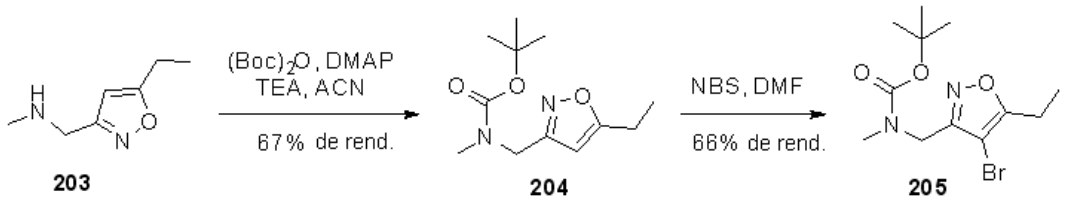
Preparación de ácido 2-{(1*R*)-1-[(2-amino-5-bromopiridin-3-il)oxi]etil}-4-fluorobenzoico (202)



7 **202**

El procedimiento descrito en la etapa 2 para el **Ejemplo 41** se usó para preparar el **compuesto 202** (731 mg, 95%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 13,43 (br. s., 1 H) 7,97 (dd, *J*=8,59, 6,06 Hz, 1 H) 7,47 - 7,64 (m, 2 H) 7,18 - 7,30 (m, 1 H) 6,87 (s, 1 H) 6,20 - 6,48 (m, 3 H) 1,58 (d, *J*=6,32 Hz, 3 H).

Preparación de [(4-bromo-5-etil-1,2-oxazol-3-il)metil]metilcarbamato de ter-butilo (205).



203 **204** **205**

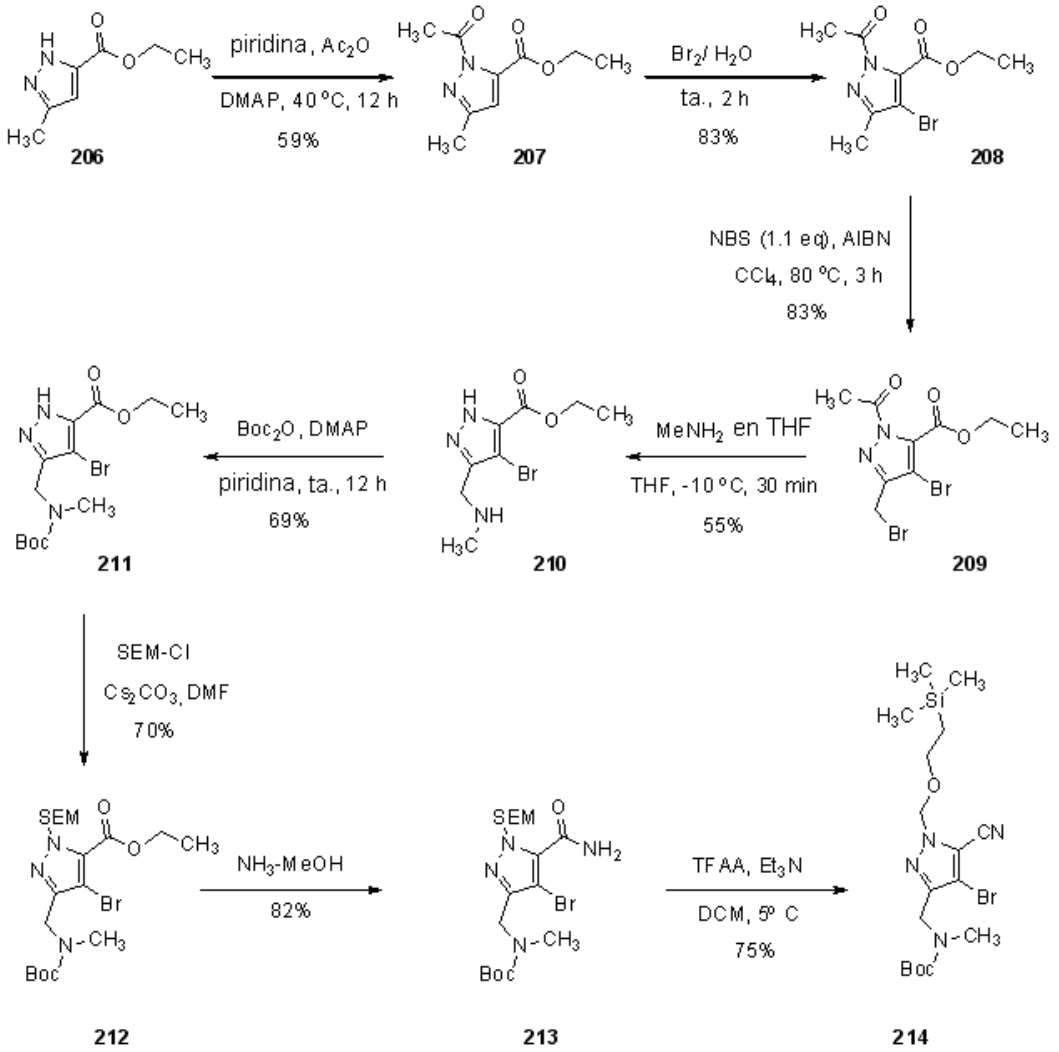
Etapa 1:

A una suspensión a 0 ºC de **compuesto 203** (1,81 g, 12,9 mmol), TEA (9,10 mL, 64,6 mmol) y DMAP (0,315 g, 2,58 mmol) en ACN (50 mL) se añadió dicarbonato de di-t-butilo (3,38 g, 15,5 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. Se añadieron agua y EtOAc a la mezcla de reacción. La capa acuosa se extrajo por 2x EtOAc. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (2 a 30 % de EtOAc/Heptano) para obtener el **compuesto 204** (2,09 g, 67%) en forma de un aceite incoloro. ^{1}H RMN (400 MHz, METANOL-d4) δ 1,28 (t, J=7,58 Hz, 3 H) 1,47 (br. s., 9 H) 2,77 (q, J=7,58 Hz, 2 H) 2,88 (s, 3 H) 4,42 (s, 2 H) 6,04 (s, 1 H).

Etapa 2:

A una solución de **compuesto 204** (500 mg, 2,08 mmol) en DMF (2,2 mL) se añadió N-bromosuccinimida (444 mg, 2,50 mmol). La mezcla de reacción se calentó hasta 60 ºC durante 1 hora. Se añadió EtOAc (22 mL) a la mezcla de reacción, y luego se lavó con agua (1 x 22 mL) y salmuera (22 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró al vacío. El residuo se purificó por cromatografía en columna (3% al 30% de EtOAc/Heptano) para obtener el **compuesto 205** (441 mg, 66%) en forma de un aceite incoloro. ^{1}H RMN (400 MHz, METANOL-*d*$_4$) δ 1,28 (t, *J*=7,71 Hz, 3 H) 1,48 (s, 4 H) 1,43 (s, 5 H) 2,82 (q, *J*=7,66 Hz, 2 H) 2,89 (s, 3 H) 4,50 (s, 2 H).

Síntesis de ((4-bromo-5-ciano-1-((-2-(trimetilsilil)etoxi)metil)-1*H*-pirazol-3-il)metil)carbamato de ter-butilo (compuesto 214)



Etapa 1:

A una solución de **compuesto 206** (120 g, 0,779 mol) en piridina (800 mL) se añadió Ac_2O (400 mL) y luego una cantidad catalítica de DMAP (13 g, 0,106 mol) a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente durante 12 horas. La TLC (éter de petróleo/EtOAc = 3:1) mostró que la reacción estaba completa. La mezcla se concentró al vacío para obtener el residuo, que se dividió entre CH_2Cl_2 (1 L) y H_2O (200 mL). La capa orgánica se separó, se lavó con salmuera (100 mL), se secó sobre Na_2SO_4 y se concentró al vacío para obtener el producto crudo. El producto crudo se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc = 10:1) para obtener el **compuesto 207** (90 g, 59%) en forma de un sólido blanco. ^1H RMN (400 MHz, $CDCl_3$) δ 6,57 (s, 1H), 4,40-4,35 (q, 2H), 2,74 (s, 3H), 2,57 (s, 3H), 1,39-1,35 (t, 3H).

Etapa 2:

A una suspensión de **compuesto 207** (50 g, 0,255 mol) en H_2O (1,5 L) se añadió gota a gota Br_2 (44 g, 0,281 mol) a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente durante 3 horas. La TLC (éter de petróleo/EtOAc = 5:1) mostró que la reacción estaba completa. La mezcla se extrajo con EtOAc (500 mL x 3). Las capas orgánicas se combinaron, se lavaron con $NaHCO_3$ acuoso saturado (200 mL), H_2O (100 mL) y salmuera (100 mL), se secaron sobre Na_2SO_4 y se concentraron al vacío para obtener el producto crudo, que se purificó por recristalización en éter de petróleo/EtOAc (5:1, 120 mL) para obtener el **compuesto 208** (58 g, 83%) en forma de un sólido amarillo. ^1H RMN (400 MHz, $CDCl_3$) δ 4,47-4,42 (q, 2H), 2,77 (s, 3H), 2,63 (s, 3H), 1,44-1,40 (t, 3H).

Etapa 3:

A una suspensión de **compuesto 208** (56 g, 0,204 mol) en CCl_4 (800 mL) se añadieron NBS (40 g, 0,225 mol) y AIBN (9,6 g) a temperatura ambiente en una atmósfera de nitrógeno. La mezcla resultante se calentó a reflujo durante 3 horas. La TLC (éter de petróleo/EtOAc = 3:1) mostró que la reacción estaba completa. La mezcla se enfrió hasta temperatura ambiente y luego se filtró, y los sólidos se lavaron con CH_2Cl_2 (200 mL). El filtrado se lavó con solución acuosa saturada de $NaHCO_3$ (100 mL x 2), H_2O (100 mL) y salmuera (100 mL), se secó sobre Na_2SO_4 y se concentró al vacío para obtener el producto crudo, que se recristalizó en éter de petróleo/EtOAc (5:1, 120 mL) para obtener el **compuesto 209** (60 g, 83%) en forma de un sólido amarillo. ^1H RMN (400 MHz, $CDCl_3$) δ 4,88 (s, 2H), 4,48-4,42 (q, 2H), 2,80 (s, 3H), 1,45-1,41 (t, 3H).

Etapa 4:

A una solución de **compuesto 209** (59 g, 0,167 mol) en THF (300 mL) se añadió gota a gota CH_3NH_2 en THF (2 N, 419 mL, 0,835 mol) a -10 °C. La mezcla resultante se agitó a -10 °C durante 30 minutos. La TLC (éter de petróleo/EtOAc = 3:1) mostró que la reacción estaba completa. La mezcla se filtró y el filtrado se concentró al vacío a 25 °C durante 20 minutos y luego a mayor temperatura para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice (CH_2Cl_2/MeOH = 100:1~20:1, R_f = 0,3 en CH_2Cl_2/MeOH = 10:1) para obtener el **compuesto 210** (24 g, 55%) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,90-7,55 (br, 2H), 6,85 (s, 1H), 5,29 (s, 0,62H, CH_2Cl_2 residual), 4,36-4,31 (q, 2H), 4,21 (s, 2H), 3,49 (s, 1,56H, MeOH residual), 2,68 (s, 3H), 1,37-1,24 (t, 3H).

Etapa 5:

A una solución de **compuesto 210** (24 g, 0,092 mol) en piridina (300 mL) se añadieron DMAP (5,66 g, 0,046 mol) y Boc_2O (29,81 g, 0,138 mol) a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente durante la noche. La TLC (éter de petróleo/EtOAc = 3:1) mostró que la reacción estaba completa. La mezcla se concentró al vacío para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc= 10:1~2:1) para obtener el **compuesto 211** (23 g, 69%) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,44-4,38 (m, 4H), 2,91 (s, 3H), 1,49 (s, 9H), 1,25-1,24 (t, 3H).

Etapa 6:

A una suspensión de **compuesto 211** (23 g, 0,0637 mol) en DMF anhidra (400 mL) se añadió Cs_2CO_3 (46,8 g, 0,14 mol) a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente durante 30 minutos. Después de 30 minutos, se añadió SEM-Cl (24,39 g, 0,146 mol) a la mezcla. La mezcla resultante se agitó a temperatura ambiente durante 2 horas. La TLC (éter de petróleo/EtOAc = 3:1) mostró que la reacción estaba completa. La mezcla se diluyó con EtOAc (1 L) y salmuera (200 mL). La capa orgánica se separó y se lavó con H_2O (200 mL x 2) y salmuera (100 mL), se secó sobre Na_2SO_4 y se concentró al vacío para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc = 10:1) para obtener el **compuesto 212** (22 g, 70%) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 5,90-5,76 (s, 1H), 4,72-4,65 (m, 2H), 4,47-4,40 (q, 2H), 3,55-3,51 (m, 2H), 2,95-2,76 (m, 3H), 1,49 (s, 9H), 1,43-1,39 (t, 3H), 0,96-0,85 (m, 2H), 0-0,05 (m, 9H).

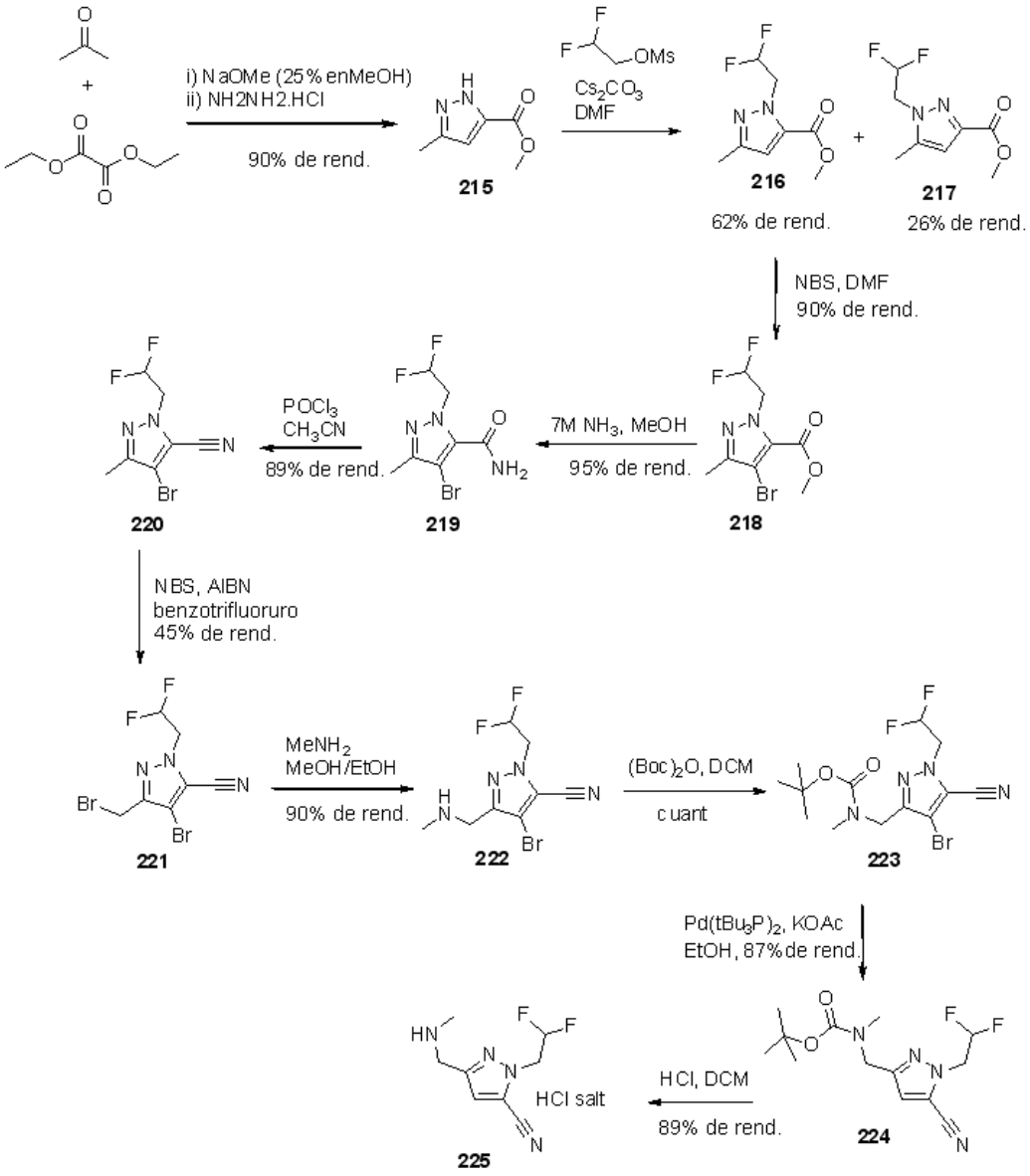
Etapa 7:

Una solución de **compuesto 212** (22 g, 0,0448 mol) en NH_3-MeOH (5 N, 350 mL) se calentó a 60 °C durante 12 horas en un tubo sellado. La TLC (éter de petróleo/EtOAc = 1:1) mostró que la reacción estaba completa. La mezcla se concentró al vacío para obtener el residuo, que se dividió entre CH_2Cl_2 (200 mL) y ácido cítrico (2 N, 30 mL). La capa orgánica se separó y se lavó con $NaHCO_3$ acuoso (2 N, 30 mL) y salmuera (20 mL) y se secó sobre Na_2SO_4, se filtró y se concentró al vacío para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc = 5:1~3:1) para obtener el **compuesto 213** (17 g, 82%) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,89 (s, 1H), 5,80 (s, 1H), 5,75 (s, 1H), 4,53-4,48 (m, 2H), 3,62-3,55 (m, 2H), 2,83-2,77 (m, 2H), 1,48 (s, 9H), 0,93-0,87 (m, 2H), 0 (s, 9H).

Etapa 8:

A una solución de **compuesto 213** (16 g, 0,0346 mol) en CH_2Cl_2 anhidro (250 mL) se añadió Et_3N (14,4 mL, 0,104 mol) y luego TFAA (9,6 mL) a 0 °C. La mezcla resultante se agitó a 0 °C durante 2 horas. La TLC (éter de petróleo/EtOAc = 3:1) mostró que la reacción estaba completa. La mezcla se concentró al vacío para obtener el producto crudo, que se dividió entre CH_2Cl_2 (150 mL) y ácido cítrico (40 mL, 2 N). La capa orgánica se separó, se lavó con $NaHCO_3$ acuoso (2 N, 50 mL) y salmuera (20 mL), se secó sobre Na_2SO_4, se filtró y se concentró al vacío para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc = 50:1) para obtener el **compuesto 214** (11,5 g, 74,8%) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 5,52 (s, 2H), 4,61-4,42 (m, 2H), 3,63-3,51 (m, 2H), 2,83-2,79 (m, 2H), 1,47 (s, 9H), 0,95-0,86 (m, 2H), 0 (s, 9H). LC-MS *m/z* 468 $[M+Na]^+$.

Preparación de {[4-bromo-5-ciano-1-(2,2-difluoroetil)-1*H*-pirazol-3-il]metil}metilcarbamato de ter-butilo (225)



Etapa 1:

A un recipiente de 5 litros equipado con un agitador superior se añadió solución de NaOMe (25% en MeOH, 500 mL, 2,31 mol) en una atmósfera de N_2. A ello se añadió MeOH (1,50 L) seguido de una solución de oxalato de dietilo (337 g, 2,31 mol) en acetona (168 mL, 2,31 mol) lentamente durante 50 min (después de 35 min, la reacción se volvió sólida, de modo que se añadieron otros 500 mL de MeOH). Al completar la adición, la mezcla de reacción amarilla pálida espesa se dejó reposar a temperatura ambiente durante 2 días bajo N_2. La reacción luego se enfrió hasta 0 ºC con agitación y se añadió lentamente HCl concentrado acuoso al 37% (190 mL, 2,31 mol) seguido de la adición lenta de monohidrato de hidrazina (112 mL, 2,31 mol)

durante 60 min, manteniendo una temperatura de reacción interna de menos de 20 ºC. La reacción se agitó luego a temperatura ambiente durante la noche. La reacción se filtró a través de Celite, lavando el taco con MeOH (200 mL). El solvente se eliminó hasta un volumen muy bajo y el residuo se dividió entre EtOAc (2,5 L) y agua/salmuera (2,0 L, 1:1). La fase orgánica se recogió y la fase acuosa se extrajo con EtOAc adicional (500 mL). Las capas orgánicas combinadas se lavaron con salmuera 1,0 L), se secaron sobre Na_2SO_4 y se evaporaron hasta sequedad para obtener el **compuesto 215** (226 g, 70%) en forma de un sólido de color crema. ^{1}H RMN (400 MHz, Cloroformo-d) δ 11,64 (s, 1H), 6,58 (d, J = 0,8 Hz, 1H), 3,89 (s, 3H), 2,37 (d, J = 0,7 Hz, 3H), [MH]+ 140,99.

Etapa 2:

Una mezcla de **compuesto 215** (30,8 g, 0,22 mol), 2,2-difluoroetilmetansulfonato (38,0 g, 0,24 mol) y Cs_2CO_3 (94,3 g, 0,29 mol) en DMF (150 mL) se agitó a 80 ºC durante 3,5 horas. Después de enfriarse, la reacción se diluyó con EtOAc (200 mL) y agua (800 mL). La capa orgánica se recogió y la capa acuosa se extrajo con EtOAc (2 x 300 mL). Las capas orgánicas combinadas se lavaron con agua (500 mL) y salmuera (500 mL), se secaron (Na_2SO_4) y se evaporaron. La purificación por cromatografía flash (20% al 50% de EtOAc en heptanos) produjo el **compuesto 216** (28 g, 62%) y **compuesto 217** (12 g, 26%).

Compuesto 216: 1H RMN (400 MHz, Cloroformo-d) δ 6,64 (s, 1H), 6,09 (tt, J = 55,9, 4,5 Hz, 1H), 4,87 (td, J = 13,1, 4,5 Hz, 2H), 3,86 (s, 3H), 2,26 (s, 3H).

Compuesto 217: 1H RMN (400 MHz, Cloroformo-d) δ 6,55 (s, 1H), 6,09 (tt, J = 55,5, 4,5 Hz, 1H), 4,41 (td, J = 13,1, 4,5 Hz, 2H), 3,86 (s, 3H), 2,30 (s, 3H), [MH]+ 205,06,

Etapa 3:

Se añadió NBS (32,0 g, 180 mmol) a una solución de **compuesto 216** (35,0 g, 172 mmol) en DMF (100 mL) y se agitó a 20 ºC durante 20 h. Se añadieron agua (200 mL) y $NaHSO_4$ acuoso al 2% (150 mL) y la mezcla se agitó durante 10 min y luego se extrajo en EtOAc/heptanos (2:1, 400 mL). La capa orgánica se separó y se lavó con salmuera (200 mL), se secó (Na_2SO_4) y se evaporó para obtener el **compuesto 218** (41 g, 90%) en forma de un aceite. ^{1}H RMN (400 MHz, DMSO-d6) δ 6,36 (tt, J = 55,0, 3,8 Hz, 1H), 4,90 (td, J = 14,6, 3,8 Hz, 2H), 3,88 (s, 3H), 2,20 (s, 3H), [MH]+ 283 y 285 (100%).

Etapa 4:

Una mezcla de **compuesto 218** (41 g, 0,145 mol) y NH_3 7 M en MeOH (500 mL) se agitó a 25 ºC durante 5 días. La mezcla de reacción luego se evaporó para

obtener el **compuesto 219** (37 g, 95%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d6) δ 8,04 (s, 1H), 7,77 (s, 1H), 6,31 (tt, J = 55,1, 3,7 Hz, 1H), 4,74 (td, J = 15,0, 3,7 Hz, 2H), 2,16 (s, 3H), [MH]+ 268 y 270 (100%).

Etapa 5:

Se añadió POCl3 (74 g, 0,483 mol) a una solución de **compuesto 219** (37 g, 0,138 mol) en acetonitrilo (250 mL) a 25 ºC. La reacción se agitó luego a reflujo durante 6 horas. Después de enfriarse, la reacción se vertió lentamente en agua (1000 mL) mientras se controlaba la exotermia manteniendo la mezcla a menos de 40 ºC mediante la adición de hielo a la capa acuosa de ser necesario. Después de agitar durante 5 minutos y no notar ninguna exotermia, la mezcla se extrajo en EtOAc/heptanos (1:1, 500 mL). La capa orgánica se separó y se lavó con $NaHCO_3$ acuoso saturado (200 mL), se secó (Na_2SO_4) y se evaporó para obtener el **compuesto 220** (27 g, 78%) en forma de un sólido marrón claro. ^{1}H RMN (400 MHz, DMSO-d6) δ 6,43 (tt, J = 53,9, 2,9 Hz, 1H), 4,81 (td, J = 15,9, 2,8 Hz, 2H), 2,23 (s, 3H).

Etapa 6:

Una mezcla de **compuesto 220** (15 g, 60 mmol), NBS (14,95 g, 84 mmol) y AIBN (492 mg, 3,0 mmol) en benzotrifluoruro (200 mL) se agitó a 80 ºC durante 12 horas. Después de enfriarse, la mezcla se filtró a través de un taco corto de gel de sílice y la torta filtrante se lavó con tolueno (20 mL). El filtrado se evaporó para obtener el **compuesto 221** (9,0 g, 45% de rendimiento) en forma de un aceite amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d6) δ 6,72 – 6,21 (m, 1H), 5,03 – 4,72 (m, 2H), 4,64 (s, 2H).

Etapa 7:

Se añadió lentamente una solución de **compuesto 221** (18 g, 27,4 mmol) en EtOH (50 mL) a una solución de $MeNH_2$ (40% en MeOH, 56 mL, 0,55 mol) en EtOH adicional (50 mL) a 0 ºC durante 15 min. Después de completar la adición, la reacción se agitó a 0 ºC durante 2 horas. La mezcla luego se concentró al vacío a aproximadamente 50 mL en volumen. Se añadió EtOH (50 mL) y la mezcla se concentró otra vez al vacío a aproximadamente 40 mL de volumen. Se añadió HCl acuoso 1 M (90 mL), seguido de TBME (150 mL) y la mezcla se agitó vigorosamente durante 5 minutos. La capa acuosa se recogió y se lavó una vez más con TBME (100 mL). La capa acuosa se recogió y se alcalinizó a aproximadamente pH 12-13 (papel de pH) usando NH_3 conc ac. La mezcla resultante se extrajo en DCM (3 x 150 mL). Las capas orgánicas se secaron (Na_2SO_4) y se evaporaron para obtener el **compuesto 222** (6,8 g, 90%) en forma de un aceite marrón pálido que solidificó al

reposar. ^{1}H RMN (400 MHz, DMSO-d6) δ 6,44 (tt, J = 53,8, 2,8 Hz, 1H), 4,84 (td, J = 15,9, 2,8 Hz, 2H), 3,63 (s, 2H), 2,24 (s, 3H), [MH]+ 279,0 y 281,0 (60%).

Etapa 8:

Se añadió dicarbonato de di-ter-butilo (5,6 g, 25,6 mmol) en porciones (sólido) a una solución de **compuesto 222** (6,8 g, 24,4 mmol) en DCM (100 mL) a 20 ºC durante 5 minutos. La mezcla luego se concentró al vacío y el residuo se purificó por cromatografía flash (20% de EtOAc en heptano) para obtener el **compuesto 223** (9,24 g, cuant) en forma de un aceite. ^{1}H RMN (400 MHz, DMSO-d6) δ 6,44 (tt, J = 53,7, 2,7 Hz, 1H), 4,86 (td, J = 16,0, 2,7 Hz, 2H), 4,42 (s, 2H), 2,78 (s, 3H), 1,47 – 1,28 (m, 9H), [MH-Boc]+ 268 y 270 (40%).

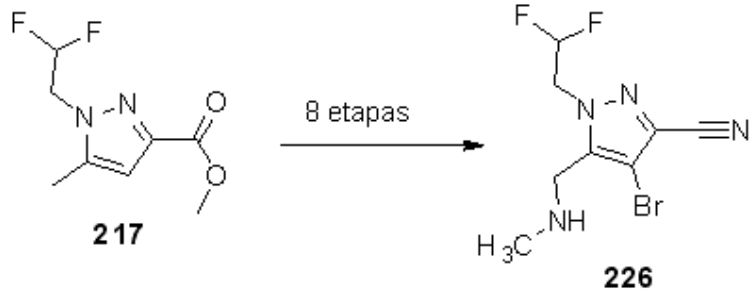
Etapa 9:

Se añadió Pd(t-$Bu_3P)_2$ (240 mg) en una porción a una mezcla de **compuesto 223** (1,80 g, 4,75 mmol) y KOAc (1,39 g, 14,3 mmol) e IMS desgasificado (95% de EtOH, 18,0 mL). La mezcla se agitó luego con irradiación de microondas (120 ºC) durante 60 min. Después de enfriar, la mezcla se concentró y se purificó por cromatografía en columna (30% de EtOAc en heptanos) para obtener el **compuesto 224** (1,25 g, 87%) en forma de un aceite. ^{1}H RMN (400 MHz, DMSO-d6) δ 7,08 (s, 1H), 6,42 (tt, J = 54,0, 2,9 Hz, 1H), 4,80 (td, J = 15,8, 2,9 Hz, 2H), 4,36 (s, 2H), 2,79 (s, 3H), 1,38 (s, 9H), [MH-Boc]+ 201,06.

Etapa 10:

Se añadió HCl (4 M en dioxano, 5,0 mL) a una solución de **compuesto 224** (1,40 g, 4,66 mmol) y la mezcla se agitó a 25 ºC durante la noche. La mezcla se concentró al vacío y el residuo se suspendió con EtOAc (10 mL) y se recolectó por filtración. El **compuesto 225** (980 mg, 89%) se obtuvo en forma de la sal clorhidrato (sólido de color crema). ^{1}H RMN (400 MHz, DMSO-d6) δ 9,47 (s, 2H), 7,44 (s, 1H), 6,46 (tt, J = 53,8, 2,8 Hz, 1H), 4,88 (td, J = 16,0, 2,7 Hz, 2H), 4,18 (s, 2H), 2,54 (s, 3H), [MH]+ 201,11.

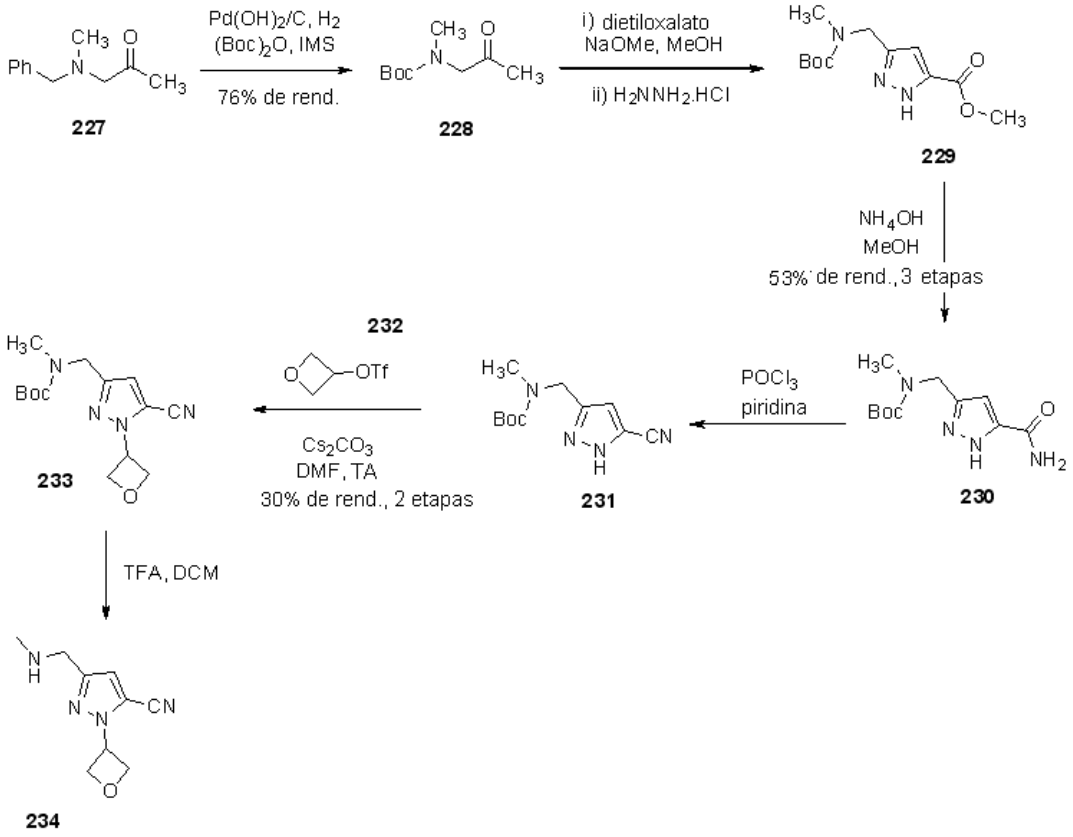
Preparación de {[4-bromo-5-ciano-1-(2,2-difluoroetil)-1*H*-pirazol-3-il]metil}metilcarbamato de ter-butilo (226)



217 **226**

Los procedimientos descritos en las etapas 3-10 para el **compuesto 225** se usaron para preparar el **compuesto 226** (30% de rendimiento). ^{1}H NMR (400 MHz, DMSO-d6) δ 9,57 (s, 2H), 7,30 (s, 1H), 6,47 (tt, J = 54,2, 3,4 Hz, 1H), 4,96 (td, J = 15,2, 3,4 Hz, 2H), 4,36 (s, 2H), 2,59 (s, 3H), [MH + CH3CN]+ 242,04.

Síntesis de ((5-ciano-1-oxetan-3-il)-1*H*-pirazol-3-il)metil)(metil)carbamato de ter-butilo (compuesto 234)



227 **228** **229** **230** **231** **232** **233** **234**

Etapa 1:

El **compuesto 227** (45,3 g, 0,256 mol) se disolvió en IMS (475 mL) y se añadieron $(Boc)_2O$ (58,6 g, 0,269 mol) y $Pd(OH)_2/C$ (4,0 g, 9% en peso). La mezcla de

reacción se agitó luego a temperatura ambiente en una atmósfera de hidrógeno (50 psi) durante tres horas antes de calentarla a 50 °C durante otras dos horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se filtró a través de Celite, eluyendo con IMS adicional, y el filtrado se concentró para obtener un aceite marrón. La mayor parte del material crudo (43,2 g) se purificó por cromatografía flash en gel de sílice (10% al 30% de EtOAc en heptanos) para obtener el **compuesto 228** en forma de un aceite amarillo (29,5 g, 76% de rendimiento, > 95% de pureza por 1H RMN). 1H RMN indica una mezcla ~1:1,1 de tautómeros. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,01 (s, 2H), 3,90 (s, 2H), 2,92 (s, 3H), 2,89 (s, 3H), 2,12 (s, 6H), 1,47 (s, 9H), 1,42 (s, 9H).

Etapa 2:

Una solución de NaOMe 5,4 M en MeOH (29,2 mL, 0,157 mol) se diluyó con más MeOH (150 mL) y se agitó a temperatura ambiente bajo nitrógeno. Se añadió una solución de **compuesto 228** (29,5 g, 0,157 mol) y dietiloxalato (21,3 mL, 0,157 mol) en MeOH (40 mL) desde un embudo de goteo durante 10 minutos y la mezcla de reacción amarilla resultante se calentó hasta 50 °C. Después de 3 horas, se añadió más dietiloxalato (2 mL, 0,015 mol) y solución de NaOMe (2 mL, 0,011 mol) y el calentamiento continuó durante otros 30 minutos. La reacción se enfrió hasta 5-10 °C y se añadió monoclorhidrato de hidrazina (10,7 g, 0,157 mol) en porciones durante 10 minutos, manteniendo la temperatura en este rango. La reacción luego se calentó hasta temperatura ambiente y se agitó durante 60 horas. Se añadieron H2O (200 mL) y salmuera (100 mL) a la mezcla de reacción antes de extraerla con EtOAc (3 x 200 mL). Los extractos orgánicos combinados se lavaron con salmuera (100 mL), se secaron sobre MgSO4 y se concentraron para obtener el **compuesto 229** en forma de un aceite amarillo, que se usó sin purificación (43,2 g). ^{1}H RMN (400 MHz, CDCl3) δ 6,72 (s, 1H), 4,47 – 4,32 (m, 2H), 3,91 (s, 3H), 2,86 (s, 3H), 1,47 (s, 9H). LC-MS ES m/z 268 [M+H]+.

Etapa 3:

El **compuesto 229** (21,1 g, 78,3 mmol) se disolvió en MeOH (60 mL) y se añadió una solución acuosa de NH_3 al 33% (100 mL) antes de agitar la solución de reacción a temperatura ambiente durante la noche. El volumen de MeOH se redujo al vacío, hasta que justo comenzó a formarse un precipitado. La mezcla se dejó cristalizar y el precipitado se recolectó por filtración, se lavó con H_2O (2 x 30 mL) y se secó intensamente en un horno de vacío (40 °C, durante la noche) para obtener una mezcla tautomérica (~1:1) de **compuesto 230** en forma de un sólido blanquecino (10,4

g, 53% de rendimiento en dos etapas). ^{1}H RMN indica una mezcla ~1:1,2 de tautómeros. ^{1}H RMN (400 MHz, DMSO-d_6) δ 13,27 (s, 1H), 13,11 (s, 1H), 7,91 (s, 1H), 7,55 – 7,33 (m, 2H), 7,15 (s, 1H), 6,68 (d, J = 2,0 Hz, 1H), 6,43 (d, J = 1,9 Hz, 1H), 4,37 (s, 2H), 4,30 (s, 2H), 2,79 (s, 3H), 2,75 (s, 3H),1,41 (s, 18H). LC-MS ES *m/z* 252 $[M+H]^+$.

Etapa 4:

El **compuesto 230** (10,5 g, 41,3 mmol) se disolvió en piridina (105 mL) y se añadió lentamente $POCl_3$ (9,6 mL, 103,2 mmol) desde un embudo de goteo, manteniendo la temperatura a aproximadamente 15 °C usando un baño de enfriamiento de hielo /H_2O. La mezcla de reacción se agitó durante 90 minutos, durante lo cual se volvió amarilla y luego de color marrón más oscuro. En porciones, la mezcla se vertió luego en H_2O (250 mL), manteniendo la temperatura a aproximadamente 30 °C mediante la adición de hielo. Una vez hidrolizada, la mezcla se extrajo con EtOAc (3 x 100 mL) y los extractos orgánicos combinados se lavaron con solución acuosa saturada de $NaHCO_3$ (150 mL) antes de secarlos sobre $MgSO_4$ y concentrarlos. El residuo se azeotropó con tolueno (3 x 100 mL) y luego heptanos (3 x 100 mL) para eliminar la piridina residual y obtener el **compuesto 231** en forma de una goma marrón que se usó sin purificación (9,1 g, >85% de pureza por 1H RMN). ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,56 (s, 1H), 4,31 (s, 2H), 2,89 (s, 3H), 1,48 (s, 9H). LC-MS ES *m/z* 235 $[M+H]^+$.

Etapa 5:

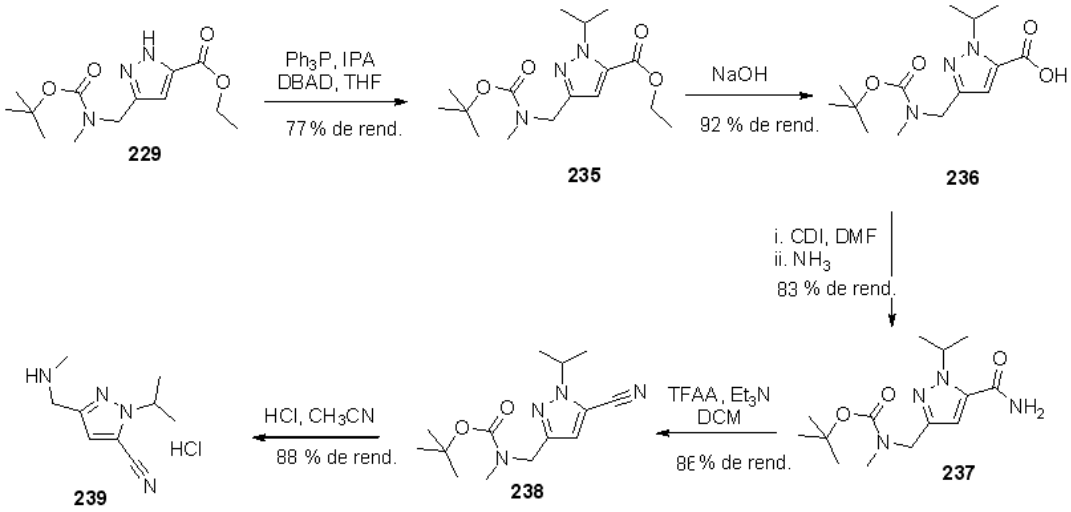
El **compuesto 231** crudo (9,1 g) se disolvió en DMF (85 mL) bajo nitrógeno y se añadió Cs_2CO_3 (37,6 g). Luego se añadió lentamente una solución de trifluorometansulfonato de oxetan-3-ilo **232** (9,5 g) en DMF (15 mL) desde un embudo de goteo, manteniendo la temperatura entre 15-20 °C. Después de completar la adición, la mezcla de reacción se agitó durante 90 minutos antes de diluirla con H_2O (100 mL) y se extrajo con EtOAc (3 x 100 mL). Los extractos orgánicos combinados se lavaron con salmuera (100 mL), se secaron sobre $MgSO_4$ y se concentraron para obtener un residuo marrón. El material crudo se purificó por cromatografía flash en gel de sílice (1:2 EtOAc;heptanos, luego 1:1 EtOAc:heptanos) para obtener el **compuesto 233** en forma de un aceite amarillo (4,00 g, 30% de rendimiento en dos etapas). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,14 – 6,89 (m, 1H), 5,71 (tt, *J* = 7,6, 6,0 Hz, 1H), 4,96 (t, *J* = 7,2 Hz, 2H), 4,88 (t, *J* = 6,5 Hz, 2H), 4,41 (s, 2H), 2,81 (s, 3H), 1,47 – 1,34 (m, 9H). La posterior elución produjo el pirazol regioisomérico en forma de un sólido incoloro

(3,28 g, 25% de rendimiento en dos etapas). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,93 (s, 1H), 5,77 (s, 1H), 4,91 – 4,81 (m, 4H), 4,47 (s, 2H), 2,72 (s, 3H), 1,41 (s, 9H).

Etapa 6:

El **compuesto 233** (0,50 g, 1,71 mmol) se disolvió en DCM (5 mL) y se enfrió en un baño de agua helada bajo nitrógeno. Luego se añadió TFA (5 mL) y la mezcla de reacción se agitó durante dos horas, durante lo cual se calentó hasta temperatura ambiente. La reacción se concentró y el TFA residual se eliminó del residuo por coevaporación con DCM (2 x 10 mL) y luego tolueno (2 x 10 mL). La sal de TFA del **compuesto 234** se obtuvo en forma de una goma amarilla (0,85 g). ^{1}H RMN (400 MHz, DMSO-d6) δ 9,00 (s, 2H), 7,25 (s, 1H), 5,78 (tt, J = 7,6, 5,9 Hz, 1H), 5,00 (t, J = 7,2 Hz, 2H), 4,89 (t, J = 6,4 Hz, 2H), 4,27 (t, J = 5,6 Hz, 2H), 2,61 (t, J = 5,2 Hz, 3H).

Preparación de clorhidrato de 3-[(metilamino)metil]-1-(propan-2-il)-1*H*-pirazol-5-carbonitrilo (1:1) (239)



Etapa 1:

Se añadió diterbutilazodicarboxilato (6,5 g, 28,2 mmol) en porciones (sólido) a una solución de **compuesto 229** (8,0 g, 28,2 mmol), Ph_3P (7,4 g, 28,2 mmol) e isopropanol (2,55 g, 42,5 mmol) en THF (80 mL) a 0 ºC durante 5 minutos. La reacción se agitó luego de 0 ºC a 20 ºC durante 2 horas. La reacción se concentró y el residuo se purificó por cromatografía flash (10% al 40% de EtOAc en heptanos) para obtener el **compuesto 235** (7,1 g, 77%). ^{1}H RMN (400 MHz, DMSO-d6) δ 6,63 (d, J = 15,6 Hz, 1H), 5,36 (hept, J = 6,6 Hz, 1H), 4,37 – 4,23 (m, 4H), 2,76 (s, 3H), 1,39 (t, J = 5,6 Hz, 15H), 1,29 (t, J = 7,1 Hz, 3H), [MH]+ 326,12.

Etapa 2:

Se disolvió NaOH (3,4 g, 87,3 mmol) en agua (6,0 mL), se añadió la solución a una solución de **compuesto 235** en MeOH y la reacción se agitó a 25 ºC durante 2 horas. La mezcla luego se diluyó con agua (250 mL) y se acidificó a aproximadamente pH 2 (papel de pH) usando $NaHSO_4$ acuoso al 5%. La mezcla luego se extrajo en EtOAc (2 x 120 mL). Las capas orgánicas se lavaron con salmuera (100 mL), se secaron (Na_2SO_4) y se evaporaron para obtener el **compuesto 236** (6,0 g, 92%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d6) δ 13,26 (s, 1H), 6,58 (d, J = 11,4 Hz, 1H), 5,42 (hept, J = 6,6 Hz, 1H), 4,30 (s, 2H), 2,76 (s, 3H), 1,38 (m, 15H), [MH]+ 298,07.

Etapa 3:

Se añadió carbonildiimidazol (3,56 g, 22,0 mmol) a una solución de **compuesto 236** en DMF (35 mL) a temperatura ambiente. Después de agitar durante 45 minutos, la reacción se enfrió hasta 0 ºC y se burbujeó gas amoníaco a través de la mezcla durante 10 minutos. La reacción se agitó durante 2 horas a temperatura ambiente, antes de diluirla con agua (250 mL). La mezcla se extrajo en EtOAc (2 x 100 mL). Las capas orgánicas combinadas se lavaron con salmuera (200 mL), se secaron (Na_2SO_4) y se evaporaron para obtener el **compuesto 237** (4,9 g, 83%) en forma de un aceite que se convirtió en sólido al reposar. ^{1}H RMN (400 MHz, DMSO-d6) δ 7,92 (s, 1H), 7,44 (s, 1H), 6,65 (s, 1H), 5,51 (hept, J = 6,6 Hz, 1H), 4,38 – 4,24 (m, 2H), 2,76 (s, 3H), 1,40 (d, J = 4,1 Hz, 9H), 1,34 (d, J = 6,6 Hz, 6H), [MH]+ 297,11.

Etapa 4:

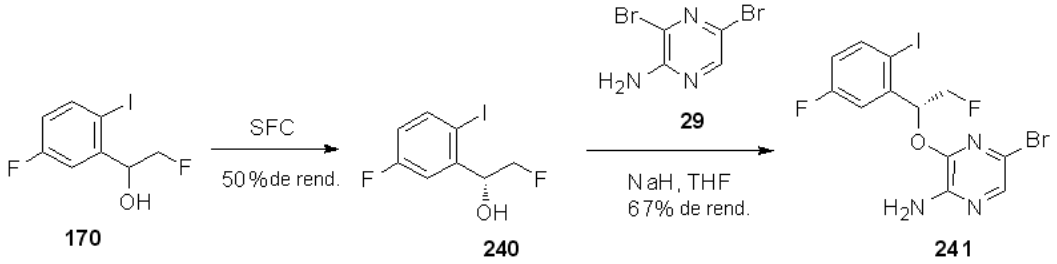
Se añadió lentamente una solución de anhídrido trifluoroacético en DCM (50 mL) a una solución de **compuesto 237** (4,90 g, 16,55 mmol) y Et_3N (5,10 g, 50,0 mmol) en DCM (50 mL) a 0 ºC durante 10 minutos. La reacción se agitó a 0 ºC durante 60 minutos, antes de la adición de agua (100 mL) y se agitó durante 10 minutos. La capa orgánica se separó, se secó (Na_2SO_4) y se evaporó. El residuo se purificó por cromatografía flash (20% de EtOAc en heptanos) para obtener el **compuesto 238** (3,95 g, 86%) en forma de un aceite incoloro. ^{1}H RMN (400 MHz, DMSO-d6) δ 6,95 (d, J = 15,2 Hz, 1H), 4,72 (hept, J = 6,6 Hz, 1H), 4,34 (s, 2H), 2,78 (s, 3H), 1,45 (d, J = 6,6 Hz, 6H), 1,43 – 1,34 (m, 9H), [MH-Boc]+ 179,14.

Etapa 5:

Se añadió HCl (4 M en dioxano, 5,0 mL) a una solución de **compuesto 238** (3,90 g, 14,0 mmol) en CH_3CN y se agitó a 50 ºC durante 60 min. Después de enfriar, la reacción se concentró, luego se añadió EtOAc (35 mL) y la mezcla se filtró para

recolectar el **compuesto 239** (2,20 g, 88%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d6) δ 9,49 (s, 2H), 7,34 (s, 1H), 4,79 (hept, J = 6,6 Hz, 1H), 4,16 (s, 2H), 2,53 (s, 3H), 1,47 (d, J = 6,6 Hz, 6H), [MH]+ 179,14.

Preparación de 5-bromo-3-[(1*R*)-2-fluoro-1-(5-fluoro-2-yodofenil)etoxi]pirazin-2-amina (241)



170 240 241

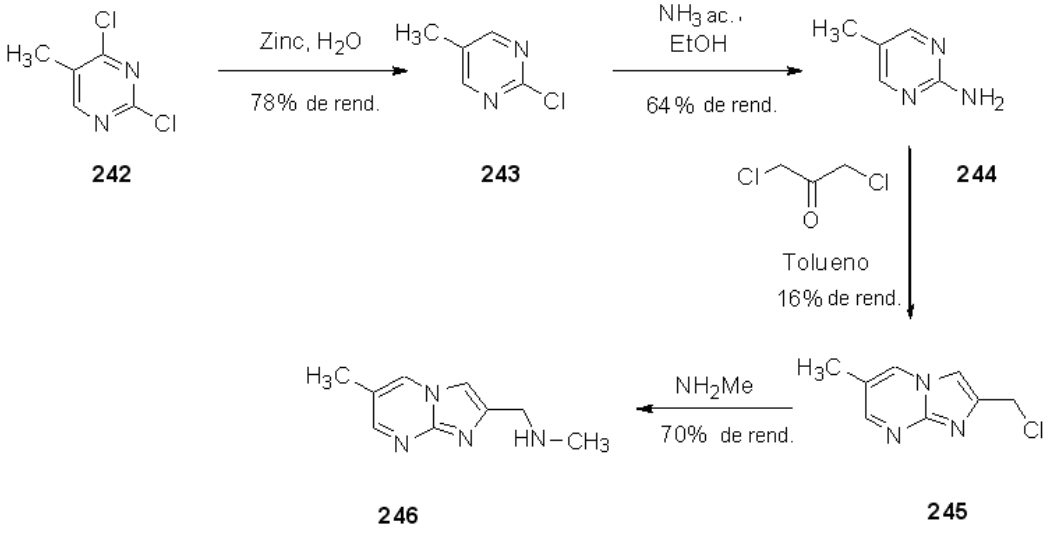
Etapa 1:

El **compuesto 170** se separó por SFC preparativa para obtener el **compuesto 240** puro (4 g, 50%) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, CDCl3): δ 7,75-7,78 (m, 1H), 7,34-7,37 (m, 1H), 6,79-6,84 (m, 1H), 5,17-5,24 (m, 1H), 4,57-4,70 (m, 1H), 4,17-4,34 (m, 1H), 2,652-2,658 (s, 1H).

Etapa 2:

A una solución de **compuesto 240** (3 g, 10,6 mmol) en THF anhidro (100 mL) se añadió NaH (464 mg, 11,6 mmol, 60% en aceite) a 0 °C bajo N_2 y la mezcla se agitó durante otros 30 min. Una solución de compuesto 12 (2,141 g, 8,5 mmol) en THF seco (10 mL) se añadió a la mezcla anterior a 0 °C y la mezcla se calentó a reflujo durante 10 horas. Se eliminó THF a presión reducida y el residuo se diluyó con H_2O (100 mL)/EtOAc (100 mL). La mezcla se filtró y el filtrado se extrajo con EtOAc (100 mL × 3). Las capas orgánicas combinadas se lavaron con salmuera (100 mL), se secaron sobre Na_2SO_4 y se concentraron para obtener residuo que se purificó por columna en gel de sílice que se eluyó con éter de petróleo : EtOAc = 60/1 ~ 10/1 para obtener el **compuesto 241** (2,6 g, 67%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,81-7,84 (m, 1H), 7,67 (s, 1H), 7,09-7,12 (d, 1H), 6,79-6,84(t, 1H), 6,35-6,42 (q, 1H), 4,91 (s, 2H), 4,59-4,81 (m, 2H), [M+H]+ 457,8.

Síntesis de N-metil-1-(6-metilimidazo[1,2-a]pirimidin-2-il)metanamina (compuesto 246)



Etapa 1:

Una suspensión de **compuesto 242** (50,0 g, 307 mmol) y Zn recién activado (lavado con ácido) (59,8 g, 920 mmol) en agua (500 mL) se calentó a reflujo durante 3 horas. La TLC mostró el consumo de SM. La mezcla de reacción se enfrió hasta temperatura ambiente, se filtró a través de un taco de Celite y se enjuagó con CH_2Cl_2 (500 mL). Las fases del filtrado se separaron y la fase orgánica se lavó con salmuera (300 mL), se secó sobre $MgSO_4$, se filtró y se concentró al vacío con cuidado para obtener el **compuesto 243** en forma de un polvo beige (30,6 g, 78% de rendimiento, 95% de pureza por ^{1}H RMN). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,63 (d, *J* = 0,9 Hz, 2H), 2,27 (t, *J* = 0,8 Hz, 3H).

Etapa 2:

El **compuesto 243** (30,6 g, 239 mmol) se disolvió en etanol (300 mL) y amoníaco acuoso (35%, 300 mL). La solución se colocó en una bomba de reacción y se calentó a 200 °C durante 6 horas, se enfrió a temperatura ambiente y luego se dejó abierta a esta temperatura durante 72 horas. El etanol se había evaporado y se añadió otra vez amoníaco acuoso (35%, 200 mL). La solución se calentó a 200 °C durante 22 horas y luego se enfrió hasta temperatura ambiente. La mezcla se concentró al vacío, luego se añadió agua (50 mL) y la suspensión obtenida se filtró. El polvo beige obtenido se secó en un horno de vacío durante 20 horas para obtener el **compuesto 244** puro (16,7 g, 64% de rendimiento, >95% de pureza por ^{1}H RMN). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,07 (s, 2H), 6,33 (s, 2H), 2,03 (s, 3H). LC-MS *m/z* 109 $[M+H]^+$.

Etapa 3:

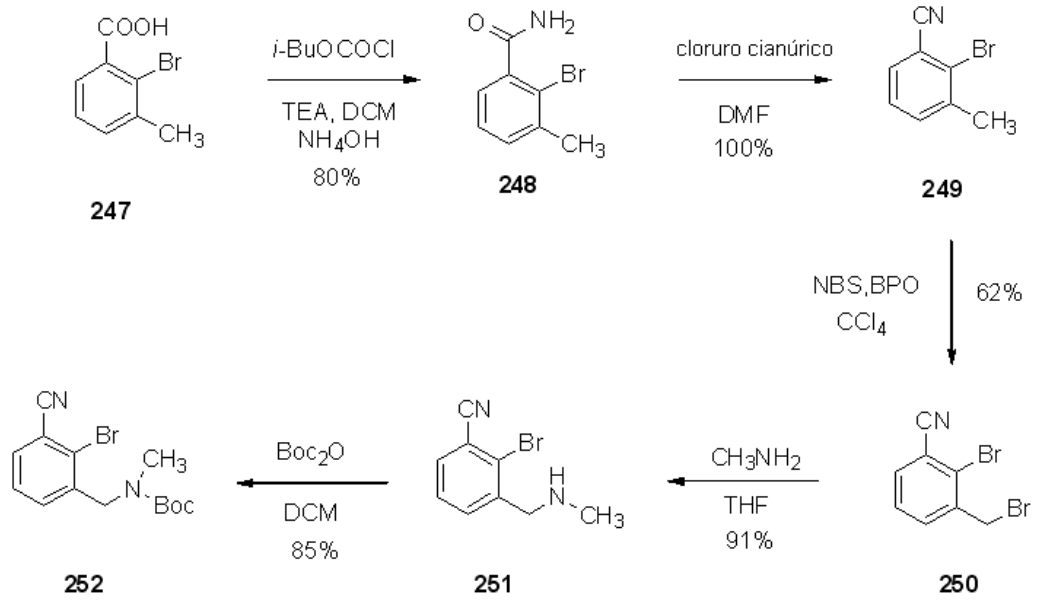
El **compuesto 244** (5,0 g, 45,9 mmol) y dicloroacetona (29,1 g, 229,3 mmol) se mezclaron con tolueno (1 L). El recipiente se equipó con un aparato de Dean-Stark y la

mezcla se calentó a 155 °C durante 1 hora (no bien se observó el reflujo de tolueno en la parte superior de Dean-Stark). La reacción se enfrió hasta temperatura ambiente y se añadieron CH_2Cl_2 (500 mL) y sílice. La mezcla obtenida se colocó directamente en la parte superior de una cromatografía en columna y se purificó por esta vía (eluyentes CH_2Cl_2/MeOH de 100:0 a 80:20). Las fracciones que contenían el **compuesto 245** se combinaron, se concentraron al vacío y se purificaron por columna SCX-2. Las fracciones que contenían el **compuesto 245** esperado se purificaron otra vez por cromatografía en columna en gel de sílice (eluyentes CH_2Cl_2/MeOH de 100:0 a 95:5) para obtener el **compuesto 245** esperado en forma de aceite amarillo pálido (1,4 g, 16% de rendimiento, 95% de pureza por LC-MS). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,76 (dq, J = 2,3, 1,1 Hz, 1H), 8,45 (d, J = 2,4 Hz, 1H), 7,88 (s, 1H), 4,85 (d, J = 0,6 Hz, 2H), 2,29 (d, J = 1,1 Hz, 3H). LC-MS *m/z* 182/184 $[M+H]^+$.

Etapa 4:

El **compuesto 245** (1,4 g, 7,7 mmol) se disolvió en CH_2Cl_2 (70 mL) y esta solución se añadió a una solución de N-metilamina en MeOH/THF (2 M, 145 mL, MeOH/THF = 1:4). El recipiente se selló y la solución amarilla se agitó a temperatura ambiente durante 24 horas. La TLC mostró el consumo de SM. Una solución de HCl en dioxano (1 mL, 4 M) se añadió gota a gota a la solución. La mezcla se concentró y luego se añadió CH_2Cl_2 (10 mL). La suspensión obtenida se filtró para obtener un sólido beige que contenía la sal clorhidrato tanto de la amina esperada como de la N-metilamina. Los sólidos se disolvieron en MeOH (150 mL) y se añadió Amberlist A-26 (40 mL). La mezcla se concentró al vacío y luego se filtró. El filtrado se concentró para obtener el **compuesto 246** (500 mg, 37% de rendimiento, 99% de pureza por LC-MS). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,73 (dq, *J* = 2,3, 1,1 Hz, 1H), 8,35 (d, *J* = 2,4 Hz, 1H), 7,65 (s, 1H), 3,73 (d, *J* = 0,8 Hz, 2H), 2,32 (s, 3H), 2,28 (d, *J* = 1,0 Hz, 3H). LC-MS *m/z* 177 $[M+H]^+$.

Preparación de 2-bromo-3-cianobencil(metil)carbamato de ter-butilo (compuesto 252)



Etapa 1:

A una solución de **compuesto 247** (15 g, 69,8 mmol) en CH2Cl2 (100 mL) se añadieron TEA (7,76 g, 76,7 mol) e iso-butilcloroformiato (10,4 g, 76,7 mmol) a 0 °C. Después de la adición, la mezcla se agitó a 0 °C durante 30 minutos. La TLC (CH_2Cl_2 / MeOH = 10:1) mostró que la reacción estaba completa. A continuación, se añadió NH_3•H_2O (27,9 g, 0,28 mol, 35% en H_2O) a la mezcla 0 °C. La mezcla resultante se agitó a esta temperatura durante 30 minutos. La TLC (éter de petróleo / EtOAc = 8:1) mostró que la reacción estaba completa. La mezcla se vertió en agua helada (200 mL). El sólido se filtró y la torta húmeda se lavó con H_2O (50 mL) y se secó para obtener el **compuesto 248** (12 g, 80%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-*d*$_6$) δ 7,70 (brs, 1H), 7,55 (brs, 1H), 7,35 (m, 1H), 7,30 (m, 1H), 7,15 (m, 1H), 2,38 (s, 3H).

Etapa 2:

A una solución de **compuesto 248** (12 g, 56,1 mmol) en DMF (100 mL) se añadió una solución de cloruro cianúrico (15,47 g, 84,1 mol) en DMF (50 mL) a 0 °C en una atmósfera de nitrógeno. Después de la adición, la mezcla se agitó a temperatura ambiente durante la noche. La TLC (éter de petróleo / EtOAc = 1:1) mostró que la reacción estaba completa. La mezcla se vertió en agua (500 mL) y se extrajo con EtOAc (200 mL x 2). Las capas orgánicas combinadas se lavaron con Na_2CO_3 acuoso saturado (200 mL x 2) y salmuera (200 mL x 4), se secaron sobre Na_2SO_4 y se concentraron para obtener el **compuesto 249** (11 g, 100%) en forma de un sólido

blanquecino. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,51-7,45 (m, 2H), 7,33-7,29 (m, 1H), 2,47 (s, 3H).

Etapa 3:

Una mezcla de **compuesto 249** (11 g, 56,1 mmol), NBS (10 g, 56,1 mmol) y BPO (81 mg, 0,34 mmol) en CCl_4 (150 mL) se calentó a reflujo durante la noche. La TLC (éter de petróleo / EtOAc = 5:1) mostró que la reacción estaba completa. La mezcla se filtró y el filtrado se concentró. El residuo se purificó por cromatografía en columna en gel de sílice (éter de petróleo / EtOAc = 20:1) para obtener el **compuesto 250** (9,6 g, 62%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,69-7,67 (d, 1H), 7,63-7,61 (d, 1H), 7,45-7,41 (t, 1H), 4,61 (s, 2H).

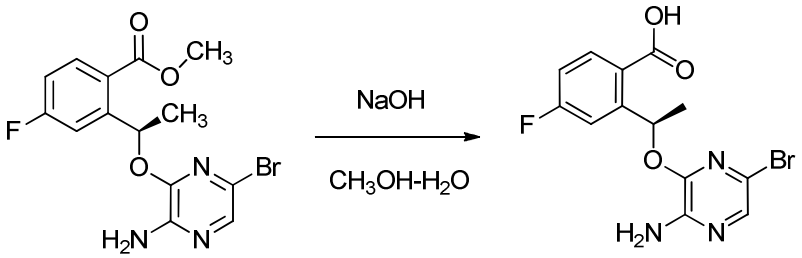
Etapa 4:

A una solución de **compuesto 250** (11,9 g, 43,3 mmol) en THF (100 mL) se añadió una solución de metilamina (2 M en THF, 215 mL, 0,43 mol) a -10 °C ~ 0 °C en una atmósfera de nitrógeno. Después de la adición, la mezcla se calentó hasta temperatura ambiente y se agitó durante 2 horas. La TLC (éter de petróleo / EtOAc = 5:1) mostró que la reacción estaba completa. La mezcla se diluyó con agua (200 mL) y se extrajo con EtOAc (200 mL x 2). Las capas orgánicas combinadas se lavaron con salmuera (200 mL), se secaron sobre Na_2SO_4 y se concentraron para obtener el **compuesto 251** (8,9 g, 91%).en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,67-7,65 (d, 1H), 7,58-7,56 (d, 1H), 7,43-7,39 (t, 1H), 3,87 (s, 2H), 2,47 (s, 3H).

Etapa 5:

A una solución de **compuesto 251** (8,7 g, 38,6 mmol) en CH_2Cl_2 (100 mL) se añadieron TEA (11,7 g, 0,11 mol) y Boc_2O (8,9 g, 40,5 mmol) a temperatura ambiente. La mezcla se agitó a temperatura ambiente durante 3 horas. La TLC (CH_2Cl_2 / MeOH = 10:1) mostró que la reacción estaba completa. La mezcla se concentró y se purificó por cromatografía en columna en gel de sílice (éter de petróleo / EtOAc = 40:1) para obtener el **compuesto 252** (10,71 g, 85%) en forma de una goma incolora. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,58 (m, 1H), 7,45-7,38 (m, 2H), 4,56-4,50 (m, 2H), 2,93-2,89 (m, 3H), 1,52-1,40 (m, 9H). MS *m/z* 347 $[M+Na]^+$.

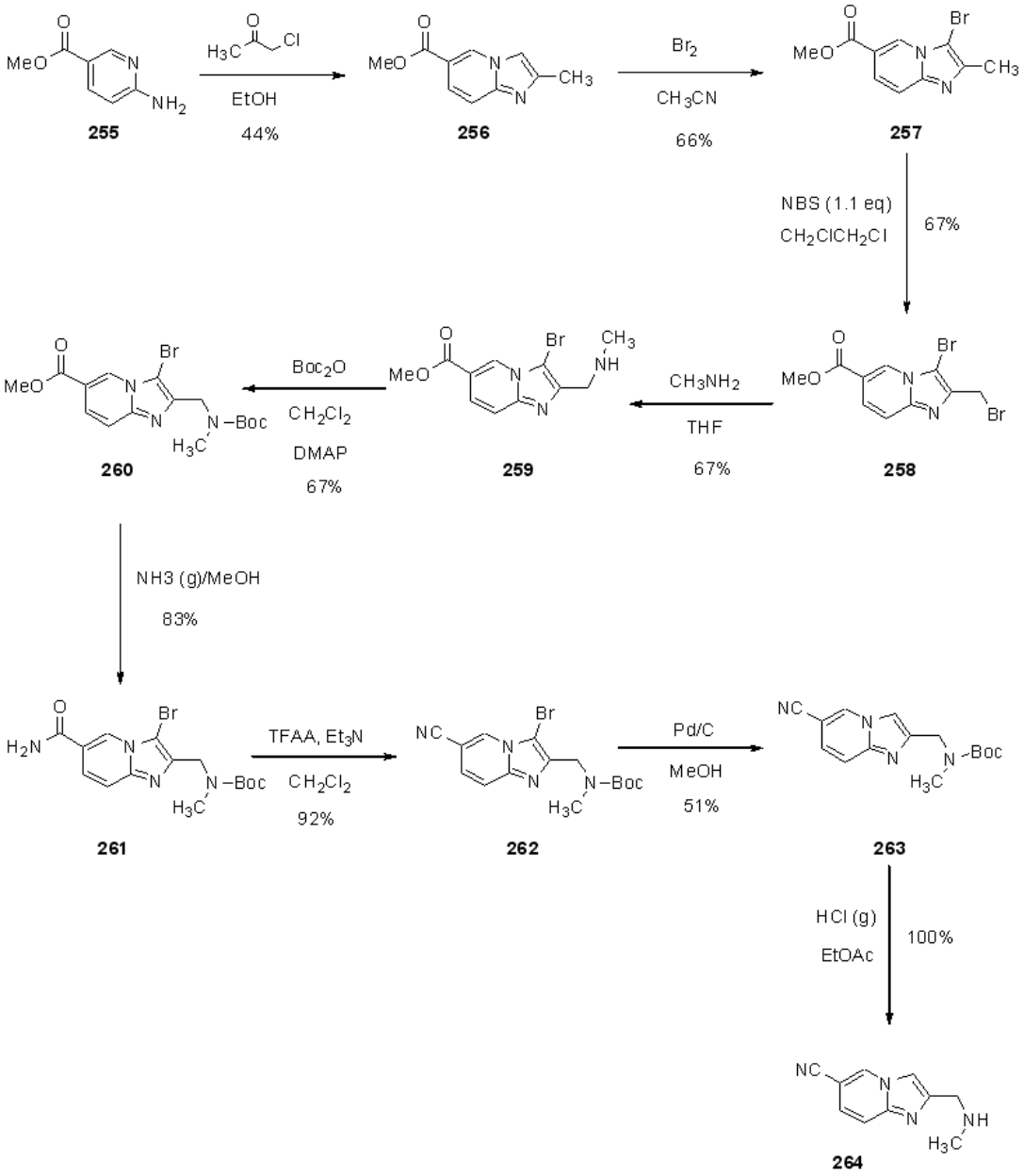
Preparación de ácido 2-{(1*R*)-1-[(3-amino-6-bromopirazin-2-il)oxi]etil}-4-fluorobenzoico (254)



253 **254**

El procedimiento descrito en la etapa 2 para el **Ejemplo 41** se usó para preparar el **compuesto 254** (0,56 g, 89% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d6) δ 7,92 (dd, J = 8,7, 6,0 Hz, 1H), 7,67 (dd, J = 10,5, 2,7 Hz, 1H), 7,52 (s, 1H), 7,19 (td, J = 8,4, 2,7 Hz, 1H), 6,88 (q, J = 6,4 Hz, 1H), 6,68 (s, 2H), 1,57 (d, J = 6,3 Hz, 3H), [MH]+ 356,03 (8%) y 357,95 (8%).

Preparación de 2-((metilamino)metil)imidazo[1,2-a]piridin-6-carbonitrilo (264)



Etapa 1:

Una mezcla de **compuesto 255** (50 g, 0,329 mmol) y 1-cloropropan-2-ona (448,4 g, 4,87 mol) en EtOH (150 mL) se calentó a reflujo durante 24 horas. La TLC (éter de petróleo/EtOAc = 1:1) mostró que quedó aproximadamente la mitad del **compuesto 255**. No se observó ningún cambio después del reflujo durante otras 12 horas. La mezcla se concentró al vacío para obtener el residuo, que se disolvió en CH_2Cl_2 (200 mL), se lavó con solución acuosa de $NaHCO_3$ (2 N, 50 mL) y salmuera (50 mL), se secó sobre Na_2SO_4 y se concentró al vacío para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice (éter de

petróleo/EtOAc = 2:1~1:1) para obtener el **compuesto 256** (18 g, 44%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,82 (s, 1H), 7,67-7,65 (m, 1H), 7,81-7,48 (m, 1H), 7,41 (s, 1H), 3,94 (s, 1H), 2,47 (s, 1H)

Etapa 2:

A una solución de **compuesto 256** (16 g, 0,089 mol) en CH_3CN (400 mL) se añadió Br_2 (15,62 g, 0,098 mol) a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente durante 1 hora. La TLC (EtOAc) mostró que la reacción estaba completa. La mezcla se diluyó con CH_2Cl_2 (500 mL) y luego se lavó con solución acuosa saturada de $NaHCO_3$ (100 mL) y salmuera (100 mL), se secó sobre Na_2SO_4 y se concentró al vacío para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice (éter de petróleo/CH_2Cl_2 = 2:1~1:1) para obtener el **compuesto 257** (15 g, 66%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,02 (s, 1H), 8,44-8,42 (m, 1H), 8,37-8,34 (m, 1H), 4,07 (s, 3H), 2,74 (s, 3H).

Etapa 3:

A una mezcla de **compuesto 257** (16 g, 0,0625 mol) y NBS (9,95 g, 0,05625 mol) en CH_2ClCH_2Cl (375 mL) se añadió AIBN (1,025 g, 0,00625 mol) a temperatura ambiente en una atmósfera de nitrógeno. La mezcla resultante se calentó a reflujo durante 2 horas. La TLC (éter de petróleo/EtOAc = 3:1) mostró que la mayor parte del **compuesto 257** se había consumido. La mezcla se enfrió hasta temperatura ambiente y se lavó con solución acuosa saturada de $NaHCO_3$ (50 mL) y salmuera (50 mL), se secó sobre Na_2SO_4, se concentró al vacío para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc = 4:1~1:1) y luego se recristalizó de éter de petróleo/EtOAc (5:1, 30 mL) en el **compuesto 258** (14 g, 67%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,85-8,75 (m, 1H), 7,88-7,80 (m, 1H), 7,62-7,55 (m, 1H), 4,67 (s, 2H), 4,00 (s, 3H).

Etapa 4:

A una solución de **compuesto 258** (14 g, 41,92 mmol) en THF anhidro (200 mL) se añadió metilamina en THF (520 mL, 1,048 mol, 2 M en THF) durante un minuto. La mezcla resultante se agitó a 0 ℃ durante 1 hora y luego a temperatura ambiente durante 1 hora. La TLC (éter de petróleo/EtOAc = 3:1) mostró que la mayor parte del **compuesto 258** se había consumido. La mezcla se concentró al vacío a 25 ℃ durante 20 minutos y luego a mayor temperatura para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice, (éter de petróleo/EtOAc

= 1:1~CH_2Cl_2/MeOH = 50:1) para obtener el **compuesto 259** (8,4 g, 67%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,85 (m, 1H), 7,84-7,81 (m, 1H), 7,60-7,52 (m, 1H), 4,18-4,15 (s, 2H), 4,00 (s, 3H), 2,65 (s, 3H).

Etapa 5:

A una suspensión de **compuesto 259** (8,4 g, 28,28 mmol) en CH2Cl2 (250 mL) se añadieron Boc_2O (12,5 g, 56,56 mmol) y DMAP (3,47 g, 28,28 mmol) a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente durante 12 horas. La TLC (CH_2Cl_2/MeOH = 20:1) mostró que la reacción estaba completa. La mezcla se concentró al vacío para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc= 10:1~5:1) para obtener el **compuesto 260** (7,5 g, 67%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,86 (s, 1H), 7,80-7,78 (m, 1H), 7,59-7,56 (m, 1H), 4,68 (s, 2H), 4,00 (s, 3H), 3,95 (s, 3H), 1,50 (s, 9H)

Etapa 6:

La reacción se corrió en lotes 3 x 1 g: Una solución de **compuesto 260** (1 g, 2,519 mmol) en NH_3(g)/MeOH (7 N, 70 mL) se selló y se calentó a 80 °C durante 12 horas. La TLC (éter de petróleo/EtOAc = 1:1) mostró que la reacción estaba completa. Las reacciones se combinaron y se concentraron al vacío para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc = 5:1~1:1) para obtener el **compuesto 261** (2,4 g, 83%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, Metanol-d_4) δ 8,90 (s, 1H), 7,90-7,82 (m, 1H), 7,65-7,55 (m, 1H), 4,65 (s, 2H), 2,95-2,84 (m, 3H), 1,45 (s, 9H).

Etapa 7:

A una solución de **compuesto 261** (2,4 g, 6,28 mmol) en CH_2Cl_2 anhidro (50 mL) se añadió Et_3N (2,6 mL, 18,85 mmol) y luego TFAA (1,73 mL, 12,57 mmol) gota a gota a 0 °C. La mezcla resultante se agitó a 0 °C durante 2 horas. La TLC (éter de petróleo/EtOAc = 1:1) mostró que la reacción estaba completa. La mezcla se concentró al vacío para obtener el residuo, que se dividió entre CH_2Cl_2 (100 mL) y salmuera (20 mL). La capa orgánica se separó, se lavó con ácido cítrico (1 N, 10 mL), solución acuosa saturada de $NaHCO_3$ (10 mL) y salmuera (10 mL), se secó sobre Na_2SO_4 y se concentró al vacío para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice (éter de petróleo/EtOAc = 5:1~1:1) para obtener el **compuesto 262** (2,1 g, 92%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,55 (s, 1H), 7,68-7,65 (m, 1H), 7,35-7,26 (m, 1H), 4,66 (s, 2H), 2,93 (s, 3H), 1,47 (s, 9H). LCMS *m/z* 308 $[M-55]^+$.

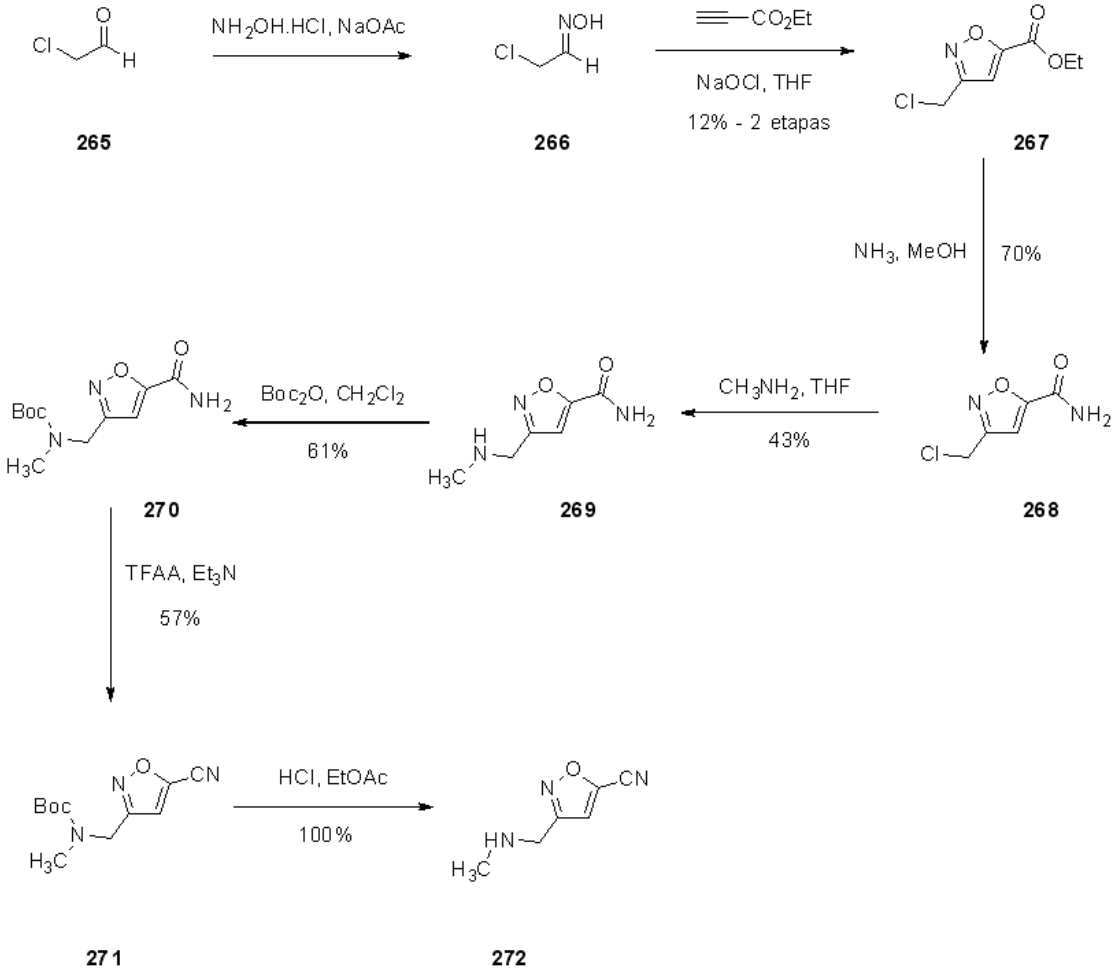
Etapa 8:

A una solución de **compuesto 262** (0,45 g, 1,23 mmol) en MeOH (80 mL) se añadió Pd/C (150 mg) a temperatura ambiente. La mezcla resultante se purgó con H_2 tres veces y se agitó bajo una presión de H_2 (15 psi) a temperatura ambiente durante 2 horas. La TLC (éter de petróleo/EtOAc = 3:1) mostró que la reacción estaba completa. La mezcla se filtró y se lavó con MeOH (30 mL). El filtrado se concentró al vacío para obtener el producto crudo, que se purificó por cromatografía en columna en gel de sílice, (éter de petróleo/EtOAc = 5:1) para obtener el **compuesto 263** (0,18 g, 51%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, Metanol-d_4) δ 8,52 (s, 1H), 7,64-7,50 (m, 2H), 7,27 (s, 1H), 4,59 (s, 2H), 2,98 (s, 3H), 1,50 (s, 9H).

Etapa 9:

A una solución de **compuesto 263** (0,18 g, 0,627 mmol) en CH_2Cl_2 (10 mL) se añadió HCl (g)/EtOAc (7 N, 20 mL) a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente durante 12 h. La mezcla se concentró al vacío para obtener el **compuesto 264** (0,15 g, 100%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, Metanol-d_4) δ 9,48 (s, 1H), 8,48 (s, 1H), 8,15-8,05 (m, 2H), 4,58 (s, 2H), 2,85 (s, 3H).

Preparación de 3-((metilamino)metil)isoxazol-5-carbonitrilo (compuesto 272)



Etapa 1:

A una solución agitada de **compuesto 265** (52 g, 0,64 mol) en H_2O (830 mL) se añadieron $NH_2OH.HCl$ (50 g, 0,71 mol) y NaOAc (59 g, 0,71 mol) a temperatura ambiente. Después de la adición, la mezcla se agitó a temperatura ambiente durante 1 hora. A continuación, la solución se extrajo con MTBE (2 x 500 mL), las capas orgánicas combinadas se lavaron con salmuera (200 mL x 3), se secaron sobre Na_2SO_4 y se concentraron para obtener el **compuesto 266** crudo (40 g) en forma de un aceite amarillo claro, que se usó en la siguiente etapa sin purificación.

Etapa 2:

A una solución agitada de **compuesto 266** (40 g, 0,437 mol) en THF (150 mL) se añadió gota a gota propiolato de etilo (50 mL, 0,5 mol) a 0 °C. Se añadió gota a gota NaOCl (10%, 1,5 L) a la mezcla anterior a 0 °C. Después de la adición, la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró para eliminar THF y se extrajo con EtOAc (2 x 500 mL). Las capas orgánicas combinadas

se lavaron con salmuera (200 mL x 3), se secaron sobre Na_2SO_4 y se concentraron para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice (Rf ~ 0,5, éter de petróleo/EtOAc = 10:1-5:1) para obtener el **compuesto 267** (11 g, 12,2 %) en forma de un sólido amarillo claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,05 (s, 1H), 4,64 (s, 2H), 4,49-4,41 (m, 2H), 11,46-1,43 (t, 3H).

Etapa 3:

A una solución agitada de NH_3 (g) en MeOH (12N, 100 mL) se añadió el **compuesto 267** (11 g, 0,058 mol) a 0 °C. Después de la adición, la mezcla se agitó a temperatura ambiente durante 10 minutos. La TLC (éter de petróleo/EtOAc = 1:1) indicó que la reacción estaba completa. La mezcla se concentró para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice (Rf = 0,2, éter de petróleo/EtOAc = 1:1-2:1) para obtener el compuesto **268** (6,5 g, 70 %) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,06 (s, 1H), 6,2 (s, 1H), 5,74 (s, 1H), 4,63 (s, 2H).

Etapa 4:

Esta reacción se corrió en lotes 3 x 2 g. Una mezcla de **compuesto 268** (2 g, 13 mmol) y metilamina (2 M en THF, 15 mL) se calentó en un recipiente sellado a 110 °C durante 18 horas. La TLC (EtOAc) indicó que la reacción estaba completa. Las reacciones se combinaron y se filtraron, y los filtrados se concentraron para obtener el **compuesto 269** crudo (2,5 g, 43%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,00 (s, 1H), 3,89-3,88 (s, 1H), 2,44 (s, 3H).

Etapa 5:

A una solución agitada de **compuesto 269** (2,5 g, 16 mmol) y Boc_2O (5,2 g, 24 mmol) en THF seco (30 mL) se añadió TEA (3,2 g, 32 mol) a 0 °C. Después de la adición, la mezcla se agitó a temperatura ambiente durante 2 horas. La TLC (éter de petróleo/EtOAc =1:1) indicó que la reacción estaba completa. La mezcla se concentró para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice (Rf = 0,46, éter de petróleo/EtOAc = 3:1) para obtener el **compuesto 270** (2,5 g, 61 %) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,96 (s, 1H), 6,51 (s, 1H), 6,02 (s, 1H), 4,52 (s, 2H), 2,89-2,86 (s, 3H), 1,47 (s, 9H).

Etapa 6:

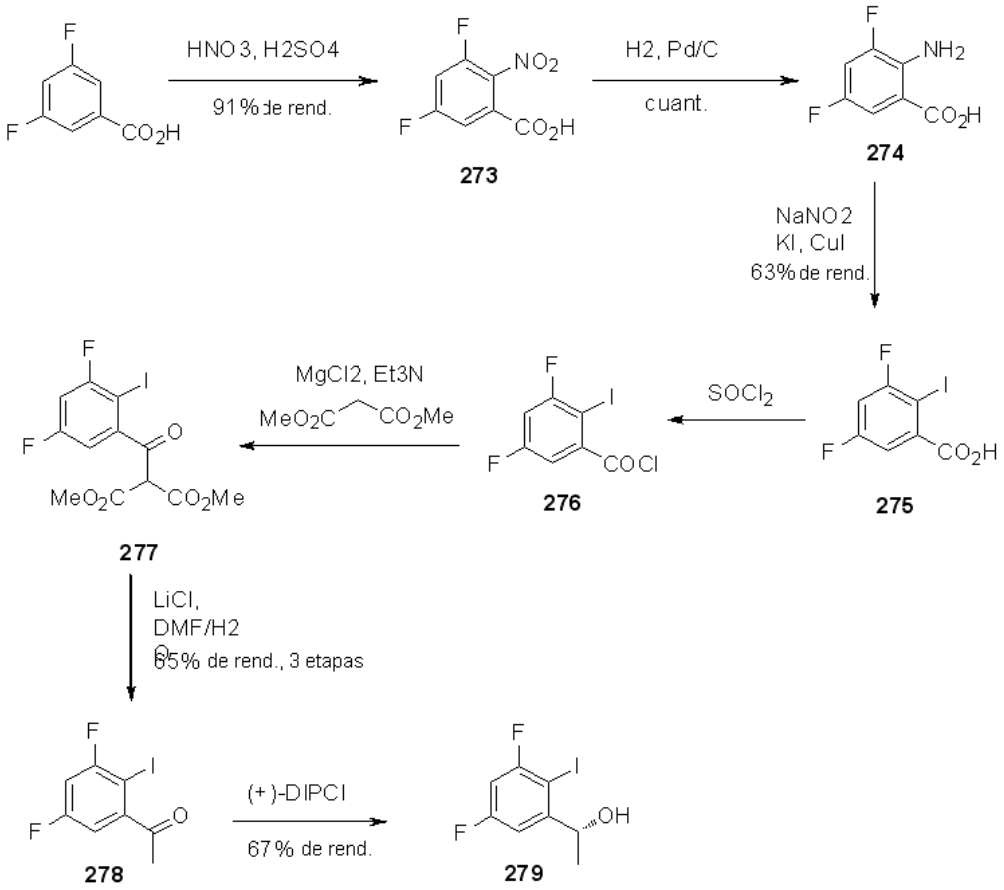
A una solución agitada de **compuesto 270** (2,5 g, 10 mmol) y TEA (4,2 mL, 30 mmol) en DCM seco (30 mL) se añadió TFAA (4,32 g, 20 mol) a 0 °C en una atmósfera de nitrógeno. Después de la adición, la mezcla se agitó a 0 °C durante 12 horas. La TLC (éter de petróleo/EtOAc =3:1) indicó que la reacción estaba completa.

La mezcla se lavó con solución acuosa saturada de $NaHCO_3$ (50 mL) y salmuera (50 mL x 2), se secó sobre Na_2SO_4 y se concentró para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice (Rf = 0,4, éter de petróleo/EtOAc = 10:1) para obtener el **compuesto 271** (1,3 g, 56,5 %) en forma de un aceite amarillo claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,96 (s, 1H), 4,52 (s, 2H), 2,87 (s, 3H), 1,47 (s, 9H).

Etapa 7:

A una solución agitada de **compuesto 271** (1,3 g, 5,5 mmol) en EtOAc (2 mL) se añadió HCl (g)/EtOAc (6N, 10 mL) a temperatura ambiente. Después de la adición, la mezcla se agitó a temperatura ambiente durante 2 horas. La TLC (éter de petróleo/EtOAc =1:1) indicó que la reacción estaba completa. La mezcla se concentró para obtener el **compuesto 272** (1 g, 100%) en forma de sal de clorhidrato. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,72 (s, 2H), 7,85 (s, 1H), 4,43 (s, 2H), 2,63 (s, 3H).

Preparación de (1*R*)-1-(3,5-difluoro-2-yodofenil)etanol (compuesto 279)



Etapa 1:

Se agitaron ácido 3,5-difluorobenzoico (80 g, 506 mmol) y ácido sulfúrico (250 ml) a temperatura ambiente durante una hora. Luego se añadió ácido nítrico (90 ml), manteniendo la temperatura interna a menos de 45 ºC con un baño de agua. La mezcla se mantuvo a temperatura ambiente durante la noche. La reacción se vertió lentamente en hielo y el sólido resultante se filtró y se lavó con agua fría para obtener el **compuesto 273** en forma de un sólido blanco (93,0 g, 91% de rendimiento). Este material se usó en la siguiente etapa sin otra purificación. ^{1}H RMN (400 MHz, DMSO-d6) δ 8,01(ddd, J=10,9, 8,5, 2,8 Hz, 1H), 7,71(dt, J= 8,4, 2,2 Hz, 1H).

Etapa 2:

El **compuesto 273** (80 g, 394 mmol) y paladio sobre carbón (9 g, 10% en peso) en EtOAc (900 ml) se agitaron a temperatura ambiente en una atmósfera de H2 (50 bar) durante 4 horas. La mezcla de reacción se filtró en un taco de sílice y Celite y el solvente se eliminó al vacío para obtener el **compuesto 274** en forma de un sólido amarillo pálido (67,39 g, 99% de rendimiento, ~95% de pureza de RMN). Este material se usó en la siguiente etapa sin otra purificación. ^{1}H RMN (400 MHz, DMSO-d6) δ 7,39 (ddd, J= 11,5, 8,4, 3,0Hz, 1H), 7,3 (ddd, J=9,6, 3,0, 1,8 Hz, 1H).

Etapa 3:

El **compuesto 274** (53,8 g, 311 mmol) se disolvió en una solución acuosa de HCl (2 M, 800 ml) y se enfrió hasta 0-5 ºC. Se disolvió nitrito de sodio (21,44 g, 311 mmol) en agua (344 ml) y se añadió a la solución previa durante un período de 15 minutos. Esta mezcla se agitó a 0-5 ºC durante 2 horas, luego se transfirió a un recipiente cónico y se mantuvo fría. En un nuevo recipiente de base redonda, se añadieron yoduro de potasio (103,25 g, 622 mmol) y yoduro de cobre (29,61 g, 156 mmol) en agua (344 ml). Esta mezcla se enfrió a 0-5 ºC, y luego la mezcla previa se añadió lentamente. Después de la adición, la mezcla de reacción se calentó hasta temperatura ambiente y se agitó durante 16 horas. La suspensión se filtró y el sólido resultante se suspendió en acetato de etilo (860 ml) durante 1 hora. Esta solución se filtró otra vez y los licores madre se lavaron con metabisulfato de sodio (10%, 4*600 ml) y salmuera (600 ml). Después de secar en MgSO4 y eliminar los solventes al vacío, el **compuesto 275** se aisló en forma de un sólido amarillo pálido (55,35 g, 63% de rendimiento, 90% de pureza de RMN). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,60 (ddd, J=8,5, 2,9, 1,5 Hz, 1H), 7,07 (J=7,8, 2,8 Hz, 1H), [M-H+]-282,74.

Etapa 4:

Se añadió cloruro de tionilo (142 ml, 1940 mmol) al **compuesto 275** (55,0 g, 194 mmol) y la mezcla se calentó a 80 ºC durante 3,5 horas. La reacción luego se enfrió hasta temperatura ambiente, se eliminó el cloruro de tionilo a presión reducida y luego se azeotropó con tolueno. El **compuesto 276** se aisló en forma de un aceite anaranjado (56 g, cuantitativo). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,6 (ddd, J=8,4, 2,8, 1,4 Hz, 1H), 7,09 (td, J= 7,7, 2,8 Hz, 1H), [M+H+]-298.

Etapa 5:

Esta reacción se fijó en 7 lotes de 5 g cada uno de **compuesto 276**. Se suspendieron cloruro de magnesio (2,35 g, 24,6 mmol) y malonato de dietilo (3,95 g, 24,6 mmol) en acetonitrilo (50 ml). La mezcla resultante se enfrió hasta 0 ºC, luego se añadió trietilamina (3,42 ml, 24,6 mmol) gota a gota a 0 ºC y la reacción se agitó durante 45 min a 0 ºC. Se añadió rápidamente una solución de **compuesto 276** (5 g, 16,4 mmol) en acetonitrilo (20 ml) a esta mezcla a 0 ºC. La solución se calentó hasta temperatura ambiente y se agitó durante 3 horas. Los solventes se eliminaron a presión reducida y el residuo se diluyó con EtOAc (350 ml) y una solución acuosa de HCl (1 M, 300 ml). La fase acuosa se lavó con EtOAc (3*300 ml), luego las fases orgánicas se combinaron, se secaron sobre MgSO4 y se filtraron, y los solventes se eliminaron a presión reducida para obtener el **compuesto 277** en forma de un aceite anaranjado (68,9 g crudos combinados). ^{1}H RMN (400 MHz, DMSO-d6) δ 7,49-7,43 (m, 1H), 7,22 (ddd, J= 8,5, 2,7, 1,2 Hz, 1H), 4,11-3,99 (m, 4H), 1,99 (s, 1H), 1,20 (m, 6H); [M-H+]= 424,89, 426,14, 426,92 (10/1).

Etapa 6:

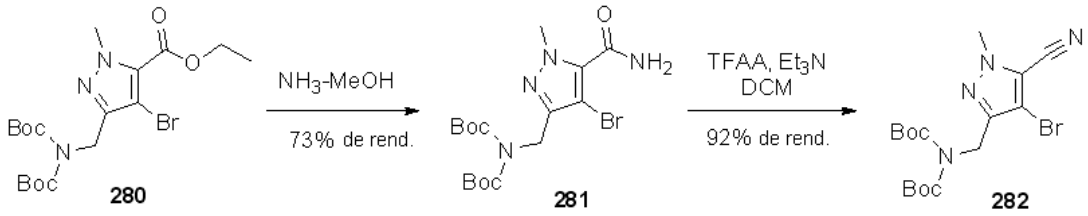
Esta reacción se realizó en 2 lotes que se combinaron antes de la elaboración (37,6 g + 31,34 g).

El **compuesto 277** (37,6 g, 88,2 mol) y cloruro de litio (3,74 g, 88,2 mmol) se disolvieron en DMF (170 ml) y agua (17 ml) y se calentaron a 100 ºC durante 4 horas. La reacción se dejó enfriar hasta temperatura ambiente, y luego se añadieron agua (150 ml) y TBME (150 ml). Las fases se separaron y la capa acuosa se lavó con TBME (3*150 ml). Las fases orgánicas se combinaron y se lavaron con agua (500 ml), se secaron sobre MgSO4, se filtraron y luego se evaporaron a presión reducida. El residuo se purificó por cromatografía flash seca (eluyente: Hept/EtOAc 98:2 a 9:1) para obtener el **compuesto 278** en forma de un sólido anaranjado (21,34 g, 65% de rendimiento en 3 etapas, 88% puro por LCMS). ^{1}H RMN (400 MHz, DMSO-d6) δ 7,53-7,51 (m, 1H), 7,50-7,48 (m, 1H), 2,57 (s, 3H), [M-F+MeCN]= 293,03, 293,79(1/10).

Etapa 7:

Una solución de (+)DIP-Cl (17,1 g, 53,2 mmol) en THF (24 ml) se enfrió hasta -35 ºC. Luego se añadió gota a gota una solución de **compuesto 278** (7,5 g, 26,5 mmol) en THF (20 ml) manteniendo la temperatura interna de la reacción entre -35 y -30 ºC. La reacción se calentó hasta temperatura ambiente y se agitó durante 12 horas. El análisis de TLC confirmó que la reacción estaba completa. Los solventes se eliminaron al vacío y el residuo se diluyó en TBME (64,5 ml). Se añadió una mezcla de dietanolamina (9,16 g, 87,45 mmol) en etanol/THF (3,75 ml / 7,5 ml). La mezcla de reacción se agitó durante 3 horas a reflujo, luego se enfrió hasta temperatura ambiente y se filtró. Los líquidos madre se concentraron al vacío y el residuo resultante se purificó por cromatografía en columna (eluyente: Hep/EtOAc 99:1 a 9:1). El aceite incoloro obtenido luego se purificó por recristalización en heptano para obtener el **compuesto 279** en forma de un sólido blanco (5,02 g, 67% de rendimiento, 95% puro por RMN, 99% ee-análisis de GC quiral). ^{1}H RMN (400 MHz, d6-DMSO) δ 7,28-7,12 (m, 2H), 5,64 (d, J= 4,2 Hz, 1H), 4,86 (q, J= 6,4 Hz, 1H), 1,27 (d, J+ 6,4 Hz, 3H), [M-F+H2O-H+]-279,12/280,92 (1:1), HPLC (columna CP-chiralsil-dex-CB): 99% ee; Rt(menor)- 18,23 min; Rt(mayor)-18,55 min; 40 ºC a 225 ºC a 6 ºC por minuto.

Preparación de [(4-bromo-5-ciano-1-metil-1*H*-pirazol-3-il)metil]imido-dicarbonato de di-ter-butilo (compuesto 282)



Etapa 1:

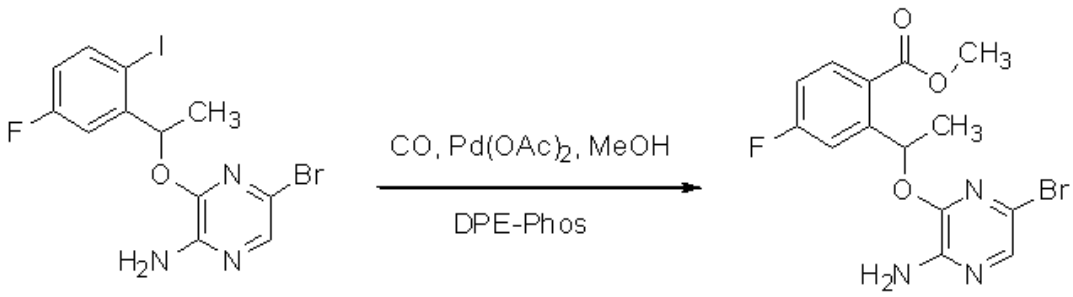
Una solución de **compuesto 280** (10 g, 0,21 mol) en NH_3(g)/MeOH (150 mL) se agitó a 45 ºC durante la noche en un tubo sellado. La TLC (éter de petróleo/EtOAc = 3: 1) indicó el consumo del compuesto 9. La mezcla de reacción se concentró. El residuo se recristalizó en CH_2Cl_2/éter de petróleo para obtener el **compuesto 281** (6,6 g, 72,6%) en forma de un sólido marrón pálido. ^{1}H RMN (400 MHz, DMSO) δ 8,00 (s, 1H),7,82 (s, 1H), 4,64 (s, 2H), 3,85 (s, 3H), 1,38 (s, 18H).

Etapa 2:

A una mezcla de **compuesto 281** (58 g, 20,5 mol) y Et_3N (4,6 g, 45,6 mmol) en CH_2Cl_2 seco (100 mL) se añadió TFAA (6,4 g, 30,5 mol) gota a gota a 0 ~ -5 ºC. Después de la adición, la mezcla se agitó a 0 ºC durante 1,5 horas. La TLC (éter de

petróleo: EtOAc = 1:1) mostró que la reacción estaba completa. La mezcla se diluyó con CH_2Cl_2 (100 mL), se lavó con 5% de ácido cítrico (50 mL), $NaHCO_3$ sat. (50 mL) y salmuera (50 mL), se secó sobre sulfato de sodio y se concentró. El residuo se purificó por Biotage (éter de petróleo/EtOAc 6/1, Rf = 0,5) para obtener el **compuesto 282** (5,8 g, 92,2%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 4,797 (s, 2H), 3,988 (s, 3H), 1,481 (s, 18H). LC-MS: m/z for C16H23BrN4O4 [M+Na]+ 439,2.

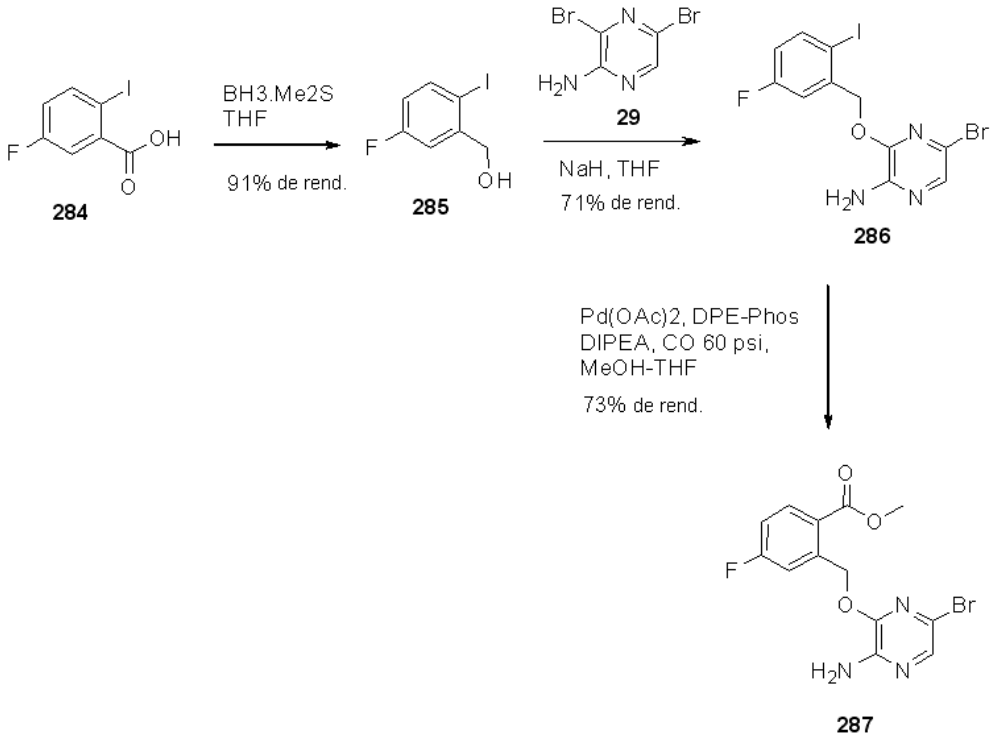
Preparación de 2-{1-[(3-amino-6-bromopirazin-2-il)oxi]etil}-4-fluorobenzoato de metilo (283).



30 283

El procedimiento descrito en la etapa 1 para el **Ejemplo 89** se usó para preparar el **compuesto 283.**

Preparación de 2-{[(3-amino-6-bromopirazin-2-il)oxi]metil}-4-fluorobenzoato de metilo (compuesto 287)



Etapa 1:

El **compuesto 284** (5,00 g, 18,80 mmol) se disolvió en THF (50 mL) y se enfrió hasta 0 ºC bajo nitrógeno. Se añadió borano-dimetilsulfuro (3,57 mL, 37,60 mmol) gota a gota con agitación y la mezcla de reacción se calentó hasta temperatura ambiente. Se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se neutralizó con cuidado vertiéndola sobre hielo y añadiendo una solución acuosa de K_2CO_3 al 10% (50 mL). La mezcla se extrajo con DCM (2 x 50 mL) y los extractos orgánicos combinados se secaron sobre $MgSO_4$ y se concentró al vacío para obtener el **compuesto 285** en forma de un sólido incoloro (4,80 g, 91% de rendimiento). ^{1}H RMN (400 MHz, CDCl3): δ 7,68 (dd, 1H, J = Hz), 7,19 (dd, 1H, J = Hz), 6,70 (td, 1H, J = Hz), 4,57 (d, 2H, J = Hz), 1,95 (t, 1H, J = Hz).

Etapa 2:

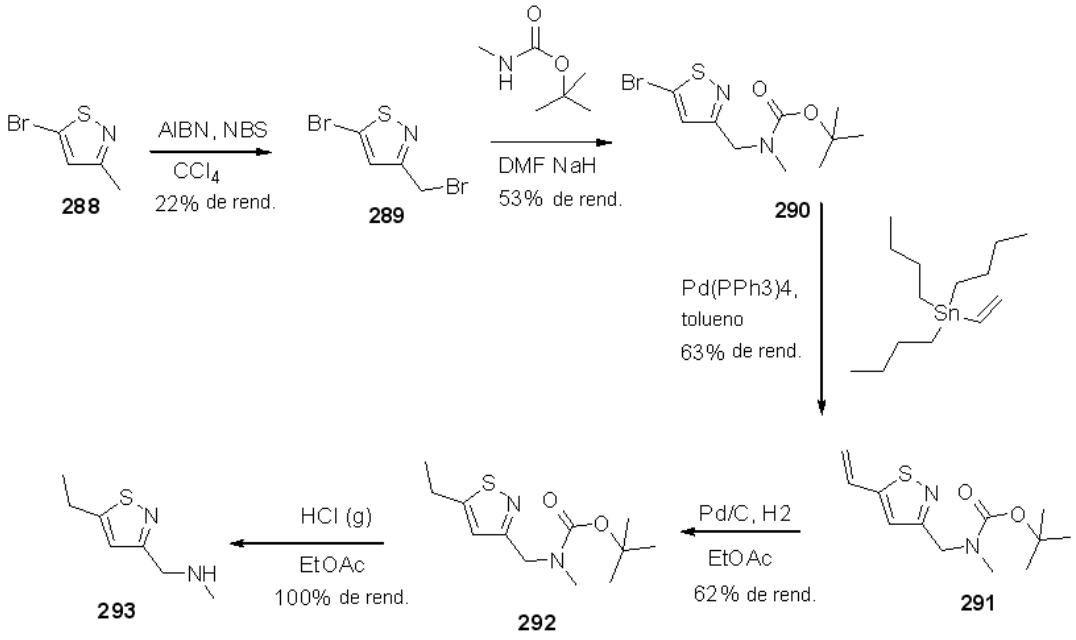
El **compuesto 285** (4,80 g, 19,05 mmol) se disolvió en THF seco (80 mL) y se enfrió hasta 0 ºC bajo nitrógeno. Se añadió NaH (60% de dispersión en aceite mineral, 831 mg, 20,77 mmol) en porciones y la mezcla se agitó durante 30 minutos temperatura ambiente. Se volvió a enfriar hasta 0 ºC y se añadió una solución de 3,5-dibromopirazin-2-amina (4,38 g, 17,31 mmol) en THF (40 mL). La mezcla de reacción se calentó luego a reflujo durante 18 horas. Después de enfriar hasta temperatura ambiente, la mezcla se evaporó al vacío para obtener un aceite marrón oscuro. A este

aceite se añadió una solución acuosa de K_2CO_3 al 10% (100 mL) y se extrajo con EtOAc (3 x 100 mL). Los extractos orgánicos combinados se lavaron con salmuera (100 mL), se secaron sobre $MgSO_4$ y se evaporaron al vacío para obtener un sólido beige. Esto se purificó por cromatografía flash eluyendo con DCM:heptanos 3:1 y luego DCM para obtener el **compuesto 286** en forma de un sólido amarillo pálido (5,80 g, 79% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,84 (dd, 1H, J = 8,7, 5,5 Hz), 7,70 (s, 1H), 7,21 (dd, 1H, J = 9,7, 3,0 Hz), 6,84 (td, 1H, J = 8,3, 3,0 Hz), 5,38 (s, 2H), 4,82 (br. s, 2H); [MH+]-425,80.

Etapa 3:

El **compuesto 286** (5,20 g, 12,26 mmol) se suspendió parcialmente en MeOH (50 mL) y se añadió THF (25 mL) para disolver en una bomba de reacción. Se añadieron DIPEA (10,61 mL, 61,30 mmol), DPE-Phos (792 mg, 12% en moles) y $Pd(OAc)_2$ (165 mg, 6 % en moles). La bomba de reacción se llenó con CO (60 psi) y la mezcla de reacción se calentó hasta 40 °C durante 3 horas. La reacción se enfrió hasta temperatura ambiente y luego se evaporó al vacío para obtener un sólido malva. Este sólido se trituró en DCM caliente y luego se enfrió antes de filtrar un sólido amarillo de compuesto 4 esencialmente puro (2,65 g, 61% de rendimiento). El filtrado se purificó por cromatografía flash eluyéndolo con 25-33% de EtOAc en heptanos para obtener más **compuesto 287** en forma de un sólido marrón pálido (540 mg, 12% de rendimiento). Se obtuvo un total de 3,19 g (73% de rendimiento). ^{1}H RMN (400 MHz, CDCl3): δ 8,06 (dd, 1H, J = 8,7, 5,9 Hz), 7,69 (s, 1H), 7,24 (dd, 1H, J = 9,9, 2,6 Hz), 7,08 (ddd, 1H, J = 8,7, 7,8, 2,7 Hz), 5,82 (s, 2H), 4,81 (br. s, 2H), 3,90 (s, 3H), [MH+]-358,02.

Preparación de 1-(5-etil-1,2-tiazol-3-il)-N-metilmetanamina (293).



Etapa 1:

Una mezcla de **compuesto 288** (13 g, 73 mmol), AIBN (1,19 g, 7,3 mmol) y NBS (32,5 g, 182,5 mmol) en cloroformo (200 mL) se calentó a reflujo bajo nitrógeno durante 24 horas. La mezcla de reacción se concentró al vacío para obtener el residuo, que se purificó por cromatografía en columna en gel de sílice eluyendo con éter de petróleo/EtOAc 200/1 para obtener el **compuesto 289** (4 g, 21,5%) en forma de un aceite amarillo.

Etapa 2:

A una solución agitada de metilcarbamato de ter-butilo (2,4 g, 18,7 mmol) en DMF (30 mL) se añadió NaH (0,75 g, 17,8 mmol, 60% en aceite mineral) a 0 ºC bajo nitrógeno. Después de la adición, la mezcla de reacción se agitó a 0 ºC durante 1 hora. Se añadió el **compuesto 289** (4 g, 15,6 mmol) a la mezcla a 0 ºC y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se diluyó con H2O (100 mL) y se extrajo con EtOAc (100 mL × 3). Las capas orgánicas combinadas se lavaron con salmuera (100 mL × 3), se secaron sobre Na2SO4 y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice eluyendo con éter de petróleo/ EtOAc 20/1 para obtener el **compuesto 290** (2,5 g, 53,2%) en forma de un aceite amarillo.

Etapa 3:

Una mezcla de **compuesto 290** (2,5 g, 8,2 mmol), tributil(etenil)estanano (3,7 g, 12,3 mmol) y $Pd(PPh_3)_4$ (0,474 g, 0,41 mmol) en tolueno seco (30 mL) se calentó a

reflujo bajo nitrógeno durante 4 horas. La mezcla de reacción se concentró al vacío para obtener el residuo, que se purificó por cromatografía en columna en gel de sílice eluyendo con éter de petróleo/EtOAc 50/1~10/1 para obtener el **compuesto 291** (1,6 g, 62,5%) en forma de un aceite amarillo.

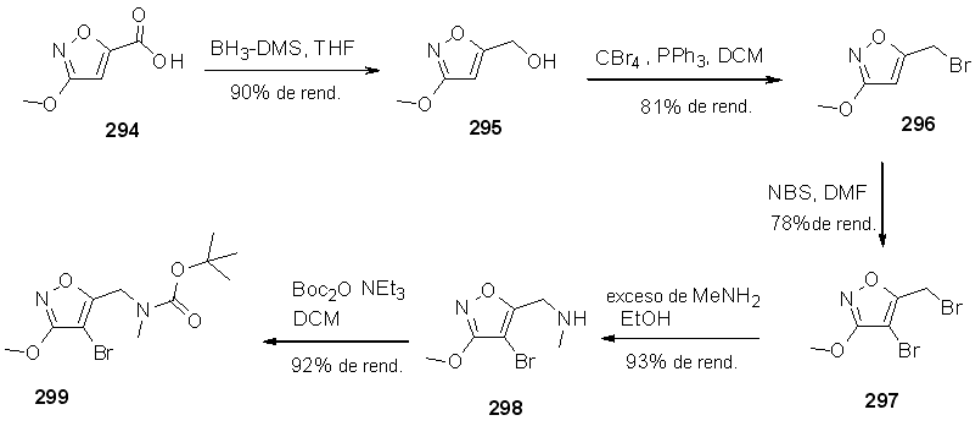
Etapa 4:

Una mezcla de **compuesto 291** (1,6 g, 6,3 mmol) y Pd/C (180 mg) en EtOAc (30 mL) se agitó a 30 °C bajo nitrógeno durante 16 horas. La mezcla de reacción se filtró y el filtrado se concentró al vacío para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice eluyendo con éter de petróleo/ EtOAc 50/1~10/1 para obtener el **compuesto 292** (1,0 g, 62,1%) en forma de aceite amarillo claro. ^{1}H RMN (400 MHz, MeOD): δ 6,973 (s, 1H), 4,50 (s, 2H), 2,96-3,0 (q, 2H), 2,93-2,91 (t, 3H), 1,53 (s, 9H), 1,35-1,28 (t, 3H) LC-MS: 127144-146-P m/z para C12H20N2O2S [M-boc+H]+ 157,0

Etapa 5:

A una solución de **compuesto 292** (0,42 g, 1,6 mmol) en EtOAc (10 mL) se añadió gota a gota HCl (g)/ EtOAc (5 mL) y se agitó a temperatura ambiente durante 5 horas. La mezcla se concentró para obtener el **compuesto 293** en forma de un sólido amarillo (0,32 g, 100%). ^{1}H RMN (400 MHz, D2O): δ 7,17 (s, 1H), 4,33 (s, 2H), 2,98-2,92 (q, 2H), 2,77 (s, 3H), 1,32-1,29 (t, 3H).

Preparación de [(4-bromo-3-metoxi-1,2-oxazol-5-il)metil]metilcarbamato de ter-butilo (299).



Etapa 1:

A una solución de ácido 3-metoxiisoxazol-5-carboxílico **294** (7,6 g, 53,14 mmol) en tetrahidrofurano anhidro (80 ml) a 0 °C bajo nitrógeno, se añadió gota a gota durante 10 minutos una solución de complejo de borano-dimetilsulfuro (5,18 g, 6,47 ml,

69,0 mmol) en THF (30 ml). La mezcla se calentó hasta temperatura ambiente, luego se calentó hasta 60 ºC durante 2 horas y posteriormente se enfrió hasta temperatura ambiente. La mezcla se neutralizó con cuidado por adición gota a gota de 10 ml de agua, se agitó durante 10 minutos, luego se extrajo con EtOAc (2 x 80 ml), se secó sobre Na_2SO_4, se filtró y el solvente se eliminó al vacío para obtener el **compuesto 295** en forma de un aceite amarillo pálido (6,0 g, 88%). ^{1}H RMN (400 MHz, d6-DMSO): δ 6,087 (s, 1H), 4,438 (s, 2H), 5,60 (br.s, 1H), 3,867 (s, 3H), [M+H 130,03].

Etapa 2:

A una solución de **compuesto 295** (411 mg, 3,18 mmol) en diclorometano (5 ml) a 0 ºC bajo nitrógeno, se añadieron trifenilfosfina (833 mg, 3,18 mmol) y tetrabromuro de carbono (1,029 g, 3,10 mmol) (que recién se había secado azeotropándolo 3 veces con tolueno). La mezcla, que se había vuelto anaranjada, se agitó a 0 ºC durante 1 hora y luego se calentó hasta temperatura ambiente. La mezcla se concentró mediante la eliminación del solvente al vacío y luego se purificó por cromatografía flash en columna eluyendo con 3:1 heptano:EtOAc que produjo el **compuesto 296** en forma de un aceite incoloro (486 mg, 81%). ^{1}H RMN (400 MHz, d6-DMSO): δ 6,350 (s, 1H), 4,696 (s, 2H), 3,889 (s, 3H, [M+H 192,2 y 194,2].

Etapa 3:

A una solución de **compuesto 296** (4,4g, 23 mmol) en dimetilformamida anhidra (20 ml) se añadió a temperatura ambiente N-bromosuccinimida (4,1 g, 23,1 mmol) y la mezcla se calentó hasta 45 ºC durante 2 horas. Se añadió más N-bromosuccinimida (2,0 g, 11,3 mmol) y la mezcla se agitó a 45 ºC durante 2 horas. Se añadió más N-bromosuccinimida (1,3g, 7,4 mmol) y la mezcla se agitó durante la noche a temperatura ambiente. Se añadió más N-bromosuccinimida (1,1 g, 11,3 mmol) y la mezcla se agitó a 45 ºC durante la noche. La mezcla se concentró mediante la eliminación del solvente al vacío, luego se extrajo con EtOAc (2 x 100 ml), la capa orgánica se lavó con agua (50 ml) y salmuera (20 ml), se secó sobre Na_2SO_4, se filtró y el solvente se eliminó al vacío. El residuo se añadió a 0,9 g de producto impuro de otra reacción idéntica y se purificó por cromatografía flash en columna eluyendo con 100:0 – 80:20 heptano:EtOAc, que produjo el **compuesto 297** en forma de un aceite incoloro, que luego se cristalizó al reposar en un sólido incoloro (5,66 g, 91% - sin embargo, teniendo en cuenta el material añadido a la columna, el rendimiento calculado fue del 78%). ^{1}H RMN (400 MHz, d6-DMSO): δ 4,72 (s, 2H), 3,98 (s, 3H).

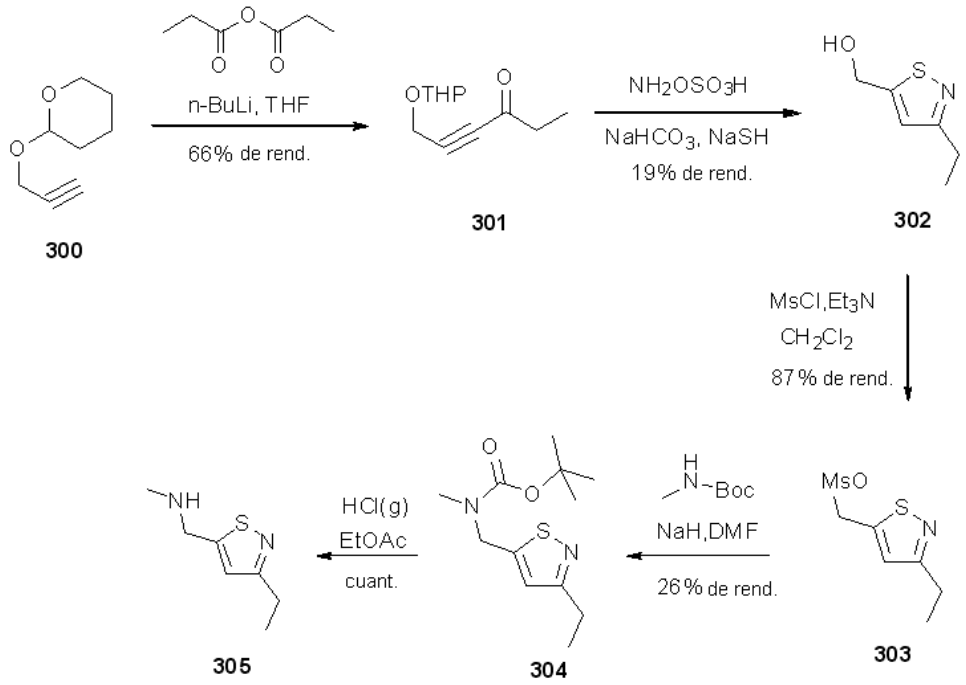
Etapa 4:

A una solución de metilamina 33% en etanol (77 ml, 653 mmol) a 0 ºC bajo nitrógeno, se añadió gota a gota durante 10 minutos una solución de **compuesto 297** en etanol (20 ml) y la mezcla se calentó hasta temperatura ambiente durante la noche. La mezcla se concentró mediante la eliminación de solvente al vacío, luego se añadió hidrógeno-carbonato de sodio acuoso saturado (20 ml), la mezcla se extrajo con EtOAc (100 ml), se secó sobre Na_2SO_4, se filtró y el solvente se eliminó al vacío para obtener el **compuesto 298** en forma de aceite amarillo pálido 4,5 g (93,5%).^{1}H RMN (400 MHz, d6-DMSO): δ 3,956 (s, 3H), 3,686 (s, 2H), 2,287 (br.s, 1H), 2,234 (s, 3H), [M+H 220,95 y 222,95].

Etapa 5:

A una solución de **compuesto 298** (4,5 g, 20,4 mmol) en diclorometano a temperatura ambiente bajo nitrógeno se añadió trietilamina (2,12 g, 2,92 ml, 21 mmol) y luego di-ter-butildicarbonato (4,58 g, 21 mmol) en porciones durante 3 minutos. Se observó una muy leve efervescencia. La mezcla se agitó a temperatura ambiente bajo nitrógeno durante 3 horas. La mezcla se concentró mediante la eliminación de solvente al vacío, se azeotropó con 150 ml de heptano, y luego el residuo se dividió entre EtOAc (100 ml) y agua (20 ml). La capa orgánica se secó sobre Na_2SO_4, se filtró y el solvente se eliminó al vacío para obtener el **compuesto 299** (6 g, 92% de rendimiento).

Preparación de 1-(3-etil-1,2-tiazol-5-il)-*N*-metilmetanamina (305).



Etapa 1:

A una solución de **compuesto 300** (55 g, 0,39 mol) en THF seco (600 mL) se añadió n-BuLi (157 mL, 0,39 mol, 2,5 M) gota a gota a -70 ºC bajo N_2. Después de la adición, la mezcla se agitó a -70 ºC durante 1 hora. La mezcla se calentó hasta -20 ºC y se agitó a esta temperatura durante 20 min. La mezcla de reacción se enfrió hasta -70 ºC y se transfirió por medio de una aguja de doble punta a una solución de anhídrido propanoico (61,3 g, 0,47 mol) en THF seco (400 mL) también mantenida a -70 ºC. La mezcla de reacción se calentó hasta temperatura ambiente lentamente y se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con solución saturada de NH_4Cl (500 mL) y EtOAc (500 mL) y se separó. La capa acuosa se extrajo con EtOAc (500 mL × 3). Las capas orgánicas combinadas se lavaron con salmuera (500 mL), se secaron sobre Na_2SO_4 y se concentraron. El residuo se destiló a presión reducida para obtener el **compuesto 301** (50 g, 65,7%) en forma de un aceite amarillo.

Etapa 2:

A una mezcla de **compuesto 301** (58 g, 0,296 mol) en H_2O (1 L) se añadió NH_2OSO_3H (36,78 g, 0,326 mol) a 0 ºC y la mezcla se agitó a temperatura ambiente durante 4 horas. Se añadió $NaHCO_3$ (27,38 g, 0,326 mol) a la mezcla con cuidado. A continuación, se añadió NaSH (24,86 g, 0,444 mol) y la mezcla se calentó a reflujo durante la noche. La TLC (éter de petróleo: EtOAc = 3:1) mostró que la reacción estaba completa. La mezcla se filtró. El filtrado se extrajo con EtOAc (500 mL × 3). Las capas orgánicas combinadas se lavaron con salmuera (500 mL), se secaron sobre Na_2SO_4 y se concentraron. El residuo se purificó con columna en gel de sílice eluyendo con éter de petróleo/ EtOAc 15/1 ~ 10/1 para obtener el **compuesto 302** (8 g, 19%) en forma de un aceite marrón.

Etapa 3:

A una solución de **compuesto 302** (8 g, 55,9 mmol) y Et_3N (16,9 g, 0,168 mol) en CH_2Cl_2 seco (100 mL) se añadió MsCl (8,32 g, 72,7 mmol) gota a gota a 0 ºC. Después de la adición, la mezcla se agitó a temperatura ambiente durante 2 horas. La TLC (éter de petróleo: EtOAc = 3:1) mostró que la reacción estaba completa. La mezcla se diluyó con EtOAc (250 mL) y se filtró. El filtrado se lavó con salmuera (50 mL), se secó sobre Na_2SO_4 y se concentró para obtener el **compuesto 303** (11 g, 87%) en forma de un líquido marrón.

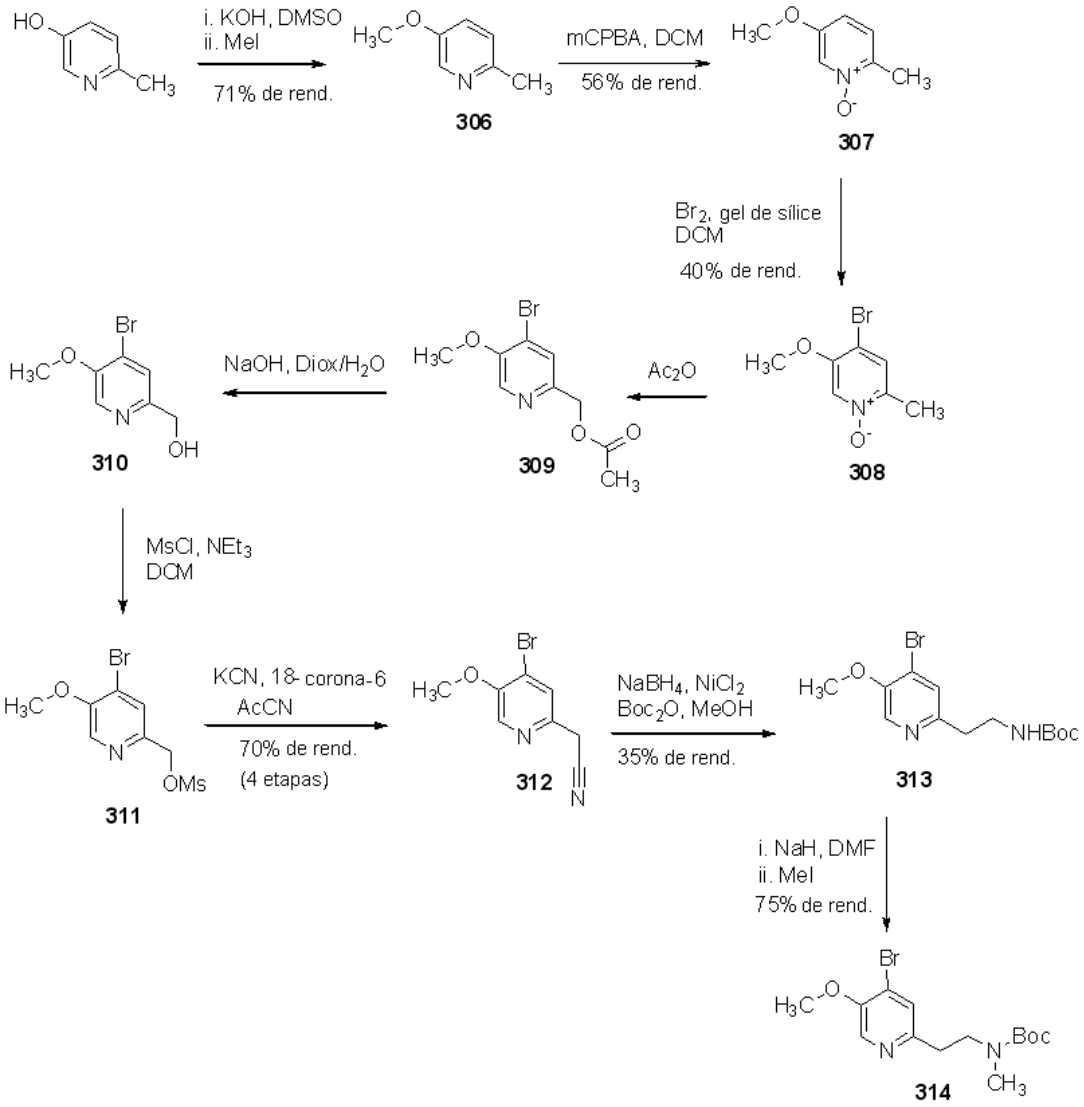
Etapa 4:

A una solución de metilcarbamato de ter-butilo (11 g, 90,5 mmol) en DMF seca (100 mL) se añadió NaH (3,6 g, 90,5 mmol, 60% en aceite) en porciones a 0 ºC bajo N_2. Después de la adición, la mezcla de reacción se agitó a 0 ºC durante 30 min. El **compuesto 303** (10 g, 45,2 mmol) se añadió a la mezcla a 0 ºC y la mezcla se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se diluyó con H_2O (100 mL)) y se extrajo con EtOAc (100 mL × 3). Las capas orgánicas combinadas se lavaron con salmuera (100 mL × 3), se secaron sobre Na_2SO_4 y se concentraron. El residuo se purificó por HPLC preparativa en condiciones básicas para obtener el **compuesto 304** (3 g, 26%) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 6,926 (s, 1H), 4,626 (s, 2H), 2,94 (s, 3H), 2,84-2,86 (q, 2H), 1,53 (s, 9H), 1,33-1,36 (t, 3H), [M+H]+ 257,

Etapa 5:

A una solución de **compuesto 304** (0,42 g, 1,6 mmol) en EtOAc (10 mL) se añadió gota a gota HCl (g)/ EtOAc (5 mL) y se agitó a temperatura ambiente durante 8 horas. La mezcla se concentró para obtener el **compuesto 305** (0,32 g, 100%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, D_2O): δ 7,30 (s, 1H), 4,51 (s, 2H), 2,81-2,75 (q, 2H), 2,72 (s, 3H), 1,222-1,18 (t, 3H).

Preparación de [2-(4-bromo-5-metoxipiridin-2-il)etil]metil-carbamato de ter-butilo (314).



Etapa 1:

Se añadió KOH (141 g, 2,52 mol) a una solución de 2-metil-3-hidroxipiridina (55,0 g, 0,50 mol) en DMSO (840 mL). La mezcla se agitó a temperatura ambiente durante 1 hora (KOH no disuelto por completo) y luego se enfrió a 0 ºC. Se añadió MeI (34,6 mL, 0,55 mol) gota a gota, y luego la reacción se agitó a temperatura ambiente durante 18 horas. Se añadió agua (1,25 L) lentamente a la mezcla de reacción. La fase acuosa se extrajo con MTBE (3 x 500 mL) y luego con EtOAc (3 x 400 mL). La fase acuosa se saturó con NaCl, luego se extrajo otra vez con EtOAc (3 x 200 mL). Las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron con cuidado al vacío (el producto es volátil). El aceite obtenido se purificó por cromatografía en columna (eluyente: heptanos:EtOAc de 1:1 a 0:1) para obtener el **compuesto 306** (44,1 g, 71% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,14

(d, J = 3,1 Hz, 1H), 7,27 (dd, J = 8,5, 3,1 Hz, 1H), 7,16 (d, J = 8,5 Hz, 1H), 3,78 (s, 3H), 2,38 (s, 3H).

Etapa 2:

A una solución de **compuesto 306** (44,1 g, 358 mmol) en DCM (890 mL) se añadió Na_2SO_4 (76,2 g, 537 mmol). La mezcla se agitó a temperatura ambiente durante 15 min, y luego se añadió mCPBA (88,0 g, 358 mmol) en porciones (proceso exotérmico). La reacción se agitó a temperatura ambiente durante 20 horas. Se añadió una cantidad adicional de mCPBA (8,0 g, 36 mmol) y la mezcla se agitó a temperatura ambiente durante 3 horas. La reacción se filtró y luego se lavó con KOH 1 M (500 mL). La fase acuosa se extrajo con DCM (3 x 200 mL), y luego las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron al vacío. El aceite obtenido se disolvió en DCM (600 mL), y luego se añadió Na_2SO_4 (17 g) seguido de mCPBA (8,0 g). La mezcla se agitó a temperatura ambiente durante 20 horas y luego se lavó con KOH 1 M (500 mL). La fase acuosa se saturó con NaCl y se extrajo con DCM (3 x 300 mL). Las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron al vacío para obtener el **compuesto 307** en forma de un sólido blanco (28,7 g, 56% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,07 (d, J = 2,4 Hz, 1H), 7,36 (d, J = 8,8 Hz, 1H), 6,96 (dd, J = 8,8, 2,5 Hz, 1H), 3,78 (s, 3H), 2,27 (s, 3H).

Etapa 3:

Se añadió agua (100 mL) gota a gota al gel de sílice (280 g). La mezcla se agitó 30 min a temperatura ambiente para obtener un polvo fluido. Se añadió DCM (420 mL), la mezcla se agitó para obtener una suspensión homogénea, y luego se añadió una solución de **compuesto 307** (27,7 g, 199 mmol) en DCM (275 mL). Después de obtener una suspensión homogénea, se añadió una solución de Br_2 en DCM (1 M, 285 mL, 199 mmol) gota a gota durante 30 min. La mezcla se agitó a temperatura ambiente durante 18 horas. Se añadieron una porción adicional de gel de sílice (100 g) y una solución de Br_2 en DCM (1 M, 142 mL, 100 mmol). La mezcla se agitó a temperatura ambiente durante 8 horas, y luego se añadieron la misma cantidad de gel de sílice y de solución de Br_2. La mezcla se agitó a temperatura ambiente durante 18 horas y luego se filtró. El taco de sílice se enjuagó con EtOAc (500 mL) y luego con una mezcla DCM/MeOH (8:2, 400 mL). Los licores madre se concentraron al vacío, se redisolvieron en DCM (500 mL) y esta solución se lavó con una solución acuosa de metabisulfito de sodio al 10% (250 mL). Las fases se separaron. La fase acuosa se saturó con NaCl, y luego se extrajo con cuidado con DCM (8 x 150 mL). Las

fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron. El aceite obtenido se purificó rápidamente por cromatografía en columna (eluyentes: EtOAc/MeOH de 15:1 a 8:1). Los sólidos aislados (27 g, mezcla entre 4-bromo y 2-bromopiridina ~6:4) se suspendieron en EtOAc (100 mL) y se trituraron durante 1 hora. El sólido se filtró (polvo blanco, 24 g), se suspendió en DCM (100 mL) y se agitó a reflujo durante 2 horas. La suspensión se enfrió hasta temperatura ambiente y el sólido se filtró para obtener el **compuesto 308**. Los licores madre se concentraron y se suspendieron en DCM; la trituración se repitió para obtener un segundo lote de **compuesto 308** (polvo blanco, 14,9 g, 34% de rendimiento). Las fracciones mezcladas residuales (8,0 g, mezcla 1:1) se purificaron por cromatografía en columna (eluyentes: EtOAc/MeOH from 15:1 a 8:1) para obtener un **compuesto 308** adicional en forma de un polvo blanco (2,6 g, 6% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,23 (d, J = 2,3 Hz, 1H), 7,79 (d, J = 2,6 Hz, 1H), 3,88 (s, 3H), 2,27 (s, 3H).

Etapa 4:

El **compuesto 308** (2,8 g, 13 mmol) se disolvió en Ac_2O (24 mL) y la solución se calentó a 60 ºC durante 18 horas. La mezcla se concentró al vacío. Se añadió ciclohexano (50 mL) y la mezcla se concentró al vacío. Esto se repitió 3 veces. El aceite obtenido se disolvió en EtOAc (150 mL) y la solución se lavó con una solución acuosa saturada de $NaHCO_3$ (100 mL). Las fases se separaron y la fase acuosa se extrajo con EtOAc (2 x 100 mL). Las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron al vacío para obtener **compuesto 309** crudo que se usó en la siguiente etapa sin otra purificación (cristales marrones claros, 3,18 g). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,36 (s, 1H), 7,70 (s, 1H), 5,06 (s, 2H), 3,97 (s, 3H), 2,09 (s, 3H).

Etapa 5:

El **compuesto 309** (3,2 g, 12 mmol) se disolvió en dioxano (86 mL) y luego se añadió una solución acuosa de NaOH (2 M, 28 mL). La mezcla se agitó a temperatura ambiente durante 18 horas. La solución se acidificó con una solución acuosa de HCl 1 M hasta pH 7. La fase acuosa se extrajo con EtOAc (3 x 150 mL). Las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron para obtener el **compuesto 310** en forma de un aceite amarillo pálido (2,5 g) que se usó en la siguiente etapa sin otra purificación. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,28 (s, 1H), 7,64 (s, 1H), 5,43 (t, J = 6,0 Hz, 1H), 4,49 (d, J = 5,6 Hz, 2H), 3,95 (s, 3H).

Etapa 6:

El **compuesto 310** (2,5 g, 12 mmol) se disolvió en DCM (80 mL), luego se añadió trietilamina (2,0 mL, 15 mmol) y la solución se enfrió a 0 ºC. Se añadió cloruro de metansulfonilo (1,0 mL, 13 mmol) gota a gota y la mezcla se agitó a 0 ºC durante 1 hora. Se añadió agua (100 mL) con cuidado a la solución enfriada. Después de dejarla a temperatura ambiente durante 30 min, las fases se separaron y la fase acuosa se extrajo con DCM (2 x 100 mL). Las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron al vacío (baño de rotavapor a temperatura ambiente) para obtener el **compuesto 311** en forma de un aceite marrón (3,4 g) que se usó directamente en la siguiente etapa (degradación observada si se mantiene a temperatura ambiente durante 24 horas). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,42 (s, 1H), 7,83 (s, 1H), 5,23 (s, 2H), 4,00 (s, 3H), 3,27 (s, 3H).

Etapa 7:

El **compuesto 311** (3,4 g, 12 mmol) se disolvió en ACN (8,5 mL) y se añadieron 18-corona-6 (4,8 g, 18 mmol) y luego KCN (1,0 g, 15 mmol). La mezcla se calentó a 50 ºC durante 1,5 horas y luego se enfrió hasta temperatura ambiente. Se añadió una solución acuosa de NaOH (1 M, 200 mL). Las fases se separaron y la fase acuosa se extrajo con EtOAc (3 x 100 mL). Las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron al vacío. El aceite obtenido se purificó por cromatografía en columna (eluyentes heptano/EtOAc de 3:1 a 1:1) para obtener el **compuesto 312** en forma de un sólido beige (2,5 g, 70% de rendimiento en 4 etapas). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,37 (s, 1H), 7,71 (s, 1H), 4,13 (s, 2H), 3,97 (s, 3H).

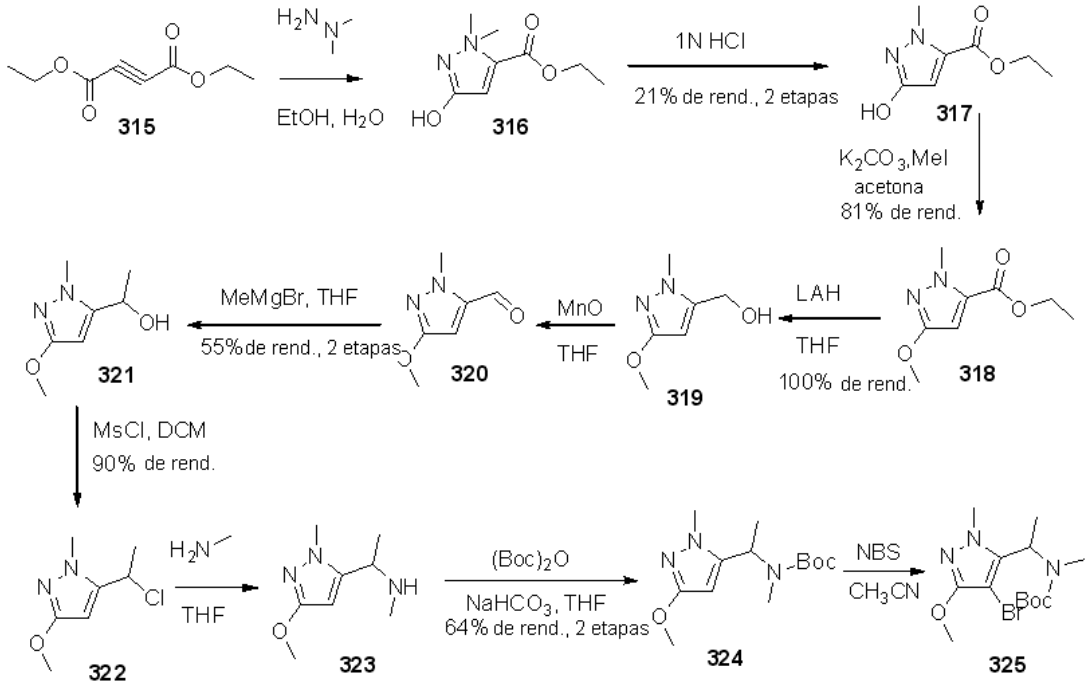
Etapa 8:

El **compuesto 312** (2,0 g, 8,8 mmol) se disolvió en MeOH (135 mL) y se añadieron $NiCl_2$,$6H_2O$ (0,21 g, 0,88 mmol) y luego Boc_2O (3,9 g, 18 mmol). La mezcla se enfrió a -10 ºC, y luego se añadió $NaBH_4$ (1,0 g, 27 mmol) en porciones durante 9 horas. Se añadió dietilentriamina (2 mL) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró al vacío, y luego se añadió EtOAc (100 mL). La solución se lavó con una solución acuosa saturada de $NaHCO_3$ (100 mL). Las fases se separaron y la fase acuosa se extrajo con EtOAc (3 x 100 mL). Las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron al vacío. El aceite obtenido se purificó por cromatografía de fase inversa (eluyentes H_2O/AcCN de 95:5 a 5:95). El **compuesto 313** se obtuvo en forma de aceite incoloro (1,0 g, 35% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,35 (s, 1H), 7,51 (s, 1H), 6,85-6,81 (m, 1H), 3,96 (s, 3H), 3,24-3,20 (m, 2H), 2,80-2,76 (m, 2H), 1,38 (s, 9H).

Etapa 9:

El **compuesto 313** (1,0 g, 3,0 mmol) se disolvió en DMF (135 mL). La solución se enfrió a 0 ºC, luego se añadió NaH (60% en aceite, 180 mg, 4,5 mmol) en porciones durante 10 min. La mezcla se agitó a 0 ºC durante 1 hora, y luego se añadió MeI (0,19 mL, 3,0 mmol) gota a gota durante 10 min. La mezcla se agitó a temperatura ambiente durante 3 horas. La solución se enfrió otra vez a 0 ºC, y luego se añadió H_2O (100 mL) con cuidado. La mezcla se extrajo con Et_2O (3 x 150 mL). Las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron. El aceite obtenido se combinó con otras dos muestras (a partir de 100 mg cada una) y se purificó por cromatografía en columna (eluyentes heptanos/EtOAc de 3:1 a 1:1). Se observó 10 % de SM, de modo que la muestra previa se disolvió en DMF (30 mL), la solución se enfrió hasta 0 ºC, y luego se añadió NaH (37 mg, 1,0 mmol) en porciones. La mezcla se agitó a 0 ºC durante 1 hora, y luego se añadió MeI (29 µL, 0,45 mmol). La mezcla se agitó a temperatura ambiente durante 2 horas y luego se enfrió a 0 ºC. Se añadió agua (50 mL) con cuidado y se extrajo con Et_2O (3 x 100 mL). Las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron para obtener el **compuesto 314** en forma de un aceite amarillo pálido (920 mg, 75% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,28 (s, 1H), 7,54 (s, 1H), 3,92 (s, 3H), 3,54-3,36 (m, 2H), 2,84 (t, J = 6,8 Hz, 2H), 2,74 (s, 3H), 1,48-1,11 (m, 9H).

Preparación de [1-(4-bromo-3-metoxi-1-metil-1*H*-pirazol-5-il)etil]metilcarbamato de ter-butilo (325).



Etapa 1:

A una mezcla de **compuesto 315** (55 mL, 0,35 mol) en 1:1 EtOH/ H2O (600 mL) se añadió lentamente a 0 ºC una solución de 1,1-dimetilhidrazina (25,74 g, 0,44 mol p/p 40% en agua) en 1:1 EtOH/ H2O (200 mL). La solución se agitó a 0 ºC durante 30 min y luego se calentó hasta temperatura ambiente durante 1 h. La mezcla se concentró y el residuo se dividió entre agua (300 mL) y EtOAc (300 mL). La capa acuosa se concentró para obtener el **compuesto 316**, que se usó para la siguiente etapa directamente.

Etapa 2:

Una mezcla de **compuesto 316** en HCl 1 N (200 mL) se agitó a temperatura ambiente durante 1,5 h. La mezcla se extrajo con DCM (150 mL), y la capa acuosa se concentró para obtener el residuo, que se purificó por cromatografía en columna (gel de sílice, éter de petróleo / EtOAc = 6:1) para obtener el **compuesto 317** (13 g, 21%) en forma de un sólido blanco. $_1$H RMN (400 MHz, $CDCl_3$): δ 6,148 (s, 1H), 4,34-4,26 (m, 2H), 3,99 (s, 3H), 1,38-1,30 (m, 3H).

Etapa 3:

Una mezcla de **compuesto 317** (4 g, 23,5 mmol), K2CO3 (9,7 g, 70,5 mmol) y MeI (16,8 g, 0,11 mol) se calentó hasta reflujo durante 3 horas. La TLC (éter de petróleo / EtOAc = 6:1) mostró que la reacción estaba completa. La mezcla se filtró y el filtrado se concentró para obtener el residuo, que se purificó por cromatografía en

columna (gel de sílice, éter de petróleo / EtOAc = 20:1) para obtener el **compuesto 318** (3,5 g, 81%) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 6,18 (s, 1H), 4,34-4,29 (q, 2H), 4,05 (s, 3H), 3,83 (s, 3H), 1,38-1,34 (t, 3H).

Etapa 4:

A una mezcla de **compuesto 318** (2 g, 11,5 mmol) en THF (50 mL) se añadió LiAlH4 (0,52 g, 13,8 mmol) en porciones a 0 ºC. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante la noche. La TLC (éter de petróleo/EtOAc 1/1) mostró que la mezcla de reacción estaba completa. La mezcla de reacción se neutralizó con NaOH acuoso al 20% (4 mL). La mezcla se filtró y el filtrado se concentró al vacío para obtener el **compuesto 319** (1,7 g, ~100 %) en forma de un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$): δ 5,58 (s, 1H), 4,55 (s, 2H), 4,83 (s, 3H), 3,65 (s, 3H).

Etapa 5:

Una solución de **compuesto 319** (2 g, 14,3 mmol), MnO2 (6,2 g, 71,4 mmol) en THF seco (50 mL) se calentó hasta reflujo durante la noche. La TLC (éter de petróleo/EtOAc 6/1) mostró que la mezcla de reacción estaba completa. La mezcla de reacción se filtró y el filtrado (**compuesto 320**) se usó para la siguiente etapa directamente.

Etapa 6:

A una solución de **compuesto 320** (~14,3 mmol) en THF seco (100 mL) se añadió MeMgBr (24 mL, 71,4 mmol, 3,0 M) a -50 ºC. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 15 horas. La TLC (éter de petróleo/EtOAc 6/1) mostró que la mezcla de reacción estaba completa. La mezcla de reacción se neutralizó con NH4Cl saturado (20 mL). La mezcla se extrajo luego con EtOAc (100 mL x 3). Los extractos combinados se lavaron con salmuera (100 mL x 2), se secaron sobre Na2SO4 y se concentraron al vacío para obtener el residuo, que se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc 10/1) para obtener el **compuesto 321** (1,2 g, 55 %) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, $CDCl_3$): δ 5,58-5,57 (d, 1H), 4,84-4,80 (q, 1H), 3,83 (s, 3H), 3,73-3,72 (d, 3H), 2,03-2,02 (bs, 1H), 1,55-1,53 (d, 3H).

Etapa 7:

A una solución de **compuesto 321** (1,2 g, 7,6 mmol) y Et3N (1,1 g, 11,4 mmol) en DCM seco (30 mL) se añadió gota a gota MsCl (1,3 g, 11,4 mmol) a 0 ºC. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 12 horas. La TLC (éter de petróleo/EtOAc 1/1) mostró que la mezcla de reacción estaba

completa. La mezcla de reacción se lavó con salmuera (20 mL), se secó sobre Na2SO4 y se concentró al vacío para obtener el residuo crudo, que se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc 20/1) para obtener el **compuesto 322** (1,2 g, 90 %) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, CDCl3): δ 5,61 (s, 1H), 5,04-4,99 (q, 1H), 3,85 (s, 3H), 3,76 (s, 3H), 1,88-1,86 (d, 3H).

Etapa 8:

Una solución de **compuesto 322** (0,3 g, 1,72 mmol) en una solución de CH3NH2 (20 mL, 2 M en THF) se calentó hasta 80 ºC en un tubo sellado durante 12 horas. La TLC (éter de petróleo/EtOAc 6/1) mostró que la mezcla de reacción estaba completa. El **compuesto 323** se usó para la siguiente etapa directamente.

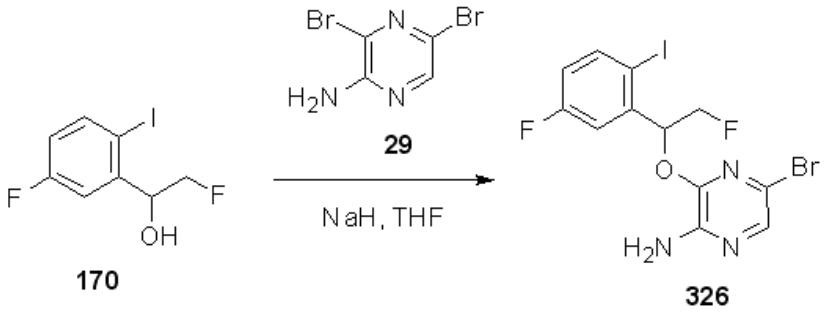
Etapa 9:

A una mezcla de **compuesto 323** en DCM (20 mL) se añadieron Et3N (347 mg, 3,44 mmol) y (Boc)2O (743 mg, 3,44 mmol), y la mezcla se agitó a temperatura ambiente durante la noche. La TLC (éter de petróleo/EtOAc 6/1) mostró que la mezcla de reacción estaba completa. La mezcla de reacción se dividió entre agua (20 mL) y DCM (50 mL). La capa orgánica separada se lavó con salmuera (50 mL), se secó sobre Na2SO4 y se concentró al vacío para obtener el residuo, que se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc 20/1) para obtener el **compuesto 324** (300 mg, 64% en dos etapas) en forma de un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$): δ 5,59 (s, 1H), 5,47 (br, 1H), 3,83 (s, 3H), 3,62 (s, 3H), 2,54 (s, 3H), 1,48 (s, 9H); LCMS: m/z para C13H23N3O3 270,3 [M+H]+.

Etapa 10:

A una solución de **compuesto 324** (2,1 g, 7,78 mmol) en DCM (20 mL) se añadió en porciones NBS (1,46 g, 8,16 mmol) a 0 ºC. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La TLC (éter de petróleo/EtOAc 6/1) mostró que la mezcla de reacción estaba completa. La mezcla de reacción se lavó con $NaHCO_3$ saturado (30 mL x 4) y salmuera (30 mL), se secó sobre Na_2SO_4 y se concentró al vacío para obtener el **compuesto 325** (2,5 g, 91 %) en forma de un aceite amarillo. ^{1}H RMN (400 MHz, CDCl3): δ 5,79 (s, 1H), 3,92 (s, 3H), 3,68 (s, 3H), 2,70 (s, 3H), 1,66-1,64 (d, 3H), 1,47 (s, 9H).

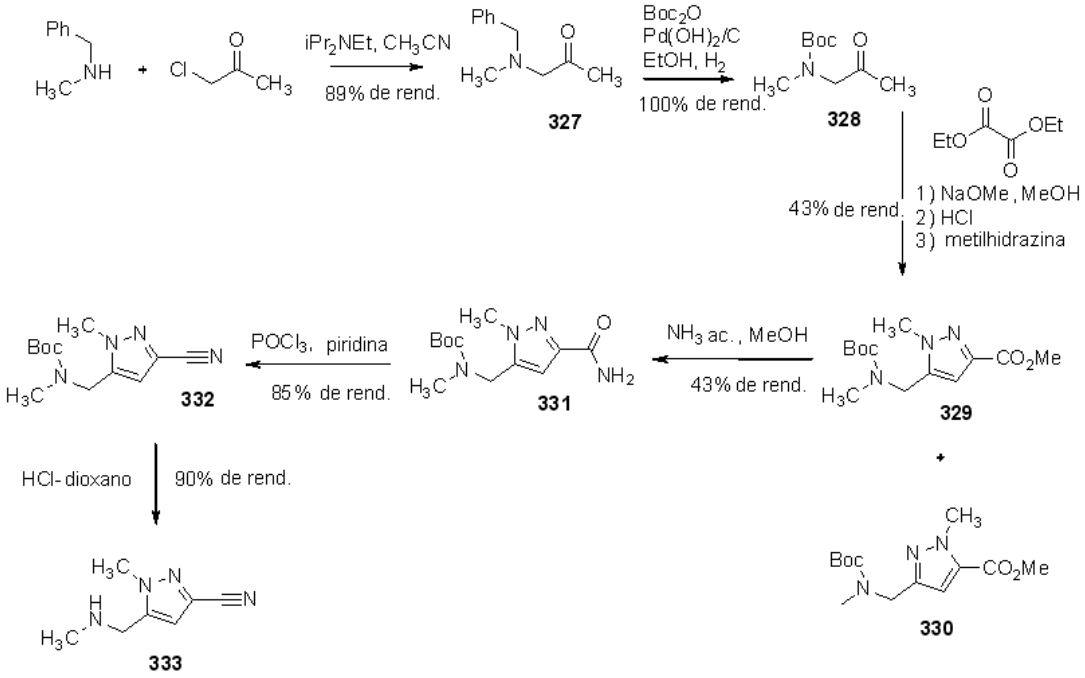
Preparación de 5-bromo-3-[2-fluoro-1-(5-fluoro-2-yodofenil)etoxi]pirazin-2-amina (326).



170 326

El procedimiento descrito en la etapa 2 para el **compuesto 241** se usó para preparar el **compuesto 326.**

Preparación de 1-metil-5-[(metilamino)metil]-1*H*-pirazol-3-carbonitrilo (333).



Etapa 1:

Se añadió cloroacetona (207 mL, 2,59 mol) gota a gota durante 45 min a una solución de DIEA (410 mL, 310 g, 2,40 mol) y N-metilbencilamina (286 g, 2,36 mol) en acetonitrilo (1500 mL), manteniendo la temperatura entre 18 y 20 °C por enfriamiento moderado con un baño de agua fría. Una vez completa la adición, el baño de enfriamiento se mantuvo en el lugar durante otros 30 min antes de retirarlo. Se continuó agitando durante otras 5,5 h, durante lo cual la temperatura interna de la reacción se elevó a 27 °C durante 1 hora, se niveló durante 2 horas y luego se disminuyó lentamente. La mezcla de reacción se concentró al vacío a

aproximadamente 1 L y luego se dejó reposar durante la noche. El precipitado cristalino se eliminó por filtración, se lavó con acetonitrilo (50 mL) y el filtrado se concentró al vacío. El filtrado concentrado se extrajo en EtOAc (1 L) y se filtró a través de un taco corto de sílice (1200 mL sílice) lavándolo con más EtOAc (2 x 1L). El filtrado se concentró al vacío para obtener el **compuesto 327** en forma de un aceite anaranjado-marrón (374 g, 89%). ^{1}H RMN (400 MHz, Cloroformo-d) δ 7,39 – 7,22 (m, 5H), 3,59 (s, 2H), 3,16 (s, 2H), 2,30 (s, 3H), 2,14 (s, 3H).

Etapa 2:

Se añadieron hidróxido de paladio sobre carbón (20%, 36 g) y dicarbonato de di-ter-butilo (565 g, 2,59 mol) a una solución de **compuesto 327** (439 g, 2,48 mol) en etanol (3,25 L) y la mezcla se hidrogenó a 50 °C y 50 psi de presión de H_2 durante 8 horas. El calentamiento se detuvo y la reacción se mantuvo bajo hidrógeno durante el fin de semana. El catalizador se eliminó por filtración a través de Celite, lavándolo con metanol y el solvente se eliminó al vacío para obtener el **compuesto 328** en forma de un aceite marrón con una pequeña cantidad de sólido suspendido (476,5 g). Este material se usó sin otra purificación. ^{1}H RMN (400 MHz, Cloroformo-d) 2 rotámeros δ 4,00 y 3,90 (2 x s, 2H), 2,92 y 2,88 (2 x s, 2H), 2,12 (s, 3H), 1,47 y 1,42 (2 x s, 9H).

Etapa 3:

Se añadió una mezcla de oxalato de dietilo (187 mL, 1,38 mol) y **compuesto 328** (258 g, 1,38 mol) en MeOH (200 mL) gota a gota durante 30 min a una solución de NaOMe en MeOH (5,38 M, 257 mL, 1,38 mol) en MeOH (1800 mL). Una vez completa la adición, la reacción se calentó hasta 55 °C y se agitó durante 2 horas. La reacción luego se calentó a 65 °C durante 30 min antes de enfriarla hasta -7 °C. Luego se añadió gota a gota una solución de clorhidrato de metilhidrazina en MeOH (preformada por la adición gota a gota de HCl concentrado [115 mL, 1,38 mol] a una solución helada de metilhidrazina [72,7 mL, 63,6 g, 1,38 mol] en MeOH [100 mL]), de modo que la temperatura se mantuvo a menos de -5 °C. Una vez completa la adición, la reacción se calentó lentamente hasta temperatura ambiente y se agitó durante la noche. La mezcla de reacción se filtró y se concentró al vacío. La masa semisólida marrón se extrajo en 10% de DCM en heptano (500 mL + 250 mL para lavar), se filtró y se combinó con el material de una segunda reacción (207 g de metil(2-oxopropil)carbamato de ter-butilo, 1,10 mol). Los filtrados combinados se aplicaron a la parte superior de una columna flash seca (3,7 L de sílice) y la columna se eluyó con heptanos/EtOAc (5-25%) para obtener los **compuestos 329 y 330** (relación 3:1).

Compuesto 329: (302 g, 43%). ^{1}H RMN (400 MHz, DMSO-d6) δ 6,65 (s, 1H), 4,30 (s, 2H), 4,04 (s, 3H), 3,82 (s, 3H), 2,76 (s, 3H), 1,40 (s, 9H).

Etapa 4:

El **compuesto 330** (7,55 g, 26,6 mmol) se disolvió en MeOH (7 mL), y luego se añadió una solución acuosa de amoníaco (35%, 70 mL). La solución se agitó a temperatura ambiente durante 18 horas. La suspensión formada se filtró y el sólido blanco aislado se secó para obtener el **compuesto 331** (3,4 g, 43% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,42 (s, 1H), 7,17 (s, 1H), 6,49 (s, 1H), 4,46 (s, 2H), 3,81 (s, 3H), 2,76 (s, 3H), 1,41 (s, 9H).

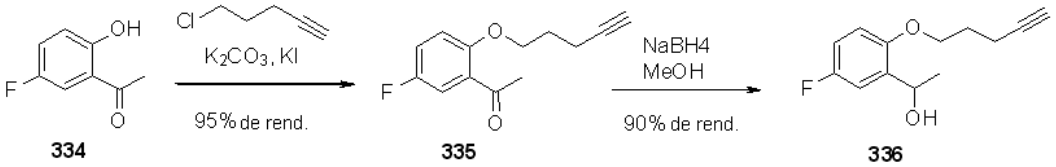
Etapa 5:

El **compuesto 331** (3,4 g, 13 mmol) se disolvió en piridina (34 mL) y la solución se enfrió a 0 °C. Se añadió $POCl_3$ (2,32 mL, 25,4 mmol) gota a gota manteniendo la temperatura a menos de 25 °C. La mezcla se agitó luego a 0 °C durante 5 minutos más y luego a temperatura ambiente durante 20 minutos. La reacción se neutralizó mediante la adición lenta de agua (200 mL). La temperatura de la mezcla se mantuvo a menos de 30 °C mediante la adición de hielo. Al final de la adición, la mezcla se agitó a temperatura ambiente durante 40 minutos y luego se extrajo con EtOAc (3 x 200 mL). Las fases orgánicas se combinaron, se lavaron con una solución saturada acuosa de $NaHCO_3$ (200 mL) y salmuera (200 mL), se secaron sobre $MgSO_4$, se filtraron y se concentraron al vacío. El aceite marrón obtenido se purificó por cromatografía en columna para obtener el **compuesto 332** en forma de un aceite amarillo (2,71 g, 85% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 6,84 (s, 1H), 4,49 (s, 2H), 3,87 (s, 3H), 2,77 (s, 3H), 1,40 (s, 9H).

Etapa 6:

El **compuesto 332** (2,71 g, 10,8 mmol) se disolvió en DCM (15 mL) y la solución se enfrió a 0 °C. Se añadió HCl (4 M en dioxano, 15 mL, 60 mmol) gota a gota, y la solución se agitó a 0 °C durante 10 minutos y luego a temperatura ambiente durante 3 horas. La suspensión obtenida se concentró al vacío hasta obtener la mitad del volumen inicial. La suspensión se filtró, los sólidos se enjuagaron con DCM (10 mL) y se secaron para obtener el **compuesto 333** clorhidrato en forma de un sólido blanco (1,80 g, 90% de rendimiento). ^{1}H RMN (400 MHz, Metanol-d_4) δ 6,99 (s, 1H), 4,42 (s, 2H), 4,03 (s, 3H), 2,81 (s, 3H).

Preparación de 1-[5-fluoro-2-(pent-4-in-1-iloxi)fenil]etanol (336).



334 335 336

Etapa 1:

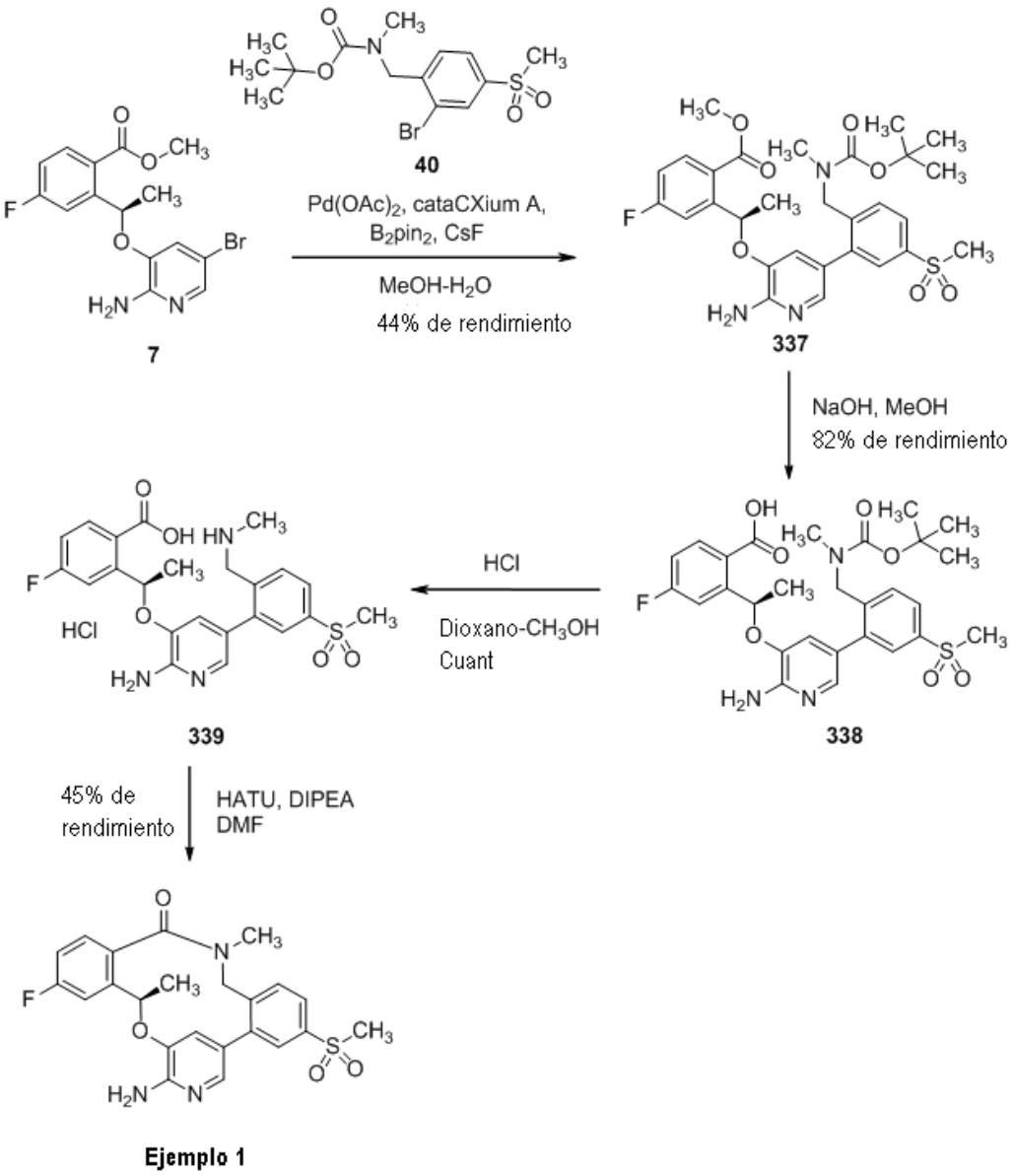
1-(5-fluoro-2-hidroxifenil)etanona **334** (5,0 g, 32,5 mmol), K_2CO_3 (8,96 g, 64,9 mmol) y KI (8,08 g, 48,7 mmol) se mezclaron en DMF (150 mL). Se añadió 5-cloropent-1-ina (5,15 mL, 48,7 mmol) y la mezcla se calentó a 80 °C durante 18 horas. La LC-MS mostró una conversión completa. La mezcla se enfrió a temperatura ambiente, se añadió EtOAc (1 L) y luego se lavó con agua (6 x 200 mL). La fase orgánica se secó sobre MgSO4, se filtró y se concentró al vacío. El aceite obtenido se purificó por cromatografía en columna (eluyentes heptanos/EtOAc de 6:1 a 3:1) para obtener el **compuesto 335** en forma de aceite amarillo pálido (6,82 g, 95% de rendimiento, 100% de pureza por LC-MS). ^{1}H RMN (400 MHz, DMSO-d6) δ 7,45 – 7,31 (m, 2H), 7,20 (dd, J = 9,1, 4,2 Hz, 1H), 4,15 (t, J = 6,1 Hz, 2H), 2,83 (t, J = 2,7 Hz, 1H), 2,55 (s, 3H), 2,37 (td, J = 7,1, 2,7 Hz, 2H), 2,10 – 1,85 (m, 2H).

Etapa 2:

El **compuesto 335** (6,62 g, 30,1 mmol) se disolvió en MeOH (120 mL). La solución se enfrió a 0 °C y se añadió NaBH4 (1,47 g, 39,1 mmol) en porciones. La mezcla se agitó a 0 °C durante 1 hora a temperatura ambiente durante 30 minutos. La TLC mostró una conversión completa. Se añadió agua (300 mL) lentamente a la mezcla y se extrajo con EtOAc (2 x 200 mL). Las fases orgánicas se combinaron, se secaron sobre MgSO4, se filtraron y se concentraron al vacío. El aceite obtenido se purificó por cromatografía en columna (eluyentes heptanos/EtOAc de 9:1 a 3:1) para obtener el **compuesto 336** en forma de aceite amarillo pálido (6,04 g, 90% de rendimiento, 97% de pureza por LC-MS). ^{1}H RMN (400 MHz, DMSO-d6) δ 7,17 (dd, J = 9,7, 3,1 Hz, 1H), 7,05 – 6,85 (m, 2H), 5,13 (d, J = 3,9 Hz, 1H), 4,95 (p, J = 6,2 Hz, 1H), 4,12 – 3,91 (m, 2H), 2,81 (t, J = 2,7 Hz, 1H), 2,34 (td, J = 7,1, 2,7 Hz, 2H), 1,96 – 1,84 (m, 2H), 1,26 (d, J = 6,3 Hz, 3H).

Ejemplos

Preparación de (5*R*)-8-amino-3-fluoro-5,17-dimetil-13-(metilsulfonil)-16,17-dihidro-7,11-(meteno)dibenzo[*g,l*][1,4,10]oxadiazaciclotetradecin-18(5*H*)-ona (Ejemplo 1).



Ejemplo 1

Etapa 1:

Acetato de paladio (II) (70 mg, 0,31 mmol) y cataCXium® A (221 mg, 0,62 mmol) se mezclaron junto en tolueno (2,5 mL, desgasificado) y la solución resultante se añadió por medio de una pipeta a una solución agitada del compuesto **7** (1,10 g, 3,1 mmol), bis-pinacolatodiboro (1,6 g, 6,2 mmol) y CsF (1,87 g, 12,4 mmol) en MeOH/H2O (4:1, 24 mL, desgasificado) a 50 ºC. Después de 4-5 minutos, la reacción se tornó de color gris oscuro/marrón y se añadió una solución del compuesto **40** (900 mg, 2,4 mmol) en metanol (5 mL, desgasificado) toda junta. La mezcla resultante se agitó luego a reflujo durante 3 hrs, en cuyo momento la TLC (EtOAc/ciclohexano 6:4) había mostrado un consumo completo tanto de bromuros de arilo como la conversión

a una nueva mancha mayor más polar (Rf = 0,35). Después de enfriar hasta temperatura ambiente, la mezcla se diluyó con EtOAc (150 mL) y se lavó con agua (100 mL), luego salmuera (100 mL), se secó (Na_2SO_4) y se evaporó. El residuo se purificó por cromatografía flash en gel de sílice, que se eluyó con 6:4 EtOAc/ciclohexano y produjo el compuesto **110** en forma de una espuma marrón claro (950 mg). TLC: Rf = 0,35 (EtOAc/ciclohexano 6:4). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,00 (dd, 1 H, *J* = 9,1, 6,1 Hz), 7,83 - 7,84 (m, 1 H), 7,63 (d, 1 H, *J* = 2,1 Hz), 7,56 - 7,59 (m, 1 H), 7,34 - 7,37 (m, 1 H), 6,97 - 7,04 (m, 2 H), 6,58 - 6,61 (m, 1 H), 6,39 - 6,45 (m, 1 H), 4,98 (br s, 2 H), 4,05 - 4,30 (m, 2 H), 3,84 (br s, 3 H), 3,05 (br s, 3 H), 2,54 - 2,68 (m, 3 H), 1,67 (d, 3 H, *J* = 6,3 Hz), 1,32 - 1,51 (m, 9 H). LCMS ES *m/z* 588 $[M+H]^+$.

Etapa 2:

A una solución del compuesto **337** (65% de pureza, 1,1 g, se asumen 1,2 mmol) en MeOH (25 mL) se añadió NaOH (1,2 g, 30 mmol) y la mezcla se agitó a temperatura ambiente durante la noche. La reacción se diluyó con agua (60 mL) y se lavó con MTBE (60 mL). La capa acuosa se acidificó luego cuidadosamente con HCl acuoso 1 M hasta aproximadamente pH 4 (papel de pH). Se añadió cloruro de sodio (10 g) a la mezcla y la mezcla se extrajo con EtOAc (80 mL). La capa orgánica se separó, se secó (Na_2SO_4) y se evaporó. El residuo se purificó por cromatografía flash sobre gel de sílice que se eluyó con 2% AcOH en EtOAc, para dar el compuesto **338** (550 mg, 82% de rendimiento) en forma de una espuma blanquecina. TLC: Rf = 0,5 (2% AcOH en EtOAc). ^{1}H RMN (400 MHz, CD_3OD) δ 7,98 (dd, 1 H, *J* = 8,2, 5,8 Hz), 7,88 (dd, 1 H, *J* = 8,0, 1,7 Hz), 7,62 (s, 1 H), 7,40 - 7,44 (m, 2 H), 7,34 (dd, 1 H, *J* = 10,1, 2,7 Hz), 7,05 - 7,09 (m, 1 H), 6,90 - 6,83 (m, 1 H), 6,53 (br s, 1 H), 4,00 - 4,33 (m, 2 H), 3,12 (s, 3 H), 2,55 - 2,75 (m, 3 H), 1,70 (d, 3 H, *J* = 6,55 Hz), 1,25 - 1,48 (m, 9 H). LCMS ES *m/z* 574 $[M+H]^+$.

Etapa 3:

Una solución de HCl en dioxano (4 M, 5,0 mL) se añadió a una solución del compuesto **338** (550 mg, 0,96 mmol) en dioxano/MeOH (4:1, 15 mL) y la reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción luego se concentró hasta secarse a presión reducida. El residuo se extrajo en MeOH (50 mL), se añadió tolueno (100 mL) y la mezcla se volvió a evaporar hasta secarse, lo que produjo el compuesto **339** en forma de un sólido blanquecino (500 mg, rendimiento cuantitativo asumido). ^{1}H RMN (400 MHz, CD_3OD) δ 8,10 (dd, 1 H, *J* = 8,0, 2,0 Hz), 8,06 (dd, 1 H, *J* = 8,9, 5,9 Hz), 7,85 (d, 1 H, *J* = 8,0 Hz), 7,78 (d, 1 H, *J* = 2,0 Hz), 7,56 (d, 1 H, *J* = 1,7 Hz), 7,48 (dd, 1 H, *J* = 9,9, 2,7 Hz), 7,26 (d, 1 H, *J* = 1,7 Hz), 7,19 (dt, 1

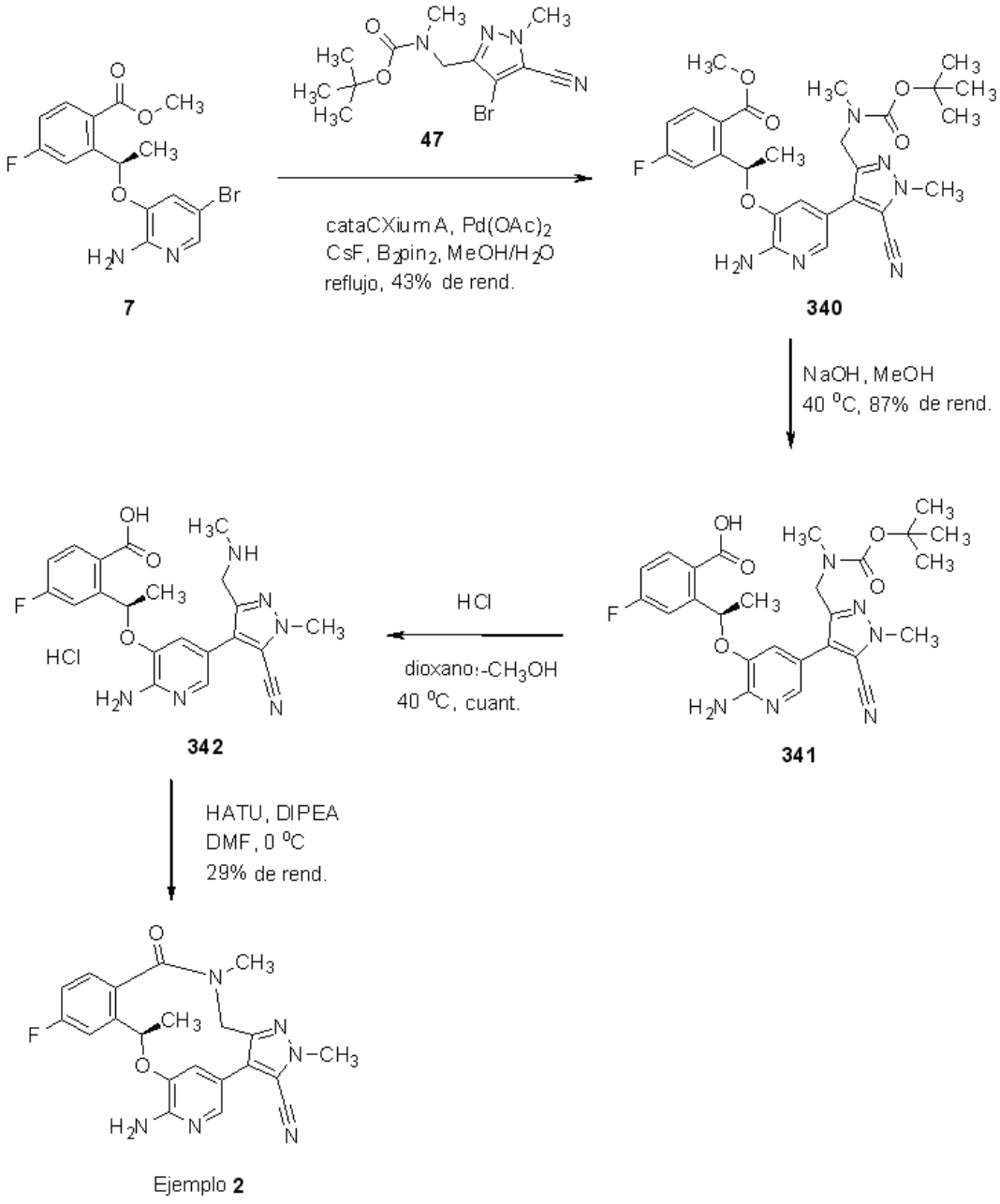
H, *J* = 8,31, 2,85 Hz), 6,70 (q, 1 H, *J* = 6,5 Hz), 4,19 (d, 1 H, *J*= 14,5 Hz), 4,13 (d, 1 H, *J* = 14,6 Hz), 3,17 (s, 3 H), 2,61 (s, 3 H), 1,76 (d, 3 H, *J* = 6,0 Hz). LCMS ES *m/z* 474 $[M+H]^+$.

Etapa 4:

Se añadió una solución del compuesto **339** (500 mg, 0,96 mmol asumidos) en forma de la sal de HCl y DIPEA (2,0 g, 15,5 mmol) en DMF (6,0 mL) y se THF (1,0 mL) gota a gota a una solución de HATU (510 mg, 1,34 mmol) en DMF (6,0 mL) a 0 ºC durante 35 minutos. Después de completar la adición, la mezcla se agitó a 0 ºC durante otros 60 min. Se añadió agua (100 mL) y la mezcla se extrajo en EtOAc (2 x 50 mL). Las capas orgánicas combinadas se lavaron con $NaHCO_3$ saturado acuoso (100 mL), salmuera (100 mL), se secaron sobre Na_2SO_4 y se evaporaron. El residuo se purificó por cromatografía en columna en gel de sílice, que se eluyó con 100% de EtOAc, para obtener un sólido pegajoso. Los sólidos se disolvieron en acetonitrilo (2,5 mL) y se añadió MTBE (30 mL) lentamente con buena agitación para precipitar el producto. Después de agitar durante 20 minutos, la mezcla se filtró y el Ejemplo **1** se recolectó en forma de un sólido de color crema (200 mg, 45% de rendimiento). TLC: R_f = 0,5 (100% de EtOAc). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,84 - 7,92 (m, 3 H), 7,69 (dd, 1 H, *J* = 10,4, 2,8 Hz), 7,51 (d, 1 H, *J* = 2,0 Hz), 7,36 (dd, 1 H, *J* = 8,8, 6,0 Hz), 7,14 (dt, 1 H, *J* = 8,4, 2,4 Hz), 7,09 (d, 1 H, 2,0 Hz), 6,13 (s, 2H), 5,71 - 5,67 (m, 1 H), 4,45 (d, 1 H, *J* = 13,2 Hz), 4,22 (d, 1 H, *J* = 13,2 Hz), 3,29 (s, 3 H), 3,01 (s, 3 H), 1,69 (d, 3 H, *J* = 6,4 Hz). LCMS ES *m/z* 456 $[M+H]^+$.

Se cultivaron cristales del Ejemplo **1** por difusión de vapor de pentano en una solución etanólica y se recolectaron los datos en una corriente de gas nitrógeno a 120(2) K. Ver la Figura 1.

Preparación de (10*R*)-7-amino-12-fluoro-2,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 2).



Ejemplo **2**

Etapa 1:

Acetato de paladio (II) (53 mg, 0,24 mmol) y cataCXium® A (180 mg, 0,5 mmol) se mezclaron juntos en tolueno (1,5 mL, desgasificado) y la solución resultante se añadió por medio de pipeta a una solución agitada de **compuesto 7** (0,9 g, 2,4 mmol), **compuesto 47** (1,0 g, 3,0 mmol), bis-pinacolato diboro (0,9 g, 3,6 mmol) y CsF (1,9 g, 12,6 mmol) en MeOH/H_2O (9:1, 12 mL, desgasifica) a 60 °C. La mezcla resultante se agitó luego a reflujo durante 3 h. Se añadió otra porción de acetato de paladio (II) (26 mg, 0,12 mmol) y cataCXium® A (90 mg, 0,25 mmol) en tolueno (1,5 mL,

desgasificado) y la mezcla de reacción amarilla se agitó a 60 ºC durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla se diluyó con EtOAc (150 mL) y se filtró a través de Celite. El filtrado se lavó con agua (100 mL) y luego salmuera (100 mL), se secó (Na_2SO_4) y se evaporó. El residuo se purificó por cromatografía flash en gel de sílice, que se eluyó con 1:1 EtOAc/ciclohexano y produjo el **compuesto 340** en forma de un aceite amarillo (570 mg, 43% de rendimiento). TLC (Rf = 0,40, 1:1 EtOAc/ciclohexano). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,03 (m, 1 H), 7,65 (s, 1 H), 7,27 (dd,1 H, *J* = 9,9, 2,7 Hz), 7,01 (m, 1 H), 6,68 (m, 1 H), 6,40 (m, 1 H), 4,90 (br s, 2 H), 4,20 - 4,30 (m, 2 H), 3,96 (s, 3 H), 3,94 (s, 3 H), 2,55 - 2,85 (m, 3 H), 1,68 (d, 3 H, *J* = 6,6 Hz), 1,24 (s, 9 H). LCMS ES *m/z* 539 $[M+H]^+$.

Etapa 2:

A una solución de **compuesto 340** (69% de pureza, 0,95 g, asumiendo 1,05 mmol) en MeOH (20 mL) se añadió una solución NaOH (1,0 g, 25 mmol) en agua (2 mL). La mezcla se agitó a 40 ºC durante 3,5 horas. La reacción se diluyó con agua (80 mL), se concentró en 20 mL para eliminar el MeOH en el rotorvap y se lavó con MTBE (100 mL). La capa acuosa se acidificó con cuidado con HCl acuoso 1 M a aproximadamente pH 2 (papel de pH). Se añadió cloruro de sodio (15 g) a la mezcla, y la mezcla se extrajo con EtOAc (100 mL). La capa orgánica se separó, se secó (Na_2SO_4) y se evaporó para obtener el **compuesto 341** en forma de un sólido amarillo pálido (480 mg, 87% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ 8,05 (m, 1 H), 7,45 (s, 1 H), 7,37 (dd,1 H, *J* = 10,4, 2,8 Hz), 7,10 (dt, 1 H, *J* = 8,5, 2,4 Hz), 6,50 - 6,60 (m, 2 H), 4,05 - 4,30 (m, 2 H), 3,99 (s, 3 H), 2,60 - 2,80 (m, 3 H), 1,72 (d, 3 H, *J* = 6,5 Hz). LCMS ES *m/z* 525 $[M+H]^+$.

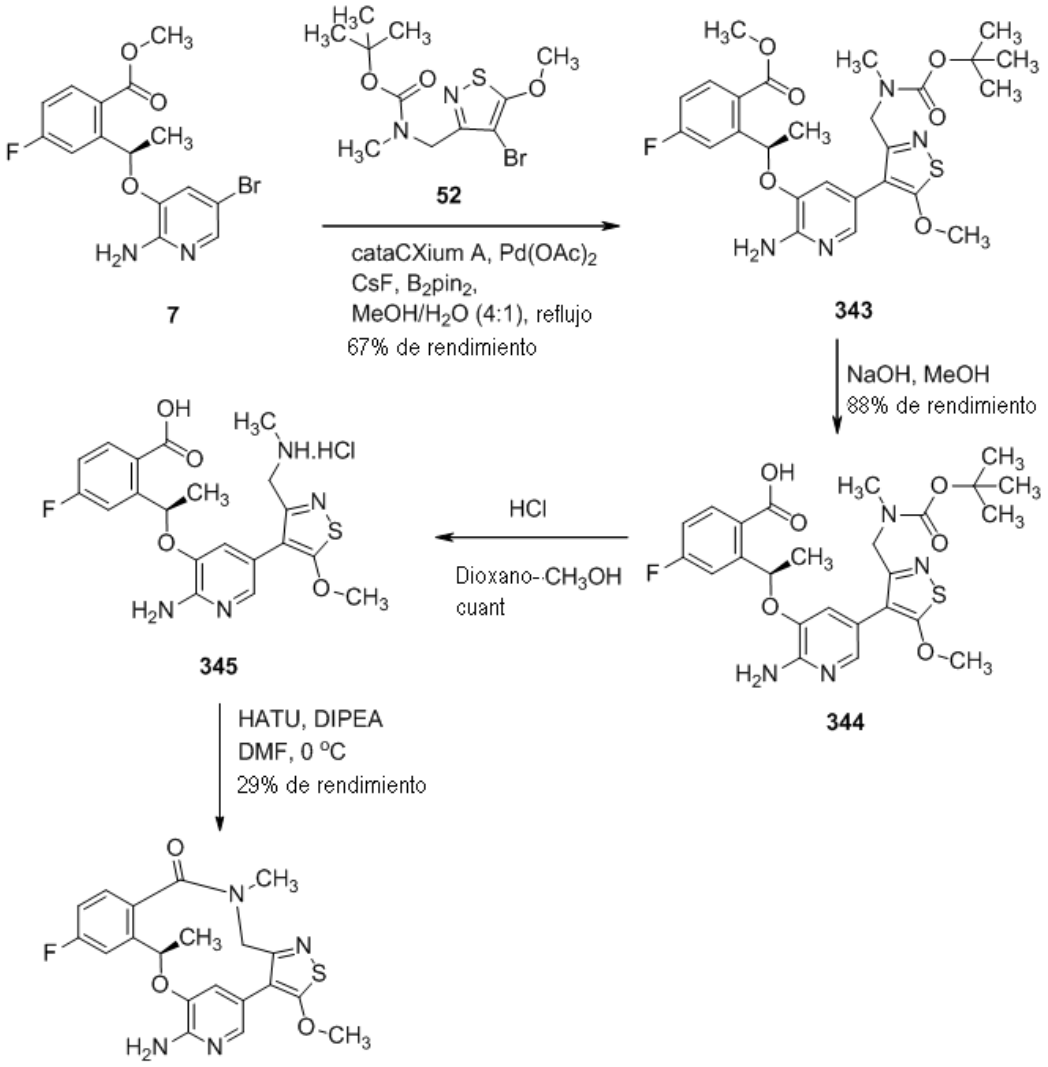
Etapa 3:

Se añadió una solución de HCl en dioxano (4 M, 6,0 mL) a una solución de **compuesto 341** (480 mg, 0,91 mmol) en MeOH (6 mL) y la reacción se agitó a 40 ºC durante 2,5 horas. La mezcla de reacción luego se concentró hasta sequedad a presión reducida. El residuo se extrajo en MeOH (50 mL), se añadió acetonitrilo (100 mL) y la mezcla se evaporó otra vez hasta sequedad para obtener el **compuesto 342** en forma de un sólido blanquecino (400 mg, 87% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ 8,07 (dd, 1 H, *J* = 8,9, 5,9 Hz), 7,51 (d, 1 H, *J* = 1,7 Hz), 7,42 (dd, 1 H, *J* = 9,8, 2,6 Hz), 7,23 (d, 1 H, *J* = 1,6 Hz), 7,16 (dt, 1 H, *J* = 8,5, 2,7 Hz), 6,73 (dd, 1 H, *J* = 11,9, 6,9 Hz), 4,22 (d, 1 H, *J* = 14,7 Hz), 4,14 (d, 1 H, *J* = 14,7 Hz), 4,07 (s, 3 H), 2,75 (s, 3 H), 1,75 (d, 3 H, *J* = 5,5 Hz). LCMS ES *m/z* 425 $[M+H]^+$.

Etapa 4:

Se añadió una solución de **compuesto 342** (400 mg, asumiendo 0,91 mmol) como la sal de HCl y DIPEA (1,17 g, 9,1 mmol) en DMF (5,0 mL) y THF (0,5 mL) gota a gota a una solución de HATU (482 mg, 1,27 mmol) en DMF (10,0 mL) a 0 °C durante 30 minutos. Después de completar la adición, la mezcla se agitó a 0 °C durante otros 30 min. Se añadió agua (70 mL) y la mezcla se extrajo en EtOAc (2 x 60 mL). Las capas orgánicas combinadas se lavaron con $NaHCO_3$ acuoso saturado (2 x 100 mL) y salmuera (100 mL), se secarpm sobre Na_2SO_4 y se evaporaron. El residuo se purificó por cromatografía en columna en gel de sílice, que se eluyó con 70% de EtOAc/ciclohexano para obtener 205 mg de un residuo amarillo pálido (semisólido). Los sólidos se disolvieron en MTBE (7 mL) y se añadió lentamente ciclohexano (20 mL) con buena agitación para precipitar el producto. Después de agitar durante 30 minutos, la mezcla se filtró y el **Ejemplo 2** se recogió en forma de un sólido blanco (110 mg, 29% de rendimiento). TLC (Rf = 0,40, 70% de EtOAc en ciclohexano).). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,83 (d, 1 H, *J* = 2,0 Hz), 7,30 (dd, 1 H, *J* = 9,6, 2,4 Hz), 7,21 (dd, 1 H, *J* = 8,4, 5,6 Hz), 6,99 (dt, 1 H, *J* = 8,0, 2,8 Hz), 6,86 (d, 1 H, *J* = 1,2 Hz), 5,75 - 5,71 (m, 1 H), 4,84 (s, 2 H), 4,45 (d, 1 H, *J* = 14,4 Hz), 4,35 (d ,1 H, *J* = 14,4 Hz), 4,07 (s, 3 H), 3,13 (s, 3 H), 1,79 (d, 3 H, *J* = 6,4Hz). LCMS ES *m/z* 407 $[M+H]^+$.

Preparación de (10*R*)-7-amino-12-fluoro-3-metoxi-10,16-dimetil-16,17-dihidro-8,4-(meteno)isotiazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 3).



Ejemplo 3

Etapa 1:

El procedimiento descrito en la etapa 1 para el Ejemplo **1** se usó para preparar el compuesto **343** (1,3 g, 67% de rendimiento). TLC (R_f = 0,30, 1:1 EtOAc/ciclohexano). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,95 (m, 1 H), 7,52 (dd, 1 H, J = 10,4, 3,0 Hz), 7,41 (m, 1 H),7,25 (m, 1 H), 6,60 (m, 1 H), 6,20 (m, 1 H), 6,00 - 6,05 (m, 2 H), 4,00 - 4,25 (m, 2 H), 3,89 (s, 3 H), 3,85 (s, 3 H), 2,70 - 2,78 (m, 3 H), 1,60 (d, 3 H, J = 6,7 Hz),1,08 - 1,38 (m, 9 H). LCMS ES *m/z* 547 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el Ejemplo **1** se usó para preparar el compuesto **344** (600 mg, 88% de rendimiento). TLC: R_f = 0,25 (EtOAc + 1% AcOH). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,95 - 8,10 (m, 3 H), 7,50 - 7,60 (m, 2 H), 7,25 (m, 1

H), 6,95 - 7,10 (m, 1 H), 6,52 (m, 1 H), 4,10 - 4,40 (m, 2 H), 3,91 (s, 3 H), 2,50 - 2,75 (m, 3 H), 1,65 (d, 3 H), 1,08 - 1,30 (m, 9 H). LCMS ES *m/z* 533 $[M+H]^+$.

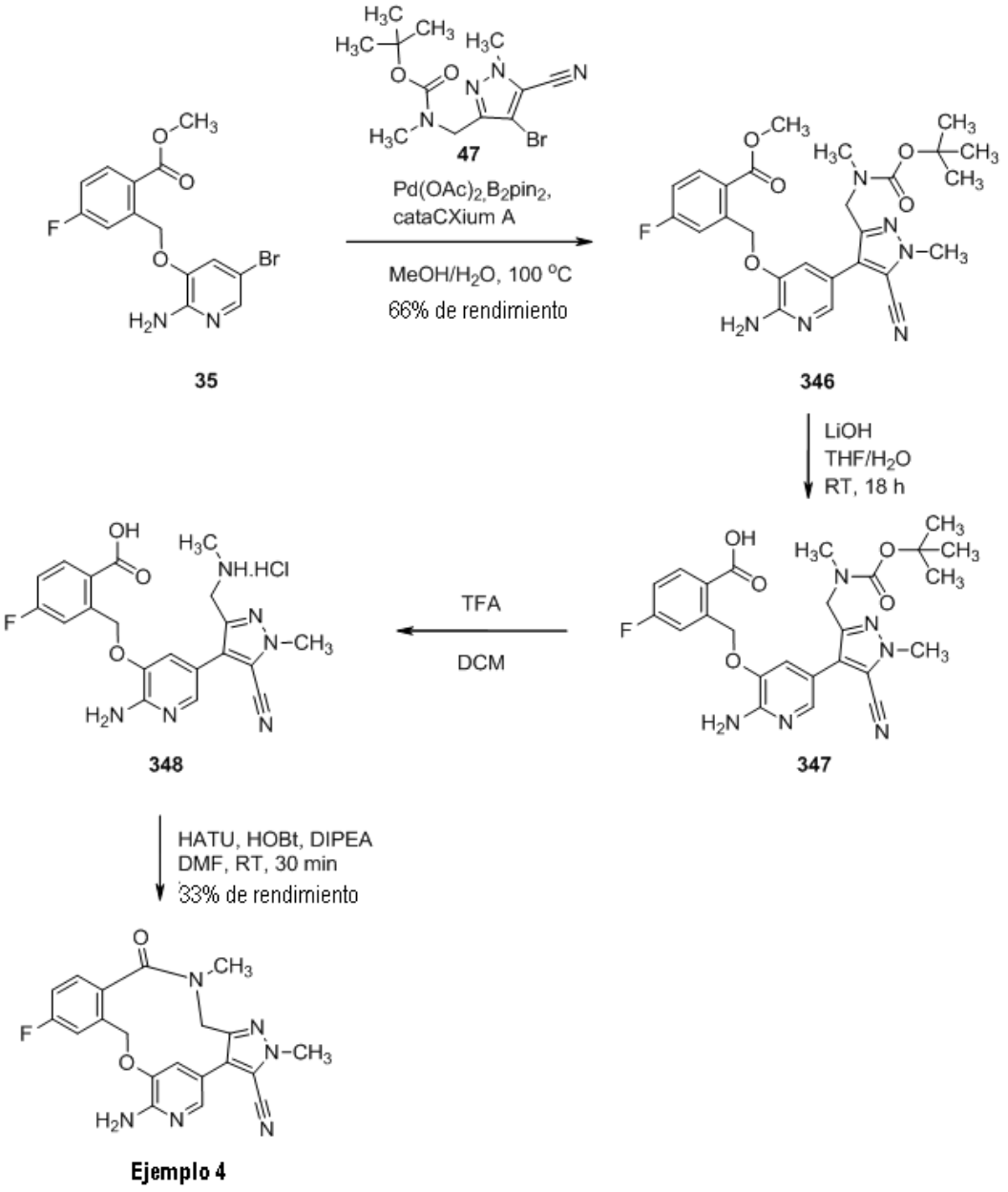
Etapa 3:

El procedimiento descrito en la etapa 3 para el Ejemplo **1** se usó para preparar el compuesto **345** (540 mg, rendimiento cuantitativo). ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,29 (br s, 2 H), 8,10 - 8,30 (m, 2 H), 8,03 (dd, 1 H, *J* = 9,4, 6,8 Hz), 7,65 (m, 1 H), 7,56 (dd, 1 H, *J* = 11,1, 2,6 Hz), 7,28 (dt, 1 H, *J* = 7,9, 2,8 Hz), 7,10 (s, 1 H), 6,52 (q, 1 H, *J* = 6,7 Hz), 4,00 - 4,20 (m, 2 H), 3,94 (s, 3 H), 2,54 - 2,57 (m, 3 H), 1,66 (d, 3 H, *J* = 6,1 Hz). LCMS ES *m/z* 433 $[M+H]^+$.

Etapa 4:

El procedimiento descrito en la etapa 4 para el Ejemplo **1** se usó para preparar el Ejemplo **3** (130 mg, 29% de rendimiento). TLC (R_f = 0,40, 100% de EtOAc). ^{1}H RMN (400 MHz, DMSOd_6) δ 7,63 (dd, 1 H, *J* = 12,0, 4,0 Hz), 7,50 (d, 1 H, *J* = 1,6 Hz), 7,42 (dd,1 H, *J* = 8,4, 5,6 Hz), 7,13 (dt, 1 H, *J* = 8,4, 2,8 Hz), 6,82 (d, 1 H, *J* = 1,6 Hz), 5,96 (s, 2 H), 5,66 - 5,62 (m, 1 H), 4,31 (d, 1 H, *J* = 13,5 Hz), 4,18 (d, 1 H, *J* =13,5 Hz), 4,05 (s, 3 H), 3,03 (s, 3 H), 1,67 (d, 3 H, *J* = 6,4 Hz). LCMS ES *m/z* 415 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-2,16-dimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 4).



Ejemplo 4

Etapa 1:

El procedimiento descrito en la etapa 1 para el Ejemplo **1** se usó para preparar el compuesto **346** (232 mg, 54% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,03 - 8,12 (m, 2 H), 7,69 - 7,75 (m, 1 H), 7,36 (dd, 1 H), 7,07 (td, 1 H), 5,56 (br s, 2 H), 5,07 (br s, 0,2 H), 4,94 (br s, 1,8 H), 4,50 (br s, 2 H), 4,02 (s, 3 H), 3,90 (s, 3 H), 2,71 (br s, 3 H), 1,35 (br s, 9 H). LCMS ES *m/z* 525 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el Ejemplo **1** se usó para preparar

el compuesto **347**, donde se usó LiOH en vez de NaOH (210 mg, rendimiento cuantitativo). LCMS ES *m/z* 511 $[M+H]^+$.

Etapa 3:

El compuesto **347** (210 mg, ~0,44 mmol) se disolvió en DCM (6 mL) y se añadió TFA (0,12 mL, 1,6 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas. Se añadió TFA (0,06 mL, 0,8 mmol) y la mezcla se agitó a temperatura ambiente durante 2 horas. La LCMS mostró el consumo del compuesto **347**. La reacción se concentró al vacío y se añadieron dietiléter (3 mL) y MTBE (3 mL). La mezcla se agitó a temperatura ambiente durante 1 hora y se decantó. Los licores madre se eliminaron y los sólidos blancos obtenidos se secaron al vacío para dar el compuesto **348** (216 mg, rendimiento cuantitativo). ^{1}H RMN (400 MHz, CD_3OD) δ 8,23 - 8,13 (m, 1 H), 7,66 (br s, 1 H), 7,58 - 7,49 (m, 2 H), 7,26 - 7,18 (m, 1 H), 5,80 - 5,77 (m, 2 H), 4,30 (s, 1 H), 4,11 (s, 2 H), 4,05 (s, 1 H), 3,21 (s, 3 H), 2,77 (s, 3 H). LCMS ES *m/z* 411 $[M+H]^+$.

Etapa 4:

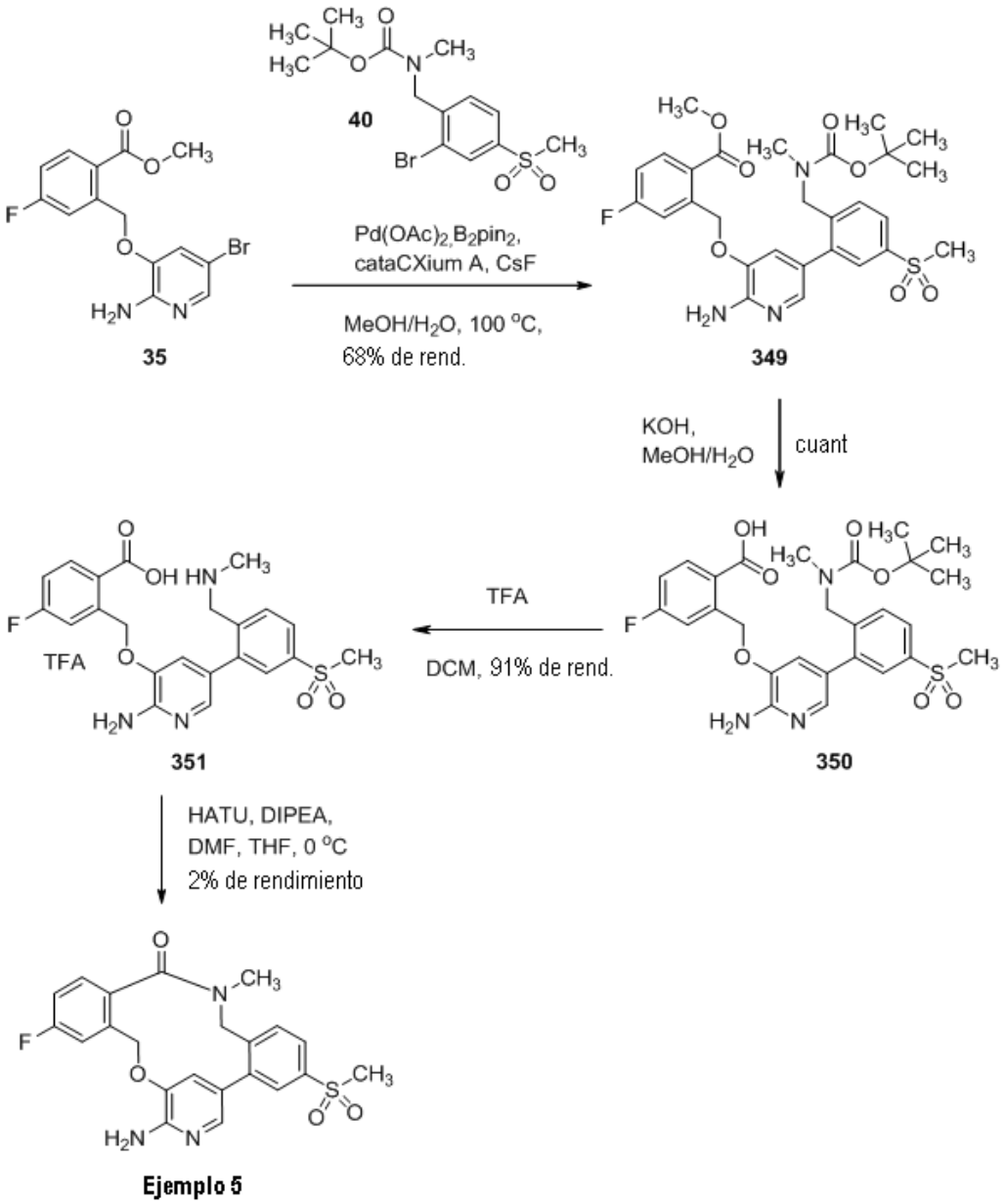
Se disolvieron HATU (380 mg, 0,99 mmol) y HOBt (20 mg, cat.) en DMF (10 mL). Una solución del compuesto **348** (210 mg, ~0,33 mmol) y DIPEA (0,42 mL, 2,31 mmol) en DMF (10 mL) se añadió gota a gota durante 25 min. Al final de la adición, la LCMS mostró el consumo de SM. Se añadió salmuera (100 mL) y se extrajo con acetato de etilo (6 x 50 mL). Las capas orgánicas se combinaron, se secaron sobre $MgSO_4$, se filtraron y se evaporaron. La purificación por cromatografía en columna en gel de sílice, que se eluyó con ciclohexano y acetato de etilo (1:1 a 0:1), produjo el Ejemplo **4** (45 mg, 35% de rendimiento en 3 etapas). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,84 (d, 1 H, *J* = 1,6 Hz), 7,34 (dd, 1 H, *J* = 9,2, 2,4 Hz), 7,22 - 7,27 (m, 1 H), 7,02 (td, 1 H, *J* = 8,4, 2,8 Hz), 6,84 (d, 1 H, *J* = 2,0 Hz), 5,49 (dd, 1 H, *J* = 13,6, 1,6 Hz), 5,23 (d, 1 H, *J* = 13,6 Hz), 4,88 (br s, 2 H), 4,48 (d, 1 H, *J* = 14,4 Hz), 4,38 (d, 1 H, *J* = 14,4 Hz), 4,07 (s, 3 H), 3,12 (s, 3 H). LCMS ES *m/z* 393 $[M+H]^+$. La separación quiral analítica por SFC se realizó usando una columna Chiralpak OD-H (4,6 mm x 250 mm, 5 micrones de tamaño de partícula), que se eluyó con 30% MeOH en CO_2 mantenido a 35 ºC a 140 bar. Una tasa de flujo de 3 mL/minutos produjo $Rt_{(pico\ 1)}$ = 4,3 minutos ($[\alpha]_d^{20}$= -121,4º (C=0,23, MeOH) y $Rt_{(pico\ 2)}$ = 5,4 minutos ($[\alpha]_d^{20}$= 103,3º (C=0,23, MeOH).

Ejemplo 4a (atropisómero pico 1): 91,6% ee. ^{1}H RMN (600 MHz, DMSO-d_6) δ 7,45 - 7,63 (3 H, m), 7,17 - 7,27 (1 H, m), 6,77 (1 H, s), 6,20 (2 H, br s), 5,29 (1 H, d, *J* = 14,3 Hz), 5,24 (1 H, d, *J* = 13,2 Hz), 4,46 (1 H, d, *J* = 14,2 Hz), 4,23 (1 H, d, *J* = 15,3 Hz),

4,02 (3 H, s), 2,97 (3 H, s).

Ejemplo 4b (atropisómero pico 2): 89,6% ee. ^{1}H RMN (600 MHz, DMSO-d_6) δ 7,45 - 7,62 (3 H, m), 7,18 - 7,27 (1 H, m), 6,77 (1 H, s), 6,20 (2 H, br s), 5,30 (1 H, d, *J* = 14,3 Hz), 5,24 (1 H, d, *J* = 13,2 Hz), 4,46 (1 H, d, *J* = 14,2 Hz), 4,23 (1 H, d, *J* = 14,2 Hz), 4,02 (3 H, s), 2,97 (3 H, s).

Preparación de 8-amino-3-fluoro-17-metil-13-(metilsulfonil)-16,17-dihidro-7,11-(meteno)dibenzo[*g*,*l*][1,4,10]oxadiazaciclotetradecin-18(5*H*)-ona (Ejemplo 5).



Etapa 1:

El procedimiento descrito en la etapa 1 para el Ejemplo **1** se usó para preparar el compuesto **349** (312 mg, 68% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ□8,09 (dd, 1 H, *J* = 8,4, 5,8 Hz), 7,89 (dd, 1 H, *J* = 8,0, 1,6 Hz), 7,77 (d, 1 H, *J* = 2,0 Hz), 7,63 (br s, 1 H), 7,43 (d, 1 H, *J* = 8,4 Hz), 7,39 (br d, 1 H, *J* = 10,0 Hz), 7,08 (dt, 1 H, *J* = 8,4, 2,4 Hz), 6,86 - 6,89 (m, 1 H), 5,55 (s, 2 H), 4,92 (br s, 2 H), 4,34 - 4,42 (m, 2 H), 3,89 (s, 3 H), 3,08 (s, 3 H), 2,68 - 2,76 (m, 3 H), 1,38 - 1,47 (m, 9 H). LCMS ES *m/z* 574 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el Ejemplo **1** se usó para preparar el compuesto **350**, donde se usó KOH en vez de NaOH (200 mg, 67% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,05 (dd, 1 H, *J* = 8,8, 6,0 Hz), 7,98 (dd, 1 H, *J* = 7,6, 2,0 Hz), 7,78 (d, 1 H, *J* = 2,0 Hz), 7,63 - 7,70 (m, 2 H), 7,46 - 7,50 (m, 2 H), 7,29 (dt, 1 H, *J* = 2,8, 8,4 Hz), 5,65 (s, 2 H), 5,39 - 4,41 (m, 2 H), 3,25 (s, 3 H), 2,66 (br s, 3 H), 1,25 - 1,36 (m, 9 H). LCMS ES *m/z* 560 $[M+H]^+$.

Etapa 3:

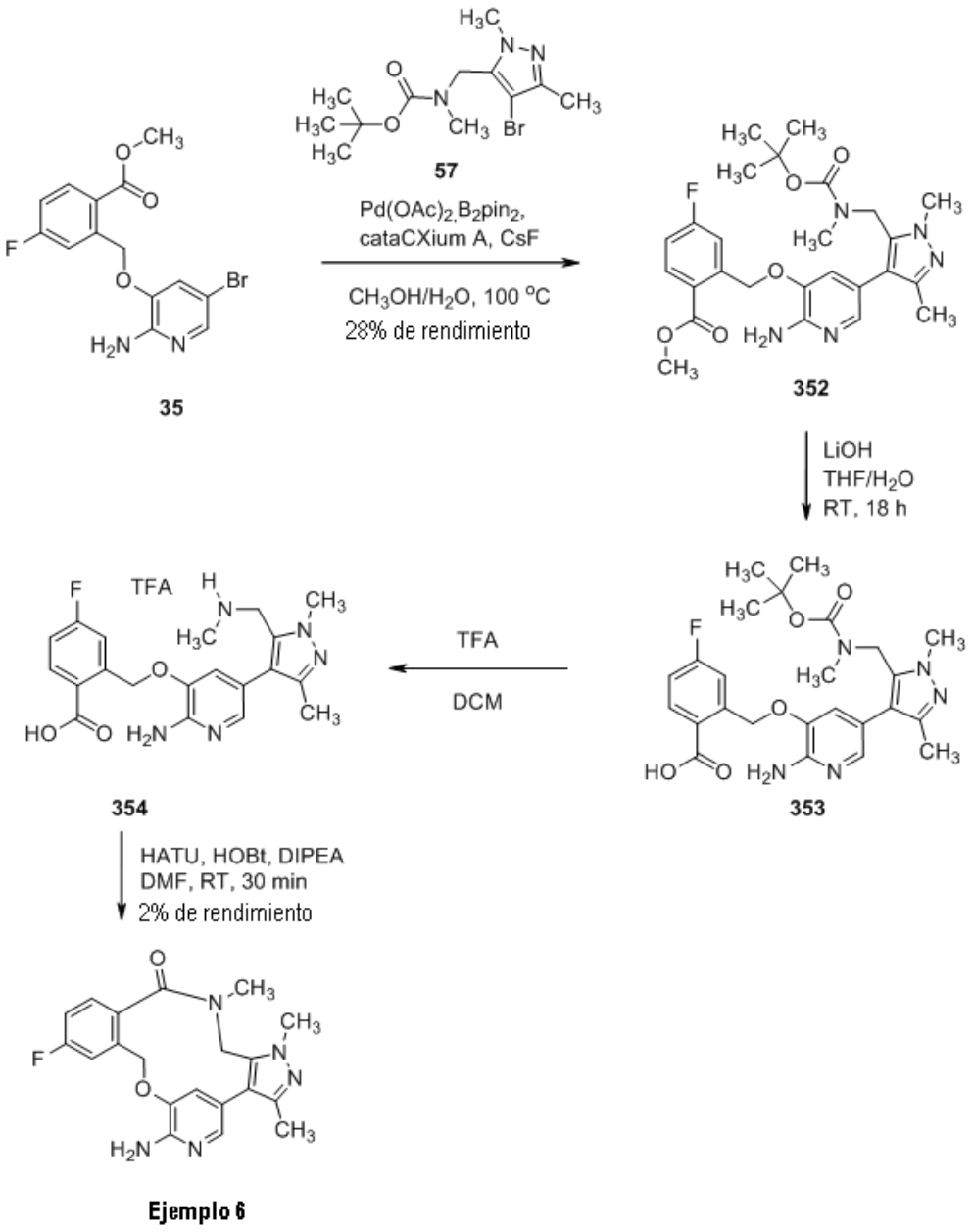
El procedimiento descrito en la etapa 3 para el Ejemplo **4** se usó para preparar el compuesto **351** (170 mg, 91% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,31 - 9,32 (m, 2 H), 8,02 - 8,09 (m, 3 H), 7,88 (d, 1 H, *J* = 2,0 Hz), 7,70 - 7,73 (m, 2 H), 7,54 (s, 1 H), 7,30 - 7,33 (m,1 H), 5,65 (s, 2 H), 4,13 - 4,15 (m, 2 H), 3,30 (s, 3 H), 3,17 (s, 3 H). LCMS ES *m/z* 460 $[M+H]^+$.

Etapa 4:

Se añadió una solución del compuesto **351** (527 mg, 1,1 mmol) y DIPEA (2,24 mL, 15,9 mmol) en DMF (9 mL) y THF (1 mL) a -10 ºC gota a gota durante 10 minutos a una solución agitada de HATU (566 mg, 1,5 mmol) en DMF (9 mL) enfriada bajo un baño de hielo/NaCl/MeOH. La LCMS mostró un consumo completo del compuesto **351**. Se añadieron agua (30 mL) y EtOAc (30 mL) y la mezcla se saturó por adición de NaCl. Las fases se separaron y la capa acuosa se extrajo otra vez con EtOAc (3 x 30 mL). Las capas orgánicas se combinaron, se secaron sobre $MgSO_4$ y el solvente se eliminó al vacío. El residuo se purificó por cromatografía en columna en gel de sílice, que se eluyó con EtOAc/heptano (8:2 a 1:0, luego EtOAc/MeOH 9:1) para obtener una fracción con el Ejemplo **5** (110 mg, ~70% de pureza pero contaminado con DMF) y una fracción más polar (componente mayor de la mezcla cruda, 83 mg, sólido blanco, $[M+H]^+$ 883) que probablemente es el dímero ciclado. La fracción primera también se purificó por cromatografía en fase inversa para obtener el Ejemplo **5** en forma de un sólido blanco (10 mg, 2% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,01 (d, 1 H, *J*

= 2,0 Hz), 7,92 (dd, 1 H, *J* = 8,0, 2,0 Hz), 7,65 (d, 1 H, *J* = 8,0 Hz), 7,59 (d, 1 H, *J* = 2,0 Hz), 7,33 (dd, 1 H, *J* = 9,2, 2,8 Hz), 7,21 (dd, 1 H, *J* = 8,6, 5,4 Hz), 7,11 (d, 1 H, *J* = 1,6 Hz), 7,00 (dt, 1 H, *J* = 8,4, 2,4 Hz), 5,59 (dd, 1 H, *J* = 13,6, 2,0 Hz), 5,22 (d, 1 H, *J* = 13,6 Hz), 4,84 (br s, 2 H), 4,63 (d, 1 H, *J* = 13,2 Hz), 4,28 (d, 1 H, *J* = 13,2 Hz), 3,12 (s, 3 H), 3,11 (s, 3 H).

Preparación de 7-amino-12-fluoro-1,3,16-trimetil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 6).



Ejemplo 6

Etapa 1:

El procedimiento descrito en la etapa 1 para el Ejemplo **1** se usó para preparar el compuesto **352** (350 mg, 28% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,09 (dd, 1 H, *J* = 8,8, 6,0 Hz), 7,55 (s, 1 H), 7,35 (dd, 1 H, *J* = 10,0, 2,8 Hz), 7,06 (td, 1 H, *J* = 8,4, 2,4 Hz), 6,74 (d, 1 H, *J* = 1,6 Hz), 5,54 (s, 2 H), 4,81 (s, 2 H), 4,40 (s, 2 H), 3,89 (s, 3 H), 3,79 (s, 3 H), 2,45 (s, 3 H), 2,10 (s, 3 H), 1,45 (s, 9 H). LCMS ES *m/z* 514 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el Ejemplo **1** se usó para preparar el compuesto **353**, donde LiOH se usó en vez de NaOH (310 mg, 88% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ 7,90 - 7,85 (m, 1 H), 7,36 (s, 1 H), 7,24 (dd,1 H, *J* = 10,0, 2,4 Hz), 6,99 (td, 1 H, *J*= 8,4, 2,4 Hz), 6,87 (s, 1 H), 5,60 (s, 2 H), 4,37 (s, 2 H), 3,75 (s, 3 H), 2,40 (s, 3 H), 2,04 - 2,00 (m, 3 H), 1,42 (s, 9 H). LCMS ES *m/z* 500 $[M+H]^+$.

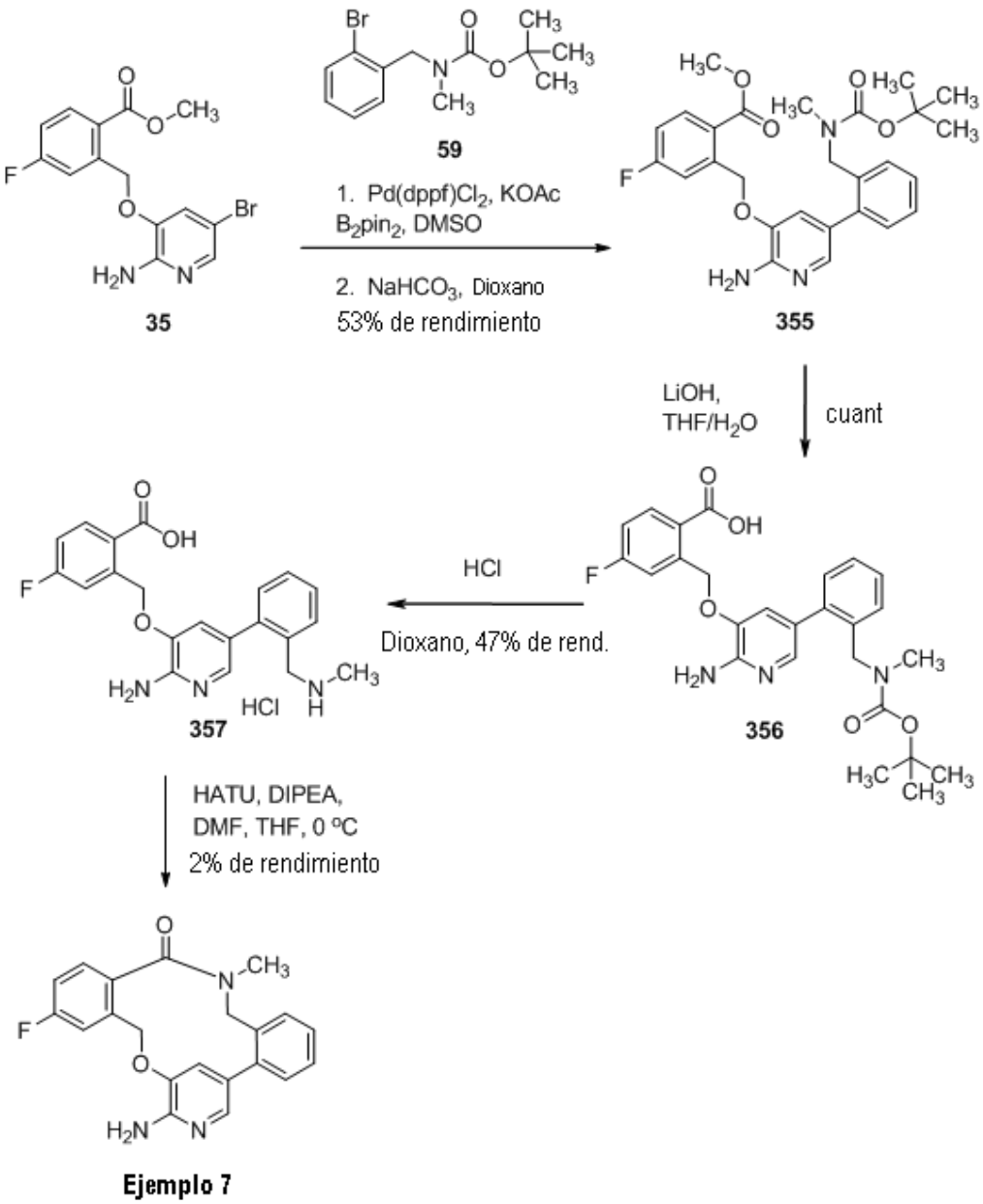
Etapa 3:

El procedimiento descrito en la etapa 3 para el Ejemplo **4** se usó para preparar el compuesto **354** (408 mg, rendimiento cuantitativo). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,75 (br s, 2 H), 8,06 (dd, 1 H, *J* = 8,4, 6,0 Hz), 7,67 (dd, 1 H, *J* = 10,0, 2,4 Hz), 7,57 (d, 1 H, *J* = 1,6 Hz), 7,26 - 7,35 (m, 2 H), 5,65 (s, 2 H), 4,20 (br s, 2 H), 3,86 (s, 3 H), 2,44 (br s, 3 H), 2,05 (s, 3 H). LCMS ES *m/z* 400 $[M+H]^+$.

Etapa 4:

El procedimiento descrito en la etapa 4 para el Ejemplo **4,** realizado a 0 ºC, se usó para preparar el compuesto Ejemplo **6** (130 mg, 29% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,56 (dd, 1 H, *J* = 9,6, 2,4 Hz), 7,44 - 7,38 (m, 2 H), 7,22 (td, 1 H, *J* = 8,4, 2,8 Hz), 6,73 (d, 1 H, *J* = 1,6 Hz), 5,82 (br s, 2 H), 5,30 (d, 1 H, *J* = 13,6 Hz), 5,17 (d, 1 H, *J* = 13,6 Hz), 4,65 (d, 1 H, *J* = 15,2 Hz), 4,20 (d, 1 H, *J* = 15,2 Hz), 3,89 (s, 3 H), 2,97 (s, 3 H), 2,54 (s, 1 H), 2,22 (s, 3 H). LCMS ES *m/z* 382 $[M+H]^+$.

Preparación de 8-amino-3-fluoro-17-metil-16,17-dihidro-7,11-(meteno)dibenzo[*g,l*][1,4,10]oxadiazaciclotetradecin-18(5*H*)-ona (Ejemplo 7).



Ejemplo 7

Etapa 1:

A una solución desgasificada del compuesto **35** (350 mg, 0,99 mmol), bis(neopentilglicolato)diboro (289 mg, 1,3 mmol) y KOAc (339 mg, 3,4 mmol) en DMSO (10 mL) se añadió $Pd(dppf)Cl_2$ (80 mg, 0,1 mmol). La mezcla resultante se agitó a 75 ºC durante 1 h. El análisis de LCMS indicó que se formó el intermediario de ácido borónico. Después de enfriar hasta temperatura ambiente, se añadieron el compuesto **59** (311 mg, 1,03 mmol) y $NaHCO_3$ (ac) (solución 1 M, 3,0 mL, 3,0 mmol) y dioxano (10 mL). La mezcla se desgasificó, seguido de la adición de $Pd(dppf)Cl_2$ (80 mg, 0,1 mmol). La mezcla resultante se agitó a 80 ºC durante 2 horas y se concentró al

vacío. Se añadieron acetato de etilo (100 mL) y agua (150 mL) y luego se dividieron. La capa acuosa se extrajo con EtOAc (2 x 100 mL) y las capas orgánicas combinadas se lavaron con salmuera (400 mL), se secaron sobre $MgSO_4$ y luego se concentraron al vacío. La purificación por cromatografía flash en columna en gel de sílice, que se eluyó con 1% de MeOH y 10% de heptano en DCM, produjo el compuesto **355** en forma de un sólido amarillo (260 mg, 53% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,06 (dd, 1 H), 7,66 (s, 1 H), 7,16 - 7,30 (m, 5 H), 7,05 (ddd, 1 H), 6,86 (d, 1 H), 5,53 (s, 2 H), 4,80 (br s, 2H), 4,33 (br s, 2 H), 3,96 (s, 3 H), 2,63 (br d, 3 H), 1,42 (br d, 9 H). LCMS ES *m/z* 440 $[M\text{-}^tBu]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el Ejemplo **1** se usó para preparar el compuesto **356**, donde LiOH se usó en vez de NaOH (123 mg, rendimiento cuantitativo). LCMS ES *m/z* 482 $[M+H]^+$.

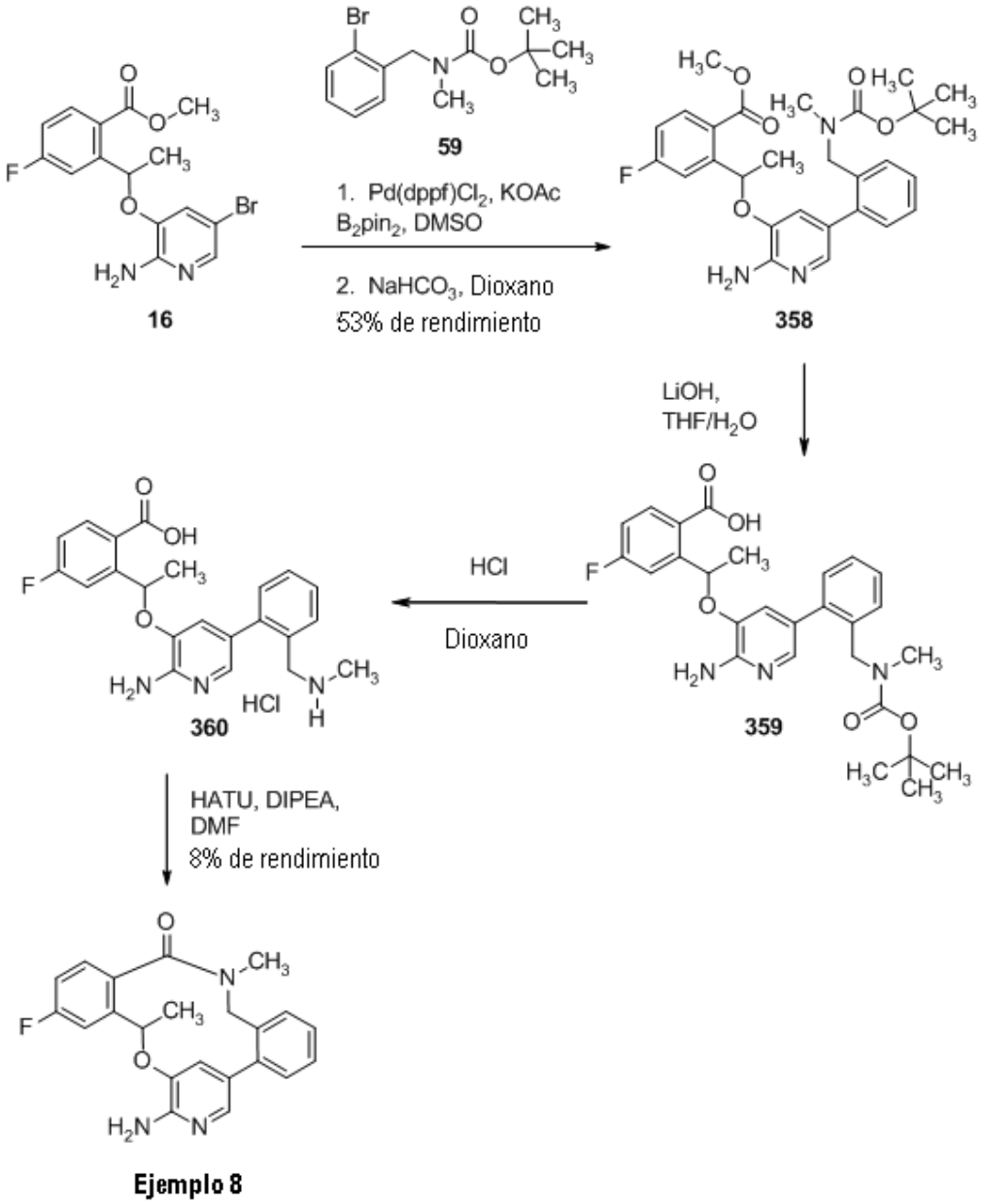
Etapa 3:

El procedimiento descrito en la etapa 3 para el Ejemplo **1** se usó para preparar el compuesto **357** (36 mg, 47% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ 7,70 (dd, 1 H), 7,63 (m, 1 H), 7,45 (m, 3 H), 7,32 (m, 2 H), 7,22 (d, 1 H), 7,02 (ddd, 1 H), 5,55 (s, 2 H), 4,08 (s, 2 H), 2,56 (s, 3 H). LCMS ES *m/z* 383 $[M+H]^+$.

Etapa 4:

A una suspensión del compuesto **357** (36 mg, 0,09 mmol) en DMF (6 mL) se añadió DIPEA (84 µL, 0,48 mmol) seguido de HATU (72 mg, 0,19 mmol). La solución resultante se agitó a temperatura ambiente durante 30 minutos. El análisis de LCMS indicó que se formaron una mezcla del producto deseado y un dímero (relación 2:1). Después de concentrarse al vacío, el residuo se purificó por HPLC preparativa en fase inversa (gradiente de agua/MeCN, corrida de 30 min), para obtener el Ejemplo **7** en forma de un sólido marrón (14 mg, 41% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ 7,56 (m, 2 H), 7,37 - 7,45 (m, 5 H), 7,15 (d, 1 H), 7,10 (ddd, 1 H), 5,53 (d, 1 H), 5,24 (d, 1 H), 4,47 (d, 1 H), 4,38 (d, 1 H), 3,10 (s, 3 H). LCMS ES *m/z* 364 $[M+H]^+$.

Preparación de 8-amino-3-fluoro-5,17-dimetil-16,17-dihidro-7,11-(meteno)dibenzo[*g,l*][1,4,10]-oxadiazaciclotetradecin-18(5*H*)-ona (Ejemplo 8).



Ejemplo 8

Etapa 1:

El procedimiento descrito en la etapa 1 para el Ejemplo **7** se usó para preparar el compuesto **358** (820 mg, 53% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,01 (dd, 1 H), 7,54 (br s, 1 H), 7,34 - 7,18 (m, 4 H), 7,07 (dd, 1 H), 6,99 (br s, 1 H), 6,62 - 6,49 (m, 1 H), 6,44 - 6,32 (m, 1 H), 4,86 (br s, 2 H), 4,11 - 4,02 (m, 2 H), 3,86 (br s, 3 H), 2,60 - 2,45 (m, 3 H), 1,67 (d, 3 H), 1,55 - 1,31 (m, 9 H). LCMS ES *m/z* 510 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el Ejemplo **1** se usó para preparar el compuesto **359**, donde el LiOH se usó en vez de NaOH (629 mg, rendimiento

cuantitativo). LCMS ES *m/z* 496 $[M+H]^+$.

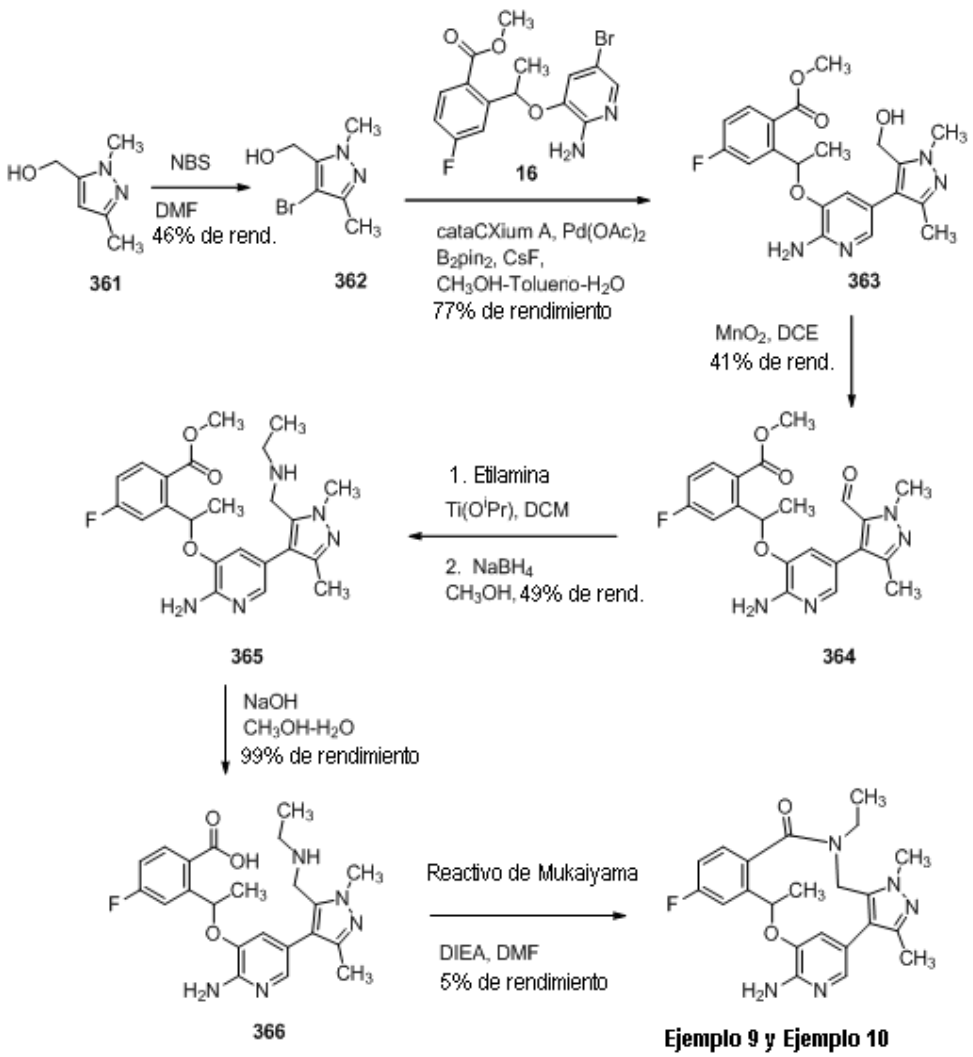
Etapa 3:

El procedimiento descrito en la etapa 3 para el Ejemplo **1** se usó para preparar el compuesto **360** (810 mg, rendimiento cuantitativo). LCMS ES *m/z* 396 $[M+H]^+$.

Etapa 4:

El procedimiento descrito en la etapa 4 para el Ejemplo **7** se usó para preparar el Ejemplo **8** (49 mg, 8% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,53 (d, 1 H, *J* = 2,0 Hz), 7,48 - 7,32 (m, 4 H), 7,28 (dd,1 H, *J* = 10,0, 2,8 Hz), 7,17 - 7,13 (m, 2 H), 6,94 (td, 1 H, *J* = 8,0, 2,4 Hz), 5,83 (qd, 1 H, *J* = 6,0, 2,0 Hz), 4,75 (br s, 2 H), 4,50 (d, 1 H, *J* = 13,2 Hz), 4,16 (d, 1 H, *J* = 13,6 Hz), 3,12 (s, 3 H), 1,78 (d, 3 H, *J* = 6,4 Hz). LCMS ES *m/z* 378 $[M+H]^+$.

Preparación de 7-amino-16-etil-12-fluoro-1,3,10-trimetil-16,17-dihidro-1H-8,4-(meteno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 9 y Ejemplo 10).



Ejemplo 9 y Ejemplo 10

Etapa 1:

A una solución del compuesto **361** (1,0 g, 7,9 mmol) en DMF (53 mL) se añadió NBS (1,4 g, 7,9 mmol). La solución se agitó a temperatura ambiente durante la noche, luego se concentró. Al sólido se añadió Na_2CO_3 1 N (10 mL) y la mezcla se concentró para eliminar agua. El sólido se suspendió en DCM/MeOH y se filtró. El licor madre se concentró y se purificó por cromatografía flash en gel de sílice, que se eluyó con DCM/7 N NH_3 en MeOH (0-10%) para obtener el compuesto **362** (749 mg, 46% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 5,31 (t, J = 5,4 Hz, 1 H), 4,43 (d, J = 5,3 Hz, 2 H), 3,77 (s, 3 H), 2,08 (s, 3 H).

Etapa 2:

En un tubo sellado, se calentó una mezcla del compuesto **16** (500 mg, 1,35 mmol), compuesto **362** (555 mg, 2,03 mmol), éster pinacólico de diboro (1,38 g, 5,42

mmol) y fluoruro de cesio (1,03 g, 6,77 mmol) en MeOH (9,0 mL) y agua (0,90 mL) a 60 ºC y se burbujeó con nitrógeno. Se añadió una solución de $Pd(OAc)_2$ (30 mg, 0,14 mmol) y di(1-adamantil)-*n*-butilfosfina (100 mg, 0, 72 mmol) en tolueno (0,5 mL) y la mezcla se calentó a 100 ºC. Después de ~6 horas, la mezcla se enfrió hasta temperatura ambiente y se diluyó con EtOAc, se lavó con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó por cromatografía flash en gel de sílice, que se eluyó con DCM/ MeOH (0-9%) y produjo el compuesto **363** en forma de una goma amarilla (433 mg, 77% de rendimiento). LCMS ES *m/z* 415 $[M+H]^+$.

Etapa 3:

A una solución del compuesto **363** (560 mg, 1,35 mmol) en DCE (13,5 mL) se añadió MnO_2 (1,2 g, 10,0 mmol). La reacción se calentó a 50 ºC durante la noche. La mezcla se filtró y el licor madre se concentró y se purificó por cromatografía flash en gel de sílice, que se eluyó con heptanos/EtOAc (0-75%) y produjo el compuesto **364** (226 mg, 41% de rendimiento durante 2 etapas). ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,40 (s, 1 H), 7,94 (dd, *J* = 5,9, 8,7 Hz, 1 H), 7,55 (dd, *J* = 2,6, 10,4 Hz, 1 H), 7,50 (d, *J* = 1,8 Hz, 1 H), 7,26 (dt, *J* = 2,8, 8,4 Hz, 1 H), 6,71 (d, *J* = 1,8 Hz, 1 H), 6,25 (q, *J* = 6,1 Hz, 1 H), 6,16 (s, 2 H), 4,00 (s, 3 H), 3,84 (s, 3 H), 1,92 (s, 3 H), 1,62 (d, *J* = 6,3 Hz, 3 H). LCMS ES *m/z* 413 $[M+H]^+$.

Etapa 4:

A una solución del compuesto **364** (226 mg, 0,548 mmol) en DCM (5,5 mL) se añadió etilamina (2 M en THF, 548 µL, 1,10 mmol) y luego $Ti(O^iPr)_4$ (642 µL, 2,19 mmol). Después de 1 hora, se añadieron MeOH (2,0 mL) y $NaBH_4$ (104 mg, 2,74 mmol) (gas producido). La reacción se neutralizó con agua y se formaron sólidos blancos. La mezcla se filtró a través de Celite y el licor madre se diluyó con EtOAc, se lavó con NH_4Cl saturado y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó por cromatografía flash en gel de sílice, que se eluyó con heptanos/EtOAc (0-100%), luego con MeOH/DCM (0-10%) y produjo el compuesto **365** (119 mg, 49% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,96 (dd, *J* = 6,0, 8,8 Hz, 1 H), 7,52 (dd, *J* = 2,5, 10,3 Hz, 1 H), 7,42 (d, *J* = 1,8 Hz, 1 H), 7,25 (dt, *J* = 2,8, 8,4 Hz, 1 H), 6,58 (d, *J* = 1,5 Hz, 1 H), 6,22 (q, *J* = 6,0 Hz, 1 H), 5,86 (s, 2 H), 3,86 (s, 3 H), 3,72 (s, 3 H), 3,48 - 3,35 (m, 2 H), 2,32 (q, *J* = 7,1 Hz, 2 H), 1,83 (s, 3 H), 1,79 (br s, 1 H), 1,61 (d, *J* = 6,3 Hz, 3 H), 0,88 (t, *J* = 7,1 Hz, 3 H). LCMS ES *m/z* 442 $[M+H]^+$.

Etapa 5:

A una solución del compuesto **365** (115 mg, 0,26 mmol) en MeOH (520 µL) se añadió 15% de NaOH (68 µL, 0,26 mmol). La reacción se calentó a 50 ºC. Una vez

completa por LCMS, la reacción se concentró para obtener la sal sódica del compuesto **366** (116 mg, 99% de rendimiento).

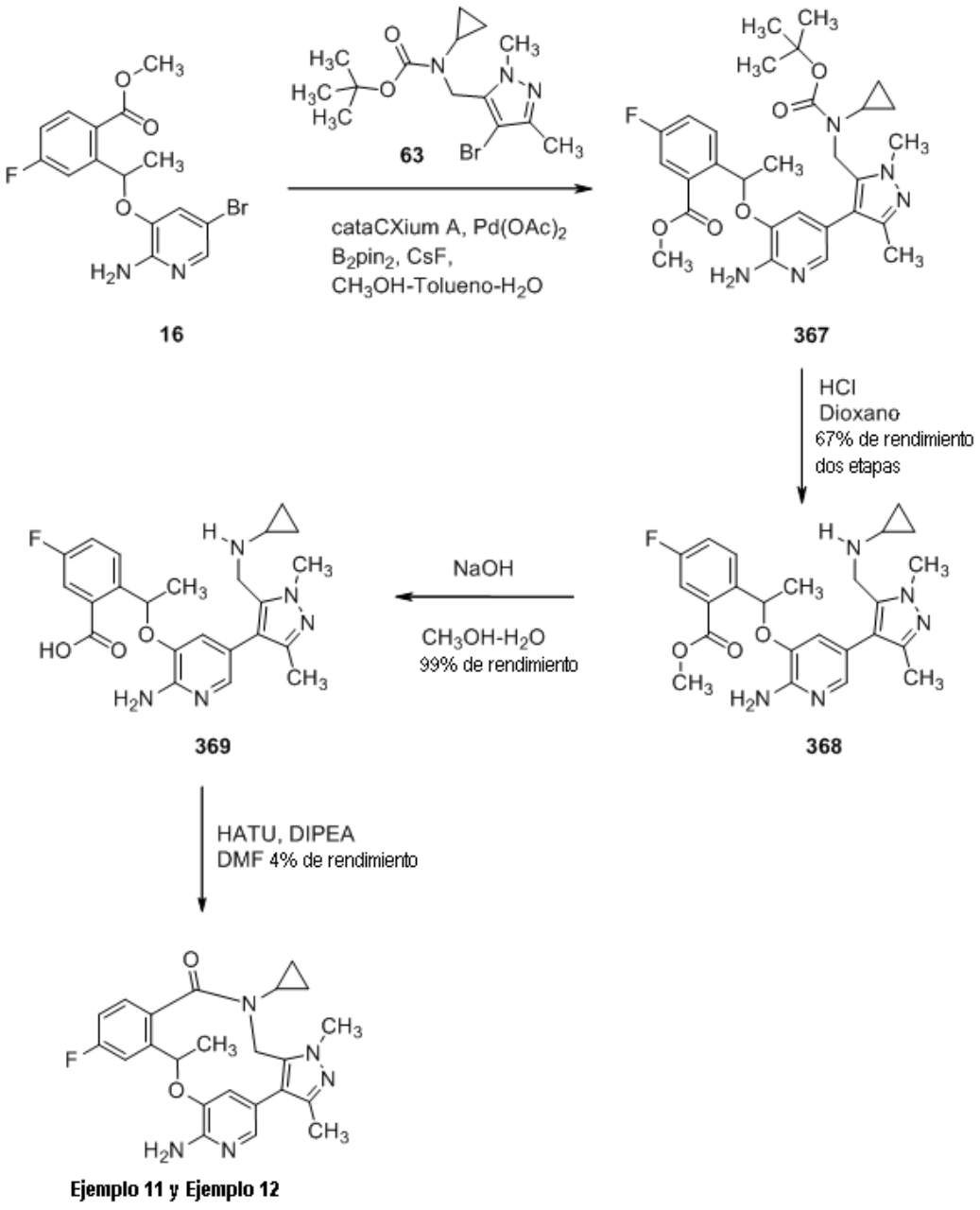
Etapa 6:

A una solución de sal sódica del compuesto **366** (90 mg, 0,20 mmol) en DMF (13 mL) se añadió DIEA (70 µL, 0,40 mmol) y luego yoduro de 2-cloro-1-metilpiridinio (57 mg, 0,22 mmol). Después de 30 min, la reacción se concentró y se purificó por cromatografía flash en gel de sílice, que se eluyó con DCM/MeOH (0-10%) y luego se sometió a separación quiral por SFC para obtener ambos enantiómeros del compuesto del título. La separación quiral analítica por SFC se realizó usando una columna Regis Whelk-01 (*S,S*) (columna de 4,6 mm x 100 mm, 5 micrones de tamaño de partícula), que se eluyó con 30% de MeOH en CO_2 mantenido a 25 ºC a 140 bar. Una tasa de flujo de 5 mL/min produjo $Rt_{(pico\ 1)}$ = 1,28 minutos y $Rt_{(pico\ 2)}$ = 1,78 minutos.

Ejemplo 9 (pico 1): 3,7 mg, >98% ee, 4,5% de rendimiento. ^{1}H RMN (DMSO-d_6, 400 MHz) δ 7,59 (dd, *J* = 2,5, 10,4 Hz, 1 H), 7,37 (s, 1 H), 7,34 (dd, *J* = 5,6, 8,4 Hz, 1 H), 7,16 (dt, *J* = 2,5, 8,4 Hz, 1 H), 6,83 (s, 1 H), 5,80 (s, 2 H), 5,60 (d, *J* = 6,4 Hz, 1 H), 4,68 (d, *J* = 15,3 Hz, 1 H), 4,07 (d, *J* = 15,5 Hz, 1 H), 3,87 (s, 3 H), 3,37 (d, *J* = 6,9 Hz, 1 H), 2,19 (s, 3 H), 1,66 (d, *J* = 6,4 Hz, 3 H), 1,02 (t, *J* = 7,0 Hz, 3 H). LCMS ES *m/z* 410 $[M+H]^+$.

Ejemplo 10 (pico 2): 4,0 mg, 90% ee, 4,9% de rendimiento. ^{1}H RMN (DMSO-d_6, 400 MHz) δ 7,59 (dd, *J* = 2,5, 10,2 Hz, 1 H), 7,37 (s, 1 H), 7,34 (dd, *J* = 5,6, 8,4 Hz, 1 H), 7,16 (d, *J* = 2,5 Hz, 1 H), 6,83 (d, *J* = 1,3 Hz, 1 H), 5,80 (s, 2 H), 5,60 (d, *J* = 5,6 Hz, 1 H), 4,68 (d, *J* = 15,3 Hz, 1 H), 4,07 (d, *J* = 15,5 Hz, 1 H), 3,87 (s, 3 H), 2,19 (s, 3 H), 1,66 (d, *J* = 6,1 Hz, 3 H), 1,02 (t, *J* = 7,0 Hz, 3 H). LCMS *m/z* 410 $[M+H]^+$.

Síntesis de 7-amino-16-ciclopropil-12-fluoro-1,3,10-trimetil-16,17-dihidro-1H-8,4-(meteno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 11 y Ejemplo 12).



Ejemplo 11 y Ejemplo 12

Etapa 1:

El procedimiento descrito en la etapa 2 para el Ejemplo **9** y **10** se usó para preparar el compuesto **367** (191 mg). ^{1}H RMN (DMSO-d_6, 400 MHz) δ 7,89 (dd, *J* = 5,8, 8,8 Hz, 1 H), 7,49 (dd, *J* = 2,4, 10,4 Hz, 1 H), 7,32 (s, 1 H), 7,20 (dt, *J* = 2,4, 8,5 Hz, 1 H), 6,49 (s, 1 H), 6,22 (q, *J* = 6,0 Hz, 1 H), 5,89 (s, 2 H), 4,34 (d, *J* = 15,9 Hz, 1 H), 4,07 (d, *J* = 15,6 Hz, 1 H), 3,85 (s, 3 H), 3,66 (s, 3 H), 1,87 (s, 3 H), 1,69 (br. s., 1 H), 1,61 (d, *J* = 6,3 Hz, 3 H), 1,35 (s, 9 H), 0,09 - 0,15 (m, 4 H). LCMS ES *m/z* 554 $[M+H]^+$.

Etapa 2:

A una solución del compuesto **367** (191 mg) en DCM (1,7 mL) se añadió HCl (4 N en dioxano, 1,7 mL). Se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado (2x) y salmuera, se secó ($MgSO_4$), se filtró y se concentró. Se purificó por cromatografía flash eluyendo con heptanos/EtOAc (50-100%), luego con DCM/MeOH (0-10%) para obtener el compuesto **368** (104 mg, 67% de rendimiento durante 2 etapas). ^{1}H RMN (DMSO-d_6, 400 MHz) δ 7,95 (dd, *J* = 5,8, 8,8 Hz, 1 H), 7,52 (dd, *J* = 2,6, 10,2 Hz, 1 H), 7,44 (d, *J* = 1,0 Hz, 1 H), 7,24 (dt, *J* = 2,8, 8,3 Hz, 1 H), 6,57 (s, 1 H), 6,22 (q, *J* = 6,1 Hz, 1 H), 5,86 (s, 2 H), 3,85 (s, 3 H), 3,69 (s, 3 H), 3,48 (s, 2 H), 2,40 (br. s., 1 H), 1,82 (s, 4 H), 1,60 (d, *J* = 6,3 Hz, 3 H), 0,24 - 0,15 (m, 2 H), 0,11 - 0,04 (m, 2 H). LCMS ES *m/z* 454 $[M+H]^+$.

Etapa 3:

El procedimiento descrito en la etapa 5 para el Ejemplo **9** y **10** se usó para preparar el compuesto **369** (105 mg de la sal sódica).

Etapa 4:

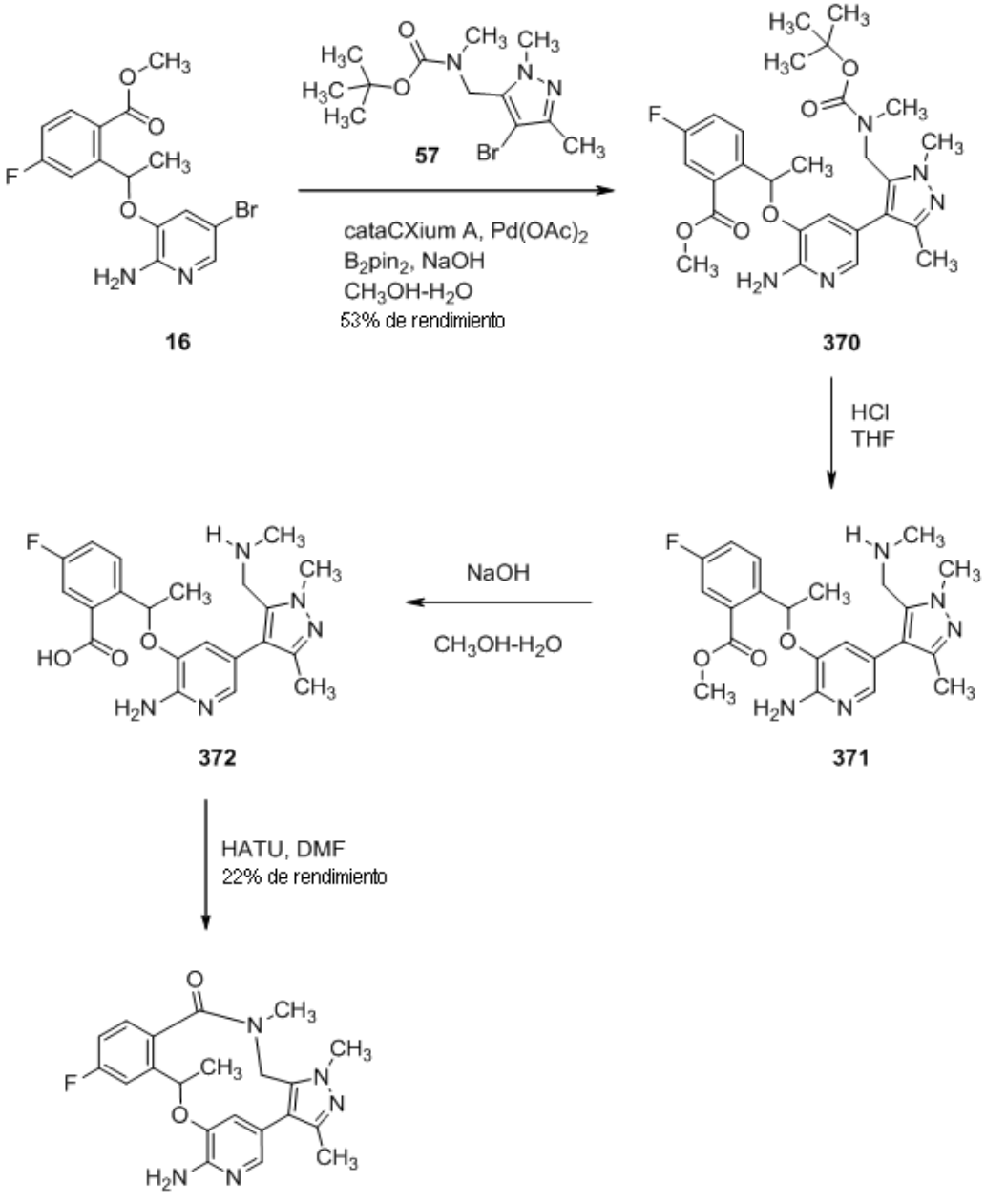
El procedimiento descrito en la etapa 6 para el Ejemplo **9** y **10** se usó para preparar los Ejemplos **11** y **12.** La separación quiral analítica por SFC se realizó usando una columna Regis Whelk-01 (*S,S*) 4,6 mm x 100 mm (5 micrones de tamaño de partícula) que se eluyó con 30% MeOH en CO_2 mantenido a 35 ºC a 120 bar. La tasa de flujo de 5 mL/min produjo $Rt_{(pico\ 1)}$ = 1,69 minutos y $Rt_{(pico\ 2)}$ = 2,73 minutos.

Ejemplo 11 (pico 2): 1,8 mg; 85% ee, 2% de rendimiento. ^{1}H RMN (DMSO-d_6, 400 MHz) δ 7,57 (dd, *J* = 2,5, 10,4 Hz, 1 H), 7,37 - 7,32 (m, 2 H), 7,13 (dt, *J* = 2,8, 8,4 Hz, 1 H), 6,74 (s, 1 H), 5,80 - 5,75 (m, 2 H), 5,70 - 5,64 (m, 1 H), 4,64 (d, *J* = 15,3 Hz, 1 H), 4,09 (d, *J* = 15,0 Hz, 1 H), 3,91 (s, 3 H), 2,44 - 2,39 (m, 1 H), 2,19 (s, 3 H), 1,65 (d, *J* = 6,1 Hz, 3 H), 1,10 (br. s, 1 H), 0,97 - 0,91 (m, 1 H), 0,86 - 0,77 (m, 2 H). LCMS ES *m/z* 422 $[M+H]^+$.

Ejemplo 12 (pico 1): 2,2 mg; 85% ee, 2% de rendimiento. ^{1}H RMN (DMSO-d_6, 400 MHz) δ 7,57 (d, *J* = 9,7 Hz, 1 H), 7,37 - 7,32 (m, 2 H), 7,13 (t, *J* = 8,4 Hz, 1 H), 6,74 (s, 1 H), 5,77 (s, 2 H), 5,70 - 5,64 (m, 1 H), 4,64 (d, *J* = 15,3 Hz, 1 H), 4,09 (d, *J* = 15,5 Hz, 1 H), 3,91 (s, 3 H), 2,44 - 2,39 (m, 1 H), 2,19 (s, 3 H), 1,65 (d, *J* = 5,8 Hz, 3 H), 1,13 - 1,06 (m, 1 H), 0,98 - 0,90 (m, *J* = 6,9 Hz, 1 H), 0,82 (br s, 2 H). LCMS ES *m/z* 422 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-1,3,10,16-tetrametil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo

13 y Ejemplo 14).



Ejemplo 13 y Ejemplo 14

Etapa 1

A una solución del compuesto **57** (689 mg, 2,2 mmol), compuesto **16** (400 mg, 1,1 mmol) y éster bispinacólico (825 mg, 3,25 mmol) en MeOH (11,6 mL) se añadió NaOH 1 N en agua (2,2 mL, 2,2 mmol). La mezcla de reacción se purgó con nitrógeno. A continuación, se añadieron secuencialmente $Pd(OAc)_2$ (30,3 mg, 0,14 mmol) y di(1-adamantil)-*n*-butilfosfina (4 mg, 0,14 mmol) y la mezcla de reacción se purgó con

nitrógeno. La mezcla de reacción se calentó a 80 ºC en un baño de aceite durante la noche y se enfrió hasta temperatura ambiente. La mezcla de reacción se filtró a través de un taco de Celite y se lavó con MeOH. La solución resultante se concentró y se purificó por cromatografía en fase inversa, y produjo el compuesto **370** en forma de un aceite (300 mg, 53% de rendimiento). LCMS *m/z* 528 $[M+H]^+$.

Etapa 2:

Al compuesto **370** (50 mg, 0,09 mmol) en THF (3 mL) se añadió 0,5 mL de 38% HCl a temperatura ambiente. La mezcla de reacción formó dos capas. La mezcla de reacción se calentó en microondas a 60 ºC durante 30 minutos, lo que produjo el compuesto **371.**

Etapa 3:

El compuesto **371** se enfrió hasta temperatura ambiente y a la mezcla de reacción se añadió 50% de NaOH (aproximadamente 1,0 mL) hasta pH ~12 y MeOH (3 mL). Después de calentar a 60 ºC durante 30 min en un baño de aceite, la reacción se concentró y se liofilizó durante la noche, lo que produjo el compuesto **372**. El rendimiento teórico asumido era de 39 mg.

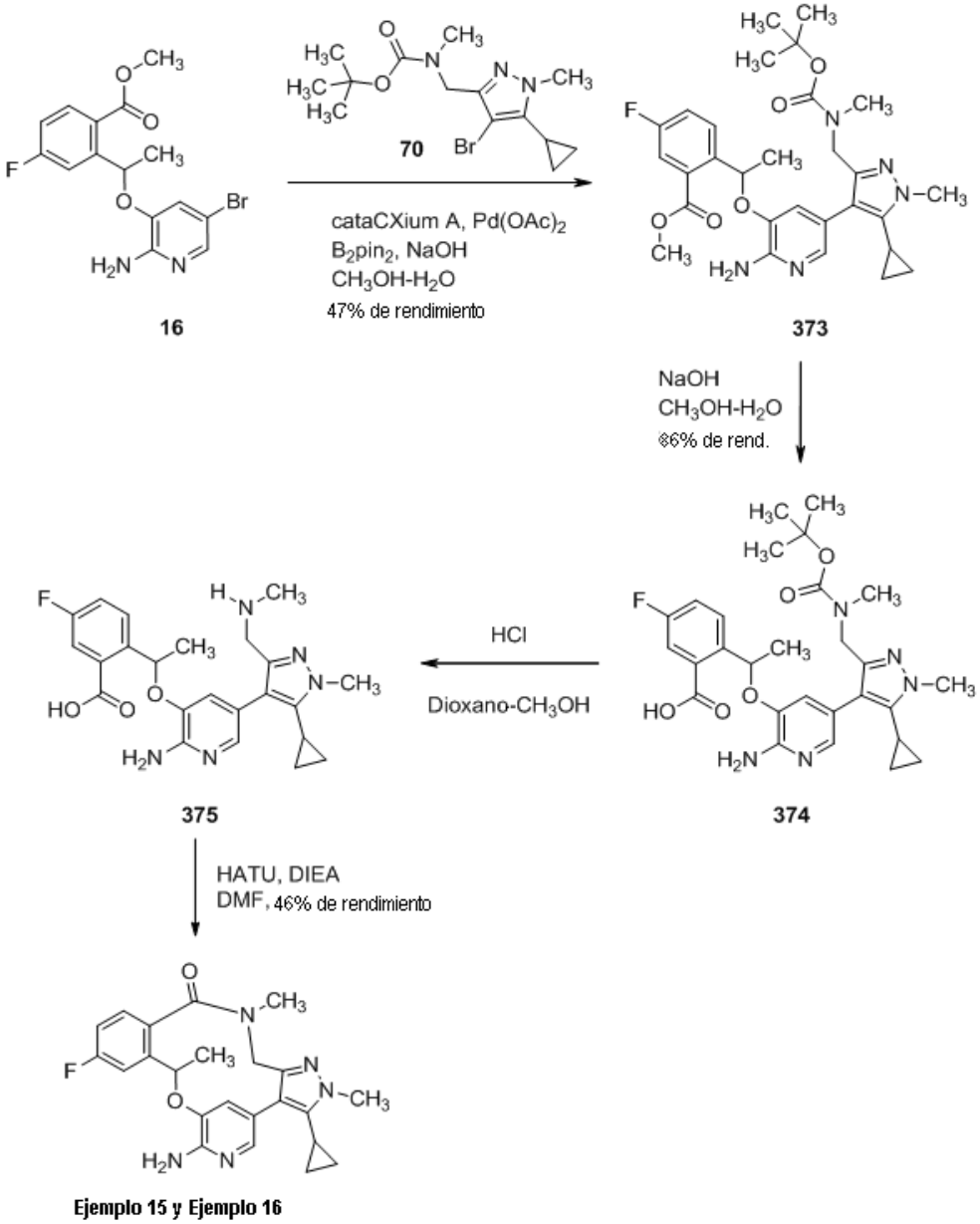
Etapa 4:

A la mezcla de reacción con el compuesto **372** (39 mg, 0,09 mmol) en DMF anhidra (3 mL) a pH ~10 se añadió HATU (72 mg, 0,18 mmol) y se agitó a temperatura ambiente. Después de 4 horas, la LCMS de la mezcla de reacción mostró la conversión completa en el producto deseado. La mezcla de reacción se diluyó con MeOH, se filtró a través de un taco de Celite y se concentró. Después de la purificación en fase inversa usando acetato de amonio como aditivo, el producto deseado se obtuvo en forma de un sólido (8 mg 22% de rendimiento). ^{1}H RMN (600 MHz, DMSO-d_6) δ 7,59 - 7,63 (m, 1 H), 7,36 - 7,41 (m, 2 H), 7,17 (d, *J* = 2,5 Hz, 1 H), 6,75 (s, 1 H), 5,81 (s, 2 H), 5,50 - 5,64 (m, 1 H), 4,61 (d, *J* = 14,9 Hz, 1 H), 4,08 (d, *J* = 15,2 Hz, 1 H), 3,87 (s, 3 H), 2,98 (s, 3 H), 2,20 (s, 3 H), 1,65 (d, *J* = 6,4 Hz, 3 H). La separación quiral analítica por SFC se realizó usando Chiralcel OD-3 (columna 4,6 mm x 100 mm, 3 micrones de tamaño de partícula) que se eluyó con 30% de MeOH en CO_2 mantenido a 25 ºC a 120 bar. La tasa de flujo de 5 mL/min produjo $Rt_{(pico\ 1)}$ = 0,75 minutos y $Rt_{(pico\ 2)}$ = 1,3 minutos.

Ejemplo 13 (pico 1): ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,62 (dd, *J* = 2,5, 10,3 Hz, 1 H), 7,33 - 7,43 (m, 2 H), 7,15 - 7,23 (m, 1 H), 6,76 (d, *J* = 1,5 Hz, 1 H), 5,81 (s, 2 H), 5,60 (br s, 1 H), 4,62 (d, *J* = 15,1 Hz, 1 H), 4,08 (d, *J* = 15,1 Hz, 1 H), 3,88 (s, 3 H), 2,99 (s, 3 H), 2,21 (s, 3 H), 1,65 (d, *J* = 6,0 Hz, 3 H).

Ejemplo 14 (pico 2): ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,57 - 7,65 (m, 1 H), 7,33 - 7,44 (m, 2 H), 7,12 - 7,23 (m, 1 H), 6,76 (s, 1 H), 5,80 (s, 2 H), 5,61 (br. s, 1 H), 4,62 (d, *J* = 15,4 Hz, 1 H), 4,09 (d, *J* = 15,1 Hz, 1 H), 3,88 (s, 3 H), 2,99 (s, 3 H), 2,21 (s, 3 H), 1,66 (d, *J* = 6,0 Hz, 3 H).

Preparación de 7-amino-3-ciclopropil-12-fluoro-2,10,16-trimetil-16,17-dihidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 15 y Ejemplo 16).



Etapa 1:

El procedimiento descrito en la etapa 1 para el Ejemplo **13** y **14** se usó para preparar el compuesto **373** (380 mg, 43% de rendimiento). LCMS *m/z* 554 $[M+H]^+$.

Etapa 2:

Una mezcla del compuesto **373** (380 mg, 0,557 mmol) y NaOH (0,55 g, 13,74 mmol) en metanol (10 mL) y agua (10 mL) se agitó a 40 ºC durante 3 horas. No se detectó nada del compuesto **374** por LCMS. La mezcla de reacción se concentró a presión reducida y el residuo resultante se disolvió en agua (20 mL). La capa acuosa se extrajo con MTBE (20 mL). La capa orgánica se descartó y la capa acuosa se acidificó con 6 N HCl hasta pH ~5. La mezcla se saturó con NaCl sólido y se extrajo con EtOAc (30 mL x 5). Las capas combinadas de EtOAc se secaron sobre Na_2SO_4 y se concentraron al vacío y produjeron el compuesto **374** en forma de un sólido amarillo (320 mg, 86% de rendimiento). LCMS *m/z* 540 $[M+H]^+$.

Etapa 3:

A una solución del compuesto **374** (320 mg, 0,515 mmol) en metanol (5 mL) se añadió gota a gota ~ 4 M HCl en dioxano (10 mL). La mezcla de reacción se agitó a 40 ºC durante 3 horas. Nada del compuesto **147** fue detectado por LCMS. La mezcla de reacción se concentró a presión reducida y el residuo resultante se disolvió en tolueno y se concentró. Esto se repitió dos veces y produjo el compuesto **375**. LCMS *m/z* 440 $[M+H]^+$.

Etapa 4:

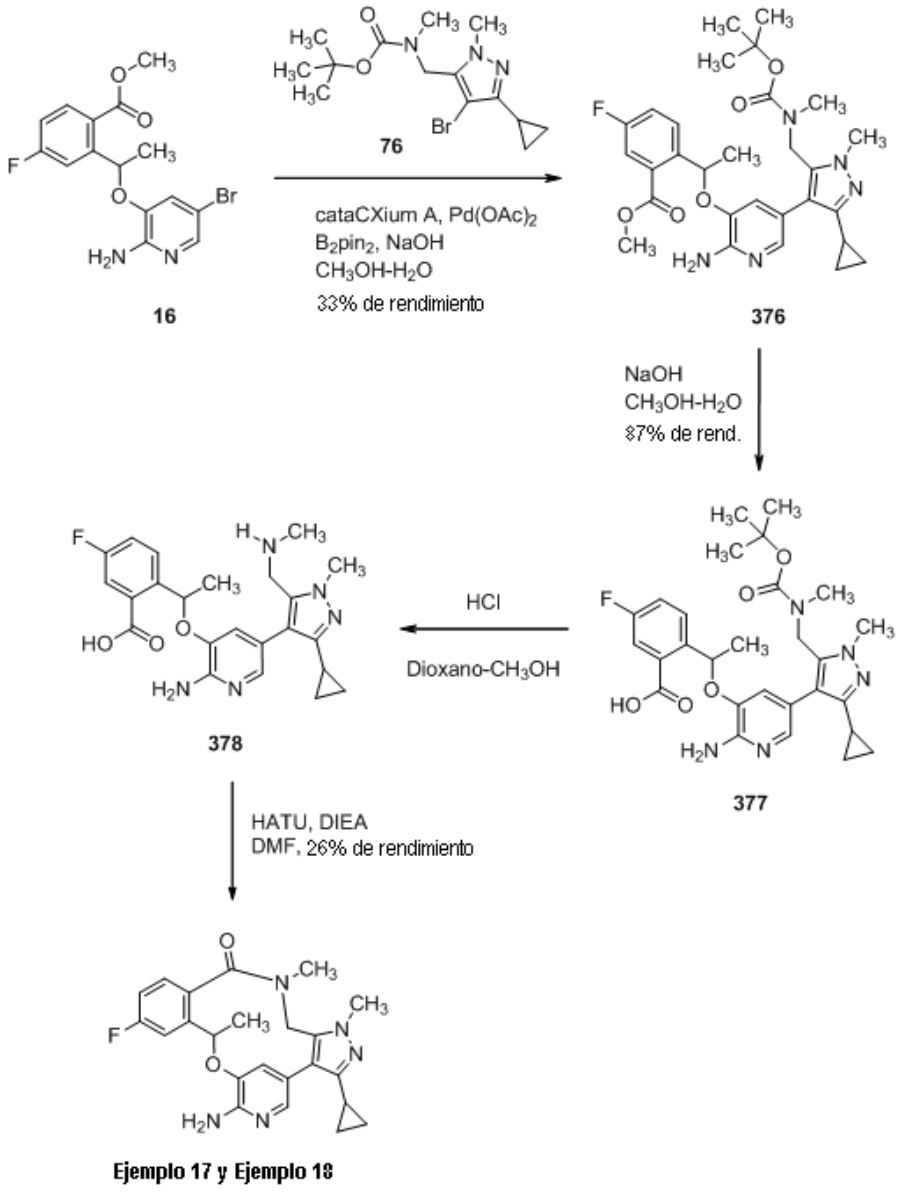
A una solución de HATU (338 mg, 0,89 mmol) en DMF (70 mL) se añadió gota a gota una solución del compuesto **375** (0,515 mmol) y DIPEA (1,2 g, 9,5 mmol) en DMF (20 mL) a 0 ºC. Después de la adición, la mezcla resultante se agitó a 0 ºC durante 1 hora. Nada del compuesto **375** fue detectado por LCMS. La mezcla se vertió en agua helada (50 mL) y la capa acuosa se extrajo con EtOAc (40 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (20 mL x 5), se secaron sobre Na_2SO_4 y se concentraron a presión reducida. El producto crudo se purificó por cromatografía flash sobre gel de sílice que se eluyó con EtOAc y produjo una mezcla pura de **Ejemplo 15 y Ejemplo 16** en forma de un sólido blanquecino (100 mg, 46% de rendimiento). La separación quiral analítica se realizó por SFC en una Chiralpak AS-H (150 x 4,6 mm I.D., 5 micrones de tamaño de partícula), que se eluyó con 5-40% de etanol (0,05% de DEA) en CO_2. La tasa de flujo de 3 mL/min dio $Rt_{(pico\ 1)}$ = 3,08 minutos y $Rt_{(pico\ 2)}$ = 3,47 minutos. La mezcla racémica se purificó por SFC preparativa y produjo el pico 1 en forma de un sólido blanco (27 mg) y en forma de un sólido

blanco **pico** 2 (22 mg).

Ejemplo 16 (pico 1): 98% ee. ^{1}H RMN (400 MHz, Metanol-d_4) δ□7,42 - 7,39 (m, 2 H), 7,29 (dd, 1 H), 7,00 (dd, 1 H), 6,77 (s, 1 H), 5,63 - 5,58 (m, 1 H), 4,22 (q, 2 H), 3,84 (s, 3 H), 2,99 (s, 3 H), 1,78 - 1,72 (m, 1 H), 1,68 - 1,67 (d, 3 H), 0,98 - 0,94 (m, 1 H), 0,86 - 0,82 (m, 1 H), 0,46 - 0,42 (m, 1 H), 0,28 - 0,24 (m, 1 H). LCMS *m/z* 422 $[M+H]^+$.

Ejemplo 15 (pico 2): 100% ee. ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,42 - 7,39 (m, 2 H), 7,29 (dd, 1 H), 7,00 (dd, 1 H), 6,77 (s, 1 H), 5,63 - 5,58 (m, 1 H), 4,22 (q, 2 H), 3,84 (s, 3 H), 2,99 (s, 3 H), 1,78 - 1,72 (m, 1 H), 1,68 - 1,67 (d, 3 H), 0,98 - 0,94 (m, 1 H), 0,86 - 0,82 (m, 1 H), 0,46 - 0,42 (m, 1 H), 0,28 - 0,24 (m, 1 H). LCMS *m/z* 422 $[M+H]^+$.

Preparación de 7-amino-3-ciclopropil-12-fluoro-1,10,16-trimetil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 17 y Ejemplo 18).



Ejemplo 17 y Ejemplo 18

Etapa 1:

El procedimiento descrito en la etapa 1 para el Ejemplo **13 y 14** se usó para preparar el **compuesto 376** (495 mg, 33% de rendimiento). LCMS *m/z* 554 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 3 para el Ejemplo **13 y 14** se usó para preparar el **compuesto 377** (420 mg, 87% de rendimiento). LCMS *m/z* 540 $[M+H]^+$.

Etapa 3:

El procedimiento descrito en la etapa 2 para el Ejemplo **13 y 14** se usó para preparar el **compuesto 378**. LCMS *m/z* 439 $[M+H]^+$.

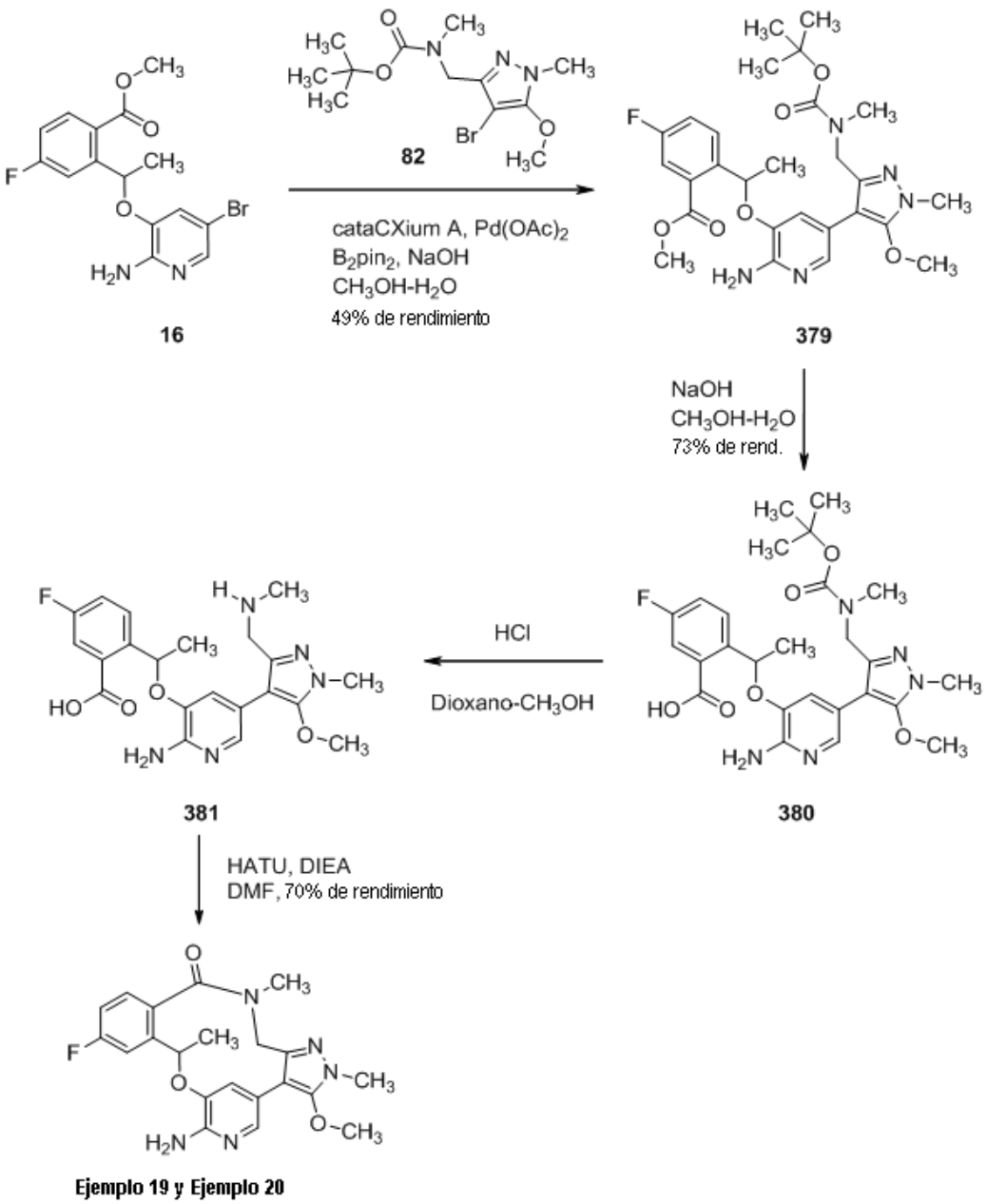
Etapa 4:

A una solución de HATU (520 mg, 1,4 mmol) en DMF (100 mL) se añadió gota a gota una solución del **compuesto 378** (0,91 mmol) y DIPEA (1,88 g, 14,6 mmol) en DMF (20 mL) a 0 ºC. La mezcla resultante se agitó a 0 ºC durante 1 hora. Nada del **compuesto 378** fue detectado por LCMS. La mezcla se vertió en agua helada (50 mL) y la capa acuosa se extrajo con EtOAc (40 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (20 mL x 5), se secaron en Na_2SO_4 y se concentraron al vacío. El producto crudo se purificó por cromatografía flash en gel de sílice, que se eluyó con EtOAc y produjo una mezcla de **Ejemplo 17 y Ejemplo 18** en forma de un sólido oscuro (100 mg, 26% de rendimiento). La separación quiral analítica se realizó por SFC en una columna Chiralcel (50 x 4,6 mm I.D., 3 micrones de tamaño de partícula), que se eluyó con 5-40% metanol (0,05% de DEA) en CO_2. La tasa de flujo de 4 mL/min dio $Rt_{(pico\ 1)}$ = 1,47 min y $Rt_{(pico\ 2)}$ = 1,74 min. La mezcla racémica se separó por SFC preparativa y produjo el pico 1 en forma de un sólido blanco (30 mg) y el pico 2 en forma de un sólido blanco (39 mg).

Ejemplo 17 (pico 1): 93,7% ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,76 - 7,75 (m, 1 H), 7,25 (dd, 1 H), 7,10 (dd, 1 H), 693 - 6,90 (m, 1 H), 6,80 (m, 1 H), 5,70 - 5,68 (s, 1 H), 4,54 (s, 2 H), 4,40 (d, 1 H), 4,22 (d, 1 H), 3,85 (s, 3 H), 3,06 (s, 3 H), 1,85 (m, 1 H), 1,70 (d, 3 H), 1,02 - 1,01 (m, 1 H), 0,95 - 0,93 (m, 1 H), 0,81 - 0,79 (m, 1 H), 0,63 (m, 1 H). LCMS *m/z* 422 $[M+H]^+$.

Ejemplo 18 (pico 2): 94,6% ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ□7,75 (s, 1 H), 7,22 (dd, 1 H), 7,18 (dd, 1 H), 693 - 6,90 (m, 1 H), 6,81 (m, 1 H), 5,70 - 5,68 (s, 1 H), 4,67 (s, 2 H), 4,32 (d, 1 H), 4,26 (d, 1 H), 3,85 (s, 3 H), 3,06 (s, 3 H), 1,85 (m, 1 H), 1,70 (d, 3 H), 1,02 - 1,01 (m, 1 H), 0,95 - 0,93 (m, 1 H), 0,81 - 0,79 (m, 1 H), 0,63 (m, 1 H). LCMS *m/z* 422 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-3-metoxi-2,10,16-trimetil-16,17-dihidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 19 y Ejemplo 20).



Ejemplo 19 y Ejemplo 20

Etapa 1:

El procedimiento descrito en la etapa 1 para el Ejemplo **13 y 14** se usó para preparar el **compuesto 379** (1,0 g, 49% de rendimiento). LCMS *m/z* 544 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 3 para el **Ejemplo 13 y 14** se usó para preparar el **compuesto 380** (700 mg, 73% de rendimiento). LCMS *m/z* 540 $[M+H]^+$.

Etapa 3:

El procedimiento descrito en la etapa 3 para el Ejemplo **15 y 16** se usó para

preparar el **compuesto 381**. LCMS *m/z* 430 $[M+H]^+$.

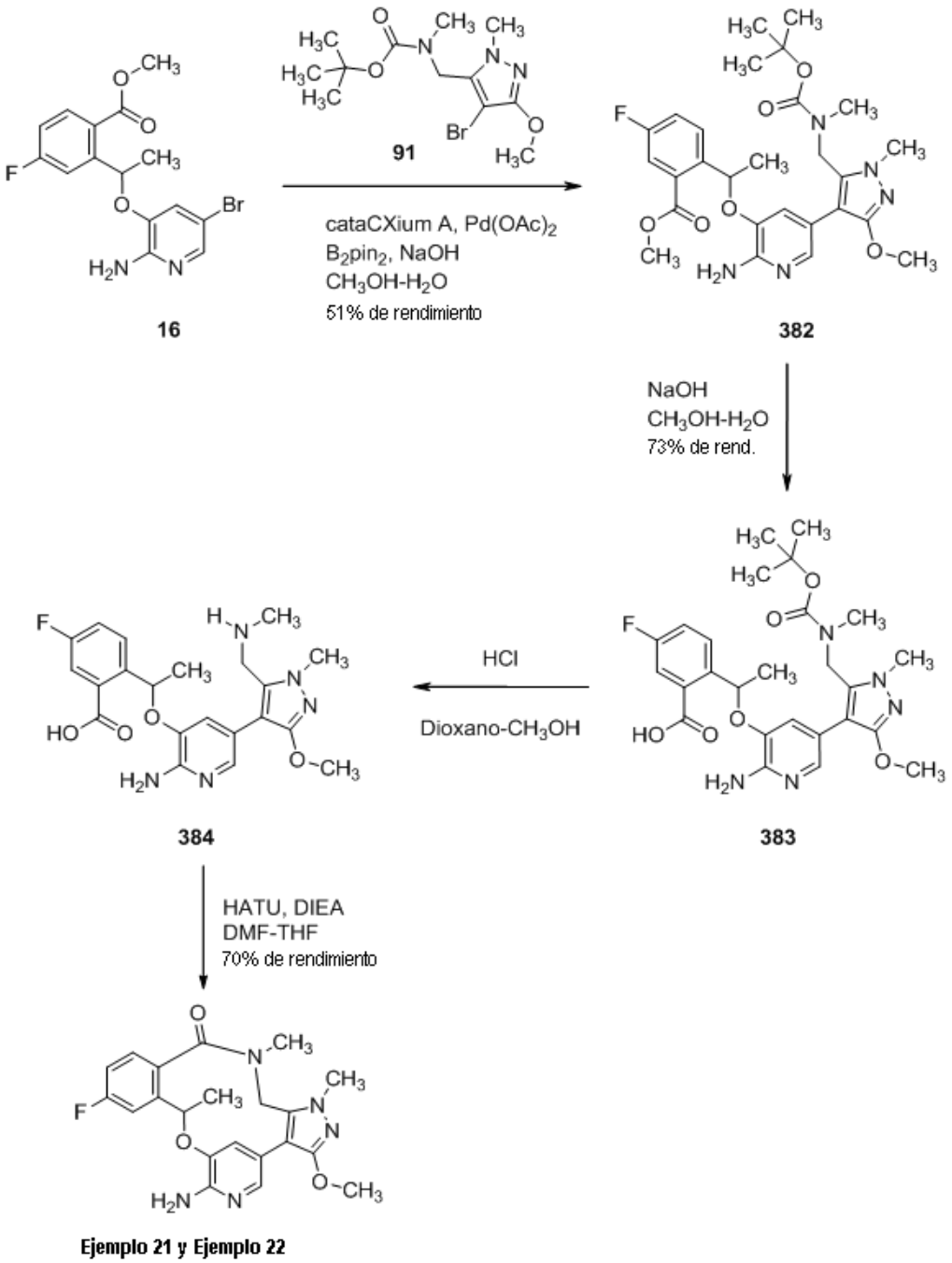
Etapa 4:

A una solución de HATU (710 mg, 1,85 mmol) en DMF (30 mL) se añadió gota a gota una solución del **compuesto 381** (1,32 mmol) y DIPEA (2,7 g, 21,1 mmol) en DMF (30 mL) y THF (6 mL) a 0 ºC. Después de la adición, la mezcla resultante se agitó a la misma temperatura durante 1 hora. La LCMS mostró que la reacción estaba completa. La mezcla se vertió en agua helada (100 mL) y la capa acuosa se extrajo con EtOAc (60 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (50 mL x 5), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo, que se purificó por cromatografía en columna en gel de sílice, que se eluyó con DCM/MeOH = 15:1 (Rf = 0,3) y produjo una mezcla de **Ejemplo 19 y Ejemplo 20** en forma de un sólido amarillo (390 mg, 70% de rendimiento). La separación quiral analítica se realizó por SFC en una columna Chiralpak AD-3 (150 x 4,6 mm I.D., 3 micrones de tamaño de partícula), que se eluyó con 5-40% de metanol (0,05% de DEA) en CO_2. $Rt_{(pico\ 1)}$ = 4,85 minutos y $Rt_{(pico\ 2)}$ = 5,79 minutos. La mezcla racémica se separó por SFC preparativa para producir el pico 1 en forma de un sólido blanco (130 mg) y el pico 2 en forma de un sólido blanco (128 mg).

Ejemplo 19 (pico 1): 100% ee. ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,41 - 7,38 (m, 2 H), 7,30 (dd, 1 H), 7,00 (dd, 1 H), 6,80 (s, 1H), 5,64 - 5,60 (m, 1 H), 4,26 (d, 1 H), 4,12 (d, 1 H), 3,73 (s, 3 H), 3,56 (s, 3 H), 3,02 (s, 3 H), 1,68 (d, 3 H). LCMS *m/z* 412 $[M+H]^+$.

Ejemplo 20 (pico 2): 98,2% ee. ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,41 - 7,38 (m, 2 H), 7,30 (dd, 1 H), 7,00 (dd, 1 H), 6,80 (s, 1 H), 5,64 - 5,60 (m, 1 H), 4,26 (d, 1 H), 4,12 (d, 1 H), 3,73 (s, 3 H), 3,61 (s, 3 H), 3,02 (s, 3 H), 1,68 (d, 3 H). LCMS *m/z* 412 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-3-metoxi-1,10,16-trimetil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 21 y Ejemplo 22).



Ejemplo 21 y Ejemplo 22

Etapa 1:

El procedimiento descrito en la etapa 1 para el Ejemplo **13 y 14** se usó para preparar el compuesto **382** en forma de un aceite marrón (300 mg, 51% de rendimiento). LCMS *m/z* 544 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 3 para el Ejemplo **13 y 14** se usó para

preparar el compuesto **383** en forma de un sólido amarillo (320 mg, 73% de rendimiento). LCMS *m/z* 529 $[M+H]^+$.

Etapa 3:

El procedimiento descrito en la etapa 2 para el Ejemplo **15 y 16** se usó para preparar el compuesto **384**. LCMS *m/z* 430 [M+H]+.

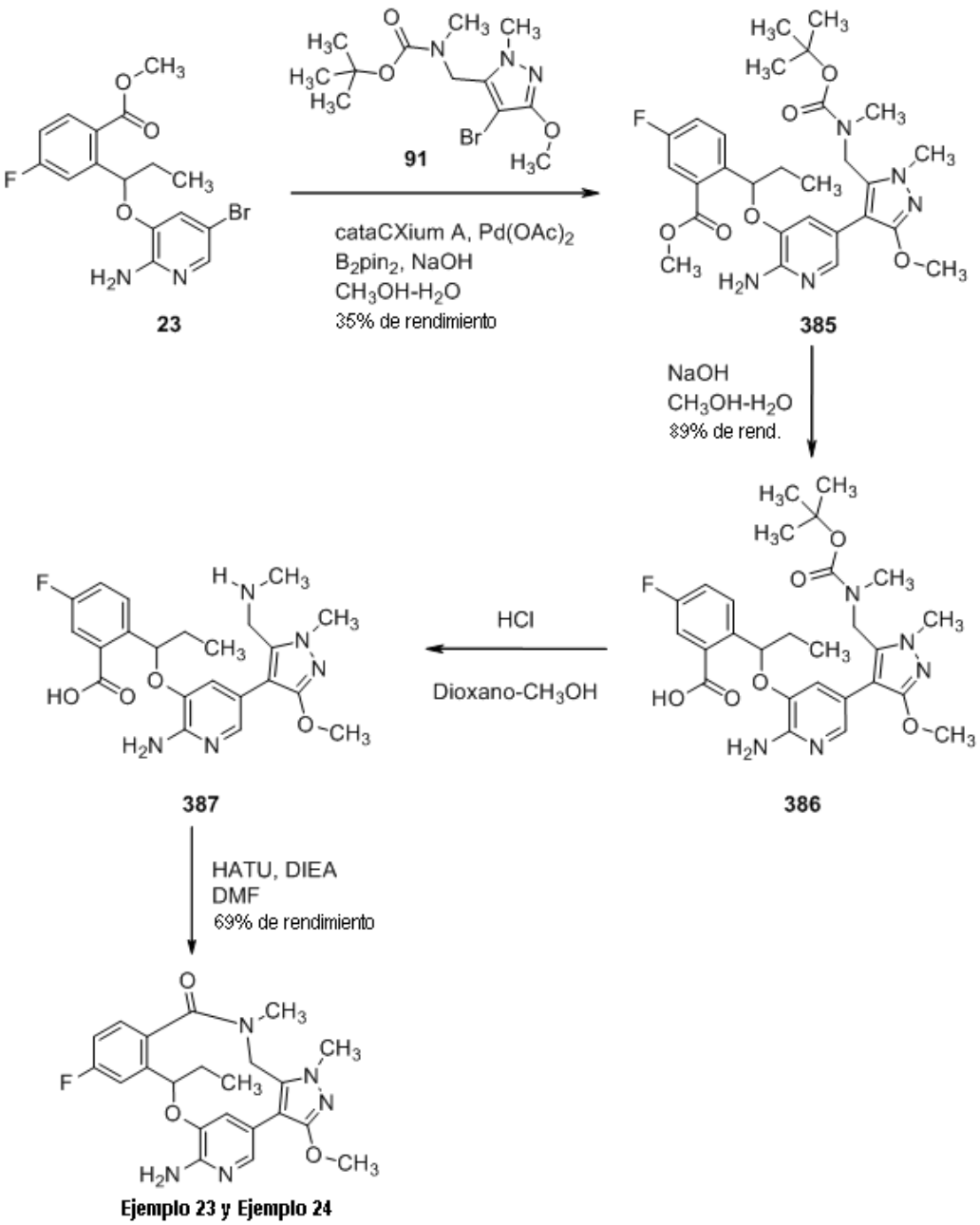
Etapa 4:

A una solución de HATU (280 mg, 0,74 mmol) en DMF (25 mL) se añadió gota a gota una solución del compuesto **384** (0,53 mmol) y DIPEA (1,09 g, 8,48 mmol) en DMF (25 mL) y THF (5 mL) a 0 ºC. La mezcla se agitó a la misma temperatura durante 1 hora. La LCMS mostró que la reacción estaba completa. La mezcla se vertió en agua helada (100 mL) y la capa acuosa se extrajo con EtOAc (60 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (50 mL x 5), se secaron en Na_2SO_4, se filtraron y se concentraron al vacío para producir un residuo, que se purificó por Biotage (DCM/MeOH = 15:1, Rf=0,3) para producir una mezcla de **Ejemplo 21 y Ejemplo 22** en forma de un sólido amarillo (170 mg, 78%). La separación quiral analítica se realizó por SFC en una columna Chiralcel OD-3 (50 x 4,6 mm I.D., 3 micrones de tamaño de partícula), que se eluyó con 5-40% de metanol (0,05% de DEA) en CO_2. $Rt_{(pico\ 1)}$ = 1,44 minutos y $Rt_{(pico\ 2)}$ = 1,59 minutos. La mezcla racémica se separó por SFC preparativa y produjo el pico 1 en forma de un sólido blanco (62 mg) y pico 2 en forma de un sólido blanco (72 mg).

Ejemplo 21 (pico 1): 96,6% ee. ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,62 (d, 1 H), 7,50 (dd, 1 H), 7,43 (dd, 1 H), 7,16 - 7,11 (m, 1 H), 6,90 (d, 1 H), 5,64 - 5,60 (m, 1 H), 4,84 (d, 1 H), 4,37 (d, 1 H), 3,92 (d, 6 H), 3,17 (s, 3 H), 1,78 (d, 3 H). LCMS *m/z* 412 $[M+H]^+$.

Ejemplo 22 (pico 2): 96,9% ee. ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,61 (d, 1 H), 7,50 (dd, 1 H), 7,42 (dd, 1 H), 7,15 - 7,10 (m, 1 H), 6,90 (d, 1 H), 5,68 - 5,64 (m, 1 H), 4,82 (d, 1 H), 4,36 (d, 1 H), 3,90 (d, 6 H), 3,15 (s, 3 H), 1,78 (d, 3 H). LCMS *m/z* 412 $[M+H]^+$.

Preparación de 7-amino-10-etil-12-fluoro-3-metoxi-1,16-dimetil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 23 y Ejemplo 24).



Ejemplo 23 y Ejemplo 24

Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 13 y 14** se usó para preparar el compuesto **385** en forma de un sólido marrón (470 mg, 35% de rendimiento).

Etapa 2:

El procedimiento descrito en la etapa 3 para el Ejemplo **13 y 14** se usó para preparar el compuesto **386** en forma de un sólido amarillo pálido (410 mg, 89% de rendimiento).

Etapa 3:

El procedimiento descrito en la etapa 2 para el Ejemplo **15 y 16** se usó para preparar el **compuesto 387** en forma de un sólido amarillo pálido (410 mg, cuantitativo).

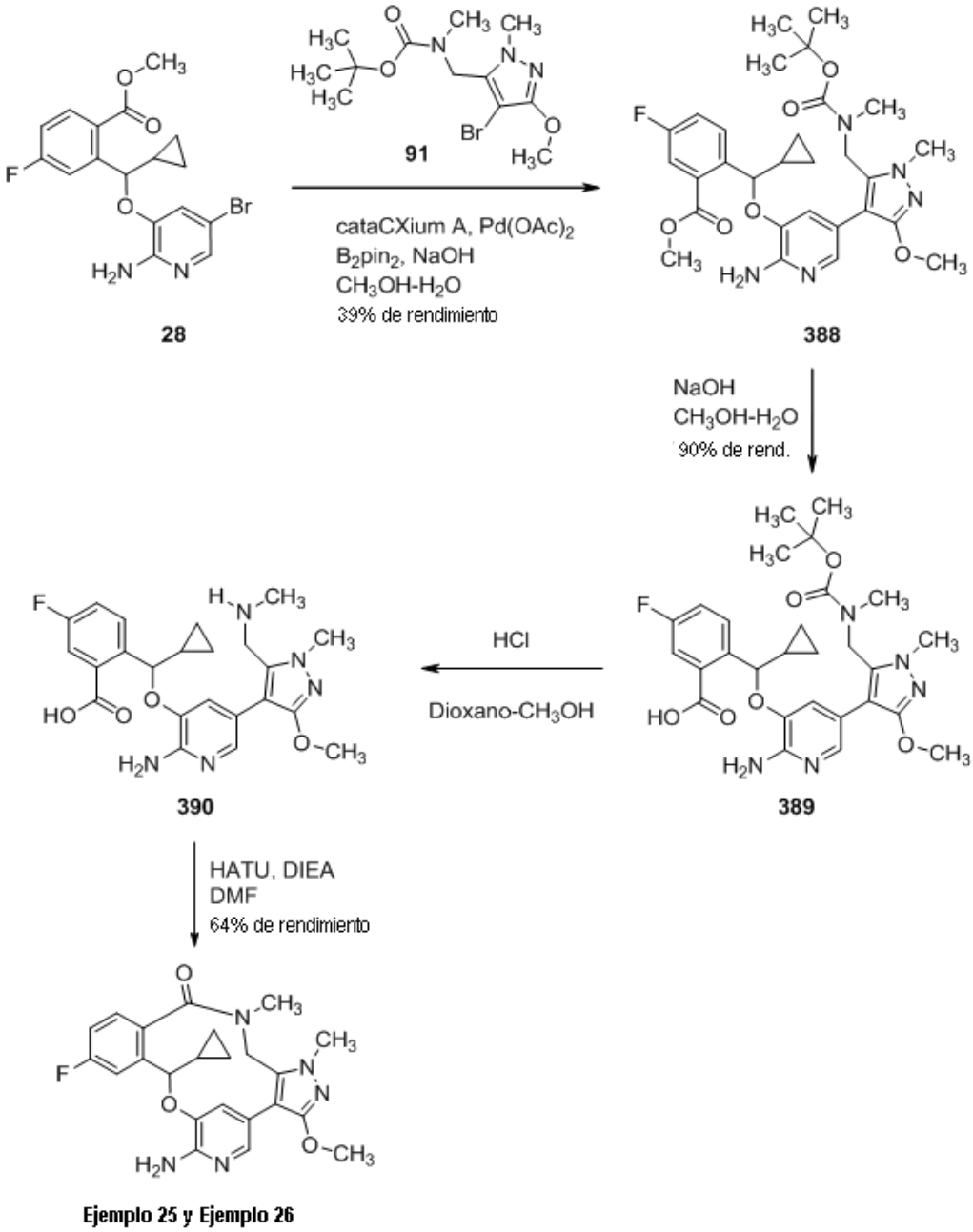
Etapa 4:

A una solución de HATU (399 mg, 1,05 mmol) en DMF (80 mL) se añadió gota a gota una solución del **compuesto 387** (0,75 mmol) y DIPEA (1,4 g, 11,3 mmol) en DMF (20 mL) a 0 ºC. Después de la adición, la mezcla resultante se agitó a la misma temperatura durante 1 hora. La LCMS mostró que la reacción estaba completa. La mezcla se vertió en agua helada (100 mL). La capa acuosa se extrajo con EtOAc (50 mL x 2). Las capas combinadas de EtOAc se lavaron con H_2O (40 mL x 2), salmuera (40 mL), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo, que se purificó por Biotage (CH_2Cl_2/MeOH de 15:1 a 10:1) para producir el **Ejemplo 23 y Ejemplo 24** en forma de un sólido blanquecino (220 mg, 69% de rendimiento). La separación quiral analítica se realizó por SFC en una columna Chiralcel AD-H (250 x 4,6 mm I.D., 5 micrones de tamaño de partícula), que se eluyó con 5-40% de etanol (0,05% de DEA) en CO_2. Una tasa de flujo de 2,3 ml/min dio $Rt_{(pico\ 1)}$ = 7,6 minutos y $Rt_{(pico\ 2)}$ = 8,7 minutos. La mezcla racémica se separó por SFC preparativa para producir el pico 1 en forma de un sólido blanquecino (65 mg) y el pico 2 en forma de un sólido blanquecino (79 mg).

Ejemplo 23 (pico 1): 99,0% ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,82 (s, 1 H), 7,28 (m, 1 H), 7,19 - 7,17 (m, 1 H), 7,01 - 6,98 (m, 1 H), 6,90 (s, 1 H), 5,41 - 5,38 (m, 1 H), 4,76 (m, 2 H), 4,44 (d, 1 H), 4,28 (d, 1 H), 3,93 (s, 3 H), 3,72 (s, 3 H), 3,13 (s, 3 H), 2,26 - 2,16 (m, 1 H), 2,04 - 1,97 (m, 1 H), 1,05 (t, 3 H). LCMS *m/z* 426 $[M+H]^+$.

Ejemplo 24 (pico 2): 94,4% ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,79 (s, 1 H), 7,27 (m, 1 H), 7,17 - 7,15 (m, 1 H), 6,94 - 6,90 (m, 1 H), 6,72 (s, 1 H), 5,35 - 5,32 (m, 1 H), 4,63 (s, 2 H), 4,38 (d, 1 H), 4,21 (d, 1 H), 3,87 (s, 3 H), 3,66 (s, 3 H), 3,08 (s, 3 H), 2,21 - 2,09 (m, 1 H), 1,97 - 1,92 (m, 1 H), 1,02 (t, 3 H). LCMS *m/z* 426 $[M+H]^+$.

Preparación de 7-amino-10-ciclopropil-12-fluoro-3-metoxi-1,16-dimetil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 25 y Ejemplo 26).



Ejemplo 25 y Ejemplo 26

Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 13 y 14** se usó para preparar el **compuesto 388** en forma de un sólido marrón pálido (550 mg, 39% de rendimiento).

Etapa 2:

El procedimiento descrito en la etapa 2 para el Ejemplo **13 y 14** se usó para preparar el **compuesto 389** en forma de un sólido amarillo pálido (482 mg, 90% de

rendimiento).

Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 13 y 14** se usó para preparar el **compuesto 390** en forma de un sólido amarillo pálido (480 mg, cuantitativo).

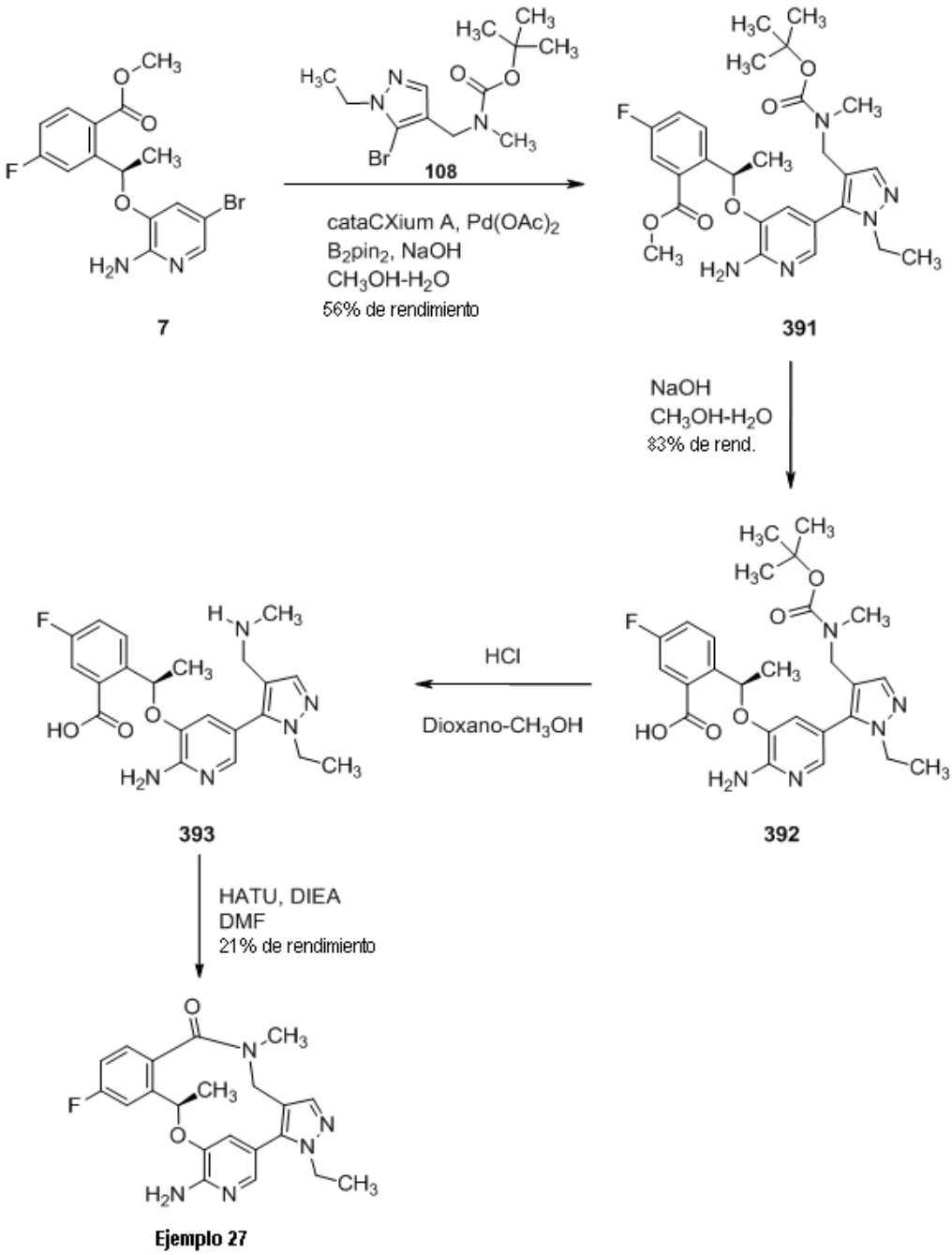
Etapa 4:

A una solución de HATU (456 mg, 1,2 mmol) en DMF (80 mL) se añadió gota a gota una solución del **compuesto 390** (0,86 mmol) y DIPEA (1,6 g, 12,4 mmol) en DMF (20 mL) a 0 ºC. Después de la adición, la mezcla resultante se agitó a la misma temperatura durante 1 hora. La LCMS mostró que la reacción estaba completa. La mezcla se vertió en agua helada (100 mL). La mezcla se extrajo con EtOAc (60 mL x 2). Las capas combinadas de EtOAc se lavaron con H_2O (50 mL x 2), salmuera (50 mL), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo, que se purificó por Biotage (CH_2Cl_2/MeOH de 15:1 a 10:1) para producir una mezcla de **Ejemplo 25 y Ejemplo 26** en forma de un sólido blanquecino (240 mg, 64% de rendimiento). La separación quiral analítica se realizó por SFC en una columna Chiralcel AD-H (250 x 4,6 mm I.D., 5 micrones de tamaño de partícula), que se eluyó con 5-40% de etanol (0,05% de DEA) en CO_2. Una tasa de flujo de 2,3 mL/min dio $Rt_{(pico\ 1)}$ = 8,1 minutos y $Rt_{(pico\ 2)}$ = 9,1 minutos. La mezcla racémica se separó por SFC preparativa para producir el pico 1 en forma de un sólido blanquecino (75 mg) y el pico 2 en forma de un sólido blanquecino (76 mg).

Ejemplo 25 (pico 1): 100% ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,75 (s, 1 H), 7,35 - 7,32 (m, 1 H), 7,16 - 7,12 (m, 1 H), 6,95 - 6,92 (m, 1 H), 6,60 (s, 1 H), 4,65 - 4,61 (m, 3 H), 4,35 (d, 1 H), 4,20 (d, 1 H), 3,86 (s, 3 H), 3,73 (s, 3 H), 3,06 (s, 3 H), 1,41 - 1,36 (m, 1 H), 0,85 - 0,82 (m, 2 H), 0,60 - 0,52 (m, 2 H). LCMS *m/z* 438 $[M+H]^+$

Ejemplo 26 (pico 2): 94,8% ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,76 (s, 1 H), 7,34 - 7,32 (m, 1 H), 7,15 - 7,12 (m, 1 H), 6,96 - 6,93 (m, 1 H), 6,61 (s, 1 H), 4,64 - 4,62 (m, 3 H), 4,34 (d, 1 H), 4,20 (d, 1 H), 3,85 (s, 3 H), 3,71 (s, 3 H), 3,04 (s, 3 H), 1,42 - 1,37 (m, 1 H), 0,84 - 0,81 (m, 2 H), 0,61 - 0,53 (m, 2 H). LCMS *m/z* 438 $[M+H]^+$.

Preparación de (10*R*)-7-amino-3-etil-12-fluoro-10,16-dimetil-16,17-dihidro-3*H*-8,4-(meteno)pirazolo[3,4-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 27).



Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 13 y 14** se usó para preparar el **compuesto 391** en forma de un sólido marrón (400 mg, 56% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,99 - 7,95 (m, 1 H), 7,45 (s, 1 H), 7,39 (s, 1 H), 7,18 - 7,15 (m, 1 H), 6,94 (d, 1 H), 6,38 (s, 1 H), 6,33 (d, 1 H), 4,93 (s, 2 H), 3,84 (d, 2 H), 3,71 (d, 3 H), 3,69 - 3,67 (m, 2 H), 2,34 (s, 3 H), 1,62 (d, 3 H), 1,36 (s, 9 H), 1,07 (t, 3 H).

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 13 y 14** se usó para preparar el **compuesto 392** en forma de un sólido amarillo (320 mg, 83% de rendimiento). LCMS *m/z* 514 $[M+H]^+$.

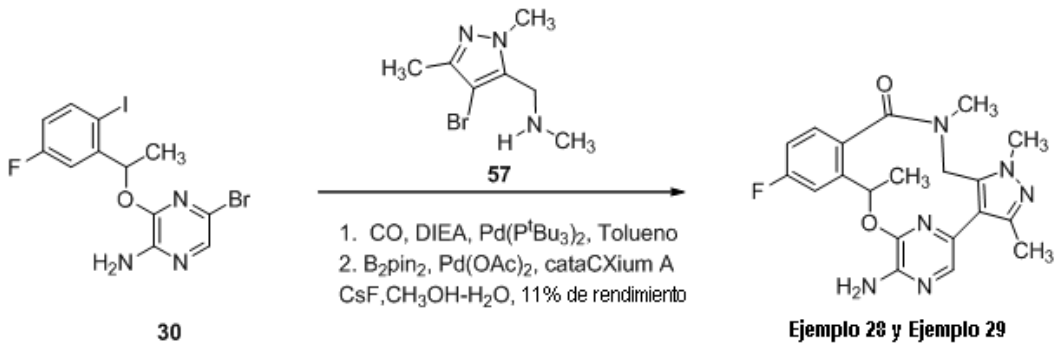
Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 13 y 14** se usó para preparar el **compuesto 393** en forma de un sólido amarillo pálido (320 mg, cuantitativo).

Etapa 4:

A una solución de HATU (684 mg, 1,8 mmol) en DMF (60 mL) se añadió gota a gota una solución del **compuesto 393** (0,62 mmol) y DIPEA (2,5 g, 19,2 mmol) en DMF (20 mL) a 0 ºC. Después de la adición, la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La LCMS mostró que la reacción estaba completa. La mezcla se vertió en agua helada (50 mL). La capa acuosa se extrajo con EtOAc (40 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (20 mL x 5), se secaron en Na_2SO_4 y se concentró al vacío para dar un residuo. El residuo se purificó por cromatografía en columna en gel de sílice, que se eluyó con éter de petróleo/EtOAc (2:1~1:2) y produjo el **Ejemplo 27** en forma de un sólido rosa (52 mg, 21% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,52 (s, 1 H), 7,48 (d, 1 H), 7,21 (s, 1 H), 7,19 (s, 1 H), 7,10 (d, 1 H), 6,85 (m, 1 H), 5,79 (s, 1 H), 4,94 (s, 2 H), 4,19 - 4,16 (m, 2 H), 4,11 (m, 2 H), 3,05 (s, 3 H), 1,72 (d, 3 H), 1,39 (t, 3 H). LCMS *m/z* 396 $[M+H]^+$.El análisis por cromatografía quiral mediante Chiralcel OD-3 (150 × 4,6 mm I.D., 3 micrones de tamaño de partícula) y elución con metanol (5% a 40% con 0,05% de DEA) en CO_2 a una tasa de flujo de 2,5mL/min dio un tiempo de retención de 6,23 minutos (100% ee).

Preparación de 7-amino-12-fluoro-1,3,10,16-tetrametil-16,17-dihidro-1H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 28 y Ejemplo 29).



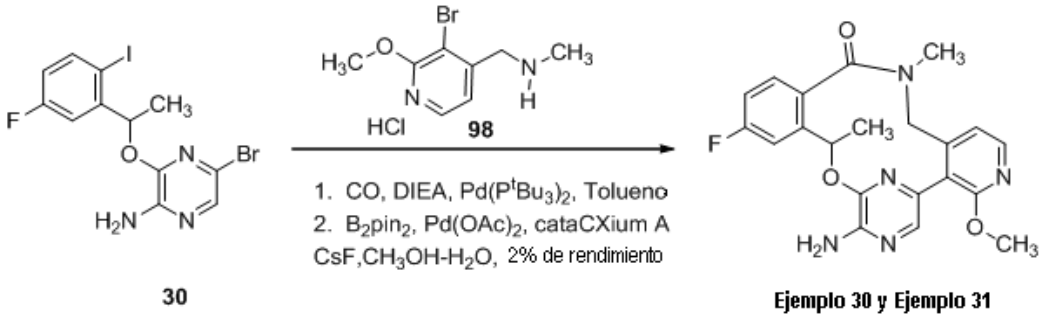
30 Ejemplo 28 y Ejemplo 29

A una solución del **compuesto 30** (266 mg, 0,607 mmol), **compuesto 57** (166 mg, 0,759) y DIEA (211 µL, 1,21 mmol) en tolueno (60 mL), se añadió $Pd(P^tBu_3)_2$ (32 mg, 0,61 mmol). La mezcla de reacción se calentó a 100 ˚C bajo 4 bar de CO durante la noche, luego se concentró. El residuo se absorbió en MeOH (12 mL) y agua (1,3 mL) y se añadió a un vial que contenía éster pinacólico de diboro (771 mg, 3,04 mmol) y CsF (461 mg, 3,04 mmol). El vial se selló y la mezcla de reacción se burbujeó con nitrógeno antes de añadir una solución de $Pd(OAc)_2$ (14 mg, 0,61 mmol) y di(1-adamantil)-n-butilfosfina (45 mg, 0,12 mmol) en tolueno (0,5 mL). Después de calentar durante 30 min a 60 ˚C, la temperatura se incrementó hasta 90 ˚C durante 6 horas. La reacción se dejó reposar a temperatura ambiente durante la noche, luego se añadieron $Pd(OAc)_2$ (14 mg, 0,61 mmol) y di(1-adamantil)-n-butilfosfina (45 mg, 0,12 mmol) en tolueno (0,5 mL). Después de calentar durante 2 horas a 100 ˚C, la mezcla de reacción se enfrió hasta temperatura ambiente y se filtró. El licor madre se diluyó con EtOAc, se lavó con agua (2x) y salmuera, se secó ($MgSO_4$), se filtró y se concentró. El producto crudo se purificó por cromatografía flash, que se eluyó con DCM/MeOH (0-8%) seguido de una segunda columna que se eluyó con heptanos/EtOAc (50-100%), luego DCM/MeOH (0-6%) y finalmente, separación quiral por SFC para obtener ambos enantiómeros del compuesto del título. La separación quiral se realizó por SFC en una columna Chiralcel OD-H (4,6 mm x 250 mm, 5 micrones de tamaño de partícula) columna que se eluyó con 25% MeOH en CO_2 mantenido a 25 ºC a 140 bar. Una tasa de flujo de 3,0 mL/min produjo el pico 1 $Rt_{(pico\ 1)}$ = 4,23 min ($[\alpha]_d^{20}$= -77,1º (C=0,23, MeOH) y el pico 2 $Rt_{(pico\ 2)}$ = 5,60 min ($[\alpha]_d^{20}$= +78,6º (C=0,24, MeOH).

Ejemplo 28 (pico 1): 14 mg, >99% ee, 6% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,51 (s, 1 H), 7,51 - 7,46 (m, 1 H), 7,36 (dd, *J* = 5,8, 8,3 Hz, 1 H), 7,17 (dt, *J* = 2,5, 8,6 Hz, 1 H), 6,29 (s, 2 H), 5,95 - 5,84 (m, 1 H), 4,47 (d, *J* = 14,7 Hz, 1 H), 4,27 (d, *J* = 14,4 Hz, 1 H), 3,87 (s, 3 H), 2,87 (s, 3 H), 2,26 (s, 3 H), 1,62 (d, *J* = 6,6 Hz, 3 H). LCMS ES *m/z* 397 $[M+H]^+$.

Ejemplo 29 (pico 2): 13 mg, 99% ee, 5% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,51 (s, 1 H), 7,49 (dd, *J* = 2,7, 10,2 Hz, 1 H), 7,36 (dd, *J* = 5,7, 8,5 Hz, 1 H), 7,17 (dt, *J* = 2,5, 8,5 Hz, 1 H), 6,29 (s, 2 H), 5,95 - 5,82 (m, 1 H), 4,47 (d, *J* = 14,7 Hz, 1 H), 4,27 (d, *J* = 14,4 Hz, 1 H), 3,87 (s, 3 H), 2,87 (s, 3 H), 2,26 (s, 3 H), 1,62 (d, *J* = 6,6 Hz, 3 H). LCMS ES *m/z* 397 $[M+H]^+$.

Preparación de 8-amino-13-fluoro-4-metoxi-11,17-dimetil-17,18-dihidro-9,5-(azeno)pirido[3,4-h][2,5,11]benzoxadiazaciclotetradecin-16(11H)-ona (Ejemplo 30 y Ejemplo 31).

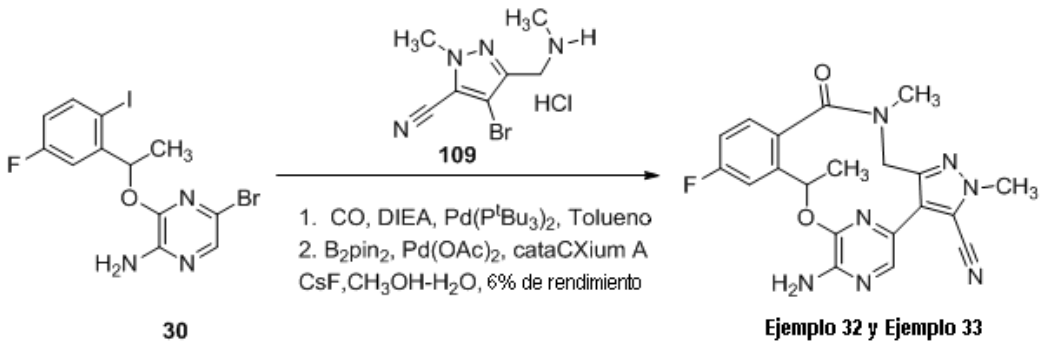


El procedimiento descrito para el Ejemplo **28** se usó para preparar el Ejemplo **30 y Ejemplo 31.** La separación quiral analítica se realizó por SFC en una columna Chiralcel OD-H (4,6 x 250 mm, 5 micrones de tamaño de partícula), que se eluyó con 25% de metanol en CO_2 a 140 bar. Una tasa de flujo de 3,0 mL/min produjo $Rt_{(pico\ 1)}$ = 4,4 minutos y $Rt_{(pico\ 2)}$ = 5,3 minutos.

Ejemplo 30 (pico 1): 4 mg; >98% ee, 1% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,14 (d, *J* = 5,3 Hz, 1 H), 7,66 (s, 1 H), 7,63 (dd, *J* = 2,5, 10,3 Hz, 1 H), 7,28 (dd, *J* = 5,8, 8,6 Hz, 1 H), 7,22 (d, *J* = 5,3 Hz, 1 H), 7,11 (dt, *J* = 2,6, 8,5 Hz, 1 H), 6,52 (s, 2 H), 6,08 - 5,98 (m, 1 H), 4,20 (d, *J* = 12,4 Hz, 1 H), 4,16 (d, *J* = 12,1 Hz, 1 H), 3,82 (s, 3 H), 2,89 (s, 3 H), 1,65 (d, *J* = 6,5 Hz, 3 H). LCMS ES *m/z* 410 $[M+H]^+$.

Ejemplo 31 (pico 2): 3 mg, ~80% ee, 1% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,14 (d, *J* = 5,0 Hz, 1 H), 7,65 (s, 1 H), 7,62 (dd, *J* = 2,6, 10,2 Hz, 1 H), 7,28 (dd, *J* = 5,7, 8,4 Hz, 1 H), 7,22 (d, *J* = 5,0 Hz, 1 H), 7,15 - 7,06 (m, 1 H), 6,51 (s, 2 H), 6,07 - 5,97 (m, 1 H), 4,20 (d, *J* = 12,3 Hz, 1 H), 4,16 (d, *J* = 12,4 Hz, 1 H), 3,82 (s, 3 H), 2,88 (s, 3 H), 1,65 (d, *J* = 6,5 Hz, 3 H). LCMS ES *m/z* 410 $[M+H]^+$.

Síntesis de 7-amino-12-fluoro-2,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 32 y Ejemplo 33).

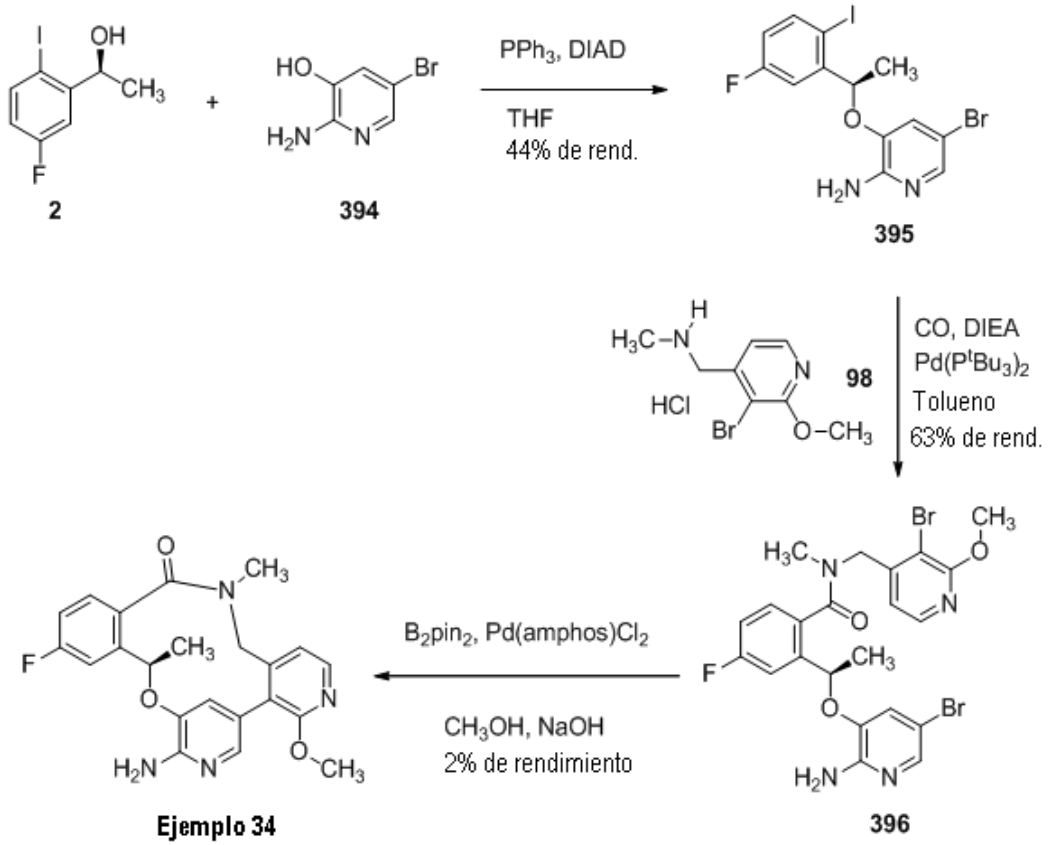


El procedimiento descrito para el Ejemplo **28 y 29** se usó para preparar el **Ejemplo 32 y Ejemplo 33.** La separación quiral analítica se realizó por SFC en una columna Regis Whelk-01 (*R, R*) (4,6 x 250 mm, 5 micrones de tamaño de partícula), que se eluyó con 20% de metanol en CO_2 a 140 bar. Una tasa de flujo de 3,0 mL/min produjo $Rt_{(pico\ 1)}$ = 4,5 minutos y $Rt_{(pico\ 2)}$ = 6,6 minutos.

Ejemplo 32 (pico 1): 8 mg; >99% ee, 3% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,77 (s, 1 H), 7,47 (dd, *J* = 2,8, 10,1 Hz, 1 H), 7,41 (dd, *J* = 5,7, 8,4 Hz, 1 H), 7,16 (dt, *J* = 2,8, 8,6 Hz, 1 H), 6,72 (s, 2 H), 5,97 - 5,81 (m, 1 H), 4,30 (AB q, *J* = 13,9 Hz, 1 H), 4,03 (s, 3 H), 2,89 (s, 3 H), 1,64 (d, *J* = 6,5 Hz, 3 H). LCMS *m/z* 408 $[M+H]^+$.

Ejemplo 33 (pico 2): 10 mg, 96% ee, 3% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,77 (1 H, s), 7,47 (1 H, dd, *J* = 10,0, 2,7 Hz), 7,41 (1 H, dd, *J* = 8,3, 5,8 Hz), 7,16 (1 H, td, *J* = 8,5, 2,7 Hz), 6,74 (2 H, s), 5,84 - 5,98 (1 H, m), 4,31 (2 H, AB q, *J* = 13,7 Hz), 4,03 (4 H, s), 2,89 (3 H, s), 1,64 (3 H, d, *J* = 6,6 Hz). LCMS *m/z* 408 $[M+H]^+$.

Preparación de (11*R*)-8-amino-13-fluoro-4-metoxi-11,17-dimetil-17,18-dihidro-9,5-(meteno)pirido[3,4-*h*][2,5,11]benzoxadiazaciclotetradecin-16(11*H*)-ona (Ejemplo 34).



Etapa 1:

A una solución del **compuesto 2** (338 mg, 1,27 mmol), **compuesto 394** (200 mg, 1,06 mmol) y trifenilfosfina (333 mg, 1,27 mmol) en THF (11 mL) se añadió DIAD (260 µL, 1,27 mmol). La solución era marrón oscura. Después de 30 minutos a temperatura ambiente, la LCMS mostró mayormente producto. El solvente se eliminó a presión reducida y el producto crudo se purificó por cromatografía en columna en gel de sílice, que se eluyó con 0 - 13% de EtOAc-DCM, que dio el compuesto **395** en forma de una goma amarilla (205 mg, 44% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,89 (dd, *J* = 5,7, 8,7 Hz, 1 H), 7,54 (d, *J* = 2,0 Hz, 1 H), 7,42 (dd, *J* = 3,0, 10,1 Hz, 1 H), 6,99 (dt, *J* = 3,0, 8,6 Hz, 1 H), 6,75 (d, *J* = 2,0 Hz, 1 H), 6,18 (s, 2 H), 5,45 (q, *J* = 6,1 Hz, 1 H), 1,54 (d, *J* = 6,3 Hz, 3 H). LCMS ES *m/z* 437/439.

Etapa 2:

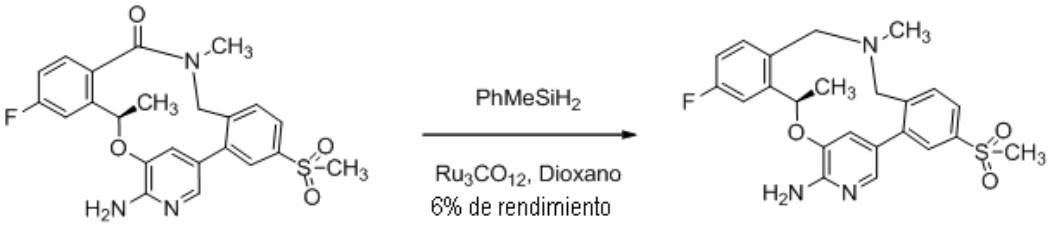
Una mezcla del **compuesto 395** (200 mg, 0,46 mmol), **compuesto 98** (135 mg, 0,50 mmol), DIEA (0,32 mL, 1,8 mmol) y Pd(P*t*-Bu$_3$)$_2$ (24 mg, 0,05 mmol) en tolueno (42 mL) se calentó a 85 ºC en una atmósfera de monóxido de carbono a 4 bar. Después de 18 horas, la mezcla de reacción se concentró y se purificó por cromatografía en columna sobre sílice, que se eluyó con 0-100% de EtOAc-heptano y

produjo el compuesto **396** (165 mg, 63% de rendimiento). LCMS ES *m/z* 566/568/571.

Etapa 3:

Una mezcla de **compuesto 396** (165 mg, 0,29 mol), éster pinacólico de diboro (368 mg, 1,45 mmol), hidróxido de sodio (58 mg, 1,45 mmol) y Pd(amfos)Cl_2 (20 mg, 0,03 mmol) en metanol (10 mL) se desgasificó y se purgó con nitrógeno. La mezcla se calentó a 100 ºC durante 18 horas y se enfrió hasta temperatura ambiente. La mezcla de reacción cruda se diluyó con EtOAc y se lavó secuencialmente con agua y salmuera. La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El producto crudo se purificó por cromatografía en columna en gel de sílice, que se eluyó con 0-100% de EtOAc-heptano seguido de purificación por cromatografía en fase inversa que produjo el **Ejemplo 34** (3 mg, 2% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,14 (d, *J* = 5,0 Hz, 1 H), 7,72 (dd, *J* = 2,5, 10,3 Hz, 1 H), 7,44 (d, *J* = 1,8 Hz, 1 H), 7,29 (dd, *J* = 5,7, 8,4 Hz, 1H), 7,22 (d, *J* = 5,3 Hz, 1 H), 7,09 (dt, *J* = 2,5, 8,4 Hz, 1 H), 6,96 (s, 1 H), 5,95 (s, 2 H), 5,73 - 5,61 (m, *J* = 6,0 Hz, 1 H), 4,26 (d, *J* = 12,8 Hz, 1 H), 4,04 (d, *J* = 12,8 Hz, 1 H), 3,81 (s, 3 H), 2,99 (s, 3 H), 1,68 (d, *J* = 6,0 Hz, 3 H). LCMS m/z 409 $[M+H]^+$.

Preparación de (5*R*)-3-fluoro-5,17-dimetil-13-(metilsulfonil)-5,16,17,18-tetrahidro-7,11-(meteno)dibenzo[*g*,*l*][1,4,10]oxadiazaciclotetradecin-8-amina (Ejemplo 35).



Ejemplo 1 **Ejemplo 35**

A una solución agitada de **Ejemplo 1** (18,2 mg, 0,04 mmol) en dioxano seco (4 mL) se añadió Ru_3CO_{12} (4,0 mg, 0,006 mmol) seguido de $PhMeSiH_2$ (200 µL, 1,6 mmol). La reacción se agitó durante la noche a 90 ˚C durante 18 horas. Después de 18 horas la reacción se concentró a 1 mL y se purificó por cromatografía preparativa en fase inversa y produjo el **Ejemplo 35** (1 mg, 6% de rendimiento). ^{1}H RMN (600 MHz, DMSO-d_6) δ 9,51 (m, 1 H), 7,87 (d, *J* = 2 Hz, 1 H), 7,76 (dd, *J* = 8,0, 2,0 Hz, 1 H), 7,56 (m, 1 H), 7,36 (m, 2 H), 7,19 (dd, *J* = 8,3, 6,0 Hz, 1 H), 6,97 (dt, *J* = 8,3, 2,8 Hz, 1 H), 6,08 (br s, 2 H), 6,00 (q, *J* = 6,4 Hz, 1 H), 4,33 (d, *J* = 10,2 Hz, 2 H), 3,17 (s, 2 H), 2,80 (d, *J* = 10,2 Hz, 1 H), 2,53 (s, 3 H), 2,35 (s, 3 H), 1,65 (d, *J* = 6,4 Hz, 3 H). LCMS *m/z* 442 $[M+H]^+$.

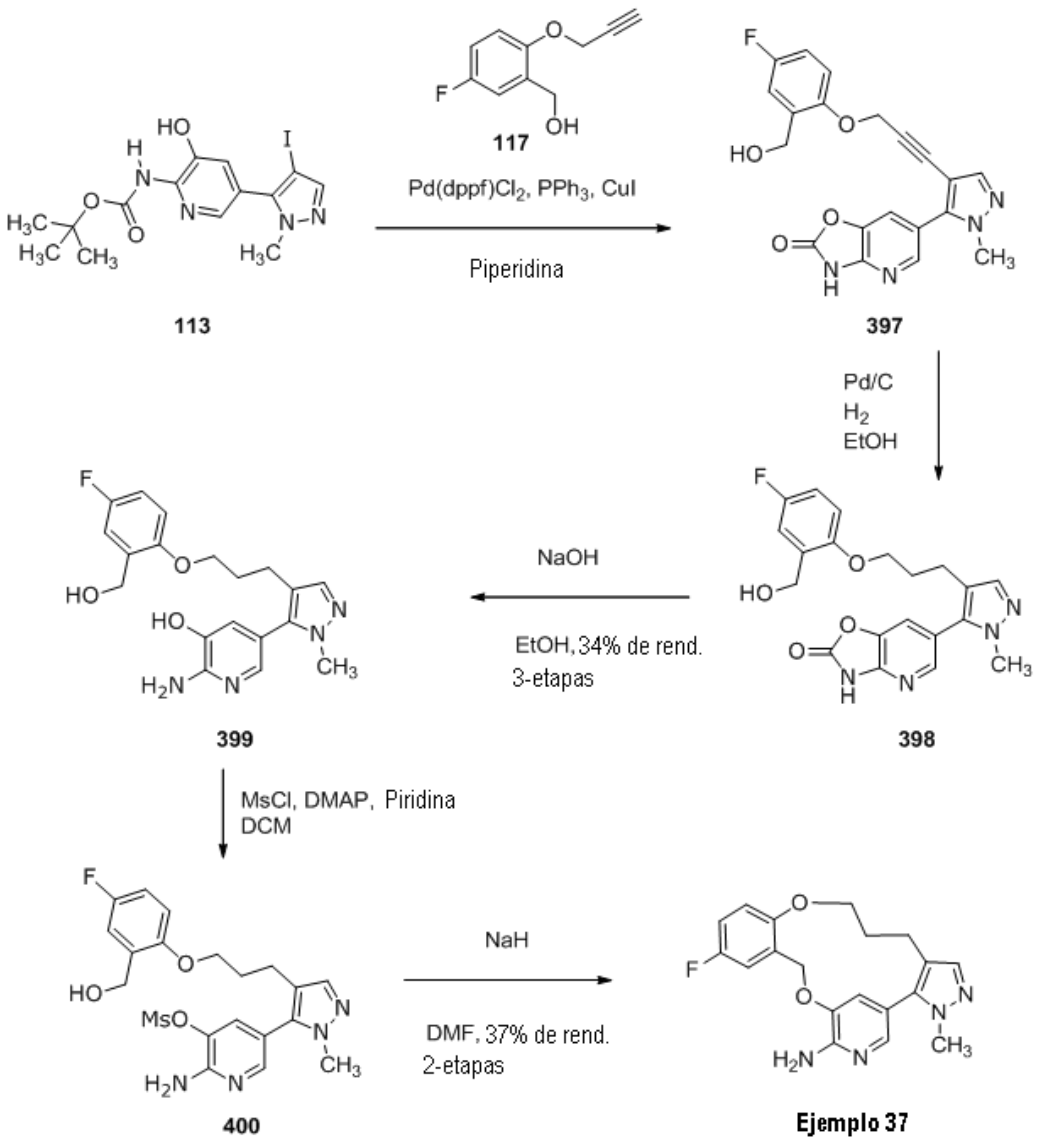
Preparación de (10*R*)-7-amino-12-fluoro-2,10,16-trimetil-10,15,16,17-tetrahidro-2*H*-4,8-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 36).



Ejemplo 2 **Ejemplo 36**

El procedimiento descrito para el **Ejemplo 2** se usó para preparar el compuesto **Ejemplo 36** (3 mg, 8%). ^{1}H RMN (600 MHz, DMSO-d_6) δ 9,64 (m, 1 H), 7,61 (m, 1 H), 7,42 (m, 1 H), 7,24 (m, 1 H), 6,98 (m, 2 H), 6,09 (br s, 2 H), 5,88 (q, *J* = 6,4 Hz, 1 H), 4,33 (d, *J* = 15,5 Hz, 2 H), 3,26 (d, *J* = 15,5 Hz, 2 H), 3,16 (d, *J* = 13,8 Hz, 2 H), 2,94 (d, *J* = 13,8 Hz, 2 H), 3,34 (s, 3 H), 1,65 (d, *J* = 6,4 Hz 3 H). LCMS *m/z* 393 $[M+H]^+$.

Síntesis de 12-fluoro-3-metil-3,16,17,18-tetrahidro-10H-8,4-(meteno)pirazolo[4,3-e][1,12,9]benzodioxazaciclopentadecin-7-amina (Ejemplo 37).



Etapa 1:

Una mezcla del **compuesto 174** (270 mg, 0,65 mmol), **compuesto 117** (176 mg, 0,974 mmol), yoduro cuproso (6 mg, 0,032 mmol), trifenilfosfina (17 mg, 0,065 mmol) y $PdCl_2(PPh_3)_2$ (23 mg, 0,032 mmol) en piperidina pura (4,3 mL) se burbujeó con nitrógeno, luego se calentó a 80 °C. Después de 5 horas, la mezcla de reacción se diluyó con EtOAc, se lavó con NH_4Cl saturado (2x) y salmuera, se secó ($MgSO_4$), se filtró y se concentró. El material se purificó por cromatografía flash en gel de sílice, que se eluyó con DCM/MeOH (0 - 5%) para obtener el **compuesto 397**.

Etapa 2:

A una solución del compuesto **397** (0,65 mmol) en EtOH (50 mL) se añadió

$Pd(OH)_2$ (50 mg). La mezcla se calentó a 50 ºC a 3-4 bar de hidrógeno durante 18 h. La mezcla de reacción se filtró a través de celite y el licor madre se concentró para obtener el **compuesto 398**.

Etapa 3:

El compuesto 398 se disolvió en EtOH (5 mL), luego se añadió el 15% de NaOH (5 mL) y la solución se calentó a 85 ºC durante la noche. La reacción se neutralizó con HCl 1 N y se extrajo con EtOAc (3x). Se añadió $NaHCO_3$ saturado a la capa acuosa que se extrajo con EtOAc (2x). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron. El residuo se purificó por cromatografía flash en gel de sílice, que se eluyó con DCM/MeOH (0-10%) para obtener el **compuesto 399** (82 mg, 34% de rendimiento en 3 etapas). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,85 (q, *J* = 6,9 Hz, 2 H), 2,42 - 2,49 (m, 2 H), 3,64 (s, 3 H), 3,87 (t, *J* = 6,2 Hz, 2 H), 4,43 (br s, 2 H), 5,11 (br. s, 1 H), 5,75 (s, 2 H), 6,80 (d, *J* = 1,5 Hz, 1 H), 6,83 (dd, *J* = 9,1, 4,5 Hz, 1 H), 6,89 - 7,00 (m, 1 H), 7,12 (dd, *J* = 9,6, 3,0 Hz, 1 H), 7,33 (s, 1 H), 7,41 (s, 1 H), 9,72 (br s, 1 H). LCMS *m/z* 373 $[M+H]^+$.

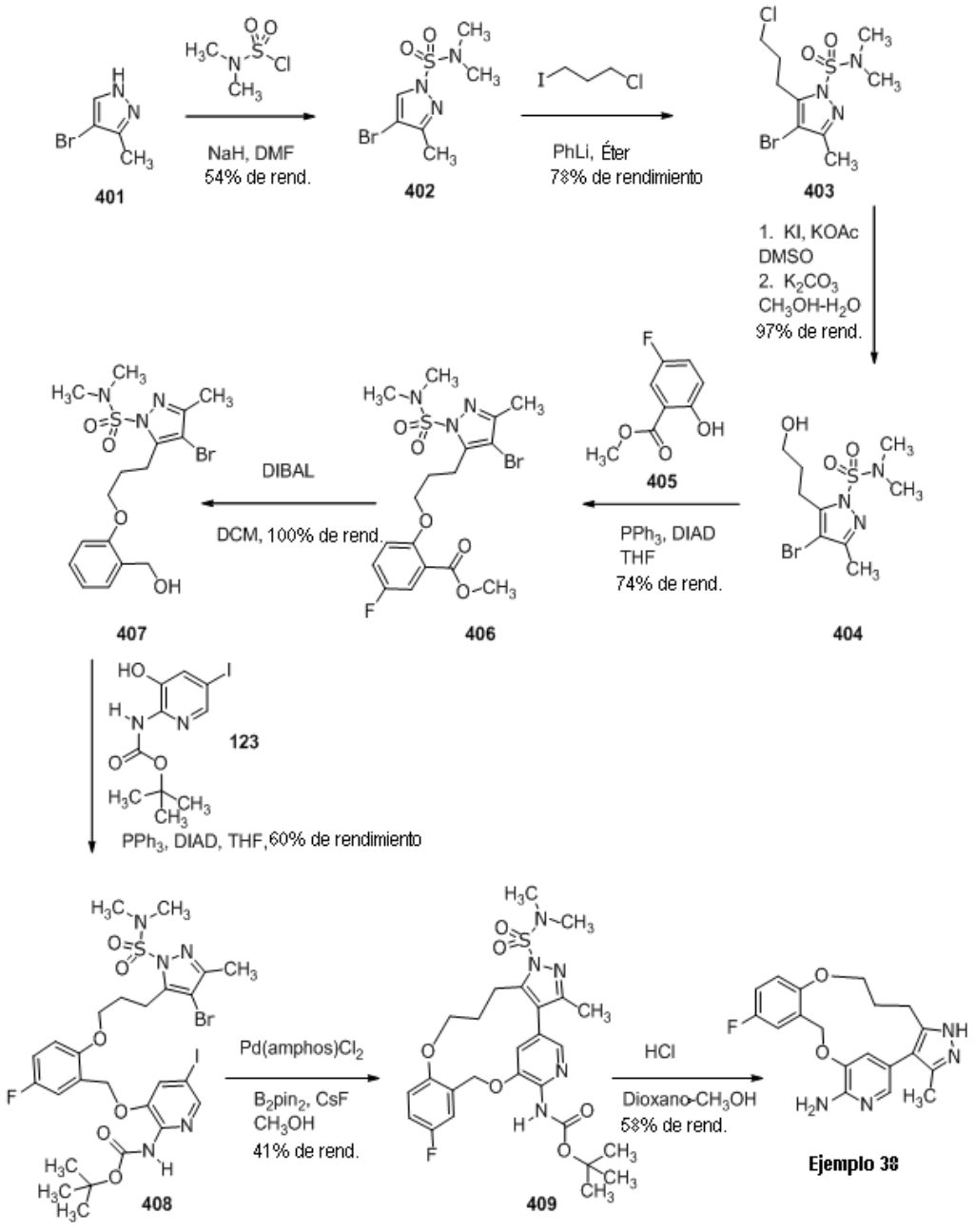
Etapa 4:

A una solución enfriada (0 ºC) de **compuesto 399** (80 mg, 0,22 mmol), DMAP (1,3 mg, 0,011 mmol) y piridina (200 µL, 2,5 mmol) en DCM (1,4 mL) se añadió una solución de MsCl (17 µL, 0,22 mmol) en DCM (0,5 mL). Después de 1 hora la reacción se diluyó con EtOAc, se lavó con NH_4Cl saturado (2x) y salmuera, se secó ($MgSO_4$), se filtró y se concentró para obtener el compuesto **400** (96 mg).

Etapa 5:

A una solución del compuesto **400** (96 mg, 0,21 mmol) en DMF (4,1 mL) se añadió NaH (60% de dispersión en aceite mineral, 9,1 mg, 0,23 mmol). La mezcla de reacción se calentó a 50 ºC durante 30 minutos, luego se diluyó con EtOAc, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía flash en gel de sílice, que se eluyó con DCM/MeOH (0-10%) para obtener el **Ejemplo 37** (27 mg, 37% de rendimiento durante 2 etapas). ^{1}H RMN (400 MHz, DMSO-d_6) δ□2,04 - 2,20 (m, 2 H), 2,65 (t, *J* = 6,8 Hz, 2 H), 3,78 (s, 3 H), 3,97 - 4,14 (m, 2 H), 5,22 (s, 2 H), 5,68 (br s, 2 H), 6,99 - 7,16 (m, 2 H), 7,25 - 7,36 (m, 2 H), 7,38 (s, 1 H), 7,65 (d, *J* = 1,5 Hz, 1 H). LCMS 355 $[M+H]^+$.

Preparación de 12-fluoro-3-metil-1,16,17,18-tetrahidro-10H-8,4-(meteno)pirazolo[3,4-e][1,12,9]benzodioxazaciclopentadecin-7-amina (Ejemplo 38).



Etapa 1:

A una solución enfriada (0 ºC) del **compuesto 401** (2,50 g, 15,5 mmol) en DMF (40 mL) se añadió NaH (60% de dispersión en aceite mineral, 745 mg, 18,6 mmol). Después de 30 min, se añadió una solución de cloruro de *N,N*-dimetilsulfamoílo (1,67 mL, 15,5 mmol) en DMF (5 mL). La mezcla de reacción se calentó gradualmente a temperatura ambiente y se agitó durante 5 horas. La reacción se neutralizó con NH_4Cl saturado y se diluyó con EtOAc. La capa orgánica se lavó secuencialmente con agua, salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El

producto crudo se purificó por cromatografía flash en gel de sílice que se eluyó con heptanos/EtOAc (0-30%) y dio el **compuesto 402** en forma de un sólido ceroso blanco (2,3 g, 54% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,47 (s, 1 H), 2,85 (s, 6 H), 2,23 (s, 3 H).

Etapa 2:

A una solución enfriada (-78 ºC) del **compuesto 402** (2,3 g, 8,4 mmol) en Et_2O (25,5 mL) se añadió gota a gota fenil-litio (1,8 M en éter dibutílico, 5,2 mL, 9,3 mmol) manteniendo la temperatura interna a menos de -65 ºC. Se formó un precipitado blanco y la mezcla se volvió espesa. La mezcla se calentó hasta 0 ºC y se agitó durante 30 minutos, se volvió a enfriar hasta -78 ºC y se añadió una solución de 1-cloro-3-yodopropano (2,7 mL, 25,3 mmol) en THF (5,0 mL). La reacción se calentó hasta temperatura ambiente y se agitó durante la noche. La solución se diluyó con EtOAc, se lavó secuencialmente con NH_4Cl saturado y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El producto crudo se purificó por cromatografía flash en gel de sílice, que se eluyó con heptanos/EtOAc (0-20%) y produjo el **compuesto 403** en forma de una goma transparente (2,3 g, 78% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,67 (t, J = 6,3 Hz, 2 H), 3,03 - 2,97 (m, 2 H), 2,95 (s, 6 H), 2,20 (s, 3 H), 2,07 - 1,93 (m, 2 H).

Etapa 3:

Una mezcla del **compuesto 403** (1,82 g, 5,28 mmol), yoduro de potasio (544 mg, 3,27 mmol) y acetato de potasio (1,04 g, 10,6 mmol) en DMSO (13,2 mL) se calentó a 80 ºC durante la noche. La mezcla de reacción se diluyó con EtOAc, se lavó con agua (2x) y salmuera, luego se concentró para obtener una goma. El residuo se disolvió en metanol (26 mL), luego se añadieron agua (870 µL) y K_2CO_3 (737 mg, 5,33 mmol). Después de 30 minutos la reacción se diluyó con EtOAc, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró para obtener el **compuesto 404** en forma de una goma anaranjada amarillenta clara (1,67 g, 97% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 4,57 (t, J = 5,3 Hz, 1 H), 3,47 - 3,37 (m, 2 H), 2,94 (s, 6 H), 2,89 - 2,82 (m, 2 H), 2,19 (s, 3 H), 1,77 - 1,58 (m, 2 H).

Etapa 4:

A una solución del **compuesto 404** (1,1 g, 3,37 mmol), **compuesto 405** (602 mg, 3,54 mmol) y trifenilfosfina (1,11 g, 4,22 mmol) en THF (16,9 mL) se añadió DIAD (859 µL, 4,22 mmol) gota a gota, muy lentamente durante 1,5 horas. Después de agitar a temperatura ambiente durante la noche la reacción se concentró y se purificó por cromatografía flash, que se eluyó con heptanos/EtOAc (0-30%) para obtener el

compuesto 406 en forma de una goma transparente (1,2 g, 74 % de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,91 - 2,05 (m, 2 H), 2,19 (s, 3 H), 2,95 (s, 6 H), 3,04 (dd, *J* = 8,6, 6,8 Hz, 2 H), 3,81 (s, 3 H), 4,04 (t, *J* = 5,8 Hz, 2 H), 7,15 (dd, *J* = 9,2, 4,4 Hz, 1 H), 7,38 (m, 1 H), 7,44 (dd, *J* = 8,8, 3,3 Hz, 1 H).

Etapa 5:

A una solución enfriada (-78 ºC) del **compuesto 406** (1,2 g, 2,51 mmol) en DCM (12,5 mL) se añadió DiBAL (1 M en hexanos, 6,27 mL, 6,27 mmol) gota a gota. Una vez completa la adición completa, la reacción se neutralizó con metanol a -78 ºC. El baño de hielo se retiró, se añadió tartrato de sodio y potasio saturado (5 mL) y el recipiente se rellenó con EtOAc. Una vez que se formó una solución transparente, la mezcla bifásica se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró para obtener el **compuesto 407** en forma de una goma transparente (1,2 g, 100% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ ,95 - 2,05 (m, 2 H), 2,14 - 2,23 (m, 3 H), 2,87 - 2,99 (m, 6 H), 2,98 - 3,09 (m, 2 H), 3,91 - 4,01 (m, 2 H), 4,50 (d, *J* = 5,8 Hz, 2 H), 5,15 (t, *J* = 5,7 Hz, 1 H), 6,83 - 6,92 (m, 1 H), 6,92 - 7,03 (m, 1 H), 7,14 (dd, *J* = 9,6, 3,3 Hz, 1 H).

Etapa 6:

A una solución del **compuesto 407** (660 mg, 1,47), **compuesto 123** (493 mg, 1,47 mmol) y trifenifosfina (481 mg, 1,83 mmol) en THF (9,8 mL) se añadió DIAD gota a gota durante 1 hora. Después de agitar a temperatura ambiente durante 1 hora, la solución se concentró y se purificó por cromatografía flash, que se eluyó con heptanos/EtOAc (0-40%) para obtener el **compuesto 408** (660 mg, 60% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,40 (s, 9 H), 1,98 - 2,10 (m, 2 H), 2,19 (s, 3 H), 2,96 (s, 6 H), 3,02 - 3,12 (m, 2 H), 4,07 (t, *J* = 5,5 Hz, 2 H), 5,12 (s, 2 H), 6,98 - 7,06 (m, 1 H), 7,13 (td, *J* = 8,7, 3,3 Hz, 1 H), 7,36 (dd, *J* = 9,2, 3,2 Hz, 1 H), 7,78 (d, *J*=1,8 Hz, 1 H), 8,16 (d, *J* = 1,8 Hz, 1 H), 9,01 (s, 1 H).

Etapa 7:

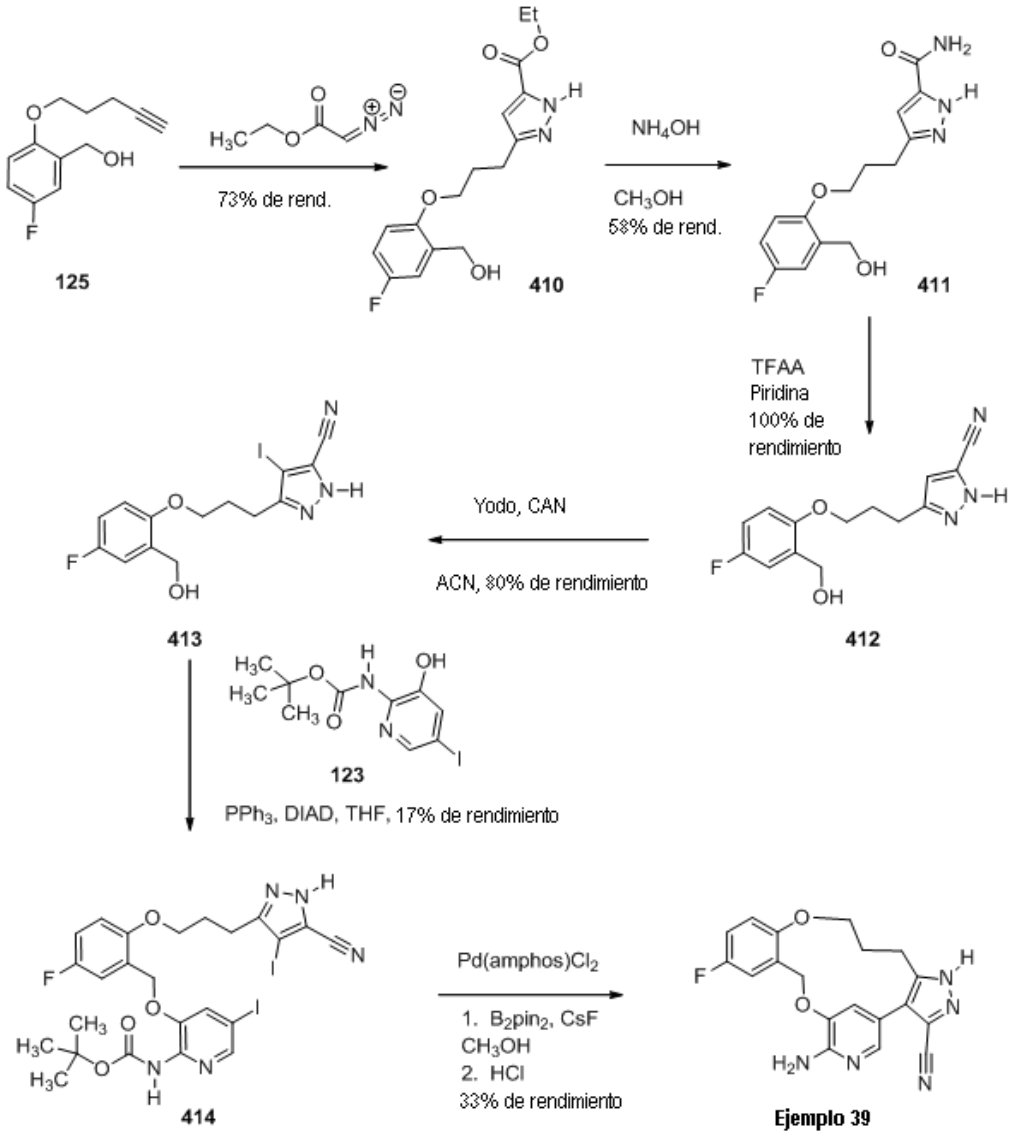
Una solución caliente (60 ºC) del **compuesto 408** (569 mg, 0,740 mmol), éster pinacólico de diboro (752 mg, 2,96 mmol) y fluoruro de cesio 1 N (3,7 mL) en MeOH (37 mL) se burbujeó con nitrógeno. Se añadió una solución de bis(di-*ter*-butil(4-dimetilaminofenil)fosfina)-dicloropaladio (II) (79 mg, 0,11 mmol) en tolueno (0,5 mL). La mezcla se calentó a 60 ºC durante 30 minutos, luego se diluyó con EtOAc, se lavó con salmuera (2x), se secó ($MgSO_4$), se filtró, se concentró y se purificó por cromatografía flash, que se eluyó con DCM/MeOH (0-6%). Las fracciones que contenían el producto deseado se concentraron y los sólidos resultantes se suspendieron en 25% de

EtOAc/heptanos. Los sólidos se recolectaron por filtración al vacío para obtener el **compuesto 409** en forma de un sólido de color crema (170 mg, 41% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ1,46 (s, 9 H), 2,31 (s, 5 H), 2,91 - 3,06 (m, 8 H), 4,19 (br s, 2 H), 5,29 (br s, 2 H), 7,04 - 7,23 (m, 2 H), 7,39 (dd, J = 8,9, 2,9 Hz, 1 H), 7,69 (d, J = 1,5 Hz, 1 H), 7,94 (d, J = 1,5 Hz, 1 H), 8,85 (s, 1 H).

Etapa 8:

A una solución del compuesto **409** (170 mg, 0,303 mmol) en dioxano (3,0 ml) se añadió HCl (4 N en dioxano, 1,52 mL, 6,06 mmol). Se añadió metanol (0,5 mL) y la solución se calentó a 40 ºC. Después de 4 horas, la mezcla de reacción se diluyó con EtOAc, se lavó con bicarbonato de sodio saturado y salmuera, se secó ($MgSO_4$), se filtró, se concentró. El residuo se suspendió en DCM y los sólidos se recolectaron por filtración al vacío para dar el **Ejemplo 38** en forma de un sólido blanco (62 mg, 58% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,19 (s, 5 H), 2,71 - 2,98 (m, 2 H), 4,04 (br s, 2 H), 5,18 (br s, 2 H), 5,56 (s, 2 H), 6,99 - 7,16 (m, 2 H), 7,19 - 7,35 (m, 2 H), 7,48 (s, 1 H), 12,32 (br s, 1 H). LCMS *m/z* 355 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-2,16,17,18-tetrahidro-10H-8,4-(meteno)pirazolo[3,4-e][1,12,9]benzodioxazaciclopentadecin-3-carbonitrilo (Ejemplo 39).



Etapa 1:

El diazoacetato de etilo (2,44 mL, 23,5 mmol) y el **compuesto 125** (4,45 g, 21,4 mmol) se calentaron a 100 ºC en un tubo sellado durante 2 días. El producto crudo se purificó por cromatografía flash, que se eluyó con heptanos/EtOAc (0-75%) para obtener el **compuesto 410** en forma del pirazol regioisomérico mayor (5,0 g, mezcla 4:1 de regioisómeros, 73% de rendimiento).

Etapa 2:

En un tubo sellado una solución del **compuesto 410** (5,0 g, 16 mmol) en MeOH (31 mL) se calentó a 60 ºC durante 1 hora. El hidróxido de amonio se añadió y la solución se calentó a 60 ºC durante la noche. La mezcla de reacción se enfrió hasta 0 ºC y los sólidos se recolectaron por filtración al vacío para obtener un único

regioisómero del **compuesto 411** (2,7 g, 58% de rendimiento).

Etapa 3:

A una mezcla enfriada (0 ºC) del **compuesto 411** (1,50 g, 5,11 mmol) en piridina (26 mL) se añadió TFAA (2,87 mL, 20,5 mmol) gota a gota. Después de 1 hora a 0 ºC la solución se diluyó con EtOAc, se lavó con $NaHCO_3$ saturado (2x), salmuera, HCl 1 N (2x), salmuera, se secó (Na_2SO_4), se filtró y se concentró. El residuo se disolvió en 20% de MeOH/DCM y se pasó a través de un cartucho SCX y el licor madre se concentró para obtener el **compuesto 412** (1,4 g, 100% de rendimiento). ^{1}H RMN (400 MHz ,DMSO-d_6) δ 13,71 (br s, 1 H), 7,14 (dd, *J* = 3,1, 9,4 Hz, 1 H), 7,03 - 6,94 (m, 1 H), 6,94 - 6,88 (m, 1 H), 6,76 (s, 1 H), 4,48 (s, 2 H), 3,96 (t, *J* = 6,0 Hz, 2 H), 2,82 (t, *J* = 7,7 Hz, 2 H), 2,12 - 1,96 (m, 2 H).

Etapa 4:

A una solución del **compuesto 412** (1,4 g, 5,1 mmol) y nitrato de cerio y amonio (1,95 g, 3,56 mmol) en ACN (45 mL) se añadió una solución de yodo (904 mg, 3,56 mmol) en ACN (5 mL). La reacción se calentó a 60 ºC y se agitó durante 2 horas. La mezcla de reacción se diluyó con EtOAc, se lavó con $Na_2S_2O_3$ saturado (2x) y salmuera, se secó (Na_2SO_4), se filtró y se concentró. El producto crudo se purificó por cromatografía flash, que se eluyó con heptanos/EtOAc (0-50%) para obtener el **compuesto 413** (1,2 g, 80% puro) que contiene 20% del aldehído. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,15 (dd, *J* = 3,1, 9,4 Hz, 1 H), 7,02 - 6,94 (m, 1 H), 6,91 - 6,87 (m, 1 H), 4,50 (s, 2 H), 3,94 (t, *J* = 5,9 Hz, 2 H), 2,81 (t, *J* = 7,6 Hz, 2 H), 2,08 - 1,99 (m, 2 H).

Etapa 5:

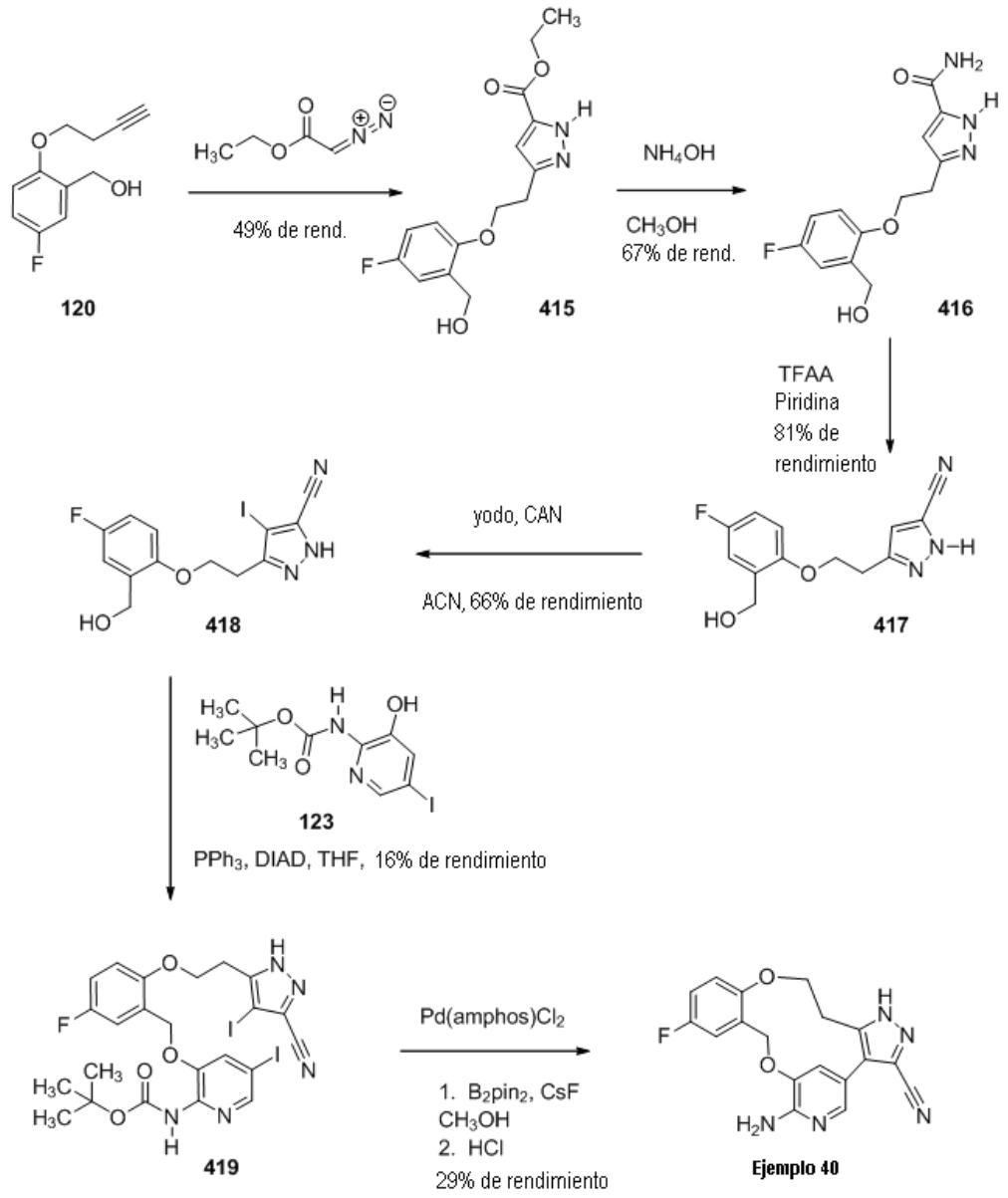
A una solución del **compuesto 413** (500 mg, 80% puro, 1,0 mmol), **compuesto 123** (340 mg, 1,0 mmol) y trifenilfosfina (327 mg, 1,25 mmol) en THF (6,7 mL) se añadió DIAD (254 µL, 1,25 mmol) gota a gota durante 1 hora. Una vez completa la reacción por LCMS, la solución se concentró y se purificó por cromatografía flash, que se eluyó con heptanos/EtOAc (0 - 50%). Las fracciones que contenían el producto deseado se concentraron y los sólidos se trituraron con Et_2O para obtener el **compuesto 414** (125 mg, 17% de rendimiento). ^{1}H RMN (400 MHz ,DMSO-d_6) δ 1,40 (s, 9 H), 1,99 - 2,15 (m, 2 H), 2,85 (t, *J* = 7,4 Hz, 2 H), 4,02 (t, *J* = 5,7 Hz, 2 H), 5,12 (s, 2 H), 7,02 (dd, *J* = 9,2, 4,4 Hz, 1 H), 7,13 (td, *J* = 8,8, 3,2 Hz, 1 H), 7,35 (dd, *J* = 9,2, 3,2 Hz, 1 H), 7,80 (d, *J* = 1,5 Hz, 1 H), 8,15 (d, *J* = 1,5 Hz, 1 H), 9,00 (s, 1 H), 14,14 (br s, 1 H).

Etapa 6:

En un vial sellado una mezcla del **compuesto 414** (120 mg, 0,17 mmol), éster

pinacólico de diboro (212 mg, 0,84 mmol) y fluoruro de cesio (127 mg, 0,835 mmol) en MeOH (8,4 mL) y agua (0,80 mL) se burbujeó con nitrógeno. Una solución de bis(di-*ter*-butil(4-dimetilaminofenil)fosfin)dicloropaladio (II) (18 mg, 0,025 mmol) en tolueno (0,5 mL) se añadió. La mezcla se calentó a 60 ºC durante 1 hora, luego se diluyó con EtOAc, se lavó con salmuera (2x), se secó (Na_2SO_4), se filtró, se concentró. El residuo se disolvió en DCM (1 mL) y se añadió HCl (4 N en dioxano, 1 mL, 4,2 mmol). Después de agitar a temperatura ambiente durante la noche, la reacción se concentró y se purificó por cromatografía flash, que se eluyó con DCM/7 N NH_3 MeOH (0-6%). Las fracciones que contenían el producto deseado se concentraron y los sólidos resultantes se trituraron con Et_2O para obtener el **Ejemplo 39** (20 mg, 33% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 2,23 (br s, 2 H), 3,03 (br s, 2 H), 3,55 - 4,55 (m, 2 H), 5,21 (br s, 2 H), 5,90 (s, 2 H), 7,04 - 7,16 (m, 2 H), 7,30 (dd, *J* = 8,9, 2,4 Hz, 1 H), 7,38 (d, *J* = 2,0 Hz, 1 H), 7,75 (d, *J* = 1,8 Hz, 1 H), 13,88 (br s, 1 H). LCMS *m/z* 366 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-16,17-dihidro-1H,10H-8,4-(meteno)pirazolo-[3,4-d][1,11,8]benzodioxazaciclotetradecin-3-carbonitrilo (Ejemplo 40).



Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 39** se usó para preparar el **compuesto 415** (1,6 g, 49% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ□□1,28 (t, J = 7,0 Hz, 3 H), 3,07 (br. s, 2 H), 4,13 - 4,22 (m, 2 H), 4,25 (d, J = 6,6 Hz, 2 H), 4,40 (s, 2 H), 4,95 - 5,34 (m, 1 H), 6,63 (br. s, 1 H), 6,89 - 7,06 (m, 2 H), 7,13 (dd, J = 9,4, 2,6 Hz, 1 H), 13,29 (br s, 1 H).

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 39** se usó para preparar el **compuesto 416** (930 mg, 67% de rendimiento). ^{1}H RMN (400 MHz ,DMSO-d_6) δ 12,97 (br s, 1 H), 7,38 (br s, 1 H), 7,18 - 7,05 (m, 2 H), 7,02 - 6,90 (m, 2

H), 6,49 (s, 1 H), 5,19 (t, *J* = 5,4 Hz, 1 H), 4,41 (d, *J* = 5,0 Hz, 2 H), 4,18 (t, *J* = 6,4 Hz, 2 H), 3,06 (t, *J* = 5,9 Hz, 2 H).

Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 39** se usó para preparar el **compuesto 417** (700 mg, 81% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,10 (t, *J* = 6,2 Hz, 2 H), 4,19 (t, *J* = 6,3 Hz, 2 H), 4,37 (s, 2 H), 6,82 (s, 1 H), 6,91 - 7,05 (m, 2 H), 7,13 (dd, *J* = 9,6, 3,0 Hz, 1 H), 13,77 (br s, 1 H).

Etapa 4:

El procedimiento descrito en la etapa 4 para el **Ejemplo 39** se usó para preparar el **compuesto 418** (630 mg, 66% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,10 (t, *J* = 6,2 Hz, 2 H), 4,20 (t, *J* = 6,2 Hz, 2 H), 4,34 (s, 2 H), 6,91 - 7,05 (m, 2 H), 7,13 (dd, *J* = 9,4, 3,2 Hz, 1 H).

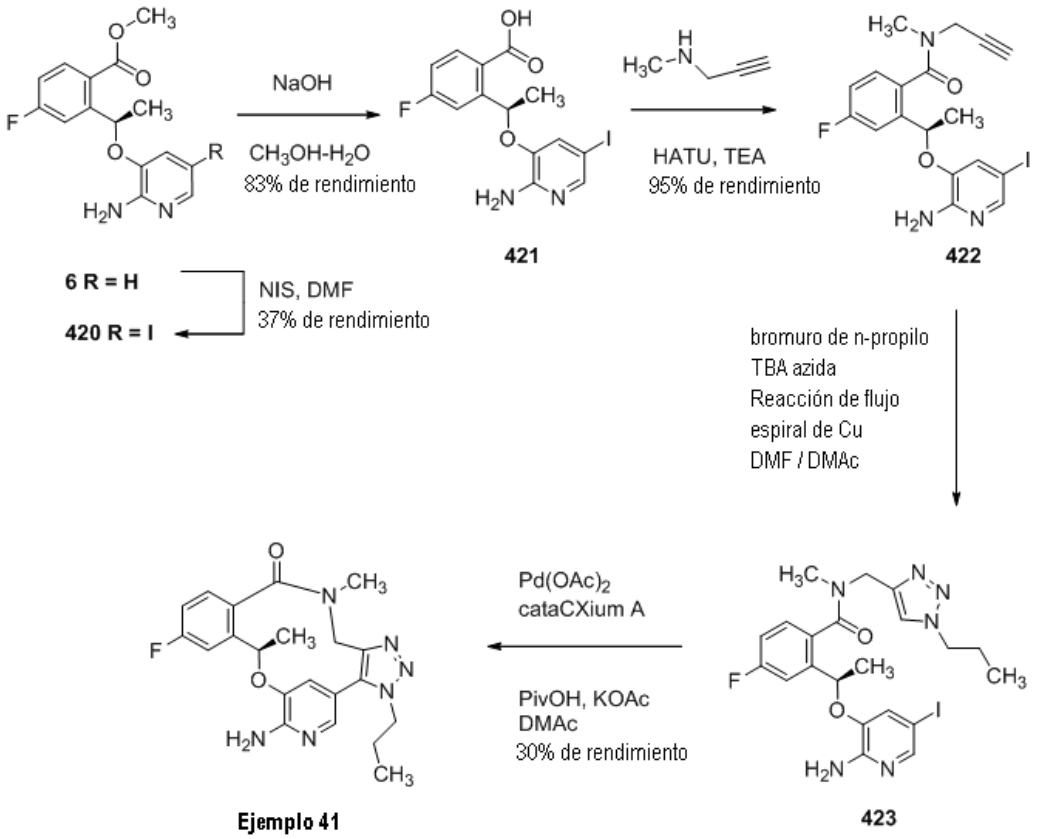
Etapa 5:

El procedimiento descrito en la etapa 5 para el **Ejemplo 39** se usó para preparar el **compuesto 419** (180 mg, 16% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,41 (s, 9 H) 3,16 (t, *J* = 6,2 Hz, 2 H) 4,25 (t, *J* = 6,3 Hz, 2 H) 5,00 (s, 2 H) 6,96 - 7,19 (m, 2 H) 7,33 (dd, *J* = 9,3, 3,0 Hz, 1 H) 7,74 (d, *J* = 1,8 Hz, 1 H) 8,17 (d, *J* = 1,8 Hz, 1 H) 9,03 (s, 1 H) 14,23 (br s, 1 H).

Etapa 6:

El procedimiento descrito en la etapa 6 para el **Ejemplo 39** se usó para preparar el **Ejemplo 40** (25 mg, 29% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 3,06 - 3,17 (m, 2 H), 4,51 (br s, 2 H), 5,19 (br s, 2 H), 5,54 (br s, 2 H), 7,02 - 7,19 (m, 2 H), 7,37 (dd, *J* = 9,1, 3,0 Hz, 1 H), 7,67 (d, *J* = 1,8 Hz, 1 H), 7,86 (d, *J* = 1,8 Hz, 1 H), 13,46 (s, 1 H). LCMS ES *m/z* 352 $[M+H]^+$.

Preparación de (10*R*)-7-amino-12-fluoro-10,16-dimetil-3-propil-16,17-dihidro-3*H*-8,4-(meteno)[1,2,3]triazolo[4,5-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 41).



Etapa 1:

El **compuesto 6** (7,6 g, 26,2 mmol) se disolvió en DMF (76 mL) para dar una solución marrón que se enfrió hasta -5 ºC en una atmósfera de nitrógeno. *N*-yodosuccinimida (5,9 g, 26,2 mmol) se añadió en porciones (7 porciones) sin detectar una exotermia observable. Después de calentar hasta temperatura ambiente, una TLC (50% de EtOAc/heptano) mostró que el **compuesto 6** estaba presente. La mezcla de reacción se reenfrió hasta 0 ºC y se añadió más NIS (5,6 g, 24,9 mmol) durante 2,5 h. La reacción se neutralizó con 10% de tiosulfato de sodio acuoso (50 mL) y bicarbonato de sodio saturado (30 mL). La mezcla marrón se evaporó hasta obtener un residuo (aproximadamente 60 mL) que se dividió en EtOAc (200 mL) y 10% de tiosulfato de sodio acuoso (200 mL). Después de la separación, la capa orgánica se lavó con bicarbonato de sodio saturado acuoso (100 mL) y luego salmuera (100 mL). La capa acuosa se reextrajo con EtOAc (50 mL). Las capas combinadas de EtOAc se secaron en $MgSO_4$, se filtraron y se evaporaron para dar un residuo oleoso marrón (aproximadamente 7 g). El producto crudo se absorbió en sílice y se purificó por cromatografía en columna (eluyente: 20 a 40% de EtOAc/heptano) y produjo el **compuesto 420** en forma de un sólido marrón (4,0 g, 37% de rendimiento). ^{1}H RMN

(400 MHz, DMSO-d_6) δ 7,88 (1 H, m), 7,57 (2 H, m), 7,21 (1 H, t), 6,91 (1 H, s), 6,13 (1 H, m), 6,10 (2 H, s), 3,85 (3 H, s), 1,51 (3 H, d). LCMS ES *m/z* 417 $[M+H]^+$.

Etapa 2:

A una solución del **compuesto 420** (400 mg, 0,961 mmol) en MeOH, se añadió NaOH 2 M (1,0 mL, 2,0 mmol). La mezcla se agitó a temperatura ambiente. Después de 6 horas, la reacción estaba completa sólo en ~20% por LCMS. Se añadió NaOH 4 M adicional (1,0 mL, 4,0 mmol). La mezcla se agitó a temperatura ambiente. Después de 11 h, la reacción estaba completa. Aproximadamente el 70% del solvente se eliminó a presión reducida y el residuo se ajustó a pH = ~7 con HCl 2 N. El precipitado se recolectó por filtración y se enjuagó con MeOH/agua para obtener el **compuesto 421** en forma de un sólido (321 mg, 83% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,56 (d, *J* = 6,3 Hz, 3 H), 6,19 (br s, 2 H), 6,33 (q, *J* = 6,4 Hz, 1 H), 6,93 (d, *J* = 1,5 Hz, 1 H), 7,23 (td, *J* = 8,5, 2,8 Hz, 1 H), 7,54 (dd, *J* = 10,4, 2,5 Hz, 1 H), 7,61 (d, *J* = 1,8 Hz, 1 H), 7,97 (dd, *J* = 8,7, 5,9 Hz, 1 H), 13,42 (br s, 1 H). LCMS APCI *m/z* 403 $[M+H]^+$.

Etapa 2:

A una solución del compuesto **421** (300 mg, 0,746 mmol), la *N*-metilpropargilamina (57 mg, 0,82 mmol), DIEA (289 mg, 2,24 mmol) en DMF (3 mL) se añadió HATU (340 mg, 0,895). La mezcla resultante se agitó a temperatura ambiente. Después de 1,5 h, la reacción estaba completa sólo ~15%. La mezcla de reacción se calentó hasta 55 °C. Después de 1 h, la reacción estaba completa. El solvente se eliminó a presión reducida. El residuo se diluyó con EtOAc y se lavó con agua, $NaHCO_3$ saturado y salmuera. La capa orgánica se filtró, se concentró y se purificó por cromatografía flash en gel de sílice, que se eluyó con 3% al 50% de EtOAc/heptano y dio el **compuesto 422** en forma de una goma marrón clara (323 mg, 95% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 1,54 (d, *J* = 6,3 Hz, 3 H), 2,85 (s, 3 H), 3,07 (s, 1 H), 4,33 - 4,40 (m, 2 H), 5,35 - 5,50 (m, 1 H), 6,12 (s, 1 H), 7,17 - 7,28 (m, 1 H), 7,30 - 7,37 (m, 1 H), 7,50 (d, *J* = 8,1 Hz, 1 H), 7,62 (d, *J* = 1,8 Hz, 1 H). LCMS APCI *m/z* 454 $[M+H]^+$.

Etapa 3:

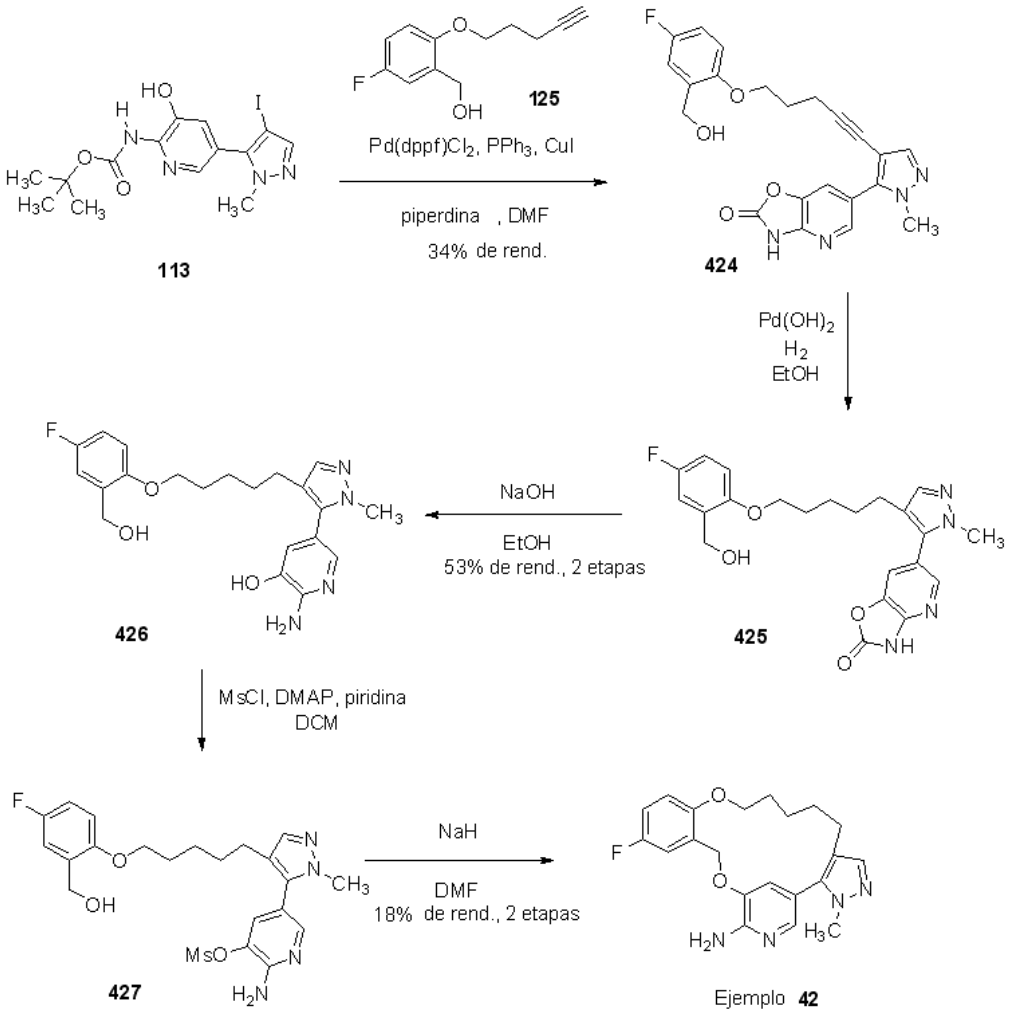
A una solución agitada de 1-bromopropano (0,4 mmol) en DMAc (200 µL) se añadió azida de tetrabutilamonio (0,4 mmol) gota a gota (200 µL/min) en forma de una solución en DMF (400 µL). A esta solución, luego se añadió el compuesto **422** (91 mg, 0,2 mmol) gota a gota (200 µL/min) en forma de una solución en DMAc (200 µL). Después de 30 segundos, el segmento de reacción (800 µL) se inyectó en un

dispositivo de reactor de flujo y se pasó a través de una espiral de tubos de cobre durante 3 minutos a 150 ˚C. El segmento de reacción luego se enfrió y se recolectó por un recolector de fracción disparada por UV (280 nm). El análisis de LCMS de este segmento mostró la presencia de la masa iónica deseada para el **compuesto 423**. LCMS *m/z* 539 $[M+H]^+$.. El solvente se eliminó en una purga de N_2 a 50 ˚C y se usó crudo en la etapa posterior.

Etapa 4:

Al compuesto **423** (108 mg, 0,2 mmol) se añadió DMAc seco desgasificado (3 mL), $Pd(OAc)_2$ (0,0021 mmol), cataCXium® A (0,0042 mmol), ácido piválico (0,0067 mmol) y KOAc (0,167 mmol) en condiciones controladas de caja de guantes (<50 ppm O_2, <50 ppm H_2O). La mezcla de reacción se agitó a 110 ˚C durante 18 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con agua y EtOAc. La capa orgánica se recolectó y se lavó con $NaHCO_3$ saturado y agua. La capa orgánica se filtró y el filtrado se concentró a presión reducida. El producto crudo se purificó por cromatografía en columna en gel de sílice, que se eluyó con 30-90% de EtOAc-heptano y produjo producto impuro. La muestra se repurificó por cromatografía en fase inversa que dio el **Ejemplo 41** en forma de un sólido blanco (16 mg, 30% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,55 - 7,72 (m, 2 H), 7,44 (dd, *J* = 5,7, 8,5 Hz, 1 H), 7,16 (dt, *J* = 2,8, 8,5 Hz, 1 H), 6,77 (s, 1 H), 6,33 (s, 2 H), 5,65 (q, *J* = 7,2, 3,6 Hz, 1 H), 4,51 (d, *J* = 14,4 Hz, 1 H), 4,29 - 4,43 (m, 2 H), 4,15 (d, *J* = 14,7 Hz, 1 H), 2,99 (s, 3 H), 1,73 - 1,83 (m, 2 H), 1,67 (d, *J* = 6,1 Hz, 3 H), 0,78 (t, *J* = 7,3 Hz, 3 H). LCMS APCI *m/z* 412 $[M+H]^+$.

Preparación de 12-fluoro-1-metil-1,4,5,6,7,8-hexahidro-14H-16,20-(meteno) pirazolo[4,3-g][1,14,11]benzodioxazaciclohexadecin-17-amina (Ejemplo 42).



Etapa 1:

Una mezcla de **compuesto 113** (300 mg, 0,72 mmol), **compuesto 125** (300 mg, 1,4 mmol), yoduro cuproso (6,9 mg, 0,036 mmol), trifenilfosfina (9,4 mg, 0,036 mmol) y $PdCl_2(PPh_3)_2$ (50,5 mg, 0,072 mmol) en una mezcla de DMF (4,81 mL) y piperidina (4,81 mL) se burbujeó con nitrógeno y luego se calentó en un baño de aceite hasta 90 °C. Después de 4 horas, la reacción se dejó enfriar y se diluyó con acetato de etilo. La solución se lavó con NH_4Cl acuoso saturado (3 x) y salmuera y las capas orgánicas se secaron sobre $MgSO_4$. La solución se filtró, se concentró y el residuo se sometió a cromatografía en columna en gel de sílice (50-100% EA/heptano) para obtener el **compuesto 424** (102 mg, 34%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 12,69 (br. s., 1 H), 8,22 (d, J =1,77 Hz, 1 H), 7,88 (d, J =1,77 Hz, 1 H), 7,64 (s, 1 H), 7,12 (dd, J = 9,35, 3,28 Hz, 1 H), 6,90 - 6,99 (m, 1 H), 6,82, (dd,

J = 8,84, 4,55 Hz, 1 H), 5,12 (br. s., 1 H), 4,45 (br. s., 2 H), 3,96 (t, *J* = 6,06 Hz, 2 H), 3,80 (s, 3 H), 1,88 (quin, J= 6,51 Hz, 2 H). LCMS *m/z* 423 $[M+H]^+$.

Etapa 2:

El **compuesto 424** (100 mg, 0,237 mmol) se disolvió en etanol (0,5 mL) y se añadió hidróxido de paladio 25 mg, 20% sobre carbón). La mezcla se inundó con nitrógeno y luego se presurizó a 3-4 bar de hidrógeno. La reacción se agitó y se calentó hasta 60 °C durante 12 horas. El recipiente de reacción se dejó enfriar y la LCMS indicó que el producto mayor era el deseado acompañado por cantidades menores de carbamato de etilo. La reacción se filtró a través de un cartucho de Celite para eliminar el catalizador y se lavó con metanol. El filtrado se concentró y al residuo (**compuesto 425**) se añadieron NaOH acuoso 2 N (2 mL) y metanol (0,8 mL). La reacción se calentó hasta 90 °C durante 4 horas, se dejó enfriar y se agitó durante otras 48 horas. La mezcla se diluyó con EtOAc y se lavó con NH_4Cl acuoso saturado. La capa acuosa se ajustó a pH 6 usando HCl 4 N y luego se extrajo con EtOAc. Las capas orgánicas se secaron sobre $MgSO_4$, se concentraron y se purificaron por cromatografía en columna en gel de sílice (0-10% MeOH/DCM) para obtener el **compuesto 426** (5 mg, 53%) en forma de un sólido incoloro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,72 (br. s., 1 H), 7,40 (d, *J* = 1,76 Hz, 1 H), 7,31 (s, 1 H), 7,12 (dd, *J* = 9,57, 3,27 Hz, 1 H), 6,93 - 7,02 (m, 1 H), 6,83 - 6,92 (m, 1 H), 6,79 (d, *J* =1,76 Hz, 1 H), 5,75 (s, 2 H), 5,13 (br. s., 1 H), 4,45 (s, 2 H), 3,88 (t, *J* = 6,42 Hz, 2 H), 3,63 (s, 3 H), 2,31 (t, *J* = 7,55 Hz, 2 H), 1,56 - 1,69 (m, 2 H), 1,41 - 1,56 (m, 2 H), 1,27 - 1,41 (m, 2 H). LCMS *m/z* 401 $[M+H]^+$.

Etapa 3:

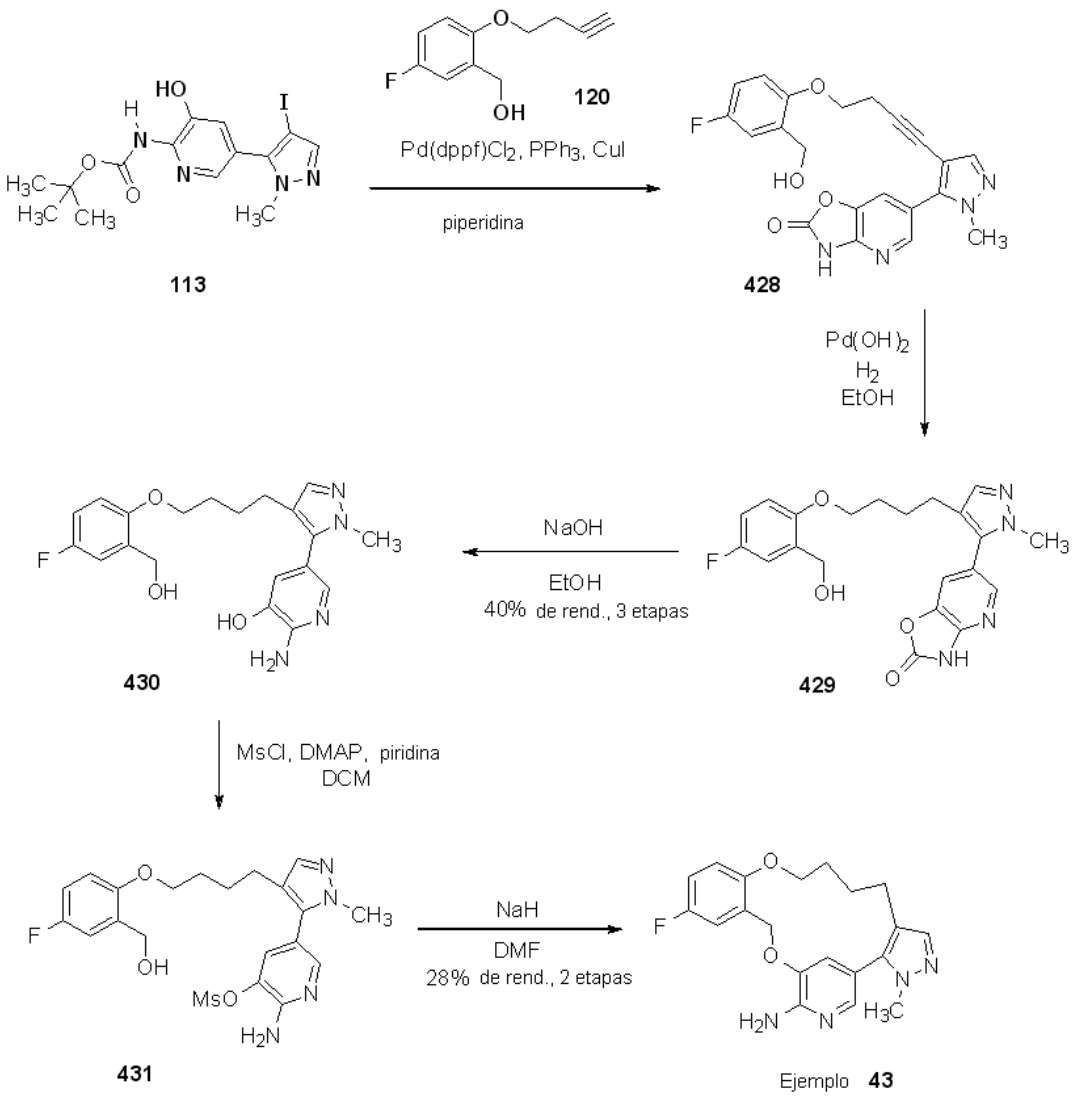
A una solución enfriada a 0 °C de **compuesto 426 en** DCM (500 µL) se añadieron TEA (20,9 µL, 0,15 mmol) y una cantidad catalítica de DMAP (0,6 mg), seguido de una solución de MsCl (9,7 µl, 0,125 mmol) en DCM (250 µL). La reacción se calentó lentamente hasta temperatura ambiente y, después de una hora, la LCMS indicó que el producto deseado era el mayor componente formado. La reacción se diluyó con DCM y se lavó con agua. Las capas orgánicas se secaron ($MgSO_4$), se filtraron y se concentraron. Después de secar durante la noche a alto vacío, el **compuesto 427** (53 mg, 89%), se aisló en forma de un sólido espumoso claro, que se usó sin purificación en la etapa de ciclación. LCMS m/z 479 $[M+H]^+$.

Etapa 4:

A una solución de **compuesto 427** (50 mg, 0,1 mmol) en DMF (2,08 mL) se añadió NaH (5,6 mg, 0,15 mmol, 60% de dispersión). La reacción se calentó hasta 50

ºC durante 3 horas. Se añadió otra porción de NaH (5 mg) y la reacción se calentó durante otra hora. La reacción se diluyó con EtOAc, se lavó con una mezcla de NH_4Cl acuoso saturado / agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía en columna en gel de sílice (0-10% MeOH/DCM) para obtener el **Ejemplo 42** (6 mg, 20%) en forma de un sólido crema amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,55 (s, 1 H), 7,23 - 7,30 (m, 2 H), 7,02 - 7,10 (m, 1 H), 6,95 - 7,02 (m, 1 H), 6,86 (s, 1 H), 5,77 (br. s., 2 H), 5,26 (s, 2 H), 4,01 (t, *J* = 5,41 Hz, 2 H), 3,65 (s, 3 H), 2,30 (t, *J* = 6,29 Hz, 2 H), 1,68 (m, *J* = 5,29 Hz, 2 H) 1,41 - 1,58 (m, 4 H). LCMS APCI *m/z* 383 $[M+H]^+$.

Preparación de 12-fluoro-3-metil-16,17,18,19-tetrahidro-3*H*,10*H*-8,4-(meteno)-pirazolo[4,3-*f*][1,13,10]benzodioxazaciclohexadecin-7-amina (Ejemplo 43)



Etapa 1:

Una mezcla de **compuesto 113** (400 mg, 0,96 mmol), **compuesto 120** (233 mg, 1,2 mmol), yoduro cuproso (9,1 mg, 0,048 mmol), trifenilfosfina (25,2 mg, 0,096 mmol) y $PdCl_2(PPh_3)_2$ (33,7 mg, 0,048 mmol) en piperidina (6,4 mL) se burbujeó con nitrógeno y luego se calentó en un baño de aceite hasta 90 °C. Después de 4 horas, la reacción se dejó enfriar y se diluyó con EtOAc. La solución se lavó con NH_4Cl acuoso saturado (3x) y salmuera, y las capas orgánicas se secaron sobre $MgSO_4$. La solución se filtró, se concentró y el residuo se sometió a cromatografía en columna en gel de sílice (0-10% MeOH/DCM) para obtener el **compuesto 428** en forma de un sólido gomoso contaminado con exceso de piperidina. Este material se usó sin otra purificación en la siguiente etapa. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,22 (s, 1 H), 8,06 (d, *J* = 2,01 Hz, 1 H), 7,64 (s, 1 H) 7,45 (d, *J* = 1,76 Hz, 1 H), 7,13 (dd, *J* = 9,32, 2,77 Hz, 1 H), 6,92 - 7,01 (m, 2 H), 5,13 (br. s., 1 H), 4,48 (d, *J*= 2,27 Hz, 2 H), 4,06 (t, *J* =6,67 Hz, 2 H), 3,82 (s, 3 H), 2,78 (t, *J* =6 .55 Hz, 2 H). LCMS *m/z* 409 $[M+H]^+$.

Etapa 2:

El **compuesto 428** (400 mg, 0,979 mmol) se disolvió en etanol (9,8 mL) y se añadió hidróxido de paladio (40 mg, 20% sobre carbón). La mezcla se inundó con nitrógeno y luego se presurizó bajo 3-4 bar de hidrógeno. La reacción se agitó y se calentó hasta 50 °C durante 18 horas. El recipiente de reacción se dejó enfriar y la LCMS indicó que el producto mayor era el deseado acompañado por cantidades menores de carbamato de etilo. La reacción se filtró a través de un cartucho de Celite para eliminar el catalizador y se lavó con metanol. El filtrado se concentró, se disolvió en etanol (10 mL) y se añadió NaOH acuoso al 15% (7,83 mL). La reacción se calentó hasta 85 °C durante 12 horas y se dejó enfriar. La mezcla se neutralizó con HCl acuoso 1 N y se extrajo con EtOAc. Las capas orgánicas se secaron sobre $MgSO_4$, se concentraron y se purificaron por cromatografía en columna en gel de sílice (0-10% MeOH/DCM) para obtener el **compuesto 430** (151 mg, 40%) en forma de un sólido incoloro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,72 (br. s., 1 H), 7,41(d, *J* = 1,76 Hz, 1 H), 7,33 (s, 1 H), 7,12 (dd, *J* = 9,44, 3,15 Hz, 1 H), 6,91 - 7,02 (m, 1 H), 6,85 (dd, *J* = 8,81, 4,53 Hz, 1 H), 6,79 (d, *J* = 2,01 Hz, 1 H), 5,75 (s, 2 H), 5,13 (br. s.,1 H), 4,45 (s, 2 H), 3,87 (t, *J* = 6,04 Hz, 2 H), 3,64 (s, 3 H), 2,35 (t, *J* = 7,30 Hz, 2 H), 1,47 - 1,74 (m, 4 H). LCMS *m/z* 387 $[M+H]^+$.

Etapa 3:

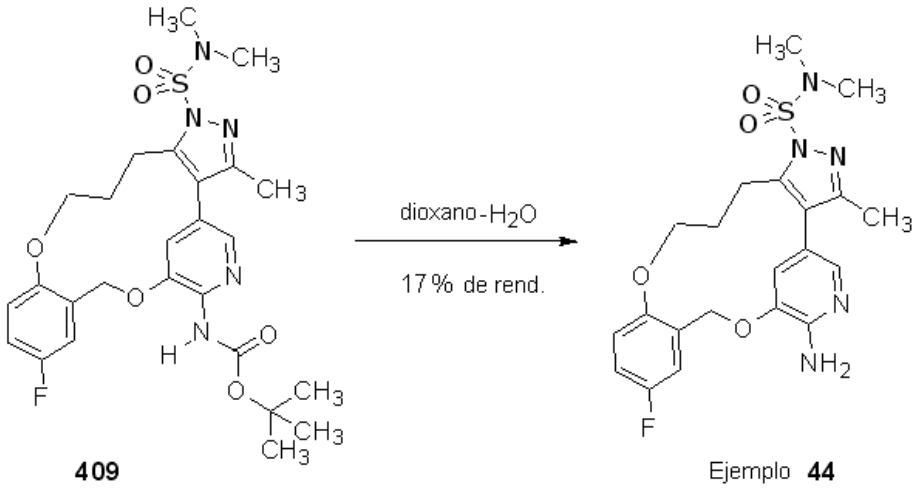
A una solución enfriada a 0 °C de **compuesto 430** (150 mg, 0,388 mmol) en DCM (2 mL) se añadieron TEA (65 µL, 0,47 mmol) y una cantidad catalítica de DMAP (2-3 mg), seguido de una solución de MsCl (30 µL, 0,39 mmol) en DCM (0,5 mL). La

reacción se calentó lentamente hasta temperatura ambiente. Después de 2 horas, se añadieron piridina (2 mL) y MsCl (15 µL, 0,2 mmol) a la reacción, que se dejó agitar durante otra hora. La reacción se diluyó con EtOAc y se lavó con NH_4Cl acuoso saturado y salmuera. Las capas orgánicas se secaron ($MgSO_4$), se filtraron y se concentraron. Después de secarlo durante la noche a alto vacío, el **compuesto 431** (156 mg, 86%) se aisló en forma de una goma anaranjada que se usó sin purificación en la etapa de ciclación.

Etapa 4:

A una solución de **compuesto 431** (156 mg, 0,34 mmol) en DMF (2,08 mL) se añadió NaH (13,4 mg, 0,34 mmol, 60% de dispersión). La reacción se calentó hasta 50 ºC durante 2 horas. La reacción se diluyó con EtOAc, se lavó con una mezcla de NH_4Cl acuoso saturado / agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía en columna en gel de sílice (0-8% MeOH/DCM) para obtener el **Ejemplo 43** (40 mg, 32%) en forma de un sólido crema amarillo. ^{1}H RMN (400 MHz, 80 ºC, DMSO-d_6) δ 7,50 - 7,57 (m, 2 H), 7,29 - 7,33 (m, 2 H), 7,01 - 7,09 (m, 1 H), 6,92 - 7,00 (m, 1 H), 5,77 (br. s., 2 H), 5,28 (s, 2 H), 4,02 (t, *J* = 5,54 Hz, 2 H), 3,69 (s, 3 H), 2,18 - 2,34 (m, 2 H), 1,71 - 1,89 (m, 4 H). LCMS APCI *m/z* 369 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-*N*,*N*,3-trimetil-17,18-dihidro-10*H*-8,4-(meteno)-pirazolo[3,4-*e*][1,12,9]benzodioxazaciclopentadecin-1(16*H*)-sulfonamida (Ejemplo 44)

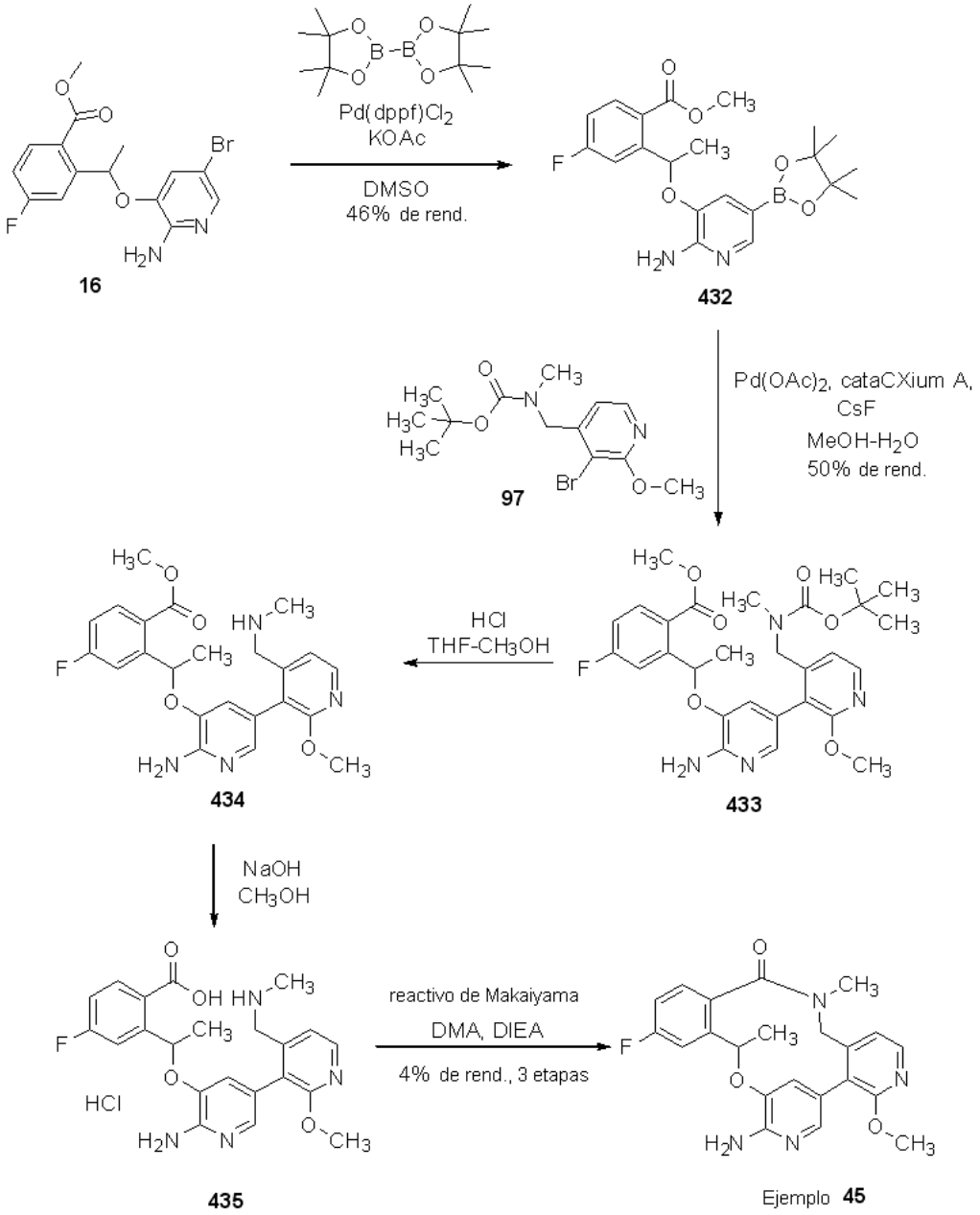


409 Ejemplo **44**

El **compuesto 409** (30 mg, 0,053 mmol) se disolvió en dioxano/agua (500 µL/50 µL) y se calentó hasta 100 ºC durante 14 horas. La reacción se concentró y se

purificó por cromatografía en columna en gel de sílice (0-60% de EtOAc/DCM), seguido de HPLC de fase inversa para obtener el **Ejemplo 44** (13 mmol, 17% - determinado por análisis de ELSD de solución de DMSO), que se sometió directamente a análisis. ^{1}H RMN (600 MHz, DMSO-d_6) δ 7,51 (d, *J* = 1,65 Hz, 1 H), 7,37 (dd, *J* =8,78, 2,74 Hz, 1 H), 7,33 (d, *J*=1,65 Hz, 1 H), 7,07 - 7,17 (m, 2 H), 5,85 (s, 2H), 5,22 (s, 2 H), 4,18 (m, *J* = 4,94 Hz, 2 H), 2,96 (s, 6 H), 2,88 (br. s., 2 H), 2,30 (s, 2 H), 2,24 (s, 3 H). LCMS ES *m/z* 462 $[M+H]^+$.

Preparación de 8-amino-13-fluoro-4-metoxi-11,17-dimetil-17,18-dihidro-9,5-(meteno)pirido[3,4-*h*][2,5,11]benzoxadiazaciclotetradecin-16(11*H*)-ona (Ejemplo 45)



Etapa 1:

Una mezcla de material de partida bromo **compuesto 16** (1,364 g, 3,70 mmol,), bis(pinacolato)diboro (1,44 g, 5,54 mmol), KOAc (1,27 g, 12,9 mmol), $Pd(dppf)Cl_2$ (272 mg, 0,333 mmol) y DMSO anhidro (17 mL) se agitó a temperatura ambiente durante 10 minutos para obtener una suspensión anaranjada oscura. La mezcla se calentó luego hasta 80 °C durante 5 horas. Se añadió EtOAc a la mezcla seguido de Si-Thiol. La suspensión se dejó enfriar hasta temperatura ambiente con agitación. Después de 30 minutos, la mezcla se filtró y los sólidos se lavaron con EtOAc. El filtrado (anaranjado

claroscuro) se diluyó con EtOAc, y se lavó con agua (2x) y luego con salmuera. Las capas acuosas se reextrajeron con EtOAc (2x). Las capas orgánicas se combinaron y se lavaron con HCl 1 M. Las capas acuosas se recolectaron y luego se enfriaron hasta 0 °C y se neutralizaron con NaOH 10 M (ac) a pH = 7. La suspensión se extrajo con EtOAc y las capas orgánicas se combinaron y se lavaron con salmuera. La capa orgánica luego se secó (Na_2SO_4), se filtró y se concentró para obtener 1,42 g de material crudo en forma de un sólido marrón. El material se disolvió en una cantidad mínima de EtOAc y luego se añadió heptano. Se formó un precipitado. La mezcla se dejó reposar durante 1 hora y luego se filtró y se lavó con heptano para obtener el **compuesto 432** (702,2 mg, 46%) en forma de un sólido marrón claro. ^{1}H RMN (600 MHz, DMSO-d_6) δ 7,94 (dd, *J* = 8,80, 5,87 Hz, 1 H), 7,74 (s, 1 H), 7,68 (dd, *J* = 10,56, 2,35 Hz, 1 H), 7,25 (td, *J* = 8,36, 2,64 Hz, 1 H), 6,87 (s, 1 H), 6,36 (s, 2 H), 6,26 (q, *J* = 6,46 Hz, 1 H), 3,91 (s, 3 H), 1,57 (d, *J* = 5,87 Hz, 3 H), 1,21 (d, J = 5,87 Hz, 12 H).

Etapa 2:

A un vial de microondas se añadió el **compuesto 97** (100 mg, 0,3 mmol), el **compuesto 432** (189 mg, 0,45 mmol), fluoruro de cesio (138 mg, 0,91 mmol), cataCXium A (12,9 mg, 0,036 mmol), acetato de paladio (8,1 mg, 0,036 mmol), metanol (3 mL) y agua (0,3 mL). La mezcla de reacción se desgasificó y el vial se selló y se calentó hasta 80 °C durante 2 horas. La mezcla se diluyó con EtOAc, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía en columna en gel de sílice (20-50% de EtOAc/Heptano, luego 5-10% de MeOH/EtOAc) para obtener el **compuesto 433** (82 mg, 50%) en forma de una goma marrón. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,96 - 8,10 (m, 2 H), 7,46 (d, *J* = 13,64 Hz, 1 H), 7,27 - 7,35 (m, 1 H), 7,00 (t, *J* = 7,33 Hz, 1 H), 6,75 (d, *J* = 5,31 Hz, 1 H), 6,51 (br. s., 1 H), 6,30 - 6,37 (m, 1 H), 4,96 (br. s., 2 H), 3,87 (s, 3 H), 3,66 - 3,77 (m, 3 H), 2,53 - 2,68 (m, 3 H), 1,63 - 1,69 (m, 3 H), 1,41 (br. s., 9 H). LCMS *m/z* 541 $[M+H]^+$.

Etapa 3:

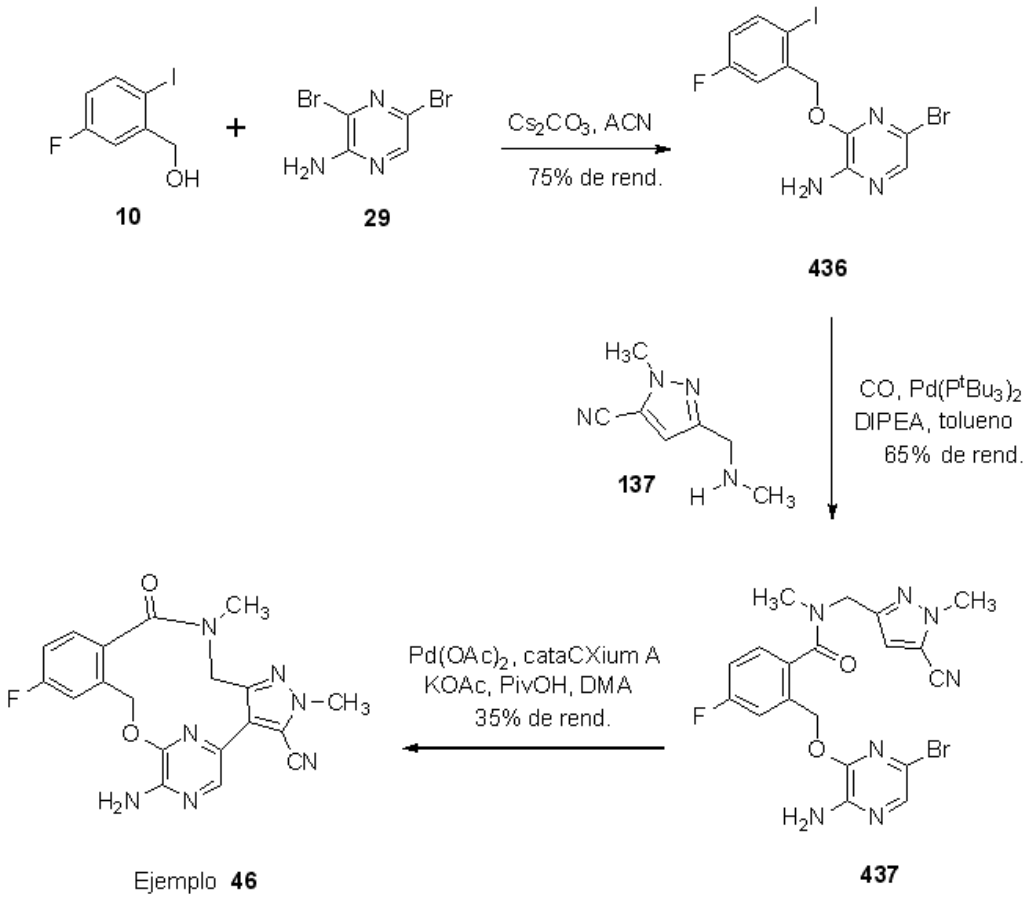
El **compuesto 433** (82 mg, 0,15 mmol) se disolvió en THF (1 mL) y MeOH (0,3 mL), antes de añadir 38% de HCl (0,1 mL). La reacción se calentó usando un baño de aceite a 50 °C durante 4 horas. La reacción se dejó enfriar hasta temperatura ambiente y se añadió NaOH acuoso al 50% hasta alcanzar el pH = 12 (~0,2 mL). Se añadieron 0,3 mL de MeOH y la reacción se calentó a 50 °C durante 1 hora. La reacción se concentró y se sometió a liofilización. El sólido se filtró y se lavó con EtOAc, seguido de MeOH/CH_2Cl_2, y los filtrados se concentraron para obtener el

compuesto 435 (126 mg) en forma de un sólido blanco, que se usó en la siguiente etapa sin otra purificación.

Etapa 4:

El **compuesto 435** (65 mg, 0,15 mmol) se disolvió en DMA (15 mL) y la solución se enfrió hasta 0 °C. Se añadió DIEA (53 µL, 0,3 mmol), seguido de CMPI (43,1 mg, 0,17 mmol) y la mezcla se agitó a 0 °C durante 30 minutos. La mezcla de reacción se diluyó con agua y se sometió a liofilización. El sólido se lavó con EtOAc y MeOH/CH_2Cl_2, los filtrados se concentraron y se purificaron por HPLC de fase inversa para obtener el **Ejemplo 45** (2,38 mg, 4%) en forma de un sólido blanquecino. ^{1}H RMN (400 MHz, Acetona-d_6) δ 8,03 - 8,15 (m, 1 H), 7,59 (dd, *J* = 10,11, 2,53 Hz, 1 H), 7,53 (d, *J* = 2,02 Hz, 1 H), 7,31 (dd, *J* = 8,46, 5,68 Hz, 1 H), 7,19 (s, 1 H), 6,96 - 7,06 (m, 2 H), 5,76 - 5,85 (m, 1 H), 5,47 (s, 1 H), 4,28 (s, 2 H), 3,79 - 3,87 (m, 3 H), 3,06 (s, 3 H), 1,69 - 1,74 (m, 3 H). LCMS APCI *m/z* 409 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-2,16-dimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(azeno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 46)



Etapa 1:

El **compuesto 10** (1,89 g, 7,5 mmol), **compuesto 29** (2,28 g, 9 mmol) y carbonato de cesio (6,11 g, 18,7 mmol) se combinaron en acetonitrilo (75 mL) y se calentaron a 80 °C durante 18 horas. Se añadió la suspensión cruda a salmuera (400 mL) y los sólidos resultantes de color hollín se recolectaron por filtración y se enjuagaron con agua. Los sólidos parcialmente secos se recristalizaron en acetonitrilo caliente (~200 mL) para obtener el **compuesto 436** (2,37 g, 75%) en forma de un sólido anaranjado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,92 (dd, 1 H), 7,58 - 7,69 (m, 2 H), 7,05 (td, J = 8,65, 3,24 Hz, 1 H), 6,69 (s, 2 H), 5,27 (s, 2 H). LCMS *m/z* 423/425 $[M+H]^+$.

Etapa 2:

El **compuesto 436** (450 mg, 1,06 mmol), **compuesto 137** (155 mg, 0,30 mmol), DIEA (0,578 mL, 3,32 mmol) y Pd (P^tBu_3)$_2$ (43,3 mg, 0,083 mmol) se disolvieron en tolueno (40 mL) en una bomba de acero inoxidable y se calentaron hasta 85 °C bajo 4 bar de presión de CO durante 15 horas. La mezcla se concentró y

se purificó por cromatografía en columna en gel de sílice (25-100% de EtOAc/heptano) para obtener el **compuesto 437** (255 mg, 65%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, 80ºC, DMSO-d_6) δ ppm 7,64 (s, 1 H), 7,51 (dd, *J* = 10,20, 2,64 Hz, 1 H), 7,40 (dd, *J* = 8,31, 5,79 Hz, 1 H), 7,15 - 7,32 (m, 1 H), 6,94 (s, 1 H), 6,23 (br. s., 2 H), 5,34 (s, 2 H), 4,13 - 4,83 (m, 2 H), 3,95 (s, 3 H), 2,87 (br. s., 3 H). LCMS *m/z* 474/476 $[M+H]^+$.

Etapa 3:

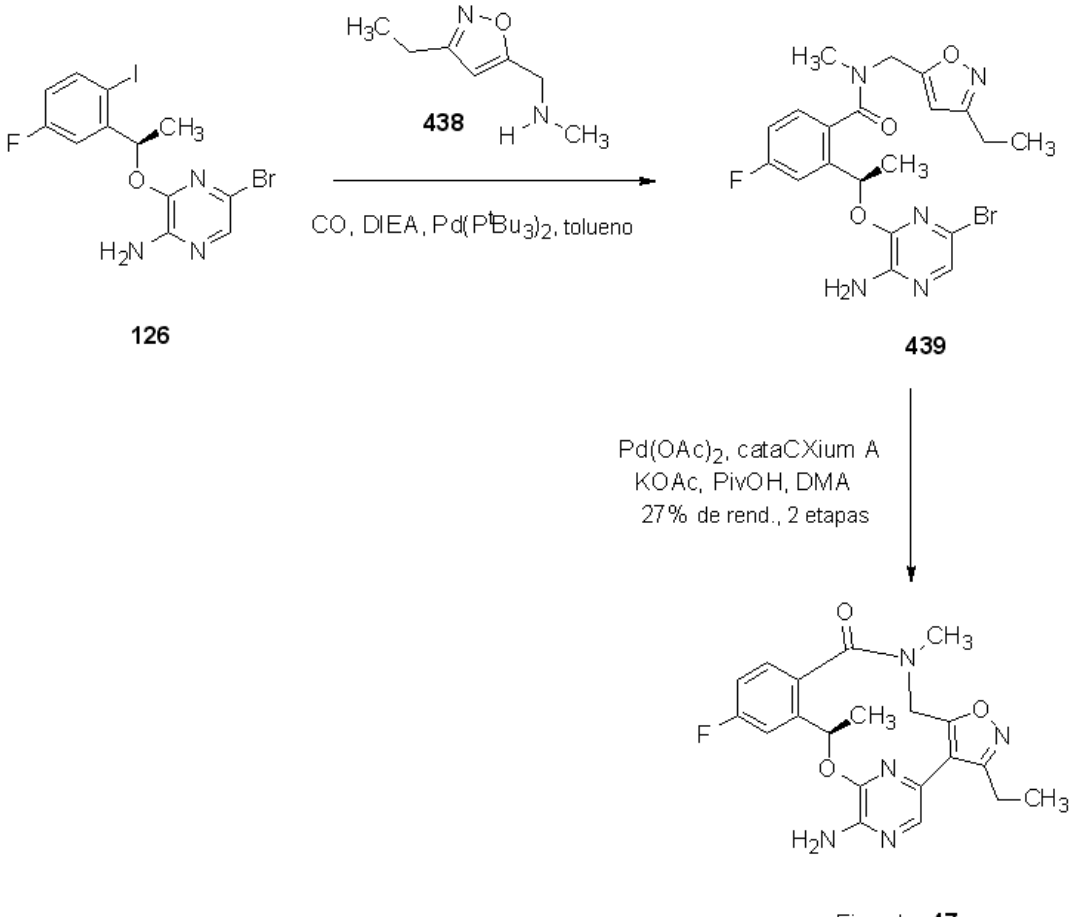
El **compuesto 437** (125 mg, 0,264 mmol), cataCXium A (29,2 mg, 0,079 mmol), acetato de paladio (9 mg, 0,04 mmol), KOAc (130 mg, 1,32 mmol) y ácido piválico (8,1 mg, 0,079 mmol) se disolvieron en DMA (5,29 mL) en un vial de microondas. El vial se inundó con nitrógeno y se calentó en el microondas a 150 ºC durante 1 hora. La mezcla se diluyó con agua y los sólidos se eliminaron por filtración. La capa acuosa se extrajo con EtOAc y se lavó con salmuera. Los sólidos se combinaron con las capas orgánicas y se secaron sobre $MgSO_4$. Las capas orgánicas se filtraron y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice (25-100% 3:1 DCM en heptanos/5% de MeOH en EtOAc). La trituración de las fracciones que contenían producto con MTBE produjo el **Ejemplo 46** (36 mg, 35%) en forma de un sólido incoloro como una mezcla de atropisómeros. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,80 (s, 1 H), 7,35 - 7,53 (m, 2 H), 7,19 (td, *J* = 8,50, 2,64 Hz, 1 H), 6,75 (s, 2 H), 5,57 (dd, *J*= 12,46, 1,64 Hz, 1 H), 5,10 (d, *J* = 12,59 Hz, 1 H), 4,23 - 4,50 (m, 2 H), 4,04 (s, 3 H), 2,88 (s, 3 H). LCMS APCI *m/z* 394 $[M+H]^+$.

La separación quiral analítica por SFC se llevó a cabo usando una columna Chiralpak OD-H (4,6 mm x 250 mm, tamaño de partícula de 5 micrones), que se eluyó con 30% de MeOH en CO_2 mantenido a 35 ºC a 140 bar. Una tasa de flujo de 3 mL/minutos produjo $Rt_{(pico\ 1)}$ = 4,85 minutos y $Rt_{(pico\ 2)}$ = 5,79 minutos.

Ejemplo 46 (Atropisómero pico 1): 99% ee. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,79 (s, 1 H), 7,37 - 7,56 (m, 2 H), 7,19 (td, *J* = 8,46, 2,78 Hz, 1 H), 6,77 (s, 2 H), 5,57 (dd, *J* = 12,51, 1,64 Hz, 1 H), 5,10 (d, *J* = 12,38 Hz, 1 H), 4,25 - 4,41 (m, 2 H), 4,04 (s, 3 H), 2,88 (s, 3 H).

Ejemplo 46 (Atropisómero pico 2): 96% ee. ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7,79 (s, 1 H), 7,37 - 7,53 (m, 2 H), 7,19 (td, *J* = 8,53, 2,65 Hz, 1 H), 6,77 (s, 2 H), 5,57 (dd, *J* = 12,38, 1,52 Hz, 1 H), 5,10 (d, *J* = 12,63 Hz, 1 H), 4,24 - 4,47 (m, 2 H), 4,04 (s, 3 H), 2,88 (s, 3 H).

Preparación de (10*R*)-7-amino-3-etil-12-fluoro-10,16-dimetil-16,17-dihidro-8,4-(azeno)[1,2]oxazolo[4,5-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 47)



Ejemplo **47**

Etapa 1:

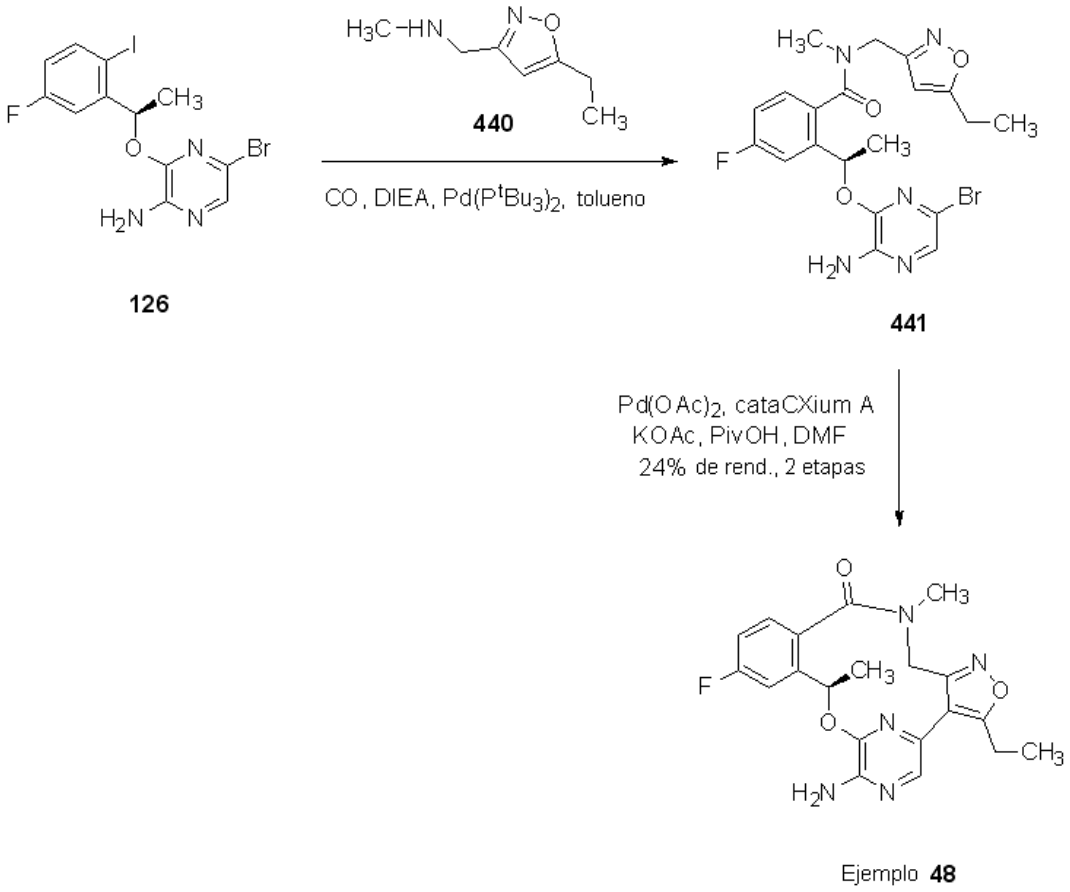
El **compuesto 126** (286 mg, 0,653 mmol), **compuesto 438** (115 mg, 0,653 mmol), DIEA (0,455 mL, 2,61 mmol), Pd ($P^tBu_3)_2$ (33,9 mg, 0,05 mmol) se disolvieron en tolueno (20 mL) en un recipiente de acero inoxidable. El reactor se presurizó en 4 bar de CO y se calentó hasta 85 °C durante 14 horas. La mezcla de reacción se diluyó con EtOAc, se lavó con agua, NH_4Cl acuoso saturado y salmuera. Las capas orgánicas se secaron ($MgSO_4$) y se concentraron. El residuo de **compuesto 439** se usó en la siguiente etapa sin otra purificación.

Etapa 2:

El **compuesto 439** (312 mg, 0,653 mmol), KOAc (320 mg, 3,26 mmol) y ácido piválico (16,8 mg, 0,163 mmol) se combinaron en DMF (4,35 mL) y la solución se

purgó con nitrógeno. Luego se añadieron $Pd(OAc)_2$ (14,6 mg, 0,065 mmol) y cataCXium A (48,4 mg, 0,131 mmol) y la reacción se calentó hasta 150 ºC durante 45 minutos en el microondas. La reacción se diluyó con EtOAc, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró. La purificación por HPLC de fase inversa produjo el **Ejemplo 47** (71 mg, 27%) en forma de un sólido incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,31 - 7,25 (m, 3 H), 7,08 (dt, *J* = 2,6, 8,2 Hz, 1 H), 6,30 - 6,22 (m, 1 H), 4,57 (d, *J* = 13,6 Hz, 1 H),4,41 (d, *J* = 13,4 Hz, 1 H), 3,12 (s, 3 H), 3,01 - 2,77 (m, 2 H), 1,84 (d, *J* = 6,6 Hz, 3 H), 1,39 (t, *J* = 7,6 Hz, 3 H). LCMS APCI *m/z* 398 $[M+H]^+$.

Preparación de (10*R*)-7-amino-3-etil-12-fluoro-10,16-dimetil-16,17-dihidro-8,4-(azeno)[1,2]oxazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 48)



Etapa 1:

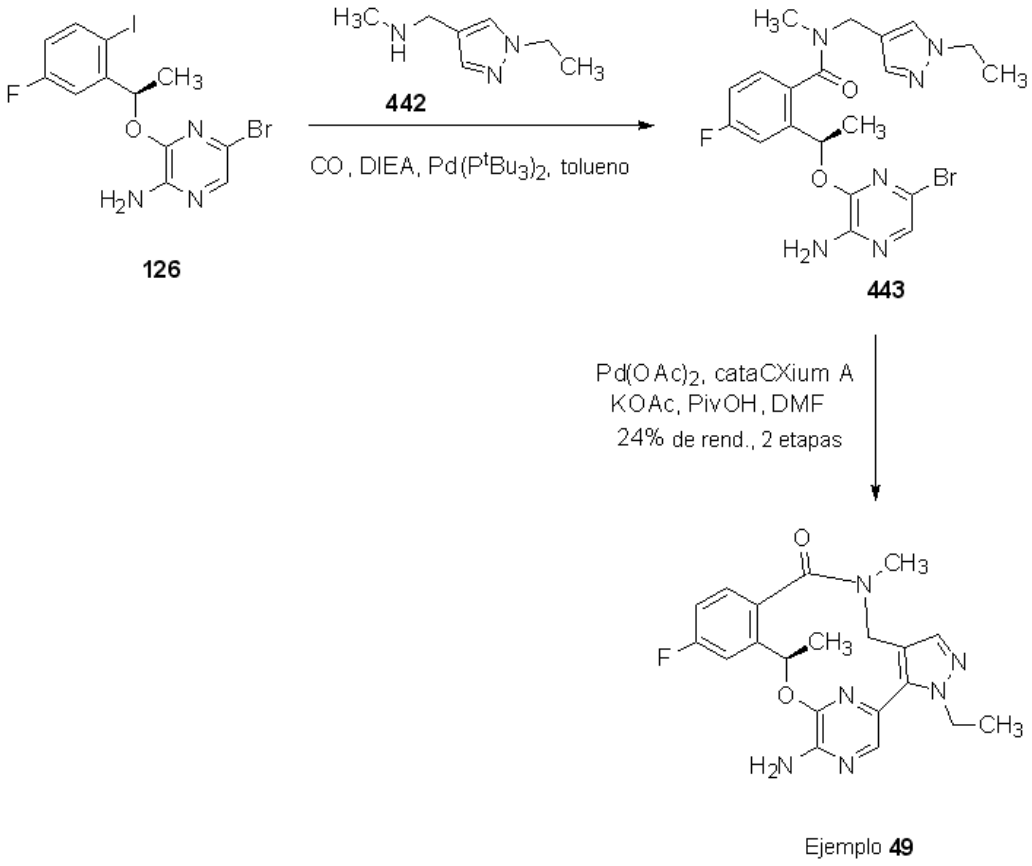
El **compuesto 126** (285 mg, 0,650 mmol), **compuesto 440** (115 mg, 0,650 mmol), DIEA (0,453 ml, 2,61 mmol), Pd (P^{t}Bu$_3$)$_2$ (33,9 mg, 0,05 mmol) se disolvieron

en tolueno (20 mL) en un recipiente de acero inoxidable. El reactor se presurizó en 4 bar de CO y se calentó hasta 85 °C durante 14 horas. La mezcla de reacción se diluyó con EtOAc, se lavó con agua, NH_4Cl acuoso saturado y salmuera. Las capas orgánicas se secaron ($MgSO_4$) y se concentraron. El residuo de **compuesto 441** se usó en la siguiente etapa sin otra purificación.

Etapa 2:

El **compuesto 441** (311 mg, 0,650 mmol), KOAc (320 mg, 3,26 mmol) y ácido piválico (16,8 mg, 0,163 mmol) se combinaron en DMF (5 mL) y la solución se purgó con nitrógeno. Luego se añadieron $Pd(OAc)_2$ (14,6 mg, 0,065 mmol) y cataCXium A (48,6 mg, 0,131 mmol) y la reacción se calentó hasta 150°C durante 45 minutos en el microondas. La reacción se diluyó con EtOAc, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró. La purificación por HPLC de fase inversa produjo el **Ejemplo 48** (62 mg, 24%) en forma de un sólido incoloro. ^{1}H RMN (400 MHz ,$CDCl_3$) δ 7,66 (s, 1 H), 7,31 - 7,27 (m, 1 H), 7,21 (dd, *J* = 5,5, 8,4 Hz, 1 H), 7,01 (dt, *J* = 2,6, 8,3 Hz, 1 H), 6,16 -6,03 (m, 1 H), 5,01 (br. s., 2 H), 4,67 (d, *J* = 14,1 Hz, 1 H), 4,33 (d, *J* = 14,1 Hz, 1 H), 3,11 (s, 3 H), 2,95 - 2,75 (m, 2 H), 1,76 (d, *J* = 6,6 Hz, 3 H),1,34 (t, *J* = 7,5 Hz, 3 H). LCMS APCI *m/z* 398 $[M+H]^+$.

Preparación de (10*R*)-7-amino-3-etil-12-fluoro-10,16-dimetil-16,17-dihidro-3*H*-8,4-(azeno)pirazolo[3,4-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 49)



Ejemplo **49**

Etapa 1:

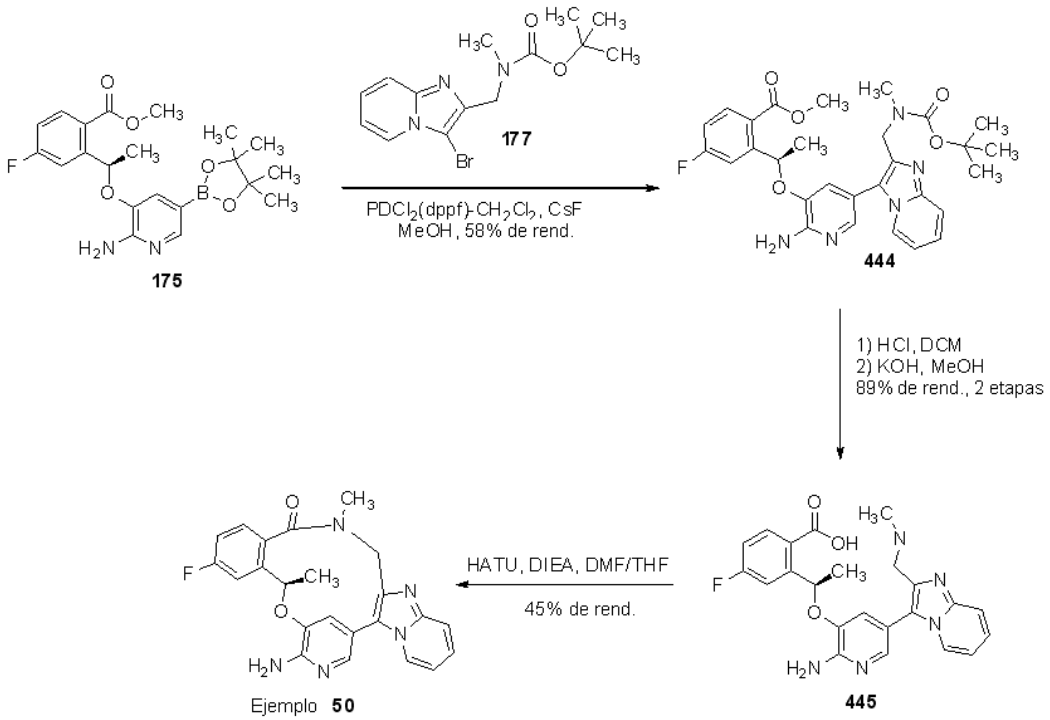
El **compuesto 126** (314 mg, 0,718 mmol), **compuesto 442** (100 mg, 0,718 mmol), DIEA (0,5 mL, 2,87 mmol) y Pd ($P^tBu_3)_2$ (37,5 mg, 0,072 mmol) se disolvieron en tolueno (20 mL) en un recipiente de acero inoxidable. El reactor se presurizó en 4 bar de CO y se calentó hasta 85 °C durante 14 horas. La mezcla de reacción se diluyó con EtOAc, se lavó con agua, NH_4Cl acuoso saturado y salmuera. Las capas orgánicas se secaron ($MgSO_4$) y se concentraron. El residuo de **compuesto 443** se usó en la siguiente etapa sin otra purificación. LCMS m/z 477/479 $[M+H]^+$.

Etapa 2:

El **compuesto 443** (258 mg, 0,540 mmol), KOAc (265 mg, 2,7 mmol) y ácido piválico (13,9 mg, 0,135 mmol) se combinaron en DMF (4 mL) y la solución se purgó con nitrógeno. Luego se añadieron $Pd(OAc)_2$ (12,1 mg, 0,054 mmol) y cataCXium A (39,9 mg, 0,108 mmol) y la reacción se calentó hasta 150 °C durante 30 minutos en el microondas. La reacción se diluyó con EtOAc, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró. La purificación por HPLC de fase inversa produjo el

Ejemplo 49 (52 mg, 24%) en forma de un sólido incoloro. ^{1}H RMN (400 MHz , DMSO-d_6) δ 7,67 (s, 1 H), 7,60 (s, 1 H), 7,54 (dd, *J* = 2,6, 10,1 Hz, 1 H), 7,31 (dd, *J* = 5,7, 8,4 Hz, 1 H), 7,12 (dt, *J* = 2,6, 8,5Hz, 1 H), 6,75 (s, 2 H), 6,09 - 5,96 (m, 1 H), 4,20 - 4,13 (m, 2 H), 4,13 - 4,04 (m, 2 H), 2,90 (s, 3 H), 1,64 (d, *J* = 6,6 Hz, 3 H), 1,33 (t, *J* = 7,2 Hz, 3H). LCMS APCI *m/z* 397 $[M+H]^+$.

Preparación de (5*R*)-8-amino-3-fluoro-5,19-dimetil-18,19-dihidro-7,11-(meteno)pirido-[2',1':2,3]imidazo[4,5-*h*][2,5,11]benzoxadiazaciclotetradecin-20(5*H*)-ona (Ejemplo 50)



Etapa 1:

Una mezcla de **compuesto 175** (355 mg, 0,852 mmol), **compuesto 177** (348 mg, 1,02 mmol) y CsF (388 mg, 2,56 mmol) en MeOH (10 mL) se purgó con nitrógeno antes de la adición de $PdCl_2(dppf).CH_2Cl_2$ (35,1 mg, 0,043 mmol). La reacción se calentó a 120 °C en el microondas durante 1 hora y luego se dividió en EtOAc y salmuera. La capa acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$) y se redujeron hasta un volumen mínimo. El residuo se purificó por cromatografía en columna en gel de sílice (0-10% de MeOH:

NH_4OH acuoso al 10% / DCM : EtOAc, 1:1) para obtener el **compuesto 444** (272 mg, 58%) del producto en forma de una espuma anaranjada pálida. LCMS m/z 550 $[M+H]^+$.

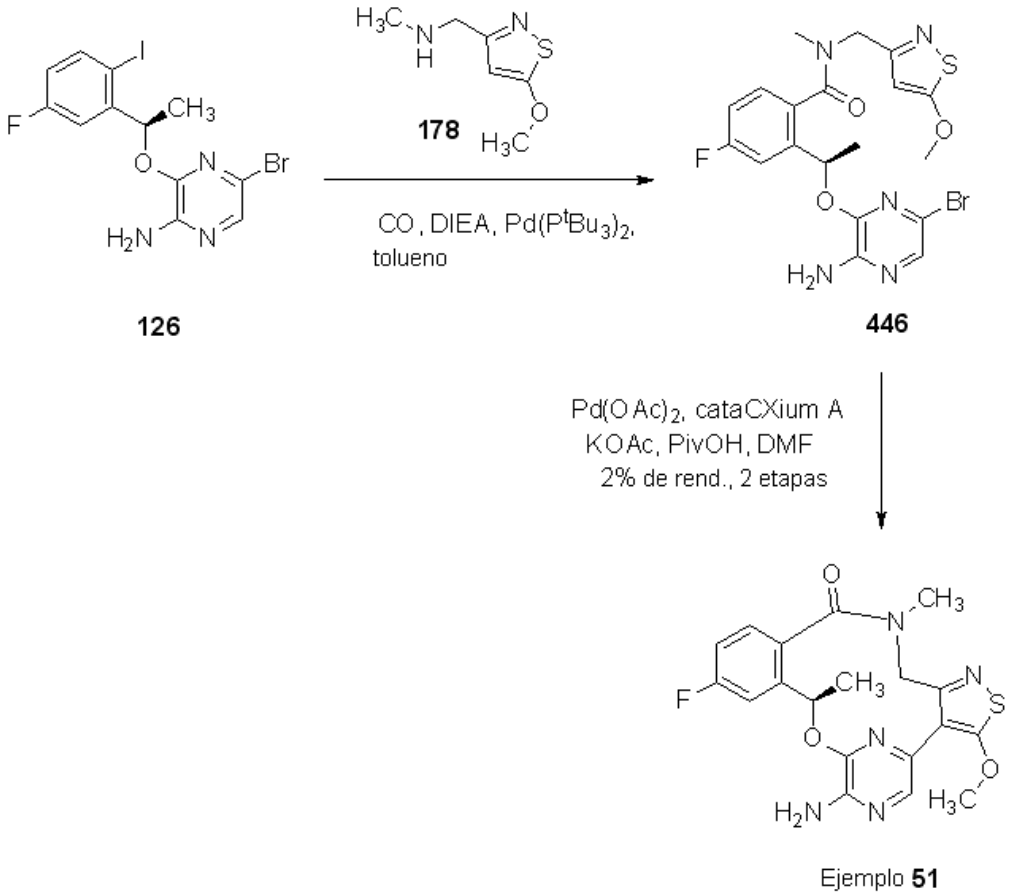
Etapa 2:

A una solución de **compuesto 444** (440 mg, 0,801 mmol) en DCM (4 mL) se añadió HCl (4 mL, 4 M en dioxano, 20 mmol). La mezcla rápidamente se volvió turbia y se formó una suspensión. La mezcla de reacción se agitó a temperatura ambiente durante 4 horas y luego se destiló hasta sequedad. El residuo se azeotropó con MTBE y se secó en un horno de vacío a ~50 °C durante 1 hora para obtener un sólido anaranjado pálido. El sólido se disolvió en MeOH (8 mL) y se añadió KOH sólido (378 mg, 6,74 mmol). La suspensión resultante se agitó a 50 °C durante la noche. El pH de la suspensión resultante se ajustó a 5-6 por adición gota a gota de HCl 6 N. La reacción se filtró y el filtrado se concentró al vacío. El residuo se azeotropó con tolueno para obtener un sólido marrón, que se secó en el horno de vacío a 50 °C durante 1 hora para obtener el **compuesto 445** (401 mg, 89%), que se usó sin purificación.

Etapa 3:

A una solución de HATU (439 mg, 1,12 mmol) en DMF /THF(20 mL/4 mL) a 0 °C se añadió gota a gota una solución de **compuesto 445** (348 mg, 0,8 mmol) y DIEA (0,7 mL, 4 mmol) en DMF /THF (20 mL/4 mL). La adición duró 35 minutos. Después de la adición, la mezcla resultante se agitó a 0 °C durante 20 minutos. La mezcla se vertió en $NaHCO_3$ acuoso (400 mL). La mezcla se filtró y el filtrado se extrajo con EtOAc (3x). Las capas combinadas de EtOAc se lavaron con agua (2x) y salmuera (1x), se secaron sobre $MgSO_4$ y se concentraron al vacío para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice (0-10% de metanol/DCM:EtOAc 1:1). Las fracciones deseadas se concentraron al vacío para obtener un residuo, que se trituró con MTBE para obtener el **Ejemplo 50** (164 mg, 45%) en forma de un sólido blanquecino. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,52 (d, 1 H), 7,79 (d, J = 1,52 Hz, 1 H), 7,59 - 7,70 (m, 2 H), 7,46 (dd, J = 8,59, 5,81 Hz, 1 H), 7,28 (ddd, J = 9,03, 6,76, 1,14 Hz, 1 H), 7,17 (td, J = 8,46, 2,78 Hz, 1 H), 6,94 (td, J = 6,82, 1,01 Hz, 1 H), 6,89 (d, J = 1,52 Hz, 1 H), 6,18 (s, 2 H), 5,62 - 5,82 (m, 1 H), 4,47 (d, J = 13,89 Hz, 1 H), 4,31 (d, J = 13,89 Hz, 1 H), 3,06 (s, 3 H), 1,69 (d, J = 6,32 Hz, 3 H). LCMS APCI *m/z* 418 $[M+H]^+$.

Preparación de (10*R*)-7-amino-12-fluoro-3-metoxi-10,16-dimetil-16,17-dihidro-8,4-(azeno)[1,2]tiazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 51)



Ejemplo **51**

Etapa 1:

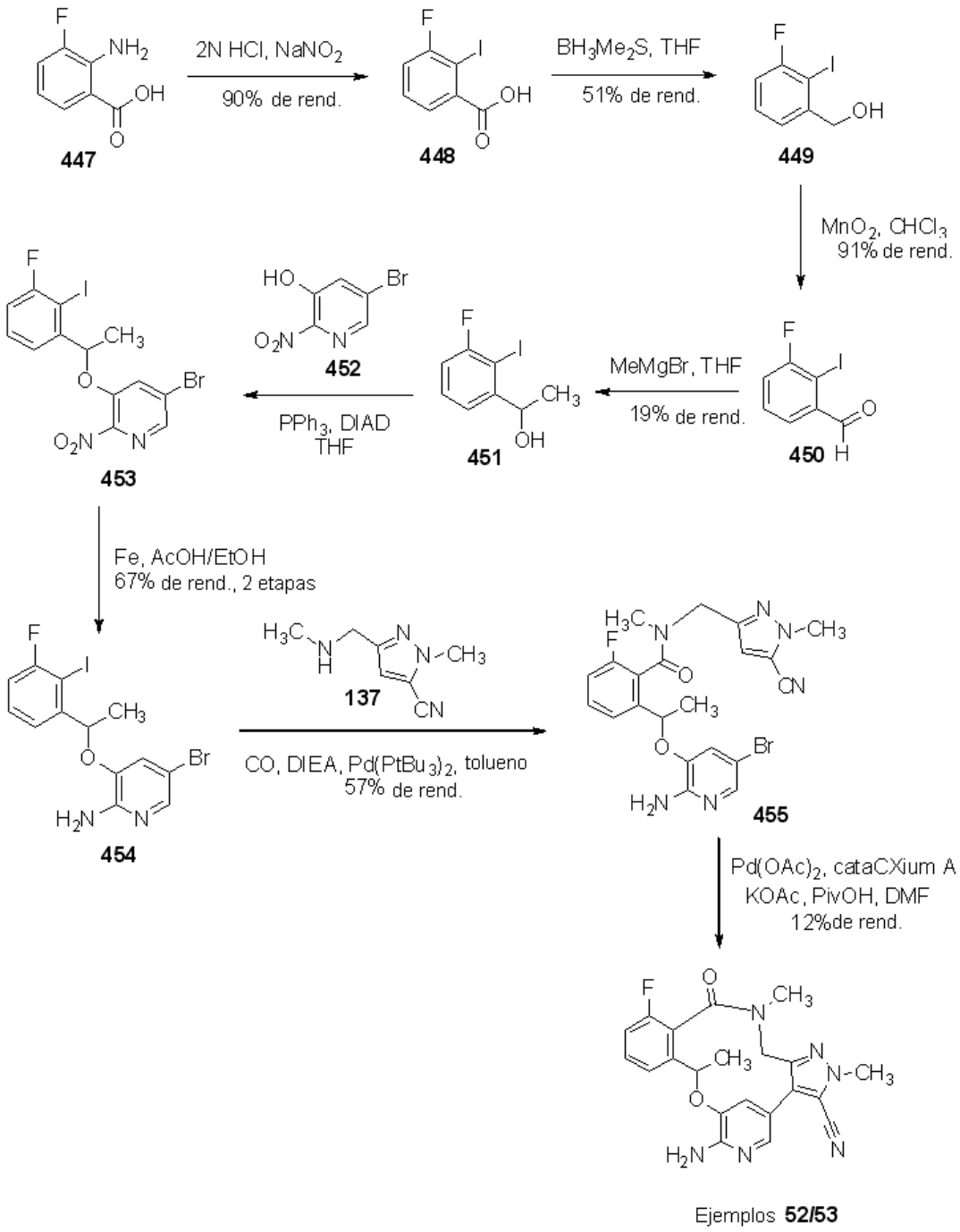
El **compuesto 126** (442 mg, 1,01 mmol), **compuesto 178** (197 mg, 1,01 mmol), DIPEA (0,704 mL, 4,04 mmol) y Pd (P^{t}Bu$_3$)$_2$ (52,7 mg, 0,101 mmol) se disolvieron en tolueno (20 mL) en un recipiente de acero inoxidable. El reactor se presurizó en 4 bar de CO y se calentó hasta 85 °C durante 14 horas. La mezcla de reacción se diluyó con EtOAc, se lavó con agua, NH_4Cl acuoso saturado y salmuera. Las capas orgánicas se secaron ($MgSO_4$) y se concentraron. El residuo del **compuesto 446** se usó en la siguiente etapa sin otra purificación. LCMS APCI *m/z* 497 $[M+H]^+$.

Etapa 2:

El **compuesto 446** (440 mg, 0,886 mmol), KOAc (435 mg, 4,43 mmol) y ácido piválico (22,9 mg, 0,222 mmol) se combinaron en DMF (9 mL) y la solución se purgó con nitrógeno. Luego se añadieron $Pd(OAc)_2$ (20 mg, 0,089 mmol) y cataCXium A (65,4 mg, 0,177 mmol) y la reacción se calentó hasta 120 °C durante 60 minutos en el microondas. La reacción se diluyó con EtOAc, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró. La purificación por HPLC de fase inversa produjo el

Ejemplo 51 (5,2 mg, 2%) en forma de un sólido incoloro. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,71 (s, 1 H), 7,51 (dd, *J* = 2,5, 10,1 Hz, 1 H), 7,38 (dd, *J* = 5,8, 8,6 Hz, 1 H), 7,14 (dt, *J* = 2,5, 8,6 Hz, 1 H), 6,50 (s, 2 H), 5,99 - 5,85 (m, 1 H), 4,36 (d, *J* = 12,8 Hz, 1 H), 4,18 (d, *J* = 12,8 Hz, 1 H), 4,08 (s, 3 H), 2,94 (s, 3 H), 1,63 (d, *J* = 6,5 Hz, 3 H). LCMS APCI *m/z* 416 $[M+H]^+$.

Preparación de 7-amino-14-fluoro-2,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplos 52 y 53)



Ejemplos **52/53**

Etapa 1:

A una solución enfriada (0 ºC) de **compuesto 447** (2,5 g, 166 mmol) en HCl acuoso 2 N (32 mL) se añadió una solución de $NaNO_2$ (1,14 g, 16,1 mmol) en 16 mL de agua, manteniendo la temperatura interna a 0-5 ºC. Una vez completa la adición, la mezcla se agitó a 0 ºC durante 1,5 horas Esta solución luego se añadió gota a gota (manteniendo la temperatura interna <10 ºC), a una mezcla de KI (5,35 g, 32,2 mmol)

y CuI (1,54 g, 8,06 mmol) en agua (16 mL). El baño de hielo se retiró y la reacción se agitó durante la noche. La mezcla se filtró y los sólidos resultantes se suspendieron en MTBE y se calentaron hasta 40 ºC durante 1 hora. Los sólidos se filtraron otra vez, y los filtrados se concentraron para obtener el **compuesto 448** (3,86 g, 90%) en forma de un sólido anaranjado. ^{1}H RMN (400 MHz, DMSO-d_6) δ 13,51 (br. s., 1 H), 7,53 - 7,44 (m, 2 H), 7,43 - 7,32 (m, 1 H).

Etapa 2:

A una solución enfriada (0 ºC) del **compuesto 448** (3,8 g, 14 mmol) en THF (30 mL) se añadió BH_3 Me_2S (28,6 mL. 1 M en THF, 28,6 mmol). El baño de hielo se eliminó y la solución se calentó hasta 60 ºC durante tres horas. La reacción se enfrió hasta temperatura ambiente y se neutralizó con NH_4Cl acuoso saturado. La reacción se extrajo con EtOAc (2x) y las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice (0-50% de EtOAc/heptanos) para obtener el **compuesto 449** (1,82 g, 51%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,42 (dt, J = 5,9, 7,9 Hz, 1 H), 7,31 (d, J = 7,6 Hz, 1 H), 7,14 (t, J = 8,1 Hz, 1 H), 5,53 (t, J = 5,7 Hz, 1 H), 4,45 (d, J = 5,0 Hz, 2 H).

Etapa 3:

A una solución del **compuesto 449** (1,82 g, 7,22 mmol) en $CHCl_3$ (40 mL) se añadió MnO_2 activado (3,77 g, 43,3 mmol). La mezcla se calentó hasta 50 ºC durante la noche, se filtró a través de un filtro de vidrio y se concentró para obtener el **compuesto 450** (1,65 g, 91%) en forma de un sólido amarillo, que se usó sin otra purificación. ^{1}H RMN (400 MHz, DMSO-d_6) δ 10,00 (s, 1 H), 7,66 - 7,61 (m, 1 H), 7,61 - 7,56 (m, 2 H).

Etapa 4:

A una solución enfriada (-78 ºC) de **compuesto 450** (1,65 g, 6,6 mmol) en THF (33 mL) se añadió MeMgBr (6,6 mL, 3 M en éter dietílico, 19,8 mmol). La reacción se agitó durante 2 horas, se neutralizó con NH_4Cl acuoso saturado y luego se extrajo con EtOAc (2x). Las capas orgánicas se secaron sobre $MgSO_4$, se filtraron y se concentraron para obtener una goma marrón anaranjada. Este residuo se purificó por cromatografía en columna en gel de sílice (0-25% de EtOAc/heptano) para obtener el **compuesto 451** (330 mg, 19%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,45 - 7,34 (m, 2 H), 7,13 (dt, J = 1,8, 7,9 Hz, 1 H), 5,49 (d, J = 4,3 Hz, 1 H), 4,90 - 4,81 (m, 1 H), 1,27 (d, J =6,3 Hz, 3 H).

Etapa 5:

A una solución de **compuesto 452** (302 mg, 1,38 mmol) y **compuesto 451** (333 mg, 1,25 mmol) en THF (6 mL) se añadió una solución de PPh_3 (410 mg, 1,56 mmol) y DIAD (330 mg, 1,56 mmol) en THF (6 mL). La reacción se agitó a temperatura ambiente durante 12 horas, se concentró y se purificó por cromatografía en columna en gel de sílice (0-25% de EtOAc/heptano) para obtener el **compuesto 453** (379 mg, 69%) en forma de un sólido incoloro. El material contenía 10-15% de DIAD reducido, pero se usó sin otra purificación en la siguiente etapa. ^{1}H RMN (400 MHz, DMSO-*d*$_6$) δ 8,29 (d, *J* = 1,8 Hz, 1 H), 7,87 (d, *J* = 1,8 Hz, 1 H), 7,48 (dt, *J* = 5,9, 8,0 Hz, 1 H), 7,30 - 7,23 (m, 2 H), 5,92 (q, *J* = 6,3 Hz, 1 H), 1,61 (d, *J* = 6,3 Hz, 3 H).

Etapa 6:

Una mezcla de **compuesto 453** (379 mg, 0,811 mmol) y hierro (453 mg, 8,11 mmol) en AcOH/EtOH (5,4 mL/5,4 mL) se calentó hasta 80 ºC. La reacción estaba completa después de 1,5 horas. Se añadió agua y la reacción se neutralizó con Na_2CO_3 sólido. La reacción se extrajo con EtOAc (2x), se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía en columna en gel de sílice (0-50% de EtOAc/heptano) para obtener el **compuesto 454** (235 mg, 67%) en forma de un sólido blanco. ^{1}H RMN (400MHz, DMSO-*d*$_6$) δ 7,52 (d, *J* = 2,0 Hz, 1 H), 7,47 - 7,37 (m, 1 H), 7,32 (dd, *J* = 1,5, 7,8 Hz, 1 H), 7,20 (dt, *J* = 1,5, 8,1 Hz, 1 H), 6,68 (d, *J* = 2,0 Hz, 1 H), 6,14 (s, 2 H), 5,54 (q, *J* = 6,4 Hz, 1 H), 1,56 (d, *J* = 6,3 Hz, 3 H). LCMS *m/z* 436/438 $[M+H]^+$.

Etapa 7:

El **compuesto 454** (230 mg, 0,526 mmol), **compuesto 137** (103 mg, 0,552 mmol), DIEA (0,366 mL, 2,1 mmol) y $Pd(P^tBu_3)_2$ (27,6 mg, 0,053 mmol) se disolvieron en tolueno (20 mL) en un recipiente de acero inoxidable. El reactor se presurizó en 4 bar de CO y se calentó hasta 85 ºC durante 14 horas. La mezcla de reacción no se mostró completa y se añadió otra vez $Pd(P^tBu_3)_2$ (27,6 mg, 0,053 mmol), y la reacción se calentó a 85 ºC bajo 4 bar de CO durante otras 4 horas. La reacción se diluyó con EtOAc, se lavó con agua, NH_4Cl acuoso saturado y salmuera. Las capas orgánicas se secaron ($MgSO_4$) y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice (0-75% de EtOAc/heptano, luego 0-10% MeOH/DCM) para obtener el **compuesto 455** (198 mg, 57%) en forma de un sólido amarillo.

Etapa 8:

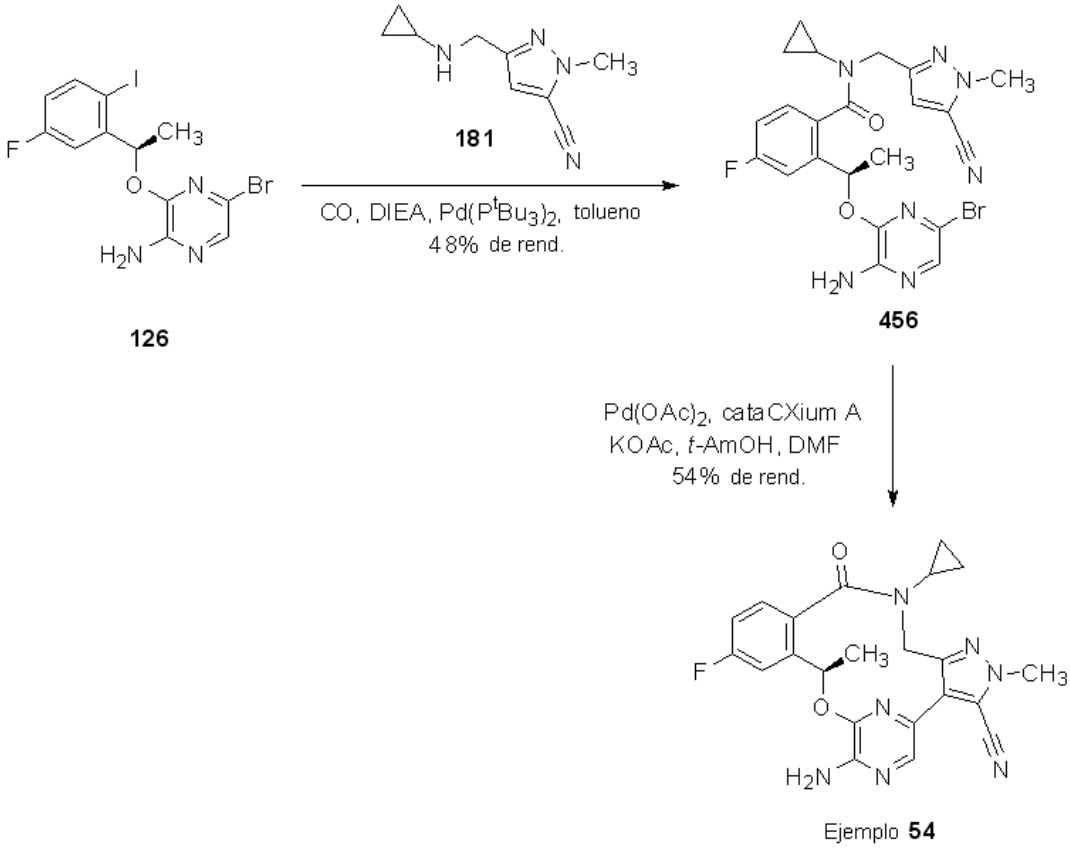
El **compuesto 455** (198 mg, 0,406 mmol), KOAc (199 mg, 2,03 mmol) y ácido piválico (10,5 mg, 0,102 mmol) se combinaron en alcohol *t*-amílico (6,44 mL) y agua (7,3 µL). La solución se purgó con nitrógeno. Luego se añadieron $Pd(OAc)_2$ (5,6 mg,

0,025 mmol) y cataCXium A (18,9 mg, 0,0510 mmol) y la reacción se calentó hasta 150 ºC durante 60 minutos en el microondas. La reacción se diluyó con EtOAc, se lavó con agua y salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía en columna en gel de sílice (0-10% MeOH/DCM) para obtener los **Ejemplos 52 y 53** como una mezcla de enantiómeros (20 mg, 12%), que se sometieron a separación quiral por SFC para obtener ambos enantiómeros del **compuesto** del título. La separación quiral analítica por SFC se llevó a cabo usando una columna Regis Whelk-01 (*R,R*) (columna 4,6 mm x 250 mm, tamaño de partícula de 5 micrones), que se eluyó con 20% de MeOH en CO_2 mantenido a 25 ºC a 140 bar. Una tasa de flujo de 3 mL/min produjo $Rt_{(pico\ 1)}$ = 1,28 minutos y $Rt_{(pico\ 2)}$ = 1,78 minutos.

Ejemplo 52 (pico 1): 5,56 mg, >99% ee, 8,3% de rendimiento. ^{1}H RMN (400MHz ,DMSO-d_6) δ 7,66 - 7,46 (m, 3 H), 7,22 (t, *J* = 8,6 Hz, 1 H), 6,90 (s, 1 H), 6,18 (s, 2 H), 5,55 (q, *J* = 5,9 Hz, 1 H), 4,36 (d, *J* =14,1 Hz, 1 H), 4,24 - 4,16 (m, 1 H), 4,04 (s, 3 H), 3,02 (s, 3 H), 1,67 (d, *J* = 6,0 Hz, 3 H). LCMS ES *m/z* 407 $[M+H]^+$.

Ejemplo 53 (pico 2): 5,06 mg, 90% ee, 7,6% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,62 - 7,55 (m, 2 H), 7,54 - 7,47 (m, 1 H), 7,22 (t, *J* = 8,8 Hz, 1 H), 6,90 (s, 1 H), 6,18 (s, 2 H), 5,55 (q, *J* = 6,1Hz, 1 H), 4,36 (d, *J* = 14,1 Hz, 1 H), 4,24 - 4,15 (m, 1 H), 4,04 (s, 2 H), 3,02 (s, 2 H), 1,67 (d, *J* = 6,3 Hz, 2 H). LCMS ES *m/z* 407 $[M+H]^+$.

Preparación de (10*R*)-7-amino-16-ciclopropil-12-fluoro-2,10-dimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(azeno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 54)



Etapa 1:

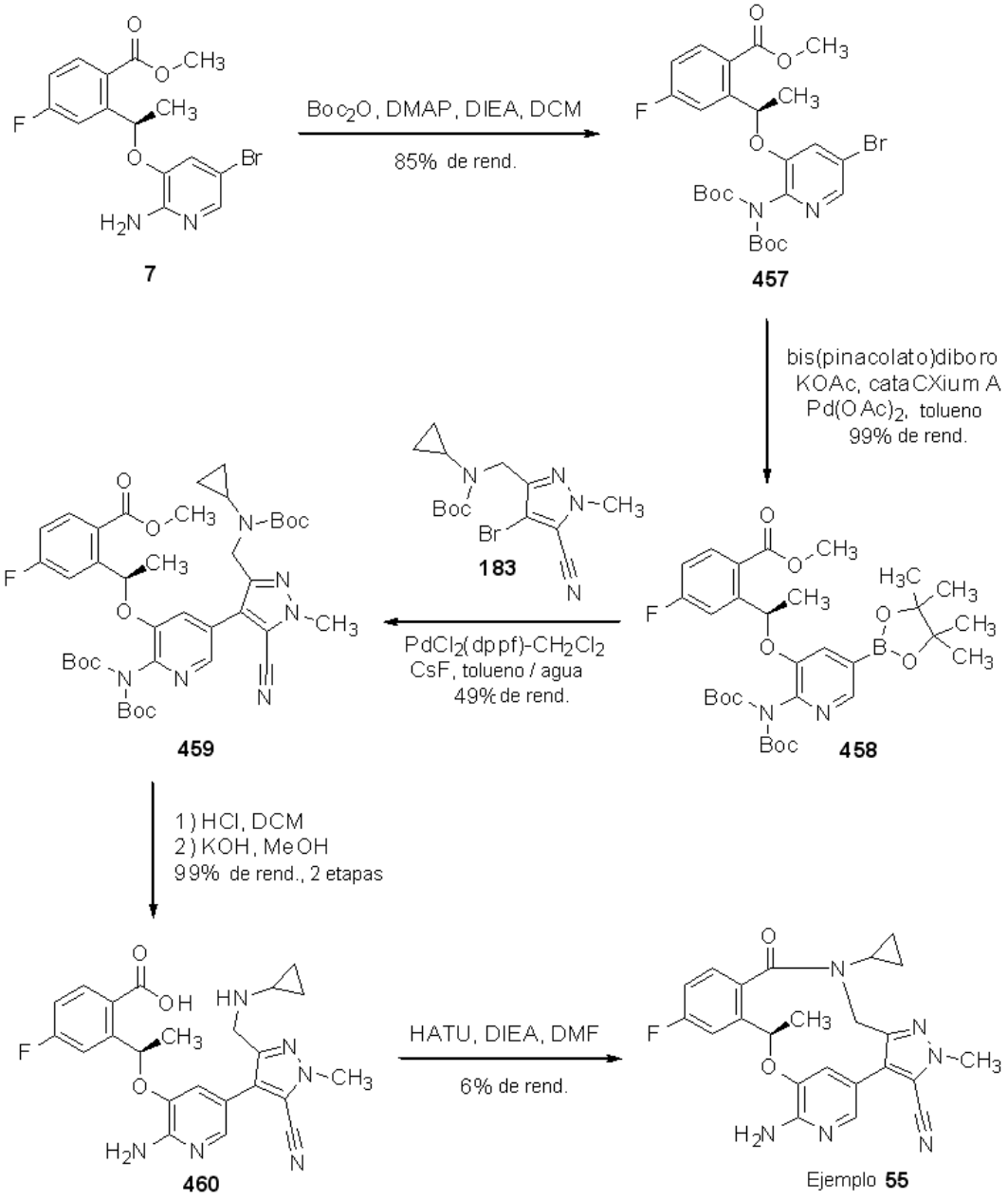
El **compuesto 126** (300 mg, 0,685 mmol), **compuesto 181** (146 mg, 0,685 mmol), DIEA (0,597 mL, 3,42 mmol) y Pd (P^{t}Bu$_3$)$_2$ (36 mg, 0,069 mmol) se disolvieron en tolueno (20 mL) en un recipiente de acero inoxidable. El reactor se presurizó en 4 bar de CO y se calentó hasta 85 °C durante 14 horas. La mezcla de reacción se concentró y se sometió a cromatografía en columna en gel de sílice (0-75% de EtOAc/heptano) para obtener el **compuesto 456** (168 mg, 48%) en forma de un sólido crema. ^{1}H RMN (400 MHz ,80°C, DMSO-*d*$_6$) δ 7,63 - 7,50 (m, 2 H), 7,47 - 7,36 (m, 1 H), 7,14 (dt, *J* = 2,8, 8,6 Hz, 1 H), 7,01 (s, 1 H), 6,41 (br. s., 2 H), 6,17(d, *J* = 5,5 Hz, 1 H), 4,74 - 4,48 (m, 2 H), 3,97 (s, 3 H), 2,83 (br. s., 1 H), 1,59 (d, *J* = 6,5 Hz, 3 H), 0,57 (br. s., 4 H).

Etapa 2:

Una mezcla de **compuesto 456** (165 mg), ácido piválico (9,9 mg, 0,096 mmol) y KOAc (158 mg, 1,6 mmol) en *t*-AmOH (8,68 mL) con 1 gota de agua añadida se purgó con nitrógeno durante 10 minutos. Se añadieron CataCXium A (35,5 mg, 0,096 mmol) y Pd(OAc)$_2$ (10,8 mg, 0,048 mmol) y el vial se calentó hasta 140 ºC durante 1 hora en el microondas. La reacción se concentró y se purificó por cromatografía en

columna en gel de sílice (0-100% de EtOAc/heptano). Las fracciones que contenían el producto deseado se suspendieron en agua, se filtraron y se secaron en el horno de vacío para obtener el **Ejemplo 54** (75 mg, 54%) en forma de un sólido crema. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,74 (s, 1 H), 7,47 (dd, *J* = 2,5, 10,1 Hz, 1 H), 7,31 (dd, *J* = 5,8, 8,6 Hz, 1 H), 7,12 (dt, *J* = 2,6, 8,5 Hz, 1 H), 6,71 (s, 2 H), 6,16 - 6,05 (m, 1 H), 4,33 - 4,26 (m, 1 H), 4,22 - 4,15 (m, 1 H), 4,02 (s, 3 H), 2,16 - 2,06 (m, 1 H), 1,66 (d, *J* = 6,5 Hz, 3 H), 1,11 -1,00 (m, 1 H), 0,97 - 0,84 (m, 1 H), 0,81 - 0,71 (m, 1 H), 0,70 - 0,61 (m, 1 H). LCMS APCI *m/z* 434 $[M+H]^+$.

Preparación de (10*R*)-7-amino-16-ciclopropil-12-fluoro-2,10-dimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 55)



Etapa 1:

A una solución de **compuesto 7** (30 g, 81,3 mmol) en DCM (325 mL) se añadieron DIEA (42,5 mL, 244 mmol), DMAP (1,99 g, 16,3 mmol) y $(Boc)_2O$ (53,2 g, 244 mmol). La reacción se agitó durante la noche y luego se concentró. La purificación por cromatografía en columna en gel de sílice (0-25% de EtOAc/heptano) produjo el **compuesto 457** (39,3 g, 85%) en forma de una goma viscosa. ^{1}H RMN (400 MHz, 30 °C, DMSO-d_6) δ 8,16 (d, J = 2,0 Hz, 1 H), 8,00 (dd, J = 5,9, 8,7 Hz, 1 H), 7,53 (d, J =

2,0 Hz, 1 H), 7,35 - 7,25 (m, 2 H), 6,38 -6,26 (m, 1 H), 3,91 (s, 3 H), 1,55 (d, *J* = 6,3 Hz, 3 H), 1,38 (s, 18 H). LCMS APCI *m/z* 469 $[M - Boc]^+$.

Etapa 2:

Una mezcla de **compuesto 457** (22 g, 39 mmol), bis(pinacolato)diboro (10,8 g, 42,5 mmol) y KOAc (11,4 g, 116 mmol) en tolueno (260 mL) se burbujeó con nitrógeno durante 30 min antes de la adición de cataCXium A (1,43g, 3,86 mmol) y $Pd(OAc)_2$ (434 mg, 1,93 mmol). La reacción se calentó hasta 100 ºC usando un baño de aceite durante 16 horas. La reacción se dejó enfriar y se diluyó con EtOAc. Las capas orgánicas se lavaron con agua (2x) y salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron. La purificación por cromatografía en columna en gel de sílice (0-10% MeOH/DCM) produjo el **compuesto 458** (24,9 g, 99%) en forma de una goma viscosa amarilla. ^{1}H RMN (400 MHz, DMSO-*d*$_6$) δ 8,17 (d, *J* = 1,3 Hz, 1 H), 8,01 (dd, *J* = 6,0, 8,8 Hz, 1 H), 7,92 (s, 1 H), 7,37 (s, 1 H), 7,36 - 7,25 (m, 2 H), 6,38 (q, *J* = 6,0 Hz, 1 H), 3,92 (s, 3 H), 1,54 (d, *J* = 6,3 Hz, 3 H), 1,37 (s, 18 H), 1,27 (d, *J* = 5,5 Hz, 12 H).

Etapa 3:

Una mezcla de **compuesto 458** (684 mg, 0,887 mmol), **compuesto 183** (315 mg, 0,887 mmol) y fluoruro de cesio (404 mg, 2,66 mmol) en tolueno/agua (6 mL/0,2 mL) se inundó con nitrógeno. Se añadió $PdCl_2(dppf).CH_2Cl_2$ (73 mg, 0,089 mmol) y la mezcla se calentó hasta reflujo durante 16 horas. La reacción se enfrió, se diluyó con EtOAc, se lavó con agua y salmuera, se secó ($MgSO_4$) y se concentró. La purificación del residuo por cromatografía en columna en gel de sílice (0-50% de EtOAc/heptano) produjo el **compuesto 459** (332 mg, 49%) en forma de un sólido vítreo. ^{1}H RMN (400 MHz, DMSO-*d*$_6$) δ 8,11 (d, *J* = 2,0 Hz, 1 H), 7,98 (dd, *J* = 5,8, 8,8 Hz, 1 H), 7,36 (dd, *J* = 2,8, 10,3 Hz, 1 H), 7,27 - 7,19 (m, 2 H), 6,35 (q, *J* = 6,0 Hz, 1 H), 4,36 - 4,26 (m, 1 H), 4,18 - 4,10 (m, 1 H), 4,01 (s, 3 H), 3,90 (s, 3 H), 2,43 - 2,33 (m, 1 H), 1,61 (d, *J* = 6,3 Hz, 3 H), 1,43 (s, 18 H), 1,30 (s, 9 H), 0,61 - 0,35 (m, 4 H).

Etapa 4:

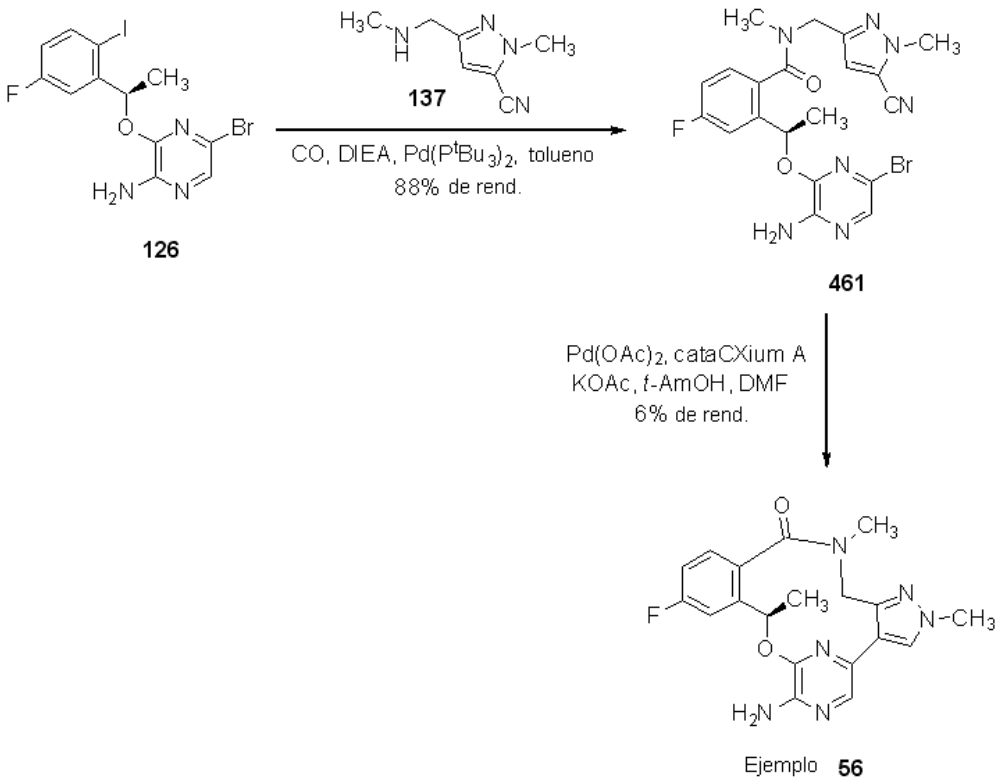
A una solución enfriada (0 ºC) del **compuesto 459** (330 mg, 0,431 mmol) en DCM (2,16 mL) se añadió HCl (2,16 mL, 4 M en dioxano, 8,63 mmol). La reacción se agitó a temperatura ambiente durante 2 horas y luego se concentró. El residuo se disolvió en MeOH (2 mL) y se añadió KOH (0,242 g, 4,31 mmol). La reacción se calentó a 50 ºC durante 48 horas. Después de enfriar hasta 0 ºC, la reacción se neutralizó con HCl concentrado. Los sólidos se filtraron y el filtrado se concentró y se secó en el horno de vacío. Este residuo se disolvió en metanol, se filtró otra vez, se

concentró y se secó para obtener el **compuesto 460** (272 mg, 99%), que se usó sin otra purificación. LCMS APCI *m/z* 451 $[M+H]^+$.

Etapa 5:

A una solución enfriada (0 ºC) de HATU (186 mg, 0,474 mmol) en DMF (8,5 mL) se añadió gota a gota una solución de **compuesto 460** (200 mg, 0,431 mmol) y DIEA (375 µL, 2,16 mmol) en DMF (8,5 mL). Una vez completa la adición, la reacción se calentó hasta temperatura ambiente y se agitó durante 14 horas. La reacción luego se concentró y el residuo se disolvió en EtOAc. Las capas orgánicas se lavaron con Na_2CO_3 acuoso saturado (2x) y salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron. La reacción se purificó por cromatografía en columna en gel de sílice (25-100% de EtOAc/heptano). Las fracciones que contenían el producto deseado se concentraron y se suspendieron en agua. Los sólidos se filtraron y se secaron en el horno de vacío durante la noche para obtener el **Ejemplo 55** (11 mg, 6%) en forma de un sólido crema. ^{1}H RMN (400MHz, DMSO-d_6) δ 7,60 (dd, *J* = 2,6, 10,2 Hz, 1 H), 7,56 (d, *J* = 1,8 Hz, 1 H), 7,39 (dd, *J* = 5,8, 8,6 Hz, 1 H), 7,15 (dt, *J* = 2,5, 8,4Hz, 1 H), 6,74 (d, *J* = 1,3 Hz, 1 H), 6,17 (s, 2 H), 5,86 - 5,70 (m, 1 H), 4,47 (d, *J* = 14,4 Hz, 1 H), 4,06 - 3,98 (m, 4 H), 2,40 - 2,23 (m, 1 H), 1,69 (d, *J* = 6,3 Hz, 3 H), 1,19 - 1,08 (m, 1 H), 0,99 - 0,87 (m, 1 H), 0,79 (td, *J* = 7,2, 14,5 Hz, 1 H), 0,75 - 0,64 (m, 1 H). LCMS APCI *m/z* 433 $[M+H]^+$.

Preparación de (10*R*)-7-amino-12-fluoro-2,10,16-trimetil-16,17-dihidro-2*H*-8,4-(azeno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 56)



Etapa 1:

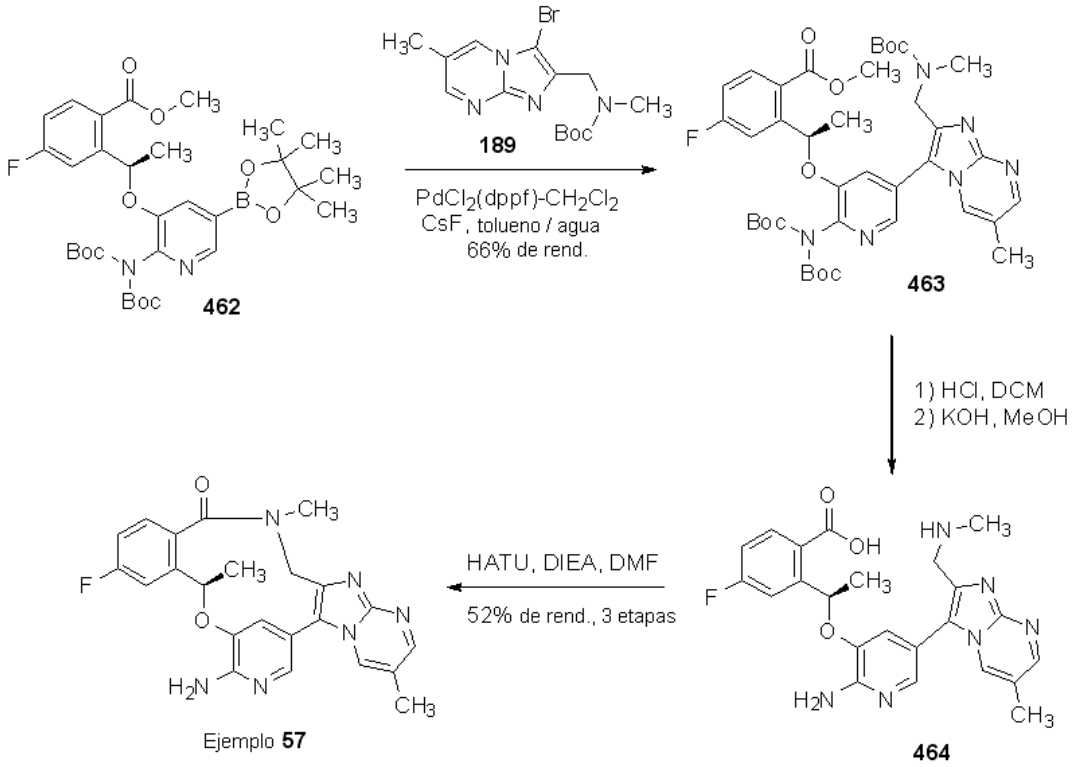
Una mezcla de **compuesto 126** (8,5 g, 19 mmol), **compuesto 137** (3,69 g, 19,8 mmol), DIEA (13,5 mL, 77,6 mmol) y Pd(P^{t}Bu$_3$)$_2$ (1,01 g, 1,94 mmol) en tolueno (320 mL) se calentó hasta 85 ºC bajo 4 bar de presión de CO durante 4 horas. La reacción se enfrió, se concentró y se purificó por cromatografía en columna en gel de sílice (0-60% de EtOAc/heptano) para obtener el **compuesto 461** (8,25 g, 88%) en forma de un sólido blanco. LCMS APCI *m/z* 488/490 $[M+H]^+$.

Etapa 2:

El **compuesto 461** (10,23 g, 20,95 mmol), KOAc (10,3 g, 105 mmol), cataCXium A (968 mg, 2,62 mmol) y Pd(OAc)$_2$ (294 mg, 1,31 mmol) se combinaron con alcohol t-amílico (300 mL) en un recipiente de acero inoxidable de 500 mL. La reacción se selló y se calentó hasta 120 ºC durante 16 horas. La reacción se dejó enfriar y el recipiente se abrió. La mezcla se diluyó con EtOAc, se lavó con agua, se secó (Na_2SO_4) y el solvente se evaporó. El residuo se purificó por cromatografía en columna en gel de sílice (1-6% MeOH/EtOAc) para obtener el **Ejemplo 56** (415 mg, 6%) en forma de un sólido amarillo. ^{1}H RMN (400MHz, $CDCl_3$) δ 7,60 (s, 1 H), 7,55 (s, 1 H), 7,18 - 7,30 (m, 2 H), 6,97 (td, *J* = 8,27, 2,65 Hz, 1 H), 6,07 (dd, *J* = 6,57, 1,77 Hz,

1 H), 4,95 (s, 2 H), 4,60 (d, *J* = 13,39 Hz, 1 H), 4,20 (d, *J* = 13,14 Hz, 1 H), 3,91 (s, 3 H), 3,04 (s, 3 H), 1,38 (d, *J* = 12,38 Hz, 3 H). LCMS APCI *m/z* 383 $[M+H]^+$.

Preparación de (5*R*)-8-amino-3-fluoro-5,14,19-trimetil-18,19-dihidro-7,11-(meteno)-pirimido[2',1':2,3]imidazo[4,5-*h*][2,5,11]benzoxadiazaciclotetradecin-20(5*H*)-ona (Ejemplo 57)



Etapa 1:

El **compuesto 462** (489 mg, 0,56 mmol), **compuesto 189** (197 mg, 0,56 mmol) y fluoruro de cesio (253 mg, 1,66 mmol) se combinaron en tolueno/agua (3,7 mL/370 µL) y la mezcla se inundó con nitrógeno. Se añadió $PdCl_2(dppf).CH_2Cl_2$ (45,7 mg, 0,056 mmol) y la mezcla de reacción se calentó a reflujo durante 14 horas. La reacción se dejó enfriar, se diluyó con EtOAc, se lavó con agua (2x) y salmuera, se secó ($MgSO_4$), se filtró y se concentró. La purificación por cromatografía en columna en gel de sílice (0-100% de EtOAc/heptano) produjo el **compuesto 463** (280 mg, 66%) en forma de una goma viscosa. ^{1}H RMN (400MHz, DMSO-d_6) δ 8,46 (s, 1H), 8,20 (s, 2H), 7,97 (dd, *J* = 6,2, 8,7 Hz, 1H), 7,44 - 7,33 (m, 2H), 7,28 - 7,21 (m, 1H), 6,41 - 6,30 (m,1H), 4,45 - 4,25 (m, 2H), 3,82 (s, 3H), 2,74 (s, 3H), 2,28 (s, 3H), 1,61 (d, *J* = 6,3 Hz, 3H), 1,47 (s, 18H), 1,30 (br. s., 9H).

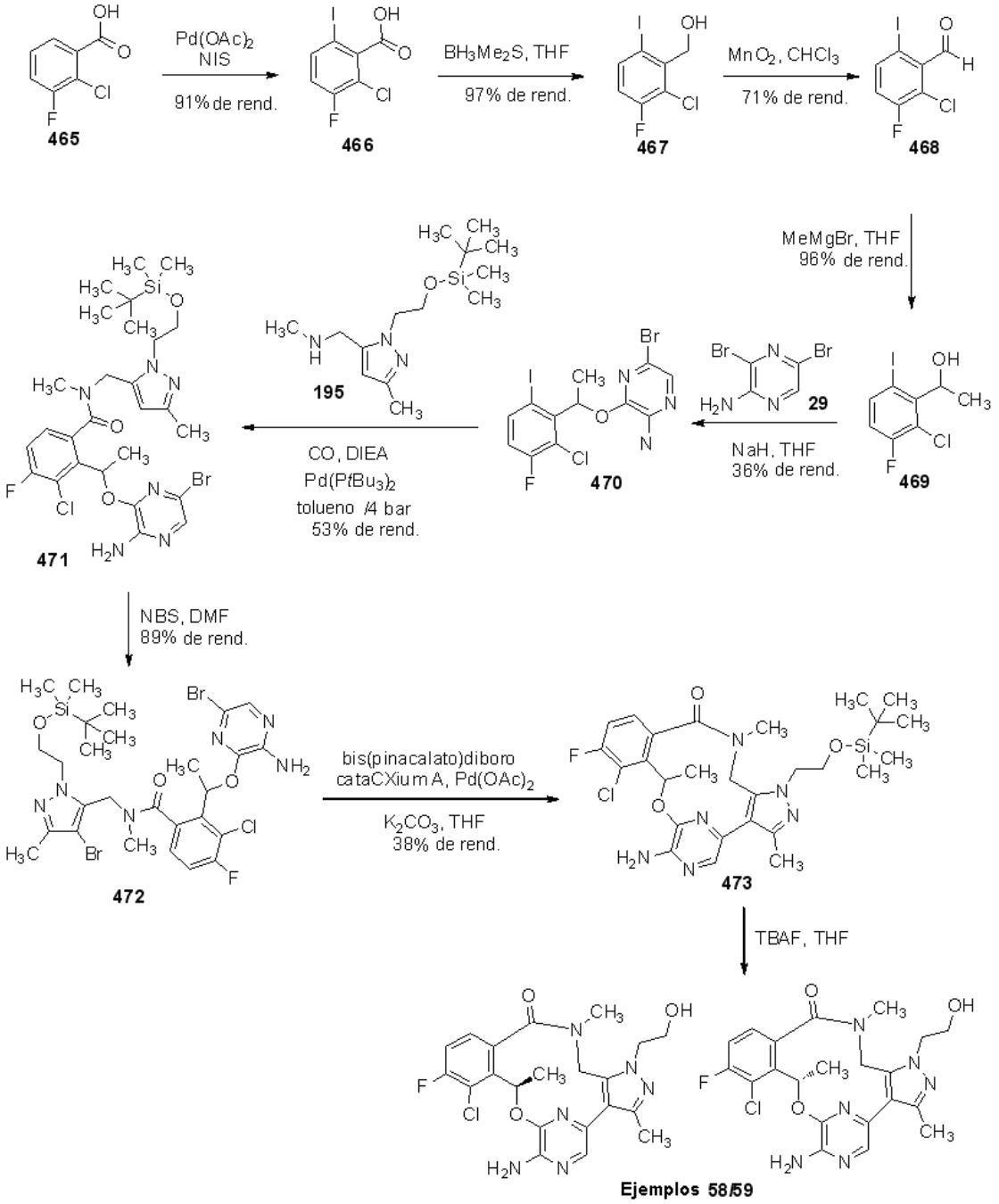
Etapa 2:

El **compuesto 463** (280 mg, 0,37 mmol) se disolvió en DCM (2 mL) y se añadió HCl (2 mL, 4M en dioxano, 7,32 mmol). La reacción se agitó durante 38 horas a temperatura ambiente. La reacción luego se concentró, el residuo se disolvió en metanol (2 mL) y se añadió KOH (0,205 g, 3,66 mmol). La reacción se calentó hasta 60 °C durante 6 horas, se enfrió y se neutralizó con HCl concentrado. Los sólidos se filtraron y el filtrado se concentró y se secó durante la noche en el horno de vacío para obtener el **compuesto 307** en forma de un sólido marrón anaranjado, que se usó sin otra purificación.

Etapa 3:

A una solución enfriada (0 ºC) de HATU (158 mg, 0,403 mmol) en DMF (7,3 mL) se añadió una solución de **compuesto 464** (165 mg, 0,366 mmol) y DIEA (0,319 mL, 1,83 mmol en DMF (7,3 mL). La reacción se calentó hasta temperatura ambiente y se agitó durante 14 horas. La mezcla se diluyó con EtOAc, se lavó con NH_4Cl acuoso saturado (3x), Na_2CO_3 acuoso saturado (3x) y salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se purificó por cromatografía en columna en gel de sílice (25-100% de EtOAc/heptano y luego 0-10% de MeOH/DCM) para obtener el **Ejemplo 57** (83 mg, 52%) en forma de un sólido amarillo. ^{1}H RMN (400MHz, DMSO-d_6) δ 8,79 (dd, *J* = 1,2, 2,1 Hz, 1H), 8,45 (d, *J* = 2,2 Hz, 1H), 7,82 (d, *J*=1,7 Hz, 1H), 7,66 (dd, *J* = 2,6, 10,3 Hz, 1H), 7,47(dd, *J* = 5,8, 8,5 Hz, 1H), 7,17 (dt, *J* = 2,7, 8,4 Hz, 1H), 6,88 (d, *J* = 1,6 Hz, 1H), 6,22 (s, 2H), 5,73 - 5,63 (m, 1H), 4,50 (d, *J* = 13,9 Hz, 1H), 4,31 (d, *J* = 13,8 Hz, 1H), 3,06 (s, 3H), 2,31 (s, 3H), 1,69 (d, *J*=6,2 Hz, 3H). LCMS APCI *m/z* 433 $[M+H]^+$.

Preparación de (10*R*)-7-amino-11-cloro-12-fluoro-1-(2-hidroxietil)-3,10,16-trimetil-16,17-dihidro-1*H*-8,4-(azeno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona / (10*S*)-7-amino-11-cloro-12-fluoro-1-(2-hidroxietil)-3,10,16-trimetil-16,17-dihidro-1*H*-8,4-(azeno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplos 58 y 59)



Etapa 1:

Se añadió $Pd(OAc)_2$ (642 mg, 2,86 mmol) a una solución desgasificada de **compuesto 465** (4,99 g, 28,61 mmol) y NIS (7,08 g, 31,5 mmol) en DMF (143 mL). La solución resultante se agitó a 100 °C durante 24 horas. La reacción se filtró, se diluyó con EtOAc y las capas orgánicas combinadas se lavaron con agua (3x) y salmuera

(2x) y se secaron (Na_2SO_4). La solución se filtró, se concentró y el residuo se purificó por cromatografía en columna en gel de sílice (0-100% de EtOAc/heptano) para obtener el **compuesto 466** (7,9 g, 91%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,74 (dd, J = 4,58, 8,74 Hz, 1H), 7,00 (t, J = 8,56 Hz, 1H).

Etapa 2:

A una solución de **compuesto 466** (7,26 g, 24,16 mmol) en THF seco (100 mL) se añadió una solución de BH_3•SMe_2 (5,32 mL, 10 M en THF, 53,2 mmol) gota a gota a 0 °C bajo nitrógeno. Una vez completa la adición, la mezcla se agitó a 0 °C durante 30 minutos y luego se calentó a reflujo durante la noche. La mezcla se neutralizó con solución acuosa saturada de NH_4Cl y la reacción se diluyó con agua y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron (Na_2SO_4) y se concentraron. La reacción se purificó por cromatografía en columna en gel de sílice (0-30% de EtOAc/heptano) para obtener el **compuesto 467** (6,7 g, 97%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,76 (dd, *J* = 5,07, 8,74 Hz, 1H), 6,90 (t, *J* = 8,50 Hz, 1H), 5,00 (d, *J* = 6,97 Hz, 2H), 2,11 (t, *J* = 7,03 Hz, 1H).

Etapa 3:

A una solución de **compuesto 467** (6,67 g, 23,35 mmol) en $CHCl_3$ (60 mL) se añadió MnO_2 activado (135 g, 140 mmol) y la reacción se calentó a reflujo (70 °C) durante 18 horas. La reacción no estaba completa, y se añadió otra porción de MnO_2 (9 g) y $CHCl_3$ (5 mL). La reacción se calentó a reflujo durante otras 12 horas. La reacción se enfrió, se filtró y los sólidos se lavaron con DCM. Las capas orgánicas se secaron (Na_2SO_4), se filtraron y se concentraron para obtener un sólido amarillo. Esto se purificó por cromatografía en columna en gel de sílice (0-20% de EtOAc/heptano) para obtener el **compuesto 468** (4,73 g, 71%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 10,13 (s, 1H), 7,91 (dd, *J* = 4,77, 8,68 Hz, 1H), 7,07 (t, *J* = 8,44 Hz, 1H).

Etapa 4:

A una solución del **compuesto 468** (4,72 g, 16,59 mmol) en THF seco (70 mL) se añadió MeMgBr (6,08 mL, 3 M en éter dietílico, 18,3 mmol) a 0 °C en nitrógeno. La reacción se agitó a 0 °C durante 10 minutos y se calentó hasta temperatura ambiente. La reacción se neutralizó con H_4Cl acuoso saturado y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice (0-30% EtOAc/heptano) para obtener el **compuesto 469** (4,8 g, 96%) en forma de un

sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,76 (dd, *J* = 5,26, 8,68 Hz, 1H), 6,81 (t, *J* = 8,50 Hz, 1H), 5,39 (dd, *J* = 6,97, 8,93 Hz, 1H), 2,85 (s, 1H), 1,62 (d, *J* = 6,85 Hz, 3H).

Etapa 5:

A una solución de alcohol **469** (4,76 g, 15,85 mmol) en THF (16 mL) se añadió NaH (697 mg, 17,4 mmol, 60% de dispersión). La reacción se agitó durante 30 minutos y luego se añadió la pirazina **29** (3,81 g, 15,1 mmol) en forma de un sólido. La reacción se agitó a 55 °C durante 4 horas. La reacción se dejó enfriar, se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos se secaron (Na_2SO_4), se filtraron y se concentraron. La trituración con éter dietílico produjo el **compuesto 470** (2,8 g, 37%) en forma de un sólido blanco. Los licores madre se combinaron, se concentraron y se purificaron por cromatografía en columna en gel de sílice (0-20% de EtOAc/heptano). La trituración de las fracciones que contenían producto con éter dietílico produjo un segundo lote de **compuesto 470** (2,7 g, 36%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,71-7,86 (m, 1H), 7,61 (s, 1H), 6,82 (t, *J* = 8,72 Hz, 1H), 6,47-6,60 (m, *J* = 6,10 Hz, 1H), 4,91 (br. s., 2H), 1,80 (d, *J* = 6,82 Hz, 3H).

Etapa 6:

El **compuesto 470** (2,97 g, 6,29 mmol), el pirazol **195** (1,87 g, 6,61 mmol), DIEA (4,39 mL, 25,2 mmol) y $Pd(P^tBu_3)_2$ (161 mg, 0,315 mmol) se combinaron en tolueno (63 mL) en un recipiente de acero inoxidable. La reacción se calentó hasta 85 °C en 4 bar de presión de CO durante 16 horas. El recipiente se dejó enfriar y la reacción se filtró. El filtrado se concentró y el residuo se sometió a cromatografía en columna en gel de sílice (0-100% de EtOAc/heptano) para obtener el **compuesto 471** (2,2 g, 53%) en forma de una goma viscosa. LCMS APCI *m/z* 655/660 $[M+H]^+$.

Etapa 7:

A una solución helada del **compuesto 471** (500 mg, 0,762 mmol) en DMF (15 mL) se añadió NBS (137 mg, 0,762 mmol). Después de 10 minutos, la reacción se diluyó con EtOAc y $NaHCO_3$ acuoso saturado. La capa orgánica se separó, se lavó con agua, se secó (Na_2SO_4), se filtró y se concentró. El residuo se purificó por cromatografía en columna en gel de sílice (0-100% de EtOAc/heptano) para obtener el **compuesto 472** (498 mg, 89%) en forma de un sólido amarillo claro. LCMS APCI *m/z* 737/740 $[M+H]^+$.

Etapa 8:

A una solución del **compuesto 472** (400 mg, 0,544 mmol), bis(pinacalato)diboro (414 mg, 1,63 mmol) en THF (5,5 mL) se añadió K_2CO_3 anhidro (376 mg, 2,72 mmol). El sistema se purgó con nitrógeno y luego se añadió cataCXium

A (50,3 mg, 0,136 mmol) seguido de $Pd(OAc)_2$ (15,3 mg, 0,068 mmol). La reacción se purgó otra vez y se agitó a 80 °C durante 7 horas. La reacción estaba completa en un 50% y se añadió una porción adicional de $Pd(OAc)_2$ (15,3 mg, 0,068 mmol) seguido de purga con nitrógeno. La reacción se calentó a 80 °C durante otras 5 horas. Después de enfriar, la reacción se filtró, se concentró y el residuo se sometió a cromatografía en columna en gel de sílice (0-100% de EtOAc/heptano) para obtener el **compuesto 473** (120 mg, 38%, 80% puro) en forma de una goma amarilla. Este material se usó directamente en la siguiente etapa. LCMS APCI *m/z* 575/578 $[M+H]^+$.

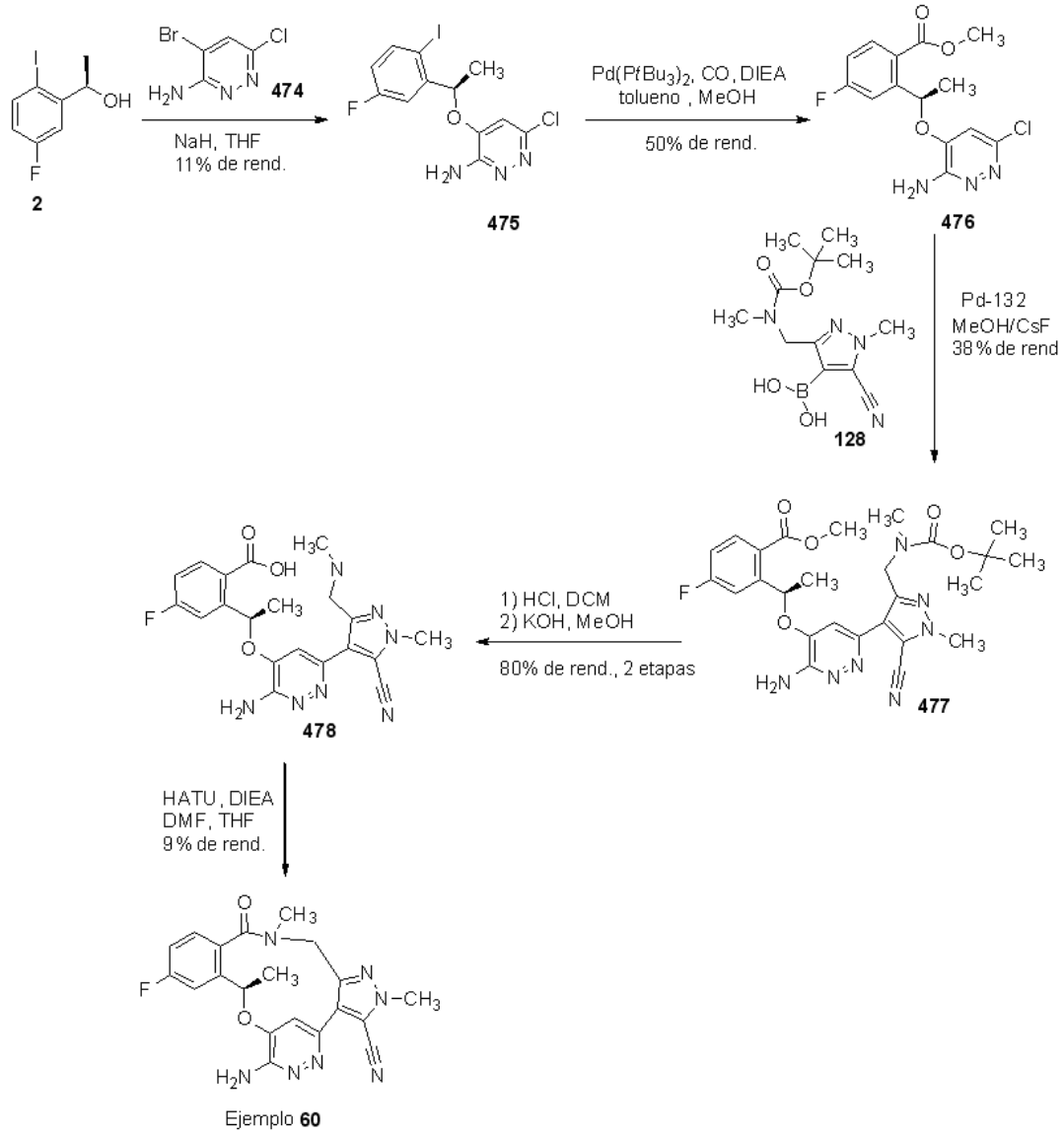
Etapa 9:

A una solución del **compuesto 473** (120 mg, 0,209 mmol) en THF (5 mL) se añadió TBAF (0,209 mL, 1 M en THF, 0,209 mmol). La reacción se agitó durante 2 horas y se concentró. El residuo se diluyó con DCM, se lavó con agua, se secó (Na_2SO_4) y se concentró para obtener 155 mg de material 80% puro en forma de una mezcla, seguido de separación quiral por SFC para obtener ambos enantiómeros del compuesto del título. La separación quiral analítica por SFC se llevó a cabo usando una columna Regis Whelk-01 (*R, R*) (columna de 4,6 mm x 100 mm, tamaño de partícula de 5 micrones), que se eluyó con 40% de MeOH en CO_2 mantenido a 25 ºC a 140 bar. Una tasa de flujo de 3 mL/min produjo $Rt_{(pico\ 1)}$ = 2,62 minutos y $Rt_{(pico\ 2)}$ = 3,61 minutos.

Ejemplo 58 (pico 1): 13,7 mg, >99% ee (-), 13% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,58 (s, 1H), 7,35-7,48 (m, 2H), 6,20 (s, 2H), 6,08-6,16 (m, *J* = 7,00 Hz, 1H), 4,78-4,89 (m, 1H), 4,60 (d, *J* = 14,43 Hz, 1H), 4,14-4,40 (m, 3H), 3,74-3,81 (m, 1H), 3,65-3,73 (m, 1H), 2,85 (s, 3H), 2,30 (s, 3H), 1,81 (d, *J* = 6,97 Hz, 3H). LCMS APCI *m/z* 461/464 $[M+H]^+$.

Ejemplo 59 (pico 2): 13,9 mg, 97% ee (+), 13% de rendimiento. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,57 (s, 1H), 7,35-7,49 (m, 2H), 6,20 (s, 2H), 6,12 (q, *J* = 6,72 Hz, 1H), 4,78-4,91 (m, 1H), 4,60 (d, J = 14,43 Hz, 1H), 4,15-4,38 (m, 3H), 3,73-3,82 (m, 1H), 3,71 (dd, *J* = 4,03, 7,46 Hz, 1H), 2,84 (s, 3H), 2,30 (s, 3H), 1,81 (d, *J* = 6,85 Hz, 3H). LCMS APCI *m/z* 461/464 $[M+H]^+$.

Preparación de (10*R*)-7-amino-12-fluoro-2,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,6,11]benzoxatriazaciclotetradecin-3-carbonitrilo (Ejemplo 60)



Etapa 1:

A una solución de **compuesto 2** (2,55 g, 9,6 mmol) en THF (50 mL) a 0 °C se añadió NaH (384 mg, 9,6 mmol, 60% de dispersión). Después de agitar a 0 °C durante 30 minutos y dejar calentar hasta temperatura ambiente, se añadió piridazina **474** (2 g, 9,6 mmol. La mezcla marrón oscura se agitó luego a 75 °C durante 18 horas. La mezcla de reacción se concentró y el residuo se extrajo en DCM. Las capas orgánicas se filtraron, se concentraron y el residuo se purificó por dos cromatografías en columna en gel de sílice (10-100% EtOAc/heptanos, seguido de 10-75% EtOAc/heptanos) para obtener el **compuesto 475** (451 mg, 11%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,92 (dd, 1 H) 7,44 (dd, *J*=10,11, 3,03 Hz, 1 H) 7,02 (td, *J*=8,46, 3,03 Hz, 1 H) 6,62 (s, 2 H) 6,52 (s, 1 H) 5,40 - 5,72 (m, 1 H) 1,57 (d, *J*=6,32 Hz, 3 H).

Etapa 2:

A una solución de **compuesto 475** (756 mg, 1,92 mmol) y DIEA (1,27 mL, 7,3 mmol) en tolueno (18 mL) y metanol (4 mL) en un recipiente de acero inoxidable se añadió $Pd(P^tBu_3)_2$ (47 mg, 0,09 mmol). La reacción se calentó hasta 85 °C en 4 bar de presión de CO durante 16 horas. El residuo se concentró y se sometió a cromatografía en columna en gel de sílice (10-75% de EtOAc/heptano). Las fracciones que contenían el producto se trituraron con MTBE y se filtraron. Los sólidos se lavaron con MTBE caliente. La evaporación del filtrado produjo el **compuesto 476** (314 mg, 50%) en forma de un sólido marrón. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,97 (dd, 1 H) 7,59 (dd, *J*=10,36, 2,78 Hz, 1 H) 7,30 (td, *J*=8,46, 2,78 Hz, 1 H) 6,69 (s, 1 H) 6,63 (s, 2 H) 6,35 (q, *J*=5,98 Hz, 1 H) 3,90 (s, 3 H) 1,62 (d, *J*=6,32 Hz, 3 H).

Etapa 3:

A la solución metanólica de **compuesto 476** (9 mL, 1,3 mmol) se añadieron el **compuesto 128** (204 mg, 0,626 mmol) y CsF (400 mg, 2,6 mmol). La mezcla luego se desgasificó y se añadió Pd-132 (22 mg, 0,031 mmol). La mezcla se calentó a 120 °C en el microondas durante 30 minutos. La LCMS indica el consumo del ácido borónico, pero la reacción no estaba completa. Se añadieron cantidades adicionales de la solución de ácido borónico (2 mL, 0,288 mmol), fluoruro de cesio (400 mg, 2,6 mmol) y Pd-132 (22 mg, 0,031 mmol), y la reacción se calentó a 120 °C en el microondas durante otros 30 minutos. La reacción se dividió entre EtOAc/salmuera y la capa acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice (10-100% EA/heptano seguido de 5% MeOH/EtOAc) para obtener el **compuesto 477** (128 mg, 38%) en forma de un sólido similar a una espuma después de triturar con MTBE. ^{1}H RMN (400 MHz, 80°C, DMSO-d_6) δ 7,97 (dd, *J*=8,69, 5,92 Hz, 1 H) 7,53 (dd, *J*=10,32, 2,77 Hz, 1 H) 7,23 (td, 1 H) 6,75 (s, 1 H) 6,39 - 6,54 (m, 1 H) 6,30 (s, 2 H) 4,48 - 4,62 (m, 1 H) 4,36 (d, *J*=15,86 Hz, 1 H) 3,98 (s, 3 H) 3,90 (s, 3 H) 2,73 (s, 3 H) 1,69 (d, *J*=6,29 Hz, 3 H) 1,26 (s, 9 H).

Etapa 4:

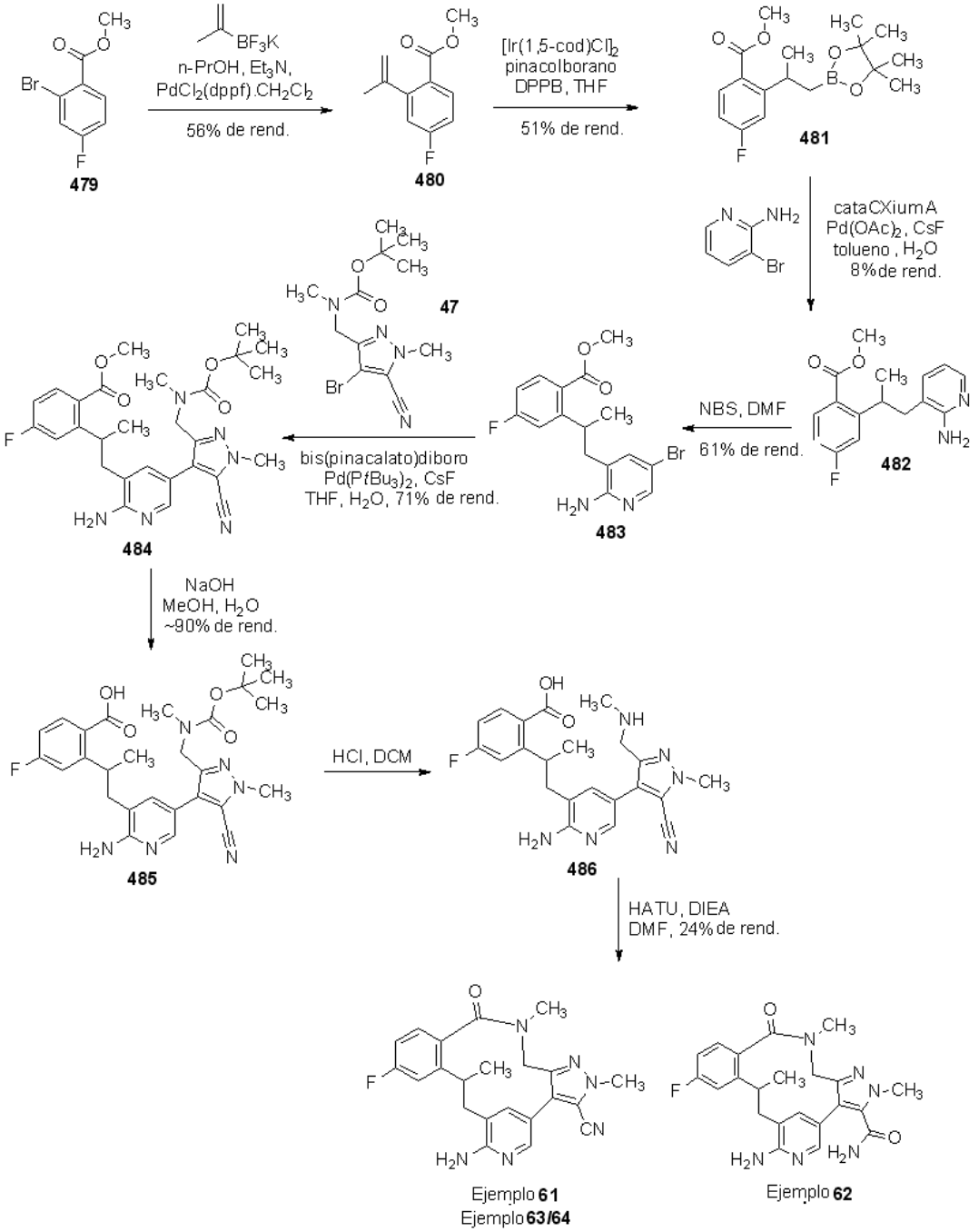
A una solución de **compuesto 477** (155 mg, 0,287 mmol) en DCM (1,5 mL) se añadió HCl (1,5 mL, 4 M en dioxano, 6 mmol). La mezcla de reacción se agitó durante 1 hora y se concentró. El residuo se azeotropó con MTBE, se concentró y se secó a 50 °C en horno de vacío durante 1 hora. El residuo se disolvió en MeOH (3 mL) y se añadió KOH (136 mg, 2,41 mmol). La reacción se calentó a 50 °C durante 8 horas. La suspensión se dejó enfriar y se neutralizó con HCl 6 N. Los sólidos se eliminaron por

filtración y el filtrado se concentró. El residuo se azeotropó con tolueno, se concentró y se secó a 50 °C en horno de vacío para obtener el **comnpuesto 478** (122 mg, 70-80% de pureza por LCMS) en forma de un sólido marrón, que se usó directamente en la siguiente etapa.

Etapa 5:

A una solución de HATU (158 mg, 0,402 mmol) en DMF (7 mL) a 0 °C se añadió gota a gota una solución de **compuesto 478** (122 mg, 0,287 mmol) y DIEA (0,3 mL, 1 mmol) en DMF/THF (7 mL/1,4 mL)**.** La adición duró 50 minutos. Después de la adición, la mezcla resultante se agitó a 0 °C durante 10 minutos. La mezcla se vertió luego en NaHCO3 acuoso saturado (400 mL) y se filtró. El filtrado se extrajo con EtOAc (3x) y las capas orgánicas se lavaron con agua (2x) y salmuera. Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice (0-10% MeOH/DCM:EtOAc 1:1) para obtener el **Ejemplo 60** (10 mg, 9%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,46 - 7,68 (m, 2 H) 7,15 - 7,31 (m, 1 H) 6,71 (s, 1 H) 6,49 (br. s., 2 H) 5,61 - 5,88 (m, 1 H) 4,50 (d, J = 14,43 Hz, 1 H) 4,29 (d, J = 14,55 Hz, 1 H) 4,07 (s, 3 H) 3,00 (s, 3 H) 1,71 (d, J = 5,75 Hz, 3 H). LCMS APCI m/z 408 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-2,10,16-trimetil-15-oxo-2,9,10,15,16,17-hexahidro-8,4-(meteno)pirazolo[3,4-*d*][2,8]benzodiazaciclotetradecin-3-carbonitrilo/ 7-amino-12-fluoro-2,10,16-trimetil-15-oxo-2,9,10,15,16,17-hexahidro-8,4-(meteno)pirazolo[3,4-*d*][2,8]benzodiazaciclotetradecin-3-carboxamida (Ejemplos 61 y 62)



Etapa 1:

Se añadieron trietilamina (13 mL, 9,44 g, 93,3 mmol), isopropeniltrifluoroborato de potasio (18,0 g, 121,6 mmol) y $PdCl_2(dppf).CH_2Cl_2$ (1,38 g, 1,70 mmol) a una solución de **compuesto 479** (21,8 g, 93,6 mmol) en *n*-propanol (640 mL) y la mezcla se calentó a reflujo durante 17 horas. El análisis de TLC (10% de 2-butanona en heptano) mostró el material de partida restante y se añadió $PdCl_2(dppf).CH_2Cl_2$ (0,69 g,

0,84 mmol) y el calentamiento continuó durante otras 4 horas. Después de enfriar hasta temperatura ambiente la mezcla se concentró hasta ~100 mL al vacío y se diluyó con EtOAc (400 mL) antes de lavar con HCl 1 M (250 mL) y salmuera (250 mL). Los lavados acuosos combinados se extrajeron con EtOAc (100 mL) y esto se lavó con salmuera (75 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$) y se concentraron al vacío para producir un aceite marrón oscuro. La purificación por cromatografía en columna (1500 mL sílice, 4% de EtOAc en heptano) produjo el producto deseado (8,63 g, 47%) en forma de un líquido incoloro, contaminado con 4-fluorobenzoato de metilo (<10%) y una mezcla del producto deseado y material de partida (5,05 g) también contaminado con 4-fluorobenzoato de metilo. La purificación adicional por cromatografía en columna (500 mL sílice, 4% de EtOAc en heptano) produjo 1,60 g (9%) más del producto deseado contaminado con 4-fluorobenzoato de metilo (<10%). El producto luego se purificó por destilación en Kugelrohr, descartando la corrida previa (70 °C, 4 mmHg) y luego aumentando la temperatura hasta 95 °C para recolectar el **compuesto 480** (95% de recuperación) con <5% de 4-fluorobenzoato de metilo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,84 (dd, *J* = 8,7, 5,9 Hz, 1H) 6,99 (ddd, *J* = 8,6, 8,0, 2,6 Hz, 1H) 6,93 (dd, *J* = 9,4, 2,6 Hz, 1H) 5,12 (p, *J* = 1,6 Hz, 1H) 4,85 (dq, *J* = 1,8, 0,9 Hz, 1H) 3,85 (s, 3H) 2,07 (t, *J* = 1,2 Hz, 3H). LCMS *m/z* 195 $[M+H]^+$.

Etapa 2:

$[Ir(1,5\text{-cod})Cl]_2$ (751 mg 1,11 mmol) y DPPB (944 mg 2,21 mmol) se agitaron en THF (100 mL) en nitrógeno a temperatura ambiente durante 5 minutos para producir una solución amarillo claro. Se añadió el **compuesto 480** (8,6 g, 44,28 mmol) en THF (10 mL) y la solución se agitó durante 10 minutos. Se añadió pinacolborano (7,95 mL, 53,1 mmol) en THF (20 mL) gota a gota y la solución de color amarillo turbio se agitó durante 48 horas. La reacción se concentró y se purificó por cromatografía en columna en gel de sílice (0-100% DCM/heptano) para producir el **compuesto 481** en forma de un aceite incoloro (7,2 g, 51%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,76 (dd, *J* = 8,68, 6,11 Hz,1H) 7,10 (dd, *J* = 10,70, 2,63 Hz,1H) 6,87 (dt, *J*= 1,00 Hz,1H) 3,84 - 3,99 (m, 4H)1,29 (d, *J* = 1,00 Hz,3H), 1,13 (d, *J*=1,00 Hz,14H). LCMS APCI *m/z* 323 $[M+H]^+$.

Etapa 3:

Al **compuesto 481** (5,7 g, 17,69 mmol) y 2-amino-3-brompiridina (6,12 g, 35,40 mmol) en tolueno (300 mL) y agua (60 mL) se añadieron $Pd(OAc)_2$ (248 mg, 1,11 mmol) y cataCXium A (793 mg, 2,21 mmol) seguido de CsF (6,72 g ,44,20 mmol). La mezcla de reacción bifásica se agitó a 120 °C durante 48 horas. La LCMS indicó sólo

el 20% de conversión en el producto deseado. La reacción se enfrió y la capa orgánica se extrajo. La capa acuosa luego se extrajo también con DCM y las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice (0-75% DCM/heptanos) para producir el **compuesto 482** en forma de un aceite marrón (401 mg, 8%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,98 (dd, *J* = 5,01, 1,71 Hz,1H) 7,91 (dd, *J* = 8,80, 6,11 Hz,1H) 7,15 - 7,23 (m,2H) 6,97 (ddd, *J* = 8,68, 7,70, 2,57 Hz,1H) 6,58 (dd, *J* = 7,21,5,01 Hz, 1H) 5,21 (brs.,2H) 4,04-4,17 (m,1H) 3,90 (s, 3H) 3,01 (dd, *J* = 13,88, 4,34 Hz,1H) 2,33 (dd, *J*= 13,88, 11,07 Hz,1H) 1,16 (d, *J* = 6,85 Hz, 3H). LCMS APCI *m/z* 323 $[M+H]^+$. LCMS APCI *m/z* 289 $[M+H]^+$.

Etapa 4:

El **compuesto 482** (720 mg, 2,50 mmol) se agitó en DMF (20 mL) en nitrógeno a temperatura ambiente. Se añadió NBS (494 mg, 2,75 mmol) y la reacción se agitó durante 14 horas. La reacción se concentró y se dividió en EtOAc y solución acuosa saturada de $NaHCO_3$. Las capas orgánicas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice (0-75% de EtOAc/heptano) para producir el **compuesto 483** en forma de un aceite marrón (558 mg, 61%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,01 (d, *J* = 2,32 Hz,1H) 7,93 (dd, *J* = 8,80, 6,11 Hz,1H) 7,33 (d, *J* = 2,32 Hz,1H) 7,17 (dd, *J* =10,39, 2,57 Hz,1H) 6,98 (ddd, *J* = 8,68, 7,70, 2,57 Hz,1H) 5,34 (brs.,2H) 4,08 (m, *J* = 1,50 Hz,1H) 3,91(s, 3H) 3,00 (dd, *J* =13,94, 4,16 Hz, 1H) 2,27 (dd, *J* = 13,82, 11,37 Hz,1H) 1,17 (d, *J* = 6,85 Hz,3H). LCMS APCI *m/z* 366/368 $[M+H]^+$.

Etapa 5:

El **compuesto 483** (478 mg, 1,30 mmol), **compuesto 47** (857 mg, 2,60 mmol), bis(pinacalato)diboro (1 g, 3,91 mmol) fluoruro de cesio (989 mg, 6,51 mmol) y $Pd(P^tBu_3)_2$ (33,9 mg, 0,065 mmol) se combinaron en THF/agua (70 mL/7 mL) y la mezcla se desgasificó con nitrógeno. La reacción se calentó a 100 °C durante 14 horas. La reacción se concentró y el residuo se disolvió en EtOAc. Las capas orgánicas se lavaron con agua, se secaron (Na_2SO_4) y se concentraron para producir un aceite amarillo. El residuo se purificó por cromatografía en columna en gel de sílice (0-100% de EtOAc/heptano) para obtener el **compuesto 484** en forma de un aceite dorado (495 mg, 71%). LCMS APCI *m/z* 537 $[M+H]^+$.

Etapa 6:

El **compuesto 484** (495 mg, 0,922 mmol) e hidróxido de sodio (192 mg, 4,80 mmol) se agitaron en agua (4,0 mL) y metanol (20 mL) durante 10 horas a 40 °C. La

reacción se concentró y se acidificó a pH-5 con AcOH 1 M. La reacción se extrajo en EtOAc, se secó (Na_2SO_4) y se concentró para obtener el **compuesto 485** en forma de un sólido marrón (430 mg 90% - se observa aproximadamente 10-15% de amida resultante de la hidrólisis de ciano). LCMS APCI *m/z* 523 $[M+H]^+$.

Etapa 7:

El **compuesto 485** (430 mg, 0,823 mmol) se agitó en HCl 4 M en dioxano (2,06 mL) y DCM (10 mL) a temperatura ambiente durante 2 horas. La solución marrón se concentró y se azeotropó con tolueno para producir el **compuesto 486** en forma de un sólido marrón que se usó directamente en la siguiente etapa. LCMS APCI *m/z* 423 $[M+H]^+$.

Etapa 8:

Una solución de **compuesto 486** (asumió 0,823 mmol) en forma de la sal de HCl y DIEA (2,30 mL, 13,20 mmol) en DMF (10 mL) se añadió gota a gota a una solución de HATU (438 mg, 1,15 mmol) en DMF (15 mL) a 0 °C durante 1 hora usando una bomba de jeringa. Después de la adición, la solución amarillo claro se calentó a temperatura ambiente y se agitó durante 14 horas. La reacción se concentró y se añadió agua. La mezcla se extrajo en EtOAc (3x) y las capas orgánicas combinadas se lavaron con Na_2CO_3 acuoso 1 M (5x), NH_4OH acuoso al 10%, agua y salmuera, se secó (Na_2SO_4) y se evaporó para producir una espuma marrón. La purificación por HPLC inversa produjo el **Ejemplo 61** (81 mg, 24%) en forma de un sólido color crema y el Ejemplo 62 (15 mg, 4%) resultante de la hidrólisis de amida, también en forma de un sólido color crema.

Ejemplo 61 (81 mg, 24%).^{1}H RMN (400 MHz, $CDCl_3$) δ 7,95 (brs, 1H) 7,39 (dt, *J* = 1,00 Hz, 1H) 7,28 (dd, *J* =1,00 Hz, 1H) 7,12 (s,1H) 7,02 (dt, *J* = 1,00 Hz,1H) 6,11 (b s, 2H) 4,42 (d, *J* = 14,31 Hz,1H) 4,24 (d, *J* = 1,00 Hz,1H) 4,0 (s, 3H) 3,61 (bs,1H) 2,97 (s,3H) 2,89 - 2,96 (m, 1H) 2,64 (bd, *J* = 1,00 Hz,1H) 1,35 (d, *J* = 6,48 Hz, 3H). LCMS APCI *m/z* 405 $[M+H]^+$.

Ejemplo 62 (15 mg, 4%).^{1}H RMN (400 MHz, $CDCl_3$) δ 7,56 - 7,90 (m,3H) 7,24 - 7,40 (m, 2H) 7,08 (s, 1H) 6,94 - 7,04 (m, 1H) 5,81 (bs, 2H) 4,29 (d, *J* = 13,82 Hz,1H) 4,11 (d, *J* = 13,82 Hz, 1H) 3,89 (s, 3H) 3,61 (bs, 1H) 2,87 - 3,07 (m, 4H) 2,56 - 2,75 (m, 2H) 1,35 (d, *J* = 6,36 Hz, 3H). LCMS APCI *m/z* 423 $[M+H]^+$.

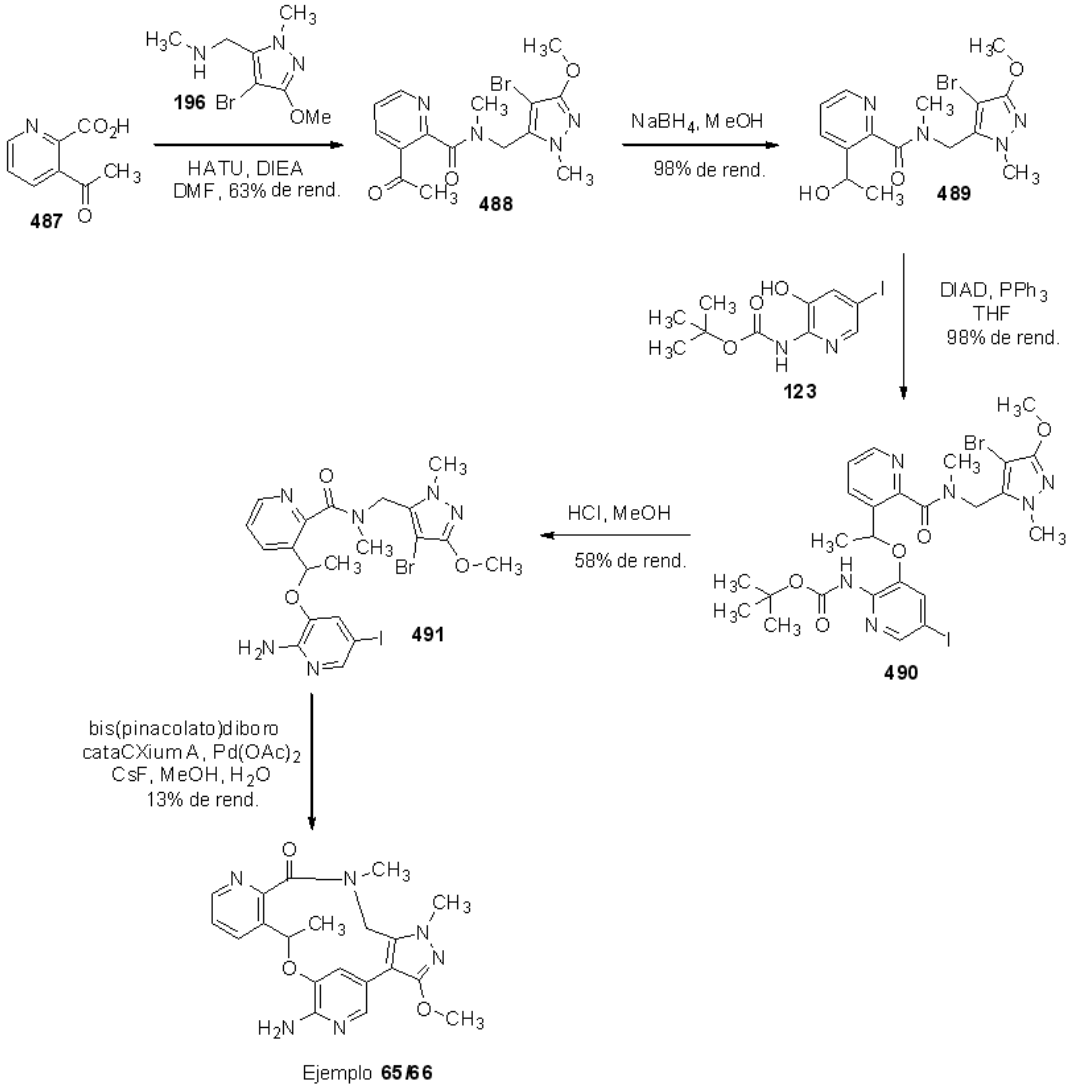
Se sometieron 68 mg del **Ejemplo 61** a separación quiral por SFC para obtener ambos enantiómeros del **compuesto** del título. La separación quiral analítica por SFC se llevó a cabo usando una columna Regis Whelk-01 (*R, R*) (columna de 4,6 mm x 100 mm, tamaño de partícula de 5 micrones), que se eluyó con 30% de MeOH en CO_2

mantenido a 140 bar. Una tasa de flujo de 3 mL/min produjo $Rt_{(pico\ 1)}$ = 3,46 minutos y $Rt_{(pico\ 2)}$ = 4,76 minutos.

Ejemplo 63 (pico 1): 25,0 mg, >99% ee (-).^{1}H RMN (400 MHz, $CDCl_3$) δ 7,95 (brs, 1H) 7,39 (dt, *J* = 1,00 Hz, 1H) 7,28 (dd, *J* =1,00 Hz, 1H) 7,12 (s,1H) 7,02 (dt, *J* = 1,00 Hz,1H) 6,11 (b s, 2H) 4,42 (d, *J* = 14,31 Hz,1H) 4,24 (d, *J* = 1,00 Hz,1H) 4,0 (s, 3H) 3,61 (bs,1H) 2,97 (s,3H) 2,89 - 2,96 (m, 1H) 2,64 (bd, *J* = 1,00 Hz,1H) 1,35 (d, *J* = 6,48 Hz, 3H). LCMS APCI *m/z* 405 $[M+H]^+$.

Ejemplo 64 (pico 2): 24,8 mg, 98% ee (+).^{1}H RMN (400 MHz, $CDCl_3$) δ 7,95 (brs, 1H) 7,39 (dt, *J* = 1,00 Hz, 1H) 7,28 (dd, *J* =1,00 Hz, 1H) 7,12 (s,1H) 7,02 (dt, *J* = 1,00 Hz,1H) 6,11 (b s, 2H) 4,42 (d, *J* = 14,31 Hz,1H) 4,24 (d, *J* = 1,00 Hz,1H) 4,0 (s, 3H) 3,61 (bs,1H) 2,97 (s,3H) 2,89 - 2,96 (m, 1H) 2,64 (bd, *J* = 1,00 Hz,1H) 1,35 (d, *J* = 6,48 Hz, 3H). LCMS APCI *m/z* 405 $[M+H]^+$.

Preparación de 7-amino-3-metoxi-1,10,16-trimetil-16,17-dihidro-1*H*-8,4-(meteno)-pirazolo[4,3-*g*]pirido[2,3-*l*][1,4,10]oxadiazaciclotetradecin-15(10*H*)-ona (Ejemplos 65 y 66)



Etapa 1:

Una suspensión de **compuesto 487** (965 mg, 5,84 mmol) y **compuesto 196** (580 mg, 5,84 mmol) en DMF (40 mL) se agitó en nitrógeno. Se añadió DIEA (3,05 mL, 17,5 mmol), y la suspensión se convirtió en un gel espeso. Se añadió HATU (2890 mg, 7,60 mmol) y la reacción se agitó durante 14 horas. Durante este tiempo, el sólido se disolvió lentamente para producir una solución marrón clara. La reacción se concentró y el residuo se disolvió en EtOAc. El extracto orgánico se lavó con $NaHCO_3$ acuoso saturado y se secó (Na_2SO_4). Las capas orgánicas se filtraron, se concentraron y el residuo se purificó por cromatografía en columna en gel de sílice (0-4% MeOH/DCM) para producir el **compuesto 488** en forma de un sólido color crema (1400 mg, 63%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,70 (dd, *J* = 4,93, 1,39 Hz,1H) 8,11 (dd, *J* = 8,08, 1,52

Hz,1H) 7,43 (dd, *J* = 7,83, 4,80 Hz,1H) 4,87 (m, 2H) 4,80-3,95 (s, 3H) 3,90 (s, 3H) 2,72 (s, 3H) 2,59 (s, 3H). LCMS APCI *m/z* 381/383 $[M+H]^+$.

Etapa 2

Una suspensión de **compuesto 488** (1324 mg, 3,473 mmol) en MeOH (60 mL) se agitó a temperatura ambiente en nitrógeno. Se añadió $NaBH_4$ (144 mg, 3,82 mmol), lo que produjo una vigorosa evolución de gas y una solución incolora transparente. La reacción se agitó durante otras 2 horas, se concentró y el residuo se disolvió en DCM. La capa orgánica se lavó con agua, se secó (Na_2SO_4) y se concentró para producir el **compuesto 489** en forma de un sólido blanco (1300 mg, 98%). LCMS APCI *m/z* 382/385 $[M+H]^+$.

Etapa 3

Al **compuesto 489** (650 mg, 1,70 mmol) y **compuesto 123** (570 mg, 1,70 mmol) en THF (40 mL) en nitrógeno a temperatura ambiente se añadió trifenilfosfina (489 mg, 1,87 mmol) seguido de la adición gota a gota de una solución de DIAD (0,37 ml, 1,87 mmol) en THF (4 mL) para producir una solución amarilla. La reacción se agitó luego durante 14 horas, se concentró y se purificó por cromatografía en columna en gel de sílice (50% DCM/EtOAc) para producir el **compuesto 490** en forma de un sólido blanco (1800 mg, 151%). RMN (CDCl3) indicó que el sólido es aproximadamente una mezcla 1:2 del producto requerido y PPh3=O. De esta manera, 1800 mg de la mezcla son equivalentes a 1008 mg de producto, rendimiento del 85%. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,55 (dd, *J* = 4,71, 1,53 Hz, 1H) 8,18 (d, *J* = 1,83 Hz, 1H) 7,86 (dd, *J* = 7,95, 1,47 Hz, 1H) 7,37 (dd, *J* = 8,07, 4,77 Hz, 1H) 7,34 (d, *J* = 1,71 Hz, 1H) 5,63 (q, *J* = 6,40 Hz, 1H) 4,80 - 5,02 (m, 2H) 3,97 (s, 3H) 3,87 (s, 3H) 2,86 (s, 3H) 1,74 (d, *J* = 6,36 Hz, 3H) 1,57 (s, 9H). LCMS APCI *m/z* 700/703 $[M+H]^+$.

Etapa 4

A una solución de **compuesto 490** (1800 mg, teoría 1,40 mmol) en MeOH (30 mL) se añadió HCl 4 M en dioxano (3,6 mL), lo que produjo una solución, que se agitó a temperatura ambiente durante 15 horas. La reacción se concentró para producir un sólido viscoso color crema. Esto se suspendió en DCM y se lavó con $NaHCO_3$ acuoso saturado para formar la base libre. Las capas orgánicas se secaron (Na2SO4), se concentraron y se purificaron por cromatografía en columna en gel de sílice (0-100% de EtOAc/DCM) para obtener el **compuesto 491** en forma de una espuma color crema (500 mg, 58%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,53 (dd, *J* = 4,77, 1,59 Hz, 1H) 7,86 (dd, *J*= 8,07, 1,47 Hz, 1H) 7,81 (d, *J* = 1,71 Hz, 1H) 7,37 (dd, *J* = 7,95, 4,77 Hz, 1H) 7,05 (d, *J* = 1,59 Hz, 1H) 5,56 (q, *J* = 6,40 Hz, 1H) 4,80 - 5,00 (m, 2H) 4,76 (bs, 1H) 3,97 (s,

3H) 3,84 - 3,90 (m, 3H) 2,84 (s, 3H) 1,71 (d, *J* = 6,36 Hz, 3H). LCMS APCI *m/z* 601/602 $[M+H]^+$.

Etapa 5

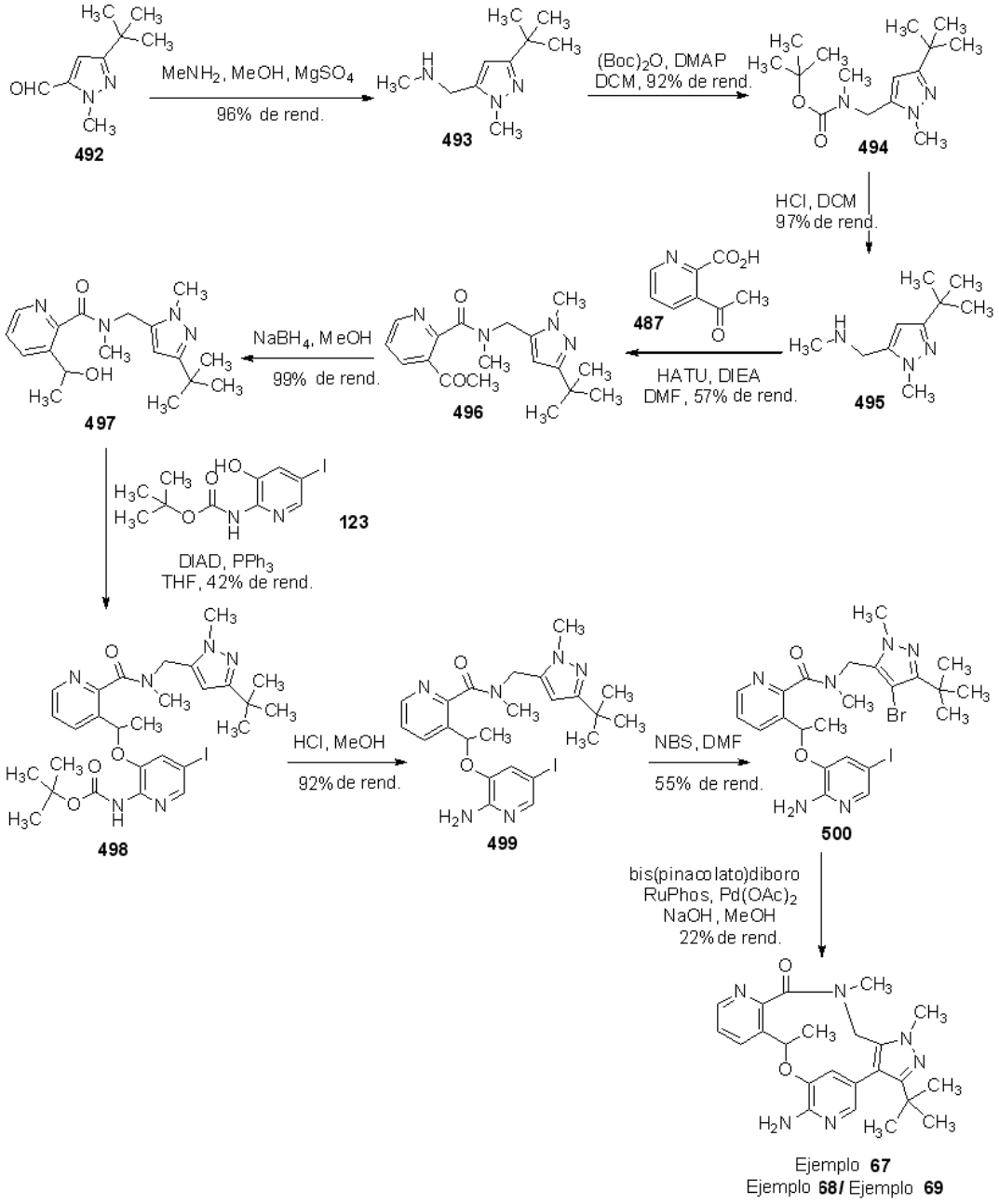
El **compuesto 491** (500 mg, 0,832 mmol), bis(pinacolato)diboro (1070 mg, 4,16 mmol), cataCXium A (60 mg, 0,166 mmol), fluoruro de cesio (638 mg, 4,16 mmol) y acetato de paladio (19 mg, 0,830 mmol) en agua (20 mL) metanol (200 mL) se calentaron a 100 ℃ durante la noche. La reacción se concentró y se dividió en agua y EtOAc. Las capas orgánicas se secaron (Na2SO4), se concentraron en un aceite amarillo, que se purificó por HPLC preparativa de fase inversa para obtener el **Ejemplo 65 y el Ejemplo 66** en forma de un polvo blanco (43 mg, 13%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,48 (dd, *J* = 4,67, 1,39 Hz, 1H) 8,15 (dd, *J* = 8,08, 1,26 Hz, 1H) 7,43 - 7,54 (m,2H) 6,75 (d, *J* = 1,26 Hz,1H) 5,73 (s, 2H) 5,56 (d, *J* = 6,32 Hz, 1H) 4,59 (d, *J* = 15,66Hz, 1H) 4,01 (d, *J* = 15,41 Hz, 1H) 3,83 (d, *J* = 7,58 Hz, 5H) 3,0 (s, 3H) 1,69 (d, *J* = 6,32 Hz, 3H). LCMS APCI *m/z* 395 $[M+H]^+$.

Una muestra de 43 mg se sometió a separación quiral por SFC para obtener ambos enantiómeros del **compuesto** del título. La separación quiral analítica por SFC se llevó a cabo usando una columna Regis Whelk-01 (*R, R*) (columna de 4,6 mm x 100 mm, tamaño de partícula de 5 micrones), que se eluyó con 30% de MeOH en CO_2 mantenido a 140 bar. Una tasa de flujo de 3 mL/min produjo $Rt_{(pico\ 1)}$ = 5,77 minutos y $Rt_{(pico\ 2)}$ = 7,01 minutos.

Ejemplo 65 (pico 1): 12 mg, 99% ee (-). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,48 (dd, *J* = 4,67, 1,39 Hz, 1H) 8,15 (dd, *J* = 8,08, 1,26 Hz, 1H) 7,43 - 7,54 (m,2H) 6,75 (d, *J* = 1,26 Hz,1H) 5,73 (s, 2H) 5,56 (d, *J* = 6,32 Hz, 1H) 4,59 (d, *J* = 15,66Hz, 1H) 4,01 (d, *J* = 15,41 Hz, 1H) 3,83 (d, *J* = 7,58 Hz, 5H) 3,0 (s, 3H) 1,69 (d, *J* = 6,32 Hz, 3H). LCMS APCI *m/z* 395 $[M+H]^+$.

Ejemplo 66 (pico 2): 15 mg, 97% ee (+). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,48 (dd, *J* = 4,67, 1,39 Hz, 1H) 8,15 (dd, *J* = 8,08, 1,26 Hz, 1H) 7,43 - 7,54 (m,2H) 6,75 (d, *J* = 1,26 Hz,1H) 5,73 (s, 2H) 5,56 (d, *J* = 6,32 Hz, 1H) 4,59 (d, *J* = 15,66Hz, 1H) 4,01 (d, *J* = 15,41 Hz, 1H) 3,83 (d, *J* = 7,58 Hz, 5H) 3,0 (s, 3H) 1,69 (d, *J* = 6,32 Hz, 3H). LCMS APCI *m/z* 395 $[M+H]^+$.

Preparación de 7-amino-3-ter-butil-1,10,16-trimetil-16,17-dihidro-1*H*-8,4-(meteno)pirazolo[4,3-*g*]pirido[2,3-*l*][1,4,10]oxadiazaciclotetradecin-15(10*H*)-ona (Ejemplos 67, 68 y 69)



Ejemplo **67**
Ejemplo **68** / Ejemplo **69**

Etapa 1:

El **compuesto 492** (2000 mg, 12,03 mmol) en MeOH (50 mL) se agitó en nitrógeno con 33% de metilamina en EtOH (1,80 mL. 5,09 mmol). Se añadió $MgSO_4$ anhidro (3000 mg) y la reacción se agitó durante otras 1,5 horas. El recipiente de reacción se enfrió en un baño de hielo y se añadió $NaBH_4$ (546 mg, 14,40 mmol). La reacción se agitó durante 14 horas, se concentró y se dividió en agua y DCM. La capa orgánica se separó y la capa acuosa se extrajo luego con DCM (2 x). Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentró para producir el

compuesto 493 en forma de un aceite incoloro (2100 mg, 96%). LCMS APCI *m/z* 182 $[M+H]^+$.

Etapa 2:

A una solución de **compuesto 493** (2100 mg, 11,58 mmol) en diclorometano (60 mL) se añadió DMAP (283 mg, 2,32 mmol), seguido de $(Boc)_2O$ (4040 mg, 18,50 mmol) para producir una solución amarilla. La reacción se agitó a temperatura ambiente durante 2 horas, y luego el solvente se eliminó a presión reducida para producir un aceite amarillo. La reacción se purificó por cromatografía en columna en gel de sílice (0-100% de EtOAc/heptano) para obtener el compuesto **494** en forma de un aceite incoloro (3000 mg, 92%).^{1}H RMN (400 MHz, $CDCl_3$) δ 5,97 (s, 1H) 4,40 (s, 2H) 3,77 (s, 3H) 2,77 (s, 3H) 1,46 (s, 9H), 1,27 (s, 9H). LCMS APCI *m/z* 282 $[M+H]^+$.

Etapa 3:

A una solución de **compuesto 494** (3800 mg, 13,50 mmol) en DCM (50 mL) se añadió HCl 4 M en dioxano (34 mL, 135 mmol) y la reacción se agitó durante 2 horas. En este momento, la reacción se volvió turbia y e añadió MeOH para producir una solución amarillo claro, que se agitó durante otras 2 horas. La reacción se concentró para obtener un sólido color crema, que se suspendió en heptanos, se filtró y se secó para producir el **compuesto 495** en forma de un sólido (3318 mg, 97%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,32 - 9,49 (m, 1H) 6,29 - 6,39 (m, 1H) 4,15 (t, 2H) 3,79-3,83 (m, 3H) 2,54 (t, 3H) 1,17 - 1,23 (m, 9H). LCMS APCI *m/z* 182 $[M+H]^+$.

Etapa 4:

A una suspensión de **compuesto 495** (965 mg, 5,84 mmol) y **compuesto 487** (1490 mg, 5,84 mmol) en DMF (40 mL) en nitrógeno se añadió DIEA (3,05 mL, 17,5 mmol) para producir una solución color marrón claro. Se añadió HATU (2890 mg, 7,60 mmol), y la reacción se agitó durante 16 horas. La reacción se concentró y el residuo se disolvió en EtOAc. Las capas orgánicas se lavaron con $NaHCO_3$ acuoso saturado, se secaron (Na_2SO_4) y se concentraron para obtener un residuo, que se purificó por cromatografía en columna en gel de sílice (0-4% MeOH/DCM) para obtener el compuesto **496** en forma de un sólido marrón (1100 mg, 57%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,71 (dd, *J* = 4,83, 1,53 Hz, 1H) 8,11 (dd, *J* = 7,95, 1,59 Hz,1H) 7,44 (dd, *J* = 7,89, 4,83 Hz, 1H) 6,17 (s, 1H) 4,81 (s, 2H) 3,93 (s, 3H) 2,75 (s, 3H) 2,61 (s, 3H) 1,32 (s, 9H).LCMS APCI *m/z* 329 $[M+H]^+$.

Etapa 5:

A una solución agitada de **compuesto 496** (1100 mg, 3,349 mmol) en MeOH (20 mL) en nitrógeno se añadió borhidruro de sodio (152 mg, 4,02 mmol) en porciones.

Se observó una vigorosa producción de gas y la reacción rápidamente se volvió una solución amarilla. La reacción se agitó durante una hora, se concentró y el residuo se disolvió en DCM. La solución orgánica se lavó con agua, se secó (Na_2SO_4) y se concentró para producir el **compuesto 497** (1100 mg, 99%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,52 (dd, *J* = 4,71, 1,65 Hz, 1H) 7,90 (dd, *J* = 7,83, 1,47 Hz, 1H) 7,37 (m, *J* = 7,90, 4,70 Hz,1H) 4,88 -4,99 (m,1H) 4,82 (q, *J* = 1,00 Hz, 2H) 3,92 (s, 3H) 2,86 (s, 3H) 1,55 (d, *J* = 6,60 Hz, 3H) 1,30 (s, 9H).LCMS APCI *m/z* 331 $[M+H]^+$.

Etapa 6:

A una solución de **compuesto 497** (1100 mg, 3,329 mmol) y **compuesto 123** (1120 mg, 3,33 mmol) en THF (40 mL) en nitrógeno a temperatura ambiente se añadió trifenilfosfina (960 mg, 3,66 mmol) seguido de la adición gota a gota de una solución de DIAD (0,72 mL. 3,66 mmol) en THF (5 mL) para obtener una solución amarilla. La reacción se agitó a temperatura ambiente durante 20 horas, se concentró y se purificó por cromatografía en columna en gel de sílice (50:50 DCM/EtOAc) para producir el **compuesto 498** en forma de un sólido amarillo (900 mg, 42%).^{1}H RMN (400 MHz, $CDCl_3$) δ 8,55 (dd, *J* = 4,65, 1,47 Hz, 1H) 8,18 (d, *J* = 1,83Hz, 1H) 7,85 (dd, *J* = 8,01, 1,41 Hz,1H) 7,37 (dd, *J* = 7,95, 4,77 Hz, 1H) 7,27-7,33 (m, 3 H) 6,14 (s, 1H) 5,62 (q, *J* = 6,50 Hz, 1H) 4,67-5,01 (m, 2H) 3,92 (s, 3H) 2,82-2,89 (m, 3H) 1,75 (d, *J* = 6,36 Hz, 3H) 1,57 (s, 9H) 1,29 (s, 9H).LCMS APCI *m/z* 649 $[M+H]^+$.

Etapa 7:

A una solución agitada de **compuesto 498** (900 mg, 1,39 mmol) en MeOH (30 mL) se añadió HCl 4 M en dioxano (3,6 mL) para obtener una solución amarilla, que se agitó a temperatura ambiente durante 16 horas. La reacción se concentró para obtener un aceite, que se dividió entre DCM y $NaHCO_3$ acuoso saturado. La capa orgánica se separó y la capa acuosa luego se extrajo con DCM (3x). Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron para producir el **compuesto 499** en forma de una espuma dorada (700 mg, 92%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,54 (dd, *J* = 4,71,1,53 Hz, 1H) 7,85 (dd, *J* = 8,07,1,47 Hz, 1H) 7,80 (d, *J* = 1,59 Hz, 1H) 7,64 - 7,72 (m, 2H) 7,03 (d, *J* = 1,59 Hz, 1H) 6,14 (s, 1H) 5,55 (q, *J* = 6,40 Hz, 1H) 4,94 (d, *J* = 15,16 Hz, 1H) 4,69-4,82 (m, 3H) 3,92 (s, 3H) 2,85 (s, 3H) 1,71 (d, *J* = 6,36 Hz, 3H) 1,29 (s, 9H). LCMS APCI *m/z* 549 $[M+H]^+$.

Etapa 8:

El **compuesto 499** (650 mg, 1,18 mmol) y NBS (234 mg, 1,30 mmol) en DMF (20 mL) se agitaron en nitrógeno durante 1 hora. La reacción se concentró y se dividió en EtOAc y $NaHCO_3$ acuoso saturado. Las capas orgánicas se secaron (Na2SO4), se

concentraron para obtener un aceite marrón, que se purificó por cromatografía en columna en gel de sílice (0-4% MeOH/DCM) para producir el **compuesto 500** en forma de una espuma marrón (411 mg, 55% - LCMS indica que una impureza de dibromo está presente). LCMS APCI *m/z* 581/583. $[M+H]^+$.

Etapa 9:

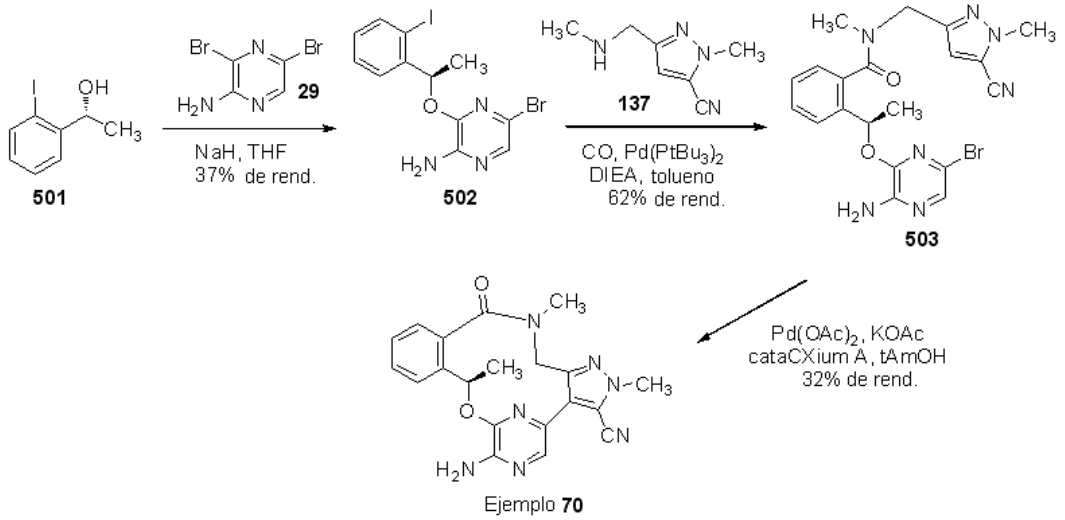
El **compuesto 500** (370 mg, 0,590 mmol), bis(pinacolato)diboro (454 mg, 1,77 mmol), RuPhos (36 mg, 0,074 mmol) y acetato de paladio (8,3 mg, 0,037 mmol) en NaOH 1 M (3 mL) y metanol (35 mL) se calentaron a 100 °C durante 14 horas. La reacción se concentró y se dividió en agua y EtOAc. Las capas orgánicas se secaron (Na_2SO_4) y se concentraron para producir un aceite amarillo, que se purificó por HPLC preparativa para producir el **Ejemplo 67** en forma de un sólido blanco (55 mg, 22%).^{1}H RMN (400 MHz, DMSO-d_6) δ 8,38 (dd, *J* = 4,66,1,64 Hz, 1H) 8,21 (dd, *J* = 8,06,1,51 Hz, 1H) 7,40 (dd, *J* = 8,06, 4,53 Hz, 1H) 7,33 (d, *J* = 2,01 Hz, 1H) 6,85 (d, *J* = 1,76 Hz, 1H) 5,72 (q, *J* = 6,30 Hz, H) 5,49 (s, 2H) 4,43 (d, *J* = 15,36 Hz, 1H) 3,97 (d, *J* = 15,11 Hz, 1H) 3,91 (s, 3H) 2,98 (s, 3H) 1,73 (d, *J* = 1,00 Hz,3H) 1,23 (s, 9H). LCMS APCI *m/z* 421 $[M+H]^+$.

Se sometieron 50 mg del **Ejemplo 67** a separación quiral por SFC para obtener ambos enantiómeros del **compuesto** del título. La separación quiral analítica por SFC se llevó a cabo usando una columna Regis Whelk-01 (*R, R*) (columna de 4,6 mm x 100 mm, tamaño de partícula de 5 micrones), que se eluyó con 30% de MeOH en CO_2 mantenido a 140 bar. Una tasa de flujo de 3 mL/min produjo $Rt_{(pico\ 1)}$ = 4,87 minutos y $Rt_{(pico\ 2)}$ = 6,99 minutos. Cada pico rápidamente se equilibró hasta obtener una mezcla 90 : 10 de atropisómeros.

Ejemplo 68 (pico 1): 12 mg, 95% ee (-).^{1}H RMN (400 MHz, DMSO-d_6) δ 8,38 (dd, *J* = 4,66,1,64 Hz, 1H) 8,21 (dd, *J* = 8,06,1,51 Hz, 1H) 7,40 (dd, *J* = 8,06, 4,53 Hz, 1H) 7,33 (d, *J* = 2,01 Hz, 1H) 6,85 (d, *J* = 1,76 Hz, 1H) 5,72 (q, *J* = 6,30 Hz, H) 5,49 (s, 2H) 4,43 (d, *J* = 15,36 Hz, 1H) 3,97 (d, *J* = 15,11 Hz, 1H) 3,91 (s, 3H) 2,98 (s, 3H) 1,73 (d, *J* = 1,00 Hz,3H) 1,23 (s, 9H). LCMS APCI *m/z* 421 $[M+H]^+$.

Ejemplo 69 (pico 2): 13 mg, 95% ee (+). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,38 (dd, *J* = 4,66,1,64 Hz, 1H) 8,21 (dd, *J* = 8,06,1,51 Hz, 1H) 7,40 (dd, *J* = 8,06, 4,53 Hz, 1H) 7,33 (d, *J* = 2,01 Hz, 1H) 6,85 (d, *J* = 1,76 Hz, 1H) 5,72 (q, *J* = 6,30 Hz, H) 5,49 (s, 2H) 4,43 (d, *J* = 15,36 Hz, 1H) 3,97 (d, *J* = 15,11 Hz, 1H) 3,91 (s, 3H) 2,98 (s, 3H) 1,73 (d, *J* = 1,00 Hz,3H) 1,23 (s, 9H). LCMS APCI *m/z* 421 $[M+H]^+$.

Preparación de (10*R*)-7-amino-2,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(azeno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 70)



Etapa 1:

A una solución helada de **compuesto 501** (1593 mg, 6,422 mmol) en THF (30 mL) en nitrógeno se añadió NaH (282 mg, 7,06 mmol, 60% de dispersión), lo que produjo una suspensión blanca con muy poca producción de gas. La suspensión se agitó durante 30 minutos y luego se añadió gota a gota una solución de **compuesto 29** (1620 mg, 6,42 mmol) en THF (8 mL). La solución color naranja brillante se calentó a 50 ºC durante 48 horas. La reacción se concentró y se dividió en EtOAc y salmuera. Los insolubles se filtraron, la capa orgánica se separó y la capa acuosa luego se extrajo con EtOAc. Las capas orgánicas combinadas se secaron (Na2SO4), se concentraron y el residuo se purificó por cromatografía en columna en gel de sílice (DCM para producir el **compuesto 502**, (R)-5-bromo-3-(1-(2-yodofenil)etoxi)pirazin-2-amina, en forma de un aceite amarillo pálido (1000 mg, 37%). LCMS APCI *m/z* 419/421 $[M+H]^+$.

Etapa 2:

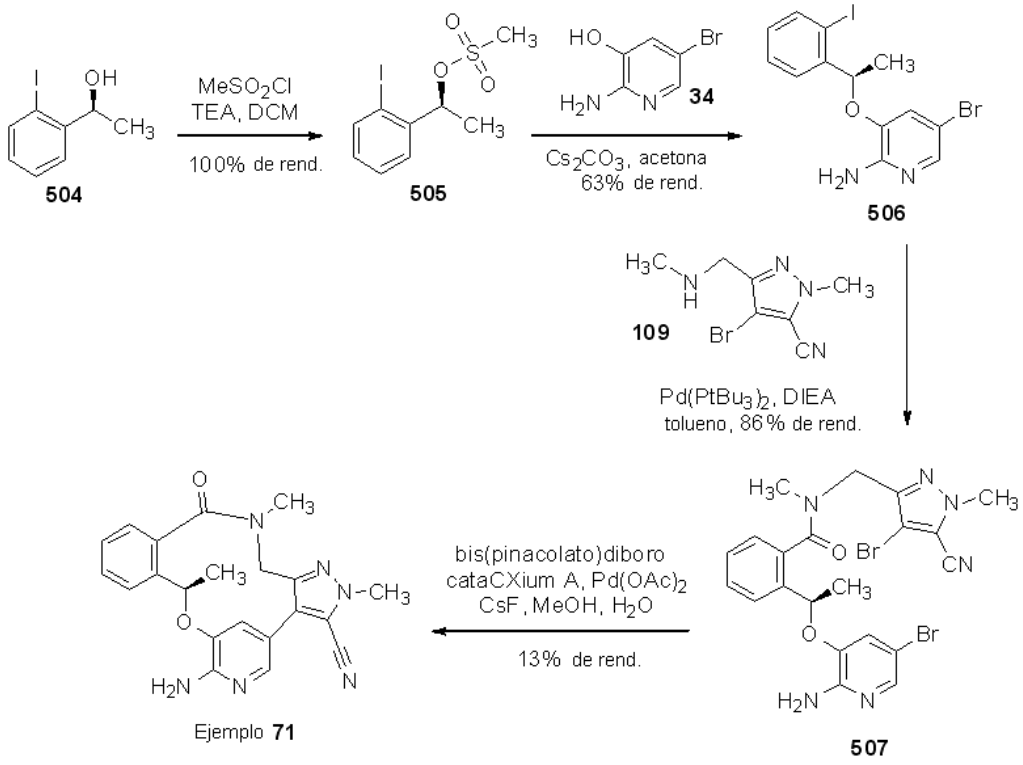
Una mezcla de **compuesto 502** (1000 mg, 2,381 mmol), **compuesto 137** (692 mg, 3,10 mmol), DIEA (1,66 mL 9,52 mmol) y Pd $(P^tBu_3)_2$ (124 mg, 0,238 mmol) en tolueno (25 mL) se agitó a 85 ºC a 4 bar de CO durante 2 horas. La reacción se concentró para obtener un aceite rojo, que se purificó por cromatografía en columna en gel de sílice (0-25% de EtOAc/heptano) para obtener el **compuesto 503**,(R)-2-(1-(3-amino-6-bromopirazin-2-iloxi)etil)-N-((5-ciano-1-metil-1H-pirazol-3-il)-metil)-N-metilbenzamida, en forma de un aceite amarillo pálido (689 mg, 62%). ^{1}H RMN (400

MHz, DMSO) δ 7,67 (d, *J* = 1,00 Hz,1H) 7,55 (s, 1H) 7,43 (dt, *J* = 1,00 Hz, 1H) 7,35 (m, 1H) 7,21-7,29 (m, 1H) 6,92-7,09 (m, 1H) 6,28 (bs, 2H) 6,10 (q, *J* = 1,00Hz, 1H) 4,70 (bs, 2H) 3,97 (s, 3H) 2,86 (bs, 3H) 1,61 (d, *J* = 6,55 Hz,3H). LCMS APCI *m/z* 470/472 $[M+H]^+$.

Etapa 3:

El **compuesto 503** (689 mg, 1,46 mmol), KOAc (733 mg, 7,47 mmol) y cataCXium A (163 mg, 0,440 mmol) se combinaron en alcohol ter-amílico (30 ml) y se burbujeó nitrógeno a través de la solución antes de añadir $Pd(OAc)_2$ (49 mg, 0,220 mmol). La reacción se calentó a 120 °C durante 3 horas en el microondas. La reacción se concentró y se dividió en agua y EtOAc. Los insolubles se filtraron y las capas orgánicas se secaron (Na_2SO_4) para producir el producto crudo en forma de un aceite amarillo, que se purificó por HPLC preparativa para producir el macrociclo en forma de una espuma amarilla. Esto se suspendió en agua durante 30 minutos, luego se filtró, luego se lavó con agua y se secó al vacío durante la noche para producir el **Ejemplo 70** (185 mg, 32%) en forma de un polvo amarillo. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,75 (s, 1H) 7,65 (d, *J* = 7,83Hz, 1H) 7,39-7,46 (m, 1H) 7,28-7,34 (m, 2H) 6,73 (bs, 2H) 5,91 (q, *J* = 6,50 Hz, 1H) 4,38 (d, *J* = 1,00 Hz, 1H) 4,28 (d, *J* = 1,00 Hz, 1H) 4,03 (s, 3H) 2,90 (s, 3H) 1,65 (d, *J*=6,60 Hz, 3H). LCMS APCI *m/z* 390 $[M+H]^+$.

Preparación de (10*R*)-7-amino-2,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(meteno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 71)



Etapa 1:

A una solución enfriada de **compuesto 504** (1283 mg, 5,172 mmol) y trietilamina (1,44 mL, 10,30 mmol) en DCM (15 mL) en nitrógeno se añadió lentamente gota a gota cloruro de metansulfonilo (0,60 mL, 7,76 mmol) para producir una suspensión color crema. La reacción se calentó a temperatura ambiente y se agitó durante 15 horas. La reacción se lavó con HCl acuoso 1 M y $NaHCO_3$ acuoso saturado. Las capas orgánicas se secaron (Na_2SO_4) y se concentraron para producir el **compuesto 505** en forma de un aceite anaranjado (1704 mg, 100%), que se usó directamente en la siguiente etapa sin otra purificación.

Etapa 2:

El **compuesto 34** (815 mg, 4,31 mmol) y **compuesto 505** (1687 mg, 5,172 mmol) se agitaron a 50 °C en acetona (50 mL) con carbonato de cesio (2810 mg, 8,62 mmol) durante 6 horas. La reacción se filtró y los sólidos se enjuagaron con acetona. El filtrado se concentró para obtener un residuo oscuro, que se purificó por cromatografía en columna en gel de sílice (0-25% de EtOAc/heptanos) para producir el **compuesto 506** en forma de un aceite anaranjado (1144 mg, 63%). LCMS APCI *m/z* 418/420 $[M+H]^+$.

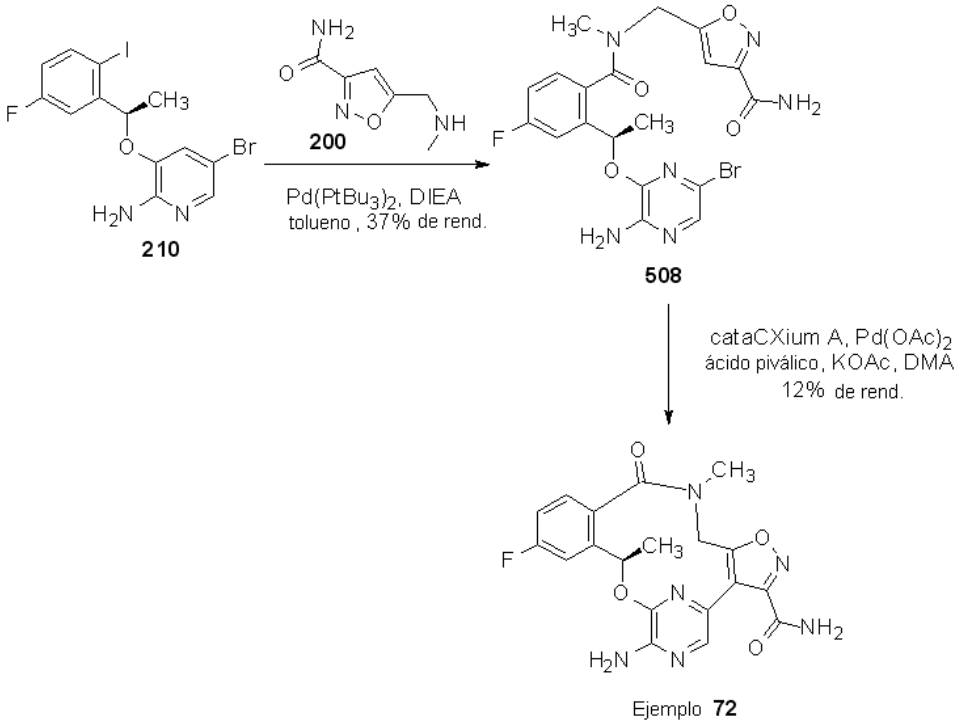
Etapa 3:

Una mezcla de **compuesto 506** (1144 mg, 1,60 mmol), **compuesto 109** (447 mg, 1,68 mmol), DIEA (1,14 mL, 6,55 mmol) y $Pd(P^tBu_3)_2$ (86 mg, 0,164 mmol) en tolueno (20 mL) se calentó a 85 ºC en una atmósfera de 4 bar de CO durante 14 horas. La reacción se concentró para producir un aceite rojo, que se purificó por cromatografía en columna en gel de sílice (0-100% de EtOAc/heptano) para producir el **compuesto 507** en forma de un sólido amarillo (770 mg, 86%). HRMN ($CDCl_3$) indica la presencia de rotámeros. LCMS APCI *m/z* 548/550 $[M+H]^+$.

Etapa 4:

El **compuesto 507** (770 mg, 1,40 mmol), bis(pinacolato)diboro (1800 mg, 7,02 mmol), cataCXium A (101 mg, 0,281 mmol), fluoruro de cesio (1070 mg 7,02 mmol) y acetato de paladio (32 mg, 0,14 mmol) en agua (10 mL) metanol (100 mL) se calentaron a 100 ºC durante la noche. La reacción luego se concentró y se dividió en agua y EtOAc. Las capas orgánicas se secaron (Na_2SO_4) y se concentraron para producir un aceite amarillo, que se sometió a cromatografía en columna en gel de sílice (0-5% de MeOH/DCM) y HPLC preparativa de fase inversa. El material obtenido se suspendió en heptano, se filtró y se secó al vacío para producir el **Ejemplo 71** (43 mg, 13%) en forma de un polvo blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,72 (d, *J* = 7,81 Hz, 1H) 7,57 (d, *J* = 2,01 Hz, 1H) 7,44 (dt, *J* = 1,00 Hz,1H) 7,29 - 7,39 (m, 2H) 6,83 (d, *J* = 1,76 Hz, 1H) 6,11 (bs, 2H) 5,59 (q, *J* = 6,30 Hz, 1H) 4,45 (d, *J* = 14,35 Hz, 1H) 4,24 (d, *J* = 14,10 Hz, 1H) 4,03 (s, 3H) 3,00 (s, 3H) 1,69 (d, *J* = 6,29 Hz, 3H). LCMS APCI *m/z* 389 $[M+H]^+$.

Preparación de (10*R*)-7-amino-12-fluoro-10,16-dimetil-15-oxo-10,15,16,17-tetrahidro-8,4-(azeno)[1,2]oxazolo[4,5-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carboxamida (Ejemplo 72)



Ejemplo **72**

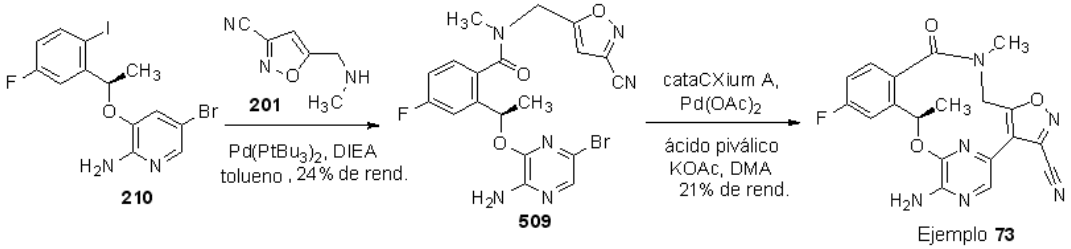
Etapa 1:

Al **compuesto 210** (150 mg, 0,342 mmol) en tolueno (10 mL) se añadieron el **compuesto 200** (55,7 mg, 0,359 mmol), DIEA (0,238 mL, 1,37 mmol) y $Pd(P^tBu_3)_2$ (17,7 mg, 0,034 mmol). La mezcla se calentó en un recipiente sellado a 85 °C en 4 bar de CO durante 16 horas. La reacción se concentró y se purificó por cromatografía en columna en gel de sílice (0-40% EtOAc/heptano – dos columnas) para producir el **compuesto 508** (62 mg, 37%) en forma de una goma amarilla. LCMS APCI *m/z* 493 $[M+H]^+$.

Etapa 2:

Al **compuesto 508** (62,0 mg, 0,13 mmol) en DMA (2,5 mL) se añadieron KOAc (61,8 mg, 0,63 mmol), ácido piválico (3,9 mg, 0,038 mmoL), cataCXium A (14,0 mg, 0,038 mmol) y $Pd(OAc)_2$ (4,3 mg, 0,019 mmol). La mezcla se inundó con nitrógeno y luego se calentó en un microondas a 120 °C durante 1 hora. Se añadió agua a la reacción, que se extrajo con EtOAc (3x), se secó (Na_2SO_4), se concentró y se purificó por HPLC de fase inversa para producir el **Ejemplo 72** (6,48 mg, 12%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,36 (s, 1 H) 8,03 (s, 1 H) 7,73 (s, 1 H) 7,52 (dd, *J* = 10,03, 2,57 Hz, 1 H) 7,41 (dd, *J* = 8,50, 5,69 Hz, 1 H) 7,20 (td, *J* = 8,53, 2,63 Hz, 1 H) 6,67 (s, 2 H) 5,89 (dd, *J* = 6,54, 1,77 Hz, 1 H) 4,44 - 4,57 (m, 2 H) 2,96 (s, 3 H)1,65 (d, *J* = 6,48 Hz, 3 H). LCMS APCI *m/z* 413 $[M+H]^+$.

Preparación de (10*R*)-7-amino-12-fluoro-10,16-dimetil-15-oxo-10,15,16,17-tetrahidro-8,4-(azeno)[1,2]oxazolo[4,5-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 73)



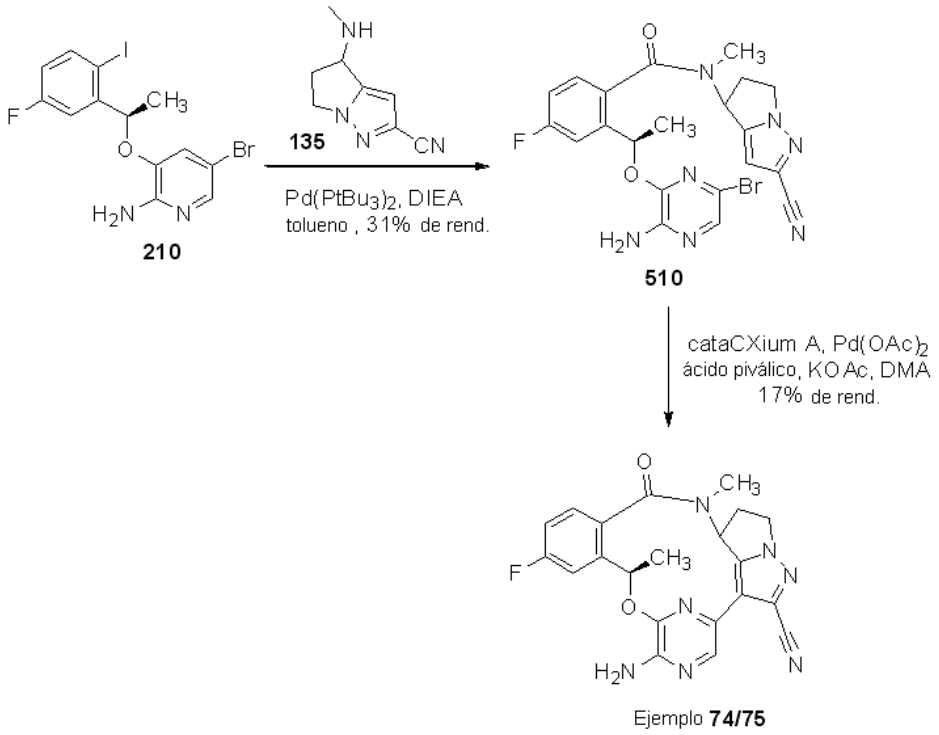
Etapa 1:

A una solución de **compuesto 210** (800 mg, 1,83 mmol) en tolueno (50 mL) se añadieron el **compuesto 360** (686 mg, 2,73 mmol), DIEA (1,27 mL, 7,30 mmol) y $Pd(P^tBu_3)_2$ (95,4 mg, 0,183 mmol). La mezcla se calentó en un recipiente sellado a 85 ºC en 4 bar de CO durante 16 horas. La reacción se concentró y se purificó por cromatografía en columna en gel de sílice (0-40% EtOAc/heptano) para producir el **compuesto 509** (212 mg, 24%) en forma de un sólido amarillento. LCMS APCI *m/z* 476 $[M+H]^+$.

Etapa 2:

A una solución de **compuesto 509** (188 mg, 0,395 mmol) en DMA (7,92 mL) se añadieron KOAc (194 mg, 1,98 mmol), ácido piválico (12,3 mg, 0,119 mmoL), cataCXium A (44,0 mg,0,30 mmol) y $Pd(OAc)_2$ (13,2 mg, 0,059 mmol). Después de purgar con nitrógeno, la mezcla se calentó en un microondas a 120 ºC durante 1 hora. Se añadió agua y la reacción se extrajo con EtOAc (3x). Las capas orgánicas combinadas se secaron (Na2SO4), se concentraron y se purificaron por HPLC de fase inversa para obtener el **Ejemplo 73** (32,12 mg, 21%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,89 (s, 1 H) 7,48 (dd, *J* = 10,03, 2,57 Hz, 1 H) 7,43 (dd, *J* = 8,50, 5,69 Hz, 1 H) 7,18 - 7,25 (m, 1 H) 6,93 (bs., 2 H) 5,85 (dd, *J* = 6,60, 1,59 Hz, 1 H) 4,54 - 4,69 (m, 2 H) 2,94 (s, 3 H) 1,65 (d, *J* = 6,48 Hz, 3 H). LCMS ES *m/z* 395 $[M+H]^+$.

Preparación de (9*R*)-6-amino-11-fluoro-9,15-dimetil-14-oxo-9,14,15,15a,16,17-hexahidro-7,3-(azeno)-8-oxa-1,5,15,17a-tetraazabenzo[11,12]ciclotetradeca[1,2,3-*cd*]pentalen-2-carbonitrilo (Ejemplos 74 y 75)



Ejemplo **74/75**

Etapa 1:

Al **compuesto 210** (250 mg, 0,571 mmol) en tolueno (20 mL) se añadieron **compuesto 135** (140 mg, 0,685 mmol), DIEA (0,398 mL, 2,28 mmol) y $Pd(P^tBu_3)_2$ (29,7 mg, 0,057 mmol). La mezcla se calentó en un recipiente sellado a 85 °C en 4 bar de presión de CO durante 16 horas. Se concentró y se purificó por cromatografía en columna en gel de sílice (0-70% EtOAc/heptano) para producir el **compuesto 510** (88 mg, 31%) en forma de una goma incolora. LCMS ES *m/z* 500 $[M+H]^+$.

Etapa 2:

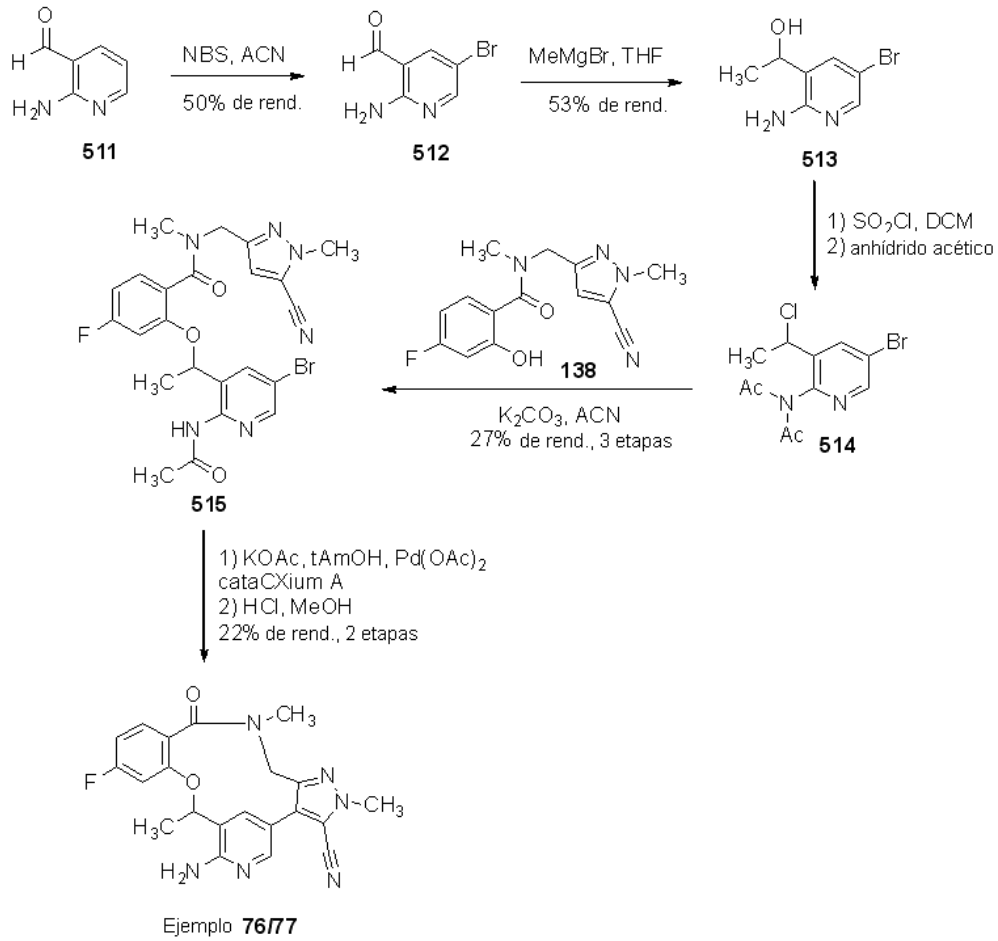
A una solución de **compuesto 510** (88 mg, 0,18 mmol) en alcohol t-amílico (6ml) se añadieron KOAc (86,4 mg, 0,88 mmol), cataCXium A (8,10 mg, 0,022 mmol) y $Pd(OAc)_2$ (8,1 mg, 0,022 mmol). Después de purgar con nitrógeno, la mezcla se calentó en un microondas a 140 °C durante 1 hora. La reacción se filtró y se sometió a separación quiral por SFC para obtener tanto el **Ejemplo 74** como el **Ejemplo 75**. La separación quiral por SFC se llevó a cabo usando una columna Chiralcel OD-H (columna 21,2 mm x 250 mm, tamaño de partícula de 5 micrones), que se eluyó con 34% de MeOH en CO_2 mantenido a 100 bar. Una tasa de flujo de 62 mL/min produjo $Rt_{(pico\ 1)}$ = 3,11 minutos y $Rt_{(pico\ 2)}$ = 4,80 minutos.

Ejemplo 74 (pico 1): 4,97 mg, > 99% ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,44 (s, 1 H) 7,42 (dd, *J* = 9,60, 2,53 Hz, 1 H) 7,21 - 7,25 (m, 1 H) 7,06 (td, *J* = 8,21, 2,53 Hz, 1 H)

6,83 (t, *J* = 8,72 Hz, 1 H) 6,59 - 6,67 (m, 1 H) 5,02 (s, 2 H) 4,39 - 4,48 (m, 1 H) 4,25 (td, *J* = 10,80, 7,20 Hz, 1 H) 3,06 - 3,21 (m, 1 H) 2,55 - 2,68 (m, 1 H) 2,43 (s, 3 H) 1,69 (d, *J* = 6,57 Hz, 3 H). LCMS ES *m/z* 420 $[M+H]^+$.

Ejemplo 75 (pico 2): 7,44 mg, > 99% ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,31 (s, 1 H) 7,33 (dd, *J* = 9,60, 2,27 Hz, 1 H) 7,17 (dd, *J* = 8,46, 5,43 Hz, 1 H) 7,03 (td, *J* = 8,21, 2,27 Hz, 1 H) 5,80 (d, *J* = 5,56 Hz, 1 H) 5,35 (d, *J* = 8,84 Hz, 1 H) 5,07 (s, 2 H) 4,44 - 4,56 (m, 1 H) 4,23 (t, *J* = 10,61 Hz, 1 H) 3,08 (dd, *J* = 14,02, 9,47 Hz, 1 H) 2,94 (s, 3 H) 2,69 (dd, *J* = 14,15, 7,58 Hz, 1 H) 1,72 (d, *J* = 6,57 Hz, 3 H). LCMS ES *m/z* 420 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-2,9,16-trimetil-15-oxo-2,15,16,17-tetrahidro-9*H*-8,4-(meteno)pirazolo[4,3-*h*][1,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplos 76 y 77)



Etapa 1:

Una mezcla de **compuesto 511** (1,0 g, 8,2 mmol) y NBS (1,5 g, 8,6 mmol) en acetonitrilo (16 mL) se calentó hasta reflujo durante 1 hora. La reacción se redujo a la

mitad del volumen y los sólidos se recolectaron por filtración para producir el **compuesto 512**, 2-amino-5-bromopiridin-3-carbaldehído (820 mg, 50%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,83 (s, 1 H) 8,31 (d, J = 2,5 Hz, 1 H) 8,24 (d, J = 2,5 Hz, 1 H) 7,68 (d, J = 2,0 Hz, 2 H).

Etapa 2:

A una mezcla enfriada (-50 °C) de **compuesto 512** (1,1 g, 5,4 mmol) en THF (36 mL) se añadió gota a gota MeMgBr (3 M en Et_2O, 18 mL, 54 mmol) manteniendo la T < - 40 °C. La reacción se agitó a 50 °C durante 1 hora, luego a 0 °C durante 1 hora antes de neutralizar con cloruro de amonio acuoso saturado. La capa acuosa se extrajo con Et_2O (3x) y las capas orgánicas combinadas se secaron en $MgSO_4$, se filtraron y se concentraron. El residuo se purificó por cromatografía en columna en gel de sílice que se eluyó con DCM/MeOH (0-5%) para producir el **compuesto 513**, 1-(2-amino-5-bromopiridin-3-il)etanol (630 mg, 53%). ^{1}H RMN (400 MHz ,DMSO-d_6) δ 7,87 (d, J = 2,5 Hz, 1 H) 7,52 (d, J = 2,3 Hz, 1 H) 5,95 (s, 2 H) 5,33 (d, J = 4,3 Hz, 1 H) 4,75 - 4,63 (m, 1 H) 1,27 (d, J = 6,5 Hz, 3 H).

Etapa 3:

A una solución enfriada (-0 °C) de **compuesto 513** (260 mg, 1,2 mmol) en diclorometano (12 mL) se añadió cloruro de tionilo (180 µL, 2,4 mmol). El baño de hielo se eliminó y después de agitar durante ~4 horas, la solución se concentró usando alto vacío. El residuo se disolvió en anhídrido acético y se calentó a 100 °C durante la noche. La solución se concentró y se azeotropó con tolueno (2x) para producir el **compuesto 514**, *N*-acetil-*N*-[5-bromo-3-(1-cloroetil)piridin-2-il]acetamida que se usó directamente en la siguiente etapa.

Etapa 4:

Una mezcla de **compuesto 514** (~1,2 mmol), **compuesto 138** (350 mg, 1,2 mmol) y carbonato de potasio (830 mg, 6,0 mmol) en acetonitrilo (8,0 mL) se calentó a 60 °C. Después de ~5 horas, la mezcla de reacción se enfrió y se diluyó con EtOAc, se lavó con agua y salmuera, se secó en $MgSO_4$, se filtró y se concentró. El material crudo se purificó por cromatografía en columna en gel de sílice que se eluyó con heptano/acetato de etilo (0-100%) para obtener el **compuesto 515**, 2-{1-[2-(acetilamino)-5-bromopiridin-3-il]etoxi}-*N*-[(5-ciano-1-metil-1*H*-pirazol-3-il)metil]-4-fluoro-*N*-metilbenzamida (170 mg, 27% en 3 etapas). ^{1}H RMN (400 MHz, 80°C, DMSO-d_6) δ 10,00 (br. s., 1 H) 8,47 (d, J = 2,5 Hz, 1 H) 7,90 (br. s., 1 H) 7,25 (dd, J = 6,8, 8,3 Hz, 1 H) 7,07 - 6,84 (m, 2 H) 6,83 - 6,69 (m, 1 H) 5,56 (q, J = 6,3 Hz, 1 H) 4,84 - 4,55

(m, 1 H) 4,31 (br. s., 1H) 3,98 (br. s., 3 H) 2,79 (br. s., 3 H) 2,14 (s, 3 H) 1,50 (d, *J* = 6,3 Hz, 3 H). LCMS APCI m/z 529/531 $[M+H]^+$.

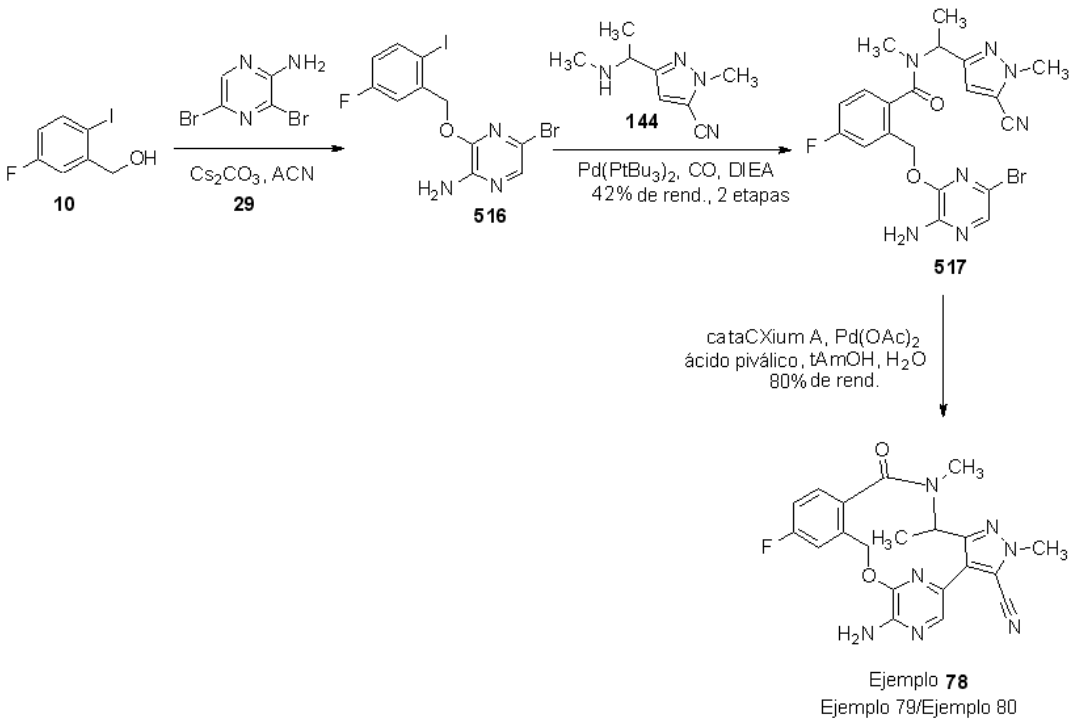
Etapa 5:

En un vial de microondas se cargó el **compuesto 515** (120 mg, 0,23 mmol), KOAc (110 mg, 1,10 mmol) y ^{t}AmOH (2,3 mL). La mezcla se burbujeó con nitrógeno, luego se añadieron acetato de paladio (II) (5,2 mg, 0,023 mmol) y cataCXium A (17 mg, 0,045 mmol). El vial se selló y la reacción se irradió en el microondas durante 30 min a 150 °C. La reacción se diluyó con EtOAc, se lavó con agua y salmuera, se secó en $MgSO_4$, se filtró y se concentró. El residuo se purificó por cromatografía en columna en gel de sílice que se eluyó con DCM/MeOH (0-10%) para producir el intermediario protegido. El residuo se disolvió en MeOH (1,0 mL), luego se añadió HCl (4 N en dioxano, 1,0 mL) y la solución se calentó a 50 °C durante la noche. La reacción se diluyó con EtOAc, se lavó con $NaHCO_3$ acuoso saturado (2x) y salmuera, se secó en $MgSO_4$, se filtró y se concentró. El residuo se purificó por cromatografía flash, que se eluyó con DCM/MeOH (0-6%) para producir una mezcla de **Ejemplo 76** y **Ejemplo 77,** La separación quiral por SFC se llevó a cabo usando una columna Regis Whelk-01 (*R, R*) (columna de 4,6 mm x 100 mm, tamaño de partícula de 5 micrones), que se eluyó con 30% de MeOH en CO_2 mantenido a 140 bar. Una tasa de flujo de 3 mL/min produjo $Rt_{(pico\ 1)}$ = 2,68 minutos y $Rt_{(pico\ 2)}$ = 4,65 minutos.

Ejemplo 76 (pico 1): 10 mg (11%), > 99% ee. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,93 (d, *J*=2,5 Hz, 1H) 7,45 (d, *J*=2,3 Hz, 1H) 7,33 (dd, *J*=6,9, 8,4 Hz, 1H) 7,21 (dd, *J*=2,3, 11,3 Hz, 1H) 6,85 (dt, *J*=2,0, 8,3 Hz, 1H) 6,26 (s, 2H) 5,88 (q, *J*=6,5 Hz, 1H) 4,30 (d, *J*=14,4 Hz, 1H) 4,13 (d, *J*=14,4 Hz, 1H) 4,04 (s, 3H) 2,95 (s, 3H) 1,48 (d, *J*=6,0 Hz, 3H).LCMS APCI *m/z* 407 $[M+H]^+$.

Ejemplo 77 (pico 2): 11 mg (11%), ~ 98% ee. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,93 (d, *J* = 2,3 Hz, 1 H) 7,45 (d, *J* = 2,3 Hz, 1 H) 7,33 (dd, *J* = 6,9, 8,4 Hz, 1 H) 7,21 (dd, *J* = 2,3, 11,3 Hz, 1 H) 6,85 (dt, *J* = 2,3, 8,3 Hz, 1 H) 6,26 (s, 2 H) 5,88 (q, *J* = 6,0 Hz, 1 H) 4,30 (d, *J* = 14,4 Hz, 1 H) 4,13 (d, *J* = 14,4 Hz, 1 H) 4,04 (s, 3 H) 2,95 (s, 3 H) 1,48 (d, *J* = 6,0 Hz, 3 H). LCMS APCI *m/z* 407 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-2,16,17-trimetil-15-oxo-10,15,16,17-tetrahidro-2*H*-8,4-(azeno)pirazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplos 78, 79 y 80)



Ejemplo **78**
Ejemplo 79/Ejemplo 80

Etapa 1:

Una mezcla de **compuesto 10** [1,89 g, ~7,5 mmol (con ~25% (5-fluoro-2-bromo-fenil)metanol)], **compuesto 29** (2,28 g, 9 mmol) y carbonato de cesio (6,11 g, 18,7 mmol) en acetonitrilo (7 mL) se calentó a 80 ˚C durante 18 horas. La suspensión cruda se añadió a salmuera (~400 mL) y los sólidos resultantes de color hollín se recolectaron por filtración y se enjuagaron con agua. Los sólidos parcialmente secos se absorbieron en acetonitrilo caliente (~200 mL) y se filtraron para eliminar insolubles oscuros finos que luego se descartaron. El filtrado se dejó reposar a temperatura ambiente durante la noche. Algunos cristales eran evidentes en el recipiente después de reposar durante la noche. El sobrenadante se eliminó y se concentró hasta secarse para producir el **compuesto 516** en forma de un sólido rojizo (2,822 g), que se usó sin otra purificación. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,92 (dd, 1 H) 7,58 - 7,69 (m, 2 H) 7,05 (td, J = 8,65, 3,24 Hz, 1 H) 6,69 (s, 2 H) 5,27 (s, 2 H).

Etapa 2:

Una mezcla de **compuesto 516** (616 mg, ~1,45 mmol), **compuesto 144** (228 mg, 1,14 mmol), DIEA (0,792 mL, 4,54 mmol) y $Pd(P^tBu_3)_2$ (59 mg, 0,114 mmol) en tolueno se calentó a 85 ˚C en 4 bar de CO durante la noche. La mezcla se concentró y se purificó por cromatografía flash usando un gradiente de 25-100% EtOAc/heptano como eluyente. Las fracciones deseadas se concentraron hasta secarse para producir

el **compuesto 517** (233 mg, 42%) en forma de un sólido espumoso. ^{1}H RMN (400 MHz, 80ºC, DMSO-d_6) δ 7,64 (s, 1 H), 7,51 (dd, *J* = 10,20, 2,64 Hz, 1 H), 7,35 - 7,46 (m, 1 H), 7,24 (td, *J* = 8,62, 2,39 Hz, 1 H), 6,99 (s, 1 H), 6,25 (br. s., 2 H), 5,86 (s, 1 H), 5,35 (s, 2 H), 3,94 (s, 3 H), 2,65 (br. s., 3 H), 1,49 (d, *J* = 7,05 Hz, 3 H).

Etapa 3:

A una solución de **compuesto 517** (179 mg, 0,367 mmol) en alcohol t-amílico (10 mL) se añadieron cataCXium A (40 mg, 0,1 mmol), ácido piválico (11 mg, 0,11 mmol), acetato de potasio (180 mg, 1,8 mmol) y agua (40 mL). La suspensión resultante se salpicó con un burbujeador de nitrógeno durante ~5 minutos. Luego se añadió acetato de paladio (12 mg, 0,055 mmol). La mezcla se selló y se calentó a 140 ºC con irradiación de microondas durante 1 hora. La LCMS indicó el producto deseado como el pico mayor. La mezcla se redujo a un volumen mínimo. El residuo se suspendió en DCM, se filtró y el filtrado se concentró y se purificó por cromatografía en columna en gel de sílice usando un gradiente de 25-100% (EtOAc con 10% de MeOH)/heptanos) como eluyente. Las fracciones deseadas se redujeron hasta un volumen mínimo para obtener el **Ejemplo 78** (120 mg, 0,294 mmol, 80%) en forma de un sólido amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,75 (s, 1 H) 7,40 - 7,60 (m, 2 H) 7,18 (td, *J* = 8,44, 3,02 Hz, 1 H) 6,75 (s, 2 H) 5,60 (dd, *J* = 12,46, 1,64 Hz, 1 H) 5,07 (d, *J* = 12,09 Hz, 1 H) 4,59 - 4,77 (m, 1 H) 4,04 (s, 3 H) 2,83 (s, 3 H) 1,61 (d, *J* = 6,80 Hz, 3H).

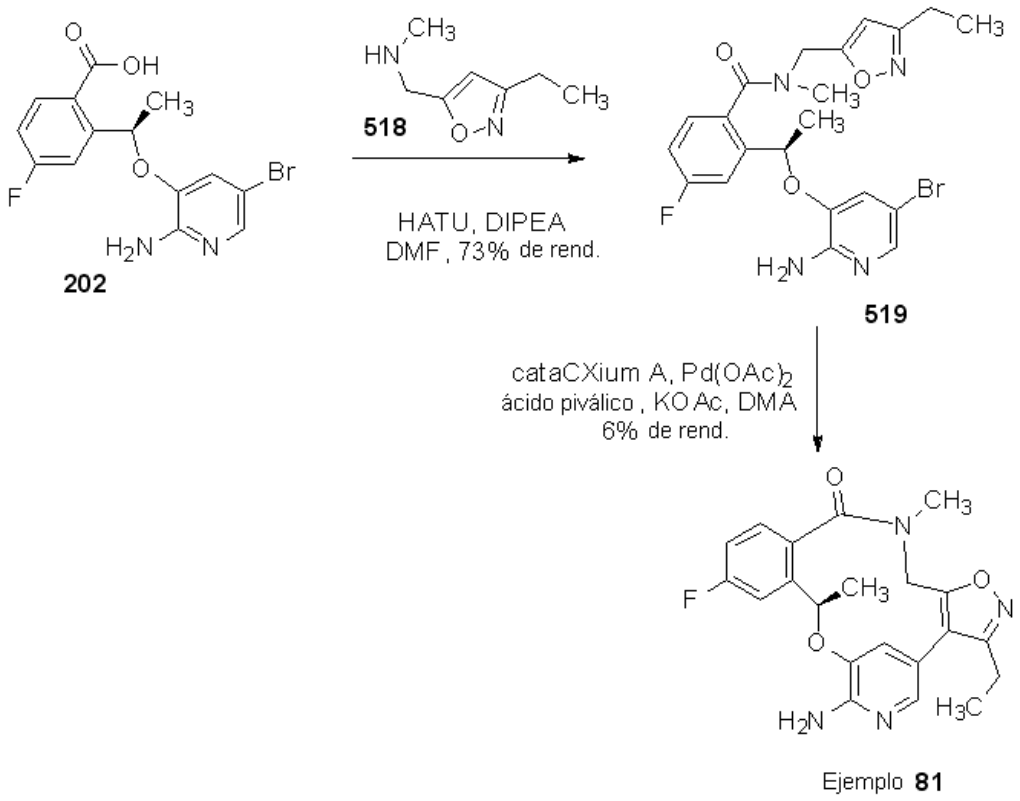
La separación quiral por SFC se llevó a cabo usando una columna Chiralcel OJ-H (columna de 4,6 mm x 250 mm, tamaño de partícula de 5 micrones), que se eluyó con 30% de MeOH en CO_2 mantenido a 140 bar. Una tasa de flujo de 3 mL/min produjo $Rt_{(pico\ 1)}$ = 3,67 minutos y $Rt_{(pico\ 2)}$ = 4,97 minutos.

Ejemplo 79 (pico 1): 44,9 mg > 99% ee (-). ^{1}H RMN (600 MHz, DMSO-d_6) δ 7,72 (s, 1 H) 7,41 - 7,58 (m, 2 H) 7,18 (td, *J* = 8,52, 2,54 Hz, 1 H) 6,78 (s, 2 H) 5,55 (d, *J* = 12,46 Hz, 1 H) 5,08 (d, *J* = 12,46 Hz, 1 H) 4,64 (q, *J* = 6,87 Hz, 1 H) 4,02 (s, 3 H) 2,81 (s, 3 H) 1,59 (d, *J* = 6,87 Hz, 3 H). LCMS APCI *m/z* 407 $[M+H]^+$.

Ejemplo 80 (pico 2): 45,2 mg > 99% ee (+). ^{1}H RMN (600 MHz, DMSO-d_6) δ 7,72 (s, 1 H) 7,42 - 7,58 (m, 2 H) 7,17 (td, *J* = 8,52, 2,54 Hz, 1 H) 6,78 (s, 2 H) 5,55 (d, *J* = 12,46 Hz, 1 H) 5,08 (d, *J* = 12,46 Hz, 1 H) 4,64 (q, *J* = 7,04 Hz, 1 H) 4,02 (s, 3 H) 2,81 (s, 3 H) 1,59 (d, *J* = 6,87 Hz, 3 H). LCMS APCI *m/z* 407 $[M+H]^+$.

Preparación de (10*R*)-7-amino-3-etil-12-fluoro-10,16-dimetil-16,17-dihidro-8,4-(meteno)[1,2]oxazolo[4,5-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona

(Ejemplo 81)



Etapa 1:

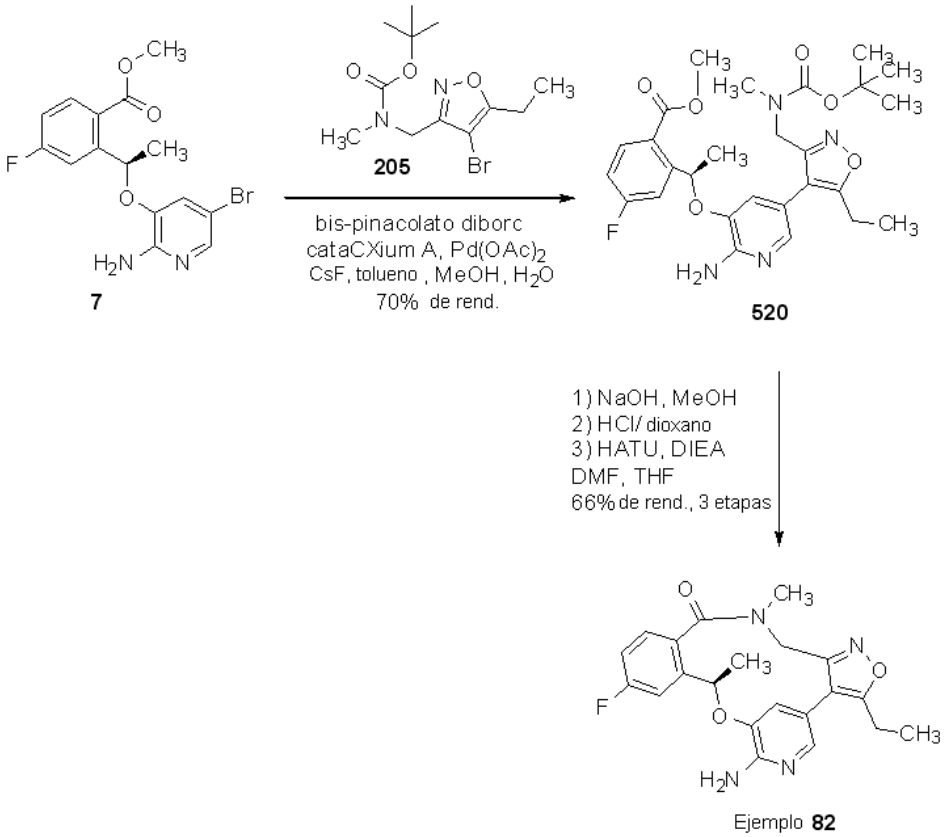
A una solución de **compuesto 518** (41 mg, 0,3 mmol), **compuesto 202** (70 mg, 0,2 mmol), DIPEA (76 mg, 3,0 equiv) en DMF (0,8 mL, 0,25 M) se añadió HATU (90 mg, 1,2 equiv). La mezcla resultante se agitó a temperatura ambiente durante 1 hora. El solvente se eliminó a presión reducida. El residuo se diluyó con EtOAc y se lavó con agua, solución acuosa saturada de $NaHCO_3$ y salmuera. La concentración y purificación por HPLC preparativa de fase inversa produjo el **compuesto 519** (69 mg, 73%) en forma de un sólido blanco. LCMS APCI *m/z* 477 $[M+H]^+$.

Etapa 2:

A una solución del compuesto **519** (63 mg, 0,13 mmol) y ácido pivalico (6 mg, 0,4 equiv) en DMA (2,6 mL) se añadió KOAc sólido (65 mg, 5 equiv), seguido de $Pd(OAc)_2$ (6 mg, 0,20 equiv) y cataCXium A (20 mg, 0,4 equiv) eno argón. La reacción se calentó en el microondas a 160 ºC durante 65 minutos y se purificó por HPLC de fase inversa para obtener el **Ejemplo 81** (3,3 mg, 6%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,63 (dd, *J* = 2,5, 10,4 Hz, 1H) 7,53 (d, *J* = 1,5 Hz, 1H) 7,42 (dd, *J* = 5,8, 8,6 Hz, 1H) 7,18 (dt, *J* = 2,7, 8,4 Hz, 1H) 6,69 (s, 1H) 6,07 (s, 2H) 5,57 - 5,67 (m, 1H) 4,57 (d, *J* = 15,2 Hz, 1H) 4,28 (d, *J* = 14,9 Hz, 1H) 3,02 (s, 3H) 2,69

- 2,85 (m, 2H) 1,66 (d, *J* = 6,3 Hz, 3H) 1,18 (t, *J* = 7,5 Hz, 3H). LCMS APCI *m/z* 397 $[M+H]^+$.

Preparación de (10*R*)-7-amino-3-etil-12-fluoro-10,16-dimetil-16,17-dihidro-8,4-(meteno)[1,2]oxazolo[4,3-*h*][2,5,11]benzoxadiazaciclotetradecin-15(10*H*)-ona (Ejemplo 82)



Ejemplo **82**

Etapa 1:

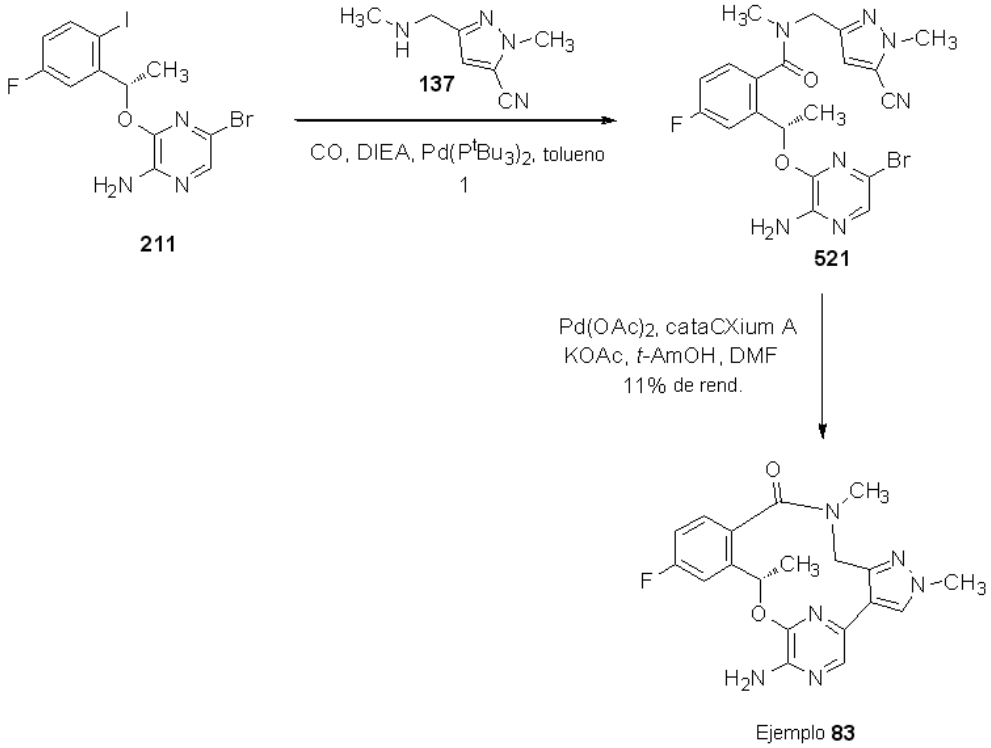
Acetato de paladio (II) (82,4 mg, 0,367 mmol) y cataCXium A (271 mg, 0,733 mmol) se mezclaron en tolueno (3,0 mL, desgasificado) y la solución resultante se añadió por medio de pipeta a una solución agitada del **compuesto 7** (1,35 g, 3,67 mmol), bis-pinacolatodiboro (1,86 g, 7,33 mmol) y CsF (2,23 g, 14,7 mmol) en MeOH/H_2O (4:1, 25,5 mL, desgasificado) a 50 ºC. Después de 5 minutos, se añadió una solución de **compuesto 205** (900 mg, 2,82 mmol) en MeOH (5,8 mL, desgasificado). La mezcla resultante se agitó a 80 ˚C. Después de agitar durante 1,5 horas, la reacción se consideró completa por análisis de LCMS. Después de enfriar hasta temperatura ambiente, la mezcla se diluyó con EtOAc, se lavó con agua, salmuera, se secó en Na_2SO_4 y se concentró al vacío para producir un residuo, que se

purificó por cromatografía en columna en gel de sílice (0-5% MeOH/DCM) para obtener el **compuesto 520** (1,045 g, 70%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,88 - 7,99 (m, 1 H) 7,50 (dd, *J* = 10,48, 2,65 Hz, 1 H) 7,39 (d, *J* = 1,77 Hz, 1 H) 7,24 (td, *J* = 8,46, 2,53 Hz, 1 H) 6,54 (br. s., 1 H) 6,22 (br. s., 1 H) 6,08 (br. s., 2 H) 3,85 (s, 3 H) 2,64 (s, 3 H) 2,43 - 2,48 (m, 2 H) 1,62 (d, *J* = 6,32 Hz, 3 H) 1,31 (br. s., 3 H) 1,12 - 1,28 (m, 6 H) 1,00 (t, *J* = 7,58 Hz, 3 H). LCMS APCI *m/z* 529 $[M+H]^+$.

Etapa 2:

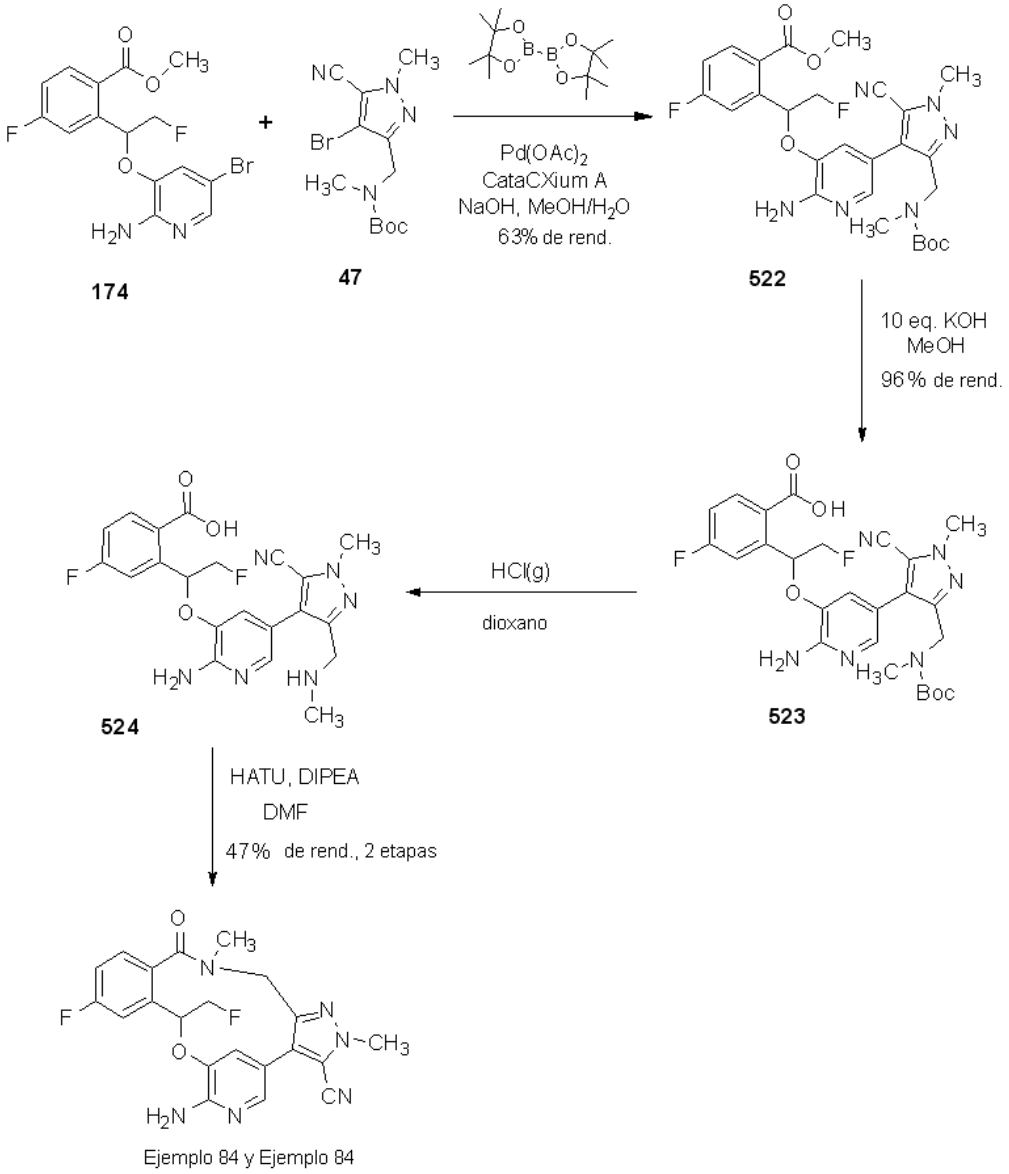
Se añadió NaOH (1,84 g, 46,1 mmol) en 1 mL agua a una solución de **compuesto 520** (995 mg, 1,8 mmol) en MeOH (30 mL) y agua (3 mL). La mezcla de reacción se agitó a temperatura ambiente. Después de agitar durante 2,5 horas, la reacción se completó y se añadió HCl 4 M en dioxano (15 mL) lentamente. La mezcla se agitó a temperatura ambiente durante 20 horas. La mezcla de reacción se concentró a presión reducida para producir el producto desprotegido crudo que se usó directamente en la etapa de ciclación sin otra purificación. A una solución de HATU (1,0 g, 2,56 mmol) en DMF (76 mL) se añadió gota a gota una solución del producto crudo y DIEA (5,1 mL, 29,3 mmol) en DMF (76 mL) y THF (7,6 mL) a 0 ºC. Después de la adición, la mezcla resultante se agitó a 0 ˚C durante 1 hora. La mezcla se vertió en agua helada (400 mL) y la capa acuosa se extrajo con EtOAc. Las capas combinadas de EtOAc se lavaron con salmuera, se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo, que se purificó por cromatografía en columna en gel de sílice (0-10% MeOH/DCM). Después de la purificación, la ^{19}F RMN indicó que el producto estaba contaminado por $PF6^-$. El producto de tipo cola se disolvió en EtOAc y se lavó con Na_2CO_3 acuoso al 10% (3x) y luego se secó sobre sulfato de sodio y se concentró a presión reducida para obtener el **Ejemplo 82** en forma de un sólido blanco (480 mg, 66%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,63 (dd, *J* = 10,32, 2,77 Hz, 1H) 7,47 (dd, *J* = 8,56, 5,79 Hz, 1 H) 7,40 (d, *J* = 1,76 Hz, 1 H) 7,17 (td, *J* = 8,50, 2,64 Hz, 1 H) 6,78 (d, *J* = 1,76 Hz, 1 H) 6,03 (s, 2 H) 5,65 (dd, *J* = 6,29, 1,76 Hz, 1 H) 4,47 (d, *J* = 14,35 Hz, 1 H) 4,21 (d, *J* = 14,35 Hz, 1 H) 3,01 (s, 3 H) 2,82 - 2,92 (m, 2 H) 1,67 (d, *J* = 6,29 Hz, 3 H) 1,22 (t, *J* = 7,55 Hz, 3 H). LCMS APCI *m/z* 397 $[M+H]^+$.

Preparación de (10S)-7-amino-12-fluoro-2,10,16-trimetil-16,17-dihidro-2H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 83)



Usando el procedimiento de dos etapas del **Ejemplo 56**, se preparó el **Ejemplo 83** (41,4 mg, 11%) en forma de un sólido blanco. ^{1}H RMN (600 MHz, DMSO-d_6) δ 8,02 (s, 1 H), 7,63 (s, 1 H) 7,44 (dd, *J* = 10,09, 2,63 Hz, 1 H) 7,40 (dd, *J* = 8,57, 5,53 Hz, 1 H) 7,15 (td, *J* = 8,57, 2,76 Hz, 1 H) 6,25 (s, 2 H) 5,74 - 6,04 (m, 1 H) 4,33 (d, *J* = 13,27 Hz, 1 H) 4,18 (d, *J* = 13,27 Hz, 1 H) 3,83 (s, 3 H) 2,87 (s, 3 H) 1,62 (d, *J* = 6,36 Hz, 3 H). LCMS APCI *m/z* 383 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-10-(fluorometil)-2,16-dimetil-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(meteno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplos 84 y 85)



Ejemplo 84 y Ejemplo 84

Etapa 1:

A una solución de **compuesto 174** (0,7 g, 1,81 mmol), **compuesto 47** (1,22 g, 3,07 mmol) y bis-(pinacalato)diboro (1,38 g, 5,42 mmol) en metanol seco (280 mL) se añadió NaOH (145 mg, 3,62 mmol) en agua (10 mL) en gas nitrógeno a temperatura ambiente. Después de que la mezcla se desgasificó tres veces con nitrógeno, se añadieron cataCXium A (68 mg, 0,18 mmol) y $Pd(OAc)_2$ (21 mg, 0,09 mmol). La mezcla resultante se desgasificó con nitrógeno tres veces y se calentó a reflujo durante 16 horas. La TLC (éter de petróleo/EtOAc 1/1) mostró que la mezcla de reacción estaba completa. La mezcla de reacción se diluyó con EtOAc (300 mL). La mezcla luego se lavó con salmuera (2x), se secó en Na_2SO_4 y se concentró al vacío

para producir el residuo, que se purificó por Biotage (éter de petróleo/EtOAc = 1:1, Rf =0,1) para producir el **compuesto 522** (0,7 g, 62,8 %) en forma de un sólido marrón. LCMS m/z 579 $[M+Na]^+$

Etapa 2:

Una mezcla de **compuesto 522** (0,5 g, 0,90 mmol) y KOH (0,5 g, 8,99 mmol) en metanol (20 mL) se calentó a 50 °C durante 24 horas. La LC-MS mostró que la reacción estaba completa. La mezcla de reacción se concentró al vacío para producir un residuo. El residuo se acidificó con HCl 1 N a pH ~5. La mezcla se extrajo con EtOAc (3x). Las capas combinadas de EtOAc se lavaron con salmuera, se secaron en Na_2SO_4 y se concentraron al vacío para producir el residuo, que se purificó por cromatografía flash en gel de sílice (DCM/MeOH=25:1, Rf=0,3) para producir el **compuesto 523** (320 mg, 95,5% de pureza, 62%) en forma de un sólido amarillo. LCMS m/z 543 $[M+H]^+$.

Etapa 3:

A una solución agitada de **compuesto 523** (320 mg, 95% puro, 0,56 mmol) en DCM (10 mL) se añadió gota a gota ~ HCl 4 M (g) en dioxano (2 mL) a temperatura ambiente. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La LC-MS indicó que la reacción estaba completa. La mezcla de reacción se concentró al vacío para producir el **compuesto** crudo **524**, que se usó en la siguiente etapa sin otra purificación. LCMS *m/z* 443 $[M+H]^+$.

Etapa 4

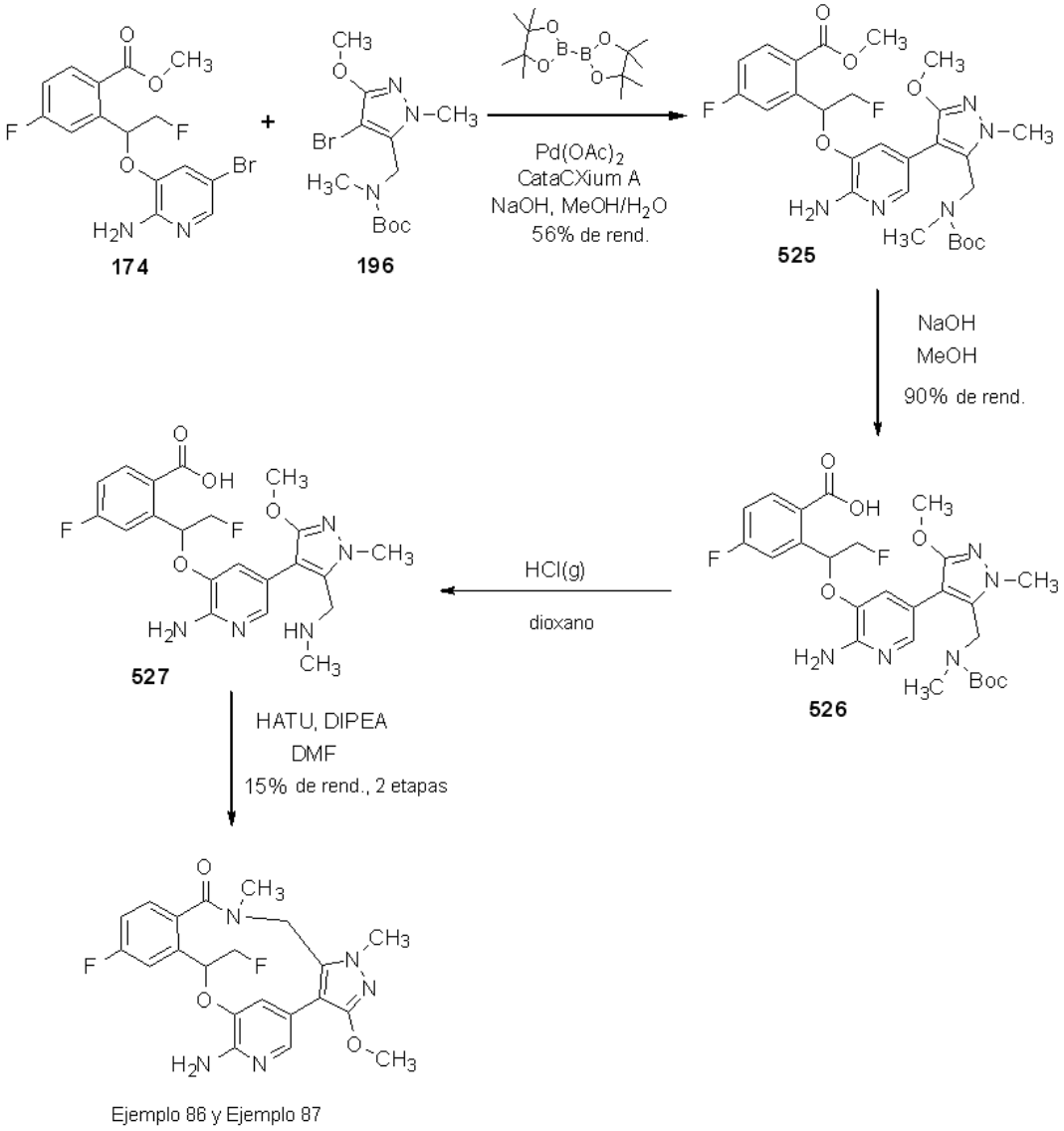
A una solución de HATU (155 mg, 0,4 mmol) en DMF (8 mL) se añadió gota a gota una solución de **compuesto 424** (~0,29 mmol) y DIEA (0,60 g, 4,64 mmol) en DMF seca (8 mL) y THF seco (1 mL) a 0 °C. Después de la adición, la mezcla resultante se agitó a la misma temperatura durante 1 hora. La LC-MS mostró que la reacción estaba completa. La mezcla se vertió en agua helada (30 mL). La mezcla se extrajo con EtOAc (30 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (30 mL x 5), se secaron en Na_2SO_4 y se concentraron al vacío para producir el residuo, que se purificó por cromatografía en columna en gel de sílice (DCM/MeOH = 25:1, Rf=0,3) para producir una mezcla de **Ejemplo 84** y **Ejemplo 85** (80 mg, 52,6%) en forma de un sólido amarillo. La separación quiral se llevó a cabo por SFC preparativa en una columna Chiralcel OJ-H (50 x 4,6 mm I.D., tamaño de partícula de 3 micrones), que se eluyó con 5-40% de metanol (0,05% DEA) a 140 bar de CO_2 con una tasa de flujo de 4 mL/min. $Rt_{(pico\ 1)}$ = 5,93 minutos y $Rt_{(pico\ 2)}$ = 9,28 minutos y

produjo el pico 1 en forma de un sólido blanco (33 mg, 27%) y el pico 2 en forma de un sólido blanco (30 mg, 20%).

Ejemplo 84 (pico 1): 100% ee. ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,70 (bs, 1H), 7,54-7,48 (m, 2H), 7,22-7,18 (m, 1H), 6,98 (s, 1H), 5,91-5,90 (m, 1H), 5,16-4,98 (m, 1H), 4,88-4,84 (m, 1H), 4,57-4,53 (d, 1H), 4,49-4,48 (d, 1H), 4,03 (s, 3H), 3,15 (s, 3H). LCMS ES *m/z* 425 $[M+H]^+$.

Ejemplo 85 (pico 2): 100% ee. ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,71 (bs, 1H), 7,54-7,48 (m, 2H), 7,232-7,18 (m, 1H), 6,99 (s, 1H), 5,92-5,56 (dd, 1H), 5,12-4,95 (m, 1H), 4,87-4,83 (m, 1H), 4,53-4,50 (d, 1H), 4,43-4,40 (d, 1H), 4,09 (s, 3H), 3,15 (s, 3H). LCMS ES *m/z* 425 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-10-(fluorometil)-3-metoxi-1,16-dimetil-16,17-dihidro-1H-8,4-(meteno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 86/Ejemplo 87)



Ejemplo 86 y Ejemplo 87

Etapa 1:

A una solución de **compuesto 174** (0,98 g, 2,5 mmol), **compuesto 196** (1,01 g, 3,03 mmol) y bis(pinacalato)diboro (1,905 g, 7,5 mmol) en metanol (320 mL) se añadió NaOH (200 mg, 5 mmol) en agua (11 mL) en nitrógeno a temperatura ambiente. Después de que la mezcla se desgasificó tres veces con nitrógeno, se añadieron cataCXium A (116 mg, 0,325 mmol) y $Pd(OAc)_2$ (74 mg, 0,325 mmol). La mezcla resultante se desgasificó con nitrógeno tres veces y se calentó a reflujo durante 16 horas. La TLC (éter de petróleo/EtOAc 1/1) mostró que la reacción estaba completa. La mezcla de reacción se diluyó con EtOAc (300 mL). Las capas combinadas de EtOAc se lavaron con salmuera (100 mL x 2), se secaron en Na_2SO_4 y se

concentraron al vacío para producir un residuo, que se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc de 3/1 a 1/1) para producir el **compuesto 525** (800 mg, 94% de pureza, 56%) en forma de un sólido marrón. ^{1}H RMN (400 MHz, CDCl3): δ 8,07-8,03 (dd, 1H), 7,53 (s, 1H), 7,31-7,28 (dd, 1H), 7,03-6,99 (m, 1H), 6,55-6,54 (d, 1H), 6,53-6,42 (d, 1H), 6,43-6,37 (dd, 1H), 4,78 (s, 2H), 4,69-4,65 (m, 2H), 4,20-4,08 (m, 2H), 3,89-3,85 (t, 3H), 3,69 (s, 3H), 3,59 (s, 3H),2,30 (s, 3H), 1,39 (s, 9H).

Etapa 2:

Una mezcla de **compuesto 525** (800 mg, 1,42 mmol) y NaOH (1,14 g, 28,5 mmol) en metanol (30 mL) y agua (10 mL) se agitó a temperatura ambiente durante 18 horas. La LC-MS mostró que la reacción estaba completa. Se eliminó MeOH al vacío para producir un residuo. El residuo se acidificó con HCl 6 N a pH ~5. La mezcla se saturó con NaCl sólido y luego se extrajo con EtOAc (30 mL x 5). Las capas combinadas de EtOAc se secaron en Na_2SO_4 y se concentraron al vacío para producir el **compuesto 526** (700 mg, 89,7%) en forma de un sólido amarillo. LCMS m/z 514 $[M+H]^+$.

Etapa 3:

A una solución de **compuesto 526** (700 mg, 1,28 mmol) en dioxano (5 mL) se añadió gota a gota ~ HCl 4 M (g) en dioxano (10 mL) a temperatura ambiente. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La TLC (EtOAc) mostró que la reacción estaba completa. La mezcla de reacción se concentró al vacío para producir el **compuesto** crudo **527**, que se usó para la siguiente etapa sin otra purificación. LCMS m/z 448 [M+H]+.

Etapa 4:

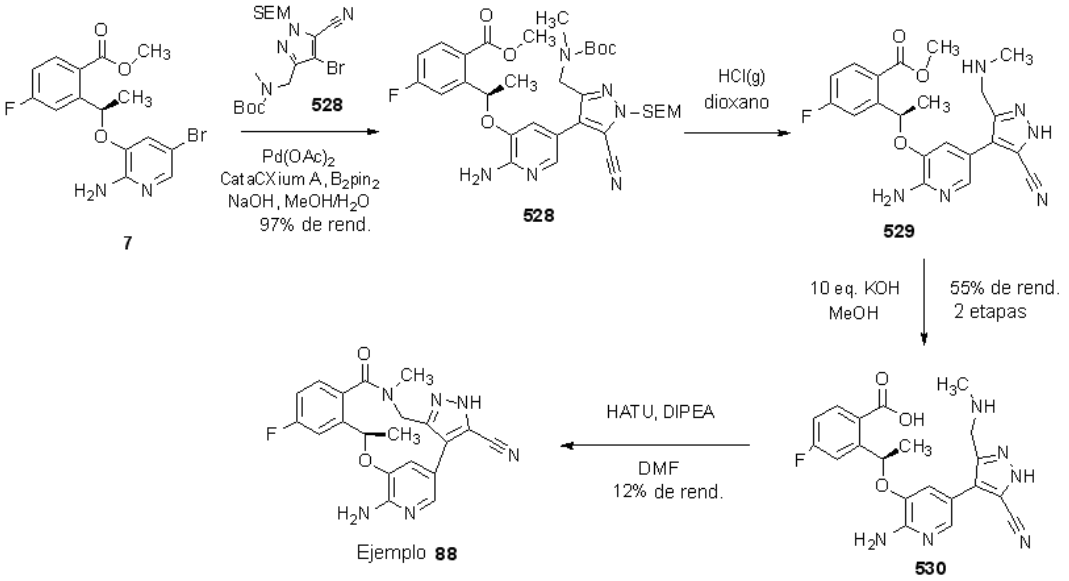
A una solución de HATU (813 mg, 2,14 mmol) en DMF (80 mL) se añadió gota a gota la mezcla de **compuesto 527** (~636 mg, 1,13 mmol) y DIPEA (3,69 g, 28,6 mmol) en DMF (20 mL) a 0 °C. Después de la adición, la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La LC-MS mostró que la reacción estaba completa. La mezcla se vertió en agua helada (50 mL). La mezcla se extrajo con EtOAc (40 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (20 mL x 5), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo. El residuo se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc 30-70%) para producir una mezcla de **Ejemplo 86** y **Ejemplo 87** (0,2 g, 36,3%) en forma de un sólido rosado. La separación quiral se llevó a cabo por SFC preparativa en una columna Chiralcel OD-3 (50 x 4,6 mm I.D., tamaño de partícula de 3 micrones),

que se eluyó con 5-40% de etanol (0,05% DEA) en CO_2 con una tasa de flujo de 4 mL/min. $Rt_{(pico\ 1)}$ = 1,47 minutos y $Rt_{(pico\ 2)}$ = 1,71 minutos y produjo el pico 1 en forma de un sólido rosado (38 mg, 7%) y el pico 2 en forma de un sólido rosado (42 mg, 8%).

Ejemplo 86 (pico 1): 100% ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,87-7,86 (d, 1H), 7,34-7,31 (dd, 1H), 7,28-7,25 (m, 1H), 7,09-7,04 (m, 1H), 6,81 (s, 1H), 5,78-5,73 (d, 1H), 4,91-4,78 (m, 4H), 4,45-4,41 (d, 1H), 4,33-4,30 (d, 1H), 3,94-3,91 (d, 3H), 3,74 (d, 3H), 3,16 (s, 3H). LCMS ES *m/z* 430 $[M+H]^+$.

Ejemplo 87 (pico 2): 100% ee. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,80 (s, 1H), 7,27-7,24 (dd, 1H), 7,22-7,19 (m, 1H), 7,03-7,0 (m, 1H), 6,76-6,75 (s, 1H), 5,71-5,67 (d, 1H), 4,85-4,72 (m, 4H), 4,38-4,35 (d, 1H), 4,27-4,23 (d, 1H), 3,89 (s, 3H),.3,81 (s, 3H), 3,09 (s, 3H). LCMS ES *m/z* 430 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-10,16-dimetil-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(meteno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 88)



Etapa 1:

A una solución de **compuesto 7** (600 mg, 1,62 mmol), **compuesto 214** (1,08 g, 2,44 mmol) y bis-(pinacalato)diboro (1,23 g, 4,86 mmol) en metanol (120 mL) se añadieron cataCXium A (80 mg, 0,2 mmol) y $Pd(OAc)_2$ (50 mg, 0,20 mmol). Después de que la mezcla se desgasificó tres veces con nitrógeno, se añadió una solución de NaOH (130 mg, 3,2 mmol) en agua (10 mL) en nitrógeno a temperatura ambiente. La mezcla resultante se desgasificó con nitrógeno tres veces y luego se calentó a reflujo

durante 16 horas. La TLC (éter de petróleo/EtOAc 3/1) mostró que la reacción estaba completa. La mezcla de reacción se diluyó con EtOAc (100 mL x 3). Las capas combinadas de EtOAc se lavaron con salmuera (50 mL x 3), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo, que se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc = 1:1, Rf= 0,3) para producir el **compuesto 528** (650 mg, 96,8% de pureza, 59%) en forma de un sólido amarillo. LCMS m/z 655 $[M+H]^+$.

Etapa 2:

A una solución agitada de **compuesto 529** (350 mg, 96,8% de pureza, 0,55 mmol) en DCM (5 mL) se añadió gota a gota ~ HCl 4 M (g) en dioxano (5 mL) a temperatura ambiente. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La LC-MS mostró que la reacción estaba completa. La mezcla de reacción se concentró al vacío para producir el **compuesto 529 crudo**, que se usó para la siguiente etapa sin otra purificación. LCMS m/z 424 $[M+H]^+$

Etapa 3:

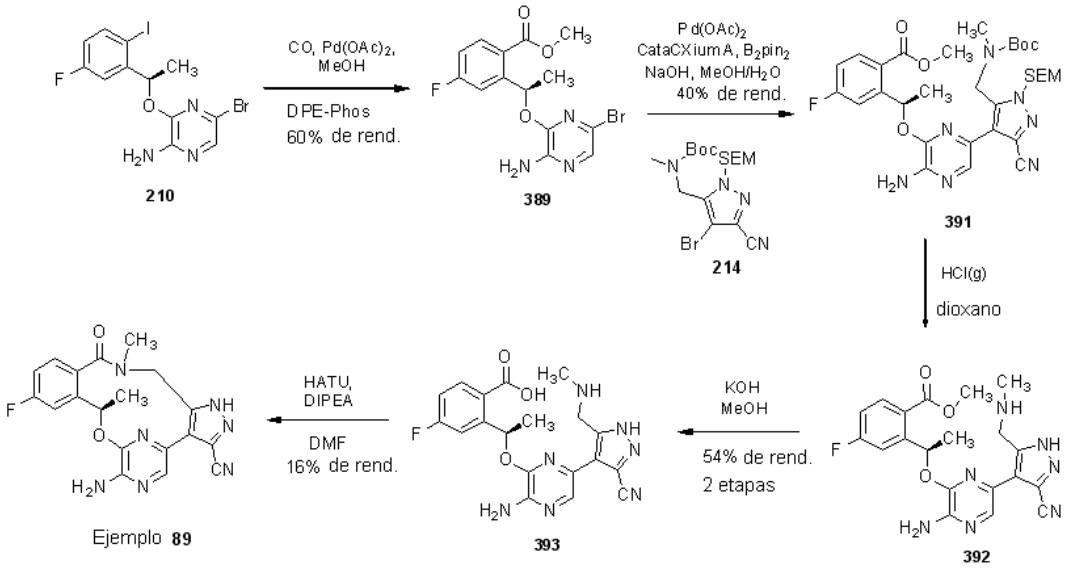
Una mezcla de **compuesto 529** (~0,47 mmol) y KOH (0,65 g, 11,7 mmol) en metanol (15 mL) se agitó a 50 °C durante 36 horas. La LC-MS mostró que la reacción estaba completa. MeOH se eliminó al vacío para obtener el residuo, que se acidificó con HCl acuoso 1 N hasta pH ~6. La mezcla se extrajo con EtOAc (20 mL x2). La capa acuosa se liofilizó para producir el producto crudo, que se diluyó con DCM/MeOH (5:1, 20 mL) y se filtró. El filtrado se concentró para producir el **compuesto 530** (140 mg, 75% de pureza, 54,4%) en forma de un sólido marrón. LCMS m/z 411 $[M+H]^+$.

Etapa 4:

A una solución de HATU (137 mg, 0,35 mmol) en DMF (20 mL) se añadió gota a gota una solución de **compuesto 530** (140 mg, 75% de pureza, 0,25 mmol) y DIEA (516 mg, 4 mmol) en DMF (10 mL) a 0 °C. Después de la adición, la mezcla resultante se agitó a 0 °C durante 1 hora. LC-MS mostró que la reacción estaba completa. La mezcla se vertió en agua (50 mL). La mezcla se extrajo con EtOAc (50 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (40 mL x 5), se secaron en Na_2SO_4 y se concentraron al vacío para obtener un residuo. El residuo se purificó por cromatografía en columna en gel de sílice (DCM/MeOH =25:1, Rf = 0,3) para obtener material crudo, que luego se purificó por SFC preparativa (Chiralcel OD-3, 150×4,6mm I.D., 3 µm. Tiempo de retención 6,93 min fase móvil: metanol (0,05% DEA) en CO_2 del 5% al 40% tasa de flujo: 3 mL/min) seguido de HPLC preparativa para obtener el

Ejemplo 88 (12 mg, 12%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, Metanol-d4) δ 7,70 (s, 1H), 7,54-7,51 (dd, 1H), 7,46-7,42 (m, 1H), 7,15-7,11 (m, 1H), 6,91 (s, 1H), 5,76-5,73 (t, 1H), 4,54 (s, 2H), 3,15 (s, 3H), 1,81-1,80 (d, 3H). LCMS *m/z* 392 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-10,16-dimetil-15-oxo-10,15,16,17-tetrahidro-1H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 89)



Etapa 1:

Una mezcla de **compuesto 210** (1,5 g, 3,42 mmol), DIPEA (1,76 g, 13,68 mmol), DPE-Phos (0,3 g, 0,58 mmol) y $Pd(OAc)_2$ (77 mg, 0,34 mmol) en MeOH (50 mL) se agitó a 40 °C en 10 bar de presión de CO durante la noche. La TLC (éter de petróleo / EtOAc = 3:1) mostró que la reacción estaba casi completa. La mezcla se filtró, y el filtrado se concentró. El residuo se purificó por cromatografía en columna en gel de sílice (éter de petróleo / EtOAc = 3:1, Rf: 0,5) para obtener el **compuesto 531** (0,76 g, 60%) en forma de un sólido amarillo.

Etapa 2:

A una solución de **compuesto 531** (300 mg, 0,81 mmol), **compuesto 214** (541 mg, 1,22 mmol) y bis-(pinacalato)-diboro (617 mg, 2,43 mmol) en metanol (60 mL) se añadieron cataCXium A (40 mg, 0,1053 mmol) y Pd(OAc)2 (25 mg, 0,1053 mmol). Después de que la mezcla se desgasificó tres veces con nitrógeno, se añadió una solución de NaOH (65 mg, 1,62 mmol) en agua (12 mL) en nitrógeno a temperatura ambiente. La mezcla resultante se desgasificó con nitrógeno tres veces y luego se

calentó a reflujo durante 16 horas. La TLC (éter de petróleo/EtOAc 3/1) mostró que la reacción estaba completa. La mezcla de reacción se diluyó con EtOAc (50 mL x 3). Las capas combinadas de EtOAc se lavaron con salmuera (20 mL x 3), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo, que se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc de 10/1 a 3/1) para obtener el **compuesto 532** (400 mg, 53% de pureza, 40%) en forma de un sólido marrón. LCMS m/z 655 $[M+H]^+$.

Etapa 3:

A una solución agitada de **compuesto 532** (400 mg, 53% de pureza, 0,32 mmol) en DCM (2 mL) se añadió gota a gota ~ HCl 4 M (g) en dioxano (10 mL) a temperatura ambiente. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La LC-MS mostró que la mezcla de reacción estaba completa. La mezcla de reacción se concentró al vacío para producir el **compuesto 533** crudo, que se usó para la siguiente etapa sin otra purificación. LCMS m/z 425 $[M+H]^+$.

Etapa 4:

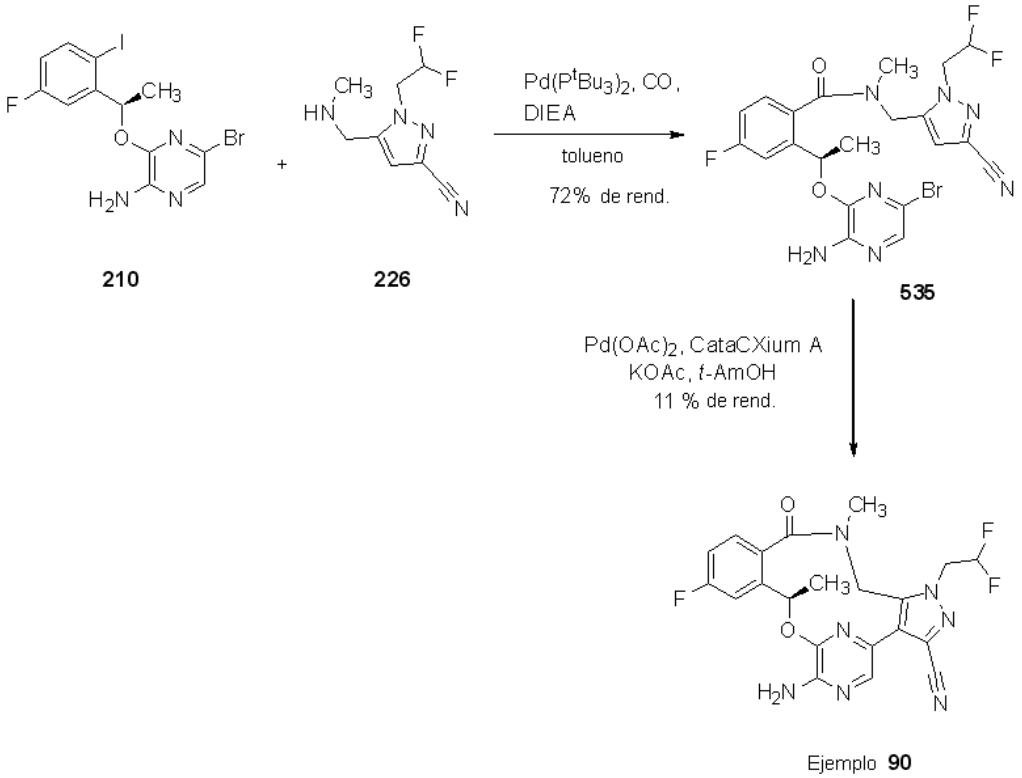
Una mezcla de **compuesto 533** (~300 mg) y KOH (0,395 g, 7,0 mmol) en metanol (15 mL) se agitó a 50 °C durante 36 horas. La LC-MS mostró que la reacción estaba completa. El MeOH se eliminó al vacío para producir el residuo, que se acidificó con HCl acuoso 1 a pH ~5. La mezcla se saturó con NaCl sólido y luego se extrajo con EtOAc (30 mL x 5). Las capas combinadas de EtOAc se secaron en Na_2SO_4 y se concentraron al vacío para producir el **compuesto 534** (180 mg, 39,8% de pureza, 53,8%) en forma de un sólido marrón. LCMS m/z 411 $[M+H]^+$.

Etapa 5:

A una solución de HATU (250 mg, 0,66 mmol) en DMF (25 mL) se añadió gota a gota una solución de **compuesto 534** (180 mg, 0,44 mmol) y DIEA (908 mg, 7,04 mmol) en DMF (10 mL) a 0 °C. Después de la adición, la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La LC-MS mostró que la reacción estaba completa. La mezcla se vertió en agua helada (50 mL). La mezcla se extrajo con EtOAc (40 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (20 mL x 5), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo. El residuo se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc 2:1~1:2) para obtener el **Ejemplo 89** (10,5 mg, 15,8%) en forma de un sólido blanco. ^1H RMN (400 MHz, $CDCl_3$) δ 8,13 (s, 1H), 7,30-7,26 (dd, 1H), 7,23-7,20 (m, 1H), 7,01-

7,00 (m, 1H), 6,19-6,14 (m, 1H), 5,07 (s, 2H), 4,75-4,72 (d, 1H), 4,28-4,25 (d, 1H), 3,04 (s, 3H), 1,17-1,15 (d, 3H). LCMS ES *m/z* 393 $[M+H]^+$.

Preparación de (10R)-7-amino-1-(2,2-difluoroetil)-12-fluoro-10,16-dimetil-15-oxo-10,15,16,17-tetrahidro-1H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 90)



210 **226** **535**

Ejemplo **90**

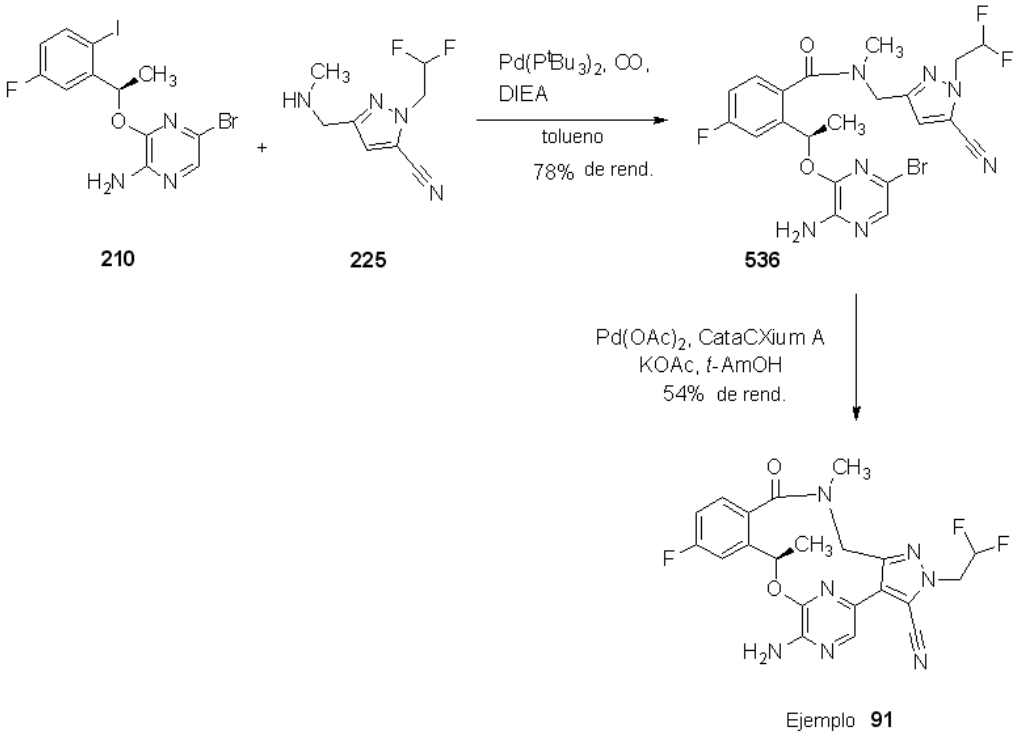
Etapa 1:

Se añadió Pd(P^{t}Bu$_3$)$_2$ (97 mg, 0,191 mmol) a una mezcla de **compuesto 226** (450 mg, 1,91 mmol), **compuesto 210**, (R)-5-bromo-3-(1-(5-fluoro-2-yodofenil)etoxi)-pirazin-2-amina (838 mg, 1,91 mmol) y DIEA (1,23 g, 9,55 mmol) en tolueno desgasificado (50 mL) y la mezcla se agitó en una atmósfera de CO (4 bar) a 80 °C durante 18 horas. Después de enfriar, los volátiles se eliminaron y el residuo se purificó por cromatografía flash en gel de sílice (1:1 EtOAc/heptano), lo que produjo el **compuesto 535** (750 mg, 72%) en forma de una espuma de color crema. ^{1}H RMN (400 MHz, DMSO-*d*$_6$) δ 7,64 – 7,08 (m, 5H), 6,75 (s, 2H), 6,51 (tt, *J* = 54,4, 3,5 Hz, 1H), 5,96 (d, J = 6,6 Hz, 1H), 5,01 – 4,35 (m, 4H), 2,95 (d, *J* = 44,5 Hz, 3H), 1,58 (d, *J* = 6,4 Hz, 3H). LCMS *m/z* 538/540 $[M+H]^+$.

Etapa 2:

$Pd(OAc)_2$ (24,0 mg, 0,11 mmol) y cataCXium A (78,0 mg, 0,22 mmol) se añadieron a una mezcla de **compuesto 535** (300 mg, 0,56 mmol), KOAc (274 mg, 2,8 mmol) y se desgasificó alcohol t-amílico (12,0 mL) en un vial de microondas de 20 mL y se agitó bajo irradiación de microondas (130 °C) durante 2,5 horas. Después de enfriar, las sustancias volátiles se eliminaron y el residuo se purificó por cromatografía en columna (70% de EtOAc en heptanos). Las fracciones que contenían el producto (Rf = 0,35) se evaporaron (producto no limpio por TLC). El residuo se repurificó por cromatografía en columna (20% de acetona en DCM). Las fracciones que contenían el producto se evaporaron (una impureza de corrida cercana aún estaba presente por TLC). El residuo se repurificó por cromatografía en columna (70% de TBME en heptanos). Las fracciones que contenían el producto se evaporaron y el residuo se disolvió en MeOH (1,0 mL). Se añadió lentamente agua (aproximadamente 4 mL) mientras se agitaba para precipitar el producto. El solvente se decantó con cuidado de los sólidos resultantes que se secaron al vacío durante la noche para producir el **Ejemplo 90** (28,0 mg, 11% de rendimiento) en forma de un polvo amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,86 (s, 1H), 7,48 (dd, *J* = 10,0, 2,6 Hz, 1H), 7,32 (dd, *J* = 8,5, 5,6 Hz, 1H), 7,23 (td, *J* = 8,5, 2,6 Hz, 1H), 6,76 (s, 2H), 6,66 – 6,32 (m, 1H), 5,93 – 5,78 (m, 1H), 5,19 – 4,87 (m, 2H), 4,72 (d, *J* = 14,9 Hz, 1H), 4,37 (d, *J* = 14,9 Hz, 1H), 2,86 (s, 3H), 1,64 (d, *J* = 6,6 Hz, 3H). LCMS ES *m/z* 458 $[M+H]^+$.

Preparación de (10R)-7-amino-2-(2,2-difluoroetil)-12-fluoro-10,16-dimetil-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclo-tetradecin-3-carbonitrilo (Ejemplo 91)



210 225 536

Ejemplo **91**

Etapa 1:

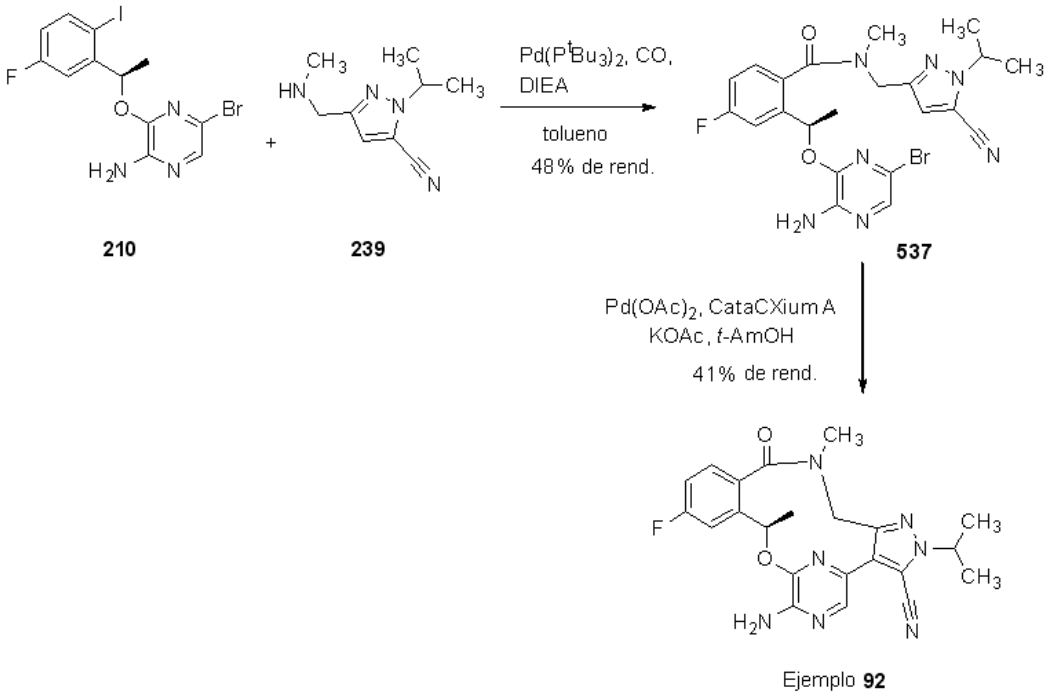
Se añadió Pd(P^{t}Bu^3)^2 (32 mg, 0,064 mmol) a una mezcla de **compuesto 210**, (R)-5-bromo-3-(1-(5-fluoro-2-yodofenil)etoxi)pirazin-2-amina (280 mg, 0,64 mmol), **compuesto 225** (150 mg, 0,64 mmol) y DIEA (413 mg, 3,2 mmol) en tolueno desgasificado (20 mL). La mezcla se agitó luego en una atmósfera de CO (4 bar) a 80 °C durante 6 horas. La mezcla se concentró y el residuo se purificó por cromatografía en columna (40% al 75% de EtOAc en heptanos), lo que produjo el **compuesto 536** (270 mg, 78%) en forma de una espuma amarilla pálida. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,70 – 7,06 (m, 5H), 6,73 (s, 2H), 6,43 (tt, J = 54,0, 3,0 Hz, 1H), 6,04 (d, J = 6,5 Hz, 1H), 4,95 – 4,27 (m, 4H), 2,93 (m, 3H), 1,57 (d, J = 6,5 Hz, 3H). LCMS *m/z* 538/540 [M+H]$^+$.

Etapa 2:

Una mezcla de **compuesto 536** (108 mg, 0,20 mmol), Pd(OAc)$_2$ (6,60 mg, 0,03 mmol), cataCXium A (21,4 mg, 0,06 mmol), KOAc (98 mg, 1,0 mmol) en alcohol t-amílico desgasificado (7,0 mL) se agitó bajo irradiación de microondas (120 °C) durante 2 horas. Después de enfriar, la mezcla se concentró, luego se purificó por cromatografía en columna (1:1 EtOAc/heptanos), lo que produjo el **Ejemplo 91** (75 mg, 54%) en forma de un polvo color crema. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,78 (s,

1H), 7,48 (dd, *J* = 10,1, 2,7 Hz, 1H), 7,42 (dd, *J* = 8,5, 5,7 Hz, 1H), 7,17 (td, *J* = 8,5, 2,7 Hz, 1H), 6,83 (s, 2H), 6,49 (tt, *J* = 53,9, 2,8 Hz, 1H), 5,91 (qd, *J* = 6,5, 1,8 Hz, 1H), 4,88 (td, *J* = 15,8, 2,8 Hz, 2H), 4,35 (q, *J* = 13,7 Hz, 2H), 2,88 (s, 3H), 1,64 (d, *J* = 6,5 Hz, 3H). LCMS *m/z* 458 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-10,16-dimetil-15-oxo-2-(propan-2-il)-10,15,16,17-tetrahidro-2H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 92)



Ejemplo **92**

Etapa 1:

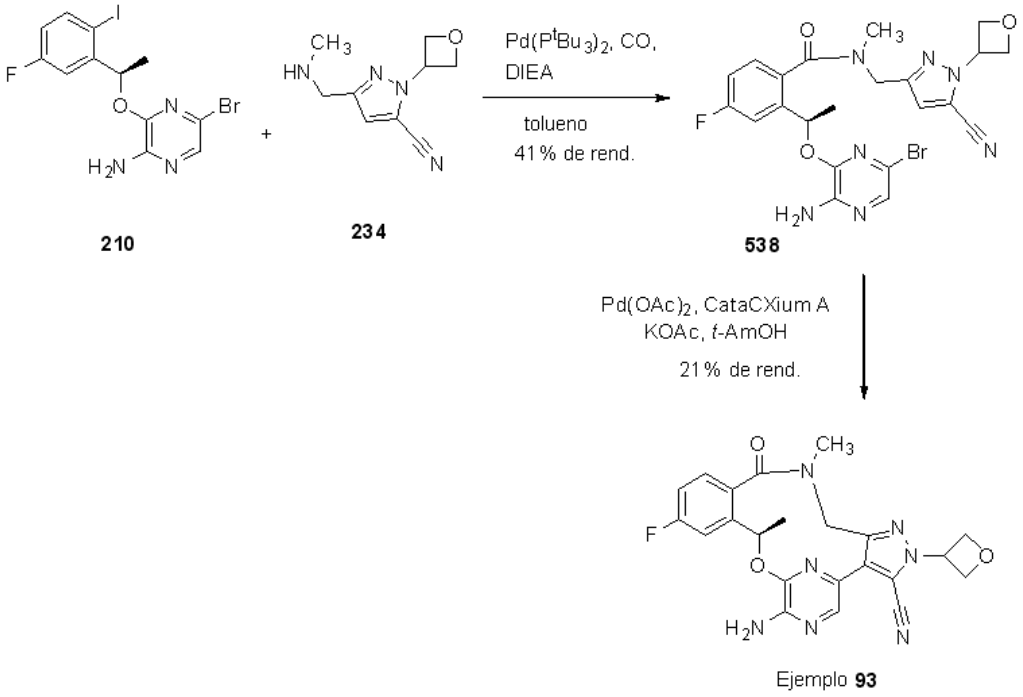
El procedimiento descrito en la etapa 1 para el **Ejemplo 91** se usó para preparar el **compuesto 537** (200 mg, 48%) en forma de una espuma amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,69 – 6,98 (m, 5H), 6,74 (s, 2H), 6,17 – 5,90 (m, 1H), 4,95 – 4,22 (m, 3H), 2,93 (m, 3H), 1,57 (d, *J* = 6,4 Hz, 3H), 1,42 (dd, *J* = 8,3, 6,6 Hz, 6H). LCMS ES *m/z* 516/518 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 91** se usó para preparar el **Ejemplo 92** (70 mg, 41%) en forma de un polvo color crema. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,77 (s, 1H), 7,47 (dd, *J* = 10,1, 2,6 Hz, 1H), 7,40 (dd, J = 8,5, 5,7 Hz, 1H), 7,17 (td, *J* = 8,5, 2,7 Hz, 1H), 6,75 (s, 2H), 5,90 (qd, *J* = 6,4, 1,9 Hz, 1H), 4,77

(hept, *J* = 6,7 Hz, 1H), 4,41 – 4,24 (m, 2H), 2,88 (s, 3H), 1,64 (d, *J* = 6,5 Hz, 3H), 1,50 (dd, *J* = 6,6, 1,1 Hz, 6H). LCMS ES *m/z* 436 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-10,16-dimetil-2-(oxetan-3-il)-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 93)



210 234 538

Ejemplo **93**

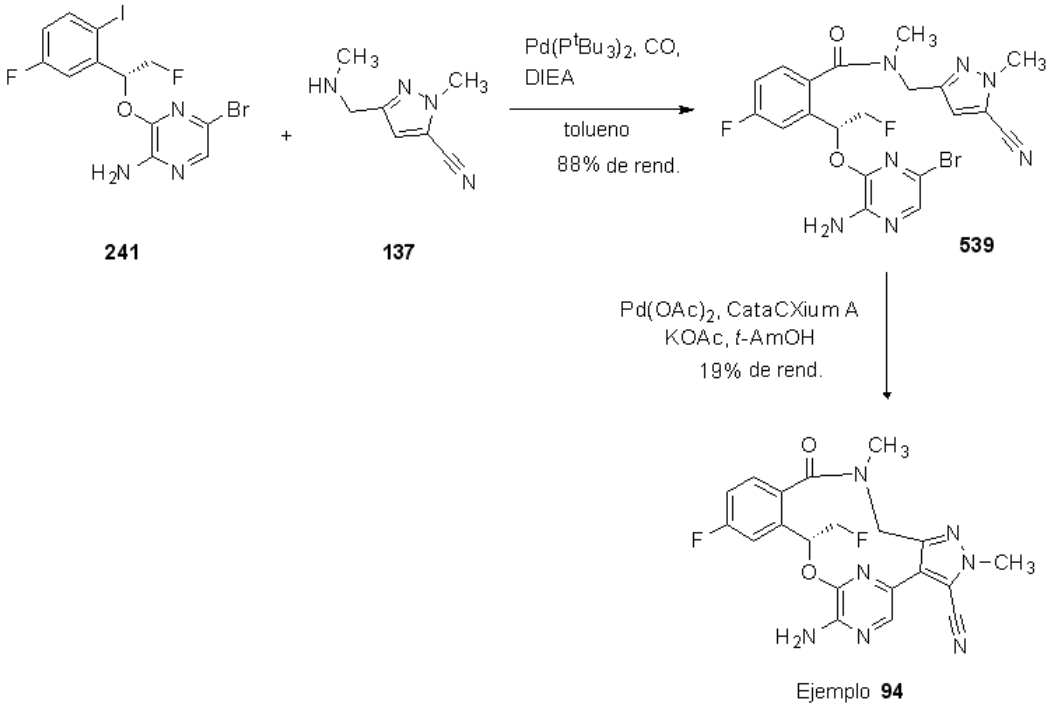
Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 91** se usó para preparar el **compuesto 538** (376 mg, 41%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,57 (s, 1H), 7,23 (dd, *J* = 8,5, 5,5 Hz, 1H), 7,15 (dd, *J* = 9,7, 2,6 Hz, 1H), 7,01 (td, J = 8,3, 2,6 Hz, 1H), 6,92 (s, 1H), 6,10 (q, *J* = 6,4 Hz, 1H), 5,66 (tt, *J* = 7,7, 6,2 Hz, 1H), 5,17 – 4,98 (m, 7H), 4,65 (d, *J* = 15,0 Hz, 1H), 3,04 (s, 3H), 1,74 (d, *J* = 6,5 Hz, 3H). LCMS ES *m/z* 530/532 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 91** se usó para preparar el **Ejemplo 93** en forma de un sólido amarillo (63 mg, 21% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,76 (s, 1H), 7,48 (dd, J = 10,1, 2,7 Hz, 1H), 7,43 (dd, J = 8,5, 5,7 Hz, 1H), 7,18 (td, *J* = 8,5, 2,7 Hz, 1H), 6,79 (s, 2H), 5,96 – 5,87 (m, 1H), 5,76 (tt, *J* = 7,5, 6,0 Hz, 1H), 5,04 – 4,91 (m, 4H), 4,39 (s, 2H), 2,94 (s, 3H), 1,65 (d, *J* = 6,6 Hz, 3H). LCMS ES *m/z* 450 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-10-(fluorometil)-2,16-dimetil-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclo-tetradecin-3-carbonitrilo (Ejemplo 94)



Ejemplo **94**

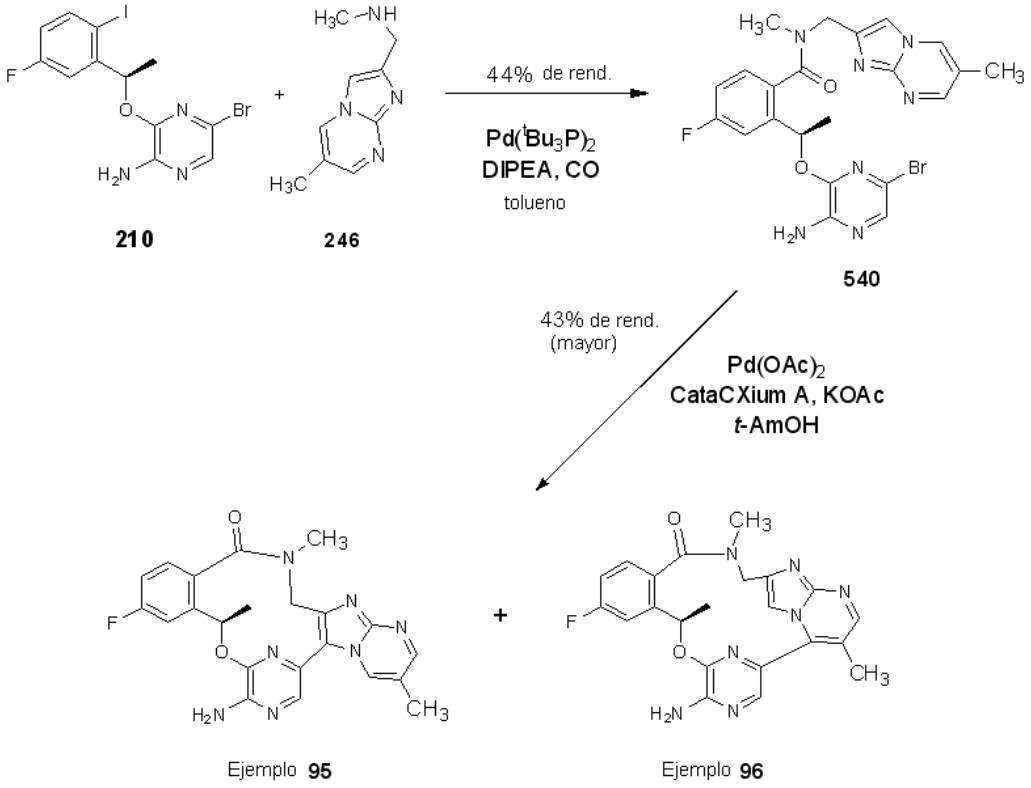
Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 91** se usó para preparar el **compuesto 539** (0,08 g, 88%) en forma de un sólido amarillo.

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 91** se usó para preparar el **Ejemplo 94** (16 mg, 19%) en forma de un sólido blanco (63 mg, 21% de rendimiento). ^{1}H RMN (400 MHz, Metanol-*d*$_4$) δ 7,94 (s, 1H), 7,50-7,43 (m, 2H), 7,21-7,17 (m, 1H), 6,17-6,11 (m, 1H), 5,06-5,01 (m, 1H), 4,74-4,71 (m, 1H), 4,56-4,53 (d, 1H), 4,40-4,37 (d, 1H), 4,14 (s, 3H), 3,05 (s, 3H). LCMS ES *m/z* 426 [M+H]$^+$.

Preparación de 12-fluoro-1,14-dimetil-1,4,5,6,7,8-hexahidro-14H-16,20-(meteno)-pirazolo[4,3-g][1,14,11]benzodioxazaciclohexadecin-17-amina (Ejemplo 95) y (11R)-8-amino-13-fluoro-4,11,17-trimetil-17,18-dihidro-9,5:19,1-di(azeno)pirimido[6,1-h][2,5,9,13]benzoxatriazaciclohexadecin-16(11H)-ona (Ejemplo 96)



Etapa 1:

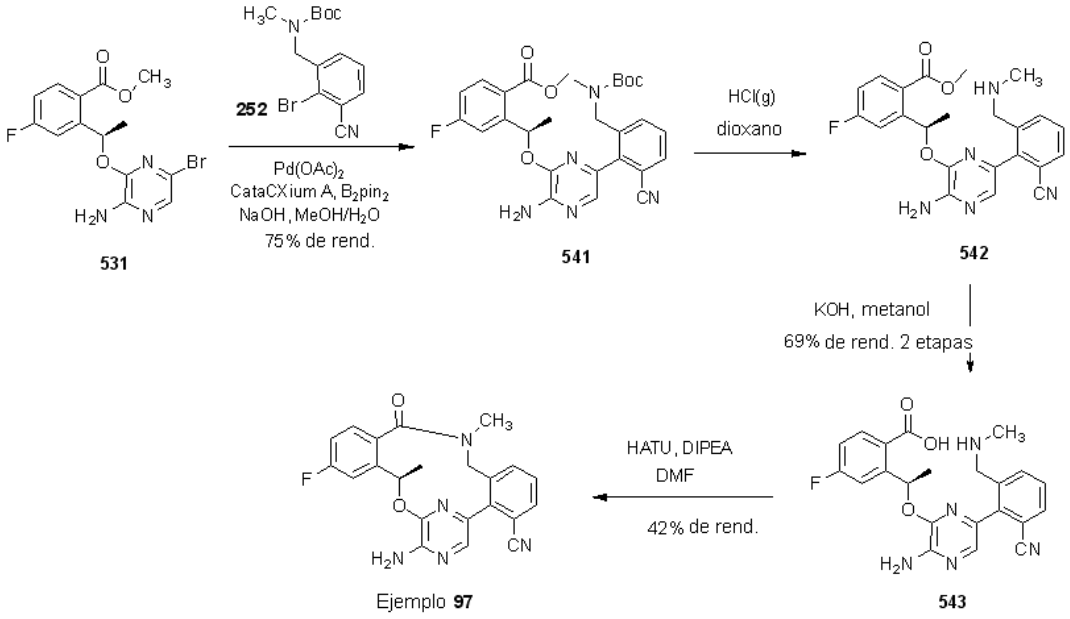
El procedimiento descrito en la etapa 1 para el **Ejemplo 91** se usó para preparar el **compuesto 540** (245 mg, 44%) en forma de una espuma amarilla pálida. ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,72 (dt, J = 2,6, 1,3 Hz, 1H), 8,63 (s, 1H), 8,49 – 8,25 (m, 1H), 7,83 (s, 1H), 7,69 (s, 1H), 7,63 – 7,46 (m, 2H), 7,37 (dd, J = 8,3, 5,8 Hz, 0H), 7,27 – 7,05 (m, 1H), 6,72 (d, J = 7,1 Hz, 2H), 6,09 (t, J = 6,5 Hz, 0H), 6,00 (d, J = 16,3 Hz, 0H), 4,97 – 4,67 (m, 1H), 4,45 (t, J = 18,3 Hz, 1H), 3,06 (s, 2H), 2,93 (s, 1H), 2,28 (d, J = 7,4 Hz, 4H), 1,59 (dt, J = 5,8, 2,4 Hz, 4H). LCMS ES m/z 511/513 $[M+H]^+$.

Etapa 2:

El **compuesto 540** (230 mg, 0,45 mmol) y KOAc (219 mg, 2,23 mmol) se mezclaron en alcohol ter-amílico (15 mL). La mezcla se desgasificó (burbujeando nitrógeno durante 30 minutos), luego se añadieron $Pd(OAc)_2$ (20 mg, 0,09 mmol) y cataCXium A (64 mg, 0,18 mmol). La mezcla se desgasificó otra vez, luego se calentó en el microondas durante 2 horas a 120 °C. La LC-MS de la mezcla cruda mostró que la reacción estaba terminada. La mezcla se filtró a través de un taco de celite y se enjuagó con EtOAc (50 mL). El filtrado se lavó con agua (100 mL), se secó en $MgSO_4$, se filtró y se concentró al vacío. El aceite obtenido se purificó por cromatografía en columna (eluyentes EtOAc/MeOH de 100:0 a 90:10). El vidrio amarillo obtenido

(macrociclo puro que aún contenía EtOAc) se disolvió en MeOH (20 mL) y se añadió agua (20 mL). La mezcla se concentró al vacío, luego se liofilizó para producir el **Ejemplo 95** en forma de un sólido amarillo pálido (82 mg, 43% de rendimiento, 97% de pureza por LC-MS). ^{1}H RMN (400 MHz, DMSO-*d*$_6$) δ 8,84 (dd, *J* = 2,5, 1,3 Hz, 1H), 8,45 (d, *J* = 2,2 Hz, 1H), 7,92 (s, 1H), 7,54 (dd, *J* = 10,1, 2,7 Hz, 1H), 7,42 (dd, *J* = 8,5, 5,7 Hz, 1H), 7,17 (td, *J* = 8,5, 2,7 Hz, 1H), 6,75 (s, 2H), 6,18 – 5,92 (m, 1H), 4,62 – 4,19 (m, 2H), 2,96 (s, 3H), 2,32 (d, *J* = 1,1 Hz, 3H), 1,66 (d, J = 6,5 Hz, 3H). LCMS ES *m/z* 434 [M+H]$^+$. Las fracciones mixtas de la columna se purificaron por HPLC de fase inversa para producir el **Ejemplo 96** (15 mg, 7% de rendimiento, 92% de pureza por LC-MS) en forma de una mezcla de dos confórmeros por ^{1}H RMN (aproximadamente mezcla 1:1). ^{1}H RMN (400 MHz, Metanol-*d*$_4$) δ 8,32 (d, *J* = 8,4 Hz, 1H), 7,84 (s, 1H), 7,81 – 7,72 (m, 1H), 7,61 (dd, *J* = 8,5, 5,7 Hz, 0,5H), 7,48 (dd, *J* = 10,4, 2,7 Hz, 0,5H), 7,38 (dd, *J* = 8,5, 5,5 Hz, 0,5H), 7,34 (s, 0,5H), 7,04 (td, *J* = 8,3, 2,7 Hz, 1H), 6,86 (d, *J* = 6,4 Hz, 0,5H), 6,14 (d, *J* = 6,3 Hz, 0,5H), 5,24 (dd, *J* = 15,9, 8,5 Hz, 1H), 4,08 (dd, *J* = 38,3, 15,9 Hz, 1H), 2,97 (s, 1,5H), 2,93 (d, *J* = 1,9 Hz, 1,5H), 2,39 (s, 1,5H), 2,32 (s, 1,5H), 1,63 (dd, *J* = 9,0, 6,5 Hz, 1,5H), 1,40 (d, *J* = 6,4 Hz, 1,5H). LCMS ES *m/z* 434 [M+H]$^+$.

Preparación de (5R)-8-amino-3-fluoro-5,17-dimetil-18-oxo-5,16,17,18-tetrahidro-7,11-(azeno)dibenzo[g,l][1,4,10]oxadiazaciclotetradecin-12-carbonitrilo (Ejemplo 97)



Etapa 1:

A una solución de **compuesto 531** (300 mg, 0,81 mmol), **compuesto 252** (393 mg, 1,21 mmol) y bis-(pinacalato)diboro (610 mg, 2,43 mmol) en metanol (60 mL) se añadieron catacxium A (38 mg, 0,1053 mmol) y $Pd(OAc)_2$ (24 mg, 0,1053 mmol). Después de que la mezcla se desgasificó tres veces con nitrógeno, se añadió una solución de NaOH (65 mg, 1,62 mmol) en agua (12 mL) a la mezcla anterior en nitrógeno a temperatura ambiente. La mezcla resultante se desgasificó con nitrógeno tres veces y luego se calentó a reflujo durante 16 horas. La TLC (éter de petróleo/EtOAc 3/1) mostró que la reacción estaba completa. La mezcla de reacción se diluyó con EtOAc (50 mL x 3). Las capas combinadas de EtOAc se lavaron con salmuera (20 mL x 2), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo, que se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc de 10/1 a 5/1) para producir el **compuesto 541** (400 mg, 80% de pureza, 75%) en forma de un sólido marrón. LCMS m/z 535 $[M+H]^+$.

Etapa 2:

A una solución agitada de **compuesto 541** (400 mg, 80% de pureza, 0,61 mmol) en DCM (2 mL) se añadió gota a gota ~ HCl 4 M (g) en dioxano (10 mL) a temperatura ambiente. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La LC-MS mostró que la mezcla de reacción estaba completa. La mezcla de reacción se concentró al vacío para producir el **compuesto 542** crudo, que se usó para la siguiente etapa sin otra purificación. LCMS m/z 435 $[M+H]^+$.

Etapa 3:

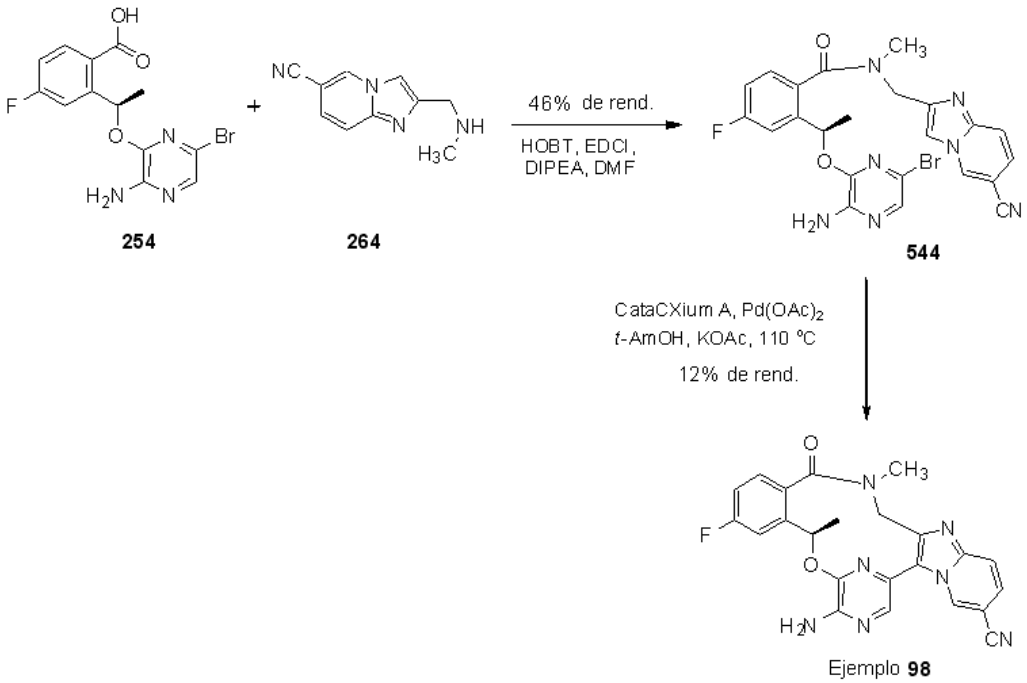
Una mezcla de **compuesto 542** (~300 mg) y KOH (316 mg, 5,65 mmol) en metanol (20 mL) se agitó a temperatura ambiente durante 36 horas. La LC-MS mostró que la reacción estaba completa. La mezcla se concentró al vacío. El residuo se diluyó con agua y se ajustó a pH ~ 5 con HCl 0,5 N. La capa acuosa se extrajo con EtOAc (30 mL x 5). Las capas combinadas de EtOAc se secaron en Na_2SO_4 y se concentraron al vacío para producir el **compuesto 543** (0,2 g, 69%) en forma de un sólido amarillo. LCMS m/z 422 $[M+H]^+$.

Etapa 4:

A una solución de HATU (271 mg, 0,69) en DMF (60 mL) se añadió gota a gota la solución de mezcla de **compuesto 543** (200 mg, 0,47 mmol) y DIPEA (980 mg, 7,6 mmol) en DMF (10 mL) a 0 °C. Después de la adición, la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La LC-MS mostró que la reacción estaba

completa. La mezcla se vertió en agua helada (20 mL). La mezcla se extrajo con EtOAc (40 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (20 mL x 5), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo. El residuo se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc 5:1~1:1) para producir el **Ejemplo 97** (80,8 mg, 42%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,81-7,78 (m, 2H), 7,67-7,65 (m, 1H), 7,50-7,47 (m, 1H), 7,29-7,27 (m, 1H), 7,18-7,17 (m, 1H), 6,98-6,94 (m, 1H), 6,34-6,29 (m, 1H), 5,10 (s, 2H), 4,65-4,62 (d, 1H), 4,15-4,12 (d, 1H), 2,94 (s, 3H), 1,79-1,78 (d, 3H). LCMS ES *m/z* 404 $[M+H]^+$.

Preparación de (5R)-8-amino-3-fluoro-5,19-dimetil-20-oxo-5,18,19,20-tetrahidro-7,11-(azeno)pirido[2',1':2,3]imidazo[4,5-h][2,5,11]benzoxadiazaciclotetradecin-14-carbonitrilo (Ejemplo 98)



254 264 544

Ejemplo **98**

Etapa 1:

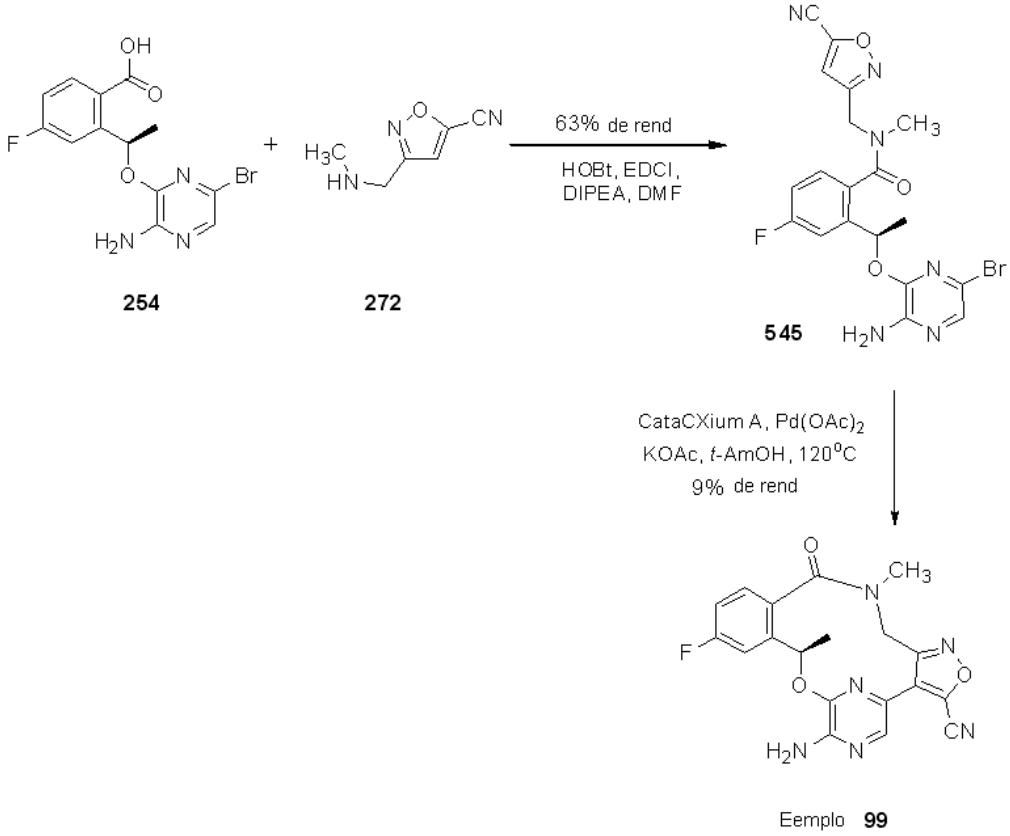
A una mezcla de **compuesto 254** (0,217 g, 0,611 mmol), **compuesto 264** (0,15 g, 0,673 mmol) en DMF (20 mL) se añadieron EDCI (0,176 g, 0,916 mmol), HOBt (0,124 g, 0,916 mmol) y DIPEA (0,394 g, 3,055 mmol) a -35 °C. La mezcla resultante se agitó a -30 °C durante 30 min y se agitó a temperatura ambiente durante la noche. La TLC (éter de petróleo/EtOAc = 1:1) mostró que la mayor parte del **compuesto 254** se había consumido. La mezcla se diluyó con EtOAc (50 mL) y H_2O (10 mL). La capa

orgánica se separó y la capa acuosa se extrajo con EtOAc (20 mL x 2). Las capas orgánicas se combinaron, se lavaron con salmuera (10 mL x 5), se secaron en Na_2SO_4, se filtraron y se concentraron al vacío para producir el producto crudo, que se purificó por TLC preparativa para obtener el **compuesto 544** (150 mg, 46%) en forma de un sólido blanco.

Etapa 2:

La reacción se corrió en tres lotes de 50 mg en idénticas condiciones. A una mezcla de **compuesto 544** (0,05 g, 0,095 mmol), cataCXium (4,25 mg, 0,0118 mmol), *t*-AmOH (1,94 mg, 0,019 mmol) y KOAc (46,55 mg, 0,475 mmol) en DMAc recién destilado (8 mL) se añadió $Pd(OAc)_2$ (2,66 mg, 0,0118 mmol) a temperatura ambiente en una atmósfera de nitrógeno. La mezcla resultante se selló y se calentó a 110 °C durante 12 h. La LC-MS mostró que la reacción estaba completa. La mezcla se diluyó con EtOAc (25 mL) y luego se lavó con salmuera (5 mL x 4). La capa orgánica se separó y se secó en Na_2SO_4, se filtró y se concentró al vacío para producir el producto crudo, que se purificó por TLC preparativa y luego se repurificó por HPLC preparativa de fase inversa para obtener el **Ejemplo 98** (15,4 mg, 12%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, Metanol d_4 + D_2O): δ 9,38-9,37 (m, 1H), 7,98-7,91 (m, 2H), 7,85-7,80 (m, 1H), 7,55-7,45 (m, 2H), 7,25-7,15 (m, 1H), 6,25-6,15 (m, 1H), 4,80-4,75 (m, 2H), 4,60-4,52 (m, 1H), 3,15 (s, 3H), 1,84-1,82 (dd, 3H). LCMS *m/z* 444 $[M+1]^+$.

Preparación de (10R)-7-amino-12-fluoro-10,16-dimetil-15-oxo-10,15,16,17-tetrahidro-8,4-(azeno)[1,2]oxazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 99)



254 272 545

Eemplo **99**

Etapa 1:

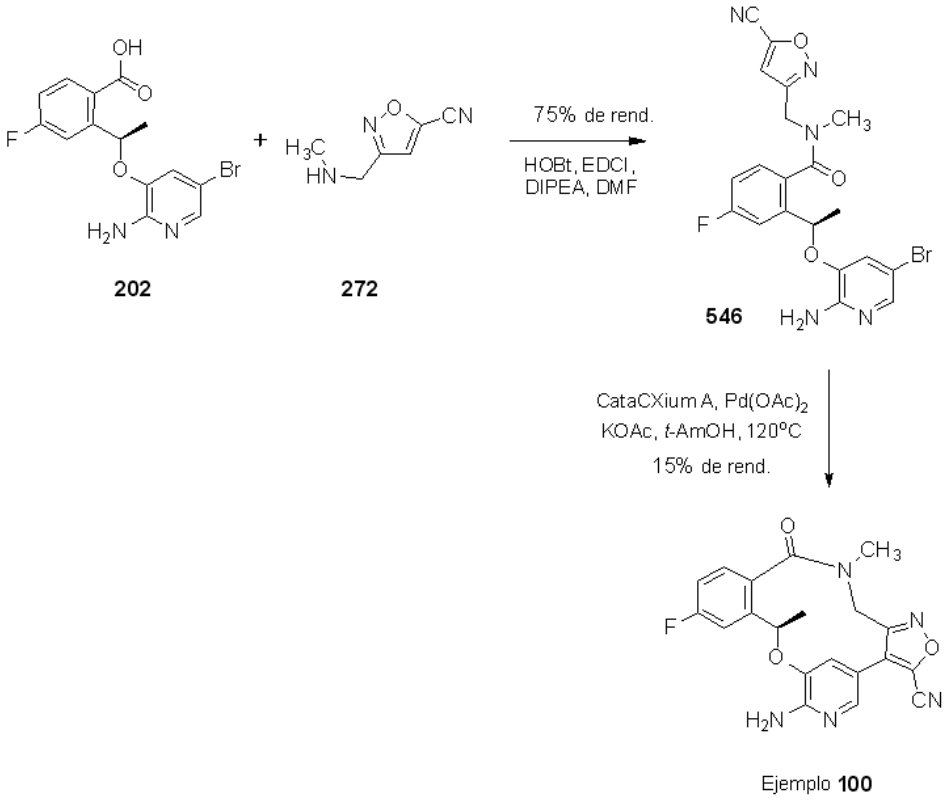
A una solución agitada de **compuesto 254** (250 mg, 0,7 mmol), **compuesto 272** (145 mg, 0,7 mmol) y DIPEA (271 mg, 2,1 mmol) en DMF (15 mL) se añadieron HOBt (143 mg, 1,05 mmol) y EDCI (135 mg, 1,05 mmol) a -35 °C en N_2, Después de la adición, la mezcla se agitó a temperatura ambiente durante 24 horas. La TLC (éter de petróleo/EtOAc = 1:1) indicó que la reacción estaba completa. La mezcla se vertió en agua helada (20 mL), se extrajo con EtOAc (20 mL x 5), las capas orgánicas combinadas se lavaron con salmuera (20 mL x 5), se secaron sobre Na_2SO_4, se concentraron para producir un residuo, que se purificó por cromatografía en columna (gel de sílice Rf = 0,3, éter de petróleo/EtOAc = 2:1-1:1) para producir el **compuesto 545** (210 mg, 63%) en forma de un aceite amarillo claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,60 (s, 1H), 7,22-7,21 (m, 2H), 7,18 (s, 1H), 7,04-7,02 (m, 1H), 6,12 (m, 1H), 5,02-4,98 (d, 1H), 4,89 (s, 2H), 4,77-4,74 (d, 2H), 3,04 (s, 3H), 1,74-1,72 (d, 3H).

Etapa 2:

Una mezcla de **compuesto 545** (200 mg, 0,42 mmol), KOAc (0,21 g, 2,15 mmol), cataCXium A (18 mg, 0,0504 mmol) y $Pd(OAc)_2$ (5,6 mg, 0,025 mmol) en *t*-AmOH (20 mL) se agitó a 120 °C durante 18 horas. La LC-MS indicó el ~30% del

compuesto deseado. La mezcla se vertió en agua helada (20 mL), se extrajo con EtOAc (30 mL x 5), las capas orgánicas combinadas se lavaron con salmuera (5 mL), se secaron en Na_2SO_4 y se concentraron para producir un residuo, que se purificó por HPLC preparativa de fase inversa para producir el **Ejemplo 99** (14,1 mg, 9 %) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,12 (S, 1H), 7,29-7,28 (d, 1H), 7,23-7,22 (d, 1H), 7,05-7,00 (m, 1H), 6,08-6,05 (s, 1H), 5,24(s, 2H), 4,7- 4,45 (dd, 2H), 3,08 (s, 3H), 1,78-1,76 (d, 3H). LCMS *m/z* 395 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-10,16-dimetil-15-oxo-10,15,16,17-tetrahidro-8,4-(meteno)[1,2]oxazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 100)



Etapa 1:

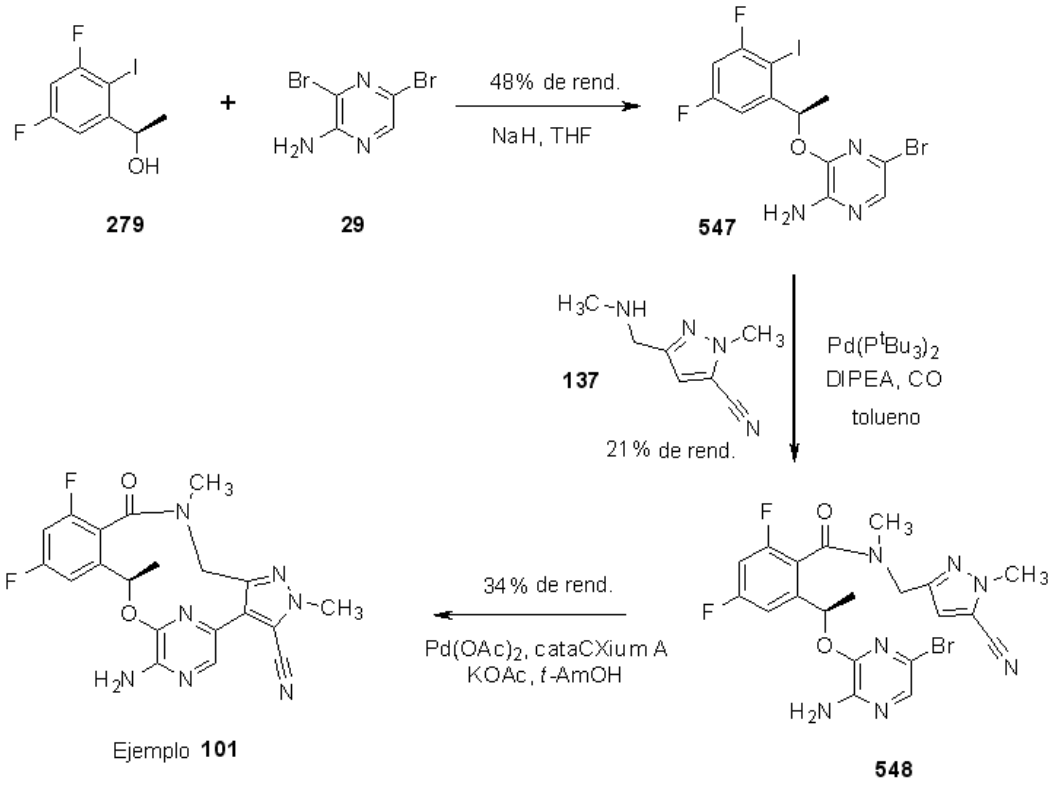
A una solución agitada de **compuesto 202** (400 mg, 1,13 mmol), **compuesto 272** (234 mg, 1,13 mmol) y DIPEA (437 mg, 3,4 mmol) en DMF (20 mL) se añadieron HOBt (230 mg, 1,7 mmol) y EDCI (219 mg, 1,7 mmol) a -35 °C en N_2, Después de la adición, la mezcla se agitó a temperatura ambiente durante 24 horas. La TLC (éter de petróleo/EtOAc =1:1) indicó que la reacción estaba completa. La mezcla se vertió en

agua helada (20 mL), se extrajo con EtOAc (20 mL x 5), las capas orgánicas combinadas se lavaron con salmuera (20 mL x 5), se secaron en Na_2SO_4, se concentraron para producir un residuo, que se purificó por cromatografía en columna (gel de sílice Rf =0,2, éter de petróleo/EtOAc = 2:1-1:1) para producir el **compuesto 546** (400 mg, 75%) en forma de un aceite amarillo claro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,68 (s, 1H), 7,26-7,21 (m, 2H), 7,07 (s, 1H), 7,04-6,98 (m, 1H), 5,50-5,46 (m, 1H), 4,94-4,91 (d, 1H), 4,74 (s, 2H), 4,80-4,76 (d, 1H), 3,14 (s, 3H), 1,66-1,65 (d, 3H).

Etapa 2:

Una mezcla de **compuesto 546** (170 mg, 0,358 mmol), KOAc (0,175 g, 1,8 mmol), cataCXium A (15 mg, 0,043 mmol) y $Pd(OAc)_2$ (5 mg, 0,022 mmol) en *t*-AmOH (20 mL) se agitó a 120 °C durante 18 horas. La LC-MS indicó el ~30% del compuesto deseado. La mezcla se vertió en agua helada (20 mL), se extrajo con EtOAc (30 mL x 5), las capas orgánicas combinadas se lavaron con salmuera (5 mL), se secaron en Na_2SO_4, se concentraron para producir un residuo, que se purificó por cromatografía en columna en gel de sílice (Rf ~ 0,38, éter de petróleo/EtOAc =3 : 1) para producir el **Ejemplo 100** (21 mg, 15 %) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, CDCl3): δ 7,92-7,91 (S, 1H), 7,32-7,26 (m, 1H), 7,24-7,23 (d, 1H), 7,07-7,02 (m, 1H), 6,84 (s, 1H), 5,72-5,70 (s, 2H), 4,59 (s, 2H), 3,18 (s, 3H), 1,81-1,79 (d, 3H). LCMS *m/z* 394 $[M+H]^+$.

Preparación de (10R)-7-amino-12,14-difluoro-2,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 101)



Etapa 1:

Una solución de **compuesto 279** (4,24 g, 14,9 mmol) en THF seco (24 mL) se añadió gota a gota a una suspensión enfriada (0 °C) de NaH (60% en aceite, 746 mg, 18,6 mmol) en THF seco (24 mL). La mezcla se agitó 10 min a 0 °C, luego 30 min a temperatura ambiente antes de añadir una solución de **compuesto 29** (3,14 g, 12,4 mmol) en THF seco (24 mL) de una vez. La mezcla se agitó a 60 °C durante 18 horas, luego se enfrió a temperatura ambiente. Se añadió salmuera (200 mL) con cuidado y la mezcla se extrajo con EtOAc (3 x 200 mL). Las fases orgánicas se combinaron, se secaron en MgSO4, se filtraron y se concentraron al vacío. El aceite obtenido se purificó por cromatografía en columna (eluyentes: heptanos/EtOAc de 98:2 a 75:25). El sólido viscoso obtenido (4,6 g) se suspendió en heptanos (~100 mL) durante 72 horas. La suspensión obtenida se filtró y el sólido se secó al vacío para producir el **compuesto 547** (2,73 g, 48% de rendimiento, 99% de pureza por LC-MS) en forma de un polvo beige. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,59 (s, 1H), 7,55 – 7,42 (m, 1H), 7,31 (td, J = 8,7, 2,8 Hz, 1H), 6,75 (s, 2H), 6,23 (q, J = 6,5 Hz, 1H), 1,53 (d, J = 6,4 Hz, 3H). LCMS *m/z* 455/457 $[M+H]^+$.

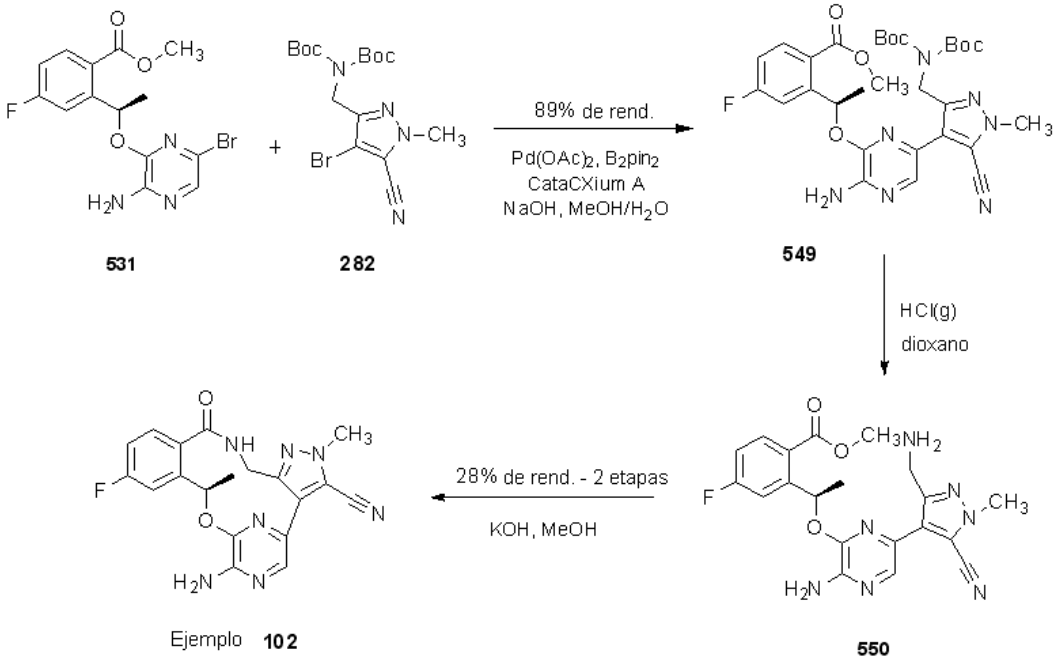
Etapa 2:

El **compuesto 547** (2,0 g, 4,4 mmol), **compuesto 137** (sal de HCl, 974 mg, 4,4 mmol) y DIEA (3,8 mL, 21,9 mmol) se disolvieron en tolueno (127 mL). Se añadió $Pd(P^tBu_3)_2$ (224 mg, 0,44 mmol) (la reacción se volvió negra) y la mezcla se calentó a 85 °C en CO (4 bar) durante 18 horas. La mezcla se enfrió a temperatura ambiente, se filtró a través de un taco de Arbocel, se enjuagó con EtOAc (~100 mL) y los licores madre se concentraron. El aceite obtenido se purificó por cromatografía en columna en gel de sílice (eluyentes heptanos/EtOAc de 4:1 a 1:1) para producir el **compuesto 548** (460 mg, 21% de rendimiento, 89% de pureza por LC-MS) en forma de una espuma sólida incolora. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,56 (d, *J* = 1,1 Hz, 1H), 7,44 (m, 1H), 7,39 – 7,26 (m, 1H), 7,03 (s, 1H), 6,78 (d, *J* = 4,1 Hz, 2H), 5,98 (q, *J* = 6,5 Hz, 1H), 4,83 (d, *J* = 15,0 Hz, 1H), 4,62 (d, *J* = 15,0 Hz, 1H), 3,96 (d, *J* = 1,0 Hz, 3H), 2,90 (s, 3H), 1,59 (d, *J* = 6,5 Hz, 2H). LCMS *m/z* 506/508 $[M+H]^+$.

Etapa 3:

Una solución de **compuesto 548** (230 mg, 0,45 mmol) en alcohol ter-amílico (9 mL) se desgasificó (3 ciclos N_2/vacío) a 100 °C. Se añadieron $Pd(OAc)_2$ (15 mg, 0,07 mmol), cataCXium A (49 mg, 0,14 mmol) y KOAc (227 mg, 2,3 mmol) y la mezcla se desgasificó (3 ciclos N_2/vacío) a 100 °C. La mezcla luego se calentó en un microondas a 120 °C durante 2 horas. La reacción se enfrió a temperatura ambiente, se concentró al vacío, se añadió DCM (50 mL) y la suspensión se filtró. Los licores madre se concentraron al vacío y el aceite obtenido se purificó por cromatografía en columna (eluyentes: heptanos/EtOAc de 3:1 a 1:1) para producir el macrociclo en forma de un polvo beige (102 mg, 53% de rendimiento, 99% de pureza por LC-MS). Este polvo se suspendió en MeOH (~2 mL) y se suspendió durante la noche. La suspensión se filtró y los sólidos blancos obtenidos se secaron con cuidado al vacío (0,3 mBar) a 80 °C durante 6 horas. El **Ejemplo 101** se obtuvo en forma de un polvo blanco (65 mg, 34% de rendimiento, 100% de pureza por LC-MS). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,81 (s, 1H), 7,38 (dd, *J* = 9,6, 2,5 Hz, 1H), 7,29 (td, *J* = 9,3, 2,4 Hz, 1H), 6,79 (s, 2H), 5,94 – 5,73 (m, 1H), 4,42 (dd, *J* = 13,8, 1,9 Hz, 1H), 4,22 (d, *J* = 13,6 Hz, 1H), 4,04 (s, 3H), 2,90 (s, 3H), 1,63 (d, *J* = 6,5 Hz, 3H). LCMS ES *m/z* 426 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-2,10-dimetil-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 102)



Etapa 1:

A una solución de **compuesto 531** (0,2 g, 0,54 mol), **compuesto 282** (336 mg, 0,81 mmol) y bis-(pinacalato)diboro (407 g, 1,62 mmol) en metanol (40 mL) se añadieron cataCXium A (25 mg, 0,07 mmol) y $Pd(OAc)_2$ (16 mg, 0,07 mmol). Después de que la mezcla se desgasificó tres veces con nitrógeno, se añadió una solución de NaOH (65 mg, 1,62 mmol) en agua (12 mL) a la mezcla anterior en gas nitrógeno a temperatura ambiente. La mezcla resultante se desgasificó con gas nitrógeno tres veces y luego se calentó a reflujo durante 16 horas. La TLC (éter de petróleo/EtOAc 3/1) mostró que la reacción estaba completa. La mezcla de reacción se diluyó con EtOAc (500 mL x 3). Las capas combinadas de EtOAc se lavaron con salmuera (100 mL x 2), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo, que se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc de 10/1 a 5/1) para producir el **compuesto 549** (400 mg, 75% de pureza, 89%) en forma de un sólido marrón. LCMS m/z 648 $[M+Na]^+$.

Etapa 2:

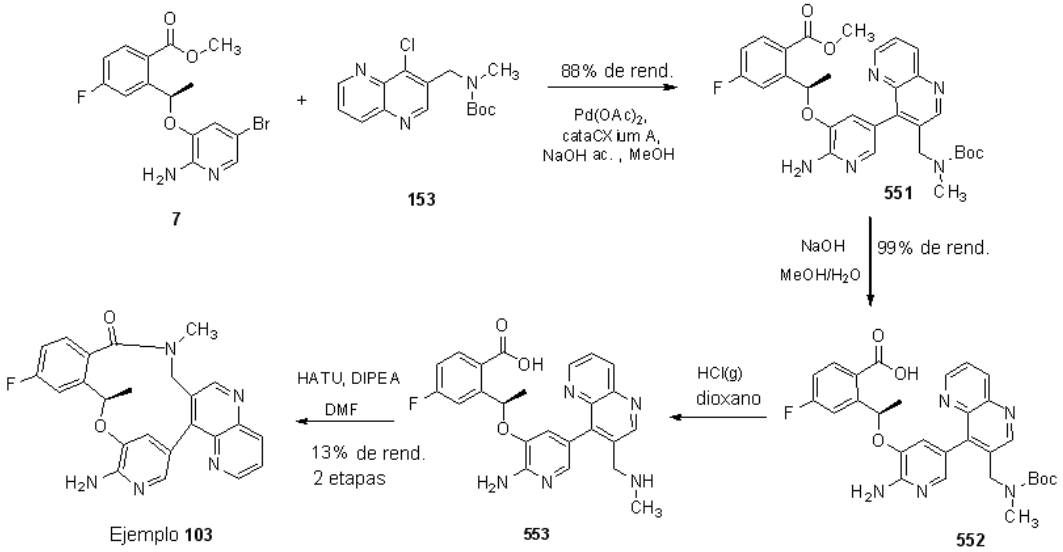
A una solución agitada de **compuesto 549** (400 mg, 75% de pureza, 0,48 mmol) en DCM (2 mL) se añadió gota a gota ~ HCl 4 M (g) en dioxano (10 mL) a temperatura ambiente. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La LC-MS mostró que la mezcla de reacción estaba completa. La mezcla de reacción se concentró al vacío para obtener el

compuesto 550 crudo, que se usó para la siguiente etapa sin otra purificación. LCMS m/z 426 $[M+H]^+$.

Etapa 3:

Una mezcla de **compuesto 550** (~300 mg) y KOH (316 mg, 5,65 mmol) en metanol (20 mL) se agitó a temperatura ambiente durante 4 horas. La LC-MS mostró que la reacción estaba completa. La mezcla se vertió en HCl 0,5 N (20 mL), se extrajo con EtOAc (30 mL x 5). Las capas combinadas de EtOAc se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo, que se purificó por cromatografía en columna (gel de sílice, éter de petróleo/EtOAc de 5/1-1/1) para obtener el **Ejemplo 102** (53,5 mg, 28%) en forma de un sólido marrón. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,96 (s, 1H), 7,32-7,28 (m, 2H), 7,05-7,00 (m, 1H), 6,19-6,14 (m, 1H), 5,08 (s, 2H), 4,30-4,26 (d, 1H), 4,22-4,18 (d, 1H), 3,49 (s, 3H), 2,17 (s, 3H). LCMS m/z 394 $[M+H]^+$.

Preparación de (11R)-8-amino-13-fluoro-11,17-dimetil-17,18-dihidro-9,5-(meteno)-[1,5]naftiridino[4,3-h][2,5,11]benzoxadiazaciclotetradecin-16(11H)-ona (Ejemplo 103)



Etapa 1:

A una solución de **compuesto 7** (0,3 g, 0,81 mmol), **compuesto 153** (400 mg, 1,29 mmol) y bis-(pinacalatodiboro) (618 mg, 2,43 mmol) en metanol (100 mL) se añadieron cataCXium A (37,8 mg, 0,105 mmol) y $Pd(OAc)_2$ (23,7 mg, 0,105 mmol) en nitrógeno a temperatura ambiente. Después de que la mezcla se desgasificó tres veces con nitrógeno, se añadió NaOH (64,8 mg, 1,62 mmol) en agua (12 mL). La mezcla resultante se desgasificó con nitrógeno tres veces y luego se calentó a reflujo

durante 3 horas. La TLC (EtOAc) mostró que la mezcla de reacción estaba completa. La mezcla de reacción se diluyó con EtOAc (300 mL). La mezcla luego se lavó con salmuera (100 mL x 2), se secó en Na_2SO_4 y se concentró al vacío para producir residuo, que se purificó por cromatografía en columna en gel de sílice (DCM/MeOH 20:1, Rf, 0,41) para obtener el **compuesto 551** (400 mg, 88%) en forma de un sólido marrón. LCMS m/z 308 $[M+Na]^+$.

Etapa 2:

Una mezcla de **compuesto 551** (400 mg, 0,71 mmol) y NaOH (0,57 g, 14,2 mmol) en metanol (15 mL) y agua (2 mL) se agitó a 40 °C durante 3 horas. La LC-MS mostró que la mezcla de reacción estaba completa. La mezcla de reacción se concentró al vacío para producir un residuo. El residuo se disolvió con agua (20 mL) y se extrajo con MTBE (20 mL). La capa acuosa luego se acidificó con HCl 6 N a pH ~5. La mezcla se saturó con NaCl sólido y luego se extrajo con EtOAc (20 mL x 5). Las capas combinadas de EtOAc se secaron en Na_2SO_4 y se concentraron al vacío para producir el **compuesto 552** (388 mg, 99%) en forma de un sólido amarillo. LCMS m/z 548 $[M+H]^+$.

Etapa 3:

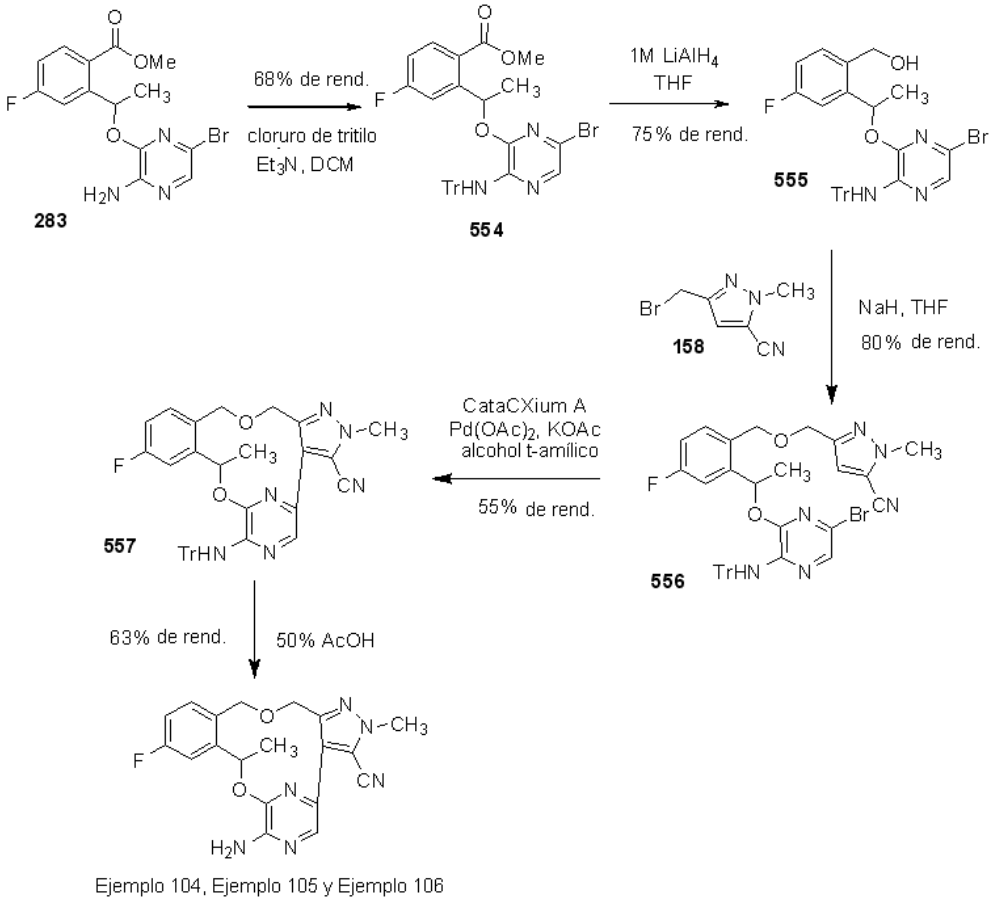
A una solución de **compuesto 552** (388 mg, 0,7 mmol) en dioxano (5 mL) se añadió gota a gota ~ HCl 4 M (g) en dioxano (20 mL) a temperatura ambiente. Después de la adición, la mezcla de reacción se agitó a temperatura ambiente durante 14 horas. LC-MS mostró que la mezcla de reacción estaba completa. La mezcla de reacción se concentró al vacío para producir residuo, que se azeotropó con tolueno tres veces para producir el **compuesto 553** crudo, que se usó para la siguiente etapa sin otra purificación. LCMS m/z 448 $[M+H]^+$.

Etapa 4:

A una solución de HATU (400 mg, 0,313 mmol) en DMF (60 mL) se añadió gota a gota una solución de **compuesto 553** (~0,7 mmol) y DIEA (1,43 g, 11,2 mmol) en DMF (20 mL) a 0 °C. Después de la adición, la mezcla resultante se agitó a esta temperatura durante 1 hora. La LC-MS mostró que la reacción estaba completa. La mezcla se vertió en agua helada (50 mL). La mezcla se extrajo con EtOAc (40 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (20 mL), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo, que se purificó por cromatografía en columna en gel de sílice (DCM/MeOH 20:1 Rf, 0,27) para obtener el **Ejemplo 103** (40 mg, 13%) en forma de un sólido blanquecino. ^1H RMN (400 MHz, $CDCl_3$) δ 9,01-9,00 (m, 2H), 8,44-8,42 (d, 1H), 7,85 (s, 1H), 7,69-7,67 (m, 1H), 7,37-

7,34 (m, 1H), 7,24-7,22 (m, 2H), 7,02-6,98 (m, 1H), 5,90-5,88 (m, 1H), 4,94 (br s, 2H), 4,67-4,47 (dd, 2H), 3,18 (s, 3H), 1,83-1,81 (d, 3H). LCMS *m/z* 430 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-2,10-dimetil-2,10,15,17-tetrahidro-8,4-(azeno)pirazolo[4,3-h][2,11,5]benzodioxazaciclotetradecin-3-carbonitrilo (Ejemplos 104, 105 y 106)



Ejemplo 104, Ejemplo 105 y Ejemplo 106

Etapa 1:

A la solución de **compuesto 283** (1,48 g, 3,99 mmol) en DCM (25 mL), se añadieron Et_3N (0,84 mL, 5,98 mmol) y DMAP (20 mg, 0,163 mmol), seguido de cloruro de tritilo (1,68 g, 5,98 mmol). La mezcla de reacción se agitó durante 16 horas a temperatura ambiente. Una cantidad adicional de cloruro de tritilo (0,56 g, 1,99 mmol) se añadió a la mezcla de reacción y se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se diluyó con DCM (20 mL) y luego se extrajo con agua (10 ml) y salmuera (10 ml). La capa orgánica se eliminó y se evaporó después de secarse sobre sulfato de sodio anhidro. El crudo obtenido en forma de un sólido amarillo se purificó por cromatografía flash en gel de sílice (8% de EtOAc en tolueno)

para producir el **compuesto 554** en forma de un sólido incoloro (1,67 g, 68% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,95 (dd, *J* = 8,7, 5,8 Hz, 1H), 7,44 – 7,16 (m, 17H), 7,01 (ddd, *J* = 8,7, 7,7, 2,7 Hz, 1H), 6,89 (qd, *J* = 6,4, 1,3 Hz, 1H), 6,36 (s, 1H), 3,93 (s, 3H), 1,72 (d, *J* = 6,4 Hz, 3H).

Etapa 2:

El **compuesto 554** (1,6 g, 2,60 mmol) se disolvió en THF seco (15 mL) y se enfrió hasta 0 °C en nitrógeno. Una solución 1 M de $LiAlH_4$ en THF (2,0 mL, 2,0 mmol) se añadió lentamente durante 15 minutos y la mezcla de reacción se agitó durante 5 minutos a 0 °C. La mezcla de reacción se neutralizó por la adición cuidadosa de H_2O (1 mL) y se agitó durante 10 minutos, antes de añadir EtOAc (40 mL) y $MgSO_4$. Las sales se filtraron y el filtrado se evaporó para producir un aceite amarillo pálido, que se purificó por cromatografía en columna en gel de sílice (heptanos/EtOAc, 5:1) para producir el comp**u**esto **555** en forma de un sólido incoloro (1,13 g, 75% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,38 – 7,20 (m, 16H), 7,09 (dd, *J* = 9,7, 2,7 Hz, 1H), 6,96 (td, *J* = 8,3, 2,7 Hz, 1H), 6,42 (s, 1H), 6,31 (qd, *J* = 6,5, 1,6 Hz, 1H), 4,92 (d, *J* = 12,1 Hz, 1H), 4,68 (dd, *J* = 12,3, 7,1 Hz, 1H), 3,01 (d, *J* = 8,4 Hz, 1H), 1,70 (d, *J* = 6,5 Hz, 3H). LCMS ES *m/z* 584/586 $[M+H]^+$.

Etapa 3:

A una solución de **compuesto 555** (1,1 g, 1,189 mmol) en THF seco (15 mL) se añadió lentamente NaH (60%, 0,15 g, 3,78 mmol) en porciones a 0 °C durante 3 minutos. La reacción se agitó durante 30 minutos a 0 °C antes de añadir la solución de **compuesto 158** (0,452 g, 2,26 mmol) en THF seco (5 mL) lentamente. La reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se neutralizó cuidadosamente con agua (10 mL) seguido de extracción con EtOAc (2 x 20 mL). La fase orgánica se eliminó, se lavó con agua (10 mL) y salmuera (10 mL). El extracto de EtOAc se evaporó después de secar en sulfato de sodio anhidro. El producto crudo obtenido en forma de una goma amarilla clara se purificó por cromatografía en columna en gel de sílice usando 15% de acetona en heptano para proporcionar el **compuesto 556** en forma de un sólido incoloro (1,06 g, 80% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,36 – 7,19 (m, 16H), 7,14 (dd, *J* = 9,8, 2,7 Hz, 1H), 6,94 (td, *J* = 8,3, 2,7 Hz, 1H), 6,82 (s, 1H), 6,32 – 6,22 (m, 1H), 5,05 (d, *J* = 11,5 Hz, 1H), 4,65 – 4,42 (m, 3H), 4,03 (s, 3H), 1,64 (d, *J* = 6,5 Hz, 3H).

Etapa 4:

La reacción se realizó en dos lotes usando **compuesto 556** (0,5 g, 0,71 mmol). En un vial de microondas (20 ml de capacidad) se colocó el **compuesto 556** (0,5 g,

0,71 mmol), KOAc (0,35 g, 3,55 mmol), cataCXium A (0,0763 g, 0,213 mmol) y alcohol t-amílico (desgasificado, 14,5 ml). La mezcla de reacción luego se desgasificó durante 3 minutos antes de añadir $Pd(OAc)_2$. El vial se selló y se irradió en el microondas durante 2 horas a 120 °C. Las mezclas de reacción se combinaron, se diluyeron con EtOAc (50 ml) y se filtraron a través de celite para eliminar las sustancias inorgánicas. El filtrado amarillo transparente se lavó con agua (2 x 10 ml), salmuera (20 ml), se secó en sulfato de sodio anhidro y se evaporó para producir el producto crudo en forma de un sólido amarillo. El sólido se purificó por cromatografía en columna en gel de sílice usando 25% de acetona en heptano para obtener el **compuesto 557** en forma de un sólido amarillo claro (0,483 mg, 54,6% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,77 (s, 1H), 7,42 – 7,19 (m, 17H), 6,94 (td, *J* = 8,2, 2,7 Hz, 1H), 6,72 (qd, *J* = 6,7, 1,7 Hz, 1H), 6,52 (s, 1H), 5,35 – 5,23 (m, 1H), 4,48 (d, *J* = 12,6 Hz, 1H), 4,24 (d, *J* = 9,6 Hz, 1H), 4,11 (d, *J* = 9,6 Hz, 1H), 3,97 (s, 3H), 1,65 (d, *J* = 6,7 Hz, 3H). LCMS ES *m/z* 623 $[M+H]^+$.

Etapa 5:

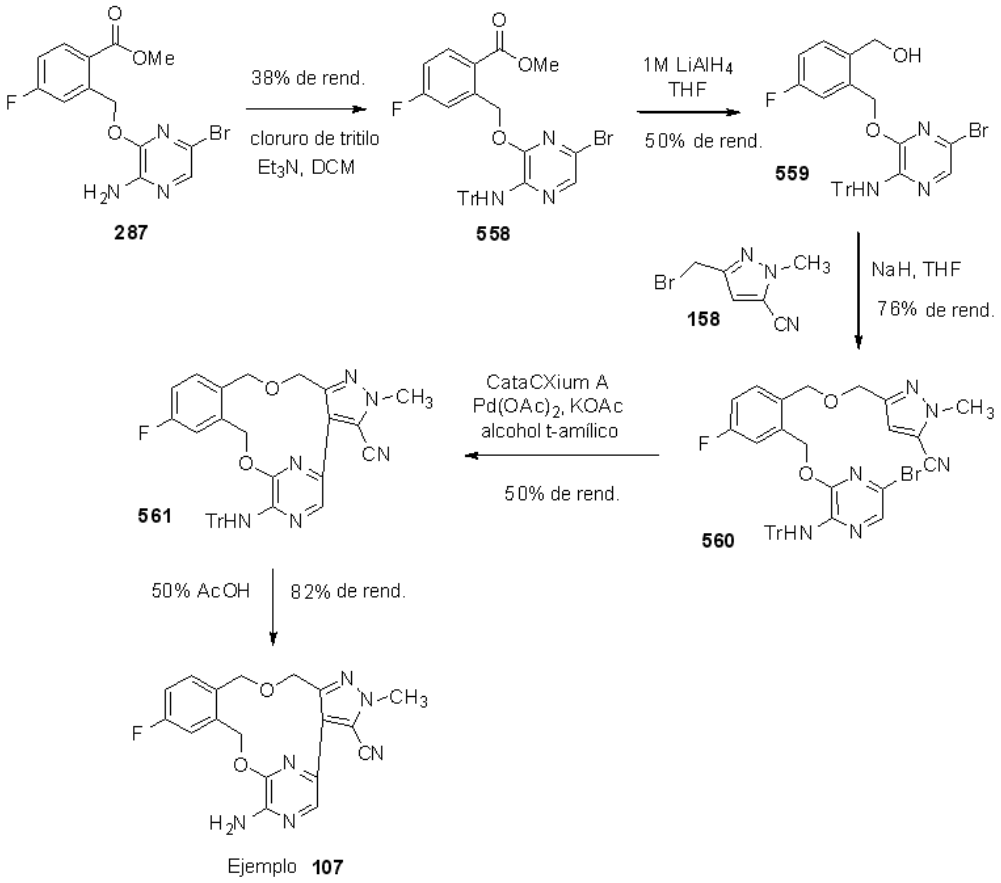
Una suspensión de **compuesto 557** (0,476 g, 0,76 mmol) en 50% de AcOH en agua (20 ml) se calentó a 80 °C durante 4 h. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con agua (20 ml). La mezcla de reacción se neutralizó con cuidado a un pH ligeramente básico (pH = 8) añadiendo lentamente $NaHCO_3$ sólido en porciones. La mezcla de reacción resultante se extrajo con EtOAc (2x 20 ml). La fase orgánica se eliminó, se lavó con agua (5 ml), salmuera (10 ml). El extracto de EtOAc de color amarillo claro se separó y se evaporó después de secar sobre sulfato de sodio anhidro. El producto crudo obtenido en forma de un sólido amarillo claro al purificar por cromatografía en columna en gel de sílice usando 25% de acetona en heptano para producir el **Ejemplo 104** en forma de un sólido incoloro (0,183 mg, 63%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,84 (s, 1H), 7,49 (dd, *J* = 10,2, 2,8 Hz, 1H), 7,38 (dd, *J* = 8,4, 5,9 Hz, 1H), 7,07 (td, *J* = 8,4, 2,8 Hz, 1H), 6,78 (s, 2H), 6,61 (qd, *J* = 6,7, 1,8 Hz, 1H), 5,17 (d, *J* = 12,3 Hz, 1H), 4,46 (d, *J* = 12,3 Hz, 1H), 4,32 (d, *J* = 9,9 Hz, 1H), 4,02 (d, 1H), 3,98 (s, 3H), 1,60 (d, *J* = 6,6 Hz, 3H). LCMS ES *m/z* 381 $[M+H]^+$.

La separación quiral se llevó a cabo por SFC preparativa en una columna Whelk-O1 (R,R) (250 x 4,6 mm I.D., tamaño de partícula de 3 micrones), que se eluyó con 20% de metanol a 140 bar de CO_2 con una tasa de flujo de 3 mL/min. $Rt_{(pico\ 1)}$ = 3,77 minutos y $Rt_{(pico\ 2)}$ = 4,95 minutos y produjo el pico 1 en forma de un sólido blanco (59 mg, 20%) y el pico 2 en forma de un sólido blanco (58 mg, 20%).

Ejemplo 105 (pico 1): > 99% ee. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,84 (s, 1H), 7,49 (dd, *J* = 10,2, 2,8 Hz, 1H), 7,38 (dd, *J* = 8,4, 5,9 Hz, 1H), 7,07 (td, *J* = 8,4, 2,8 Hz, 1H), 6,78 (s, 2H), 6,61 (qd, *J* = 6,7, 1,8 Hz, 1H), 5,17 (d, *J* = 12,3 Hz, 1H), 4,46 (d, *J* = 12,3 Hz, 1H), 4,32 (d, *J* = 9,9 Hz, 1H), 4,02 (d, 1H), 3,98 (s, 3H), 1,60 (d, *J* = 6,6 Hz, 3H). LCMS APCI *m/z* 381 $[M+H]^+$.

Ejemplo 106 (pico 2): ~ 99% ee. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,84 (s, 1H), 7,49 (dd, *J* = 10,2, 2,8 Hz, 1H), 7,38 (dd, *J* = 8,4, 5,9 Hz, 1H), 7,07 (td, *J* = 8,4, 2,8 Hz, 1H), 6,78 (s, 2H), 6,61 (qd, *J* = 6,7, 1,8 Hz, 1H), 5,17 (d, *J* = 12,3 Hz, 1H), 4,46 (d, *J* = 12,3 Hz, 1H), 4,32 (d, *J* = 9,9 Hz, 1H), 4,02 (d, 1H), 3,98 (s, 3H), 1,60 (d, *J* = 6,6 Hz, 3H). LCMS APCI *m/z* 381 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-2-metil-2,10,15,17-tetrahidro-8,4-(azeno)pirazolo[4,3-h][2,11,5]benzodioxazaciclotetradecin-3-carbonitrilo (Ejemplo 107)



Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 104** se usó para preparar el **compuesto 558** (1,77 g, 38%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,05 (dd, *J* = 8,7, 5,8 Hz, 1H), 7,39 – 7,13 (m, 17H), 7,06 (td, *J* = 8,3, 2,7 Hz, 1H), 6,37 (s, 1H), 5,83 (s, 2H), 3,83 (s, 3H).

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 104** se usó para preparar el **compuesto 559** (0,084 g, 50%) en forma de un sólido incoloro (835 mg, 50% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,39 (dd, *J* = 8,5, 5,7 Hz, 1H), 7,35 (s, 1H), 7,33 – 7,14 (m, 16H), 7,03 (td, *J* = 8,3, 2,7 Hz, 1H), 6,44 (s, 1H), 5,52 (s, 2H), 4,76 (d, *J* = 5,7 Hz, 2H), 2,01 (t, *J* = 5,7 Hz, 1H). LCMS ES *m/z* 570/572 $[M+H]^+$.

Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 104** se usó para preparar el **compuesto 560** (0,77 g, 76%) en forma de un sólido incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,39 – 7,14 (m, 18H), 7,01 (td, *J* = 8,3, 2,7 Hz, 1H), 6,82 (s, 1H), 6,35 (s, 1H), 5,48 (s, 2H), 4,64 (s, 2H), 4,51 (s, 2H), 4,00 (s, 3H). LCMS ES *m/z* 689/691 $[M+H]^+$.

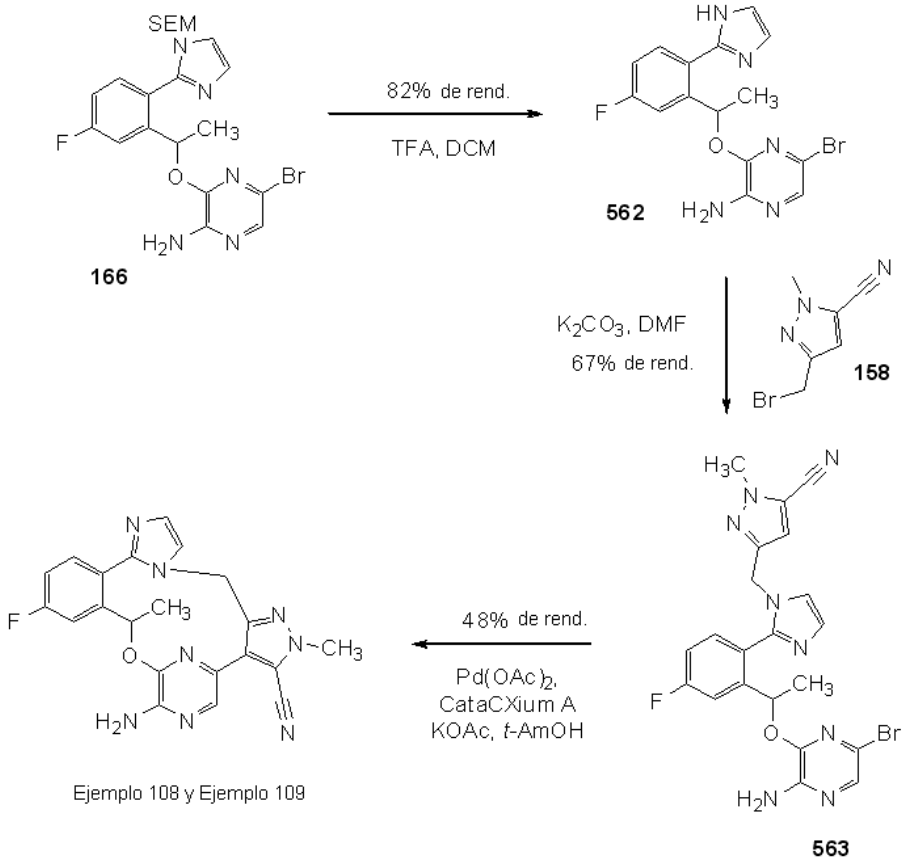
Etapa 4:

El procedimiento descrito en la etapa 4 para el **Ejemplo 104** se usó para preparar el **compuesto 561** (0,31 g, 50%) en forma de un sólido amarillo. ^{1}RMN (400 MHz, DMSO-d_6) δ 7,67 (dd, *J* = 10,2, 2,8 Hz, 1H), 7,55 (s, 1H), 7,47 – 7,16 (m, 16H), 7,10 (td, *J* = 8,5, 2,8 Hz, 1H), 6,19 – 6,06 (m, 1H), 5,38 – 5,04 (m, 1H), 4,52 – 4,38 (m, 1H), 4,37 – 4,23 (m, 1H), 4,08 – 3,90 (m, 4H). LCMS ES *m/z* 609 $[M+H]^+$.

Etapa 5:

El procedimiento descrito en la etapa 5 para el **Ejemplo 104** se usó para preparar el **Ejemplo 107** (143 mg, 82%) en forma de un sólido amarillo pálido. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,85 (s, 1H), 7,48 – 7,39 (m, 2H), 7,13 (td, *J* = 8,5, 2,9 Hz, 1H), 6,82 (s, 2H), 6,23 – 5,95 (m, 1H), 5,44 – 5,17 (m, 1H), 5,16 – 4,90 (m, 1H), 4,61 – 4,21 (m, 2H), 4,00 (s, 3H). LCMS ES *m/z* 367 $[M+H]^+$.

Preparación de 8-amino-3-fluoro-5,13-dimetil-13,15-dihidro-5H-7,11-(azeno)imidazo[1,2-k]pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-12-carbonitrilo (Ejemplos 108/109)



Etapa 1:

El **compuesto 166** (1,5 g, 2,96 mmol), se disolvió en DCM (7 mL), luego se añadió gota a gota TFA (15 mL) a esta solución. La mezcla se agitó a temperatura ambiente durante 20 horas (la TLC mostró una conversión completa). La reacción se concentró al vacío, se diluyó con EtOAc (100 mL) y se lavó con una solución acuosa saturada de $NaHCO_3$ (100 mL luego 50 mL). La fase acuosa se extrajo con EtOAc (2 x 50 mL). Las fases orgánicas se combinaron, se secaron en MgSO4, se filtraron y se concentraron al vacío. El aceite obtenido se purificó por cromatografía en columna en gel de sílice (eluyentes heptanos/EtOAc 1:1 a 1:2) para producir el **compuesto 562** en forma de una espuma sólida (919 mg, 82% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 12,42 (s, 1H), 7,70 (dd, J = 10,5, 2,8 Hz, 1H), 7,62 (dd, J = 8,7, 5,7 Hz, 1H), 7,49 (s, 1H), 7,23 (td, J = 8,5, 2,8 Hz, 2H), 7,13 (s, 1H), 7,03 – 6,90 (m, 1H), 6,66 (s, 2H), 1,64 (d, J = 6,3 Hz, 3H).

Etapa 2:

El **compuesto 562** (919 mg, 2,43 mmol), **compuesto 158** (513 mg, 2,56 mmol) y K_2CO_3 (503 mg, 3,64 mmol) se mezclaron en DMF (50 mL). La mezcla se agitó a

temperatura ambiente durante 20 horas (la LC-MS mostró una conversión completa). Se añadió agua (300 mL) y se extrajo con Et_2O (5 x 100 mL). Las fases orgánicas se combinaron, se secaron en MgSO4, se filtraron y se concentraron al vacío. El aceite obtenido se purificó por cromatografía en columna en gel de sílice (eluyentes heptanos/EtOAc 1:1 a 0:1). El **compuesto 563** se obtuvo en forma de un polvo blanco (805 mg, 67% de rendimiento). ^{1}H RMN (400 MHz, DMSO-*d*$_6$) δ 7,66 (dd, *J* = 10,2, 2,8 Hz, 1H), 7,53 (s, 1H), 7,42 – 7,30 (m, 2H), 7,22 (td, *J* = 8,4, 2,7 Hz, 1H), 7,07 (d, *J* = 1,3 Hz, 1H), 6,96 (s, 1H), 6,69 (s, 2H), 5,85 (q, *J* = 6,3 Hz, 1H), 5,14 (d, *J* = 15,7 Hz, 1H), 4,98 (d, *J* = 15,7 Hz, 1H), 3,90 (s, 3H), 1,52 (d, *J* = 6,4 Hz, 3H). LCMS *m/z* 497/499 $[M+H]^+$.

Etapa 3:

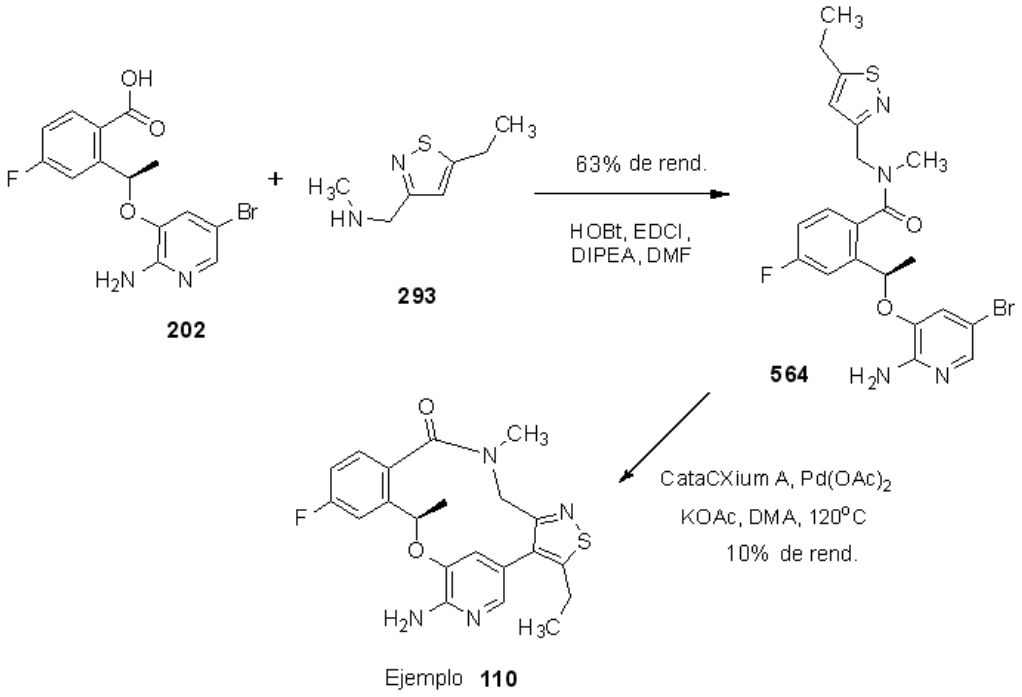
Se realizó una reacción idéntica cuatro veces debido a la limitación del volumen de los viales de microondas. El **compuesto 563** (200 mg, 0,4 mmol) se mezcló con KOAc (197 mg, 2,0 mmol) en alcohol ter-amílico (10 mL). La reacción se desgasificó durante 30 minutos (burbujeando nitrógeno), luego se añadieron $Pd(OAc)_2$ (18 mg, 0,08 mmol) y cataCXium A (58 mg, 0,16 mmol). La reacción se desgasificó otra vez durante 30 minutos, el vial de microondas se selló y se calentó a 120 °C durante 2 horas (la LC-MS mostró el 96% del producto esperado). La reacción se enfrió a temperatura ambiente, se filtró a través de un taco de celite y se enjuagó con EtOAc (100 mL). El filtrado se lavó con agua (50 mL) y salmuera (50 mL), se secó en $MgSO_4$, se filtró y se concentró al vacío. El aceite obtenido se combinó con las otras reacciones y se purificó por cromatografía en columna en gel de sílice (eluyentes heptanos/EtOAc de 1:2 a 0:1). Se obtuvo una mezcla de **Ejemplo 108** y **Ejemplo 109** en forma de un polvo beige (320 mg, 48% de rendimiento). ^{1}H RMN (400 MHz, DMSO-*d*$_6$) δ 7,70 (s, 1H), 7,58 (dd, *J* = 10,0, 2,8 Hz, 1H), 7,46 (dd, *J* = 8,5, 5,7 Hz, 1H), 7,24 (td, *J* = 8,5, 2,8 Hz, 1H), 7,01 (s, 2H), 6,75 (s, 2H), 5,71 – 5,46 (m, 1H), 5,00 (d, *J* = 14,1 Hz, 1H), 4,56 (d, *J* = 14,1 Hz, 1H), 4,08 (s, 3H), 1,66 (d, *J* = 6,6 Hz, 3H). LCMS *m/z* 417 $[M+H]^+$. La separación quiral se llevó a cabo en 32 mg de material por SFC preparativa en una columna Whelk-O1 (R,R) (250 x 4,6 mm I.D., tamaño de partícula de 3 micrones), que se eluyó con 30% de metanol a 140 bar de CO_2 con una tasa de flujo de 3 mL/min. $Rt_{(pico\ 1)}$ = 3,00 minutos y $Rt_{(pico\ 2)}$ = 3,86 minutos y produjo el pico 1 en forma de un sólido blanco (14,4 mg) y el pico 2 en forma de un sólido blanco (14,7 mg).

Ejemplo 108 (pico 1): > 99% ee. ^{1}H RMN (400MHz, DMSO-d_6) δ 7,71 (s, 1H), 7,58 (dd, *J* = 2,6, 9,9 Hz, 1H), 7,46 (dd, *J* = 5,8, 8,6 Hz, 1H), 7,24 (dt, *J* = 2,8, 8,6 Hz, 1H),

7,01 (s, 2H), 6,73 (s, 2H), 5,62 - 5,51 (m, 1H), 5,00 (d, *J* = 14,1 Hz, 1H), 4,56 (d, *J* = 13,8 Hz, 1H), 4,08 (s, 3H), 1,66 (d, *J* = 6,5 Hz, 3H). LCMS APCI *m/z* 417 $[M+H]^+$.

Ejemplo 109 (pico 2): ~ 95% ee. ^{1}H RMN (400MHz, DMSO-d_6) δ 7,71 (s, 1H), 7,58 (dd, *J*=2,6, 9,9 Hz, 1H), 7,46 (dd, *J* = 5,8, 8,6 Hz, 1H), 7,24 (dt, *J* = 2,6, 8,5 Hz, 1H), 7,01 (s, 2H), 6,73 (s, 2H), 5,62 - 5,49 (m, 1H), 5,00 (d, *J* = 14,1 Hz, 1H), 4,56 (d, *J* = 14,1 Hz, 1H), 4,08 (s, 3H), 1,66 (d, *J* = 6,5 Hz, 3H). LCMS APCI *m/z* 417 $[M+H]^+$.

Preparación de (10R)-7-amino-3-etil-12-fluoro-10,16-dimetil-16,17-dihidro-8,4-(meteno)[1,2]tiazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 110)



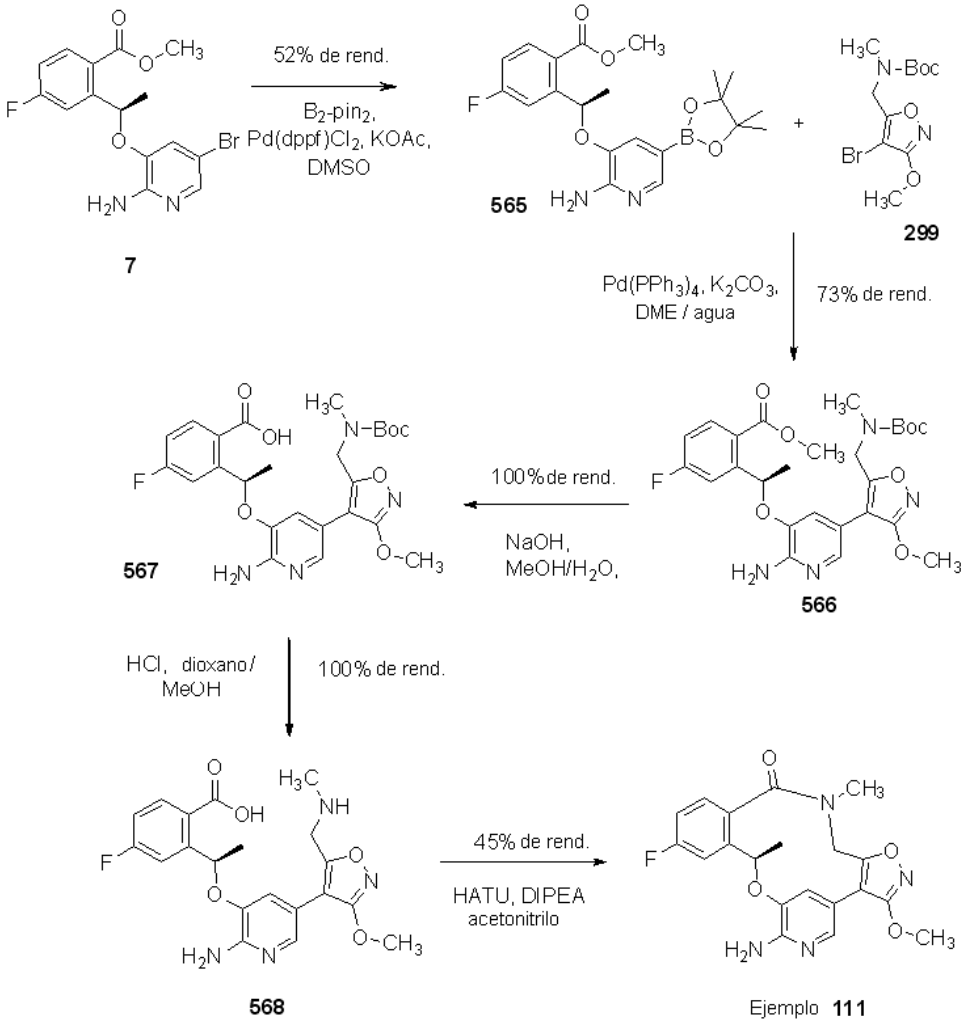
Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 100** se usó para preparar el **compuesto 564** en forma de un sólido amarillo (0,5 g, 63%). LCMS m/z 493 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 100** se usó para preparar el **Ejemplo 110** en forma de un sólido amarillo (16,8 mg, 10%). ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,59-7,56 (m, 1H), 7,48-7,42 (m, 3H), 7,19-7,14 (m, 1H), 5,99-5,98 (d, 1H), 4,56-4,47 (m, 2H), 3,18 (s, 3H), 3,09-2,99 (m, 2H), 1,88-1,87 (d, 3H), 1,38-1,35 (t, 3H). LCMS *m/z* 413 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-3-metoxi-10,16-dimetil-16,17-dihidro-8,4-(meteno)[1,2]oxazolo[4,5-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 111)



Etapa 1:

A una solución de **compuesto 7** (200 mg, 0,54 mmol) en DMSO anhidro (2 mL) se añadieron bis-(pinacolato)diboro (635 mg, 2,5 mmol), $Pd(dppf)Cl_2.CH_2Cl_2$ (40 mg, 0,054 mmol) y luego KOAc (178 mg, 1,82 mmol), y la mezcla se agitó en nitrógeno y se calentó a 80 °C durante 1 hora. La mezcla se enfrió, se añadió EtOAc (40 mL) y se filtró a través de Arbocel. El filtrado se lavó con agua, luego salmuera, después la capa orgánica se extrajo en HCl acuoso 1 M (2x). La fase acuosa se enfrió en hielo, se neutralizó a pH 7 mediante la adición cuidadosa de solución de NaOH 1 M y el precipitado resultante se extrajo en EtOAc (2x). Las capas orgánicas combinadas se

secaron en sulfato de sodio, se filtraron y el solvente se eliminó al vacío. El residuo oleoso se redisolvió en EtOAc (1 mL) y se añadió heptano (15 mL) para formar un precipitado blanquecino. El solvente se eliminó al vacío para producir 115 mg (52%) de **compuesto 565**. ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,94 (dd, 1H), 7,74 (d, 1H), 7,67 (dd, 1H), 7,25 (td, 1H), 6,87 (d, Hz, 1H), 6,35 (s, 2H), 6,26 (q, 1H), 3,91 (s, 3H), 1,57 (d, 3H), 1,21 (d, 12H). LCMS *m/z* 335 $[M+H]^+$.

Etapa 2:

Una solución de **compuesto 299** (1,26 g, 3,92 mmol), carbonato de potasio (811 mg, 5,88 mmol) en dimetoxietano (20 mL) y agua (15 mL) se calentó hasta 40 °C y se desgasificó burbujeando nitrógeno a través de la mezcla durante 20 minutos. A la mezcla se añadió una solución de **compuesto 565** (68 mg, 0,16 mmol) en dimetoxietano desgasificado (1 mL), luego $Pd(PPh_3)_4$. La mezcla se agitó en nitrógeno y se calentó luego a 100 °C. Durante este tiempo, en intervalos de 5 minutos, se añadieron otras 4 adiciones de **compuesto 565** (68 mg, 0,16 mmol) en dimetoxietano desgasificado (1 mL) a la mezcla y una vez que la reacción alcanzó los 100 °C, en intervalos de 5 minutos, se añadieron otras 7 adiciones de **compuesto 565** (68 mg, 0,16 mmol) en dimetoxietano desgasificado (1 mL) a la mezcla. (En total, se añadieron 820 mg, 1,96 mmol de **compuesto 565** en 12 mL de DME). Después de la adición final, la mezcla se agitó a 100 °C en nitrógeno durante 1,5 h, luego se enfrió. Se añadió EtOAc (120 mL), luego la mezcla se lavó con agua (2 x 50 mL), se secó en sulfato de sodio, se filtró y el solvente se eliminó al vacío. La purificación del residuo por cromatografía en columna en gel de sílice que se eluyó con heptano: EtOAc 100:0 – 30:70 produjo el **compuesto 566** en forma de un sólido incoloro (750 mg, 73%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,02 – 7,93 (m, 1H), 7,57 – 7,46 (m, 2H), 7,25 (td, 1H), 6,68 (m, 1H), 6,24 (q, 1H), 6,13 (s, 2H), 4,59 – 4,12 (m, 2H), 3,88 (s, 3H), 3,84 (s, 3H), 2,70 (m, 3H)*, 1,61 (d, J = 6,2 Hz, 3H), 1,42-1,08 (m, 9H). LCMS *m/z* 531 $[M+H]^+$.

Etapa 3:

A una solución de **compuesto 566** (1,05 g, 1,98 mmol) en metanol (25 mL) a temperatura ambiente se añadió una solución de hidróxido de sodio (1,2 g, 30 mmol) en agua (3,5 mL) y la mezcla se agitó durante 18 horas a temperatura ambiente. A la mezcla se añadió agua (100 mL), luego la mezcla se lavó con TBME (10 mL). La capa acuosa se ajustó a pH 4 con la adición cuidadosa de HCl 1 N y se formó un precipitado. La mezcla se extrajo con EtOAc (80 mL), luego se añadió cloruro de sodio (20 g) a la capa acuosa, que se extrajo luego con EtOAc (80 mL). Las capas orgánicas combinadas se secaron en sulfato de sodio, se filtraron y el solvente se eliminó al

vacío para producir el **compuesto 567** en forma de un sólido amarillo pálido (1,02 g, 100%).^{1}H RMN (400 MHz, DMSO-d_6) δ 7,99 (dd, 1H), 7,54 – 7,44 (m, 2H), 7,21 (td, 1H), 6,72 (d, 1H), 6,37 (q, 1H), 6,17 (s, 2H), 4,81 – 3,95 (m, 2H), 3,84 (s, 3H), 2,73-2,66 (m, 3H), 1,60 (d, 3H), 1,36 -1,07 (m, 9H). LCMS *m/z* 517 $[M+H]^+$.

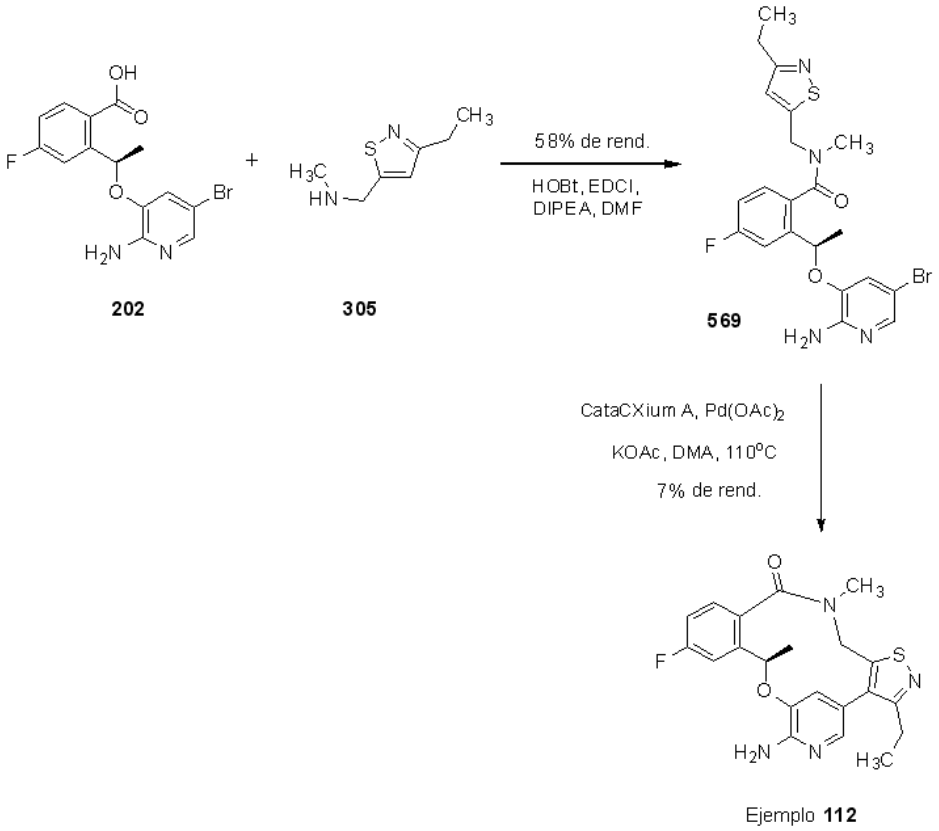
Etapa 4:

A una solución de **compuesto 567** (1,02 g, 1,98 mmol) en metanol (10 mL) y dioxano (10 mL) se añadió una solución de HCl 4 N en dioxano (6 mL) y la mezcla se agitó a 45 °C en nitrógeno durante 1,5 horas. El solvente se eliminó al vacío, luego se azeotropó con dioxano (2 x 25 mL) para producir el **compuesto 568** (1,2 g, 100%) en forma de un sólido marrón pálido. El sólido no se purificó adicionalmente y se usó en la siguiente reacción. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,67 (s, 2H), 8,28 – 8,18 (m, 1H), 8,05 (dd, 1H), 7,84 (d, 1H), 7,55 (dd, 1H), 7,29 (td, 1H), 7,10 (d, 1H), 6,56 (q, 1H), 4,28 (s, 2H), 3,87 (s, 3H), 2,55 (s, 3H), 1,66 (d, 3H). LCMS *m/z* 417 $[M+H]^+$.

Etapa 5:

A una suspensión de **compuesto 568** (1,1 g, 1,654 mmol para impurezas) en acetonitrilo (1,05 L) a temperatura ambiente se añadió DIEA (1,92 g, 2,59 mL, 14,88 mmol) y la mezcla se convirtió en una solución. A la mezcla se añadió HATU (660 mg, 1,74 mmol) y la mezcla se agitó en nitrógeno a temperatura ambiente durante 1 hora. El solvente se eliminó al vacío, luego el residuo se redisolvió en EtOAc (200 mL), se lavó con agua (3 x 40 mL), salmuera (20 mL), se secó en sulfato de sodio, se filtró y el solvente se eliminó al vacío. Se purificó el residuo por cromatografía en columna en gel de sílice y se eluyó con EtOAc, y luego se azeotropearon las fracciones con hexano (30 ml), lo que produjo el producto deseado en forma de un sólido incoloro, 1H y 19F RMN indicó una traza de sal de PF_6, de modo que el material se redisolvió en EtOAc (100 mL), se lavó con Na_2CO_3 acuoso al 10% (3x 40 mL), salmuera (2 x 20 mL), se secó en sulfato de sodio, se filtró y el solvente se eliminó al vacío. A continuación, el residuo se redisolvió en EtOAc (2 mL), se añadió hexano (30 mL) y se formó un precipitado blanco. El solvente se eliminó al vacío para producir el **Ejemplo 111** en forma de un sólido incoloro (323 mg, 45%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,58 (dd, J = 10,3, 2,7 Hz, 1H), 7,55 (d, J = 1,8 Hz, 1H), 7,44 (dd, J = 8,6, 5,7 Hz, 1H), 7,21 (td, J = 8,4, 2,7 Hz, 1H), 6,67 (d, J = 1,8 Hz, 1H), 6,07 (s, 2H), 5,60 – 5,49 (m, 1H), 4,52 (d, J = 15,2 Hz, 1H), 4,33 (d, J = 15,2 Hz, 1H), 3,98 (s, 3H), 3,03 (s, 3H), 1,66 (d, J = 6,2 Hz, 3H). LCMS ES *m/z* 399 $[M+H]^+$.

Preparación de (10R)-7-amino-3-etil-12-fluoro-10,16-dimetil-16,17-dihidro-8,4-(meteno)[1,2]tiazolo[4,5-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 112)



Ejemplo **112**

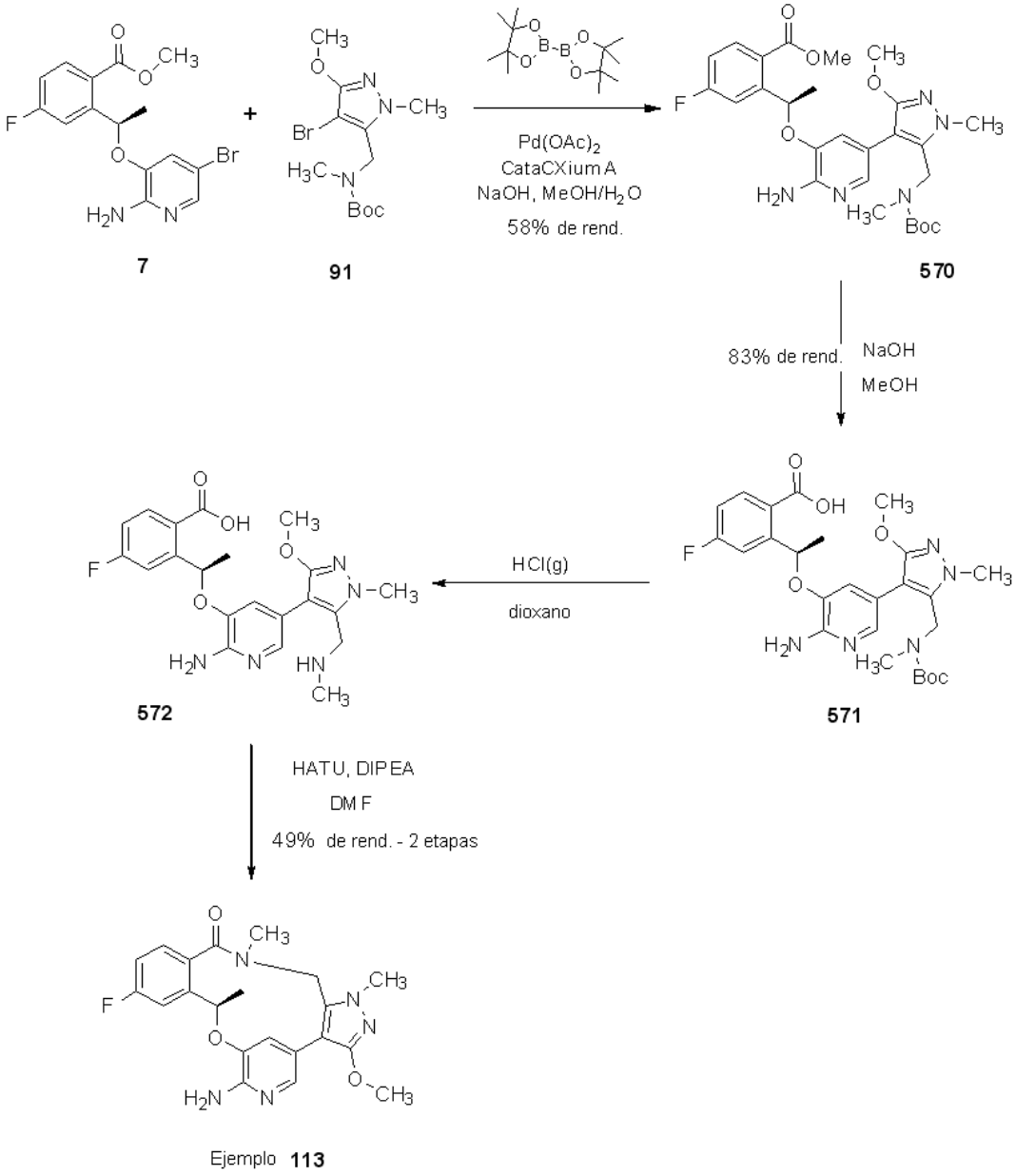
Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 100** se usó para preparar el **compuesto 569** (0,4 g, 58%) en forma de un sólido amarillo. LCMS ES *m/z* 493 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 100** se usó para preparar el **Ejemplo 112** (12,5 mg, 7%) en forma de un sólido blanco. ^{1}RMN (400 MHz, Metanol-d_4) δ 7,60-7,57 (m, 1H), 7,46 (s, 1H), 7,39-7,36 (m, 1H), 7,1-7,09 (d, 1H), 7,02-7,01 (d, 1H), 5,85-5,84 (d, 1H), 4,73-4,52 (m, 2H), 3,22 (s, 3H), 2,91-2,87 (d, 2H), 1,82-1,81 (d, 3H), 1,29-1,26 (t, 3H). LCMS ES *m/z* 413 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-3-metoxi-1,10,16-trimetil-16,17-dihidro-1H-8,4-(meteno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 113)



Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 86** y **Ejemplo 87** se usó para preparar el **compuesto 570** (1,4 g, 58%) en forma de un sólido marrón. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,99-7,95 (dd, 1H), 7,48 (s, 1H), 7,21-7,18 (dd, 1H), 6,94-6,89 (m, 1H), 6,53-6,52 (d, 1H), 6,31-6,26 (dd, 1H), 4,73 (s, 2H), 3,87-3,83 (t, 3H), 3,70 (s, 3H), 3,59 (s, 3H), 2,27 (s, 3H), 1,61-1,57 (t, 3H), 1,39 (s, 9H).

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 86** y **Ejemplo 87** se usó para preparar el **compuesto 571** (1,0 g, 83%) en forma de un sólido amarillo. LCMS ES *m/z* 530 $[M+H]^+$.

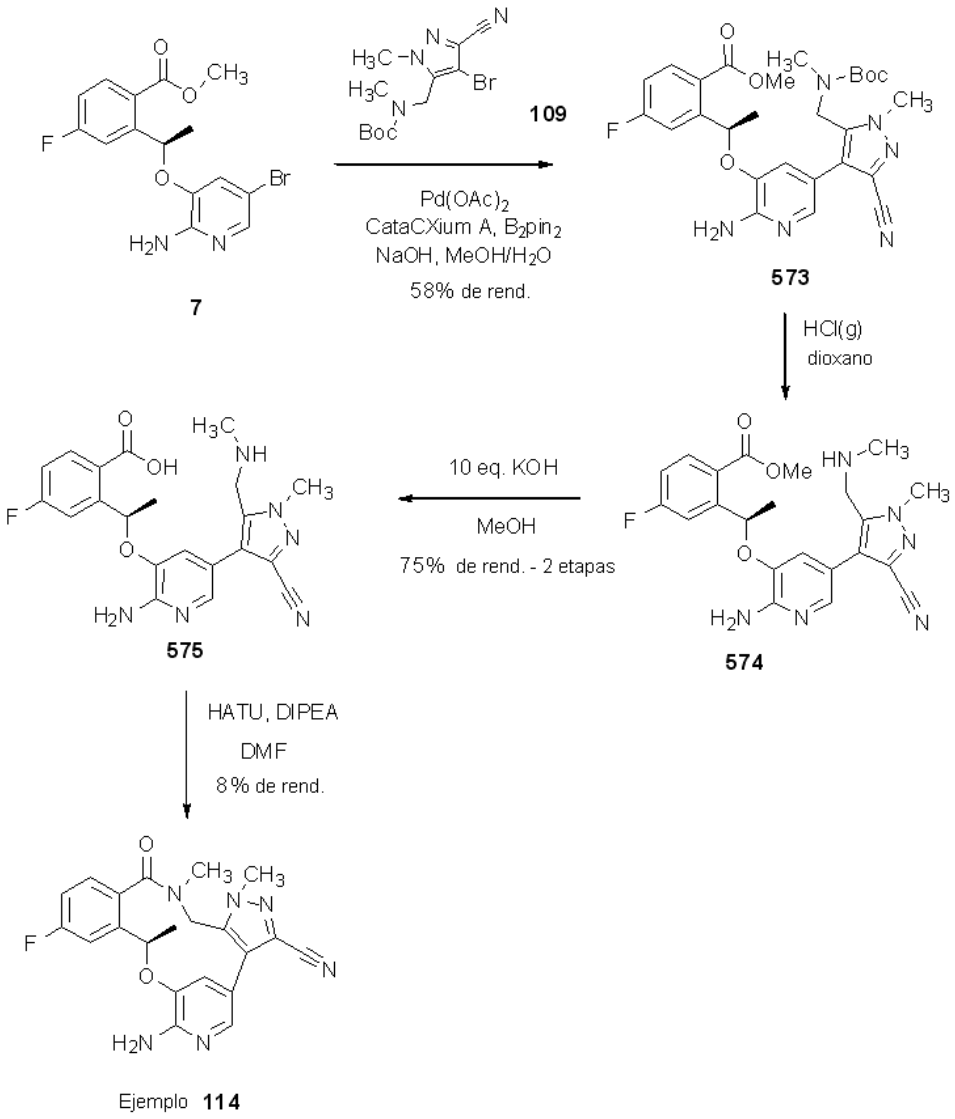
Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 86** y **Ejemplo 87** se usó para preparar el **compuesto 572**, que se usó en la siguiente etapa directamente. LCMS m/z 430 $[M+H]^+$.

Etapa 4:

El procedimiento descrito en la etapa 4 para el **Ejemplo 86** y **Ejemplo 87** se usó para preparar el **Ejemplo 113** en forma de un sólido blanquecino (380 mg, 49%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,76 (d, 1H), 7,25-7,22 (m, 1H), 7,14-7,12 (m, 1H), 6,94-6,92 (d, 1H), 6,74-6,73 (d, 1H), 5,61-5,57 (m, 1H), 4,64 (s, 2H), 4,42-4,21 (dd, 2H), 3,87-3,84 (d, 3H),3,80-3,67 (s, 3H), 3,09 (s, 3H), 1,70-1,69 (d, 3H). LCMS ES *m/z* 412 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-1,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-1H-8,4-(meteno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 114)



Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 88** se usó para preparar el **compuesto 573** (600 mg, 58%) en forma de un sólido marrón. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,04-7,99 (m, 1H), 7,57-7,56 (d, 1H), 7,24 (s, 1H), 7,03-6,97 (m, 1H), 6,63-6,62 (d, 1H), 6,42-6,40 (m, 1H), 5,01 (s, 2H), 4,54-4,31 (m, 2H), 3,99-3,95 (d, 3H), 3,94-3,86 (m, 3H), 2,307 (s, 3H), 1,69-1,64 (d, 3H), 1,29 (s, 9H).

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 88** se usó para preparar el **compuesto 574**, que se usó para la siguiente etapa sin otra purificación. LCMS m/z 439 $[M+H]^+$.

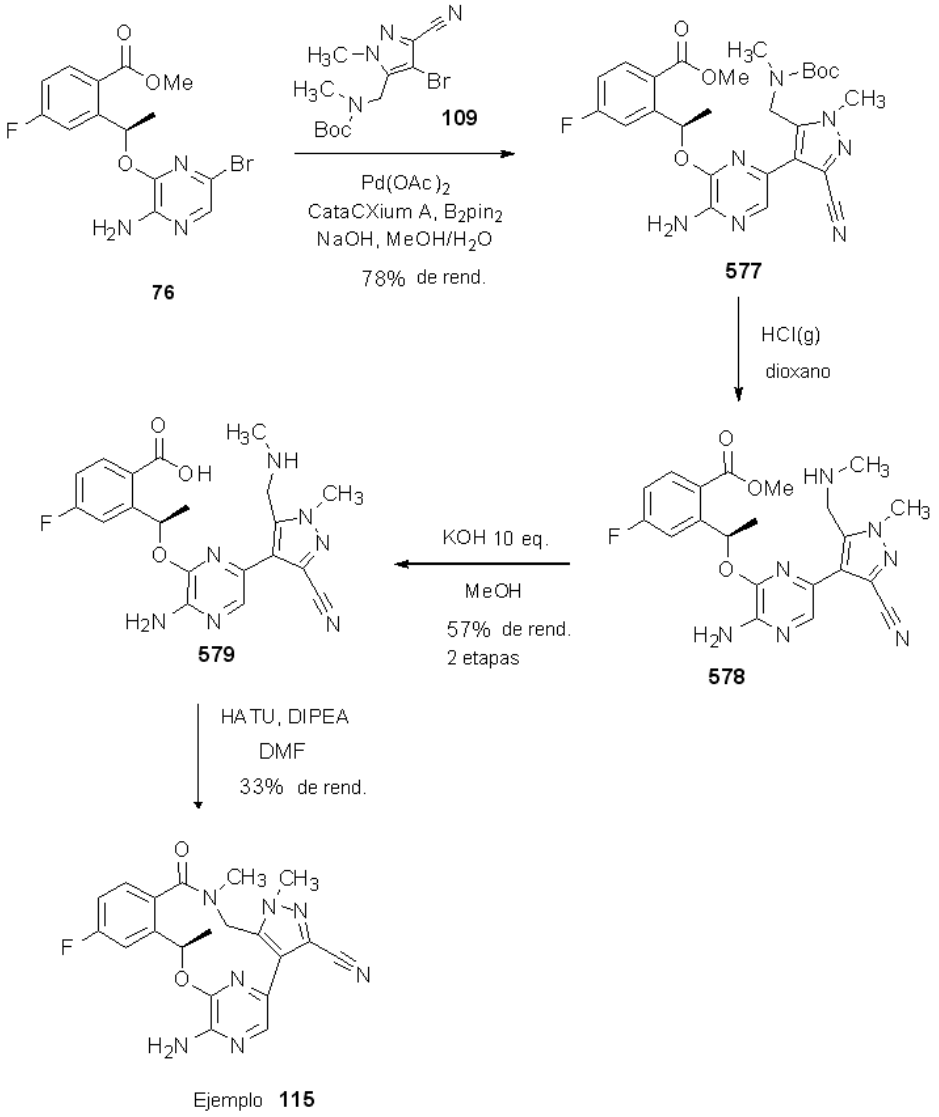
Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 88** se usó para preparar el **compuesto 575** (320 mg, 75%) en forma de un sólido marrón. LCMS m/z 425 $[M+H]^+$.

Etapa 4:

El procedimiento descrito en la etapa 4 para el **Ejemplo 88** se usó para preparar el **Ejemplo 114** (24,1 mg, 8%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,89 (s, 1H), 7,33-7,30 (d, 1H), 7,26-7024 (m, 1H), 7,19-7,18 (m, 1H), 7,02-7,00 (m, 1H), 5,71-5,70 (m, 1H), 4,84 (s, 2H), 4,59-4,37 (m, 2H), 4,10 (s, 3H), 3,16 (s, 3H), 1,79-1,64 (d, 3H). LCMS *m/z* 407 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-1,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-1H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 115)



Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 88** se usó para preparar el **compuesto 577** (400 mg, 78%) en forma de un sólido marrón. LCMS m/z 562 $[M+Na]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 88** se usó para preparar el **compuesto 578**, que se usó para la siguiente etapa sin otra purificación. LCMS m/z 440 $[M+H]^+$.

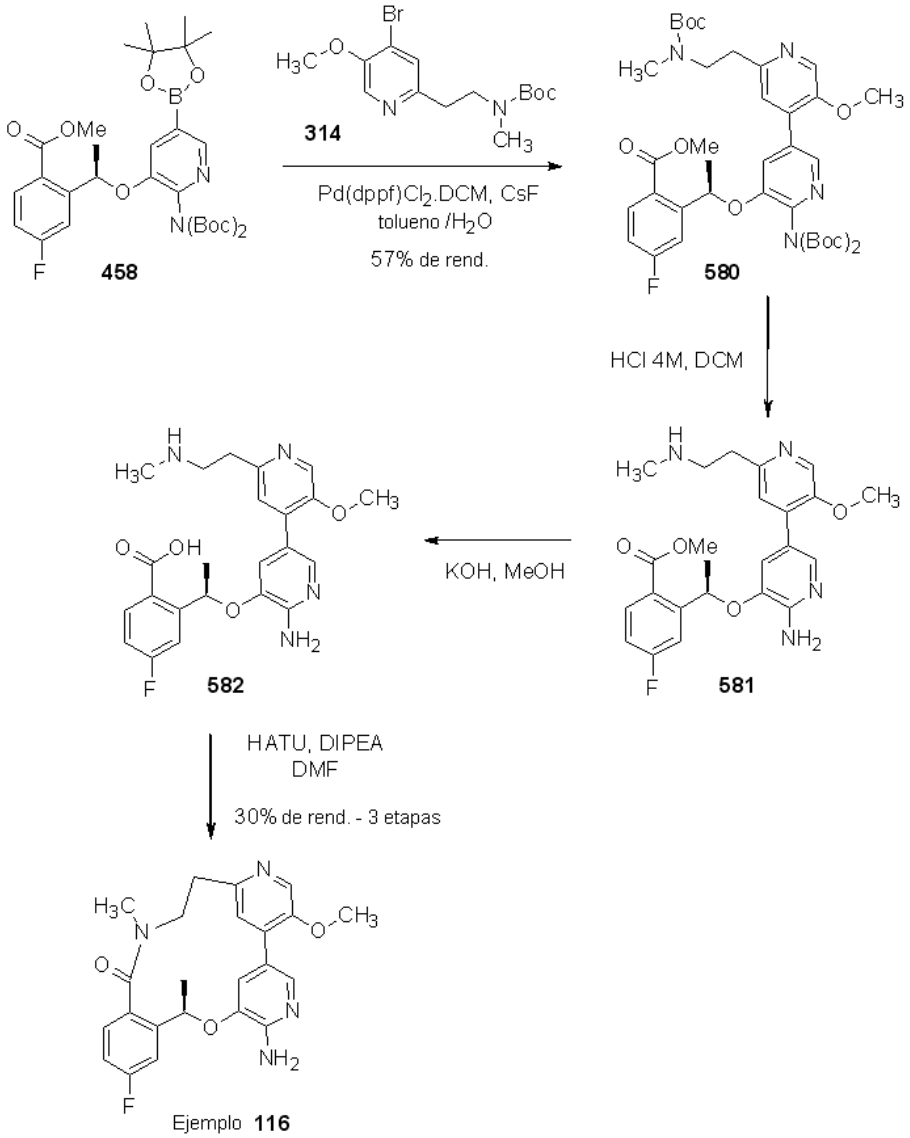
Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 88** se usó para preparar el **compuesto 579** (300 mg, 65% de pureza, 57%) en forma de un sólido marrón. LCMS m/z 426 $[M+H]^+$.

Etapa 4:

El procedimiento descrito en la etapa 4 para el **Ejemplo 88** se usó para preparar el **Ejemplo 115** (61,5 mg, 33%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,17 (s, 1H), 7,30-7,22 (m, 1H), 7,21-7,19 (m, 1H), 7,02-6,97 (m, 1H), 6,01-5,98 (m, 1H), 5,02 (s, 2H), 4,76-4,24 (dd, 2H), 4,08 (s, 3H), 3,02 (s, 3H), 1,76-1,74 (d, 3H). LCMS ES *m/z* 408 $[M+H]^+$.

Preparación de (1R)-4-amino-19-fluoro-9-metoxi-1,15-dimetil-14,15-dihidro-1H-3,7:8,12-di(meteno)-2,5,11,15-benzoxatriazaciclooctadecin-16(13H)-ona (Ejemplo 116)



Etapa 1:

El **compuesto 458** (475 mg, 0,77 mmol), **compuesto 314** (280 mg, 0,81 mmol) y CsF (351 mg, 2,3 mmol) se disolvieron en una mezcla de tolueno/H_2O (6,6 mL, 10:1). La solución se calentó a 60 °C y se desgasificó (3 ciclos N_2/vacío). Se añadió $Pd(dppf)Cl_2.CH_2Cl_2$ (69 mg, 0,08 mmol), la mezcla se desgasificó (3 ciclos N_2/vacío) y se calentó a 100 °C durante 18 horas. La mezcla se enfrió a temperatura ambiente, luego se filtró a través de un taco de sílice, luego se enjuagó con EtOAc (~100 mL). Las fases se separaron y la fase acuosa se extrajo con EtOAc (2 x 50 mL). Las fases orgánicas combinadas se secaron en $MgSO_4$, se filtraron y se concentraron al vacío para producir un aceite marrón, que se purificó por cromatografía en columna en gel de sílice (eluyente heptanos/EtOAc de 1:1 a 0:1). El **compuesto 580** se obtuvo en

forma de espuma sólida anaranjada (870 mg, 57% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,33 (s, 1H), 8,17 (d, *J* = 6,8 Hz, 1H), 8,05 (dd, *J* = 8,8, 5,7 Hz, 1H), 7,46 -7,16 (m, 5H), 6,35 (d, *J* = 6,3 Hz, 1H), 3,87 (d, *J* = 1,1 Hz, 3H), 3,69 (s, 3H), 3,47 (q, *J* = 6,4 Hz, 2H), 2,86 (t, *J* = 6,8 Hz, 2H), 2,76 (s, 2H), 1,57 (d, *J* = 6,2 Hz, 3H), 1,43 (s, 16H), 1,34-0,92 (m, 10H). LCMS ES *m/z* 755 $[M+H]^+$.

Etapa 2:

El **compuesto 580** (876 mg, 1,16 mmol) se disolvió en DCM (6 mL) y se añadió gota a gota la solución se enfrió a 0 °C. HCl 4 M en dioxano (5,8 mL). La mezcla se agitó a temperatura ambiente durante 18 horas, luego se concentró al vacío. La sal de HCl de **compuesto 581** se obtuvo en forma de un sólido blanco (713 mg, 100% de pureza por LC-MS) y se usó en la siguiente etapa sin otra purificación. ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,48-8,90 (m, 2H), 8,38 (d, *J* = 37,4 Hz, 3H), 7,98-7,76 (m, 2H), 7,60 (s, 1H), 7,48 (dd, *J* = 10,2, 2,6 Hz, 1H), 7,32 (d, *J* = 1,5 Hz, 1H), 7,18 (td, *J* = 8,4, 2,6 Hz, 1H), 6,30 (q, *J* = 6,2 Hz, 1H), 3,73 (s, 3H), 3,64 (s, 3H), 3,17 (d, *J* = 6,3 Hz, 4H), 2,41 (t, *J* = 5,2 Hz, 3H), 1,52 (d, *J* = 6,1 Hz, 3H). LCMS ES *m/z* 455 $[M+H]^+$.

Etapa 3:

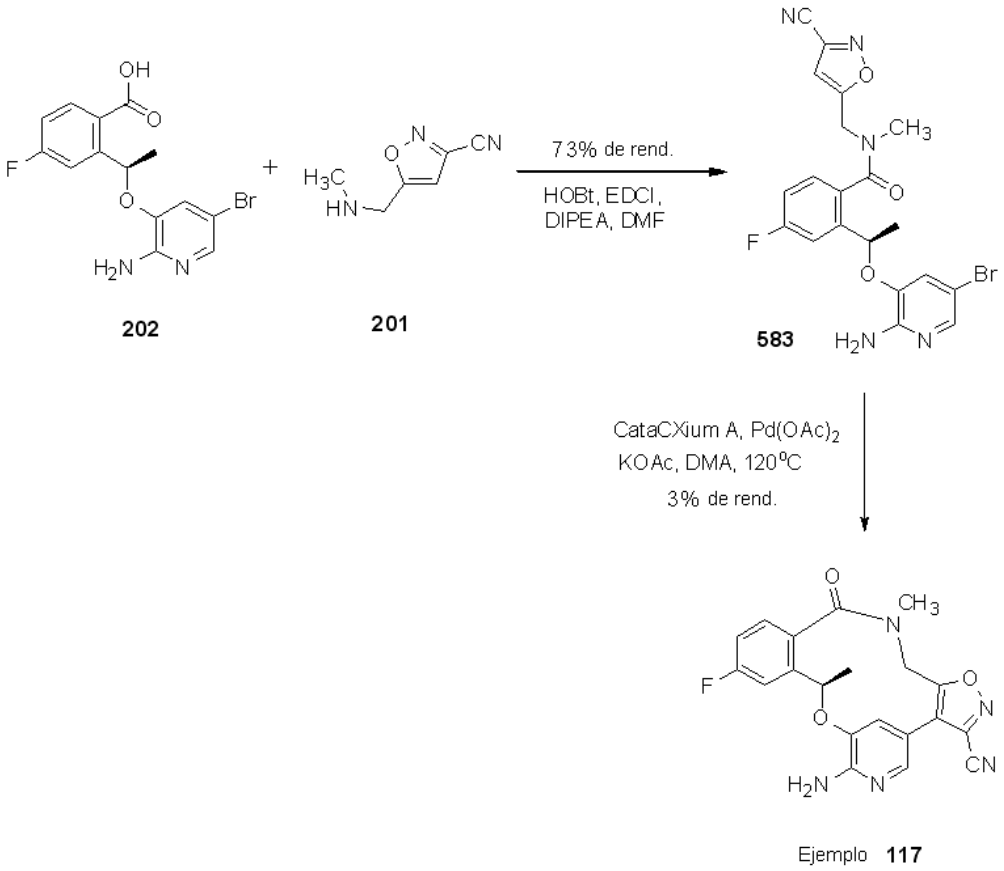
El **compuesto 581** (713 mg, 1,16 mmol) y KOH (520 mg, 9,3 mmol) se disolvieron en MeOH (12,3 mL) usando ultrasonido. La solución se calentó a 50 °C durante 5 horas, a 40 °C durante 18 horas, luego a 60 °C durante 2 horas. La mezcla se enfrió a 0 °C, luego se acidificó con cuidado usando HCl concentrado a pH 4 (formación de sólidos blancos). La suspensión se filtró. Los licores madre se concentraron al vacío para producir un sólido beige que se suspendió en MeOH (5 mL). Los sólidos se filtraron. Los licores madre se concentraron al vacío para producir la sal de clorhidrato del **compuesto 582** en forma de sólidos marrón pálido (640 mg). ^{1}H RMN (400 MHz, DMSO-d_6) δ 9,20 (s, 2H), 8,49 (d, *J* = 22,0 Hz, 4H), 8,05 (dd, *J* = 8,8, 5,9 Hz, 1H), 7,97 (d, *J* = 1,7 Hz, 1H), 7,75-7,50 (m, 2H), 7,45 (d, *J* = 1,7 Hz, 1H), 7,29 (td, *J* = 8,4, 2,7 Hz, 1H), 6,58 (q, *J* = 6,2 Hz, 1H), 3,79 (s, 3H), 3,36-3,19 (m, 4H), 2,56 (t, *J* = 5,2 Hz, 3H), 1,67 (d, *J* = 6,1 Hz, 3H). LCMS ES *m/z* 441 $[M+H]^+$.

Etapa 4:

A una solución enfriada de HATU (390 mg, 1,0 mmol) en DMF (12 mL) a 0 °C se añadió gota a gota una solución de **compuesto 582** (450 mg, 0,82 mmol) y DIPEA (0,68 mL, 4,1 mmol) en DMF (21 mL) durante 1 hora. Diez minutos después de terminada la adición, se añadió H_2O (300 mL) y la mezcla se extrajo con EtOAc (6 x 50 mL). Las fases orgánicas se combinaron, se secaron en $MgSO_4$ y se purificaron directamente sin concentrarse por columna SCX-2 (10 g, eluyentes: EtOAc (desde la

elaboración), luego MeOH, el MeOH/NH_3). Las fracciones obtenidas por elución con MeOH/NH_3 se combinaron, se concentraron al vacío y se purificaron por cromatografía en columna en gel de sílice (eluyentes DCM/MeOH de 95:5 a 90:10) para producir el **Ejemplo 116** en forma de sólidos amarillo pálido (146 mg, 42% de rendimiento, 90% de pureza por ^{1}H RMN). Esta muestra se suspendió en agua (2 mL), se filtró, se suspendió con TBME (3 mL), luego se secó. El **Ejemplo 116** se obtuvo en forma de un polvo amarillo pálido (106 mg, 30% de rendimiento en tres etapas finales). ^{1}H RMN (400 MHz, Metanol-d_4) δ 8,63 (s, 1H), 8,53 (s, 1H), 8,33 (d, *J* = 1,6 Hz, 1H), 8,17 (s, 1H), 7,34 (dd, *J* = 9,6, 2,6 Hz, 1H), 6,96 (t, *J* = 6,8 Hz, 1H), 6,81 (dt, *J* = 8,9, 4,5 Hz, 1H), 5,66 (q, *J* = 6,4 Hz, 1H), 4,47 (t, *J* = 10,6 Hz, 1H), 4,09 (s, 3H), 3,93 – 3,65 (m, 2H), 2,84 (s, 3H), 1,65 (d, *J* = 6,4 Hz, 3H). LCMS ES *m/z* 423 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-10,16-dimetil-15-oxo-10,15,16,17-tetrahidro-8,4-(meteno)[1,2]oxazolo[4,5-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 117)



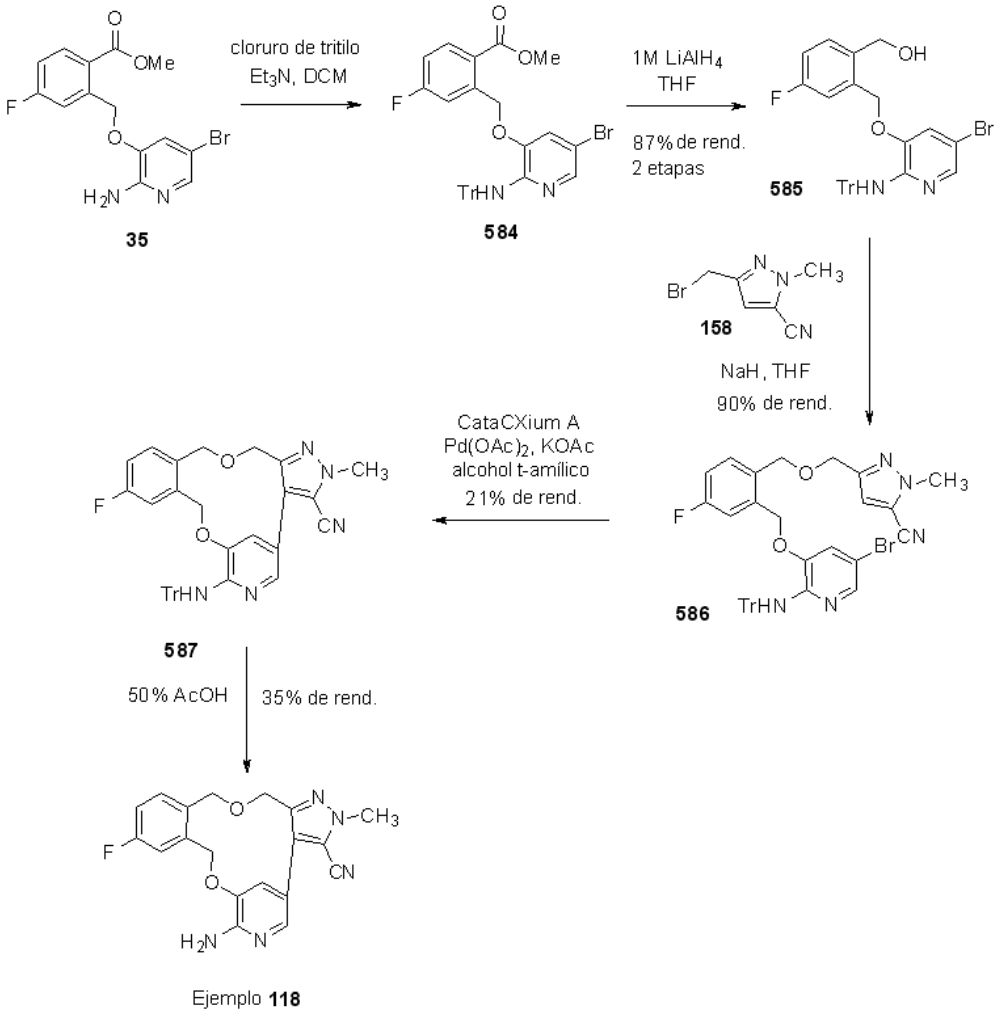
Etapa 1:

El procedimiento descrito en la etapa 3 para el **Ejemplo 99** se usó para preparar el **compuesto 583** (400 mg, 73%) en forma de un aceite incoloro. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,72-7,68 (s, 1H), 7,22-7,20 (m, 2H), 7,08-7,03 (m, 1H), 6,92 (s, 1H), 6,55-6,52 (s, 1H), 5,47-5,42 (m, 1H), 4,98-4,86 (dd, 2H), 4,75 (s, 2H), 2,88 (s, 3H) δ 1,66-1,64 (d, 3H).

Etapa 2:

El procedimiento descrito en la etapa 3 para el **Ejemplo 99** se usó para preparar el **Ejemplo 117** (4,2 mg, 3%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,79 (s, 1H), 7,56--7,59 (d, 1H), 7,39-7,49 (d, 1H), 7,12-7,21 (m, 1H), 6,89 (s, 1H), 5,79-5,71 (s, 1H), 4,7-4,65 (dd, 2H), 3,21 (s, 3H), 1,72 (s, 3H). LCMS m/z 394 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-2-metil-2,10,15,17-tetrahidro-8,4-(meteno)pirazolo-[4,3-h][2,11,5]benzodioxazaciclotetradecin-3-carbonitrilo (Ejemplo 118)



Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 104** se usó para preparar el **compuesto 584** en forma de un sólido cristalino blanquecino (5,23 g). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,11 (dd, *J* = 8,8, 5,8 Hz, 1H), 7,43 (dd, *J* = 2,0, 0,9 Hz, 1H), 7,39 – 7,17 (m, 16H), 7,08 (ddd, *J* = 8,7, 7,6, 2,7 Hz, 1H), 6,98 (d, *J* = 2,0 Hz, 1H), 6,36 (s, 1H), 5,53 (s, 2H), 3,90 (s, 3H). LCMS ES *m/z* 597/599 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 104** se usó para preparar el **compuesto 585** en forma de un sólido cristalino blanquecino (3,86 g, 87%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,43 (d, *J* = 2,0 Hz, 1H), 7,36 (dd, *J* = 8,5, 5,6 Hz, 1H), 7,34 – 7,14 (m, 17H), 7,07 – 6,99 (m, 2H), 6,33 (s, 1H), 5,21 (s, 2H), 4,70 (d, *J* = 5,6 Hz, 2H). LCMS ES *m/z* 569/571 $[M+H]^+$.

Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 104** se usó para preparar el **compuesto 586** en forma de una espuma incolora (1,23 g, 90%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,42 (dd, *J* = 2,0, 0,9 Hz, 1H), 7,37 – 7,15 (m, 17H), 7,04 – 6,97 (m, 2H), 6,32 (s, 1H), 5,20 (s, 2H), 4,59 (s, 2H), 4,49 (s, 2H), 3,99 (s, 3H). LCMS ES *m/z* 766/768/770 $[M+H]^+$.

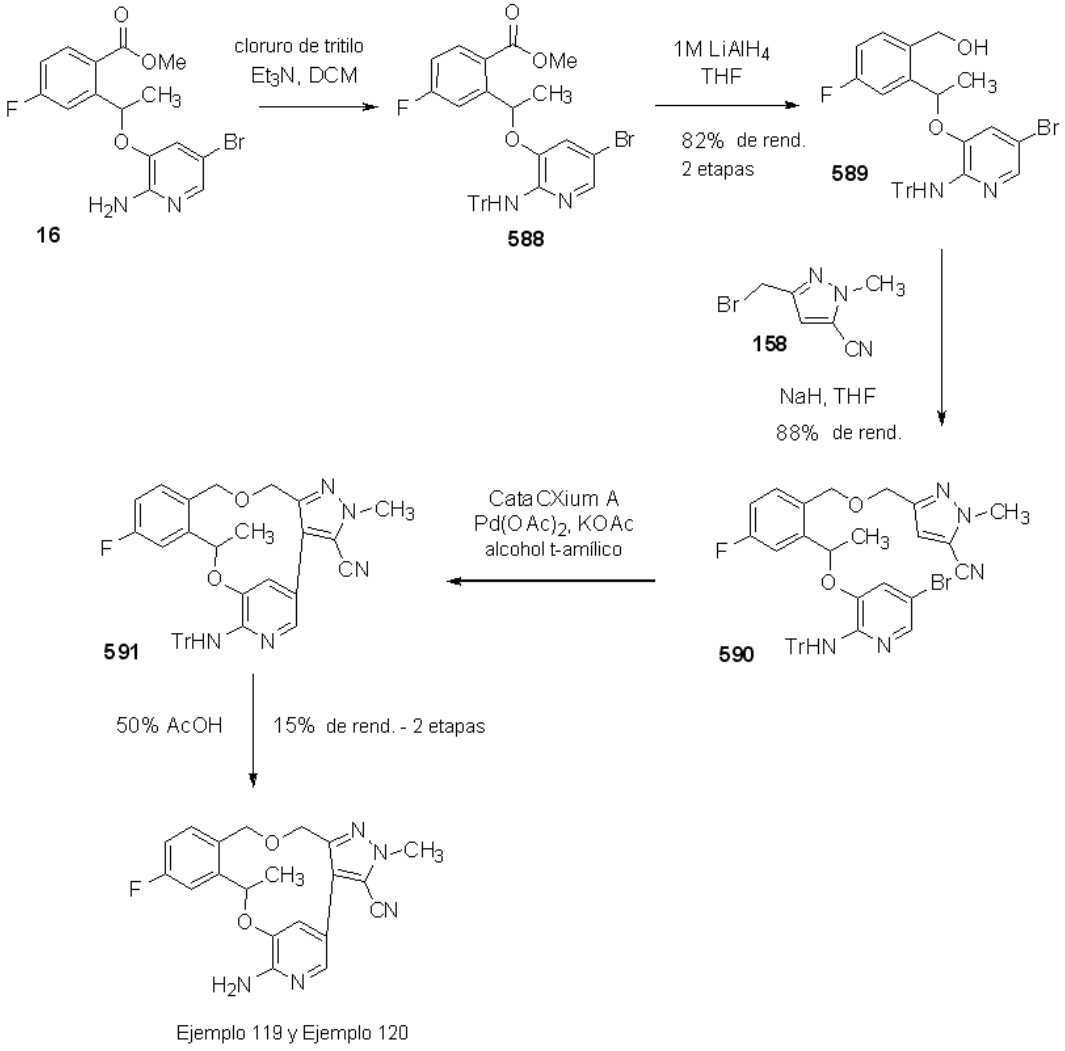
Etapa 4:

El procedimiento descrito en la etapa 4 para el **Ejemplo 104** se usó para preparar el **compuesto 587** (206 mg, 21%) en forma de un sólido amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,48 (d, *J* = 1,9 Hz, 1H), 7,59 (d, *J* = 1,8 Hz, 1H), 7,42 – 7,12 (m, 17H), 6,97 (td, *J* = 8,1, 2,7 Hz, 1H), 6,32 (s, 1H), 5,60 (d, *J* = 13,2 Hz, 1H), 5,34 – 5,16 (m, 2H), 4,46 (d, *J* = 13,2 Hz, 1H), 4,29 (d, *J* = 10,0 Hz, 1H), 4,03 (dd, *J* = 12,8, 4,0 Hz, 1H), 3,95 (s, 3H). LCMS ES *m/z* 608 $[M+H]^+$

Etapa 5:

El procedimiento descrito en la etapa 5 para el **Ejemplo 104** se usó para preparar el **Ejemplo 118** en forma de un sólido incoloro (43 mg, 35%).^{1}H RMN (400 MHz, Acetona-d_6) δ 8,60 (d, *J* = 1,8 Hz, 1H), 7,80 (d, *J* = 1,9 Hz, 1H), 7,50 – 7,43 (m, 2H), 7,05 (td, *J* = 8,4, 2,8 Hz, 1H), 5,70 (d, *J* = 13,6 Hz, 1H), 5,61 (s, 2H), 5,37 (d, *J* = 12,1 Hz, 1H), 5,28 (d, *J* = 13,1 Hz, 1H), 4,58 (d, *J* = 12,3 Hz, 1H), 4,46 (d, *J* = 10,6 Hz, 1H), 4,12 (d, *J* = 10,5 Hz, 1H), 4,03 (s, 3H). LCMS ES *m/z* 366 $[M+H]^+$.

Preparación de 7-amino-3-ter-butil-1,10,16-trimetil-16,17-dihidro-1H-8,4-(meteno)-pirazolo[4,3-g]pirido[2,3-l][1,4,10]oxadiazaciclotetradecin-15(10H)-ona (Ejemplos 119 y 120)



Ejemplo 119 y Ejemplo 120

Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 104** se usó para preparar el **compuesto 588** en forma de un sólido beige (5,82 g, cuantitativo). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,05 (dd, *J* = 8,8, 5,8 Hz, 1H), 7,39 – 7,18 (m, 17H), 7,03 (ddd, *J* = 8,7, 7,6, 2,7 Hz, 1H), 6,70 (d, *J* = 2,0 Hz, 1H), 6,38 (s, 1H), 6,35 (q, *J* = 6,4 Hz, 1H), 3,94 (s, 3H), 1,65 (d, *J* = 6,2 Hz, 3H). LCMS ES *m/z* 611/613 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 104** se usó para preparar el **compuesto 589** en forma de un sólido incoloro, en dos lotes de purezas ligeramente diferentes (5,43 g, 82%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,39 – 7,16 (m, 17H), 7,13 (dd, *J* = 9,8, 2,7 Hz, 1H), 6,96 (td, *J* = 8,2, 2,7 Hz, 1H), 6,93 (d, *J* = 2,0 Hz, 1H), 6,37 (s, 1H), 5,70 (q, *J* = 6,3 Hz, 1H), 4,79 (dd, *J* = 12,3, 6,1 Hz, 1H), 4,70 (dd, *J* =

12,3, 5,6 Hz, 1H), 1,75 – 1,69 (m, 1H), 1,66 (d, *J* = 6,3 Hz, 3H). LCMS ES *m/z* 583/585 $[M+H]^+$.

Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 104** se usó para preparar el **compuesto 590** en forma de un sólido incoloro (5,88 g, 88% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,39 – 7,17 (m, 17H), 7,11 (dd, *J* = 9,7, 2,7 Hz, 1H), 6,95 (td, *J* = 8,2, 2,7 Hz, 1H), 6,85 (d, *J* = 2,0 Hz, 1H), 6,37 (s, 1H), 5,67 (q, *J* = 6,3 Hz, 1H), 4,65 (d, *J* = 11,3 Hz, 1H), 4,60 (d, *J* = 12,1 Hz, 1H), 4,53 (d, *J* = 12,1 Hz, 1H), 4,53 (d, *J* = 11,2 Hz, 1H), 4,01 (s, 3H), 1,62 (d, *J* = 6,3 Hz, 3H). LCMS ES *m/z* 778/780/781 $[M+H]^+$.

Etapa 4:

El procedimiento descrito en la etapa 4 para el **Ejemplo 104** se usó para preparar el **compuesto 591** (1,19 g), que se usó sin otra purificación. LCMS ES *m/z* 622 $[M+H]^+$.

Etapa 5:

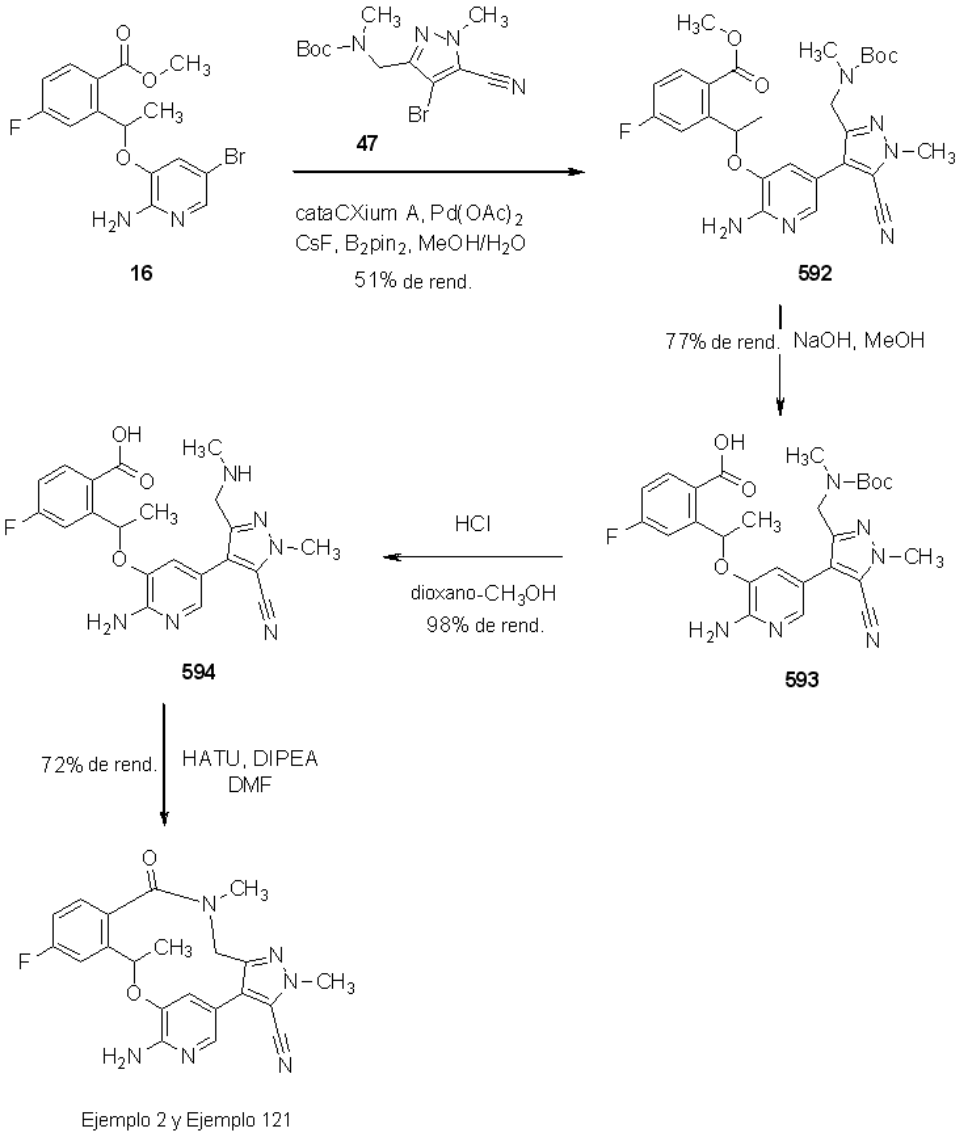
El procedimiento descrito en la etapa 5 para el **Ejemplo 104** se usó para preparar una mezcla de **Ejemplo 119** y **Ejemplo 120** en forma de un sólido incoloro (185 mg, 15% de rendimiento en dos etapas). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,34 (d, *J* = 1,9 Hz, 1H), 7,63 (d, *J* = 1,8 Hz, 1H), 7,55 (dd, *J* = 10,5, 2,8 Hz, 1H), 7,38 (dd, *J* = 8,5, 6,0 Hz, 1H), 7,08 (td, *J* = 8,4, 2,8 Hz, 1H), 6,17 (s, 2H), 6,02 – 5,92 (m, 1H), 5,24 (d, *J* = 12,0 Hz, 1H), 4,49 (d, *J* = 12,1 Hz, 1H), 4,45 (d, *J* = 10,7 Hz, 1H), 3,97 (s, 3H), 3,92 (d, *J* = 10,7 Hz, 1H), 1,64 (d, *J* = 6,2 Hz, 3H). LCMS ES *m/z* 380 $[M+H]^+$.

La separación quiral de 146 mg del material se llevó a cabo por SFC preparativa en una columna Whelk-O1 (R,R) (250 x 4,6 mm I.D., tamaño de partícula de 3 micrones), que se eluyó con 20% de metanol a 140 bar de CO_2 con una tasa de flujo de 3 mL/min. $Rt_{(pico\ 1)}$ = 4,51 minutos y $Rt_{(pico\ 2)}$ = 6,00 minutos y produjo el pico 1 en forma de un sólido blanco (58 mg) y el pico 2 en forma de un sólido blanco (57 mg). Los sólidos resultantes de ambos picos se suspendieron en agua y se secaron durante la noche en el horno de vacío.

Ejemplo 119 (pico 1): > 99% ee (47 mg). ^{1}H RMN (400 MHz, DMSO-*d*6) δ 7,63 (s, 1 H) 8,35 (s, 1 H) 7,55 (dd, *J* = 10,39, 2,57 Hz, 1 H) 7,38 (dt, *J* = 2,20 Hz, 1 H) 7,07 (dt, *J* = 2,60 Hz, 1 H) 6,15 (s, 2 H) 5,91 - 6,01 (m, 1 H) 5,24 (d, *J* = 12,10 Hz, 1 H) 4,47 (dd, *J* = 13,63, 11,68 Hz, 2 H) 3,89 - 4,02 (m, 4 H) 1,65 (d, *J*=6,11 Hz, 3 H). LCMS APCI *m/z* 380 $[M+H]^+$.

Ejemplo 120 (pico 2): ~ 98% ee (45 mg). ^{1}H RMN (400 MHz, DMSO-*d*6) δ 8,34 (d, *J* = 1,52 Hz, 1 H) 7,63 (d, *J* = 1,52Hz, 1 H) 7,55 (dd, *J* = 10,48, 2,65 Hz, 1 H) 7,38 (dd, *J* = 8,59, 6,06 Hz, 1 H) 7,07 (dt, *J* = 2,50 Hz, 1 H) 6,15 (s, 2 H) 5,97 (m, *J* = 5,80 Hz, 1 H) 5,24 (d, *J* = 11,87 Hz, 1 H) 4,47 (dd, *J* = 14,02, 11,49 Hz, 2 H) 3,85 - 4,03 (m, 4 H) 1,65 (d, *J* = 6,06 Hz, 3 H). LCMS APCI *m/z* 380 $[M+H]^+$.

Preparación de (10S)-7-amino-12-fluoro-2,10,16-trimetil-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(meteno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 121)



Ejemplo 2 y Ejemplo 121

Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 2** se usó para preparar el **compuesto 592** (800 mg, 51%) en forma de una espuma amarilla. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,02 (m, 1H), 7,58 (s, 1H), 7,23 (m, 1H), 7,03 (ddd, *J* = 8,7, 7,6, 2,7 Hz, 1H), 6,88 (m, 1H), 6,50 (m, 1H), 6,0 (m, 1H), 5,48 (m, 1H), 4,05-4,65 (m, 2H), 3,98 (s, 3H), 3,94 (s, 3H), 2,60-2,80 (m, 4H), 1,70 (d, *J* = 6,2 Hz, 3H), 1,25-1,45 (m, 9H). LCMS ES m/z 539 $[M+H]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 2** se usó para preparar el **compuesto 593** (1060 mg, 77% de rendimiento). ^{1}H RMN (400 MHz, DMSO-d_6) δ 13,36 (s, 1H), 7,94 (t, *J* = 6,9 Hz, 1H), 7,61 – 7,43 (m, 2H), 7,01-7,25 (m, 2H), 6,75 - 7,0(m, 2H), 6,47 (m, 1H), 4,59 – 4,03 (m, 2H), 3,96 (s, 3H), 2,79 – 2,51 (m, 2H), 1,62 (d, *J* = 6,2 Hz, 3H), 1,34 – 1,01 (m, 9H). LCMS ES m/z 525 $[M+H]^+$.

Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 2** se usó para preparar el **compuesto 594** (910 mg, 98%) en forma de sal de clorhidrato. ^{1}H RMN (400 MHz, DMSO-d_6) δ 13,38 (s, 1H), 9,36 – 9,16 (m, 2H), 7,98 (dd, *J* = 8,8, 6,0 Hz, 1H), 7,80 (d, *J* = 1,7 Hz, 1H), 7,58 (dd, *J* = 10,3, 2,7 Hz, 1H), 7,26 (ddd, *J* = 12,5, 6,6, 3,3 Hz, 2H), 7,20 – 7,07 (m, 2H), 6,54 (q, *J* = 6,2 Hz, 1H), 4,24 – 4,07 (m, 2H), 4,05 (s, 3H), 2,18 (d, *J* = 90,0 Hz, 2H), 1,64 (d, *J* = 6,2 Hz, 3H). LCMS ES m/z 425 $[M+H]^+$.

Etapa 4:

El procedimiento descrito en la etapa 4 para el **Ejemplo 2** se usó para preparar una mezcla de **Ejemplo 2 y Ejemplo 121** en forma de un sólido blanco (570 mg, 72%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,65 – 7,54 (m, 2H), 7,46 (dd, *J* = 8,6, 5,7 Hz, 1H), 7,18 (td, *J* = 8,5, 2,7 Hz, 1H), 6,81 (d, *J* = 1,9 Hz, 1H), 6,19 (d, *J* = 3,4 Hz, 1H), 5,60 (dt, *J* = 6,7, 3,4 Hz, 1H), 4,44 (d, *J* = 14,4 Hz, 1H), 4,19 (d, *J* = 14,4 Hz, 1H), 4,03 (s, 3H), 2,99 (s, 3H), 1,67 (d, *J* = 6,2 Hz, 3H). LCMS ES m/z 407 $[M+H]^+$.

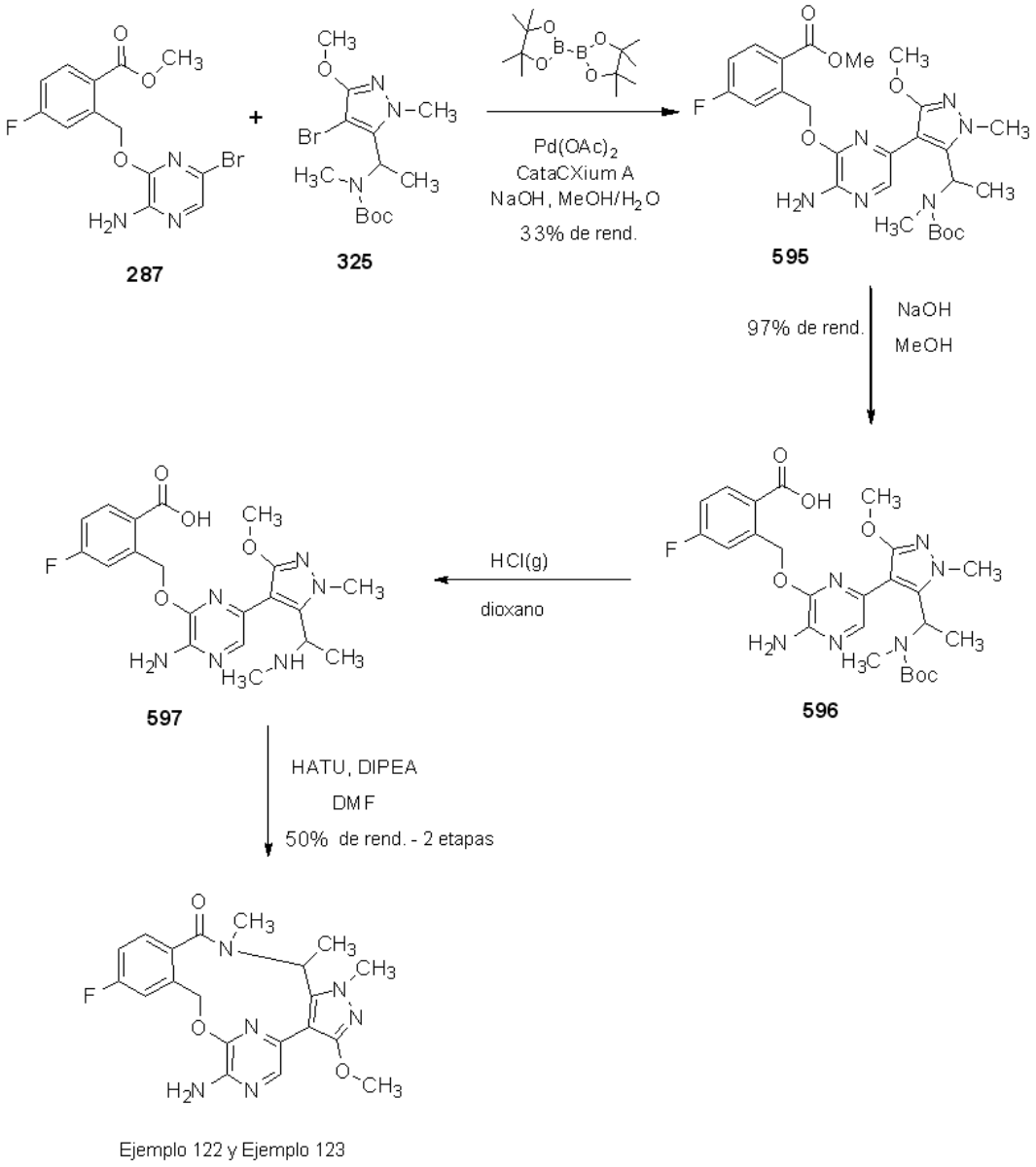
La separación quiral de 570 mg del material se llevó a cabo por SFC preparativa en una columna Whelk-O1 (R,R) (250 x 4,6 mm I.D., tamaño de partícula de 3 micrones), que se eluyó con 30% de metanol a 140 bar de CO_2 con una tasa de flujo de 3 mL/min. $Rt_{(pico\ 1)}$ = 3,06 minutos y $Rt_{(pico\ 2)}$ = 4,38 minutos, y produjo el pico 1 en forma de un sólido blanco (263 mg) y el pico 2 en forma de un sólido blanco (262 mg).

Ejemplo 2 (pico 1): > 99% ee (263 mg).

Ejemplo 121 (pico 2): ~ 98% ee (262 mg). ^{1}H RMN (400MHz, DMSO-d6) δ = 7,63 - 7,55 (m, 2H), 7,46 (dd, *J*=5,8, 8,6 Hz, 1H), 7,17 (dt, *J*=2,8, 8,4 Hz, 1H), 6,81 (d, *J*=1,5

Hz, 1H), 6,17 (s,2H), 5,66 - 5,55 (m, 1H), 4,43 (d, *J*=14,6 Hz, 1H), 4,19 (d, *J*=14,4 Hz, 1H), 4,03 (s, 3H), 2,99 (s, 3H), 1,68 (d, *J*=6,3 Hz, 3H). LCMS APCI *m/z* 407 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-3-metoxi-1,16,17-trimetil-16,17-dihidro-1H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplos 122 y 123)



Ejemplo 122 y Ejemplo 123

Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 86** y **Ejemplo 87** se usó para preparar el **compuesto 595** (500 mg, 33%, Rf = 0,3) en forma de un sólido marrón. LCMS m/z 567 $[M+Na]^+$.

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 86** y **Ejemplo 87** se usó para preparar el **compuesto 596** (470 mg, 97%) en forma de un sólido blanco. LCMS ES *m/z* 531 $[M+H]^+$.

Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 86** y **Ejemplo 87** se usó para preparar el **compuesto 597**, que se usó en la siguiente etapa directamente. LCMS m/z 431 $[M+H]^+$.

Etapa 4:

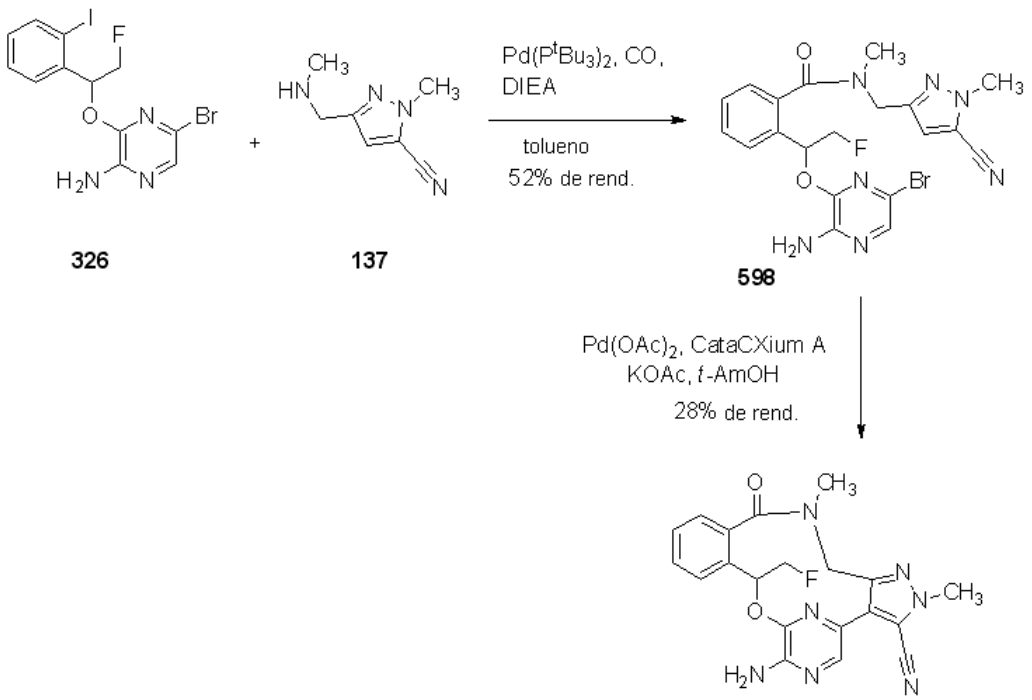
El procedimiento descrito en la etapa 4 para el **Ejemplo 86** y **Ejemplo 87** se usó para preparar una mezcla de **Ejemplo 122** y **Ejemplo 123** en forma de un sólido blanquecino (190,1 mg, 50% en dos etapas). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,66 (s, 1H), 7,50-7,44 (m, 2H), 7,20-7,19 (m, 1H), 6,34 (s, 2H), 5,54-5,51 (d, 1H), 5,03-5,00 (d, 1H), 4,81-4,79 (d, 1H), 3,97 (s, 3H), 3,85 (s, 3H), 3,01 (s, 3H), 1,67-1,65 (d, 3H). LCMS *m/z* 413 $[M+H]^+$.

La separación quiral de 70 mg del material se llevó a cabo por SFC preparativa en una columna Chiralpak AD-H (250 x 4,6 mm I.D., tamaño de partícula de 5 micrones), que se eluyó con 5-40% de etanol (0,05% de DEA) a 140 bar de CO_2 con una tasa de flujo de 4 mL/min. $Rt_{(pico\ 1)}$ = 6,93 minutos y $Rt_{(pico\ 2)}$ = 8,52 minutos, y produjo el pico 1 en forma de un sólido blanco (9 mg) y el pico 2 en forma de un sólido blanco (6 mg). La separación requirió dos corridas. Cada pico en aislamiento se equilibró hasta obtener una mezcla 90 : 10 de atropisómeros.

Ejemplo 122 (pico 1): > 99% ee. ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,79 (s, 1H), 7,54-7,51 (m, 2H), 7,16-7,11 (m, 1H), 5,68-5,65 (m, 1H), 5,07-5,01 (m, 2H), 4,06 (s, 3H), 3,98 (s, 3H), 3,15 (s, 3H), 1,78-1,76 (d, 3H). LCMS APCI *m/z* 413 $[M+H]^+$.

Ejemplo 123 (pico 2): ~ 98% ee. ^{1}H RMN (400 MHz, Metanol-d_4) δ 7,79 (s, 1H), 7,54-7461 (m, 2H), 7,16-7,11 (m, 1H), 5,68-5,65 (m, 1H), 5,07-5,02 (m, 2H), 4,06 (s, 3H), 3,98 (s, 3H), 3,15 (s, 3H), 1,78-1,76 (d, 3H). LCMS APCI *m/z* 413 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-3-metoxi-1,16,17-trimetil-16,17-dihidro-1H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplos 124, 125 y 126)



Ejemplo 124, Ejemplo 125 y Ejemplo 126

Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 90** se usó para preparar el **compuesto 598** en forma de una espuma blanca (117 mg, 52%). ^{1}H RMN (400 MHz, Metanol-d_4, 2 rotámeros) δ 7,63 (dd, J = 7,0, 2,1 Hz, 1H), 7,54 y 7,51 (2 x s, 1H), 7,50 – 7,30 (m, 3H), 6,98 y 6,79 (2 x s, 1H), 6,33 (ddd, J = 16,1, 7,6, 2,6 Hz) y 6,29 – 6,11 (m) (1H), 5,04 (d, J = 15,0 Hz, 1H), 4,94 – 4,65 (m, 2H), 4,57 (d, J = 15,0 Hz, 1H), 4,02 y 3,99 (2 x s, 3H), 3,17 y 3,01 (2 x s, 3H). LCMS ES m/z 488/490 $[M+H]^+$

Etapa 2:

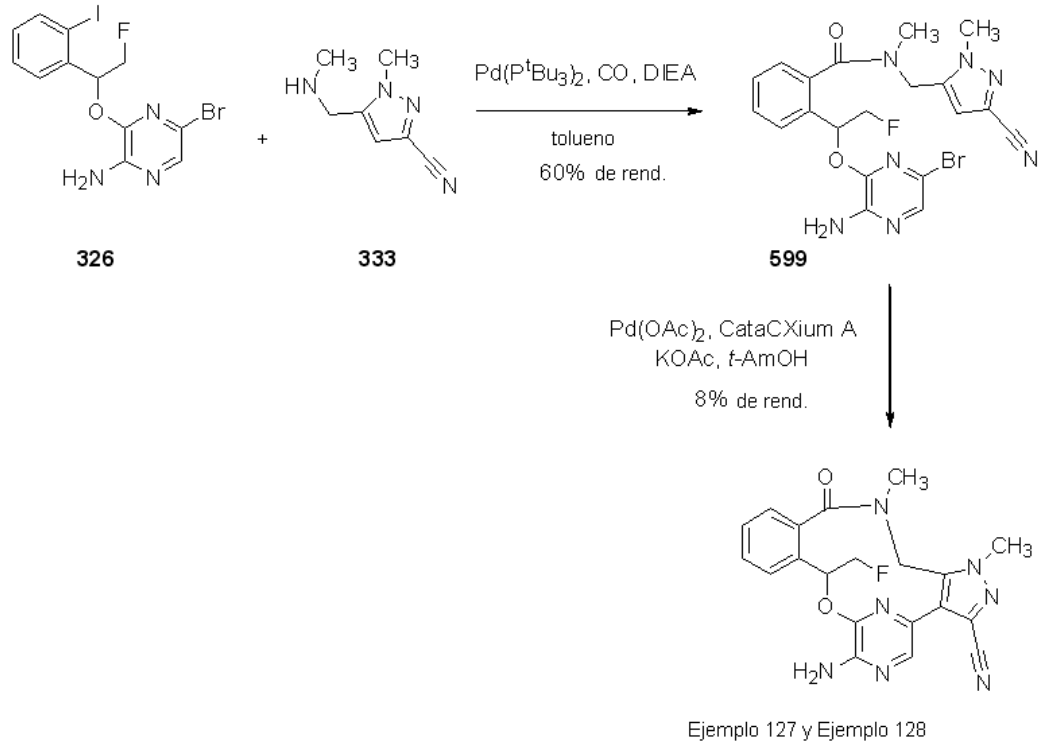
El procedimiento descrito en la etapa 2 para el **Ejemplo 90** se usó para preparar el **Ejemplo 124** en forma de un sólido incoloro (26 mg, 28%). ^{1}H RMN (400 MHz, Acetona-d_6) δ 7,90 (s, 1H), 7,65 (dd, J = 7,9, 1,8 Hz, 1H), 7,48 – 7,34 (m, 3H), 6,21 (ddd, J = 17,7, 8,1, 2,3 Hz, 1H), 4,96 (ddd, J = 48,6, 10,3, 8,2 Hz, 1H), 4,71 (ddd, J = 46,2, 10,3, 2,3 Hz, 1H), 4,53 (d, J = 13,6 Hz, 1H), 4,36 (d, J = 13,6 Hz, 1H), 4,11 (s, 3H), 2,97 (s, 3H). LCMS ES m/z 408 $[M+H]^+$.

La separación quiral de 23 mg del material se llevó a cabo por SFC preparativa en una columna Whelk-O1 (R,R) (250 x 4,6 mm I.D., tamaño de partícula de 5 micrones), que se eluyó con 35% de metanol a 120 bar de CO_2 con una tasa de flujo de 62 mL/min. $Rt_{(pico\ 1)}$ = 3,06 minutos y $Rt_{(pico\ 2)}$ = 4,60 minutos y, produjo el pico 1 en forma de un sólido blanco (8 mg) y el pico 2 en forma de un sólido blanco (8,23 mg).

Ejemplo 125 (pico 1): > 99% ee (-).[1]H RMN (400 MHz, Acetona-d_6) δ 7,90 (s, 1H), 7,65 (dd, *J* = 7,9, 1,8 Hz, 1H), 7,48 – 7,34 (m, 3H), 6,21 (ddd, *J* = 17,7, 8,1, 2,3 Hz, 1H), 4,96 (ddd, *J* = 48,6, 10,3, 8,2 Hz, 1H), 4,71 (ddd, *J* = 46,2, 10,3, 2,3 Hz, 1H), 4,53 (d, *J* = 13,6 Hz, 1H), 4,36 (d, J = 13,6 Hz, 1H), 4,11 (s, 3H), 2,97 (s, 3H). LCMS ES *m/z* 408 $[M+H]^+$

Ejemplo 126 (pico 2): ~ 98% ee (+).[1]H RMN (400 MHz, Acetona-d_6) δ 7,90 (s, 1H), 7,65 (dd, *J* = 7,9, 1,8 Hz, 1H), 7,48 – 7,34 (m, 3H), 6,21 (ddd, *J* = 17,7, 8,1, 2,3 Hz, 1H), 4,96 (ddd, *J* = 48,6, 10,3, 8,2 Hz, 1H), 4,71 (ddd, *J* = 46,2, 10,3, 2,3 Hz, 1H), 4,53 (d, *J* = 13,6 Hz, 1H), 4,36 (d, J = 13,6 Hz, 1H), 4,11 (s, 3H), 2,97 (s, 3H). LCMS ES *m/z* 408 $[M+H]^+$.

Preparación de 7-amino-12-fluoro-3-metoxi-1,16,17-trimetil-16,17-dihidro-1H-8,4-(azeno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 127 y Ejemplo 128)



326 **333** **599**

Ejemplo 127 y Ejemplo 128

Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 90** se usó para preparar el **compuesto 599** en forma de un sólido blanco (723 mg, 60%). [1]H RMN (400 MHz, DMSO-d_6) δ 7,75 – 7,65 (m, 1H), 7,58 (s, 1H), 7,52 – 7,39 (m, 3H), 7,09 (s,

1H), 6,84 (s, 2H), 6,20 – 6,00 (m, 1H), 5,06 – 4,64 (m, 4H), 3,99 (s, 3H), 2,92 (s, 3H). LCMS *m/z* 488/490 $[M+H]^+$.

Etapa 2:

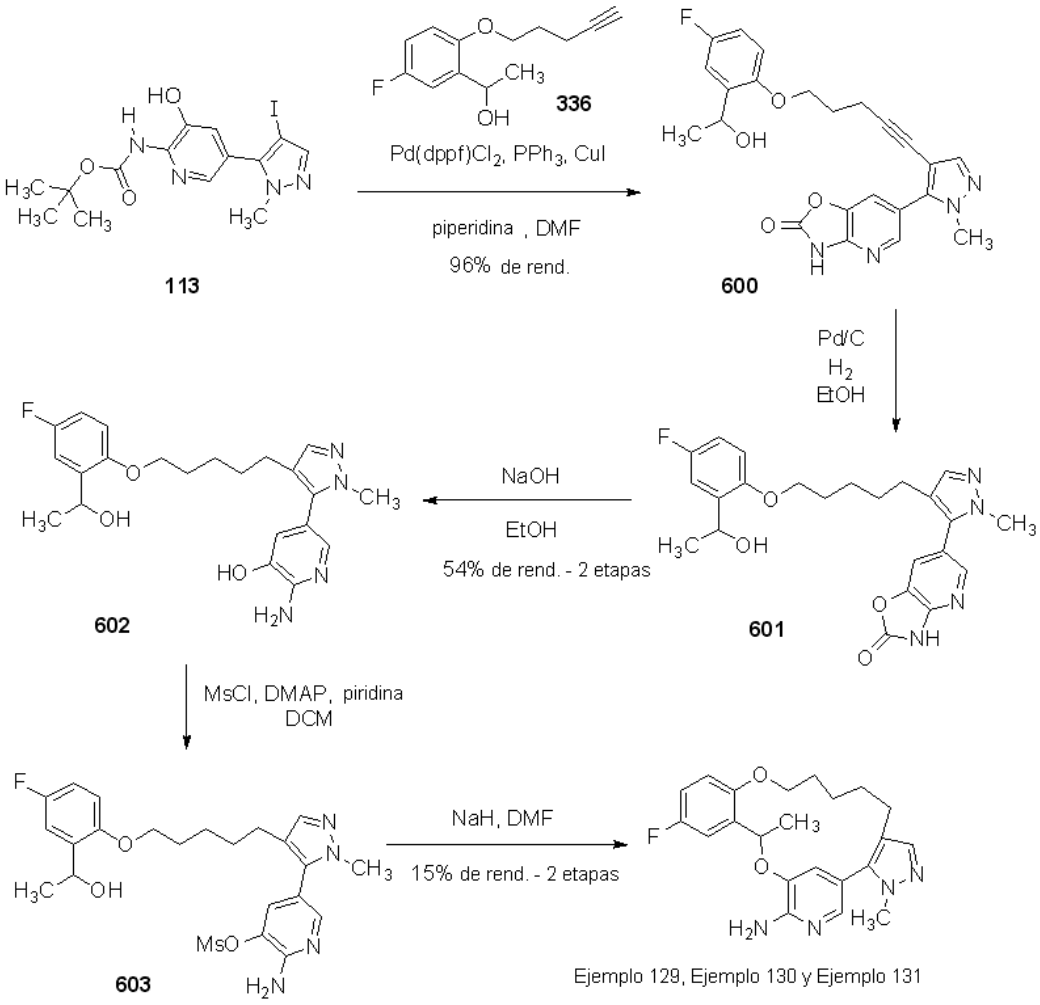
El procedimiento descrito en la etapa 2 para el **Ejemplo 90** se usó para preparar una mezcla de **Ejemplo 127 y Ejemplo 128** en forma de sólidos beige (33 mg, 8%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,87 (s, 1H), 7,67 – 7,56 (m, 1H), 7,53 – 7,35 (m, 3H), 6,79 (s, 2H), 6,01 (ddd, *J* = 17,3, 8,3, 2,3 Hz, 1H), 4,98 (ddd, *J* = 48,3, 10,2, 8,3 Hz, 1H), 4,76 – 4,53 (m, 2H), 4,36 (d, *J* = 14,8 Hz, 1H), 4,08 (s, 3H), 2,91 (s, 3H). LCMS *m/z* 408 $[M+H]^+$.

La separación quiral de 27 mg del material se llevó a cabo por SFC preparativa en una columna Whelk-O1 (R,R) (250 x 4,6 mm I.D., tamaño de partícula de 5 micrones), que se eluyó con 38% de metanol a 120 bar de CO_2 con una tasa de flujo de 62 mL/min. $Rt_{(pico\ 1)}$ = 4,19 minutos y $Rt_{(pico\ 2)}$ = 5,50 minutos y produjo el pico 1 en forma de un sólido blanco (11,99 mg) y el pico 2 en forma de un sólido blanco (10,99 mg).

Ejemplo 127 (pico 1): > 99% ee (-).^{1}H RMN (400MHz, DMSO-d_6) δ 7,87 (s, 1H), 7,60 (d, *J* = 6,8 Hz, 1H), 7,50 - 7,35 (m, 3H), 6,80 (br. s., 2H), 6,01 (dd, *J* = 7,8, 17,4 Hz, 1H), 5,11-4,84 (m, 1H), 4,73 - 4,52 (m, 2H), 4,36 (d, *J* = 15,1 Hz, 1H), 4,08 (s, 3H), 2,91 (s, 3H). LCMS APCI *m/z* 408 $[M+H]^+$

Ejemplo 128 (pico 2): > 99% ee (+).^{1}H RMN (400MHz, DMSO-d_6) δ 7,87 (s, 1H), 7,60 (d, *J* = 6,8 Hz, 1H), 7,50 - 7,35 (m, 3H), 6,80 (br. s., 2H), 6,01 (dd, *J* = 7,8, 17,4 Hz, 1H), 5,11 -4,84 (m, 1H), 4,73 - 4,52 (m, 2H), 4,36 (d, *J* = 15,1 Hz, 1H), 4,08 (s, 3H), 2,91 (s, 3H). LCMS APCI *m/z* 408 $[M+H]^+$

Preparación de 12-fluoro-1,14-dimetil-1,4,5,6,7,8-hexahidro-14H-16,20-(meteno)-pirazolo-[4,3-g][1,14,11]benzodioxazacicloheptadecin-17-amina (Ejemplo 129/Ejemplo 130/Ejemplo 131)



Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 37** se usó para preparar el **compuesto 600** en forma de un aceite amarillo (709 mg, 96%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 8,05 (d, J = 2,0 Hz, 1H), 7,63 (s, 1H), 7,45 (d, J = 2,0 Hz, 1H), 7,16 (dd, J = 9,7, 3,3 Hz, 1H), 6,93 (td, J = 8,5, 3,3 Hz, 1H), 6,84 (dd, J = 9,0, 4,6 Hz, 1H), 4,94 (q, J = 6,3 Hz, 1H), 3,98 (q, J = 5,7 Hz, 2H), 3,82 (s, 3H), 1,91 (p, J = 6,6 Hz, 2H), 1,61 (q, J = 6,0, 4,9 Hz,2H), 1,23 (d, J = 6,3 Hz, 3H). LCMS m/z 504 $[M+H]^+$

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 37** se usó para preparar el **compuesto 601** en forma de un aceite amarillo (603 mg). Esto se sometió a la siguiente etapa sin otra purificación. LCMS m/z 439 $[M+H]^+$

Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 37** se usó para preparar el **compuesto 602** en forma de un sólido blanco (350 mg, 54%). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,40 (d, *J* = 1,9 Hz, 1H), 7,31 (s, 1H), 7,15 (dd, *J* = 9,7, 3,2 Hz, 1H), 6,95 (td, *J* = 8,5, 3,2 Hz, 1H), 6,88 (dd, *J* = 9,0, 4,6 Hz, 1H), 6,78 (d, *J* = 2,0 Hz, 1H), 5,76 (s, 2H), 5,11 (d, *J* =4,4 Hz, 1H), 4,91 (p, *J* = 6,0 Hz, 1H), 3,95 – 3,83 (m, 2H), 3,63 (s, 3H), 2,31 (t, *J* = 7,4 Hz, 2H), 1,72 – 1,60 (m, 2H), 1,48 (d, *J* = 7,5 Hz, 2H), 1,38 (d, *J* = 7,1 Hz, 2H), 1,21 (d, *J* = 6,3 Hz, 3H). LCMS *m/z* 413 $[M+H]^+$.

Etapa 4:

El procedimiento descrito en la etapa 4 para el **Ejemplo 37** se usó para preparar el **compuesto 603** en forma de un aceite incoloro (233 mg, cuantitativo). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,91 (d, *J* = 2,0 Hz, 1H), 7,46 (d, *J* = 1,9 Hz, 1H), 7,38 (s, 1H), 7,12 (dd, *J* = 9,2, 3,1 Hz, 1H), 6,87 (ddd, *J* = 8,9, 7,9, 3,1 Hz, 1H), 6,74 (dd, *J* = 8,9, 4,4 Hz, 1H), 5,25 (s, 2H), 5,05 (q, *J* = 6,4 Hz, 1H), 4,00 – 3,86 (m, 2H), 3,74 (s, 3H), 3,56 (q, *J* = 7,3 Hz, 2H), 3,28 (s, 3H), 2,39 (h, *J* = 7,3 Hz, 2H), 1,77 (dd, *J* = 14,1, 7,2 Hz, 2H), 1,44 (d, *J* = 6,5 Hz, 3H). LCMS *m/z* 493 $[M+H]^+$.

Etapa 5:

El procedimiento descrito en la etapa 5 para el **Ejemplo 37** se usó para preparar el **Ejemplo 129** en forma de un sólido blanco (29 mg, 15%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,47 – 7,38 (m, 1H), 7,34 (s, 1H), 7,03 (dd, *J* = 8,9, 3,1 Hz, 1H), 6,91 (ddd, *J* = 8,9, 7,9, 3,2 Hz, 1H), 6,79 (dd, *J* = 9,0, 4,3 Hz, 1H), 6,54 (d, *J* = 1,5 Hz, 1H), 5,73 – 5,65 (m,1H), 4,29 – 4,16 (m, 2H), 3,94 – 3,84 (m, 2H), 3,76 (s, 3H), 2,64 – 2,43 (m, 1H), 2,13 – 1,99 (m, 1H), 1,83 – 1,66 (m, 2H), 1,63 (d, *J* = 6,4 Hz, 3H), 1,33 (dd, J = 9,7, 5,5 Hz, 2H). LCMS *m/z* 397 $[M+H]^+$.

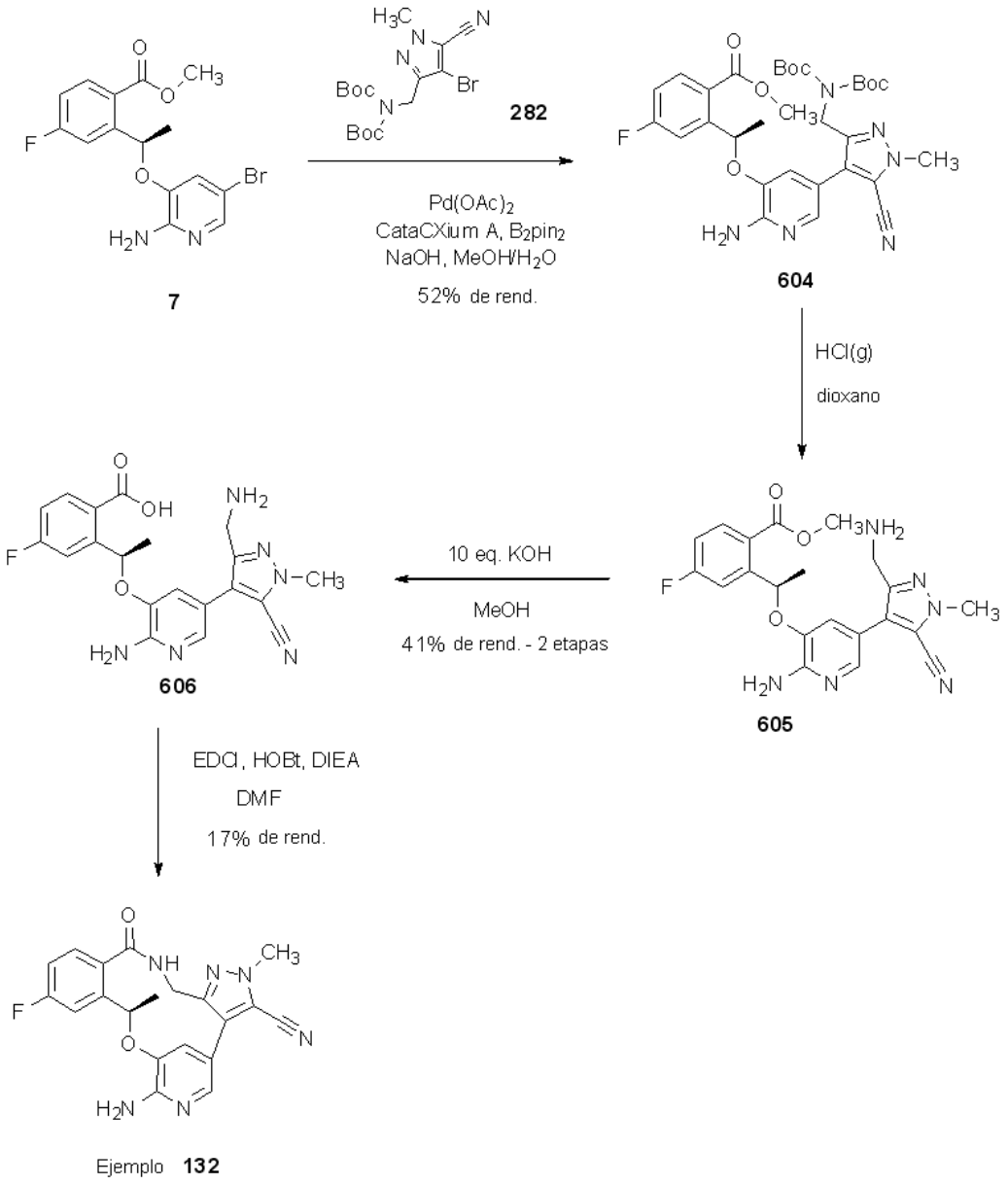
La separación quiral de 27 mg del material se llevó a cabo por SFC preparativa en una columna Chiralpak AD-H (250 x 4,6 mm I.D., tamaño de partícula de 5 micrones), que se eluyó con 38% de metanol a 140 bar de CO_2 con una tasa de flujo de 3 mL/min. $Rt_{(pico\ 1)}$ = 2,37 minutos y $Rt_{(pico\ 2)}$ = 5,70 minutos, y produjo el pico 1 en forma de un sólido blanco (4,9 mg) y el pico 2 en forma de un sólido blanco (4,9 mg).

Ejemplo 130 (pico 1): > 99% ee (+).^{1}H RMN (400MHz, DMSO-d_6) δ 7,56 (s, 1H), 7,27 (s, 1H), 7,16 (d, *J* = 8,6 Hz, 1H), 7,08 - 6,95 (m, 2H), 6,42 (s, 1H), 6,12 (s, 2H), 5,65 (d, *J* = 6,5Hz, 1H), 4,25 (br. s., 1H), 3,86 (t, *J* = 10,6 Hz, 1H), 3,66 (s, 3H), 2,48 - 2,27 (m, 2H), 2,12 - 1,93 (m, 2H), 1,82 - 1,44 (m, 6H), 1,34 - 1,20 (m, 1H). LCMS APCI *m/z* 397 $[M+H]^+$.

Ejemplo 131 (pico 2): > 99% ee (-). ^{1}H RMN (400MHz, DMSO-d_6) δ 7,56 (s, 1H), 7,27 (s, 1H), 7,16 (d, *J* = 8,6 Hz, 1H), 7,08 - 6,95 (m, 2H), 6,42 (s, 1H), 6,12 (s, 2H), 5,65 (d,

J = 6,5Hz, 1H), 4,25 (br. s., 1H), 3,86 (t, *J* = 10,6 Hz, 1H), 3,66 (s, 3H), 2,48 - 2,27 (m, 2H), 2,12 - 1,93 (m, 2H), 1,82 - 1,44 (m, 6H), 1,34 - 1,20 (m, 1H). LCMS APCI *m/z* 397 $[M+H]^+$.

Preparación de (10R)-7-amino-12-fluoro-2,10-dimetil-15-oxo-10,15,16,17-tetrahidro-2H-8,4-(meteno)pirazolo[4,3-h][2,5,11]benzoxadiazaciclotetradecin-3-carbonitrilo (Ejemplo 132)



Etapa 1:

El procedimiento descrito en la etapa 1 para el **Ejemplo 88** se usó para preparar el **compuesto 604** (340 mg, 52%) en forma de un sólido marrón. LCMS m/z 647 $[M+Na]^+$

Etapa 2:

El procedimiento descrito en la etapa 2 para el **Ejemplo 88** se usó para preparar el **compuesto 605**, que se usó para la siguiente etapa sin otra purificación. LCMS m/z 425 $[M+H]^+$

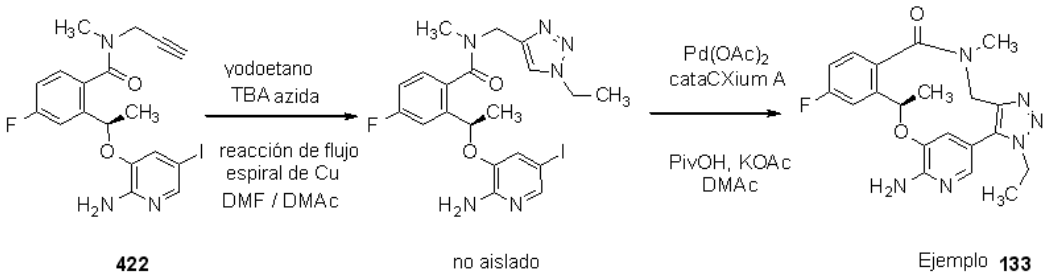
Etapa 3:

El procedimiento descrito en la etapa 3 para el **Ejemplo 88** se usó para preparar el **compuesto 606** (70 mg, 41%) en forma de un sólido blanco. LCMS m/z 411 $[M+H]^+$

Etapa 4:

A una solución de **compuesto 606** (70 mg, 0,17 mmol) y DIPEA (33 mg, 0,256 mmol) en DMF (25 mL) se añadieron HOBt (35 mg, 0,256 mmol) y EDCI (33 mg, 0,256 mmol) en DMF (10 mL) a -35 °C. Después de la adición, la mezcla resultante se agitó a 80 °C durante 72 horas. La LC-MS mostró que la reacción estaba completa. La mezcla se vertió en agua helada (50 mL). La mezcla se extrajo con EtOAc (40 mL x 5). Las capas combinadas de EtOAc se lavaron con salmuera (20 mL x 5), se secaron en Na_2SO_4 y se concentraron al vacío para producir un residuo. El residuo se purificó por TLC preparativa y luego se purificó por HPLC preparativa de fase inversa para producir el **Ejemplo 132** (11,5 mg, 17%) en forma de un sólido blanco. ^1H RMN (400 MHz, Metanol-d_4 – la muestra es una mezcla de rotámeros) δ 7,8-7,75 (m, 1H), 7,70-7,6 (m, 1H), 7,32-7,20 (m, 2H), 7,01-7,00 (m, 1H), 6,39-6,24 (m, 1H), 5,66-5,64 (d, 1H), 4,45-4,32 (d, 1H), 4,05-4,02 (s, 1H), 1,77-1,75 (d, 3H). LCMS *m/z* 392 $[M+H]^+$.

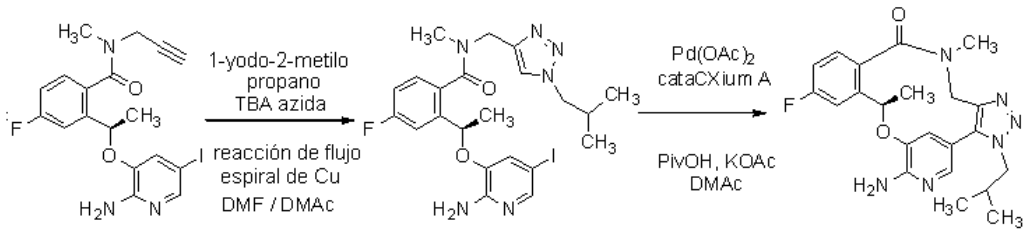
Preparación de (10R)-7-amino-3-etil-12-fluoro-10,16-dimetil-16,17-dihidro-3H-4,8-(meteno)[1,2,3]triazolo[4,5-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 133)



422 no aislado Ejemplo 133

La combinación de las etapas 3 y 4 del **Ejemplo 41** en un protocolo de biblioteca produjo el **Ejemplo 133** en forma de un sólido blanco (35,47 mg). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,62-7,64 (m, 2 H), 7,44 (dd, *J* = 5,7, 8,5 Hz, 1 H), 7,17 (dt, *J* = 2,8, 8,5 Hz, 1 H), 6,77 (bs, 1 H), 6,35 (bs, 2 H), 5,65 (q, *J* = 7,2, 3,6 Hz, 1 H), 4,51 (d, *J* = 14,4 Hz, 1 H), 4,35 - 4,46 (m, 2 H), 4,13 (d, *J* = 14,7 Hz, 1 H), 2,99 (s, 3 H), 1,67 (d, *J* = 6,1 Hz, 3 H), 1,40 (t, *J* = 7,4 Hz, 3 H). LCMS APCI *m/z* 397 $[M+H]^+$.

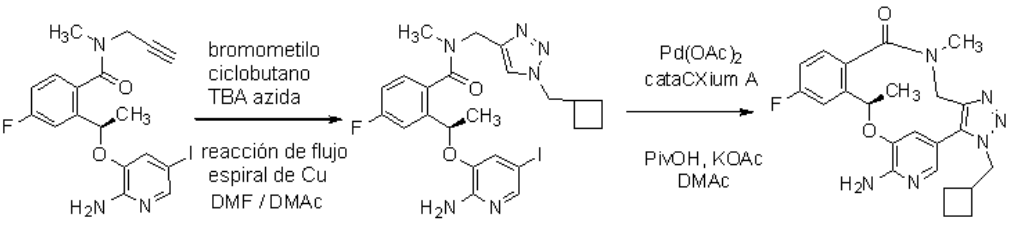
Preparación de (10R)-7-amino-12-fluoro-10,16-dimetil-3-(2-metilpropil)-16,17-dihidro-3H-8,4-(meteno)[1,2,3]triazolo[4,5-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 134)



422 no aislado Ejemplo **134**

La combinación de las etapas 3 y 4 del **Ejemplo 41** en un protocolo de biblioteca produjo el **Ejemplo 134** en forma de un sólido blanco (47,09 mg). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,62 - 7,64 (m, 2 H), 7,43 (dd, *J* = 5,7, 8,5 Hz, 1 H), 7,16 (dt, *J* = 2,8, 8,5 Hz, 1 H), 6,75 (s, 1 H), 6,33 (s, 2 H), 5,64 (q, *J* = 7,2, 3,6 Hz, 1 H), 4,51 (d, *J* = 14,4 Hz, 1 H), 4,27 - 4,31 (m, 1 H), 4,19 - 4,21 (m, 1 H), 4,13 (d, *J* = 14,7 Hz, 1 H), 2,98 (s, 3 H), 2,03-2,07 (m, 1 H), 1,65 (d, *J* = 6,1 Hz, 3 H), 0,75 (d, *J* = 6,6 Hz, 6 H). LCMS APCI *m/z* 425 $[M+H]^+$.

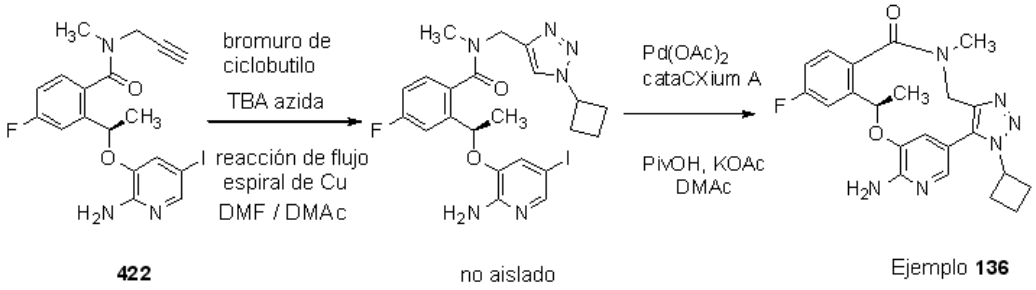
Preparación de (10R)-7-amino-3-(ciclobutilmetil)-12-fluoro-10,16-dimetil-16,17-dihidro-3H-8,4-(meteno)[1,2,3]triazolo[4,5-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 135)



422 no aislado Ejemplo **135**

La combinación de las etapas 3 y 4 del **Ejemplo 41** en un protocolo de biblioteca produjo el **Ejemplo 135** en forma de un sólido blanco (8,3 mg). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,62-7,64 (m, 2 H), 7,43 (dd, *J* = 5,7, 8,5 Hz, 1 H), 7,16 (dt, *J* = 2,8, 8,5 Hz, 1 H), 6,77 (s, 1 H), 5,65 (q, *J* = 7,2, 3,6 Hz, 1 H), 4,51 (d, *J* = 14,4 Hz, 1 H), 4,38,4,47 (m, 2 H), 4,14 (d, *J* = 14,7 Hz, 1 H), 2,97 (s, 3 H), 2,71 (m, 1 H), 1,73 - 1,90 (m, 2 H), 1,64-1,73 (m, 7 H). LCMS APCI *m/z* 437 $[M+H]^+$.

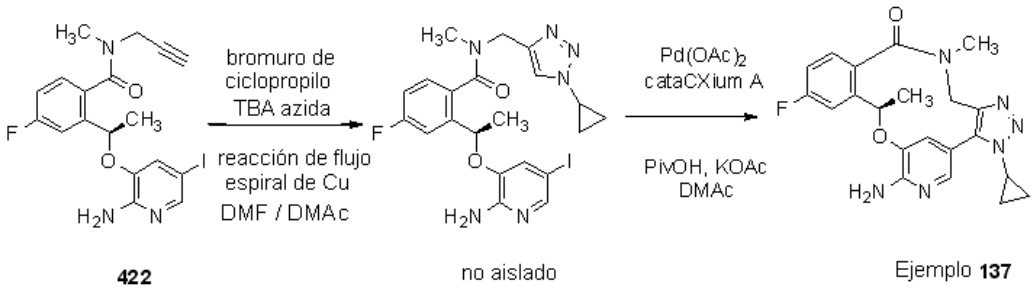
Preparación de (10R)-7-amino-3-ciclobutil-12-fluoro-10,16-dimetil-16,17-dihidro-3H-8,4-(meteno)[1,2,3]triazolo[4,5-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 136)



422 no aislado Ejemplo **136**

La combinación de las etapas 3 y 4 del **Ejemplo 41** en un protocolo de biblioteca produjo el **Ejemplo 136** en forma de un sólido blanco (56,97 mg). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,57 - 7,61 (m, 2 H), 7,44 (s, 1 H), 7,38 – 7,40 (m, 1 H), 7,12 (dt, *J* = 2,8, 8,5 Hz, 1 H), 6,73 (s, 1 H), 6,31 (s, 2 H), 5,60 (q, *J* = 7,2, 3,6 Hz, 1 H), 5,00 (m, 1 H), 4,47 (d, *J* = 14,4 Hz, 1 H), 4,09 (d, *J* = 14,7 Hz, 1 H), 2,95 (s, 3 H), 2,52 (m, 2 H), 2,65 (m, 1 H), 2,26 (m, 1 H), 1,82 (m, 1 H) 1,62 (d, *J* = 6,1 Hz, 3 H), 0,78 (t, *J* = 7,3 Hz, 3 H). LCMS APCI *m/z* 423 $[M+H]^+$.

Preparación de (10R)-7-amino-3-ciclopropil-12-fluoro-10,16-dimetil-16,17-dihidro-3H-8,4-(meteno)[1,2,3]triazolo[4,5-h][2,5,11]benzoxadiazaciclotetradecin-15(10H)-ona (Ejemplo 137)



422 no aislado Ejemplo **137**

La combinación de las etapas 3 y 4 de **Ejemplo 41** en un protocolo de biblioteca produjo el **Ejemplo 137** en forma de un sólido blanco (11,55 mg). ^{1}H RMN (400 MHz, DMSO-d_6) δ 7,59 - 7,62 (m, 2 H), 7,45 (dd, *J* = 5,7, 8,5 Hz, 1 H), 7,16 (dt, *J* = 2,8, 8,5 Hz, 1 H), 6,76 (s, 1 H), 6,35 (s, 2 H), 6,01-6,05 (m, 1 H), 5,62 (q, *J* = 7,2, 3,6 Hz, 1 H), 5,19 (dd, *J* = 1,2, 10,4 Hz, 1 H), 5,13 – 5,16 (m, 1 H), 4,98 – 4,99 (m, 1 H), 4,84 (dd, *J* = 2,2, 18 Hz, 1 H), 4,53 (d, *J* = 14,4 Hz, 1 H), 4,17 (d, *J* = 14,7 Hz, 1 H), 3,00 (s, 3 H), 1,67 (d, *J* = 6,1 Hz, 3 H). LCMS APCI *m/z* 409 $[M+H]^+$.

EJEMPLOS BIOLÓGICOS

Ensayos de la enzima ALK de tipo salvaje y de mutante L1196M de ALK

Se midió la inhibición de la enzima ALK de tipo salvaje y mutante L1196M de ALK mediante un ensayo de desplazamiento de movilidad de microfluidos. Las reacciones se llevaron a cabo en volúmenes de 50 µL en placas de 96 cavidades, y contenían dominio de quinasa ALK de tipo salvaje recombinante humana preactivada (1,3 nM) o ALK L1196M (0,5 nM) (aminoácidos 1093-1411), péptido fosfoaceptor 1,5 µM, 5 'FAM-KKSRGDYMTMQIG-CONH2 (CPC Scientific, Sunnyvale, CA), compuesto de ensayo (diluciones seriadas de 11 dosis 3 veces, 2% final de DMSO) o DMSO solo, 1 mM de DTT, 0,002% de Tween-20 y 5 mM de $MgCl_2$ en Hepes 25 mM, pH 7,1, y se iniciaron mediante la adición de ATP (concentración final 60 µM ~ nivel Km) después de una preincubación de 20 min. Las reacciones se incubaron durante 1 h a temperatura ambiente, se detuvieron mediante la adición de EDTA 0,1 M, pH 8, y se determinó la amplitud de las reacciones (una conversión de aproximadamente 15-20% sin inhibidor) después de la separación electroforética del sustrato péptido marcado con fluorescencia y producto fosforilado en una lectora LabChip EZ Reader II (Caliper Life Sciences, Hopkinton, MA). Los inhibidores mostraron ser competitivos con ATP a partir de los estudios cinéticos y cristalográficos. Los valores de Ki se calcularon mediante el ajuste del % de conversión con respecto a la ecuación para la inhibición competitiva, para lo cual se utilizó el método de regresión no lineal (GraphPad Prism, GraphPad Software, San Diego, CA) y se midió experimentalmente el ATP K_m = 58 µM para la enzima de tipo salvaje y 55 µM para la enzima L1196M. Las enzimas ALK fueron producidas en fábrica (expresión de baculovirus) y preactivadas por autofosforilación de 16 µM de enzima no activada en presencia de ATP 2 mM, $MgCl_2$ 10 mM y DTT 4 mM en 20 mM de Hepes, pH 7,5, a temperatura ambiente durante ~1 h, y se verificó la fosforilación total (~4 fosfatos por molécula de proteína) del dominio de ALK quinasa por espectrometría de masas Q-TOF.

Ensayo de ELISA fosfo-ALK (Tyr1604) celular para EML4-ALK:

Líneas celulares:

Las células NIH-3T3-ALK EML4 wt v1 y NIH-3T3 EML4-ALK v1 L1196M eran líneas celulares humanas estables en Pfizer - La Jolla, CA. Las células se mantuvieron a 37 ºC en una incubadora de CO_2 al 5% en medio DMEM (Invitrogen, Carlsbad, CA) enriquecido con L-glutamina al 1%, penicilina al 1% y estreptomicina, puromicina 1 ug/ml y suero de ternero recién nacido (NCS) al 10% en recipientes T-75.

Ensayo:

Las células se lavaron con PBS y se resuspendieron en medio DMEM enriquecido con NCS al 0,5% y penicilina al 1%/estreptomicina y se sembraron en placas de 96 cavidades con una densidad de 20.000 células/cavidad/100 µl y se incubaron en la incubadora a 37 ºC y en 5% de CO_2. Después de 20 horas de incubación, se añadieron 100 µl de medio de ensayo (DMEM) en presencia de concentraciones de compuestos PF designados o controles (DMSO) a las placas y se incubaron durante 1 hora en la incubadora. Seguidamente se retiró el medio y se añadió tampón de lisis, que contenía inhibidores de fosfato y fluoruro de fenilmetansulfonilo (PMSF), a las cavidades y se agitó a 4 ℃ durante 30 minutos para generar lisatos de proteína. Posteriormente, se utilizó un kit ELISA de sándwich quimioluminiscente PathScan fosfo - ALK (Tyr1604) (Cell Signal Technology Inc., cat N.° 7020) para evaluar la fosforilación de ALK como se indica a continuación:

Se aplicó un recubrimiento de anticuerpo de conejo fosfo-ALK (Tyr1604) sobre las microplacas de 96 cavidades. Se añadieron 50 µl de lisatos de células a la placa recubierta con anticuerpo y se incubó a temperatura ambiente durante 2 horas. Después de un exhaustivo lavado con Tween 20 al 0,1% en PBS para eliminar los materiales no unidos, se añadió ALK mAb de ratón para detectar las proteínas de fusión fosfo-ALK (Tyr1604) y fosfo-ALK capturadas. Luego se utilizó anticuerpo IgG antirratón, unido a HRP, para reconocer el anticuerpo de detección unido. Por último, se añadió el reactivo quimioluminiscente y se incubó durante 10 minutos para el desarrollo de la señal. Las placas de ensayo se leyeron en la lectora de placas Envision en el modo luminiscente. Los valores de IC_{50} se calcularon mediante un ajuste de la curva de concentración-respuesta para lo cual se utilizó un método analítico de cuatro parámetros.

Los datos de Ki e IC_{50} obtenidos con los ensayos enzimáticos ALK 1 y 2 y del ensayo ELISA celular de fosfo-ALK (Tyr1604) para WT EML4-ALK y L1196M EML4-

ALK, descritos anteriormente, se muestran en la siguiente tabla. En dicha tabla, los compuestos que no tienen datos indican que tales compuestos no se evaluaron con los ensayos enumerados en la Tabla 1.

Tabla 1

Ejemplo	Ensayo de la enzima WT ALK (Ki)	Ensayo de la enzima L1196M ALK (Ki)	Ensayo de ELISA para WT EML4-ALK (IC_{50})	Ensayo de ELISA para L1196M EML4-ALK (IC_{50})
1	<0,200 nM	0,26 nM	1,39 nM	22,8 nM
2	<0,200 nM	0,78 nM	1,33 nM	20,7 nM
3	<0,200 nM	0,20 nM	0,99 nM	22,2 nM
4	<0,200 nM	1,20 nM	28,1 nM	184 nM
5	0,340 nM	3,40 nM	12,1 nM	156 nM
6	<0,200 nM	1,93 nM	6,41 nM	97,1 nM
7	NA	14,0 nM	155 nM	2,68 µM
8	0,90 nM	10,0 nM	12,1 nM	0,68 µM
9	0,20 nM	1,06 nM	0,35 nM	9,29 nM
10	13,0 nM	34,0 nM		
11	<0,200 nM	1,10 nM	1,21 nM	27,7 nM
12	10,0 nM	29,0 nM	34,9 nM	0,70 µM
13	<0,200 nM	0,29 nM	0,70 nM	13,9 nM
14	17,0 nM	61,2 nM		
15	<0,200 nM	2,50 nM		
16	213 nM	>2,27 µM		
17	<0,200 nM	<0,100 nM	0,30 nM	4,25 nM
18	5,20 nM	24,0 nM		
19	<0,200 nM	0,90 nM	4,89 nM	110 nM
20	34,0 nM	450 nM		
21	<0,200 nM	<0,100 nM	0,18 nM	2,13 nM
22	12,0 nM	17,0 nM	192 nM	305 nM
23	<0,200 nM	0,29 nM	0,77 nM	10,1 nM
24	4,60 nM	14,0 nM		
25	<0,200 nM	0,56 nM	1,35 nM	21,9 nM
26	3,30 nM	15,0 nM	50,5 nM	0,511 µM
27	0,380 nM	5,30 nM	9,15 nM	157 nM
28	<0,200 nM	0,11 nM	<0,205 nM	1,40 nM
29	19,0 nM	31,0 nM		
30	<0,200 nM	0,67 nM	2,64 nM	67,2 nM
31	5,96 nM	15,8 nM	53,2 nM	0,66 µM
32	<0,200 nM	<0,100 nM	0,841 nM	5,36 nM
33	1,01 µM	>2,68 µM		
34	0,56 nM	15,0 nM	36,1 nM	0,89 µM
35	<0,261 nM	1,10 nM	0,98 nM	14,3 nM
36	<0,200 nM	0,560 nM	0,18 nM	2,64 nM
37	3,80 nM	29,0 nM	86,0 nM	0,654 µM
38	0,610 nM	5,70 nM	12,0 nM	201 nM
39	0,220 nM	<0,100 nM	14,9 nM	112 nM
40	0,360 nM	1,60 nM	21,8 nM	101 nM

Ejemplo	Ensayo de la enzima WT ALK (Ki)	Ensayo de la enzima L1196M ALK (Ki)	Ensayo de ELISA para WT EML4-ALK (IC_{50})	Ensayo de ELISA para L1196M EML4-ALK (IC_{50})
41	1,50 nM	19,0 nM	33,1 nM	0,68 µM
42	500 nM	2,89 nM		
43	5,23 nM	35,6 nM	0,52 µM	3,66 µM
44	12,0 nM	70,0 nM		
45	> 3,0 µM	500 nM		
46	0,15 nM	1,10 nM	10,42 nM	44,70 nM
47	0,29 nM	3,60 nM	16,41 nM	208,0 nM
48	0, 2 nM	1,20 nM	6,75 nM	68,9 nM
49	0,17 nM	1,50 nM	4,08 nM	80,8 nM
50	0,14 nM	1,2 nM	2,37 nM	29,7 nM
51	0,13 nM	0,28 nM	0,95 nM	6,25 nM
52	1,20 nM	10,2 nM	4,78 nM	296,4 nM
53	25,8 nM	164,0 nM		
54	< 0,07 nM	0,06 nM	0,332 nM	3,03 nM
55	< 0,07 nM	0,24 nM	1,03 nM	13,38 nM
56	0,2 nM	0,88 nM	1,83 nM	35,03 nM
57	0,14 nM	2,0 nM	6,79 nM	0,365 µM
58	< 0,1 nM	< 0,1 nM	0,33 nM	2,06 nM
59		14,4 nM	12,98 nM	155,93 nM
60	4,6 nM	21,5 nM		
61	0,15 nM	0,17 nM	4,82 nM	17,07 nM
62	137 nM	253,0 nM	7,605 µM	> 10 µM
63	0,12 nM	0,13 nM	1,95 nM	8,70 nM
64	34,4 nM	33,3 nM	0,407 µM	1,19 µM
65	0,88 nM	9,8 nM	9,36 nM	0,313 µM
66	19,3 nM	122,0 nM		
67	411 nM	> 1,5 µM		
68	207 nM	> 1,5 µM		
69	> 3,0 µM	> 3,0 µM		
70	< 0,16 nM	0,96 nM	6,52 nM	78,54 nM
71	< 0,249 nM	3,73 nM	10,16 nM	169,09 nM
72	5,1 nM	28,0 nM	0,347 µM	4,266 µM
73	0,33 nM	2,4 nM	12,75 nM	0,169 µM
74	0,30 nM	0,86 nM	11,41 nM	51,93 nM
75	0,065 nM	0,095 nM	0,902 nM	7,06 nM
76	3,1 nM	1,9 nM	95,65 nM	108,89 nM
77	75,0 nM	45,8 nM	3,39 µM	3,32 µM
78	2,93 nM	9,61 nM	40,83 nM	0,350 µM
79	1,18 nM	2,9 nM	42,79 nM	179,84 nM
80	> 3,0 µM	> 3,0 µM		
81	< 1,88 nM	3,9 nM	2,25 nM	51,98 nM
82	< 0, 2 nM	2,39 nM	11,15 nM	182,59 nM
83	47,6 nM	74 nM		
84	29,3 nM	90,2 nM		
85	0,070 nM	0,13 nM	0,55 nM	6,72 nM
86	< 0,2 nM	0,10 nM	0,45 nM	2,57 nM

Ejemplo	Ensayo de la enzima WT ALK (Ki)	Ensayo de la enzima L1196M ALK (Ki)	Ensayo de ELISA para WT EML4-ALK (IC_{50})	Ensayo de ELISA para L1196M EML4-ALK (IC_{50})
87	270,0 nM	51,0 nM		
88	0,2 nM	0,39 nM	15,51 nM	190,94 nM
89	0,339 nM	0,275 nM	6,43 nM	56,05 nM
90	0,079 nM	0,249 nM	1,32 nM	13,00 nM
91	0,177 nM	0,315 nM	0,68 nM	5,88 nM
92	0,23 nM	0,21 nM	0,47 nM	3,66 nM
93	0,048 nM	0,3 nM	3,23 nM	31,67 nM
94	0,93 µM	0,698 µM		
95	0,35 nM	1,9 nM	10,37 nM	169,25 nM
97	3,50 nM	24,7 nM		
98	0,115 nM	0,404 nM	2,21 nM	32,28 nM
99	3,2 nM	11,7 nM	52,38 nM	0,531 µM
100	3,1 nM	24,2 nM	146,29 nM	1,48 µM
101	0,12 nM	0,41 nM	0,92 nM	8,77 nM
102	0,33 nM	1,41 nM	11,62 nM	83,82 nM
103	9,1 nM	131,0 nM		
104	8,4 nM	57,5 nM		
105	3,0 nM	16,7 nM	115,04 nM	0,642 µM
106	> 3 µM	> 3 µM		
107	88,5 nM	179,0 nM		
108	< 0,06 nM	< 0,05 nM	0,068 nM	0,50 nM
109	8,1 nM	4,7 nM	11,029 nM	55,56 nM
110	0,56 nM	7,3 nM	9,99 nM	0,447 µM
111	0,059 nM	0,54 nM	1,42 nM	32,49 nM
112	0,32 nM	3,4 nM	9,67 nM	247,76 nM
113	0,20 nM	0,46 nM	0,68 nM	9,56 nM
114	0,271 nM	1,36 nM	3,29 nM	78,24 nM
115	< 0,08 nM	0,09 nM	0,96 nM	8,18 nM
116	> 1,5 µM	> 3 µM	> 10 µM	> 10 µM
117	2,18 nM	17,8 nM	35,22 nM	393,0 nM
118	17,8 nM	64,7 nM	217,23 nM	1,402 µM
119	1,6 nM	13,4 nM	7,79 nM	264,0 nM
120	146,0 nM	0,821 µM	2,11 µM	> 10 µM
121	132,0 nM	273,0 nM		
122	0,27 nM	0,70 nM	9,27 nM	52,31 nM
123	205,0 nM	333,0 nM	4,79 µM	> 10 µM
124	2,10 nM	7,4 nM	56,17 nM	0,873 µM
125	0,11 nM	0,49 nM	2,30 nM	49,08 nM
126	0,54 µM	1,07 µM		
127	0,099 nM	0,52 nM	2,50 nM	64,97 nM
128	138,0 nM	386,0 nM		
129	353,0 nM	> 1,5 µM		
130	> 3 µM	> 3 µM		
131	78,3 nM	0,794 µM		
132	3,32 nM	16,52 nM	35,27 nM	0,892 µM
133	3,06 nM	32,75 nM	95,77 nM	0,997 µM

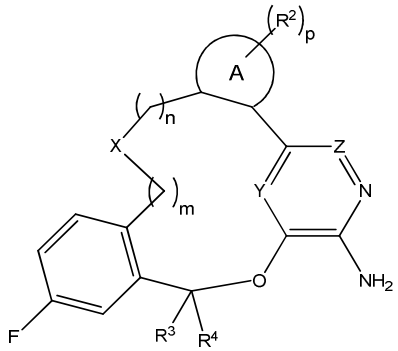
Ejemplo	Ensayo de la enzima WT ALK (Ki)	Ensayo de la enzima L1196M ALK (Ki)	Ensayo de ELISA para WT EML4-ALK (IC_{50})	Ensayo de ELISA para L1196M EML4-ALK (IC_{50})
134	3,0 nM	20,5 nM		
135	2,1 nM	12,6 nM	45,89 nM	0,814 µM
136	0,6 nM	4,8 nM	28,47 nM	0,419 µM
137	6,1 nM	72,4 nM		2,28 µM

Todas las publicaciones y solicitudes de patente citadas en la memoria descriptiva se incorporan en la presente por referencia como si cada publicación o solicitud de patente individual se indicaran específica e individualmente como incorporadas por referencia. A pesar de que la anterior invención se describió con cierto detalle a modo de ilustración y ejemplo, los expertos en la técnica descubrirán fácilmente, a la luz de las enseñanzas de esta invención, que se pueden hacer ciertos cambios y modificaciones en ella sin apartarse del espíritu o el alcance de las reivindicaciones anexas.

REIVINDICACIONES

Reivindicamos:

1. Un compuesto de la fórmula (I)



(I)

en donde:

X está seleccionado del grupo que consiste en $-(CR^5R^6)_qO(CR^5R^6)_r-$, $-(CR^5R^6)_qN(R^1)(CR^5R^6)_r-$, $-(CR^5R^6)_qC(O)N(R^1)(CR^5R^6)_r-$ y $-(CR^5R^6)_qN(R^1)C(O)(CR^5R^6)_r-$;

Y y Z son cada uno, de modo independiente, N o CH, siempre que, cuando Y es N, Z sea CH y cuando Z es N, Y sea CH;

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo

C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico

de 3-12 miembros, y heteroarilo de 5-6 miembros;

m es 0, 1, 2 o 3;

n es 0, 1, 2 o 3;

p es 0, 1, 2, 3 o 4;

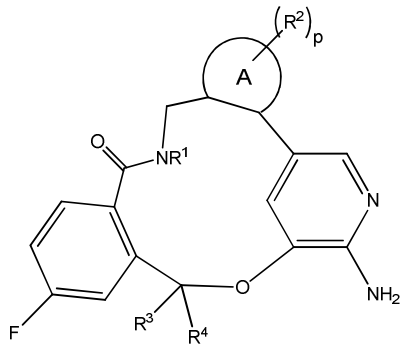
cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

2. Un compuesto de la fórmula (V)



(V)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, --$C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)N$

R^7R^8, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo

C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

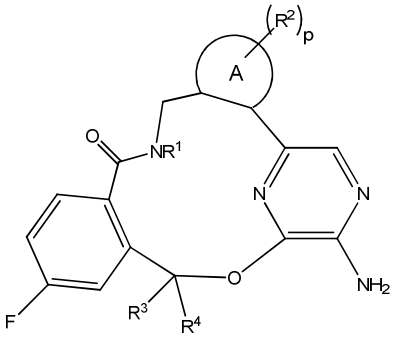
cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

3. Un compuesto de la fórmula (VI)



(VI)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, --$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo

C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 y R^4 están seleccionados cada uno, de modo independiente, de hidrógeno, alquilo C_1-C_6 y cicloalquilo C_3-C_6, en donde cada hidrógeno en alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico

de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

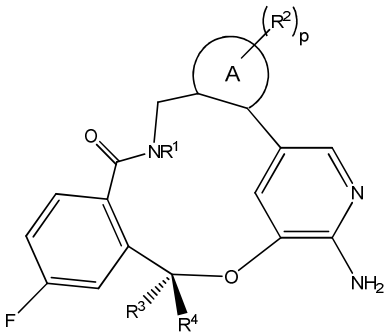
4. El compuesto de acuerdo con la reivindicación 1, 2 o 3, en donde R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6, o una de sus sales farmacéuticamente aceptables.

5. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 4, en donde cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, $-S(O)_rR^7$, $-S(O)_2NR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$, o una de sus sales farmacéuticamente aceptables.

6. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, en donde A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol, o una de sus sales farmacéuticamente aceptables.

7, El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde R^3 y R^4 están seleccionados cada uno, de modo independiente, del grupo que consiste de hidrógeno y alquilo C_1-C_6, o una de sus sales farmacéuticamente aceptables.

8. Un compuesto de la fórmula (XV)



(XV)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, --$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -$S(O)_tR^7$, -$S(O)_2NR^7R^8$, -$S(O)_2OR^7$, -NO_2, -$(CR^5R^6)_qNR^7R^8$, -$N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, -$OR^7$, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, -$C(O)R^7$, -$OC(O)R^7$, -$O(CR^5R^6)_qR^7$, -$NR^7C(O)R^8$, -$(CR^5R^6)_qC(O)OR^7$, -$(CR^5R^6)_qNR^7R^8$, -$C(=NR^7)NR^7R^8$, -$NR^7C(O)NR^7R^8$, -$NR^7S(O)_2R^8$ y -$(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en dicho alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)$

R^{10}, -C(O)OR^9, -C(=NR^9)NR^9R^{10}, -NR^9C(O)NR^9R^{10}, -$NR^9S(O)_2R^{10}$ y -C(O)NR^9R^{10}; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -C(O)R^9, -OC(O)R^9, -NR^9C(O)R^{10}, -C(O)OR^9, -C(=NR^9)NR^9R^{10}, -NR^9C(O)NR^9R^{10}, -$NR^9S(O)_2R^{10}$ o -C(O)NR^9R^{10};

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -C(O)R^9, -OC(O)R^9, -NR^9C(O)R^{10}, -C(O)OR^9, -C(=NR^9)NR^9R^{10}, -NR^9C(O)NR^9R^{10}, -$NR^9S(O)_2R^{10}$ o -C(O)NR^9R^{10};

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

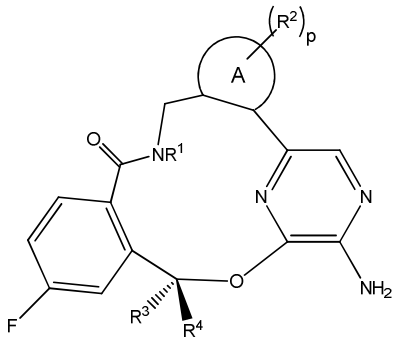
cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

9. Un compuesto de la fórmula (XVI)



(XVI)

en donde:

A es un anillo seleccionado de arilo C_6-C_{12} y heteroarilo de 5-6 miembros;

R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, --$C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^2 está seleccionado, de modo independiente, del grupo que consiste en halógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, $-S(O)_tR^7$, $-S(O)_2NR^7R^8$, $-S(O)_2OR^7$, $-NO_2$, $-(CR^5R^6)_qNR^7R^8$, $-N(CR^5R^6)(CR^5R^6)_qNR^7R^8$, $-OR^7$, $-O(CR^5R^6)(CR^5R^6)_qOR^7$, $-O(CR^5R^6)(CR^5R^6)_qR^7$, -CN, $-C(O)R^7$, $-OC(O)R^7$, $-O(CR^5R^6)_qR^7$, $-NR^7C(O)R^8$, $-(CR^5R^6)_qC(O)OR^7$, $-(CR^5R^6)_qNR^7R^8$, $-C(=NR^7)NR^7R^8$, $-NR^7C(O)NR^7R^8$, $-NR^7S(O)_2R^8$ y $-(CR^5R^6)_qC(O)NR^7R^8$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, $-OR^9$, -CN, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

R^3 es alquilo C_1-C_6 o cicloalquilo C_3-C_6 y R^4 es hidrógeno, en donde cada hidrógeno en dicho alquilo C_1-C_6 o cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ o $-C(O)NR^9R^{10}$;

cada R^5 y R^6 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, heteroarilo de 5-6 miembros, -OH, $-NH_2$, $-S(O)_tR^9$, $-S(O)_2NR^9R^{10}$, $-S(O)_2OR^9$, $-NO_2$, -CN, $-OR^9$, $-C(O)R^9$, $-OC(O)R^9$, $-NR^9C(O)R^{10}$, $-C(O)OR^9$, $-C(=NR^9)NR^9R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$ y $-C(O)NR^9R^{10}$; en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6,

cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -CN, -OR^9, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^7 y R^8 está seleccionado, de modo independiente, del grupo que consiste en hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros, en donde cada hidrógeno en dicho alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros y heteroarilo de 5-6 miembros puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ o -$C(O)NR^9R^{10}$;

cada R^9 y R^{10} está seleccionado, de modo independiente, de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_6, arilo C_6-C_{12}, heteroalicíclico de 3-12 miembros, y heteroarilo de 5-6 miembros;

p es 0, 1, 2, 3 o 4;

cada q es, de modo independiente, 0, 1, 2 o 3;

cada r es, de modo independiente, 0, 1, 2 o 3; y

cada t es, de modo independiente, 0, 1 o 2;

o una de sus sales farmacéuticamente aceptables.

10. El compuesto de acuerdo con la reivindicación 7, 8 o 9, en donde R^1 está seleccionado del grupo que consiste en hidrógeno, alquilo C_1-C_6, y cicloalquilo C_3-C_6, o una de sus sales farmacéuticamente aceptables.

11. El compuesto de acuerdo con cualquiera de las reivindicaciones 7 a 10, en donde cada R^2 está seleccionado, de modo independiente, del grupo que consiste en alquilo C_1-C_6, cicloalquilo C_3-C_6, -$S(O)_rR^7$, -$S(O)_2NR^7R^8$, -OR^7, -$O(CR^5R^6)(CR^5R^6)_qOR^7$, -$O(CR^5R^6)(CR^5R^6)_qR^7$ y -CN; en donde cada hidrógeno en dicho alquilo C_1-C_6 y cicloalquilo C_3-C_6 puede estar opcionalmente sustituido, de modo independiente, con halógeno, -OH, -NH_2, -$S(O)_tR^9$, -$S(O)_2NR^9R^{10}$, -$S(O)_2OR^9$, -NO_2, -OR^9, -CN, -$C(O)R^9$, -$OC(O)R^9$, -$NR^9C(O)R^{10}$, -$C(O)OR^9$, -$C(=NR^9)NR^9R^{10}$, -$NR^9C(O)NR^9R^{10}$, -$NR^9S(O)_2R^{10}$ y -$C(O)NR^9R^{10}$, o una de sus sales farmacéuticamente aceptables.

12. El compuesto de acuerdo con cualquiera de las reivindicaciones 7 a 11, en

donde A es un anillo seleccionado del grupo que consiste en fenilo, piridina, pirimidina, piridazina, pirazina, triazina, pirazol, imidazol, triazol, tetrazol, tiazol, isotiazol, oxazol e isoxazol, o una de sus sales farmacéuticamente aceptables.

13. El compuesto de acuerdo con cualquiera de las reivindicaciones 7 a 12, en donde R^3 es metilo y R^4 es hidrógeno, o una de sus sales farmacéuticamente aceptables.

14. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13, o una de sus sales farmacéuticamente aceptables, y un excipiente o vehículo farmacéuticamente aceptable.

15. Un método para tratar la proliferación celular anormal en un mamífero, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 13, o una de sus sales farmacéuticamente aceptables.

16. El método de acuerdo con la reivindicación 15, en donde la proliferación celular anormal es cáncer.

17. El método de acuerdo con la reivindicación 16, en donde el cáncer es mediado por quinasa de linfoma anaplásico (ALK).

18. El método de acuerdo con la reivindicación 16, en donde el cáncer es mediado por una proteína de fusión EML4-ALK.

19. El método de acuerdo con la reivindicación 16, en donde el cáncer es mediado por una proteína de fusión EML4-ALK que tiene al menos una mutación.

20. El método de acuerdo con la reivindicación 19, en donde dicha mutación es L1196M o C1156Y.

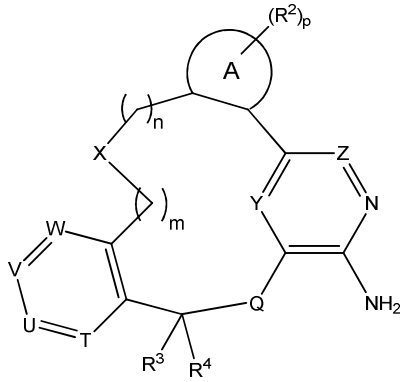
21. El método de acuerdo con cualquiera de las reivindicaciones 16 a 20, en donde el cáncer está seleccionado del grupo que consiste en cáncer pulmonar de células no pequeñas (NSCLC), carcinoma de células escamosas, cáncer de próstata refractario a las hormonas, carcinoma papilar de células renales, adenocarcinoma colorrectal, neuroblastomas, linfoma anaplásico de células grandes (ALCL) y cáncer gástrico.

22. El método de acuerdo con cualquiera de las reivindicaciones 15 a 21, en donde el mamífero es un humano.

23. El método de acuerdo con cualquiera de las reivindicaciones 15 a 21, en donde el mamífero es un perro.

RESUMEN

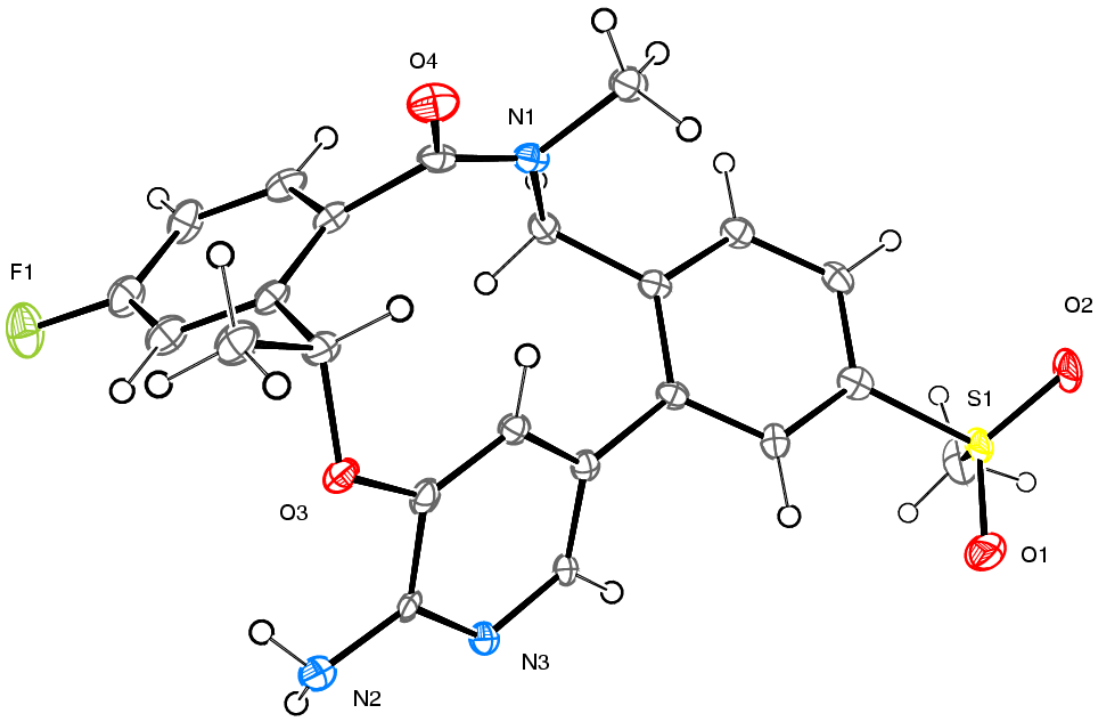
La invención se refiere a compuestos de la fórmula (Φ)



(Φ)

como se define además en la presente y a sus sales farmacéuticamente aceptables, a composiciones farmacéuticas que comprenden dichos compuestos y sales, y a sus usos. Los compuestos y las sales de la presente invención inhiben la quinasa del linfoma anaplásico (ALK) y/o EML4-ALK y son útiles para tratar o mejorar los trastornos proliferativos celulares anormales, tales como cáncer.

Figura 1



SEQUENCE LISTING

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<120> MACROCYCLIC DERIVATIVES FOR THE TREATMENT OF DISEASES

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<151> 2012-03-06

<150> US 61/759,307
<151> 2013-01-31

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