SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-132584- -00000-0000

Fecha: 2014-06-18 16:15:30 Dep. 2020 DIR.NUEVASCR
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 411 PRESENTACION Folios: 8 7

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE DIHIDRO-BENZO-OXAZINA Y DIHIDRO-PIRIDO-OXAZINA

SOLICITANTE: NOVARTIS AG,

DIRECCIÓN: Lichtstrasse 35 CH-4056 Basel, Zuisa.

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 18 de junio de 2014

P2014/000073

OLARTEMOURE

OLART SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Industria y Comercio
SUPERINTENDENCIA

No. 14-132584- -00000-0000

Fecha: 2014-06-18 16:15:30 Dep. 2020 DIR.NUEVASCR
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 411 PRESENTACION Folios: 87

...esivo de radicación.

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

P2014/000073

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) SOLICITANTE (71)

Nombre: NOVARTIS AG
Dirección: Lichtstrasse 35, CH-4056 Basel, Suiza

Nacionalidad o Domicilio: Suiza
Lugar de Constitución: Suiza

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 D.C.
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

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

(5) PCT (86)

Solicitud Internacional No. PCT/IB2012/057554 Fecha Diciembre 20, 2012

Publicación Internacional No. WO2013/093849 Fecha Junio 27, 2013

(6) Título (54) **DERIVADOS DE DIHIDRO-BENZO-OXAZINA Y DIHIDRO-PIRIDO-OXAZINA**

Clasificación Internacional (51) C07 413/14, C07D 498/04, A61K 31/536, A61K 31/5365, A61P 19/02, A61P 37/08, A61P 35/00, A61P 33/06

Prioridad

SI [X] **NO** [ ]

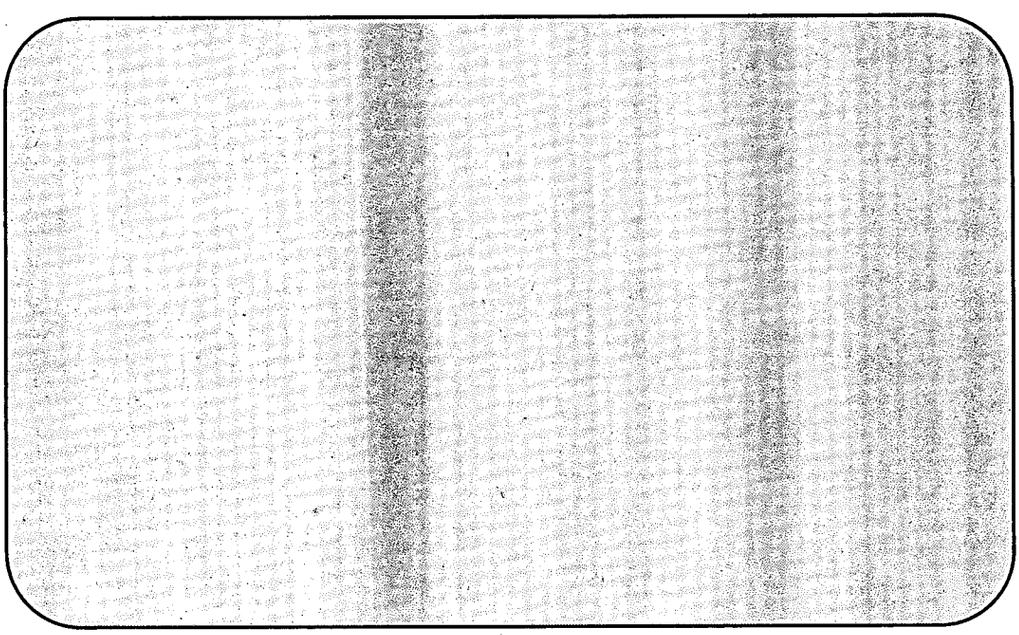
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Diciembre 22, 2011	61/579,231

(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.
- [X] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) FIGURA CARACTERÍSTICA:



(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/IB2012/057554

Giorgio CARAVATTI
Werk Klybeck, Postfach,
CH-4002 Basel
Suiza

Sylvie CHAMOIN
Postfach, CH-4002 Basel
Suiza

Pascal FURET
Werk Klybeck, Postfach,
CH-4002 Basel
Suiza

Klemens HÖGENAUER
Werk Klybeck, Postfach,
CH-4002 Basel
Suiza

Konstanze HURTH
Werk Klybeck, Postfach,
CH-4002 Basel
Suiza

Christoph KALIS
Postfach, CH-4002 Basel
Suiza

Karen KAMMERTOENS
Werk Klybeck, Postfach
CH-4002 Basel
Suiza

Ian LEWIS
Postfach, CH-4002 Basel
Suiza

Henrik MOEBITZ
Werk Klybeck, Postfach,
CH-4002 Basel
Suiza

Alexander, Baxter SMITH
Postfach CH-4002 Basel
Suiza

Nicolas SOLDERMANN
Werk Klybeck, Postfach,
CH-4002 Basel
Suiza

Romain WOLF
Postfach, CH-4002 Basel
Suiza

Frédéric ZECRI
100 Technology Square, Cambridge,
Massachusetts 02139
Estados Unidos de America

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0064910

Bogotá D.C., Junio 18 de 2014 - 15:54:16

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870 RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
RECIBO DE CA	999999999	51664	15/05/2014		21.000.00
RECIBO DE CA	999999999	56270	28/05/2014		128.000.00
RECIBO DE CA	999999999	56271	28/05/2014		128.000.00
RECIBO DE CA	999999999	63957	16/06/2014		520.000.00
RECIBO DE CA	999999999	63958	16/06/2014		520.000.00

*** 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. 14-132584- -00000-0000
Fecha: 2014-06-18 16:15:30 Dep. 2020 DIR.NUEVASCR
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 411 PRESENTACION Folios: 7

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Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: 14 / 6 / 18 (AAAA / MM / DD)	Recorrido:
2020		
Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	*No. Radicación*	*Consecutivo*	*Item*
1	14-132584	0	
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

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

Observaciones:
El CD Anexo Contiene un total de 12 Archivos, 12 en formato pdf, los cuales fueron procesados.

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-132584- -00000-0000
Fecha: 2014-06-18 16:15:30 Dep. 2020 DIR.NUEVASCR
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 411 PRESENTACION Folios: 8

7

PATENTE DE INVENCIÓN ☐ sión 486/00

- ☐ Indicación que se solici
- ☐ 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 **P2014/000073**

SOLICITUD DE:

1

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

[X] Capítulo I. [ ] Capítulo II.

2 **SOLICITANTE (71)**	**Nombre:** NOVARTIS AG **Dirección:** Lichtstrasse 35, CH-4056 Basel, Suiza **Nacionalidad o Domicilio:** Suiza **Lugar de Constitución:** Suiza **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 D.C. **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olartemoure.com	**IDENTIFICACIÓN** **C.C.** [X] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** 79782747Bta **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

5 **PCT (86)**

Solicitud Internacional No. PCT/IB2012/057554 Fecha Diciembre 20, 2012

Publicación Internacional No. WO2013/093849 Fecha Junio 27, 2013

6 **Título (54)** **DERIVADOS DE DIHIDRO-BENZO-OXAZINA Y DIHIDRO-PIRIDO-OXAZINA**

Clasificación Internacional (51) C07 413/14, C07D 498/04, A61K 31/536, A61K 31/5365, A61P 19/02, A61P 37/08, A61P 35/00, A61P 33/06

Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] **NO** [ ]	US	Diciembre 22, 2011	61/579,231

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

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.
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 4.17 (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.
x	De ser el caso, modificaciones efectuadas a la solicitud internacional.
x	Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA: _____

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/IB2012/057554

Giorgio CARAVATTI
Werk Klybeck, Postfach,
CH-4002 Basel
Suiza

Sylvie CHAMOIN
Postfach, CH-4002 Basel
Suiza

Pascal FURET
Werk Klybeck, Postfach,
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Klemens HÖGENAUER
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CH-4002 Basel
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Konstanze HURTH
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Alexander, Baxter SMITH
Postfach CH-4002 Basel
Suiza

Nicolas SOLDERMANN
Werk Klybeck, Postfach,
CH-4002 Basel
Suiza

Romain WOLF
Postfach, CH-4002 Basel
Suiza

Frédéric ZECRI
100 Technology Square, Cambridge,
Massachusetts 02139
Estados Unidos de America

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

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

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.

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

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

E-mail: treseser1@yahoo.com. No. 8346

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

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

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

Zayde Chahin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahin
Graciela Melo

Power of Attorney

The undersigned,

domiciled in

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

NOVARTIS AG

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Hilbert Camonica

Pascal Hauck

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Attestation

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

Leg.Prot.Nr. 915 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by .....
   .....
3. in his/her function as .....
4. and certified by the seal of the .....
   .....

Certified .. Aug. 2006

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. .....
9. Seal/stamp: 10. Signature:
   .....
   Heidi Fischer

STATE CHANCERY * BASLE-CITY *

PCT

Print Out (Original in Electronic Form)

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 NOVARTIS AG is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from CARAVATTI, Giorgio to Novartis Pharma AG, dated 06 November 2012 (06.11.2012)
VIII-2-1(iv)		an assignment from CHAMOIN, Sylvie to Novartis Pharma AG, dated 03 December 2012 (03.12.2012)
VIII-2-1(iv)		an assignment from FURET, Pascal to Novartis Pharma AG, dated 06 November 2012 (06.11.2012)
VIII-2-1(iv)		an assignment from HÖGENAUER, Klemens to Novartis Pharma AG, dated 19 November 2012 (19.11.2012)
VIII-2-1(iv)		an assignment from HURTH, Konstanze to Novartis Pharma AG, dated 12 November 2012 (12.11.2012)
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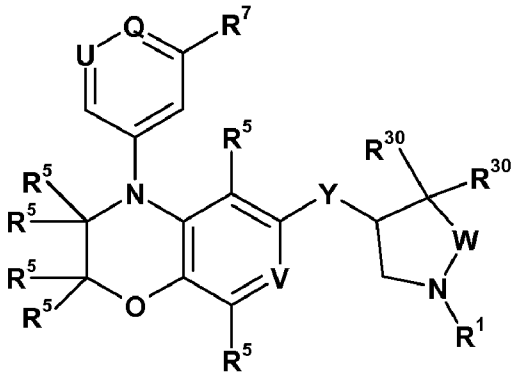
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[Continued on next page]

(54) **Title**: DIHYDRO-BENZO-OXAZINE AND DIHYDRO-PYRIDO-OXAZINE DERIVATIVES



(I)

(57) **Abstract**: The invention relates to dihydro-benzo-oxazine and dihydro-pyrido-oxazine compounds of the formula (I) and/or pharmaceutically acceptable salts and/or solvates thereof, wherein Y, V, W, U, Q, R^1, R^5, R^7 and R^{30} are as defined in the description. Such compounds are suitable for the treatment of a disorder or disease which is mediated by the activity of the PI3K enzymes.

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Dihydro-Benzo-Oxazine and Dihydro-Pyrido-Oxazine Derivatives

FIELD OF THE INVENTION

The invention relates to the preparation and use of new dihydro-benzo-oxazine and dihydro-pyrido-oxazine derivatives as drug candidates in free form or in pharmaceutically acceptable salt form with valuable druglike properties, such as e.g. metabolic stability and suitable pharmacokinetics, form for the modulation, notably the inhibition of the activity or function of the phosphoinositide 3' OH kinase family (hereinafter PI3K).

BACKGROUND OF THE INVENTION

Members of the phosphoinositide-3 kinase (PI3K) family are involved in cell growth, differentiation, survival, cytoskeletal remodeling and the trafficking of intracellular organelles in many different types of cells (Okkenhaug and Wymann, Nature Rev. Immunol. 3:317 (2003).

To date, eight mammalian PI3Ks have been identified, divided into three main classes (I, II and III) on the basis of their genetic sequence, structure, adapter molecules, expression, mode of activation, and prefered substrate.

PI3Kδ is a lipid kinase belonging to the class I PI3K family (PI3K α, β, γ and δ) that generates second messenger signals downstream of tyrosine kinase-linked receptors. PI3Kδ is a heterodimer composed of an adaptor protein and a p110δ catalytic subunit which converts phosphatidylinositol-4,5-bis-phosphate (PtdInsP2) to phosphatidylinositol-3,4,5-tri-phosphate (PtdInsP3). Effector proteins interact with PtdInsP3 and trigger specific signaling pathways involved in cell activation, differentiation, migration, and cell survival.

Expression of the p110δ and p110γ catalytic subunits is preferential to leukocytes. Expression is also observed in smooth muscle cells, myocytes and endothelial cells. In contrast, p110α and p110β are expressed by all cell types (Marone et al. Biochimica et Biophysica Acta 1784:159 (2008)).

PI3Kδ is associated with B cell development and function (Okkenhaug et al. Science 297:1031 (2002)).

B cells play also a critical role in the pathogenesis of a number of autoimmune and allergic diseases as well as in the process of transplant rejection (Martin and Chan, Annu. Rev. Immunol. 24:467 (2006)).

Chemotaxis is involved in many autoimmune or inflammatory diseases, in angiogenesis, invasion/metastasis, neurodegeneration or woud healing (Gerard et al. Nat. Immunol. 2:108 (2001)). Temporarily distinct events in leukocyte migration in response to chemokines are fully dependent on PI3Kδ and PI3Kγ (Liu et al. Blood 110:1191 (2007)).

PI3Kα and PI3Kβ play an essential role in maintaining homeostasis and pharmacological inhibition of these molecular targets has been associated with cancer therapy (Maira et al. Expert Opin. Ther. Targets 12:223 (2008)).
PI3Kα is involved in insulin signaling and cellular growth pathways (Foukas et al. Nature 441:366 (2006)). PI3Kδ isoform-selective inhibition is expected to avoid potential side effects such as hyperglycemia, and metabolic or growth disregulation.

Parasitic infections still represent one of the most important causes of morbidity and mortality worldwide. Among the parasites that cause human and animal pathology the phylum apicomplexa comprises a group of vector-borne parasites that is responsible for a wide variety of serious illnesses including but not limited to malaria, leishmaniasis and trypanosomiasis. Malaria alone infects 5-10% of humanity and causes around two milion deaths per year. *[Schofield et al, "Immunological processes in malaria pathogenesis", Nat Rev Imm 2005], [Schofiled L, "Intravascular infiltrates and organ-specific inflammation in malaria pathogenesis], [Mishra et al, "TLRs in CNS Parasitic infections", Curr Top Micro Imm 2009],[Bottieau et al, "Therapy of vector-borne protozoan infections in nonendemic settings", Expert Rev. Anti infect. Ther., 2011].*

Toll-like receptors (TLRs) are germ-line encoded, phylogenetically ancient molecules that recognize evolutionary conserved structural relevant molecules (known as pathogen – associated molecular patterns (PAMPs)) within microbial pathogens. Various different cell types including cells of the immune system express TLRs and are thereby able to detect the presence of PAMPs. Sofar 10 functional TLR family members (TLR1-10) have been described in humans, all of which recognize specific PAMP molecules. Following recognition of these specific PAMPs TLRs induce and orchestrate the immuneresponse of the host to infections with bacteria, viruses, fungi and parasites. *[Hedayat et al, "Targeting of TLRs: a decade of progress in combating infectious disease", review, Lancet Infectious disease 2011], [Kwai et al, "TLRs and their crosstalk with other innate receptors in infection and immunity", review, Immunity May-2011].*
The immune system of the infected host responds to infection with the TLR induced production of pro-inflammatory cytokines mainly of the T-helper 1 type (Th1). While

adequate amounts of these cytokines are benefical and required to clear the infection an overproduction of these mediators is harmful to the host and associated with immune mediated pathology including neuropathology and tissue damage with severe and often fatal consequences. One prominent and highly relevant example of such immune mediated pathology is acute and cerebral malaria (CM) which causes severe clinical symptoms and is often fatal. *[Schofield et al, "Immunological processes in malaria pathogenesis", Nat Rev Imm 2005], [Schofiled L, "Intravascular infiltrates and organ-specific inflammation in malaria pathogenesis], [Mishra et al, "TLRs in CNS Parasitic infections", Curr Top Micro Imm 2009], [Bottieau et al, "Therapy of vector-borne protozoan infections in nonendemic settings", Expert Rev. Anti infect. Ther., 2011] [Hedayat et al, "Targeting of TLRs: a decade of progress in combating infectious disease", review, Lancet Infectious disease 2011].* Despite progress made in treatment and eradication of malaria, the mortality rate that is associated with severe malaria, including CM remains unacceptably high. Strategies directed solely at the eradication of the parasite in the host might therefore not be sufficient to prevent neurological complications and death in all cases of CM. Development of new innovative adjunct therapeutic strategies to efficiently reduce the CM-associated mortality and morbidity that is caused, in part, by host-mediated immunopathology remains therefore an urgent medical need. *[Higgins et al, "Immunopathogenesis of falciparum malaria: implications for adjunctive therapy in the management of severe and cerebral malaria", Expert Rev. Anti Infect. Ther. 2011]*

Recently further evidence has been provided that TLR9 plays a key role in the recognition and response to parasites including but not limited to Plasmodium, Leishmania, Trypanosoma and Toxoplasma *[Gowda et al, "The Nucleosome is the TLR9-specific Immunostimulatory component of plasmodium falciparum that activates DCs", PLoS ONE, June 2011], [Peixoto-Rangel et al, "Candidate gene analysis of ocular toxoplasmosis in Brazil: evidence for a role for TLR9", Mem Inst Oswaldo Cruz 2009], [Pellegrini et al, "The role of TLRs and adoptive immunity in the development of protective or pathological immune response triggered by the Trypanosoma cruzi protozoan", Future Microbiol 2011]* and that interference with the activation of TLRs including TLR9 represents a promising strategy to prevent the deleterious inflammatory responses in severe and cerebral malaria *[Franklin et al, "Therapeutical targeting of nucleic acid-sensing TLRs prevents experimental cerebral malaria", PNAS 2011]*

Malaria is an infectious disease caused by four protozoan parasites: Plasmodium falciparum; Plasmodium vivax; Plasmodium ovale; and Plasmodium malaria. These four parasites are typically transmitted by the bite of an infected female Anopheles mosquito. Malaria is a

problem in many parts of the world and over the last few decades the malaria burden has steadily increased. An estimated 1-3 million people die every year from malaria – mostly children under the age of 5. This increase in malaria mortality is due in part to the fact that Plasmodium falciparum, the deadliest malaria parasite, has acquired resistance against nearly all available antimalarial drugs, with the exception of the artemisinin derivatives.

Leishmaniasis is caused by one or more than 20 varieties of parasitic protozoa that belong to the genus Leishmania, and is transmitted by the bite of female sand flies. Leishmaniasis is endemic in about 88 countries, including many tropical and sub-tropical areas. There are four main forms of Leishmaniasis. Visceral leishmaniasis, also called kala-azar, is the most serious form and is caused by the parasite Leishmania donovani. Patients who develop visceral leishmaniasis can die within months unless they receive treatment. The two main therapies for visceral leishmaniasis are the antimony derivatives sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantim®). Sodium stibogluconate has been used for about 70 years and resistance to this drug is a growing problem. In addition, the treatment is relatively long and painful, and can cause undesirable side effects.

Human African Trypanosomiasis, also known as sleeping sickness, is a vector-borne parasitic disease. The parasites concerned are protozoa belonging to the Trypanosoma Genus. They are transmitted to humans by tsetse fly (Glossina Genus) bites which have acquired their infection from human beings or from animals harboring the human pathogenic parasites.

Chagas disease (also called American Trypanosomiasis) is another human parasitic disease that is endemic amongst poor populations on the American continent. The disease is caused by the protozoan parasite Trypanosoma cruzi, which is transmitted to humans by blood-sucking insects. The human disease occurs in two stages: the acute stage, which occurs shortly after infection and the chronic stage, which can develop over many years. Chronic infections result in various neurological disorders, including dementia, damage to the heart muscle and sometimes dilation of the digestive tract, as well as weight loss. Untreated, the chronic disease is often fatal. The drugs currently available for treating Chagas disease are Nifurtimox and benznidazole. However, problems with these current therapies include their diverse side effects, the length of treatment, and the requirement for medical supervision during treatment. Furthermore, treatment is really only effective when given during the acute stage of the disease. Resistance to the two frontline drugs has already occurred. The antifungal agent Amphotericin b has been proposed as a second-line drug, but this drug is costly and relatively toxic.

Toxoplasmosis is endemic through most of the world, which can infect a large proportion of the adult population.1,2 However, its prevalence differs in different countries.3 It is estimated to infect at least 10% of adults in northern temperate countries and more than half of adults in Mediterranean and tropical contries.4 Toxoplasma gondii is a ubiquitous, obligate intracellular protozoan and is considered to be the most common cause of infective retinitis in humans, which depends on a variety of factors, including climate, hygiene, and dietary habits.5–7 The course of disease in immunocompetent adults is usually asymptomatic and self-limiting. As soon as infection has occurred, the parasite forms latent cysts in the retina and in other organs of the body, which can reactivate years after the initial infection giving rise to acute retinochoroiditis and the formation of new retinochoroidal lesions. *[Arevalo et al, "Ocular Toxoplasmosis in the developing world", Internat. Ophthal. Clin 2010]*

Neurocysticercosis is the most common parasitic disease of the CNS (incidence ~2.5 milion worldwide) caused by the larvae of Taenia solium. The disease has a long asymptomatic phase in humans characterized by the absence of a detectable inflammatory response surrounding the parasite. The overall immune response during the asymptomatic phase is of the Th2 phenotype. However, the destruction of larvae by therapeutic treatment or by normal parasite attrition causes a strong inflammatory response, often consisting of a chronic granulomatous reaction and manifestation of typical symptoms of the disease. The immune response in the CNS of symptomatic patients consists of an overt Th1 phenotype or a mixed Th1, Th2, and Th3 response, depending upon the absence or presence of granulomas. The hyperinflammatory response prevailing during the symptomatic phase in the CNS is responsible for the severe neuropathology and mortality associated with neurocysticercosis . *[Mishra et al, "TLRs in CNS Parasitic infections", Curr Top Micro Imm 2009]*

There is a need to provide new PI3K inhibitors that are good drug candidates. In particular, compounds of the invention should bind potently to PI3K whilst showing little affinity for other receptors and show functional activity as inhibitors. They should be well absorbed from the gastrointestinal tract, be metabolically stable and possess favourable pharmacokinetic properties. When targeted against receptors in the central nervous system they should cross the blood brain barrier freely and when targeted selectively against receptors in the peripheral nervous system they should not cross the blood brain barrier. They should be non-toxic and demonstrate few side-effects. Furthermore, the ideal drug candidate will exist in a physical form that is stable, non-hygroscopic and easily formulated.

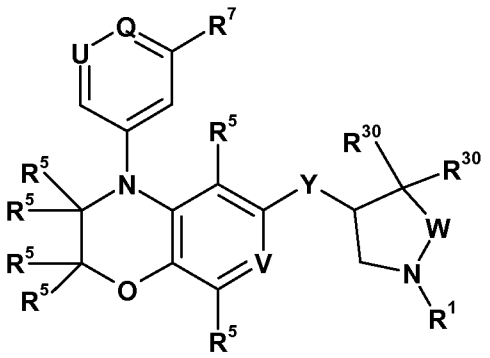
The compounds of the invention show a certain level of selectivity against the different paralogs PI3K α, β, γ and δ. In particular, show a certain level of selectivity for the isoform PI3Kδ.

The compounds of the present invention are therefore potentially useful in the treatment of a wide range of disorders, particularly disorders including but not limited to autoimmune disorders, inflammatory diseases, allergic diseases, disease or infection associated immunopathologies, airway diseases, such as asthma and COPD, transplant rejection, cancers eg of hematopoietic origin or solid tumors.

The invention also relates to the treatment, either alone or in combination, with one or more other pharmacologically active compounds, includes methods of treating conditions, diseases or disorders in which one or more of the functions of B cells such as antibody production, antigen presentation, cytokine production or lymphoid organogenesis are abnormal or are undesirable including rheumatoid arthritis, pemphigus vulgaris and related diseases, idiopathic thrombocytopenia purpura, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, Sjögren‘s syndrome, autoimmune hemolytic anemia, ANCA-associated vasculitides, cryoglobulinemia, thrombotic thrombocytopenic purpura, chronic autoimmune urticaria, allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, AMR (antibody-mediated transplant rejection), B cell-mediated hyperacute, acute and chronic transplant rejection and cancers of haematopoietic origin including but not limited to multiple myeloma; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; non-Hodgkin lymphoma; lymphomas; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Walden stroem disease as well as in disease or infection associated immunopathology.

SUMMARY OF THE INVENTION

The invention relates to dihydro-benzo-oxazine and dihydro-pyrido-oxazine compounds of the formula (I) and/or pharmaceutically acceptable salts and/or solvates thereof,



(I)

wherein

Y is selected from O or NH;

V is selected from CR^5 or N;

W is selected from CH_2, or O;

U is selected from N or CH;

Q is selected from N or CR_6;

wherein U and Q are not both N;

R^1 is selected from phenyl, pyridyl, pyrimininyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl,

or

-X-R^4

wherein X is selected from C(O), $S(O)_2$ or CH_2

and

R^4 is selected from C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, cyano-C_1-C_8-alkyl, N,N-di-C_1-C_4-alkyl-amino-C_1-C_8-alkyl, C_1-C_4-alkyl-sulfonyl-C_1-C_8-alkyl, phenyl, heterocyclyl, heterocyclyl-oxy, heterocyclyl-C_1-C_8-alkyl, C_3-C_{12}-cycloalkyl, C_3-C_{12}-cycloalkyl-oxy, C_3-C_{12}-cycloalkyl-C_1-C_8-alkyl, heteroaryl, heteroaryl-oxy, heteroaryl-C_1-C_8-alkyl, hydroxy, C_1-C_8-alkoxy, amino, N-C_1-C_8-alkyl-amino or N,N-di-C_1-C_8-alkyl-amino,

wherein C_1-C_8-alkyl in N-C_1-C_8-alkyl-amino and in N,N-di-C_1-C_8-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy,

wherein C_3-C_{12}-cycloalkyl in C_3-C_{12}-cycloalkyl and in C_3-C_{12}-cycloalkyl-C_1-C_8-alkyl may be unsubstituted or substituted by by 1-5 substituents selected from halogen, hydroxy or C_1-C_4-alkoxy;

wherein 'heterocyclyl' is a 3 to 7 membered saturated or partially unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, each of which is unsubstituted or substituted by 1-5 substituents selected from oxo, halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states,

wherein 'heteroaryl' is a 3 to 7 membered fully unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, or pyrazolo[1,5-a]pyrimidine or imidazo[2,1-b]thiazole, each of which is unsubstituted or substituted by 1-5 substituents selected from halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;

R^6 is selected from hydrogen, halogen, C_1-C_4-alkyl, halo-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkyl-sulfonyl, C_1-C_4-alkyl-sulfinyl, C_1-C_4-alkyl-sulfanyl, halo-C_1-C_4-alkoxy, C_1-C_4-alkoxy-C_1-C_4-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino;

R^7 is selected from hydrogen, halogen, cyano, nitro, C_1-C_4-alkyl, halo-C_1-C_4-alkyl, C_1-C_4-alkoxy, N(R^8)$_2$-sulfonyl, C_1-C_4-alkyl-sulfonyl, C_1-C_4-alkyl-sulfonyl-amino, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, or N,N-di-C_1-C_8-alkyl-amino;

or R^6 and R^7, together are CH=CH-CH=CH,

wherein R^8 is independently selected from hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or two R^8 together with the nitrogen they are attached to form a 4 to 7 membered heterocyclic ring containing 1-2 heteroatoms selected from N, O, S, which is unsubstituted or substituted by 1-3 substituents selected from C_1-C_4-alkyl;

R^5 is independently selected from H, D, F or C_1-C_2-alkyl;

R^{30} is independently selected from H, D or F.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is the X-ray Powder Diffraction Pattern of Example F1, crystalline anhydrous form

Figure 2 is the differential scanning calorimetry graph of Example Example F1, crystalline anhydrous form

DETAILED DESCRIPTION OF THE INVENTION

Unless specified otherwise, the term “compounds of the present invention” refers to compounds of formula (I) and subformulae thereof, salts of the compound, hydrates or solvates of the compounds and/or salts, as well as all stereoisomers (including diastereoisomers and enantiomers), tautomers and isotopically labeled compounds (including deuterium substitutions). Compounds of the present invention further comprise polymorphs of compounds of formula (I) (or subformulae thereof) and salts thereof. Where compounds of formula (I) are mentioned, this is meant to include also the tautomers and N-oxides of the compounds of formula (I).

The invention may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. As used herein, the terms "including", "containing" and "comprising" are used herein in their open, non-limiting sense.

Tautomers, such as tautomers between keto- and enol form, lactam- and lactim form, amid form and imidic acid form or enamine form and imine form, can be present for example in the R^1 portion of compounds of formula (I). Nitrogen containing heterocyclyl and heteroaryl residues may form N-oxides.

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

As used herein, the term “alkyl” refers to a fully saturated branched, including single or multiple branching, or unbranched hydrocarbon moiety having up to 20 carbon atoms. Unless otherwise provided, alkyl refers to hydrocarbon moieties having 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 7 carbon atoms, or 1 to 4 carbon atoms.

Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl, 3-methylhexyl, 2,2- dimethylpentyl, 2,3-dimethylpentyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like. Typically, alkyl groups have 1-7, more preferably 1-4 carbons.

As used herein, the term "halo-alkyl" refers to an alkyl as defined herein, which is substituted by one or more halo groups as defined herein. The halo-alkyl can be mono-halo-alkyl, di-halo-alkyl or poly-halo-alkyl including per-halo-alkyl. A mono-halo-alkyl can have one iodo, bromo, chloro or fluoro within the alkyl group. Di-halo-alky and poly-halo-alkyl groups can have two or more of the same halo atoms or a combination of different halo groups within the alkyl. Typically the poly-halo-alkyl contains up to 12, or 10, or 8, or 6, or 4, or 3, or 2 halo groups. Non-limiting examples of halo-alkyl include fluoro-methyl, di-fluoro-methyl, tri-fluoro-methyl, chloro-methyl, di-chloro-methyl, tri-chloro-methyl, penta-fluoro-ethyl, hepta-fluoro-propyl, di-fluoro-chloro-methyl, di-chloro-fluoro-methyl, di-fluoro-ethyl, di-fluoro-propyl, di-chloro-ethyl and dichloro-propyl. A per-halo-alkyl refers to an alkyl having all hydrogen atoms replaced with halo atoms.

As used herein, the term "heterocyclyl" or "heterocyclic" refers to a 3 to 7 membered monocyclic or 7 to 10 membered saturated or partially saturated ring or ring system, which contains at least one heteroatom selected from N, O and S, where the N and S can also optionally be oxidized to various oxidation states. 'Heterocyclyl' can be attached at a heteroatom or a carbon atom. 'Heterocyclyl' can include fused or bridged rings as well as spirocyclic rings.
In the context of R^4, examples of heterocycles include oxiranyl, aziridinyl, oxetanyl, thiethanyl, acetitinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, 2,3-dihydrothiophenyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl, thiomorpholinyl, oxathianyl, dioxanyl, piperazinyl, dihydropyranyl, tetrahydropyridinyl, dihydrothiopyranyl, azepanyl, thiepanyl and oxepanyl.
In the context of R^8, examples of heterocycles include pyrrolinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyridinyl and azepanyl.

As used herein, the term "heteroaryl" or "heteroarylic" refers to a 4-, 5-, 6-, or 7-membered monocyclic, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or 10-, 11-, 12-, 13-, 14- or 15-membered tricyclic unsaturated ring or ring system - carrying the highest possible number of conjugated double bonds in the ring(s), which contains at least one heteroatom selected from N, O and S, wherein the N and S can also optionally be oxidized to various oxidation states. 'Heteroaryl' can be attached at a heteroatom or a

carbon atom. 'Heteroaryl' can include fused or bridged rings as well as spirocyclic rings. Examples of heteroaryl include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl and 1,3,5-triazinyl.

As used herein, the term "cycloalkyl" refers to saturated or partially unsaturated monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-12 carbon atoms. Unless otherwise provided, cycloalkyl refers to cyclic hydrocarbon groups having between 3 and 10 ring carbon atoms or between 3 and 7 ring carbon atoms. Exemplary bicyclic hydrocarbon groups include octahydroindyl, decahydronaphthyl. Exemplary tricyclic hydrocarbon bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octy. Exemplary tetracyclic hydrocarbon groups include adamantyl.

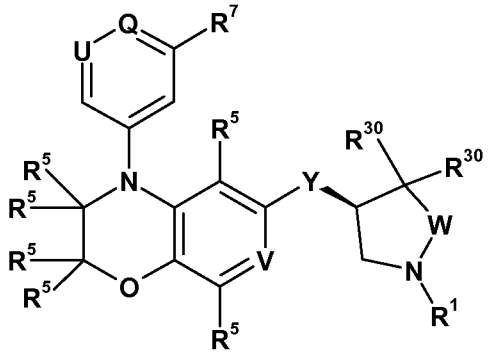
As used herein, the term "oxy" refers to an -O- linking group.

As used herein, the term "carboxy" or "carboxyl" is –COOH.

As used herein, all substituents are written in a way to show the order of functional groups (groups) they are composed of. The functional groups are defined herein above.

Various enumerated embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

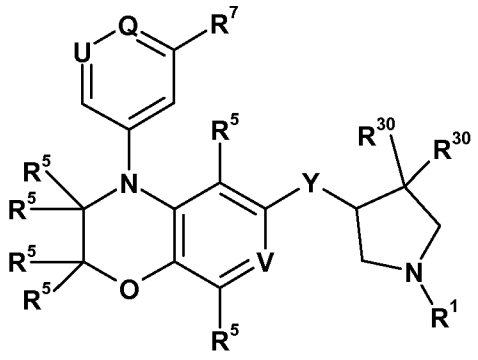
In one embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (I')



(I'),

wherein R^1, R^5, R^7, R^{30}, Y, V, W, U and Q are as defined above.

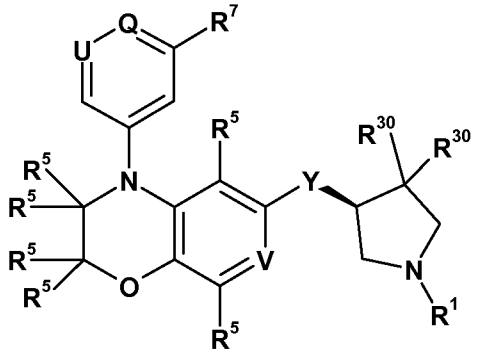
In one embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ia)



(Ia),

wherein R^1, R^5, R^7, R^{30}, Y, V, U and Q are as defined above.

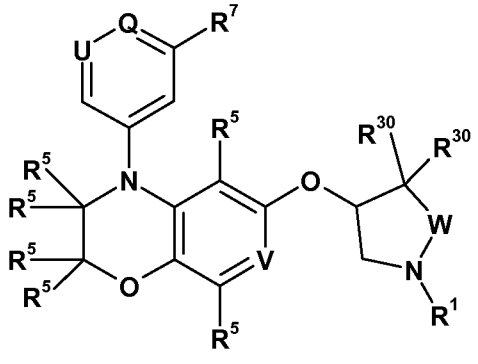
In one embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ia')



(Ia'),

wherein R^1, R^5, R^7, R^{30}, Y, V, U and Q are as defined above.

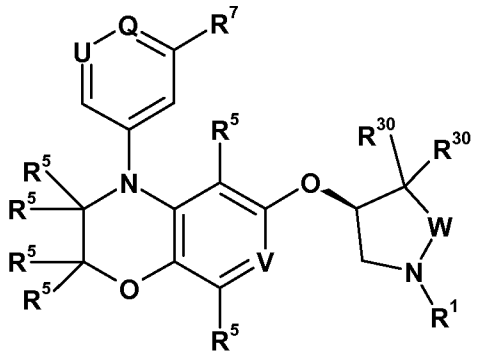
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ib)



(Ib),

wherein R^1, R^5, R^7, R^{30}, V, W, U and Q are as defined above.

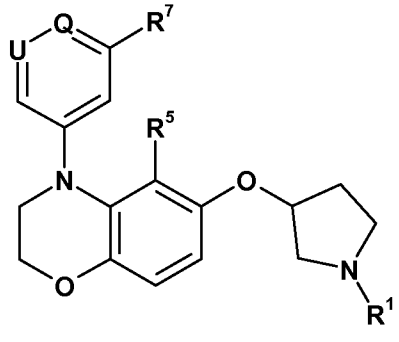
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ib')



(Ib'),

wherein R^1, R^5, R^7, R^{30}, V, W, U and Q are as defined above.

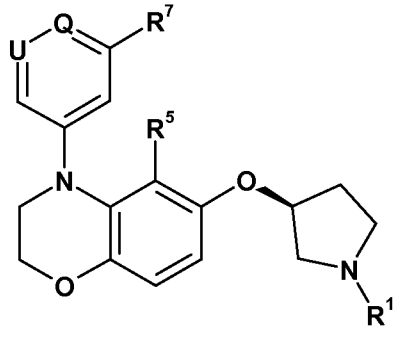
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ic)



(Ic),

wherein R^1, R^5, R^7, U and Q are as defined above.

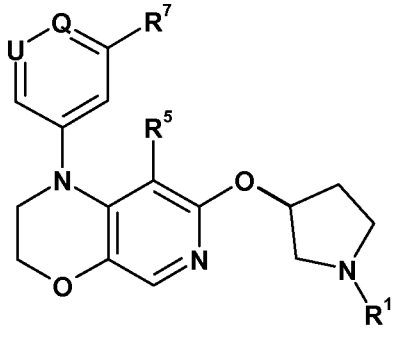
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ic')



(Ic'),

wherein R^1, R^5, R^7, U and Q are as defined above.

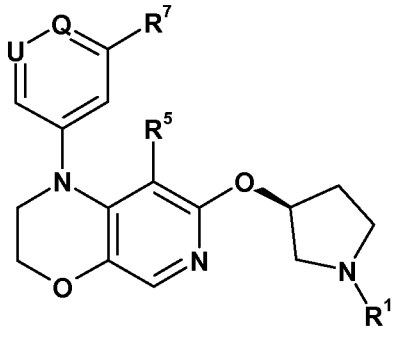
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Id)



(Id),

wherein R^1, R^5, R^7, U and Q are as defined above.

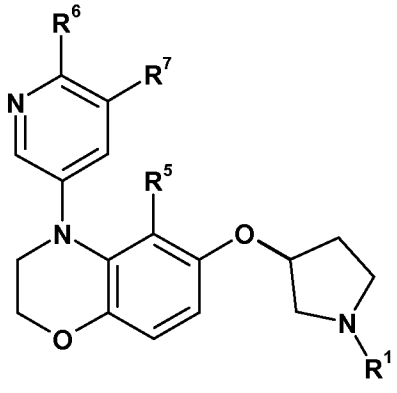
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Id')



(Id'),

wherein R^1, R^5, R^7, U and Q are as defined above.

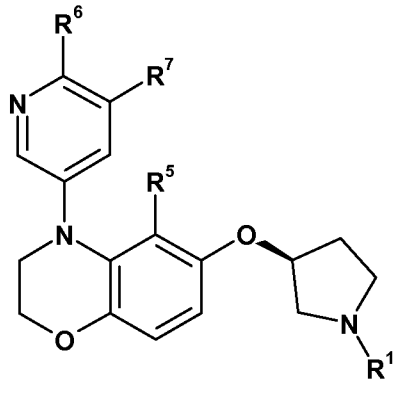
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ie)



(Ie),

wherein R^1, R^5, R^6 and R^7 are as defined above.

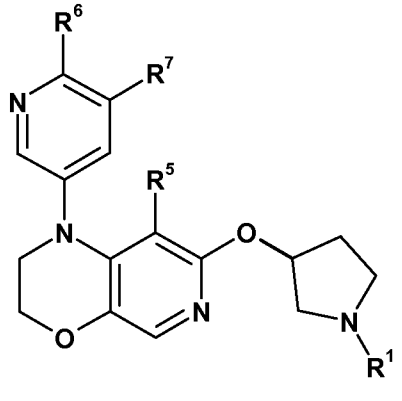
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ie')



(Ie'),

wherein R^1, R^5, R^6 and R^7 are as defined above.

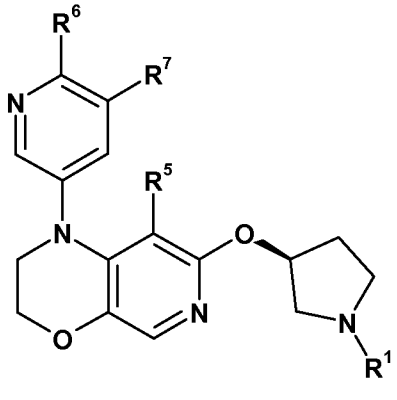
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (If)



(If),

wherein R^1, R^5, R^6 and R^7 are as defined above.

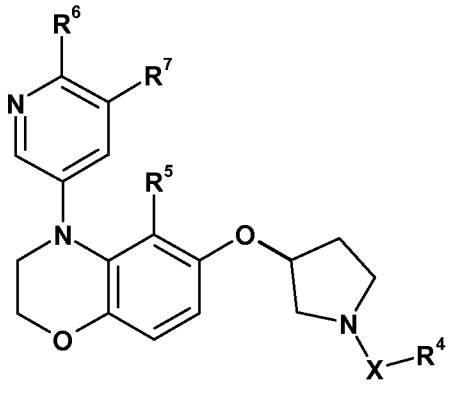
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (If')



(If'),

wherein R^1, R^5, R^6 and R^7 are as defined above.

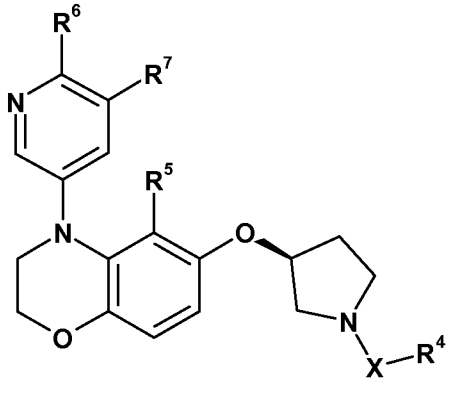
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ig)



(Ig),

wherein X, R^4, R^5, R^6 and R^7 are as defined above.

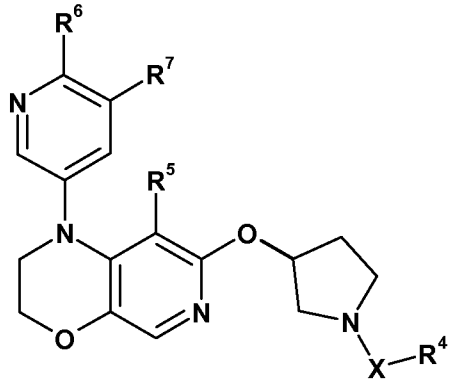
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ig')



(Ig'),

wherein X, R^4, R^5, R^6 and R^7 are as defined above.

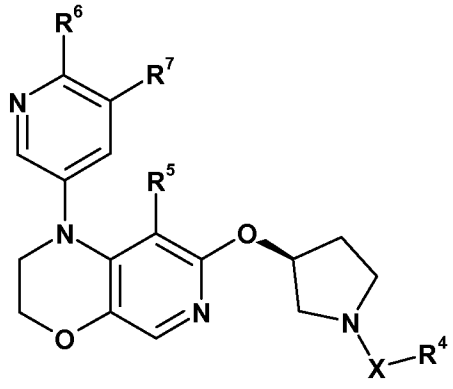
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ih)



(Ih),

wherein X, R^4, R^5, R^6 and R^7 are as defined above.

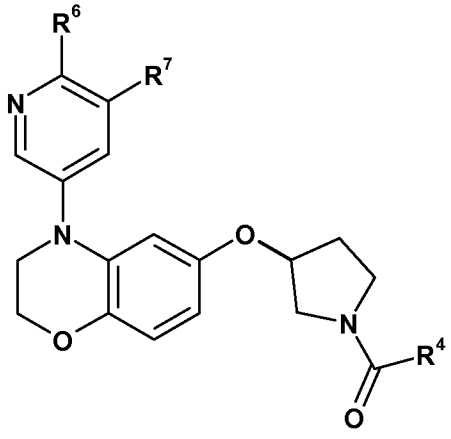
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ih')



(Ih'),

wherein X, R^4, R^5, R^6 and R^7 are as defined above.

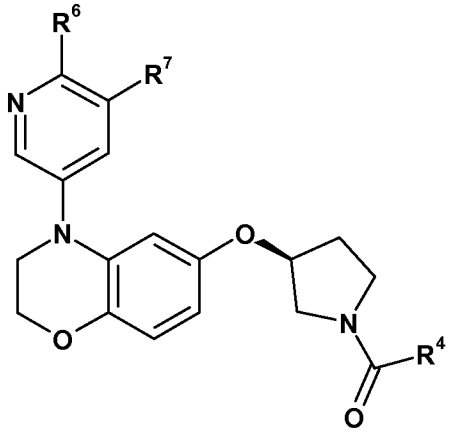
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ii)



(Ii),

wherein R^4, R^5, R^6 and R^7 are as defined above.

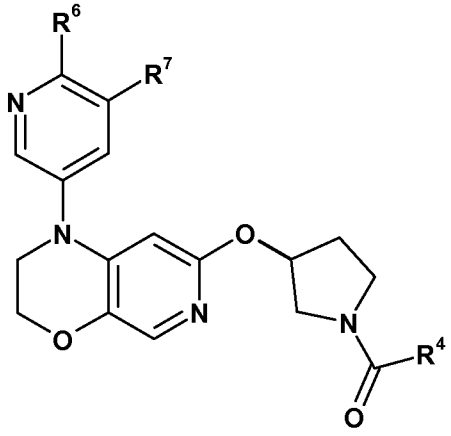
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ii')



(Ii'),

wherein R^4, R^5, R^6 and R^7 are as defined above.

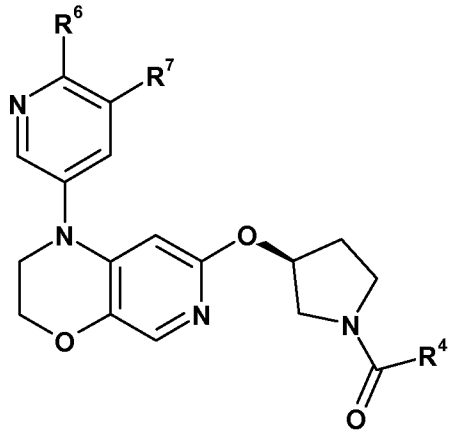
In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ij)



(Ij),

wherein R^4, R^5, R^6 and R^7 are as defined above.

In another embodiment, the invention provides a compound of the formula (I) and/or a pharmaceutically acceptable salt and/or a solvate thereof, selected from a compound of the formula (Ij')



(Ij'),

wherein R^4, R^5, R^6 and R^7 are as defined above.

In another embodiment, the invention provides a compound of the formulae (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) or (Ij') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R^4 is selected from C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, cyano-C_1-C_8-alkyl, N,N-di-C_1-C_4-alkyl-amino-C_1-C_8-alkyl, C_1-C_4-alkyl-sulfonyl-C_1-C_8-alkyl, phenyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, C_3-C_{12}-cycloalkyl, heteroaryl, heteroaryl-C_1-C_8-alkyl, C_1-C_8-alkoxy, wherein C_1-C_8-alkyl in N-C_1-C_8-alkyl-amino and in N,N-di-C_1-C_8-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy,

wherein C_3-C_{12}-cycloalkyl in C_3-C_{12}-cycloalkyl and in C_3-C_{12}-cycloalkyl-C_1-C_8-alkyl may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy;

wherein 'heterocyclyl' is a 3 to 7 membered saturated or partially unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, which is unsubstituted or substituted by 1-5 substituents selected from oxo, halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states,

wherein 'heteroaryl' is a 3 to 7 membered fully unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, or pyrazolo[1,5-a]pyrimidine or imidazo[2,1-b]thiazole, each of which is unsubstituted or substituted by 1-5 substituents selected from halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states.

In another embodiment, the invention provides a compound of the formulae (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) or (Ij') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein

R^4 is selected from C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, cyano-C_1-C_8-alkyl, N,N-di-C_1-C_4-alkyl-amino-C_1-C_8-alkyl, C_1-C_4-alkyl-sulfonyl-C_1-C_8-alkyl, phenyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, C_3-C_{12}-cycloalkyl, heteroaryl, heteroaryl-C_1-C_8-alkyl, C_1-C_8-alkoxy, wherein C_1-C_8-alkyl in N-C_1-C_8-alkyl-amino and in N,N-di-C_1-C_8-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy,

wherein C_3-C_{12}-cycloalkyl in C_3-C_{12}-cycloalkyl and in C_3-C_{12}-cycloalkyl-C_1-C_8-alkyl may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy;

wherein 'heterocyclyl' is selected from pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, piperidinyl, tetrahydrothiopyranyl, morpholinyl, dioxanyl or dihydropyranyl, each of which is unsubstituted or substituted by 1-3 substituents selected from oxo, C_1-C_8-alkyl or C_1-C_8-alkyl-carbonyl; wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states,

wherein 'heteroaryl' is selected from imidazolyl, pyrazolyl, thiazolyl, oxazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyrazolo[1,5-a]pyrimidine or imidazo[2,1-b]thiazole, each of which is unsubstituted or substituted by 1-3 substituents selected from C_1-C_8-alkyl, hydroxyl or amino; wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states.

In another embodiment, the invention provides a compound of the formulae (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) or (Ij') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R^6 is selected from halogen, C_1-C_4-alkoxy, C_1-C_4-alkyl-sulfonyl or halo-C_1-C_4-alkoxy.

In another embodiment, the invention provides a compound of the formulae (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) or (Ij') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R^7 is selected from hydrogen, halogen, cyano, C_1-C_4-alkyl, halo-C_1-C_4-alkyl or C_1-C_4-alkoxy.

In another embodiment, the invention provides a compound of the formulae (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) or (Ij') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein R^4 is selected from C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, cyano-C_1-C_8-alkyl, N,N-di-C_1-C_4-alkyl-amino-C_1-C_8-alkyl, C_1-C_4-alkyl-sulfonyl-C_1-C_8-alkyl, phenyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, C_3-C_{12}-cycloalkyl, heteroaryl, heteroaryl-C_1-C_8-alkyl, C_1-C_8-alkoxy, wherein C_1-C_8-alkyl in N-C_1-C_8-alkyl-amino and in N,N-di-C_1-C_8-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy,

wherein C_3-C_{12}-cycloalkyl in C_3-C_{12}-cycloalkyl and in C_3-C_{12}-cycloalkyl-C_1-C_8-alkyl may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy;

wherein 'heterocyclyl' is a 3 to 7 membered saturated or partially unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, which is unsubstituted or substituted by 1-5 substituents selected from oxo, halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states,

wherein 'heteroaryl' is a 3 to 7 membered fully unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, or pyrazolo[1,5-a]pyrimidine or imidazo[2,1-b]thiazole, each of which is unsubstituted or substituted by 1-5 substituents selected from halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-

C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;

and R^6 is selected from halogen, C_1-C_4-alkoxy, C_1-C_4-alkyl-sulfonyl or halo-C_1-C_4-alkoxy.

In another embodiment, the invention provides a compound of the formulae (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) or (Ij') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein

R^4 is selected from C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, cyano-C_1-C_8-alkyl, N,N-di-C_1-C_4-alkyl-amino-C_1-C_8-alkyl, C_1-C_4-alkyl-sulfonyl-C_1-C_8-alkyl, phenyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, C_3-C_{12}-cycloalkyl, heteroaryl, heteroaryl-C_1-C_8-alkyl, C_1-C_8-alkoxy, wherein C_1-C_8-alkyl in N-C_1-C_8-alkyl-amino and in N,N-di-C_1-C_8-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy,

wherein C_3-C_{12}-cycloalkyl in C_3-C_{12}-cycloalkyl and in C_3-C_{12}-cycloalkyl-C_1-C_8-alkyl may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy;

wherein 'heterocyclyl' is a 3 to 7 membered saturated or partially unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, which is unsubstituted or substituted by 1-5 substituents selected from oxo, halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states,

wherein 'heteroaryl' is a 3 to 7 membered fully unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, or pyrazolo[1,5-a]pyrimidine or imidazo[2,1-b]thiazole, each of which is unsubstituted or substituted by 1-5 substituents selected from halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;

and R^7 is selected from hydrogen, halogen, cyano, C_1-C_4-alkyl, halo-C_1-C_4-alkyl or C_1-C_4-alkoxy.

In another embodiment, the invention provides a compound of the formulae (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) or (Ij') and/or a pharmaceutically acceptable salt and/or a solvate thereof, wherein
R^4 is selected from C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, cyano-C_1-C_8-alkyl, N,N-di-C_1-C_4-alkyl-amino-C_1-C_8-alkyl, C_1-C_4-alkyl-sulfonyl-C_1-C_8-alkyl, phenyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, C_3-C_{12}-cycloalkyl, heteroaryl, heteroaryl-C_1-C_8-alkyl, C_1-C_8-alkoxy, wherein C_1-C_8-alkyl in N-C_1-C_8-alkyl-amino and in N,N-di-C_1-C_8-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy,

wherein C_3-C_{12}-cycloalkyl in C_3-C_{12}-cycloalkyl and in C_3-C_{12}-cycloalkyl-C_1-C_8-alkyl may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy;

wherein 'heterocyclyl' is a 3 to 7 membered saturated or partially unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, which is unsubstituted or substituted by 1-5 substituents selected from oxo, halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states,

wherein 'heteroaryl' is a 3 to 7 membered fully unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, or pyrazolo[1,5-a]pyrimidine or imidazo[2,1-b]thiazole, each of which is unsubstituted or substituted by 1-5 substituents selected from halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;

R^6 is selected from halogen, C_1-C_4-alkoxy, C_1-C_4-alkyl-sulfonyl or halo-C_1-C_4-alkoxy
and R^7 is selected from hydrogen, halogen, cyano, C_1-C_4-alkyl, halo-C_1-C_4-alkyl or C_1-C_4-alkoxy.

In another embodiment individual compounds according to the invention are those listed in the Examples section below.

As used herein, the term “an optical isomer” or “a stereoisomer” refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. The term "chiral" refers to molecules which have the property of non-superimposability on their mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. “Enantiomers” are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic” mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-.

Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, or as isomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. The present invention is meant to include all such possible isomers, including racemic mixtures, diasteriomeric mixtures and optically pure forms. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

As used herein, the terms “salt” or “salts” refers to an acid addition or base addition salt of a compound of the invention. “Salts” include in particular “pharmaceutical acceptable salts”. The term “pharmaceutically acceptable salts” refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, sulfosalicylate, tartrate, tosylate and trifluoroacetate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.
Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.
Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include

isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H and ^{14}C, or those into which non-radioactive isotopes, such as ^{2}H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

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, DMSO-d6.

Compounds of the invention, i.e. compounds of formula (I) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I).

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's

Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviate, inhibit, prevent and/or ameliorate a condition, or a disorder or a disease (i) mediated by PI3K or (ii) associated with PI3K activity, or (iii) characterized by activity (normal or abnormal) of PI3K or (2) reduce or inhibit the activity of PI3K or (3) reduce or inhibit the expression of PI3K. In another non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of PI3K; or at least partially reducing or inhibiting the expression of PI3K. The meaning of the term “a therapeutically effective amount” as illustrated in the above embodiment for PI3K also applies by the same means to any other relevant proteins/peptides/enzymes.

As used herein, the term “subject” refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

As used herein, the term “inhibit”, "inhibition" or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat”, "treating" or

"treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, “treat”, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

As used herein, the term "a,” "an,” "the” and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.* "such as”) provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50% enantiomeric excess, at least 60% enantiomeric excess, at least 70% enantiomeric excess, at least 80% enantiomeric excess, at least 90% enantiomeric excess, at least 95% enantiomeric excess, or at least 99% enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated double bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical

isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

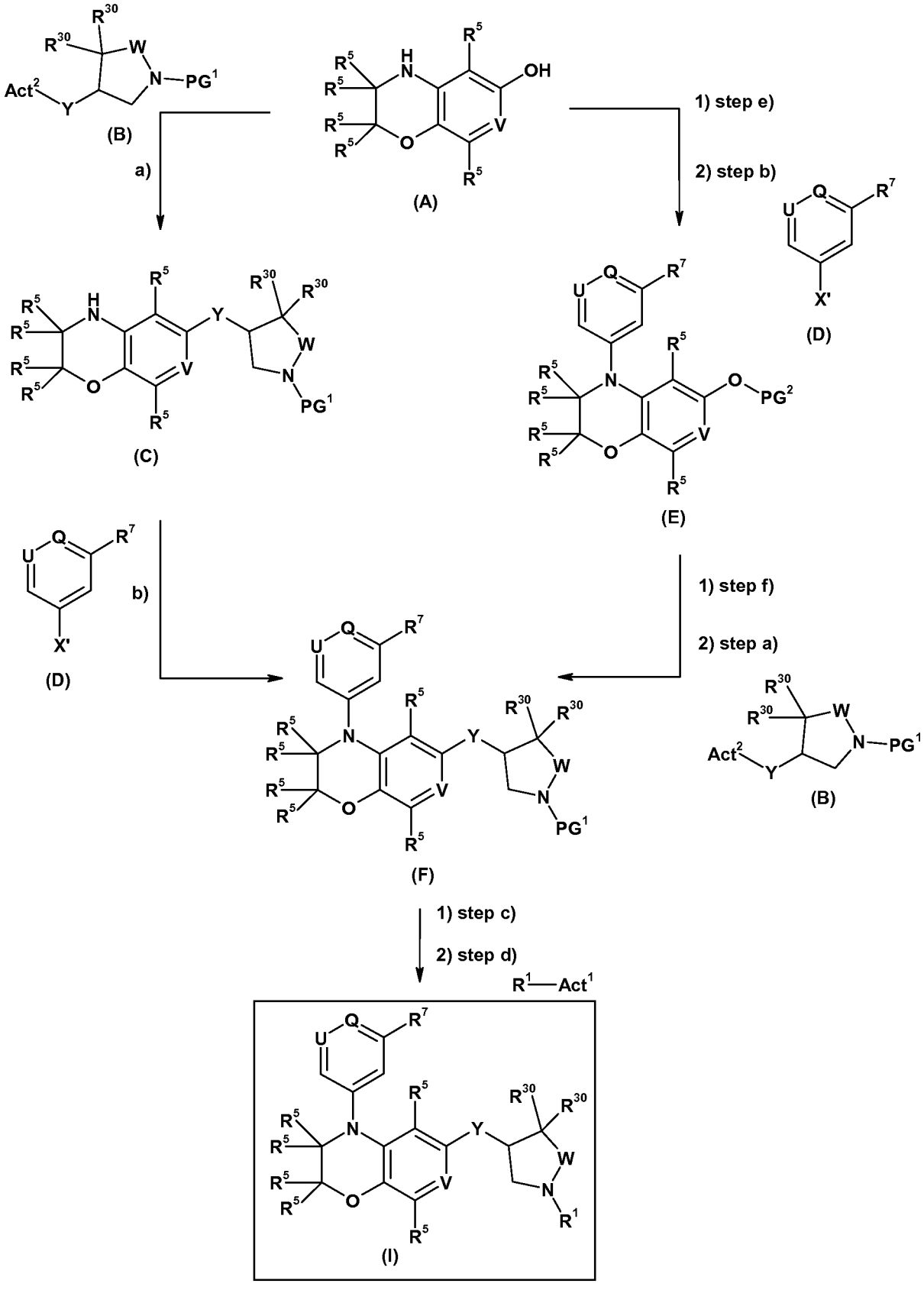
Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The compounds of the present invention, including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.

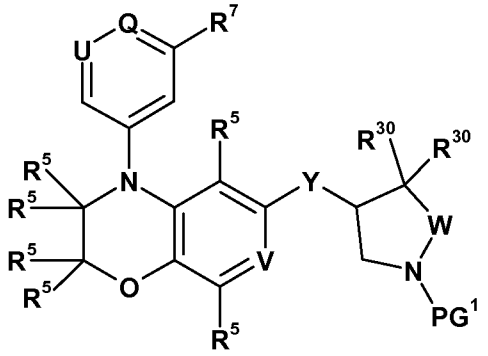
Typically, the compounds of formula (I) can be prepared according to the methods provided *infra.*

Scheme A


(B)
a)
(A)
1) step e)
2) step b)
(D)
(C)
(E)
(D)
b)
1) step f)
2) step a)
(B)
(F)
1) step c)
2) step d)
R1—Act1
(I)

In one embodiment, the invention relates to a process for manufacturing a compound of formula (I) (Method A) comprising steps a, b, c, d.

The compound of formula (I) is obtained via the step c of deprotecting PG^1 from the compound of formula (F), wherein PG^1 represents a suitable protecting group, such as a Boc group, and the other substituents are as defined above,



(F)

followed by coupling reaction step d with

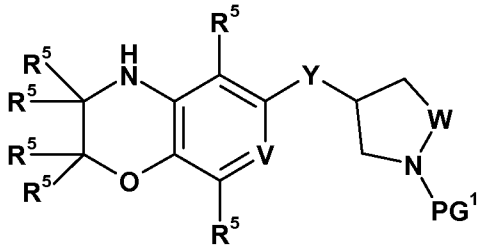
R^1-Act^1,

step c1: Where R^1 is -C(O)-R^4, or -$S(O)_2$-R^4, wherein R^4 is defined above, and Act^1 represents an activating group or a hydroxy group: The coupling reaction is an amide, urea, carbamic ester or sulfonamid formation. There are many known ways of preparing amides, urea carbamic esters or sulfonamids. The coupling reaction step can be carried out with Act^1 representing an activating group, preferably in a one step procedure or with Act^1 representing a hydroxy group either involving a one or two step procedure. For examples of amide bond formations, see Mantalbetti, C.A.G.N and Falque, V., Amide bond formation and peptide coupling, Tetrahedron, 2005, 61(46), pp10827-10852 and references cited therein. For examples of urea synthesis, see Sartori, G.; Maggi, R. Acyclic and cyclic ureas, Science of Synthesis (2005), 18, 665-758; Gallou, Isabelle. Unsymmetrical ureas Synthetic methodologies and application in drug design, Organic Preparations and Procedures International (2007), 39(4), 355-383. For examples of carbamate synthesis see Adams, Philip; Baron, Frank A. Esters of carbamic acid, Chemical Reviews (1965), 65(5), 567-602. The examples provided herein are thus not intended to be exhaustive, but merely illustrative;

step c2: Where R^1 is selected from phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl or 1,3,5-triazinyl and Act^1 represents halogen, particularly iodo or bromo: The coupling reaction is carried out in the presence of an amine base such as N,N-diisopropylethylamine. The reaction is carried out in the presence of an organic solvent or without a solvent under microwave heating. Alternatively, the reaction is carried out under customary Buchwald-Hartwig conditions such as the conditions

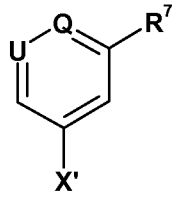
described above. The reaction is preferably carried out under an inert gas such as nitrogen or argon.

The compound of formula (F) is obtained via the step b of coupling the compound of formula (C), wherein PG^1 represents a suitable protectiong group, such as a Boc, and the other substituents are as defined above,



(C)

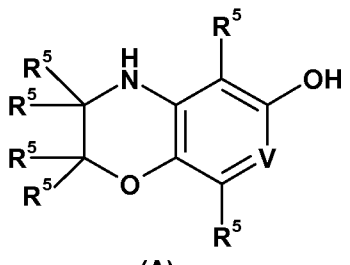
with a compound of formula (D), wherein X' represents halogen, such as iodo or bromo and the other substituents are as defined above,



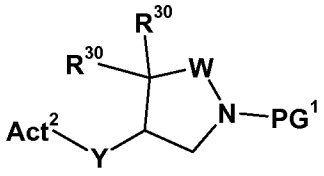
(D)

under customary Buchwald-Hartwig conditions using a suitable Pd catalyst/ligand combination such as $Pd_2(dba)_3$/2-(dicyclohexylphosphino)biphenyl or $Pd_2(dba)_3$/2-dicyclohexylphosphino-2',4',6'-triisopropyl-biphenyl, $Pd_2(dba)_3$/X-Phos, $Pd_2(dba)_3$/(rac)-BINAP, $Pd(OAc)_2$/(rac)-BINAP or bis(tri-t-butylphosphine)palladium and a suitable base, such as NaOtBu, Cs_2CO_3 or K_3PO_4 and organic solvent such as toluene, dioxane or THF. The reaction is stirred at a temperature of approximately 60-140°C, for example at 100°C to 110°C and is optionally performed in a microwave reactor. The reaction is preferably carried out under an inert gas such as nitrogen or argon.

The compound of formula (C) is obtained via the step a of coupling the compound of formula (A), wherein the substituents are as defined above with a compound of formula (B), wherein PG^1 represents a suitable protectiong group, such as a Boc group and Act^2 is an activating group or H, and the other substituents are as defined above,



(A)



(B)

step a1: Where Y is O and Act^2 represents an activating group such as a mesylate: The reaction takes place in the presence of a suitable base such as sodium hydroxide (NaH), K_2CO_3 or potassium t-butoxide (tBuOK) in a suitable polar organic solvent such as DMF, THF, 2-methyltetrahydrofuran or Dioxane at a suitable temperature such as rt - 100°C.

step a2: Where Y is O and Act^2 represents H: The reaction takes place using customary Mitsunobu conditions, for example using Ph_3P and DEAD in organic solvent such as THF under inert gas conditions at elevated temperature such as 70°C.

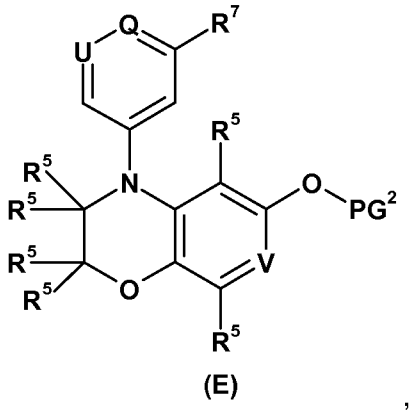
step a3: Where Y is NH and and Act^2 represents H: A base promoted phosphonium coupling reaction is employed, whereby a compound of the formula (A) in a suitable solvent such as acetonitrile is reacted with a phosphonium salt such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) in the presence of a base such as 1,8-diaza-7-bicyclo[5.4.0]undecene (DBU) followed by addition of a compound of the formula (B). The reaction mixture is stirred at a temperature of 20°C to 100°C.

In another embodiment, the invention relates to a process for manufacturing a compound of formula (I) (Method A-a) comprising steps a and b as defined above for Method A, using a compound of formula (B) wherein PG^1 represents R^1.

In another embodiment, the invention relates to a process for manufacturing a compound of formula (I) (Method B) comprising steps e, b, f, a, c and d.

The compound of formula (I) is obtained via the steps c and d as described above for Method A from the compound of formula (F).

The compound of formula (F) is obtained via the step f of deprotecting PG^2 from the compound of formula (E), wherein PG^2 is a suitable protecting group, such as a silyl protecting group, and the other substituents are as defined above



(E)

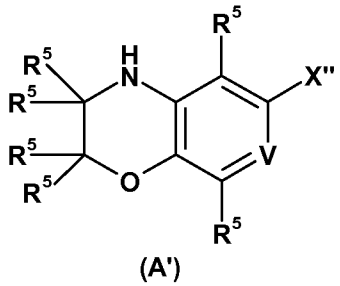
,

followed by coupling reaction step a, as described above for Method A, with the compound of formula (B).

The compound of formula (E) is obtained via the step e of protecting the compound of formula (A) with a suitable protecting group PG^2, followed by from the compound of formula (E), wherein PG^2 is a suitable protecting group, such as a silyl protecting group, followed by coupling reaction step b, as described above for Method A with the compound of formula (D).

In another embodiment, the invention relates to a process for manufacturing a compound of formula (I) (Method B-a) comprising steps e, b and f as defined above for Method B, using a compound of formula (B) wherein PG^1 represents R^1.

In another embodiment, the invention relates to a process for manufacturing a compound of formula (I) (Method C).using a compound of formula (A'), wherein X'' represents halogen and the other substituents are as defined above



(A')

comprising steps b, c and d as defined above for Method B, using a compound of formula (B) and a modified step a4:

step a4: Where Y is NH and Act^2 is H: The reaction takes place in the presence of a suitable base such as for example potassium carbonate or a suitable amine base such as triethylamine or N,N-diisopropylethylamine at elevated temperature such as 100°C to 140°C. Alternatively, the reaction is carried out under customary Buchwald-Hartwig conditions such as the conditions described above. The reaction is preferably carried out under an inert gas such as nitrogen or argon.

In another embodiment, the invention relates to a process for manufacturing a compound of formula (I) (Method C-a) comprising steps b, a4, c and d as defined above for Method B^1, using a compound of formula (B) wherein PG^1 represents R^1.

The term “activating group” as used herein relates to a group that can activate a carboxylic acid, carbonic acid or carbamic acid derivative, for coupling with an amine moiety to form an amide, urea or carbamic ester moiety, respectively (Act^1) or to a group that can activate a hydroxy group for coupling with anothe hydroxy moiety to form an ether (Act^2).
Groups that can activate a carboxylic acid, carbonic acid or carbamic acid derivative, for coupling with an amine moiety to form an amide, urea or carbamic ester moiety are chlorides, or groups resulting from the reaction of the acid derivative with an activating agent. Suitable activating agents are known to the skilled person, examples of such activating reagents are carbodiimide derivatives, pentafluorophenyl ester derivatives, triazole derivatives, imidazole derivatives.
Groups that can activate a hydroxy group for coupling with anothe hydroxy moiety to form an ether are groups are known to the skilled person, examples of such activating groups are mesylates and tosylates.

The term “protecting group” as used herein relates to a group that protects a functional group which is present in the starting materials and is not intended to take part in the reaction. In additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more protecting groups. The protecting groups are then wholly or partly removed according to one of the known methods. Protecting groups, and the manner in which they are introduced and removed are described, for example, in "Protective Groups in Organic Chemistry", Plenum Press, London, New York 1973, and in "Methoden der organischen Chemie", Houben-Weyl, 4th edition, Vol. 15/1, Georg-Thieme-Verlag, Stuttgart 1974 and in Theodora W. Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons, New York 1981. A characteristic of protecting groups is that they can be removed readily, i.e. without the occurrence of undesired secondary reactions, for example by solvolysis, reduction, photolysis or alternatively under physiological conditions.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the

remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure material.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known *to those skilled in the art*.

Intermediates and final products can be worked up and/or purified according to standard methods, *e.g.* using chromatographic methods, distribution methods, (re-) crystallization, and the like.

The following applies in general to all processes mentioned herein before and hereinafter.

All the above-mentioned process steps can be carried out under reaction conditions that are known to those skilled in the art, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, *e.g.* in the H+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190 °C, including, for example, from approximately -80 °C to approximately 150 °C, for example at from -80 to -60 °C, at room temperature, at from -20 to 40 °C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described herein above.

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or *N*-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid

anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, methycyclohexane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration, and rectal administration, etc. In addition, the pharmaceutical compositions of the present invention can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions or emulsions). The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifers and buffers, etc.

Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbents, colorants, flavors and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable compositions for oral administration include an effective amount of a compound of the invention in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Certain injectable compositions are aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

Suitable compositions for transdermal application include an effective amount of a compound of the invention with a suitable carrier. Carriers suitable for transdermal delivery include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate

controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, *e.g.*, to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.*, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, *e.g.*, for the treatment of skin cancer, *e.g.*, for prophylactic use in sun creams, lotions, sprays and the like. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

As used herein a topical application may also pertain to an inhalation or to an intranasal application. They may be conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomizer or nebuliser, with or without the use of a suitable propellant.

The present invention further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the present invention as active ingredients, since water may facilitate the degradation of certain compounds.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e.g.*, vials), blister packs, and strip packs.

The invention further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the compound of the present invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

The compounds of formula I in free form or in salt form, exhibit valuable pharmacological properties, e.g. PI3K modulating properties, e.g. as indicated in in vitro and in vivo tests as provided in the next sections, and are therefore indicated for therapy or for use as research chemicals, e.g. as tool compounds.

Compounds of the invention may be useful in the treatment of conditions, diseases or disorders including disease or infection associated immunopathology in which one or more of the functions of B cells such as antibody production, antigen presentation, cytokine production or lymphoid organogenesis are abnormal or are undesirable including rheumatoid arthritis, pemphigus vulgaris and related diseases, idiopathic thrombocytopenia purpura, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, Sjögren's syndrome, autoimmune hemolytic anemia, ANCA-associated vasculitides, cryoglobulinemia, thrombotic thrombocytopenic purpura, chronic autoimmune urticaria, allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, AMR (antibody-mediated transplant rejection), B cell-mediated hyperacute, acute and chronic transplant rejection and cancers of haematopoietic origin including but not limited to multiple myeloma; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; non-Hodgkin lymphoma; lymphomas; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Walden stroem disease.

The invention includes methods of treating conditions, diseases or disorders in which one or more of the functions of neutrophils, such as superoxide release, stimulated exocytosis, or chemoatractic migration are abnormal or are undesirable including rheumatoid arthritis, sepsis, pulmonary or resporatory disorders such as asthma, inflammatory dermatoses such as psoriasis, as well as in disease or infection associated immunopathology and others.

The invention includes methods of treating conditions, diseases or disorders in which one or more of the functions of basophil and mast cells such as chemoatractic migration or allergen-IgE-mediated degranulation are abnormal or are undesirable including allergic diseases (atopic dermatitis, contact dermatitis, allergic rhinitis) as well as other disorders such as COPD, asthma or emphysema.

The invention includes methods of treating conditions, diseases or disorders in which one or more of the functions of T cells such as cytokine production or cell-mediated

cytotoxicity abnormal or are undesirable including rheumatoid arthritis, multiple sclerosis, acute or chronic rejection of cell tissue or organ grafts or cancers of haematopoietic origin as well as in disease or infection associated immunopathology.

Further, the invention includes methods of treating neurodegenerative diseases, cardiovascular diseases and platelet aggregation.
Further, the invention includes methods of treating skin diseases such as porphyria cutanea tarda, polymorphous light eruption, dermatomyositis, solar urticaria, oral lichen planus, panniculitis, scleroderma, urticarial vasculitis.

Further, the invention includes methods of treating chronic inflammatory diseases such as sarcoidosis, granuloma annulare.

In other embodiments, the condition or disorder (e.g. PI3K-mediated) is selected from the group consisting of: polycythemia vera, essential thrombocythemia, myelofibrosis with myeloid metaplasia, asthma, COPD, ARDS, Loffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma, eosinophil-related disorders affecting the airways occasioned by drug-reaction, psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, autoimmune haematogical disorders (e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis, cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease, reperfusion injuries, retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy, and conditions characterized by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma.

In another embodiment, the compounds of the present invention are useful in the treatment, prevention, or amelioration of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, including inflammatory conditions and rheumatic diseases involving bone loss, inflammatory pain, spondyloarhropathies including ankolsing spondylitis, Reiter syndrome, reactive arthritis, psoriatic arthritis, and enterophathics arthritis, hypersensitivity (including both airways hypersensitivity and dermal hypersensitivity) and allergies. Specific auto-immune diseases for which antibodies of the invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopa-thic thrombocytopenia), acquired hemophilia A, cold agglutinin disease, cryoglobulinemia, thrombotic thrombocytopenic purpura, Sjögren's syndrome, systemic lupus erythematosus, inflammatory muscle disorders, polychondritis, sclerodoma, anti-neutrophil cytoplasmic antibody- associated vasculitis, IgM mediated neuropathy, opsoclonus myoclonus syndrome, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, pemphigus vulgaris, pemphigus foliacius, idio-pathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), endocrine ophthalmopathy, Graves' disease, sarcoidosis, multiple sclerosis, neuromyelitis optica, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior, intermediate and posterior as well as panuveitis), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephro-tic syndrome or minimal change nephropathy), tumors, inflammatory disease of skin and cornea, myositis, loosening of bone implants, metabolic disorders, such as atherosclerosis, diabetes, and dislipidemia.

In another embodiment, the compounds of the present invention are useful in the treatment of conditions or disorders selected from the group consisting of, primary cutaneous B-cell lymphoma, immunobullous disease, pemphigus vulgaris, pemphigus foliaceus, endemic form of Brazilian pemphigus (Fogo selvagem), paraneoplastic pemphigus, bullous pemphigoid, mucous membrane pemphigoid, epidermolysis bullosa acquisita, chronic graft versus host disease, dermatomyositis, systemic lupus erythematosus, vasculitis, small vessel vasculitis, hypocomplementemic urticarial vasculitis, antineutrophil cytoplasmic antibody-vasculitis, cryoglobulinemia, Schnitzler syndrome, Waldenstrom's macroglobulinemia, angioedema, vitiligo, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, multiple sclerosis, cold agglutinin

disease, autoimmune hemolytic anemia, antineutrophil cytoplasmic antibody—associated vasculitis, graft versus host disease, cryoglobulinemia and thrombotic thrombocytopenic.

Thus, as a further embodiment, the present invention provides the use of a compound of formulae (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) or (Ij') in therapy. In a further embodiment, the therapy is selected from a disease which may be treated by inhibition of PI3K. In another embodiment, the disease is selected from the afore-mentioned list, suitably from autoimmune disorders, inflammatory diseases, allergic diseases, airway diseases, such as asthma and COPD, transplant rejection; antibody production, antigen presentation, cytokine production or lymphoid organogenesis are abnormal or are undesirable including rheumatoid arthritis, pemphigus vulgaris, idiopathic thrombocytopenia purpura, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, Sjögren's syndrome, autoimmune hemolytic anemia, ANCA-associated vasculitides, cryoglobulinemia, thrombotic thrombocytopenic purpura, chronic autoimmune urticaria, allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, AMR (antibody-mediated transplant rejection), B cell-mediated hyperacute, acute and chronic transplant rejection and cancers of haematopoietic origin including but not limited to multiple myeloma; a leukaemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; non-Hodgkin lymphoma; lymphomas; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Walden stroem disease; more suitably from rheumatoid arthritis (RA), pemphigus vulgaris (PV), idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune hemolytic anemia (AIHA), acquired hemophilia type A (AHA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis (MG), Sjögren's syndrome (SS), ANCA-associated vasculitides, cryoglobulinemia, chronic autoimmune urticaria (CAU), allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, transplant rejection and cancers of haematopoietic origin as well as in disease or infection associated immunopathology, for example in severe and cerebral malaria, trypanosomiasis, leishmaniasis, toxoplasmosis and neurocysticercosis.

In another embodiment, the invention provides a method of treating a disease which is treated by inhibition of PI3K comprising administration of a therapeutically acceptable amount of a compound of formulae (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) or (Ij'). In a further embodiment, the disease is selected from the afore-mentioned list, suitably from autoimmune disorders, inflammatory diseases, allergic diseases, airway diseases, such as asthma and COPD, transplant

rejection; antibody production, antigen presentation, cytokine production or lymphoid organogenesis are abnormal or are undesirable including rheumatoid arthritis, pemphigus vulgaris, idiopathic thrombocytopenia purpura, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, Sjögren's syndrome, autoimmune hemolytic anemia, ANCA-associated vasculitides, cryoglobulinemia, thrombotic thrombocytopenic purpura, chronic autoimmune urticaria, allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, AMR (antibody-mediated transplant rejection), B cell-mediated hyperacute, acute and chronic transplant rejection and cancers of haematopoietic origin including but not limited to multiple myeloma; a leukaemia; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; non-Hodgkin lymphoma; lymphomas; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Walden stroem disease; more suitably from rheumatoid arthritis (RA), pemphigus vulgaris (PV), idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune hemolytic anemia (AIHA), acquired hemophilia type A (AHA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis (MG), Sjögren's syndrome (SS), ANCA-associated vasculitides, cryoglobulinemia, chronic autoimmune urticaria (CAU), allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, transplant rejection and cancers of haematopoietic origin as well as in disease or infection associated immunopathology, for example in severe and cerebral malaria, trypanosomiasis, leishmaniasis, toxoplasmosis and neurocysticercosis.

Thus, as a further embodiment, the present invention provides the use of a compound of formulae (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) or (Ij') for the manufacture of a medicament. In a further embodiment, the medicament is for treatment of a disease which may be treated inhibition of PI3K. In another embodiment, the disease is selected from the afore-mentioned list, suitably from autoimmune disorders, inflammatory diseases, allergic diseases, airway diseases, such as asthma and COPD, transplant rejection; antibody production, antigen presentation, cytokine production or lymphoid organogenesis are abnormal or are undesirable including rheumatoid arthritis, pemphigus vulgaris, idiopathic thrombocytopenia purpura, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, Sjögren's syndrome, autoimmune hemolytic anemia, ANCA-associated vasculitides, cryoglobulinemia, thrombotic thrombocytopenic purpura, chronic autoimmune urticaria, allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, AMR (antibody-mediated transplant rejection), B cell-mediated hyperacute, acute and chronic transplant rejection and cancers of haematopoietic origin including but not limited to multiple myeloma; a leukaemia; acute myelogenous leukemia;

chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; non-Hodgkin lymphoma; lymphomas; polycythemia vera; essential thrombocythemia; myelofibrosis with myeloid metaplasia; and Walden stroem disease; more suitably from rheumatoid arthritis (RA), pemphigus vulgaris (PV), idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune hemolytic anemia (AIHA), acquired hemophilia type A (AHA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis (MG), Sjögren's syndrome (SS), ANCA-associated vasculitides, cryoglobulinemia, chronic autoimmune urticaria (CAU), allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, transplant rejection and cancers of haematopoietic origin as well as in disease or infection associated immunopathology, for example in severe and cerebral malaria, trypanosomiasis, leishmaniasis, toxoplasmosis and neurocysticercosis.

The pharmaceutical composition or combination of the present invention can be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, *e.g.*, aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.1-500 mg/kg, or between about 1-100 mg/kg.

The compound of the present invention may be administered either simultaneously with, or before or after, one or more other therapeutic agent. The compound of the present invention may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agents.

In one embodiment, the invention provides a product comprising a compound of formula (I) and at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a disease or condition mediated by the activity of the PI3K enzymes. Products provided as a combined preparation include a composition comprising the compound of formula (I) and the other therapeutic agent(s) together in the same pharmaceutical composition, or the compound of formula (I) and the other therapeutic agent(s) in separate form, *e.g.* in the form of a kit.

In one embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I) and another therapeutic agent(s). Optionally, the pharmaceutical composition may comprise a pharmaceutically acceptable carrier, as described above.

In one embodiment, the invention provides a kit comprising two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I). In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

The kit of the invention may be used 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 of the invention typically comprises directions for administration.

In the combination therapies of the invention, the compound of the invention and the other therapeutic agent may be manufactured and/or formulated by the same or different manufacturers. Moreover, the compound of the invention and the other therapeutic may be brought together into a combination therapy: (i) prior to release of the combination product to physicians (*e.g.* in the case of a kit comprising the compound of the invention and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the patient themselves, *e.g.* during sequential administration of the compound of the invention and the other therapeutic agent.

Accordingly, the invention provides the use of a compound of formula (I) for treating a disease or condition mediated by the activity of the PI3K enzymes, wherein the medicament is prepared for administration with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition mediated by the activity

of the PI3K enzymes, wherein the medicament is administered with a compound of formula (I).

The invention also provides a compound of formula (I) for use in a method of treating a disease or condition mediated by the activity of the PI3K enzymes, wherein the compound of formula (I) is prepared for administration with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a disease or condition mediated by the activity of the PI3K enzymes, wherein the other therapeutic agent is prepared for administration with a compound of formula (I). The invention also provides a compound of formula (I) for use in a method of treating a disease or condition mediated by the activity of the PI3K enzymes wherein the compound of formula (I) is administered with another therapeutic agent. The invention also provides another therapeutic agent for use in a method of treating a disease or condition mediated by the activity of the PI3K enzymes wherein the other therapeutic agent is administered with a compound of formula (I).

The invention also provides the use of a compound of formula (I) for treating a disease or condition mediated by the activity of the PI3K enzymes, wherein the patient has previously (*e.g.* within 24 hours) been treated with another therapeutic agent. The invention also provides the use of another therapeutic agent for treating a disease or condition mediated by the activity of the PI3K enzymes, wherein the patient has previously (*e.g.* within 24 hours) been treated with a compound of formula (I).

The compounds of formula I may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, other drugs e.g. immunosuppressive or immunomodulating agents or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, or a chemotherapeutic agent, e.g a malignant cell anti-proliferative agent. For example, the compounds of formula I may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK 506; a mTOR inhibitor, e.g. rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779, ABT578, AP23573, TAFA-93, biolimus-7 or biolimus-9; an ascomycin having immuno-suppressive properties, e.g. ABT-281, ASM981, etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; leflunomide; mizoribine; mycophenolic acid or salt; mycophenolate mofetil; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; a PKC inhibitor, e.g. as disclosed in WO 02/38561 or WO 03/82859, e.g. the compound of Example 56 or 70; a JAK3 kinase inhibitor, e.g. N-benzyl-3,4-dihydroxy-benzylidene-cyanoacetamide α-cyano-(3,4-dihydroxy)-]N-benzylcinnamamide (Tyrphostin AG 490), prodigiosin 25-C

(PNU156804), [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline] (WHI-P131), [4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline] (WHI-P154), [4-(3',5'-dibromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline] WHI-P97, KRX-211, 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile, in free form or in a pharmaceutically acceptable salt form, e.g. mono-citrate (also called CP-690,550), or a compound as disclosed in WO 04/052359 or WO 05/066156; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD40, CD45, CD52, CD58, CD80, CD86 or their ligands; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or antihistamines; or antitussives, or a bronchodilatory agent; or an angiotensin receptor blockers; or an anti-infectious agent.

Where the compounds of formula I are administered in conjunction with other immunosuppressive / immunomodulatory, anti-inflammatory, chemotherapeutic or anti-infectious therapy, dosages of the co-administered immunosuppressant, immunomodulatory, anti-inflammatory, chemotherapeutic or anti-infectious compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth.

A compound of the formula (I) may also be used to advantage in combination with each other or in combination with other therapeutic agents, especially other antiproliferative agents. Such antiproliferative agents include, but are not limited to, aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active agents; alkylating agents; histone deacetylase inhibitors; compounds, which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; agents used in the treatment of hematologic malignancies;

compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors; temozolomide (TEMODAL®); and leucovorin.

The term "aromatase inhibitor", as used herein, relates to a compound which inhibits the estrogen production, i.e., the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to, steroids, especially atamestane, exemestane and formestane; and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketoconazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane can be administered, e.g., in the form as it is marketed, e.g., under the trademark AROMASIN. Formestane can be administered, e.g., in the form as it is marketed, e.g., under the trademark LENTARON. Fadrozole can be administered, e.g., in the form as it is marketed, e.g., under the trademark AFEMA. Anastrozole can be administered, e.g., in the form as it is marketed, e.g., under the trademark ARIMIDEX. Letrozole can be administered, e.g., in the form as it is marketed, e.g., under the trademark FEMARA or FEMAR. Aminoglutethimide can be administered, e.g., in the form as it is marketed, e.g., under the trademark ORIMETEN. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g., breast tumors.

The term "anti-estrogen", as used herein, relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to, tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be administered, e.g., in the form as it is marketed, e.g., under the trademark NOLVADEX. Raloxifene hydrochloride can be administered, e.g., in the form as it is marketed, e.g., under the trademark EVISTA. Fulvestrant can be formulated as disclosed in U.S. Patent No. 4,659,516 or it can be administered, e.g., in the form as it is marketed, e.g., under the trademark FASLODEX. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g., breast tumors.

The term "anti-androgen", as used herein, relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX), which can be formulated, e.g., as disclosed in U.S. Patent No. 4,636,505.

The term "gonadorelin agonist", as used herein, includes, but is not limited to, abarelix, goserelin and goserelin acetate. Goserelin is disclosed in U.S. Patent No. 4,100,274 and can be administered, e.g., in the form as it is marketed, e.g., under the trademark ZOLADEX. Abarelix can be formulated, e.g., as disclosed in U.S. Patent No. 5,843,901.

The term "topoisomerase I inhibitor", as used herein, includes, but is not limited to, topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO 99/17804). Irinotecan can be administered, e.g., in the form as it is marketed, e.g., under the trademark CAMPTOSAR. Topotecan can be administered, e.g., in the form as it is marketed, e.g., under the trademark HYCAMTIN.

The term "topoisomerase II inhibitor", as used herein, includes, but is not limited to, the anthracyclines, such as doxorubicin, including liposomal formulation, e.g., CAELYX; daunorubicin; epirubicin; idarubicin; nemorubicin; the anthraquinones mitoxantrone and losoxantrone; and the podophillotoxines etoposide and teniposide. Etoposide can be administered, e.g., in the form as it is marketed, e.g., under the trademark ETOPOPHOS. Teniposide can be administered, e.g., in the form as it is marketed, e.g., under the trademark VM 26-BRISTOL. Doxorubicin can be administered, e.g., in the form as it is marketed, e.g., under the trademark ADRIBLASTIN or ADRIAMYCIN. Epirubicin can be administered, e.g., in the form as it is marketed, e.g., under the trademark FARMORUBICIN. Idarubicin can be administered, e.g., in the form as it is marketed, e.g., under the trademark ZAVEDOS. Mitoxantrone can be administered, e.g., in the form as it is marketed, e.g., under the trademark NOVANTRON.

The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing agents and microtublin polymerization inhibitors including, but not limited to, taxanes, e.g., paclitaxel and docetaxel; vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate; vincristine, especially vincristine sulfate and vinorelbine; discodermolides; cochicine; and epothilones and derivatives thereof, e.g., epothilone B or D or derivatives thereof. Paclitaxel may be administered, e.g., in the form as it is marketed, e.g., TAXOL. Docetaxel can be administered, e.g., in the form as it is marketed, e.g., under the trademark TAXOTERE. Vinblastine sulfate can be administered, e.g., in the form as it is marketed, e.g., under the trademark VINBLASTIN R.P. Vincristine sulfate can be administered, e.g., in the form as it is marketed, e.g., under the trademark FARMISTIN. Discodermolide can be obtained, e.g., as disclosed in U.S. Patent No. 5,010,099. Also included are epothilone derivatives which are disclosed in WO 98/10121, U.S. Patent No. 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247. Especially preferred are epothilone A and/or B.

The term "alkylating agent", as used herein, includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g., under

the trademark CYCLOSTIN. Ifosfamide can be administered, e.g., in the form as it is marketed, e.g., under the trademark HOLOXAN.

The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes compounds disclosed in WO 02/22577, especially *N*-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide and pharmaceutically acceptable salts thereof. It further especially includes suberoylanilide hydroxamic acid (SAHA).

The term "antineoplastic antimetabolite" includes, but is not limited to, 5-fluorouracil or 5-FU; capecitabine; gemcitabine; DNA demethylating agents, such as 5-azacytidine and decitabine; methotrexate and edatrexate; and folic acid antagonists, such as pemetrexed. Capecitabine can be administered, e.g., in the form as it is marketed, e.g., under the trademark XELODA. Gemcitabine can be administered, e.g., in the form as it is marketed, e.g., under the trademark GEMZAR. Also included is the monoclonal antibody trastuzumab which can be administered, e.g., in the form as it is marketed, e.g., under the trademark HERCEPTIN.

The term "platin compound", as used herein, includes, but is not limited to, carboplatin, *cis*-platin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g., under the trademark CARBOPLAT. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g., under the trademark ELOXATIN.

The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds", as used herein, includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g.,

a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, e.g., a *N*-phenyl-2-pyrimidine-amine derivative, e.g., imatinib, SU101, SU6668 and GFB-111;

b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR);

c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the IGF-IR receptor, such as those compounds disclosed in WO 02/092599;

d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family;

e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

f) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor;

g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase;

h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases - (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, e.g., imatinib;

i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family and their gene-fusion products, e.g., BCR-Abl kinase, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, e.g., a *N*-phenyl-2-pyrimidine-amine derivative, e.g., imatinib, PD180970, AG957, NSC 680410 or PD173955 from ParkeDavis;

j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK and Ras/MAPK family members, or PI(3) kinase family, or of the PI(3)-kinase-related kinase family, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in U.S. Patent No. 5,093,330, e.g., midostaurin; examples of further compounds include, e.g., UCN-01; safingol; BAY 43-9006; Bryostatin 1; Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds, such as those disclosed in WO 00/09495; FTIs; PD184352; or QAN697 (a P13K inhibitor);

k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC) or tyrphostin. A tyrphostin is preferably a low molecular weight (Mr < 1500) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzylidenemalonitrile class or the S-arylbenzenemalonirile or bisubstrate quinoline class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810, AG 99,

Tyrphostin AG 213, Tyrphostin AG 1748, Tyrphostin AG 490, Tyrphostin B44, Tyrphostin B44 (+) enantiomer, Tyrphostin AG 555, AG 494, Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester, NSC 680410, adaphostin; and

l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or hetero-dimers), such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g., EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g., the compound of Example 39, or in EP 0 564 409; WO 99/03854; EP 0520722; EP 0 566 226; EP 0 787 722; EP 0 837 063; U.S. Patent No. 5,747,498; WO 98/10767; WO 97/30034; WO 97/49688; WO 97/38983 and, especially, WO 96/30347, e.g., compound known as CP 358774; WO 96/33980, e.g., compound ZD 1839; and WO 95/03283, e.g., compound ZM105180, e.g., trastuzumab (HERCEPTIN), cetuximab, Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3; and 7*H*-pyrrolo-[2,3-*d*]pyrimidine derivatives which are disclosed in WO 03/013541.

Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g., unrelated to protein or lipid kinase inhibition, e.g., thalidomide (THALOMID) and TNP-470.

Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are, e.g., inhibitors of phosphatase 1, phosphatase 2A, PTEN or CDC25, e.g., okadaic acid or a derivative thereof.

Compounds which induce cell differentiation processes are e.g. retinoic acid, α- γ- or δ-tocopherol or α- γ- or δ-tocotrienol.

The term cyclooxygenase inhibitor, as used herein, includes, but is not limited to, e.g., Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g., 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid or lumiracoxib.

The term "bisphosphonates", as used herein, includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. "Etridonic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark DIDRONEL. "Clodronic acid" can be administered, e.g., in the form as it is

marketed, e.g., under the trademark BONEFOS. "Tiludronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark SKELID. "Pamidronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark AREDIA™. "Alendronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark FOSAMAX. "Ibandronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark BONDRANAT. "Risedronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark ACTONEL. "Zoledronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark ZOMETA.

The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity, such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

The term "heparanase inhibitor", as used herein, refers to compounds which target, decrease or inhibit heparin sulphate degradation. The term includes, but is not limited to, PI-88.

The term "biological response modifier", as used herein, refers to a lymphokine or interferons, e.g., interferon γ.

The term "inhibitor of Ras oncogenic isoforms", e.g., H-Ras, K-Ras or N-Ras, as used herein, refers to compounds which target, decrease or inhibit the oncogenic activity of Ras, e.g., a "farnesyl transferase inhibitor", e.g., L-744832, DK8G557 or R115777 (Zarnestra).

The term "telomerase inhibitor", as used herein, refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, e.g., telomestatin.

The term "methionine aminopeptidase inhibitor", as used herein, refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are, e.g., bengamide or a derivative thereof.

The term "proteasome inhibitor", as used herein, refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include, e.g., PS-341 and MLN 341.

The term "matrix metalloproteinase inhibitor" or "MMP inhibitor", as used herein, includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g., hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

The term "agents used in the treatment of hematologic malignancies", as used herein, includes, but is not limited to, FMS-like tyrosine kinase inhibitors, e.g., compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-b-*D*-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors, e.g., compounds which target, decrease or inhibit anaplastic lymphoma kinase. Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, e.g., PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

The term "HSP90 inhibitors", as used herein, includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteasome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90, e.g., 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative, other geldanamycin related compounds, radicicol and HDAC inhibitors.

The term "antiproliferative antibodies", as used herein, includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1, erlotinib (Tarceva™), bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 antibody. By antibodies is meant, e.g., intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least two intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

For the treatment of acute myeloid leukemia (AML), compounds of formula (I) can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of formula (I) can be administered in combination with, e.g., farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

A compound of the formula (I) may also be used to advantage in combination with each other or in combination with other therapeutic agents, especially other anti-malarial agents. Such anti-malarial agents include, but are not limited to proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, inhaled NO, L-arginine, Dipropylenetri-amine NONOate (NO

donor), Rosiglitzone (PPARγ agonist), activated charcoal, Erythropoietin, Levamisole, and pyronaridine.

A compound of the formula (I) may also be used to advantage in combination with each other or in combination with other therapeutic agents, such as used for the treatment of Leishmaniosis, Trypanosomiasis, Toxoplasmosis and Neurocysticercosis. Such agents include, but are not limited to chloroquine sulfate, atovaquone-proguanil, artemether-lumefantrine, quinine-sulfate, artesunate, quinine, doxycycline, clindamycin, meglumine antimoniate, sodium stibogluconate, miltefosine, ketoconazole, pentamidine, amphotericin B (AmB), liposomal-AmB, paromomycine, eflornithine, nifurtimox, suramin, melarsoprol, prednisolone, benznidazole, sulfadiazine, pyrimethamine, clindamycin, trimetropim, sulfamethoxazole, azitromycin, atovaquone, dexamethasone, praziquantel, albendazole, beta-lactams, fluoroquinolones, macrolides, aminoglycosides, sulfadiazine and pyrimethamine.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International, e.g., IMS World Publications.
The above-mentioned compounds, which can be used in combination with a compound of the formula (I), can be prepared and administered as described in the art, such as in the documents cited above.
A compound of the formula (I) may also be used to advantage in combination with known therapeutic processes, e.g., the administration of hormones or especially radiation.
A compound of formula (I) may in particular be used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.
By "combination", there is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the formula (I) and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, e.g., synergistic, effect or any combination thereof. The terms “co-administration” or “combined administration” or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term “pharmaceutical combination” as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed

combination" means that the active ingredients, e.g. a compound of formula I and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of formula (I) and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

EXAMPLES

Experimental details:

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Celsius. If not mentioned otherwise, all evaporations are performed under reduced pressure, typically between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, *e.g.*, microanalysis and spectroscopic characteristics, *e.g.*, MS, IR, NMR. Abbreviations used are those conventional in the art.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

Abbreviations

ACN	acetonitrile
AcOH	acetic acid
aq.	aqueous
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
tBu	*tert*-butyl
tBuOH	*tert*-butanol
BrettPhos	2-(Dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6'-triisopropyl-1,1'-biphenyl
br s	broad singlet
COMU	(1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate
conc.	concentrated
d	day(s)
d	doublet

dd	doublet of doublets
dba	dibenzylideneacetone
DCM	dichloromethane
DEA	diethylamine
DEAD	diethyl azodicarboxylate
DEAP	diethylaminopyridine
DIPEA	diisopropylethylamine
DMF	dimethylformamide
DMME	dimethoxymethane
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
DPPF	1,1'-bis(diphenylphosphino)ferrocene
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
eq.	equivalent(s)
ESI	electrospray ionisation
Et_3N	triethylamine
Et_2O	diethylether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HBTU	O-(1H-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazane
HOBT	1-hydroxy-benztriazole
HPLC	high performance liquid chromatography
IPA	isopropanol
LCMS	liquid chromatography with mass spectrometry
mCPBA	*meta*-chloroperoxybenzoic acid
MeOH	methanol
m	multiplet
min	minute(s)
MS	mass spectrometry
mw	microwave
NMR	nuclear magnetic resonance spectrometry
NaOtBu	sodium tert-butoxide

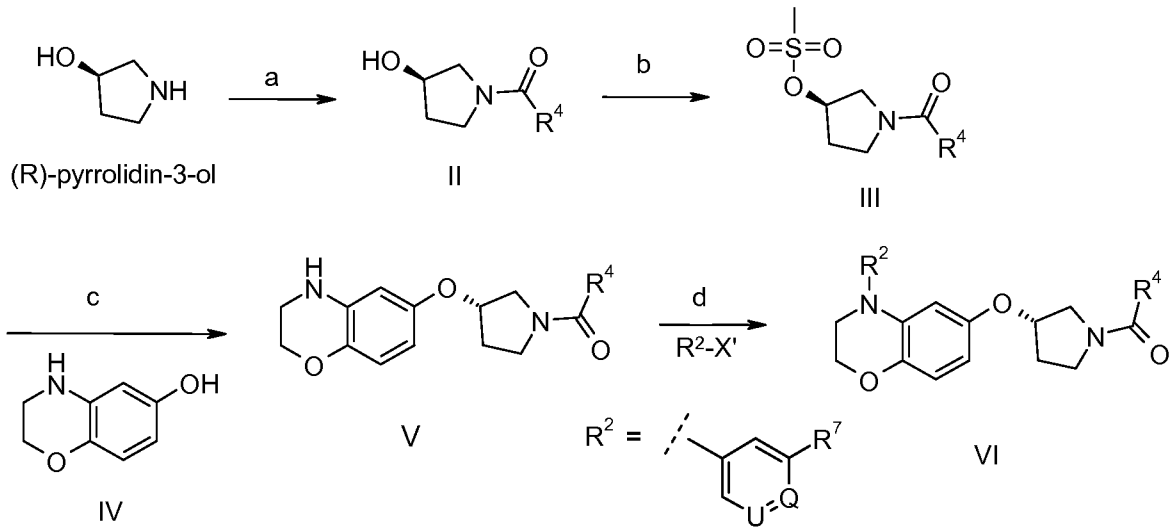
NP	normal phase
OBD	optimum bed density
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
PL-HCO_3 MP SPE	Polymer-supported bicarbonate cartridge for acid removal
prep.	preparative
PPh_3	triphenylphosphine
q	quartet
Rac-BINAP	racemic 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
RP	reversed phase
Rt	retention time
rt	room temperature
RuPhos	2-dicyclohexylphosphino-2',6'-di-isopropoxy-1,1'-biphenyl
sat.	saturated
SCX-2	polymer supported sulfonic acid macroporous polystyrene
soln.	solution
t	triplet
TBME	*tert*-butyl methyl ether
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilylchloride
Tetramethyl-t-butyl -XPhos	2-di-t-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropylbiphenyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UPLC	ultra performance liquid chromatography
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
Pd[RuPhos]	(2-dicyclohexylphosphino-2' 6'-diisopropyl-1 1'-biphenyl)(2-(2-aminoethyl)phenyl)palladium(II)

Microwave equipment used is a Biotage Initiator®

All compounds are named using AutoNom.

Preparation of Examples – General Procedures

Scheme 1



a) (R)-pyrrolidin-3-ol and an acid chloride of formula $R^4C(O)Cl$ or carboxylic acid of formula $R^4C(O)OH$ were reacted to prepare an amide of general formula **II**. Those skilled in the art will appreciate that there are many known ways of preparing amides. For example, see Mantalbetti, C.A.G.N and Falque, V., Amide bond formation and peptide coupling, Tetrahedron, 2005, 61(46), pp10827-10852 and references cited therein. The following general methods i – ii have been used.

i. A soln. of the carboxylic acid and DMF (1 eq.) in DCM was treated with oxalyl chloride (1.5 eq.) for 1 h at 3°C. The reaction mixture was concentrated under reduced pressure, dissolved in DCM and added to a soln. of (R)-pyrrolidin-3-ol hydrochloride (1.0 eq.) and Et_3N (2.5 eq.) in DCM at 3°C. The resulting mixture was stirred vigorously at 3°C for 1h, then concentrated under reduced pressure. The residue was treated with EtOAc and filtered. The residue was washed with EtOAc, and the combined filtrates were concentrated under reduced pressure and purified by flash chromatography.

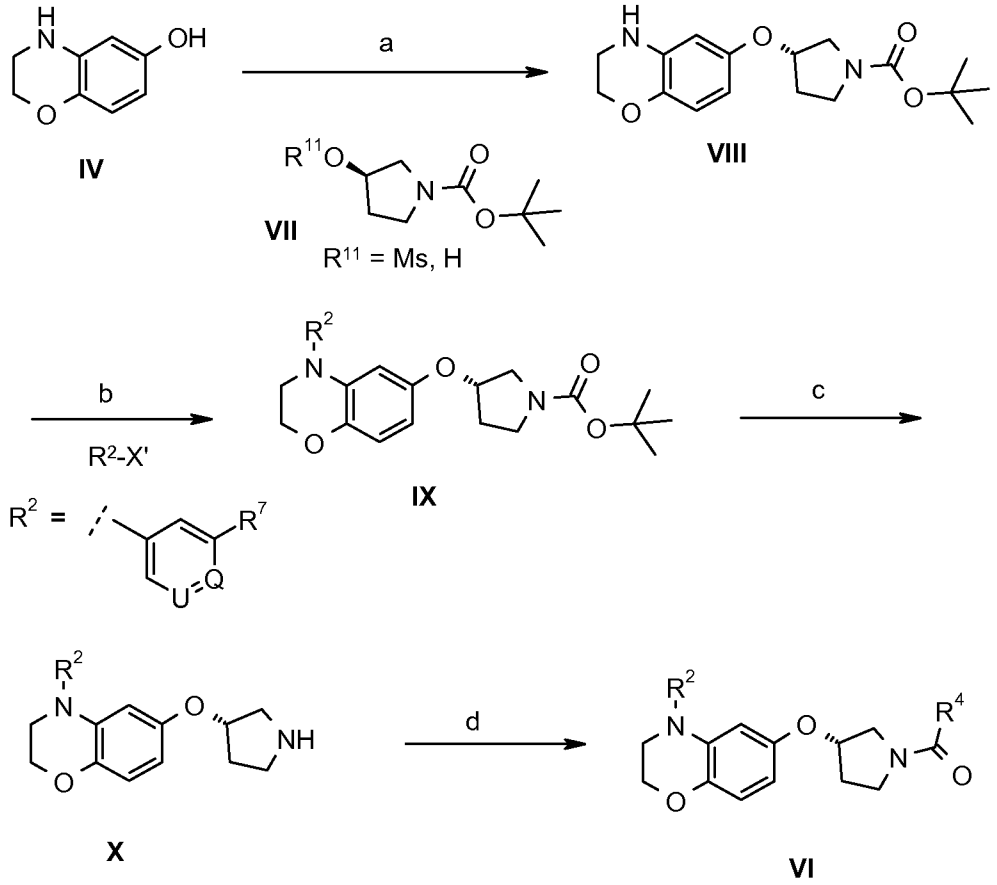
ii. A soln. of a commercial acid chloride (1.0 eq.) in DCM was added to a soln. of (R)-pyrrolidin-3-ol hydrochloride (1.0 eq.) and Et_3N (2.5 eq.) in DCM at 3°C. The resulting mixture was stirred vigorously at 3°C for 1 h, then concentrated under reduced pressure. The residue was treated with EtOAc and filtered. The residue was washed with EtOAc, and the combined filtrates were concentrated under reduced pressure and purified by flash chromatography. Typical conditions for amid bond formation reactions are exemplified in the section B) Amide bond formation conditions below.

b) The mesylates of compounds of general formula **II** were prepared by costumary conditions, perferably by reaction of **II** with methane sulfonyl chloride (2 eq.) and Et_3N (2 eq.) in DCM at 0°C.

c) Compounds of general formula **V** were prepared by reacting 3,4-dihydro-2H-benzo[1,4]oxazin-6-ol **IV** with compounds of general formula **III** in the presence of a suitable base such as sodium hydride (NaH) and polar organic solvent such as DMF under inert gas conditions at 50°C. Typical conditions for such reactions are exemplified in the section C) Side chain introduction conditions below.

d) Buchwald-Hartwig cross-coupling between **V** and an aryl halogenide of the general formula R^2-X' where X'=bromo or iodo was performed under customary Buchwald-Hartwig conditions using a Pd catalyst/ligand combination such as preferably $Pd_2(dba)_3$/2-(dicyclohexylphosphino)biphenyl or $Pd_2(dba)_3$/2-dicyclohexylphosphino-2',4',6'-triisopropyl-biphenyl or bis(tri-t-butylphosphine)palladium and a base, such as preferably NaOtBu, and organic solvent such as preferably toluene. The reaction was preferably stirred at a temperature of approximately 80-120°C, preferably 110°C and was perferably performed in a microwave reactor. The reaction was preferably carried out under an inert gas such as nitrogen or argon. The final compounds were purified by normal or reversed phase chromatography. Typical conditions for Buchwald-Hartwig cross-coupling reactions are exemplified in the section A) Buchwald aminations or hydroxylations below.

Scheme 2



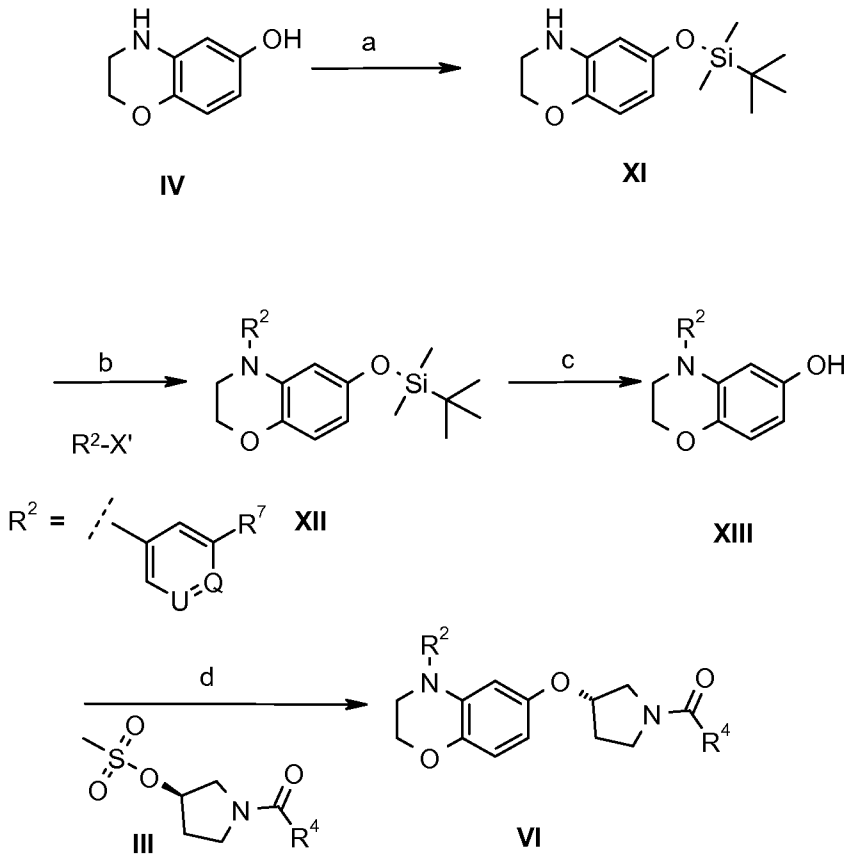
a) (S)-tert-butyl 3-((3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)pyrrolidine-1-carboxylate (compound **VIII)** was prepared by reacting 3,4-dihydro-2H-benzo[1,4]oxazin-6-ol **IV** with a compound of general formula **VII** by one of the following methods 1) for X=mesylate, compounds **IV** and **VII** were reacted in the presence of a suitable base such as sodium hydride (NaH) and a polar organic solvent DMF under inert gas conditions at room temperature ii) for X = H, compounds of general formula **IV** and **VII** were reacted using customary Mitsunobu conditions, preferably using Ph_3P (1.4 eq.) and DEAD (1.4 eq.) in organic solvent such as THF under inert gas conditions at a temperature of preferably 70°C. Typical conditions for such reactions are exemplified in the section C) Side chain introduction conditions below.

b) Buchwald-Hartwig cross-coupling between **VIII** and an aryl halogenide of the general formula R^2-X' where X'=bromo or iodo was performed under customary Buchwald-Hartwig conditions using a Pd catalyst/ligand combination such as preferably $Pd_2(dba)_3$/X-Phos, $Pd_2(dba)_3$/(rac)-BINAP, $Pd(OAc)_2$/(rac)-BINAP or bis(tri-t-butylphosphine)palladium and a base, such as preferably NaOtBu, Cs_2CO_3 or K_3PO_4 and an organic solvent such as preferably toluene, dioxane or THF. The reaction was preferably stirred at a temperature of approximately 60-120°C and was perferably be performed in a microwave reactor. The reaction was preferably carried out under an inert gas such as nitrogen or argon. Typical conditions for Buchwald-Hartwig cross-coupling reactions are exemplified in the section A) Buchwald aminations or hydroxylations below.

c) N-BOC deprotection of compounds of general formula **IX** was performed under customary BOC deprotection conditions using among the possible acids preferably trifluoro-actetic acid and organic solvent, preferably DCM. The reactionwas preferably performed at room temperature.

d) A compound of the general formula **X** and an acid chloride of formula $R^4C(O)Cl$ or a carboxylic acid of formula formula $R^4C(O)OH$ wereare reacted to prepare an amide of general formula **VI** using costumary amide coupling conditions: in addition to the methods decribed in Scheme 1, step a) preferred coupling reagents were HBTU, HOBt/EDC, COMU/DIPEA. The couplings were performed in an organic solvent such as preferably DMF or DCM and the final compounds were purified by normal or reversed phase chromatography. Typical conditions for amid bond formation reactions are exemplified in the section B) Amide bond formation conditions below.

Scheme 3



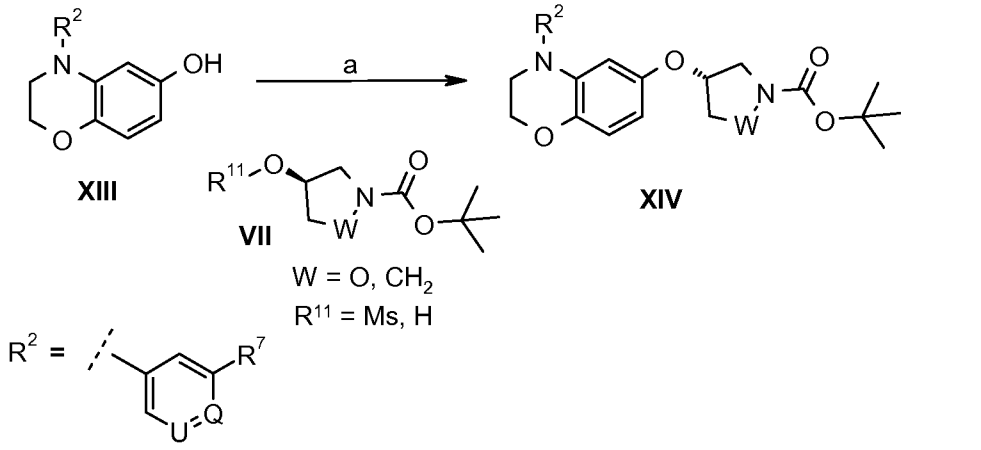
a) 3,4-Dihydro-2H-benzo[1,4]oxazin-6-ol **IV** was *O*-protected using standard silylation procedures, using a silylating reagent, preferably TBDMSCl and a base, preferably NaH, in an organic solvent, preferably THF at room temperature.

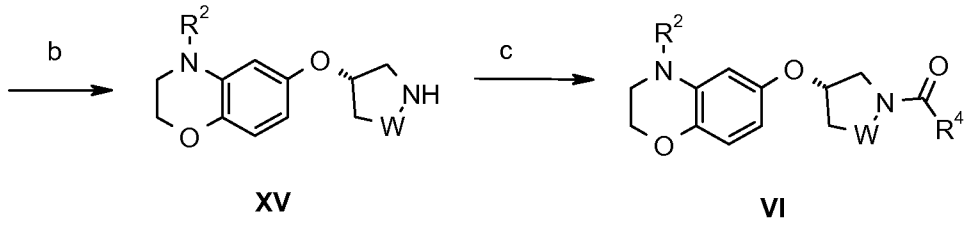
b) Buchwald-Hartwig cross-coupling between **XI** and an aryl halogenide of the general formula R^2-X' where X'=bromo or iodo was performed under customary Buchwald-Hartwig conditions using a Pd catalyst/ligand combination such as preferably $Pd_2(dba)_3$/X-Phos, $Pd_2(dba)_3$/dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl or bis(tri-t-butylphosphine)-palladium and a base, such as preferably NaOtBuand an organic solvent such as preferably toluene. The reaction was preferably stirred at a temperature of approximately 110-140°C and was perferably performed in a microwave reactor. The reaction was preferably carried out under an inert gas such as nitrogen or argon. Typical conditions for Buchwald-Hartwig cross-coupling reactions are exemplified in the section A) Buchwald aminations or hydroxylations below.

c) *O*-TBDMS deprotection of compounds of general formula **XII** was performed under customary deprotection conditions using perferably TBAF and an organic solvent, preferably THF. The reaction was preferably performed at room temperature

d) Compounds of general formula **XIII** were coupled with mesylates of general formula **III** using a suitable base such as preferably sodium hydride (NaH) or K_2CO_3 and polar organic solvent such as DMF under inert gas conditions at room temperature or elevated temperatures up to 100°C. The final compounds were purified by normal or reversed phase chromatography. Typical conditions for such reactions are exemplified in the section C) Side chain introduction conditions below.

Scheme 4



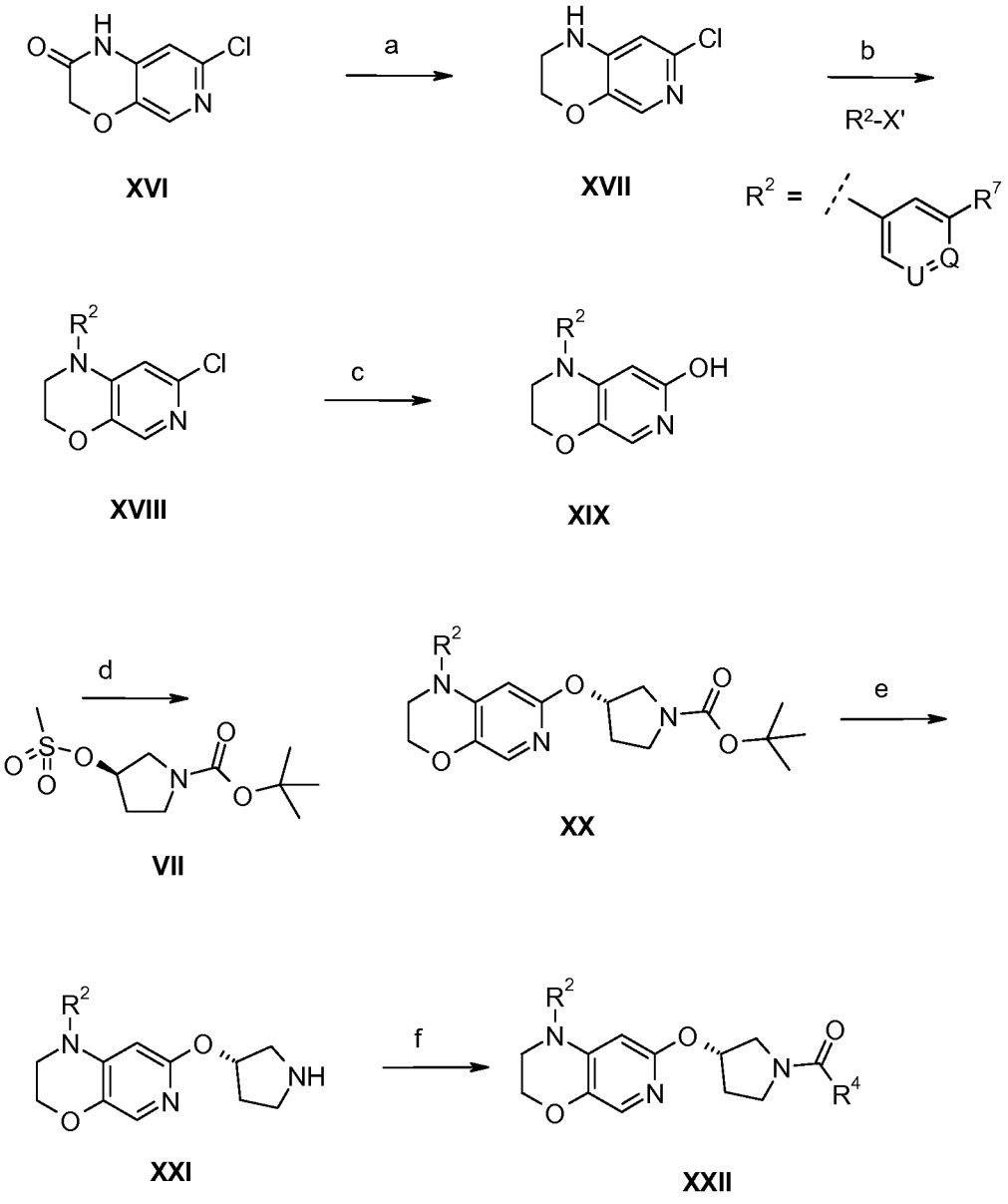


a) Compounds of general formula **XIII** (prepared as described in Scheme 3) were reacted with compounds of general formula by one of the following methods 1) for X=mesylate, compounds **XIII** and **VII** were reacted in the presence of a suitable base such as sodium hydride (NaH) and a polar organic solvent DMF under inert gas conditions at room temperature ii) for X = H, compounds of general formula **XIII** and **VII** were reacted using customary Mitsunobu conditions, preferably using Ph_3P (1.4 eq.) and DEAD (1.4 eq.) in organic solvent such as THF under inert gas conditions at a temperature of preferably 70°C. Typical conditions for such reactions are exemplified in the section C) Side chain introduction conditions below.

b) N-BOC deprotection was performed under customary BOC deprotection conditions using among the possible acid preferably trifluoro-actetic acid and organic solvent preferably CH_2Cl_2. The reaction was preferably performed at room temperature.

c) Amide bond formation was performed using compounds of general formula **XV** and an acid chloride of formula $R^4C(O)Cl$ or carboxylic acid of formula $R^4C(O)OH$ to prepare an amide of general formula **VI**; customary amide bond coupling conditions, as described in Scheme 1, step a) have been used. In addition to the methods decribed in Scheme 1, step a), coupling of carboxylic acids using HOBt/EDC or coupling using chloroformates or carbamic chlorides were used. The couplings were performed in an organic solvent such as preferably DMF or DCM and the final compounds were purified by normal or reversed phase chromatography. Typical conditions for amid bond formation reactions are exemplified in the section B) Amide bond formation conditions below.

Scheme 5



a) 7-Chloro-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine **XVII** was prepared from 7-chloro-1H-pyrido[3,4-b][1,4]oxazin-2-one **XVI** by costumary reduction methods, using as reducing agent preferably BH_3*THF and as solvent preferably THF. **XVI** is available via flow nitration of 2-chloro-5-(2-methoxy-2-oxoethoxy)pyridine-1-oxide, followed by reduction and cyclisation.

b) Cross-coupling between **XVII** and an aryl halogenide of the general formula R^2-X' where X'=bromo or iodo was performed under customary Buchwald-Hartwig conditions using a Pd catalyst/ligand combination such as preferably $Pd_2(dba)_3$/X-Phos, and a base, such as preferably Cs_2CO_3 and an organic solvent such as preferably dioxane. The reaction was preferably stirred at a temperature of approximately 100°C and could be performed in a microwave reactor. The reaction was preferably carried out under an inert gas such as nitrogen or argon. Typical conditions for Buchwald-Hartwig cross-coupling reactions are exemplified in the section A) Buchwald aminations or hydroxylations below.

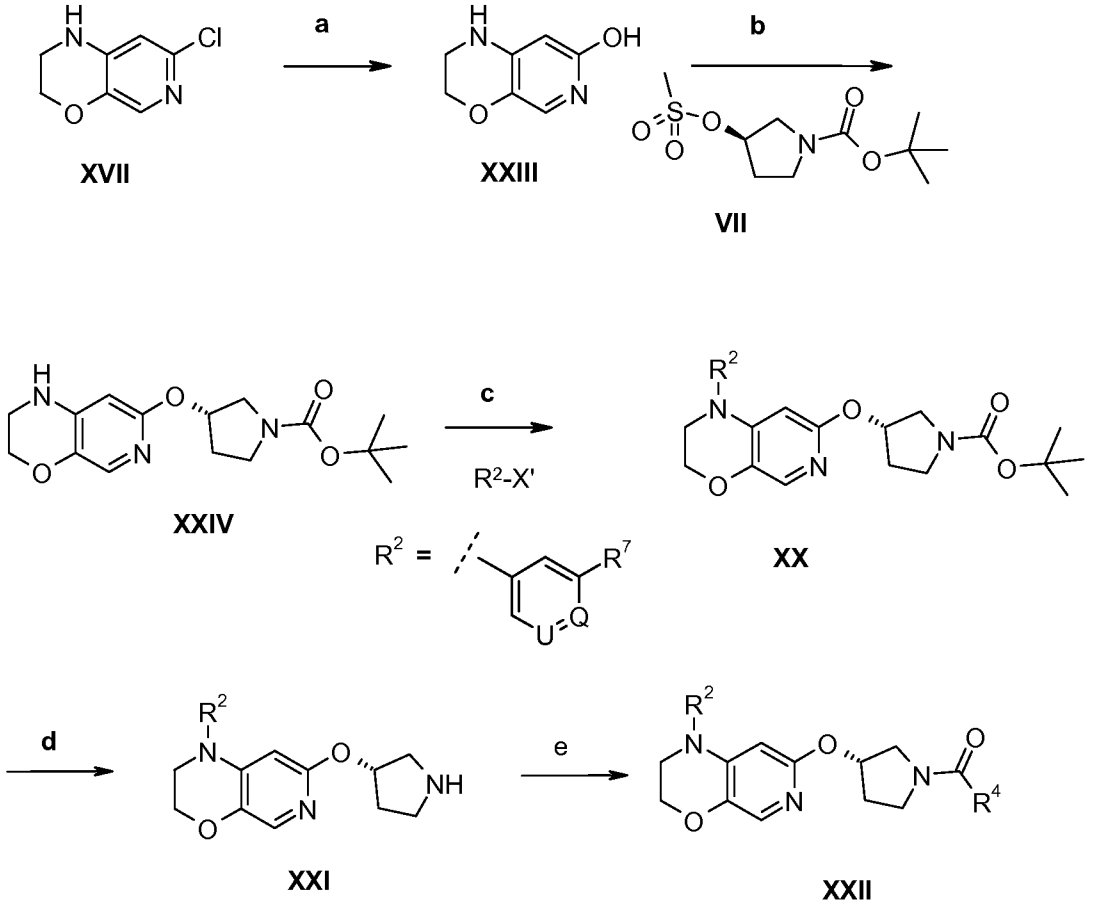
c) Hydroxylation of **XVIII** was performed using aq. KOH and a Pd catalyst/ligand combination such as preferably $Pd_2(dba)_3$/tetramethyl-tert-butyl-Xphos and an organic solvent such as preferably dioxane. The reaction was preferably stirred at a temperature of approximately 100°C. The reaction was preferably carried out under an inert gas such as nitrogen or argon.

d) Coupling of a compound of general formula **XIX** with a compound of general formula **VII** was performed using a suitable base such as sodium hydride (NaH, Cs_2CO_3, K_2CO_3) and polar organic solvent such as DMF under inert gas conditions at a temperature of perferably 60-80°C. Typical conditions for such reactions are exemplified in the section C) Side chain introduction conditions below.

e) N-BOC deprotection was performed under customary BOC deprotection conditions using among the possible acid preferably trifluoro-actetic acid and organic solvent preferably CH_2Cl_2. The reaction was preferably performed at room temperature.

f) Amide bond formation was performed using compounds of general formula **XXI** and an acid chloride of formula $R^4C(O)Cl$ or carboxylic acid of formula $R^4C(O)OH$ to prepare an amide of general formula **XXII**; customary amide bond coupling conditions, as described in Scheme 1, step a) have been used, in addotion coupling of carboxylic acids using HOBt/EDC was applied. The couplings were performed in an organic solvent such as preferably DMF or DCM and the final compounds were purified by normal or reversed phase chromatography. Typical conditions for amid bond formation reactions are exemplified in the section B) Amide bond formation conditions below.

Scheme 6



a) Hydroxylation of 7-chloro-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine **XVII** to give 2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-ol **XXIII** was performed using aq. KOH and a Pd catalyst/ligand combination such as preferably $Pd_2(dba)_3$/tetramethyl-tert-butyl-Xphos and an organic solvent such as preferably dioxane. The reaction was preferably stirred at a temperature of approximately 100°C. The reaction was preferably carried out under an inert gas such as nitrogen or argon.

b) Coupling of compound **XXIII** with mesylate **VII** was effected using a suitable base such as sodium hydride (NaH) and polar organic solvent such as DMF under inert gas conditions at a temperature of preferably 80°C. Typical conditions for such reactions are exemplified in the section C) Side chain introduction conditions below.

c) Cross-coupling between **XXIV** and an aryl halogenide of the general formula R^2-X' where X'=bromo or iodo was performed under customary Buchwald-Hartwig conditions using a Pd catalyst/ligand combination such as preferably $Pd_2(dba)_3$/X-Phos or $Pd_2(dba)_3$/(rac)-BINAP, and a base, such as preferably Cs_2CO_3 or NaOtBuand an organic solvent such as preferably dioxane or toluene. The reaction was preferably stirred at a temperature of approximately 100°C and could be performed in a microwave reactor. The reaction was preferably carried out under an inert gas such as nitrogen or argon. Typical conditions for Buchwald-Hartwig

cross-coupling reactions are exemplified in the section A) Buchwald aminations or hydroxylations below.

d) N-BOC deprotection was performed under customary BOC deprotection conditions using among the possible acid preferably trifluoro-actetic acid and organic solvent preferably CH_2Cl_2. The reaction was preferably performed at room temperature

e) Amide bond formation was performed using compounds of general formula **XXI** and an acid chloride of formula $R^4C(O)Cl$ or carboxylic acid of formula $R^4C(O)OH$ to prepare an amide of general formula **XXII**; customary amide bond coupling conditions, as described in Scheme 1, step a) have been used or coupling of carboxylic acids using HBTU, HOBt/EDC or HATU was applied. The couplings were performed in an organic solvent such as preferably DMF or DCM and the final compounds were purified by normal or reversed phase chromatography. Typical conditions for amid bond formation reactions are exemplified in the section B) Amide bond formation conditions below.

General chromatography information

LCMS method M1 (Rt_{M1})

HPLC-column dimensions:	2.1 x 50 mm
HPLC-column type:	Acquity UPLC HSS T3, 1.8 µm
HPLC-eluent:	A) water + 0.05 Vol.-% formic acid + 3.75 mM ammonium acetate B) ACN + 0.04 Vol.-% formic acid
HPLC-gradient:	2 - 98% B in 1.4 min, 98% B 0.45 min, flow = 1.2 ml / min
HPLC-column temperature:	50 °C

LCMS method M2 (Rt_{M2})

HPLC-column dimensions:	2.1 x 30 mm
HPLC-column type:	Ascentis Express C18, 2.7 µm
HPLC-eluent	A) water + 0.05 Vol.-% formic acid + 3.75 mM ammonium acetate B) ACN + 0.04 Vol.-% formic acid
HPLC-gradient:	2 - 98% B in 1.4 min, 0.75 min 98% B, flow = 1.2 ml / min
HPLC-column temperature:	50 °C

LCMS method M3 (Rt_{M3})

HPLC-column dimensions:	2.1 x 30 mm
HPLC-column type:	Ascentis Express C18, 2.7 µm
HPLC-eluent	A) water + 0.05 Vol.-% formic acid + 3.75 mM ammonium acetate B) ACN + 0.04 Vol.-% formic acid

HPLC-gradient:	2 - 98% B in 8.5 min, 1 min 98% B, flow = 1.2 ml / min
HPLC-column temperature:	50 °C

LCMS method M4 (Rt_{M4})

HPLC-column dimensions:	4.6 x 50 mm
HPLC-column type:	SunFire C18, 5 µm
HPLC-eluent	A) water + 0.1 Vol.-% TFA, B) ACN + 0.1 Vol.-% TFA
HPLC-gradient:	5 - 100% B in 8.0 min B, flow = 2 ml / min
HPLC-column temperature:	40 °C

LCMS method M5 (Rt_{M5})

HPLC-column dimensions:	0.46x25 cm
HPLC-column type:	Chiralcel OJ-H (1189)
HPLC-eluent	EtOH/MeOH 60:40
HPLC-gradient:	isocratic, flow=0.5ml/min
Detector:	UV 220 nm

LCMS method M6 (Rt_{M6})

HPLC-column dimensions:	2.1 x 30 mm
HPLC-column type:	Ascentis Express C18, 2.7 µm
HPLC-eluent	A) water + 0.05% TFA, B) ACN + 0.04% TFA
HPLC-gradient:	2 - 98% B in 1.4 min, 0.75 min 98% B, flow = 1.2 ml / min
HPLC-column temperature:	50 °C

LCMS method M7 (Rt_{M7})

HPLC-column dimensions:	2.1 x 30 mm
HPLC-column type:	Ascentis Express C18, 2.7 µm
HPLC-eluent	A) water + 0.05% TFA, B) ACN + 0.04% TFA
HPLC-gradient:	10 - 95% B in 3.0 min, 1 min 95% B, flow = 1.2 ml / min
HPLC-column temperature:	50 °C

LCMS method M8 (Rt_{M8})

HPLC-column dimensions:	2.1 x 30 mm
HPLC-column type:	Ascentis Express C18 2.7 µm
HPLC-eluent:	A) water + 0.05% formic acid + 3.75 mM ammonium acetate, B) acetonitrile +0.04% formic acid
HPLC-gradient:	10 - 95% B in 3.0 min, flow = 1.2 ml/min

LCMS method M9 (Rt_{M9})

HPLC-column dimensions:	2.1 x 30 mm
HPLC-column type:	Ascentis Express C18 2.7 µm
HPLC-eluent:	A) water + 0.05% formic acid + 3.75 mM ammonium acetate, B) acetonitrile +0.04% formic acid
HPLC-gradient:	10% B from 0.0 to 0.5 min then from 0.5 min to 3.0 min gradient 10 - 95% B, flow = 1.2 ml/min

LCMS method M10 (Rt_{M10})

HPLC-column dimensions:	2.1 x 50 mm
HPLC-column type:	Acquity UPLC BEH C18 1.7 µm
HPLC-eluent:	A) water + 0.1 Vol.-% formic acid, B) acetonitrile
HPLC-gradient:	20 - 25% B in 1.00 min, then 25 - 95% B in 3.20 min, then 95 - 100% B in 0.10 min, then 100% for 0.20 min, flow = 0.7 ml/min

LCMS method M11 (Rt_{M11})

HPLC-column dimensions:	2.1 x 50 mm
HPLC-column type:	Acquity UPLC BEH C18 1.7 µm
HPLC-eluent:	A) water + 0.1 Vol.-% formic acid, B) acetonitrile
HPLC-gradient:	5 - 10% B in 1.00 min, then 10 - 90% B in 3.00 min, then 90 - 100% B in 0.10 min, then 100% for 0.40 min, flow = 0.7 ml/min

LCMS method M12 (Rt_{M12})

HPLC-column dimensions:	2.1 x 30 mm
HPLC-column type:	Ascentis Express C18 2.7 µm
HPLC-eluent:	A) water + 0.1 Vol.-% TFA, B) acetonitrile
HPLC-gradient:	10 -95% B over 1.7 min and 1.2 mL/min as solvent flow and then 95 5 B over 0.7 min, flow = 1.4 mL/min.

LCMS method M13 (Rt_{M13})

HPLC-column dimensions:	2.1 x 30 mm
HPLC-column type:	Ascentis Express C18 2.7 µm
HPLC-eluent:	A) water + 0.05% formic acid + 3.75 mM ammonium acetate, B) acetonitrile +0.04% formic acid
HPLC-gradient:	10 - 95% B in 3.7 min, flow = 1.2 ml / min

LCMS method M14 (Rt_{M14})

HPLC-column dimensions:	2.1 x 30 mm
HPLC-column type:	Ascentis Express C18, 2.7 µm
HPLC-eluent	A) water + 0.05% formic acid + 3.75 mM ammonium acetate, B) acetonitrile +0.04% formic acid
HPLC-gradient:	10 - 95% B in 1.5 min, 1 min 95% B, flow = 1.2 ml / min

LCMS method M15 (Rt_{M15})

HPLC-column dimensions:	0.46x25 cm
HPLC-column type:	Chiralcel OD-H (1194)
HPLC-eluent	Hexan/EtOH 50:50 + 0.05% DEA
HPLC-gradient:	isocratic, flow=0.5ml/min
Detector:	UV 220 nm

LCMS method M16 (Rt_{M16})

HPLC-column dimensions:	2.1 x 50 mm
HPLC-column type:	Acquity UPLC HSS T3, 1.8 µm
HPLC-eluent:	A) water + 0.05 Vol.-% formic acid + 3.75 mM ammonium acetate B) ACN + 0.04 Vol.-% formic acid
HPLC-gradient:	5 - 98% B in 1.4 min, 98% B 0.4 min, flow = 1.0 ml / min
HPLC-column temperature:	60 °C

X-ray Powder Diffraction

Instrumentation:

Method X1

Instrument	Bruker D8 GADDS Discover
Irradiation	CuKα (40 kV, 40 mA)
Detector	HI-STAR Area detector
Scan range	6°-39° (2 theta value)

Melting Point determination:

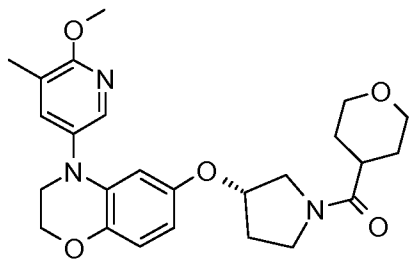
Melting point was determined by Differential Scanning calorimetry (DSC). DSC was as recorded on a TA Instruments DSC Q2000 using a heating rate of 10°C/min. A sample of 0.6 mg was weighed into standard aluminium pan (pan + lid, TA 900786.901, 900779.901). The instrument was operated using the Thermal Advantage Q-Series software V.2.6.0.367 and

the Thermal Advantage software V4.6.9. Thermal events were characterized using Universal Analysis V4.3A Build 4.3.0.6. The samples was measured against sample pan without pin hole. The sample was treated according to the protocol below:

Step 1: EQUILIBRATE AT 0°C
Step 2: Ramp 10°C/min to 300°C

Preparation of examples

Where it is stated that compounds were prepared in the manner described for an earlier 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.



Example A1: (S)-(3-((4-(6-methoxy-5-methylpyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone (according to Scheme 1)

a1) (R)-(3-hydroxypyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone

A stirred solution of tetrahydro-2H-pyran-4-carboxylic acid (CAS registry 5337-03-1) (0.200 g, 1.537 mmol) and DMF (0.012 ml, 0.154 mmol) in DCM (3 ml) was treated with oxalyl chloride (0.202 ml, 2.305 mmol) at 3°C. After 1 h at 3°C, the reaction mixture was concentrated under reduced pressure. The residue was then dissoved in DCM (2 ml), and added to a stirred solution of (R)-pyrrolidin-3-ol hydrochloride (CAS registry 104706-47-0) (0.190 g, 1.537 mmol), Et_3N (0.535 ml, 3.84 mmol) in DCM (3 ml) at 3°C. After 1 h at 3°C, the reaction mixture was concentrated under reduced pressure. The residue was treated with EtOAc (10ml) and filtered. The residue was washed with EtOAc, and the combined filtrates were concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM / methanol gradient) to provide the title compound as a white solid.

ESIMS: 200 $[(M+H)^+]$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.61-4.50 (m, 1H), 4.10-4.02 (m, 2H), 3.77-3.40 (m, 6H), 2.70-2.53 (m, 1H), 2.20-1.85 (m, 4H), 1.75-1.69 (m, 3H).

alternative method a2: instead of preparing the acid chloride in situ, a commercially available acid chloride like propanoyl chloride (CAS registry 79-03-8) was used.

b1) (R)-1-(tetrahydro-2H-pyran-4-carbonyl)pyrrolidin-3-yl methanesulfonate

A stirred solution of (R)-(3-hydroxypyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone (0.245 g, 1.230 mmol) in DCM (10 ml) was treated with Et_3N (0.343 ml, 2.459 mmol) and methanesulfonyl chloride (0.192 ml, 2.459 mmol) at 0 °C. After 1 h at 0 °C, water (20 ml) was added. The organic layer was washed with a saturated NaCl solution (20 ml), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by trituration with diethyl ether to provide the title compound as a white solid.

ESIMS: 278 [$(M+H)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40-.5.29 (m, 1H), 4.10-4.02 (m, 2H), 3.94-3.87 (m, 1H), 3.82-3.56 (m. 3H), 3.52-3.41 (m, 2H), 3.11-3.04 (m, 3H), 2.70-2.10 (m, 3H), 2.02-2.87 (m, 2H), 1.72-1.57 (m, 2H).

c1) (S)-(3-((3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone

A stirred solution of 3,4-dihydro-2H-benzoxazin-6-ol (CAS registry 26021-57-8) (0.140 g, 0.926 mmol) in DMF (3 ml) was treated with sodium hydride (60% in mineral oil, 0.445 g, 1.111 mmol) at rt. After 10 min at rt, (R)-1-(tetrahydro-2H-pyran-4-carbonyl)pyrrolidin-3-yl methanesulfonate (0.283 g, 1.019 mmol) was added. The vial was capped and heated to 50°C for 3 h. After this time, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (50 ml), and water (50 ml) was added. The organic layer was washed with a saturated NaCl solution (20 ml), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM / methanol gradient) to provide the title compound as a grey amorphous solid.

HPLC Rt_{M10}= 2.07 min; ESIMS: 333 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.55-6.50 (m, 1H), 6.15-6.11 (m, 1H), 6.07-6.00 (m, 1H), 5.77 (br s, 1H), 4.88-4.74 (m, 1H), 4.06-4.01 (m, 2H), 3.90-3.22 (m, 10H), 2.75-2.58 (m, 1H), 2.15-1.95 (m, 2H), 1.65-1.45 (m, 4H).

d1) (S)-(3-((4-(6-methoxy-5-methylpyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone

A stirred solution of (S)-(3-((3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone (0.050 g, 0.150 mmol) in toluene (1 ml) was treated with 5-bromo-2-methoxy-3-methylpyridine (CAS registry 760207-87-2) (0.030 g, 0.150 mmol), NaOtBu (0.022 g, 0.226 mmol), 2-(dicyclohexylphosphino)biphenyl (CAS registry 247940-06-3) and $Pd_2(dba)_3$ (0.004 g, 0.005 mmol) at rt under argon. The reaction vial was capped and heated to 110°C in a microwave reactor for 3 h. After this time, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (cyclohexane / EtOAc gradient) to provide the title compound as an off-white solid.

HPLC Rt_{M10}= 2.85 min; ESIMS: 454 [$(M+H)^+$].

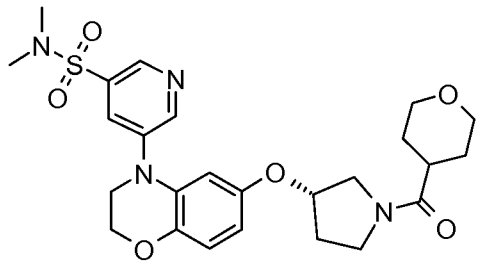
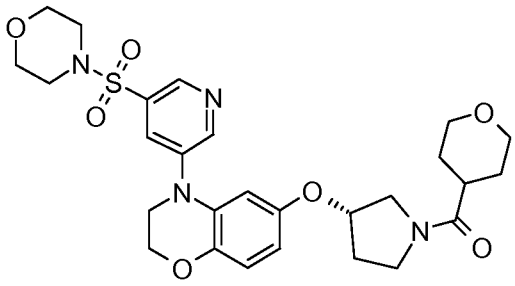
^{1}H NMR (400 MHz, CD_3OD): δ 7.90-7.85 (m, 1H), 7.49-7.44 (m, 1H), 6.76-6.69 (m, 1H), 6.32-6.24 (m, 1H), 6.07-6.02 (m, 1H), 4.86-4.73 (m, 1H), 4.29-4.23 (m, 2H), 4.02-3.92 (m, 5H), 3.80-3.40 (m, 8H), 2.85-2.60 (m, 1H), 2.25-1.91 (m, 5H), 1.85-1.50 (m, 4H).

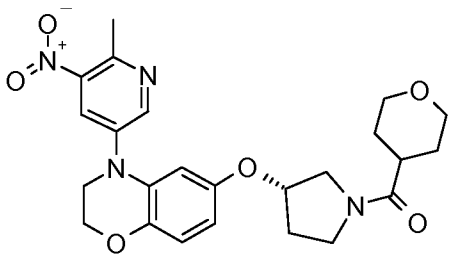
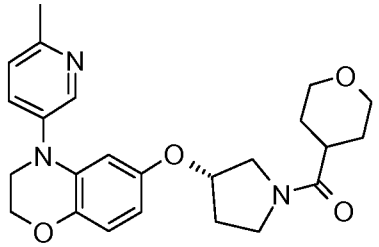
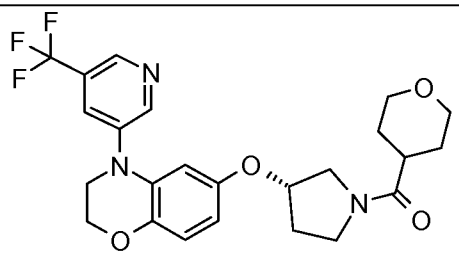
alternative method d2: 2-(dicyclohexylphosphino)biphenyl (CAS registry 247940-06-3) was replaced with 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (CAS registry 564483-18-7)

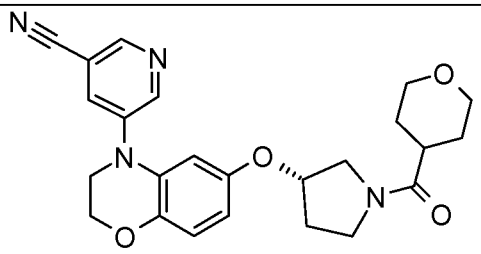
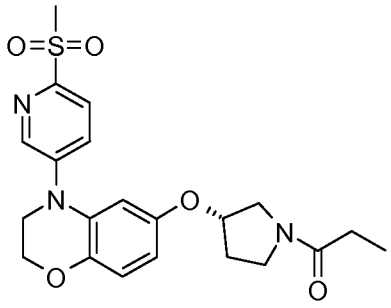
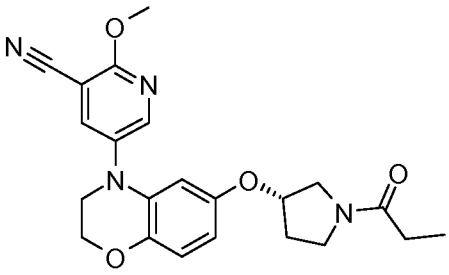
alternative method d3: 2-(dicyclohexylphosphino)biphenyl (CAS registry 247940-06-3) and $Pd_2(dba)_3$ was replaced with bis(tri-t-butylphosphine)palladium (CAS registry 53199-31-8)

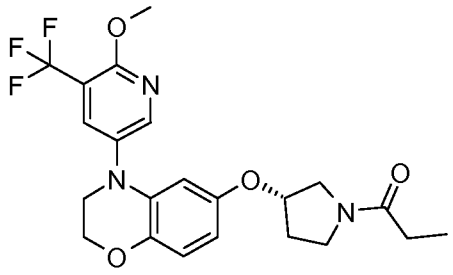
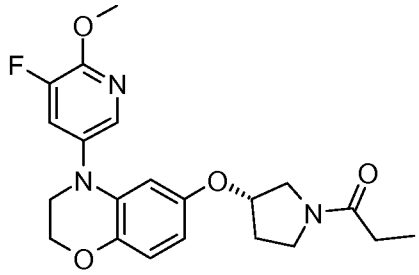
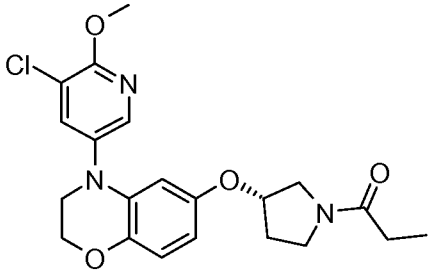
Examples A2 to A43: The compounds listed in Table 1 were prepared by a procedure analogous to that used in Example A1.

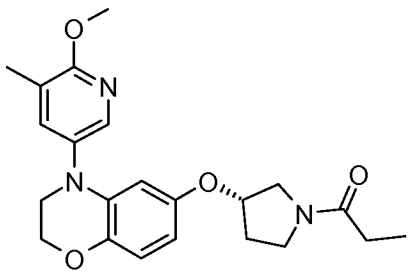
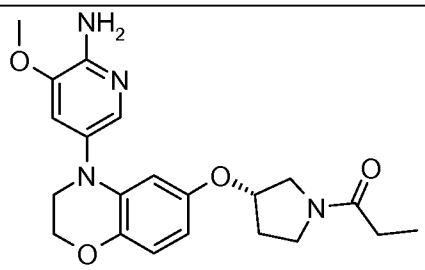
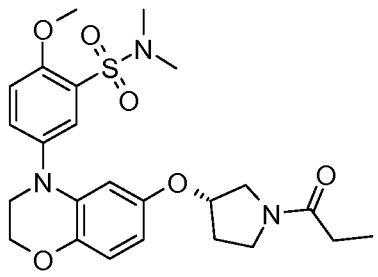
Table 1

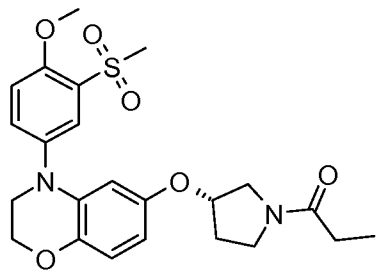
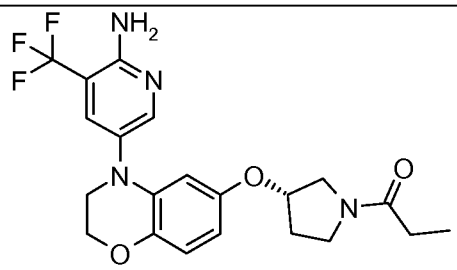
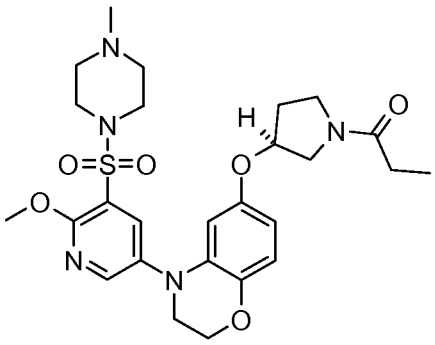
Example	Compound	HPLC Rt [min] (method)	MS [m/z; $(M+1)^+$]
A2	 5-{6-[(S)-1-(Tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-pyridine-3-sulfonic acid dimethylamide Synthetic route used: a1, b1, c1, d1 (intermediate IA13)	2.50 (M10)	517
A3	 ((S)-3-{4-[5-(Morpholine-4-sulfonyl)-pyridin-3-yl]-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy}-pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone Synthetic route used: a1, b1, c1, d1 (intermediate IA14)	1.10 (M12)	560

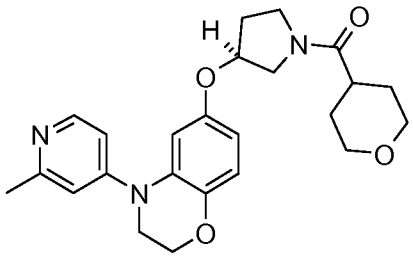
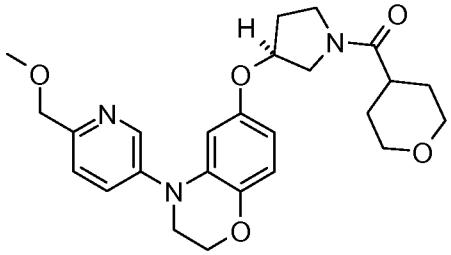
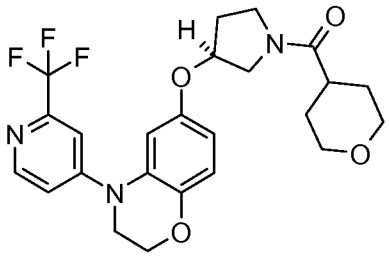
A4	 {(S)-3-[4-(6-Methyl-5-nitro-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Synthetic route used: a1, b1, c1, d1 (intermediate IA15)	1.78 (M10)	469
A5	 {(S)-3-[4-(6-Methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Synthetic route used: a1, b1, c1, d1 (intermediate IA16)	1.03 (M10)	425
A6	 (Tetrahydro-pyran-4-yl)-{(S)-3-[4-(5-trifluoromethyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Synthetic route used: a1, b1, c1, d1 (intermediate IA18)	1.21 (M12)	479

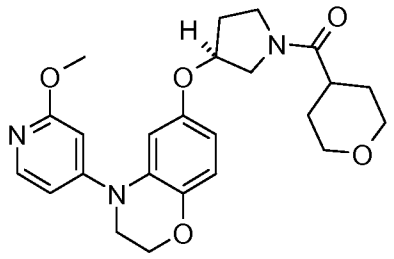
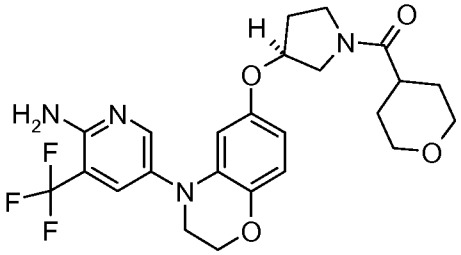
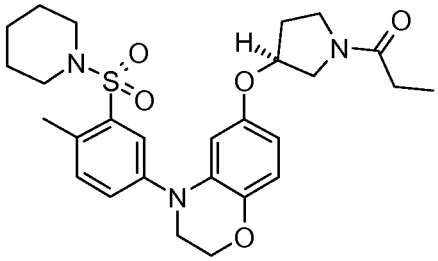
A7	 5-{6-[(S)-1-(Tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1, c1, d2 (intermediate IA17)	2.44 (M10)	435
A8	 1-{(S)-3-[4-(6-Methanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a2, b1, c1, d2 (intermediate IA40)	1.46 (M8)	432
A9	 2-Methoxy-5-[6-((S)-1-propionyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-nicotinonitrile Synthetic route used: a2, b1, c1, d2 (intermediate IA12)	2.80 (M10)	409

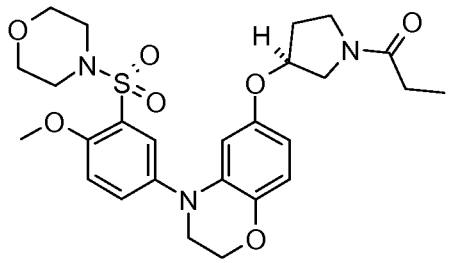
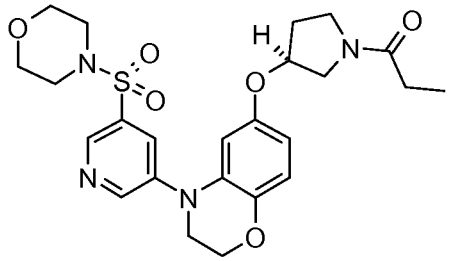
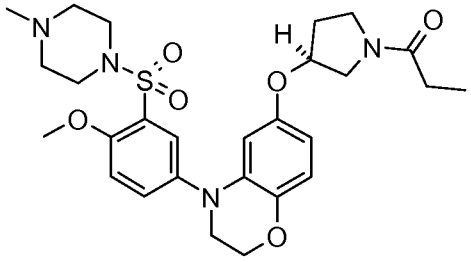
A10	 1-{(S)-3-[4-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a2, b1, c1, d2 (intermediate IA21)	2.74 (M11)	452
A11	 1-{(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a2, b1, c1, d2 (intermediate IA10)	2.86 (M10)	402
A12	 1-{(S)-3-[4-(5-Chloro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a2, b1, c1, d2 (intermediate IA11)	3.00 (M10)	418

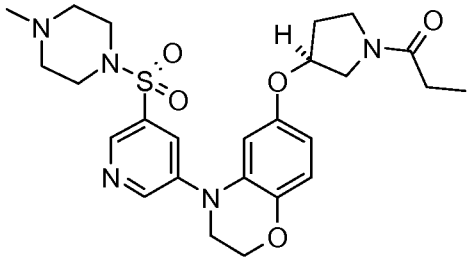
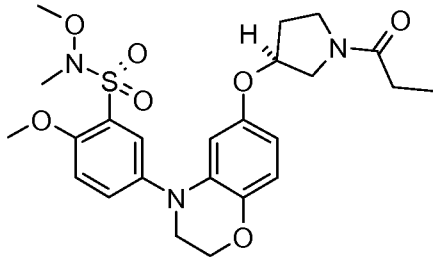
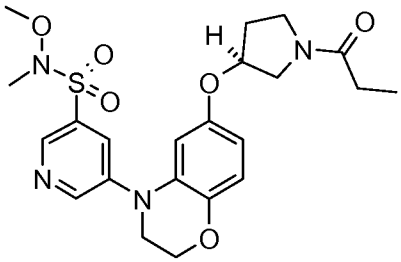
A13	 1-{(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a2, b1, c1, d2 (intermediate IA9)	2.93 (M10)	398
A14	 1-{(S)-3-[4-(6-Amino-5-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a2, b1, c1, d2 (intermediate IA46)	1.98 (M10)	399
A15	 2-Methoxy-N,N-dimethyl-5-[6-((S)-1-propionyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-benzenesulfonamide Synthetic route used: a2, b1, c1, d2 (intermediate IA60)	2.76 (M10)	490

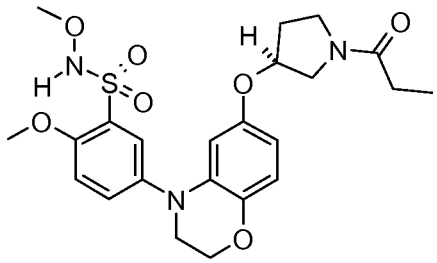
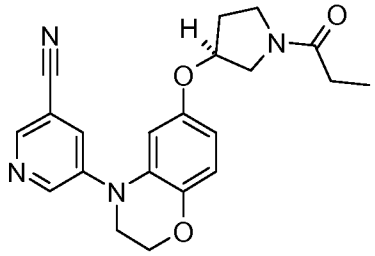
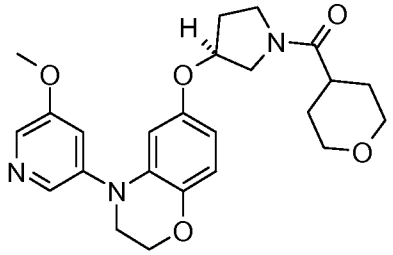
A16	 1-{(S)-3-[4-(3-Methanesulfonyl-4-methoxy-phenyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a2, b1, c1, d2 (intermediate IA59)	2.56 (M10)	461
A17	 1-{(S)-3-[4-(6-Amino-5-trifluoromethyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a2, b1, c1, d2 (intermediate IA23)	2.67 (M10)	437
A18	 1-((S)-3-{4-[6-Methoxy-5-(4-methyl-piperazine-1-sulfonyl)-pyridin-3-yl]-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy}-pyrrolidin-1-yl)-propan-1-one Synthetic route used: a2, b1, c1, d3 (intermediate IA24)	1.60 (M9)	546

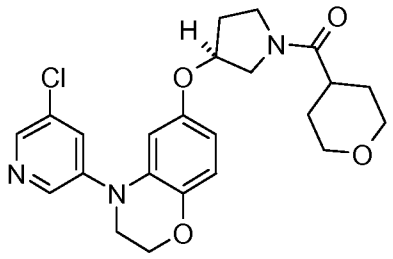
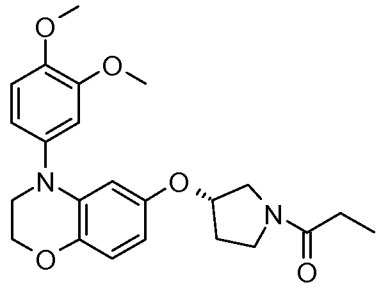
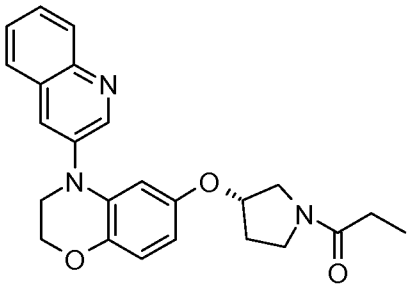
A19	 {(S)-3-[4-(2-Methyl-pyridin-4-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Synthetic route used: a1, b1, c1, d3 (intermediate IA61)	1.32 (M9)	424
A20	 {(S)-3-[4-(6-Methoxymethyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Synthetic route used: a1, b1, c1, d3 (intermediate IA25)	1.47 (M9)	454
A21	 (Tetrahydro-pyran-4-yl)-{(S)-3-[4-(2-trifluoromethyl-pyridin-4-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Synthetic route used: a1, b1, c1, d3 (intermediate IA63)	1.61 (M9)	478

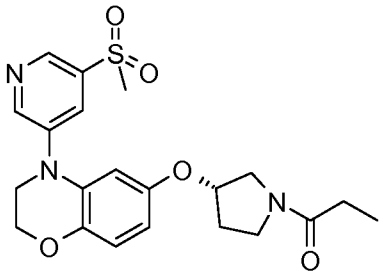
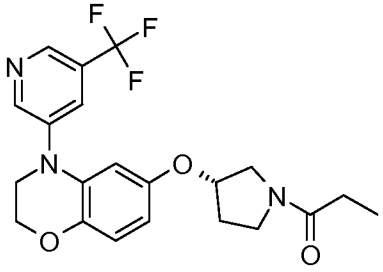
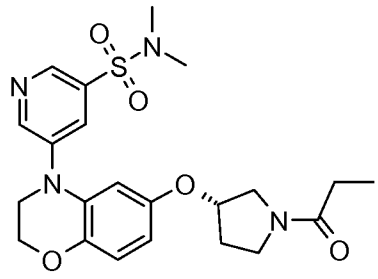
A22	 {(S)-3-[4-(2-Methoxy-pyridin-4-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Synthetic route used: a1, b1, c1, d3 (intermediate IA62)	1.43 (M9)	440
A23	 {(S)-3-[4-(6-Amino-5-trifluoromethyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Synthetic route used: a1, b1, c1, d3 (intermediate IA23)	1.57 (M9)	493
A24	 1-((S)-3-{4-[4-Methyl-3-(piperidine-1-sulfonyl)-phenyl]-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy}-pyrrolidin-1-yl)-propan-1-one Synthetic route used: a2, b1, c1, d3 (intermediate IA31)	2.04 (M9)	514

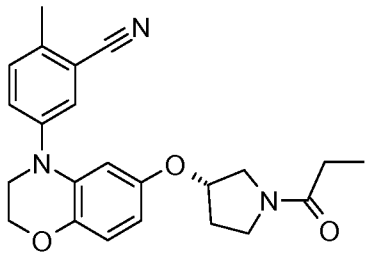
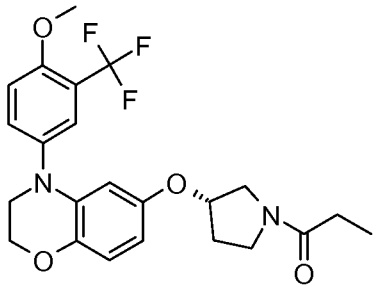
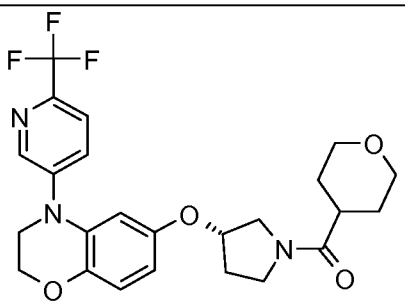
A25	 1-((S)-3-{4-[4-Methoxy-3-(morpholine-4-sulfonyl)-phenyl]-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy}-pyrrolidin-1-yl)-propan-1-oneSynthetic route used: a2, b1, c1, d3 (intermediate IA32)	1.83 (M9)	532
A26	 1-((S)-3-{4-[5-(Morpholine-4-sulfonyl)-pyridin-3-yl]-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy}-pyrrolidin-1-yl)-propan-1-one Synthetic route used: a2, b1, c1, d3 (intermediate IA33)	1.83 (M9)	503
A27	 1-((S)-3-{4-[4-Methoxy-3-(4-methyl-piperazine-1-sulfonyl)-phenyl]-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy}-pyrrolidin-1-yl)-propan-1-one Synthetic route used: a2, b1, c1, d3 (intermediate IA34)	2.22 (M9)	545

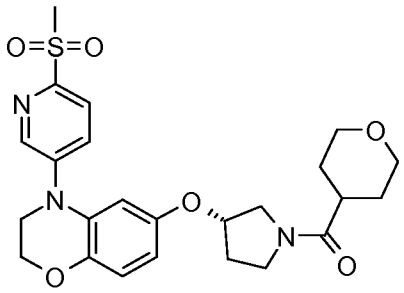
A28	 1-((S)-3-{4-[5-(4-Methyl-piperazine-1-sulfonyl)-pyridin-3-yl]-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy}-pyrrolidin-1-yl)-propan-1-one Synthetic route used: a2, b1, c1, d3 (intermediate IA35)	2.08 (M9)	516
A29	 2,N-Dimethoxy-N-methyl-5-[6-((S)-1-propionyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-benzenesulfonamide Synthetic route used: a2, b1, c1, d3 (intermediate IA36)	2.82 (M9)	506
A30	 5-[6-((S)-1-Propionyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-pyridine-3-sulfonic acid methoxy-methyl-amide Synthetic route used: a2, b1, c1, d3 (intermediate IA37)	2.69 (M9)	477

A31	 2,N-Dimethoxy-5-[6-((S)-1-propionyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-benzenesulfonamide Synthetic route used: a2, b1, c1, d3 (intermediate IA65)	2.72 (M9)	492
A32	 5-[6-((S)-1-Propionyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-nicotinonitrile Synthetic route used: a2, b1, c1, d3 (intermediate IA17)	2.49 (M9)	379
A33	 {(S)-3-[4-(5-Methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Synthetic route used: a1, b1, c1, d3 (intermediate IA38)	1.54 (M9)	440

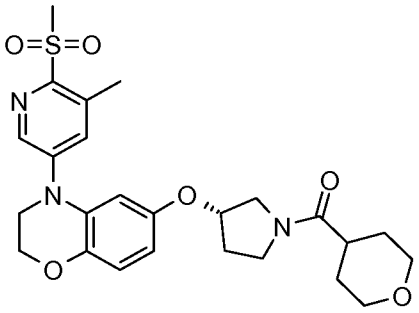
A34	 {(S)-3-[4-(5-Chloro-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Synthetic route used: a1, b1, c1, d3 (intermediate IA39)	1.76 (M9)	444
A35	 1-{(S)-3-[4-(3,4-Dimethoxy-phenyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a1, b1, c1, d3 (intermediate IA66)	1.24 (M6)	413
A36	 1-[(S)-3-(4-Quinolin-3-yl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy)-pyrrolidin-1-yl]-propan-1-one Synthetic route used: a1, b1, c1, d3 (intermediate IA54)	1.02(M6)	404

A37	 1-{(S)-3-[4-(5-Methanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a1, b1, c1, d3 (intermediate IA55)	1.03 (M6)	432
A38	 1-{(S)-3-[4-(5-Trifluoromethyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a1, b1, c1, d3 (intermediate IA18)	1.24 (M6)	422
A39	 5-[6-((S)-1-Propionyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-pyridine-3-sulfonic acid dimethylamide Synthetic route used: a1, b1, c1, d3 (intermediate IA13)	1.13 (M6)	461

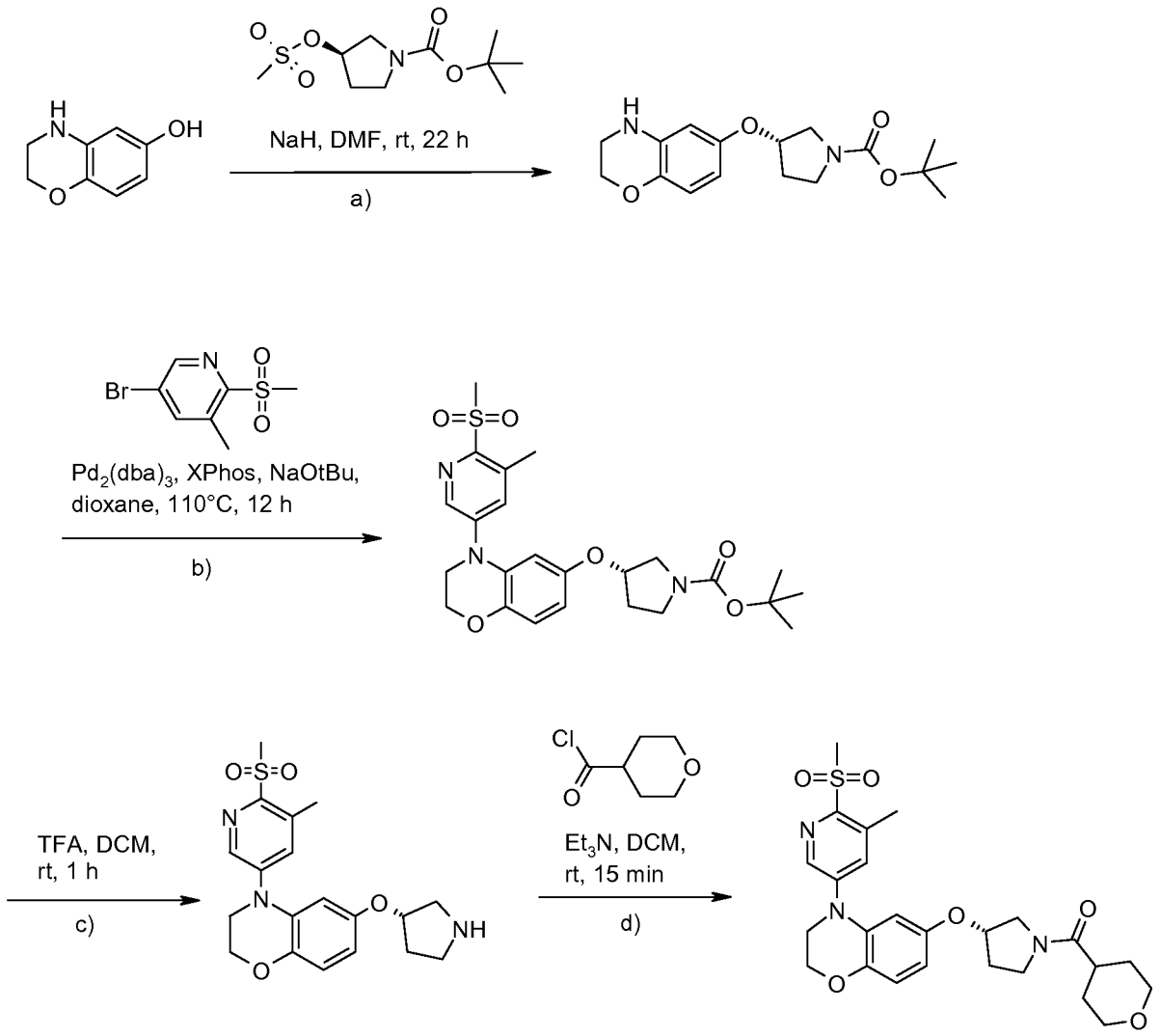
A40	 2-Methyl-5-[6-((S)-1-propionyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-benzonitrile Synthetic route used: a1, b1, c1, d3 (intermediate IA56)	1.33 (M6)	392
A41	 1-{(S)-3-[4-(4-Methoxy-3-trifluoromethyl-phenyl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Synthetic route used: a1, b1, c1, d3 (intermediate IA57)	1.44 (M6)	451
A42	 (Tetrahydro-pyran-4-yl)-{(S)-3-[4-(6-trifluoromethyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Synthetic route used: a1, b1, c1, d3 (intermediate IA26)	1.82 (M6)	478

A43	 {(S)-3-[4-(6-Methanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Synthetic route used: a1, b1, c1, d3 (intermediate IA40)	1.44 (M6)	488

5



<u>Example B1:</u> {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone (according to Scheme 2)



a) (S)-3-(3,4-Dihydro-2H-benzo[1,4]oxazin-6-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of 3,4-dihydro-2H-benzo[1,4]oxazin-6-ol (CAS registry 26021-57-8) (4.0 g, 26.5 mmol) in DMF (150 ml) was treated with NaH (2.117 g, 52.9 mmol) for 20 min at 20 °C. (R)-3-Methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester (CAS registry 127423-61-4) (9.13 g, 34.4 mmol) was added. After stirring for 22 h at rt the reaction mixture was concentrated to dryness, then taken up with EtOAc, filtered through hyflo and the filtrate was washed with sat. aq. Na_2CO_3 solution. Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography on silica gel (cyclohexane / isopropanol 100:0 to 85:15 in 40 min) to provide the title compound as a yellow oil.

HPLC Rt_{M8} =1.84 min; ESIMS: 321 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO): 6.52 (d, 1H), 6.12 (d, 1H), 6.02 (m, 1H), 5.76 (m, 1H), 4.75 (br s, 1H), 4.01-40.5 (m, 2H), 3.27-3.50 (m, 4H), 3.22-3.26 (m, 2H), 1.95-2.08 (m, 2H), 1.39 (m, 9H).

b) (S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (S)-3-(3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (2.12 g, 6.62 mmol), 5-bromo-2-methanesulfonyl-3-methyl-pyridine (Intermediate IA1) (2.091 g, 7.94 mmol), NaOtBu (1.272 g, 13.23 mmol), XPhos ligand (0.158 g, 0.331 mmol) and $Pd_2(dba)_3$ (0.303 g, 0.331 mmol) in dioxane (3.5 ml) was degassed and stirred for 12 h at 110 °C. Sat. aq. $NaHCO_3$ solution was added and the reaction mixture was extracted with EtOAc. Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography on silica gel (cyclohexane / EtOAc 100:0 to 50:50) to provide the title compound.

HPLC Rt_{M14} =1.25 min; ESIMS: 490 [$(M+H)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, 1H), 7.43 (d, 1H), 6.86 (d, 1H), 6.59 (d, 1H), 6.47 (m, 1H), 4.69-4.73 (m,12H), 4.23-4.28 (m, 2H), 3.73-3.78 (m, 2H), 3.41-3.58 (m, 4H), 3.34 (s, 3H), 2.69 (s, 3H), 1.96-2.17 (m, 2H), 1.46 (s, 9H).

c) 4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-6-((S)-pyrrolidin-3-yloxy)-3,4-dihydro-2H-benzo[1,4]oxazine

A solution of (S)-3-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (1.5 g, 3.06 mmol) and TFA (0.236 ml, 3.06 mmol) in DCM (15 ml) was stirred for 1 h at rt. The reaction mixture was cooled down to 0°C, sat. Na_2CO_3 solution was added and the reaction mixture was extracted with DCM. Combined organic layers were dried over Na_2SO_4, filtered and evaporated to provide the title compound.

HPLC Rt_{M2} =0.66 min; ESIMS: 390 [$(M+H)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, 1H), 7.43 (d, 1H), 6.86 (d, 1H), 6.58 (d, 1H), 6.47 (m, 1H), 4.68 (m, 1H), 4.22-4.27 (m, 2H), 3.73-3.78 (m, 2H), 3.33 (s, 3H), 3.12-3.22 (m, 2H), 2.86-3.04 (m, 2H), 2.68 (s, 3H), 1.88-2.08 (m, 2H).

d) {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone

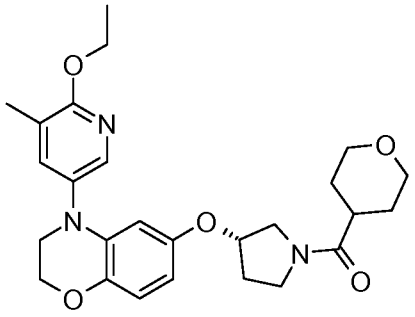
A mixture of 4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-6-((S)-pyrrolidin-3-yloxy)-3,4-dihydro-2H-benzo[1,4]oxazine (0.085 g, 0.218 mmol), tetrahydro-2H-pyran-4-carbonyl chloride (CAS registry 40191-32-0) (0.049 mg, 0.327 mmol) and Et_3N (0.046 ml, 0.327 mmol) in DCM (4 ml) was stirred at rt for 15 min. The reaction mixture was concentrated to dryness.

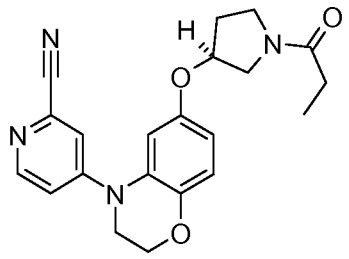
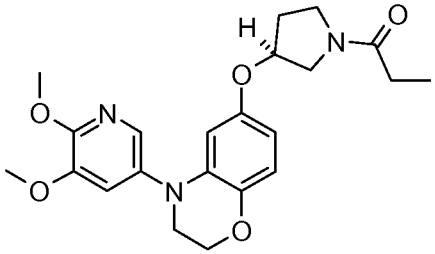
The crude product was purified by prep. RP-HPLC (column SunFire C18, H_2O + 0.1% TFA / ACN + 0.1% TFA 90:10 to 30:70 in 12 min) to provide the title compound as a white solid. HPLC Rt_{M7} =1.62 min; ESIMS: 502 [$(M+H)^+$].

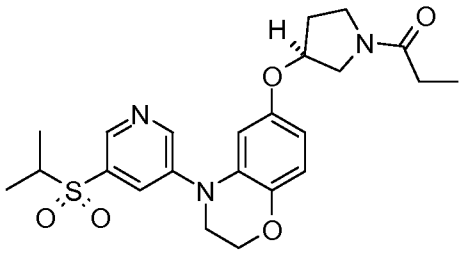
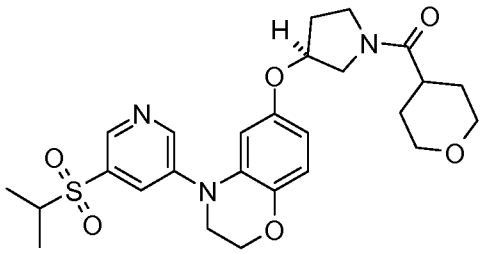
^1H NMR (400 MHz, DMSO): δ 8.38-8.42 (m, 1H), 7.72 (m, 1H), 6.84 (d, 1H), 6.67 (m, 1H), 6.50-6.57 (m, 1H), 4.82-4.94 (m, 1H), 4.20 (m, 2H), 3.31 (s, 3H), 3.28-3.88 (m, 10H), 2.59-2.73 (m, 1H), 2.56 (s, 3H), 1.95-2.13 (m, 2H), 1.44-1.62 (m, 4H).

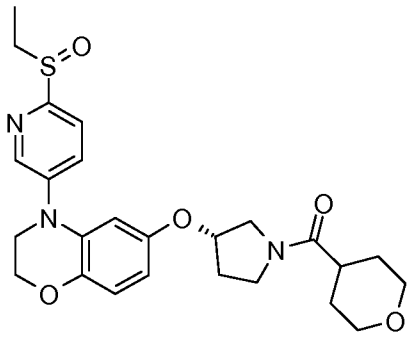
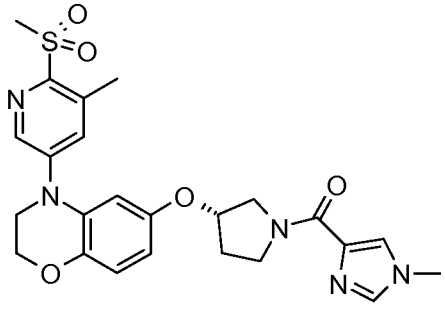
Examples B2 to B122: The compounds listed in Table 2 were prepared by a procedure analogous to that used in Example B1.

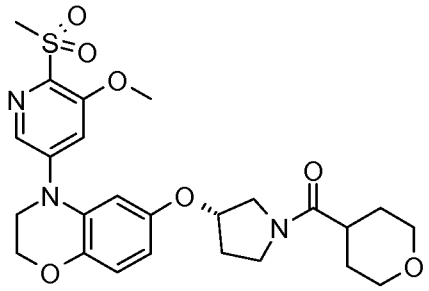
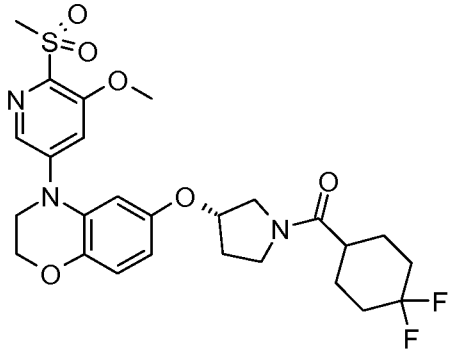
Table 2

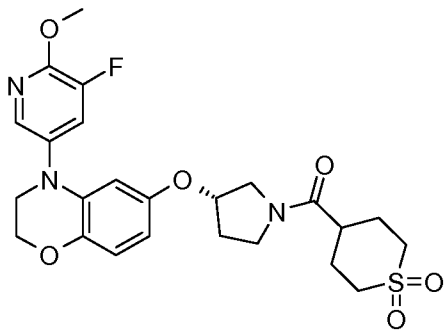
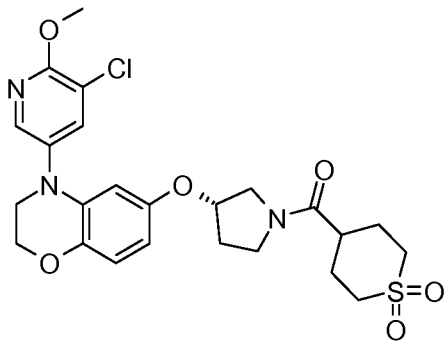
Example	Compound / Reaction Conditions	HPLC Rt [min] (method)	MS [m/z; $(M+1)^+$]
B2	 {(S)-3-[4-(6-Ethoxy-5-methyl-pyridin-3-yl)-3,4dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 ,127423-61-4, IA19, 40191-32-0	2.00 (M8)	**468**

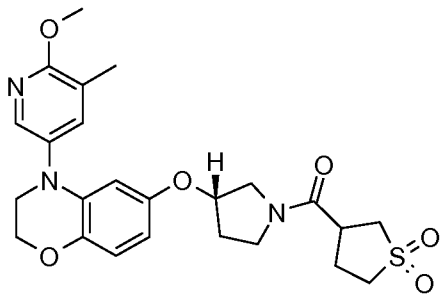
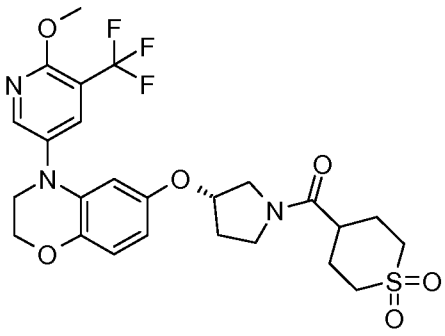
B3	 4-[6-((S)-1-Propionyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-pyridine-2-carbonitrile Buchwald amination condition: CA12 Amide bond condition: CB6 Side chain introduction condition: Precursors used: CAS 26021-57-8 ,127423-61-4, IA30, 79-03-8	1.53 (M8)	**379**
B4	 1-{(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Buchwald amination condition: CA8 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 ,127423-61-4, IA31, 79-03-8	1.58 (M9)	**414**

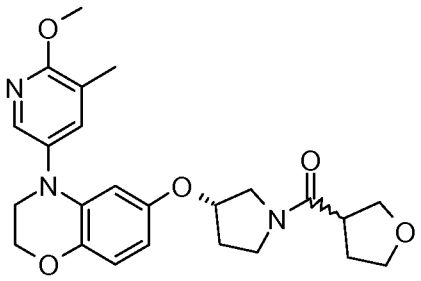
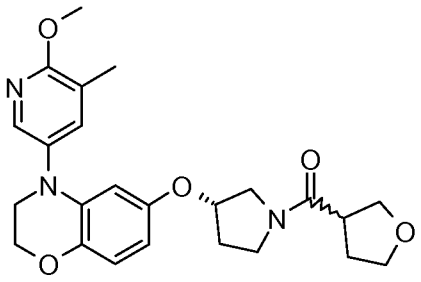
B5	 1-((S)-3-{4-[5-(Propane-2-sulfonyl)-pyridin-3-yl]-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy}-pyrrolidin-1-yl)-propan-1-one Buchwald amination condition: CA8 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 ,127423-61-4, IA30, 79-03-8	2.61 (M10)	**460**
B6	 ((S)-3-{4-[5-(Propane-2-sulfonyl)-pyridin-3-yl]-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy}-pyrrolidin-1-yl) -(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA8 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 ,127423-61-4, IA30, 40191-32-0	1.50 (M9)	**560**

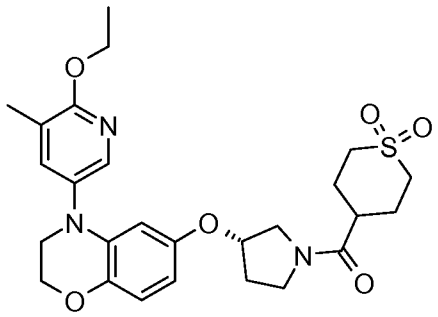
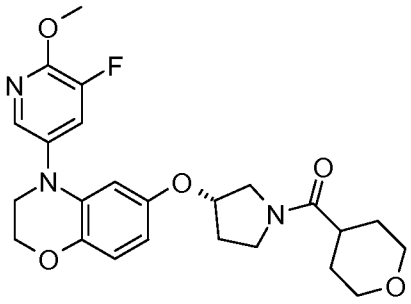
B7	 {(S)-3-[4-(6-Ethanesulfinyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA13 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 ,127423-61-4, IA58, 40191-32-0	1.37 (M8)	**486**
B8	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA14 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 ,127423-61-4, IA1, 41716-18-1	1.27 (M8)	**498**

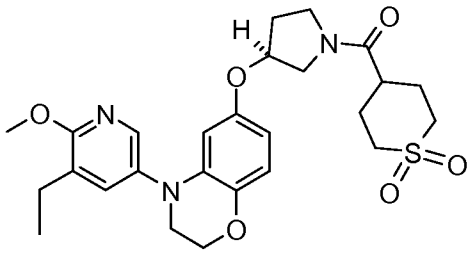
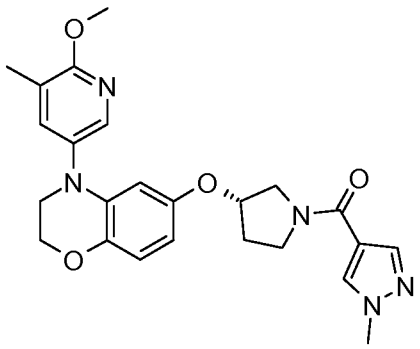
B9	 {(S)-3-[4-(6-Methanesulfonyl-5-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA14 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 ,127423-61-4, IA45, 40191-32-0	1.34 (M8)	**518**
B10	 (4,4-Difluoro-cyclohexyl)-{(S)-3-[4-(6-methanesulfonyl-5-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA14 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 ,127423-61-4, IA45, 122665-97-8	1.68 (M8)	**522**

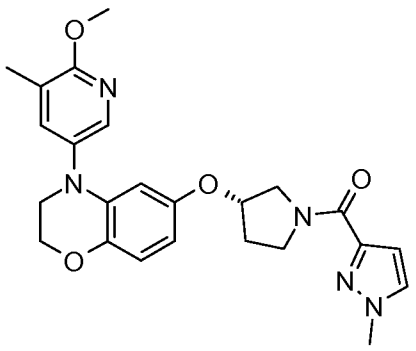
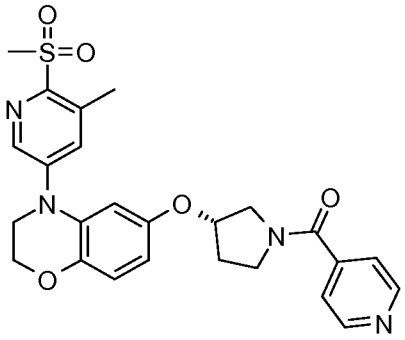
B11	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[4-(5-fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2 H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 64096-87-3	1.67 (M8)	506
B12	 {(S)-3-[4-(5-Chloro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1, 1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA11 / 64096-87-3	1.80 (M8)	522, 524

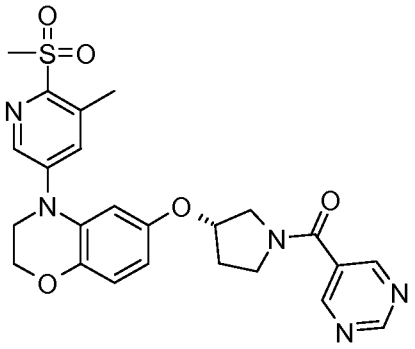
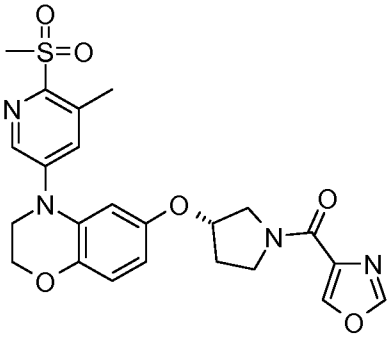
B13	 (1,1-Dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-{(S)-3-[4-(6-methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2 H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA16 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA9 /4785-67-5	1.74 (M8)	488
B14	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[4-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA21 / 64096-87-3	1.95 (M8)	556

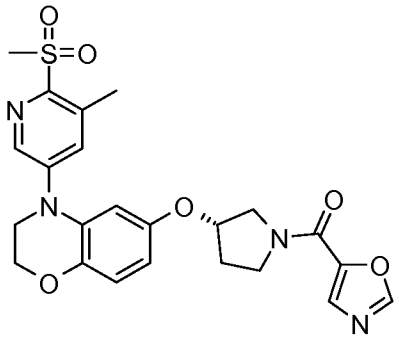
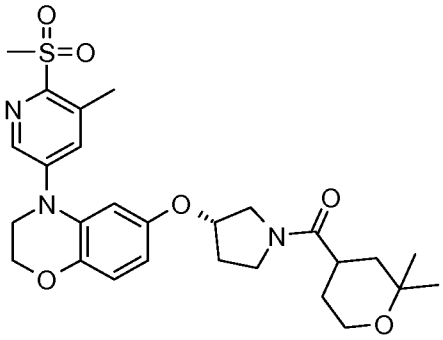
B15	 {(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-furan-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA9 / 89364-31-8 Chiral separation: CD9	1.89 (M7)	440
B16	 {(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-furan-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-614 / IA9 / 89364-31-8 Chiral separation: CD9	1.89 (M7)	440

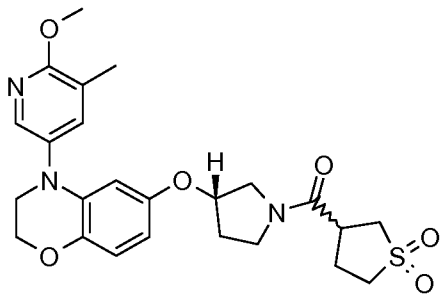
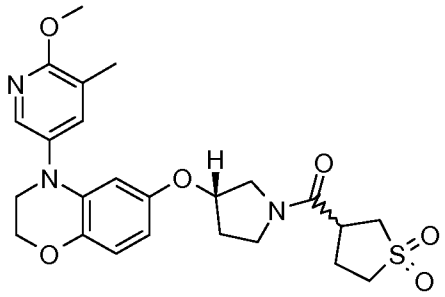
B17	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[4-(6-ethoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB7 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA19 / 64096-87-3	1.88 (M8)	516
B18	 ({(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(te trahydro-pyran-4-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 40191-32-0	1.86 (M7)	458

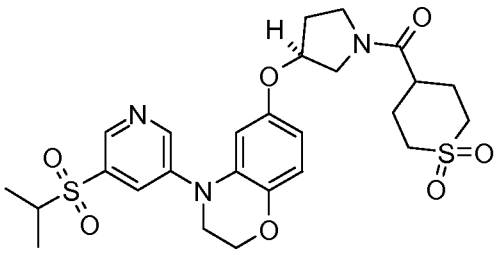
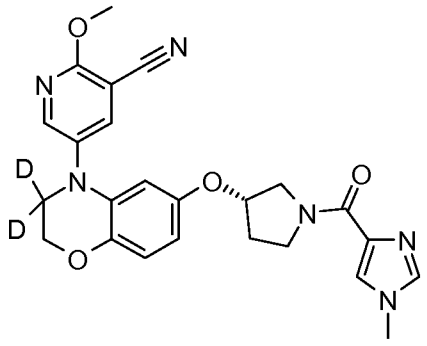
B19	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[4-(5-ethyl-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H -benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA8 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA48 / 64096-87-3	1.04 (M2)	516
B20	 {(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1- methyl-1H-pyrazol-4-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA9 / 5952-92-1	1.70 (M8)	450

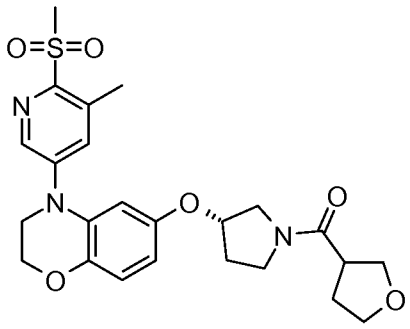
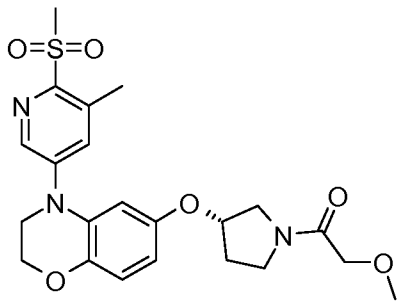
B21	 {(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-pyrazol-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA9 / 25016-20-0	1.87 (M8)	450
B22	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-pyridin-4-yl-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 55-22-1	0.85 (M6)	495

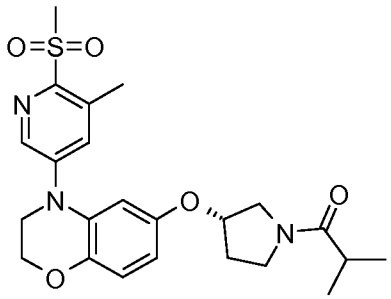
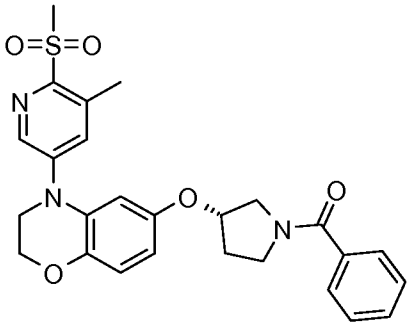
B23	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1 -yl}-pyrimidin-5-yl-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 4595-61-3	0.92 (M6)	496
B24	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1 -yl}-oxazol-4-yl-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 23012-13-7	0.95 (M6)	485

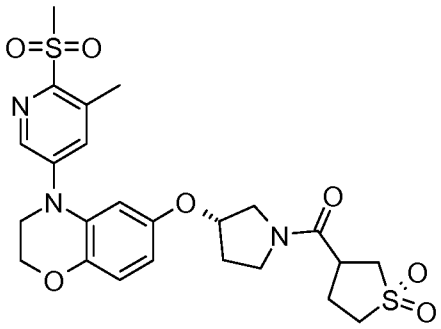
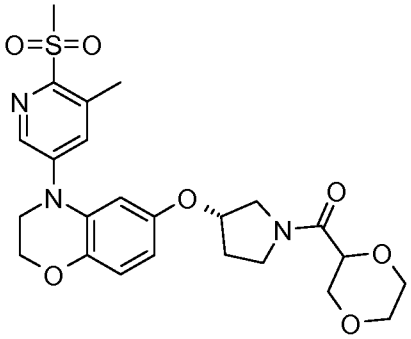
B25	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1 -yl}-oxazol-5-yl-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 118994-90-4	0.94 (M6)	485
B26	 (2,2-Dimethyl-tetrahydro-pyran-4-yl)-{(S)-3-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 52916-16-2	1.01 (M6)	530

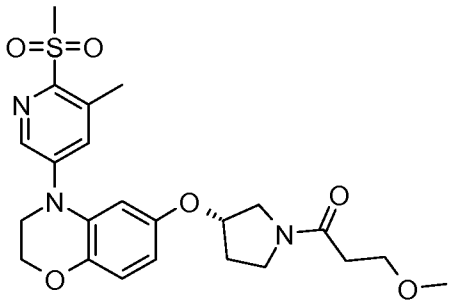
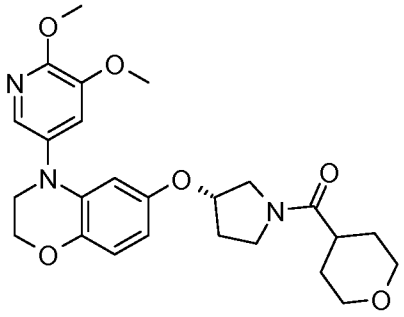
B27	 (1,1-Dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-{(S)-3-[4-(6-methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2 H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA9 /4785-67-5 Chiral separation : CD8	1.62 (M2)	488
B28	 (1,1-Dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-{(S)-3-[4-(6-methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2 H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA9 / 4785-67-5 Chiral separation: CD8	1.62 (M2)	488

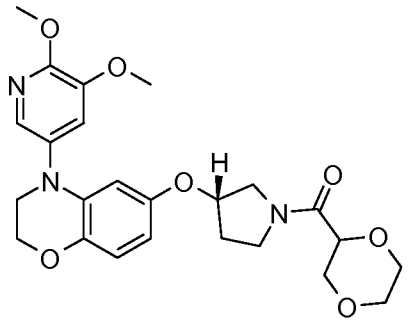
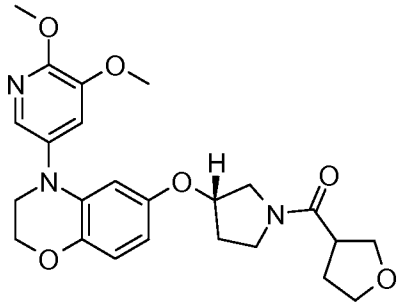
B29	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-((S)-3-{4-[5-(propane-2-sulfonyl)-pyridin-3-yl]-3,4-dihyd ro-2H-benzo[1,4]oxazin-6-yloxy}-pyrrolidin-1-yl)-methanone Buchwald amination condition: CA8 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA30/ 64096-87-3	1.53 (M6)	564
B30	 2-Methoxy-5-{6-[(S)-1-(1-methyl-1H-imidazole-4-carbonyl)-pyrrolidin-3-yloxy]-3,3-dideutero-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA15 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: ID1, CAS 127423-61-4, IA12, CAS 41716-18-1	1.50 (M9)	464

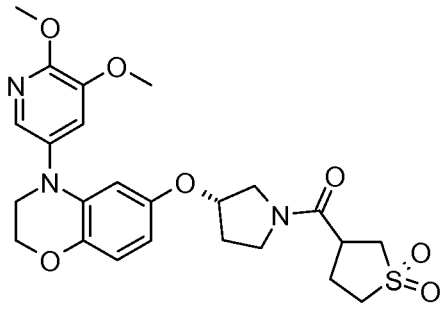
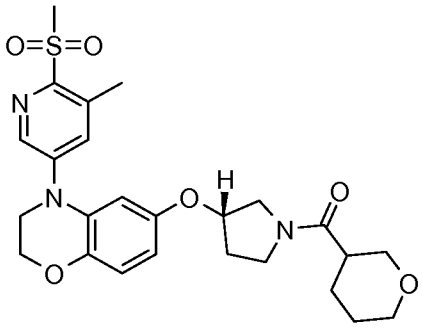
B31	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-furan-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 89364-31-8	0.94 (M6)	488
B32	 1-{(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-2-methoxy-ethanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 625-45-6	0.92 (M6)	462

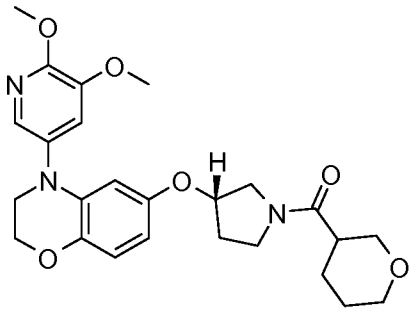
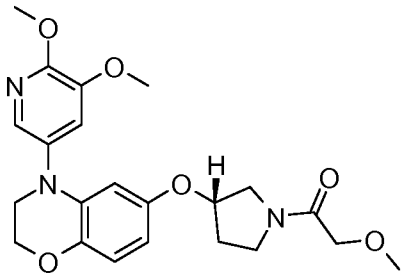
B33	 1-{(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-2-methyl-propan-1-one Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 79-31-2	1.01 (M6)	460
B34	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-phenyl-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 65-85-0	1.05 (M6)	494

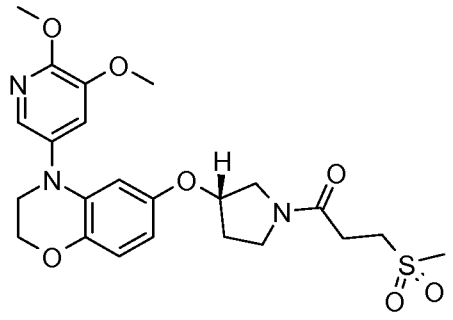
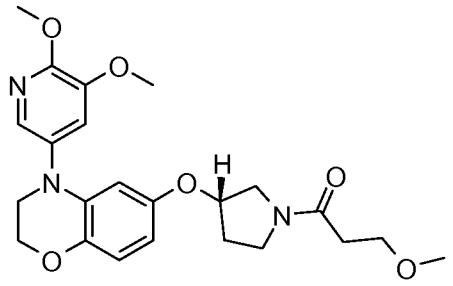
B35	 (1,1-Dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-{(S)-3-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 4785-67-5	0.87 (M2)	536
B36	 [1,4]Dioxan-2-yl-{(S)-3-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 89364-41-0	0.88 (M2)	504

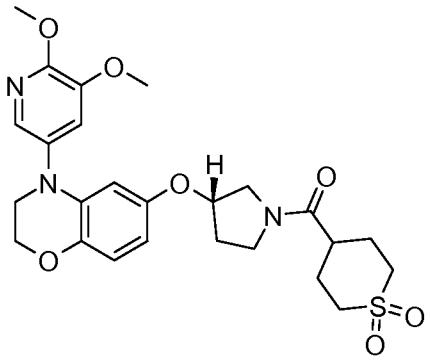
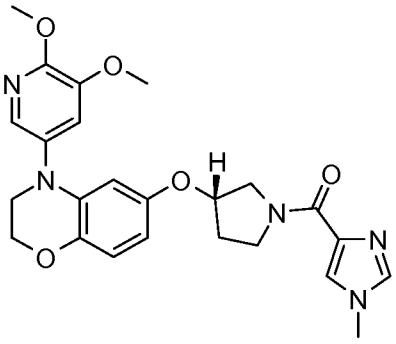
B37	 1-{(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-methoxy-propan-1-one Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 2544-06-1	0.88 (M2)	476
B38	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA8 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, CAS 127423-61-4, IA29, acyl chloride 40191-32-0	0.93 (M2)	470

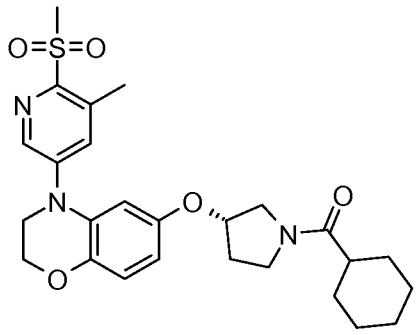
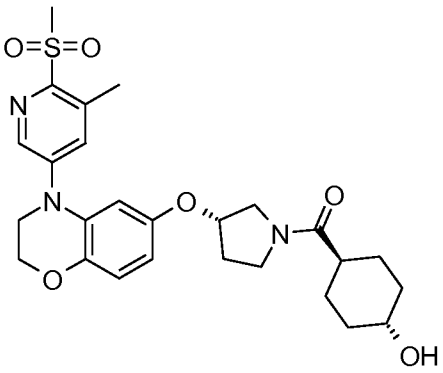
B39	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-[1,4]dioxan-2-yl-methanone Buchwald amination condition: CA8 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA29 / 89364-41-0	0.91 (M2)	472
B40	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-furan-3-yl)-methanone Buchwald amination condition: CA8 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA29 / 89364-31-8	0.92 (M2)	456

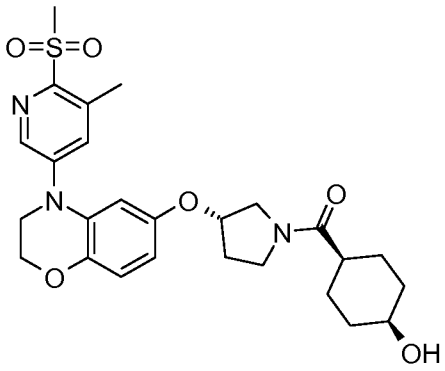
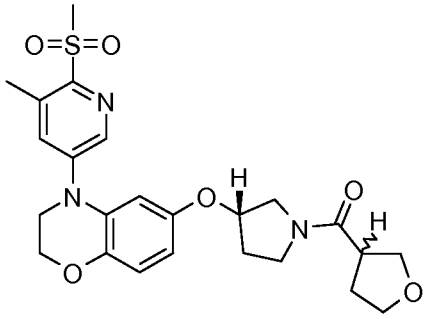
B41	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-methanone Buchwald amination condition: CA8 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA29 / 4785-67-5	0.91 (M2)	504
B42	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 873397-34-3	0.91 (M2)	502

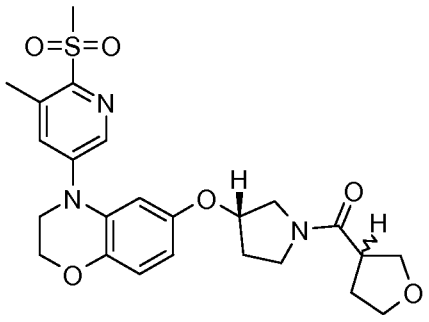
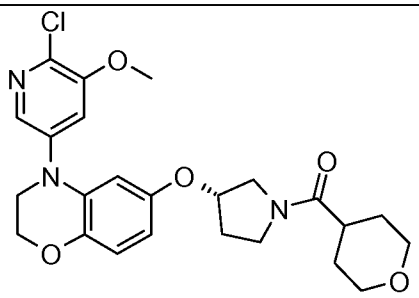
B43	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-3-yl)-methanone Buchwald amination condition: CA8 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA29 / 873397-34-3	0.96 (M2)	470
B44	 1-{(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-2-methoxy-ethanone Buchwald amination condition: CA8 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA29 / 625-45-6	0.90 (M2)	430

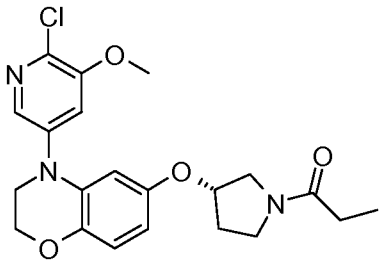
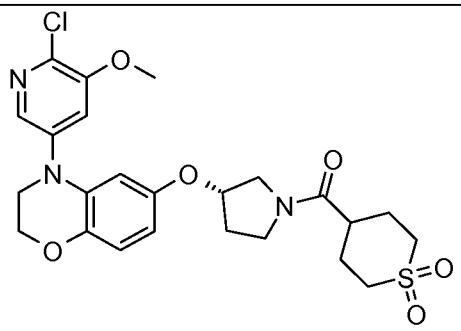
B45	 1-{(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-methanesulfonyl-propan-1-one Buchwald amination condition: CA8 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA29 / 645-83-0	0.89 (M2)	492
B46	 1-{(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-methoxy-propan-1-one Buchwald amination condition: CA8 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA29 / 2544-06-1	0.92 (M2)	444

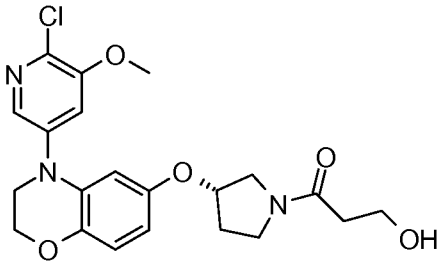
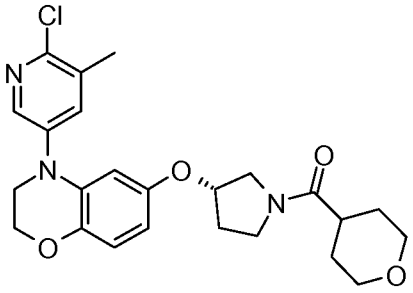
B47	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-methanone Buchwald amination condition: CA8 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA29 / 64096-87-3	0.90 (M2)	518
B48	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA8 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA29 / 41716-18-1	0.85 (M2)	466

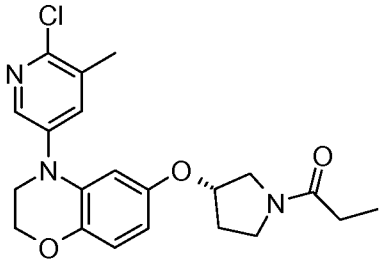
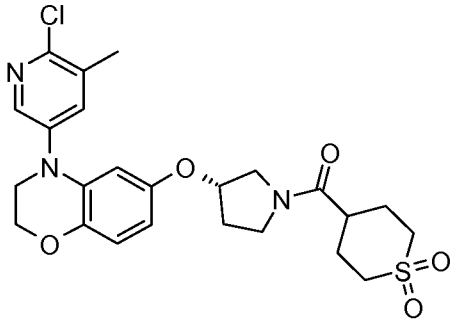
B49	 Cyclohexyl-{(S)-3-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 98-89-5	1.06 (M2)	500
B50	 (4-Hydroxy-cyclohexyl)-{(S)-3-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 3685-26-5	0.86 (M2)	516

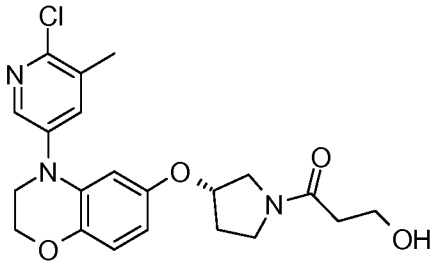
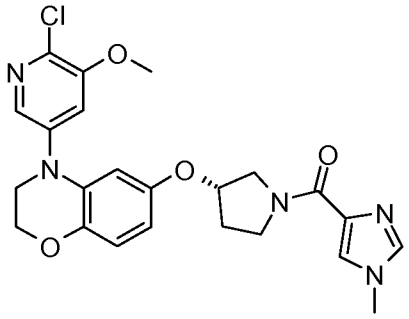
B51	 (4-Hydroxy-cyclohexyl)-{(S)-3-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 3685-22-1	0.89 (M2)	516
B52	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-furan-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 89364-31-8 Chiral separation: CD4	0.88 (M2) 15.13 (CD10)	488

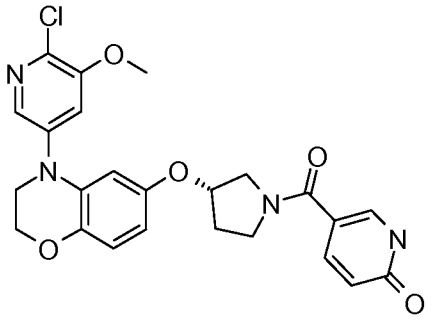
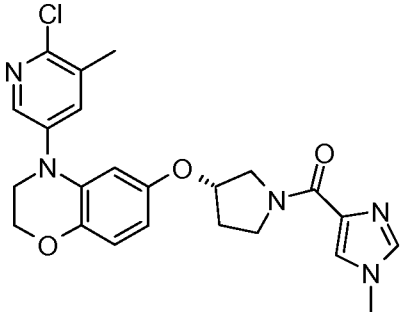
B53	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-furan-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 89364-31-8 Chiral separation: CD4	0.88 (M2) 18.70 (CD10)	488
B54	 {(S)-3-[4-(6-Chloro-5-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA9 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA49 / Acyl chloride: 40191-32-0	3.21 (M3)	474, 476

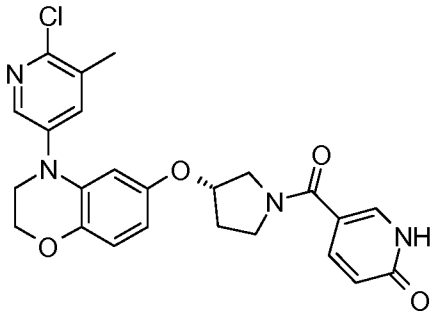
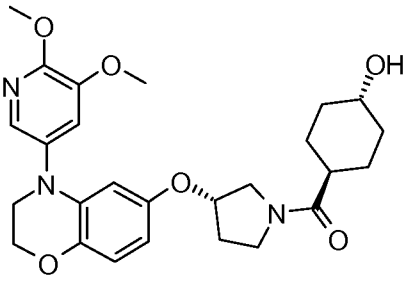
B55	 1-{(S)-3-[4-(6-Chloro-5-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Buchwald amination condition: CA9 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA49 / Acyl chloride: 79-03-8	3.30 (M3)	418, 420
B56	 {(S)-3-[4-(6-Chloro-5-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-methanone Buchwald amination condition: CA9 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA49 / 64096-87-3	3.02 (M3)	522, 524

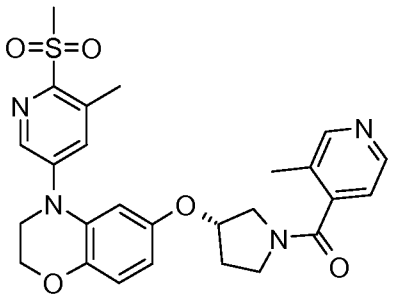
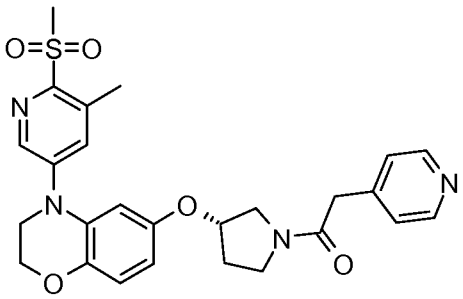
B57	 1-{(S)-3-[4-(6-Chloro-5-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-hydroxy-propan-1-one Buchwald amination condition: CA9 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA49 / 503-66-2	0.88 (M2)	434, 436
B58	 {(S)-3-[4-(6-Chloro-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA9 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA50 / Acyl chloride: 40191-32-0	3.36 (M3)	458, 460

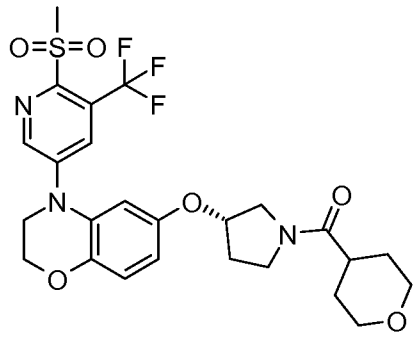
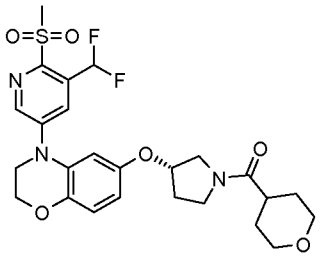
B59	 1-{(S)-3-[4-(6-Chloro-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Buchwald amination condition: CA9 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA50 / Acyl chloride: 79-03-8	3.47 (M3)	402, 404
B60	 {(S)-3-[4-(6-Chloro-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-methanone Buchwald amination condition: CA9 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA50 / 64096-87-3	3.17 (M3)	506, 508

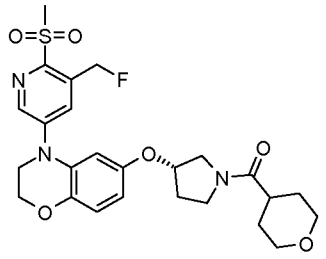
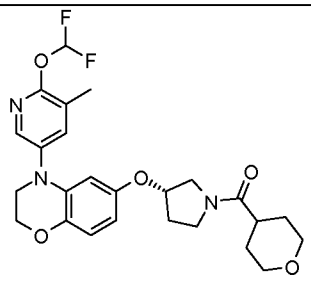
B61	 1-{(S)-3-[4-(6-Chloro-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-hydroxy-propan-1-one Buchwald amination condition: CA9 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA50 / 503-66-2	0.91 (M2)	418, 420
B62	 {(S)-3-[4-(6-Chloro-5-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA9 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA49 / 41716-18-1	2.59 (M3)	469

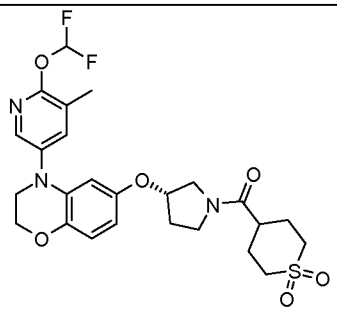
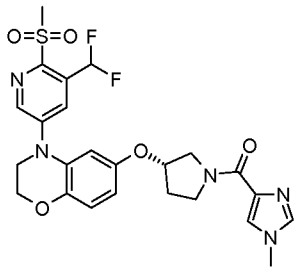
B63	 5-{(S)-3-[4-(6-Chloro-5-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carbonyl}-1H-pyridin-2-one Buchwald amination condition: CA9 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA49 / 5006-66-6	2.85 (M3)	482, 483
B64	 {(S)-3-[4-(6-Chloro-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA9 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA50 / 41716-18-1	2.71 (M3)	453

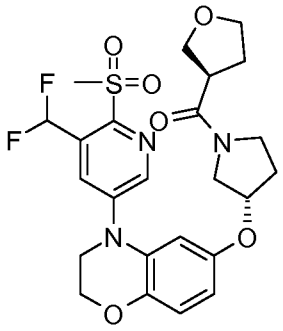
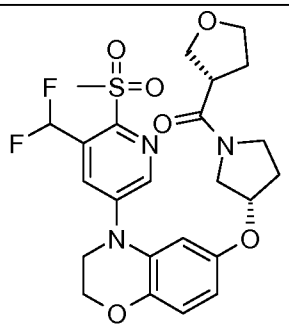
B65	 5-{(S)-3-[4-(6-Chloro-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carbonyl}-1H-pyridin-2-one Buchwald amination condition: CA9 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA50 / 5006-66-6	2.97 (M3)	466, 468
B66	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(4-hydroxy-cyclohexyl)-methanone Buchwald amination condition: CA8 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA29 / 3685-26-5	0.88 (M2)	484

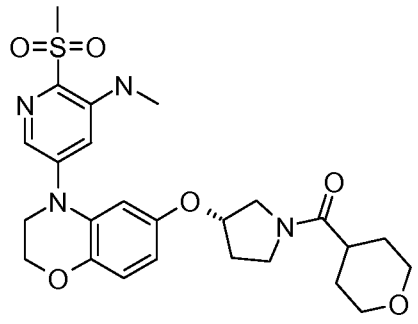
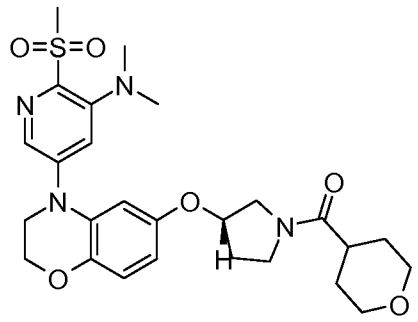
B67	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(3-methyl-pyridin-4-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 4021-12-9	0.86 (M2)	509
B68	 1-{(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-2-pyridin-4-yl-ethanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA1 / 6622-91-9	0.77 (M2)	509

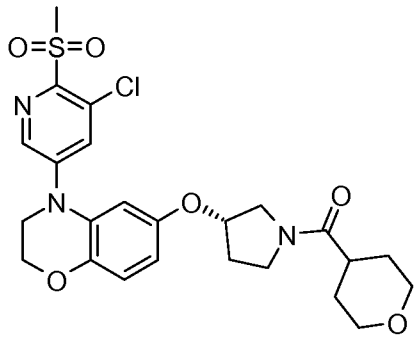
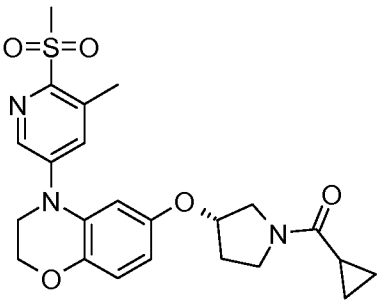
B69	 {(S)-3-[4-(6-Methanesulfonyl-5-trifluoromethyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA10 Amide bond condition: abbreviate: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA3 / Acyl chloride: 40191-32-0	0.93 (M1)	556
B70	 {(S)-3-[4-(5-Difluoromethyl-6-methanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA10 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA4 / Acyl chloride: 40191-32-0	0.91 (M1)	538

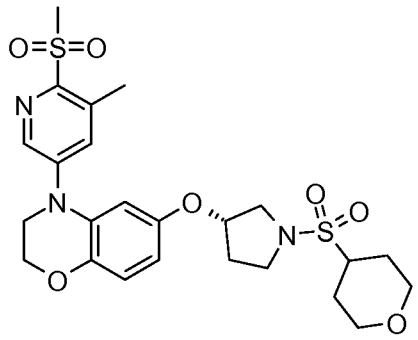
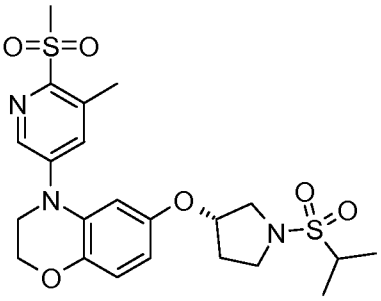
B71	 {(S)-3-[4-(5-Fluoromethyl-6-methanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA10 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA5 / Acyl chloride: 40191-32-0	0.88 (M1)	520
B72	 {(S)-3-[4-(6-Difluoromethoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA2 Amide bond condition: CB6 Side chain introduction condition: CC4 Precursors used: CAS 26021-57-8 / 109431-87-0 / IA8 / Acyl chloride: 40191-32-0	1.07 (M1)	490

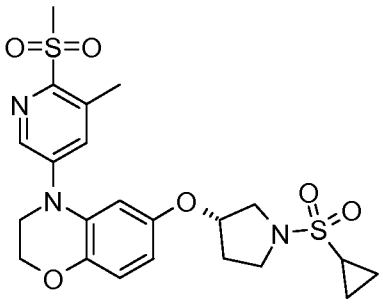
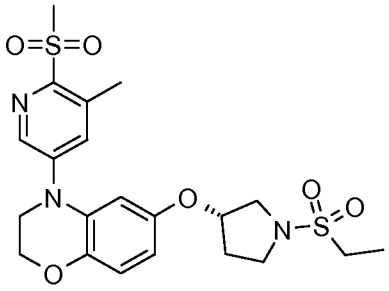
B73	 {(S)-3-[4-(6-Difluoromethoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-hexahydro-6-thiopyran-4-yl)-methanone Buchwald amination condition: CA2 Amide bond condition: CB3 Side chain introduction condition: CC4 Precursors used: CAS 26021-57-8 / 109431-87-0 / IA8 / 64096-87-3	1.01 (M1)	538
B74	 {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA10 Amide bond condition: CB3 Side chain introduction condition: CC4 Precursors used: CAS 26021-57-8 / 109431-87-0 / IA4 / 41716-18-1	0.81 (M1)	534

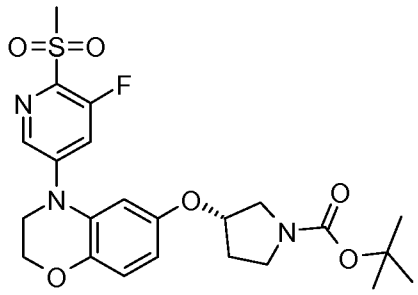
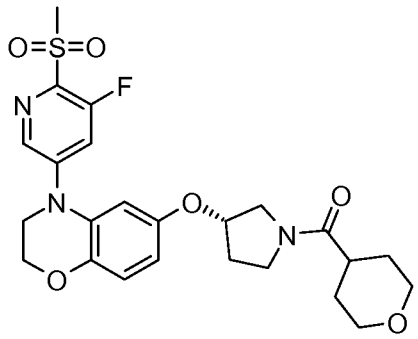
B75	 {(S)-3-[4-(5-Difluoromethyl-6-methanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(R)-tetrahydro-furan-3-yl-methanone Buchwald amination condition: CA10 Amide bond condition: CB4 Side chain introduction condition: CC4 Precursors used: CAS 26021-57-8 / 109431-87-0 / IA4 / IB1	0.88 (M1)	524
B76	 {(S)-3-[4-(5-Difluoromethyl-6-methanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(S)-tetrahydro-furan-3-yl-methanone Buchwald amination condition: CA10 Amide bond condition: CB4 Side chain introduction condition: CC4 Precursors used: CAS 26021-57-8 / 109431-87-0 / IA4 / IB2	0.88 (M1)	524

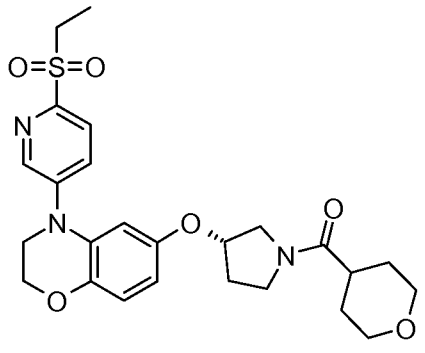
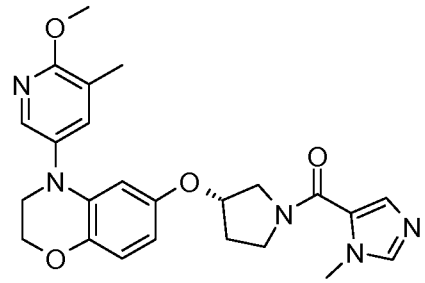
B77	 {(S)-3-[4-(6-Methanesulfonyl-5-methylamino-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA10 Amide bond condition: CB6 Side chain introduction condition: CC4 Precursors used: CAS 26021-57-8 / 109431-87-0 / IA51 / Acyl chloride: 40191-32-0	0.85 (M1)	517
B78	 {(S)-3-[4-(5-Dimethylamino-6-methanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA10 Amide bond condition: CB6 Side chain introduction condition: CC4 Precursors used: CAS 26021-57-8 / 109431-87-0 / IA52 / Acyl chloride: 40191-32-0	0.86 (M1)	531

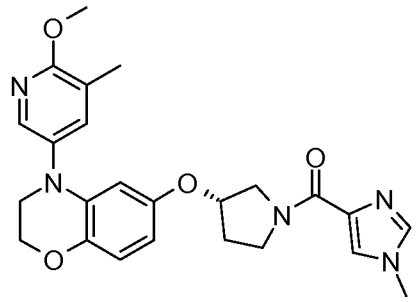
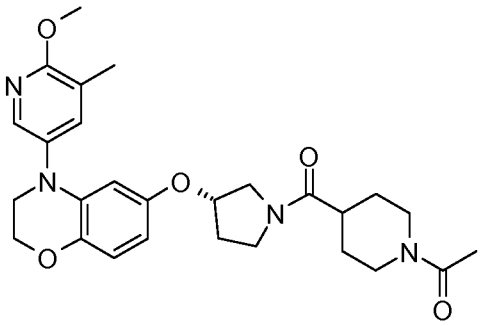
B79	 {(S)-3-[4-(5-Chloro-6-methanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA10 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA53, acyl chloride 40191-32-0	0.98 (M1)	522
B80	 Cyclopropyl-{(S)-3-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA4 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA1, acyl chloride 4023-34-1	0.94 (M1)	458

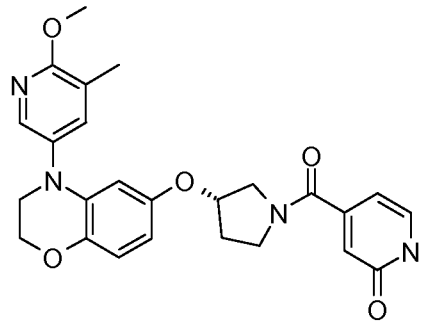
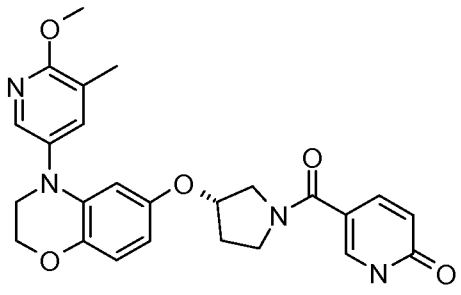
B81	 4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-6-[(S)-1-(tetrahydro-pyran-4-sulfonyl)-pyrrolidin-3-yloxy]-3,4-dihydro-2H-benzo[1,4]oxazine Buchwald amination condition: CA4 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA1, sulfonyl chloride 338453-21-7	0.95 (M1)	538
B82	 4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-6-[(S)-1-(propane-2-sulfonyl)-pyrrolidin-3-yloxy]-3,4-dihydro-2H-benzo[1,4]oxazine Buchwald amination condition: CA4 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA1, sulfonyl chloride 10147-37-2	0.99 (M1)	496

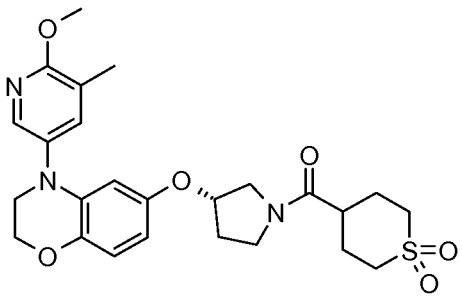
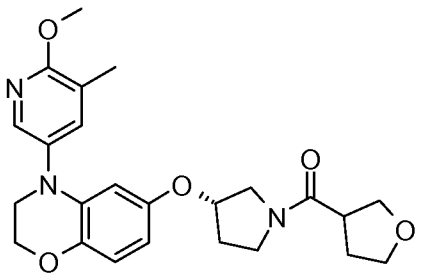
B83	 6-((S)-1-Cyclopropanesulfonyl-pyrrolidin-3-yloxy)-4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazine Buchwald amination condition: CA4 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA1, sulfonyl chloride 139631-62-2	0.96 (M1)	494
B84	 6-((S)-1-Ethanesulfonyl-pyrrolidin-3-yloxy)-4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazine Buchwald amination condition: CA4 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA1, sulfonyl chloride 594-44-5	0.94 (M1)	482

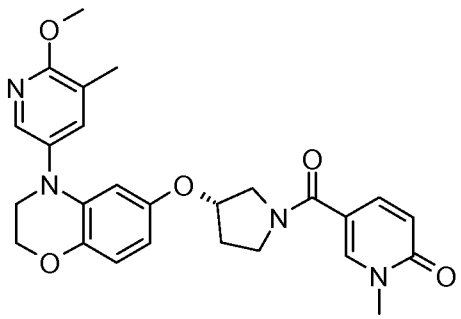
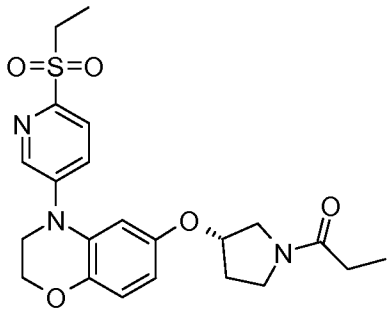
B85	 (S)-3-[4-(5-Fluoro-6-methanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester Buchwald amination condition: CA10 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA2	1.08 (M1)	494
B86	 {(S)-3-[4-(5-Fluoro-6-methanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA10 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA2, acyl chloride 40191-32-0 BOC cleavage with HCl in dioxane instead of TFA	0.80 (M1)	506

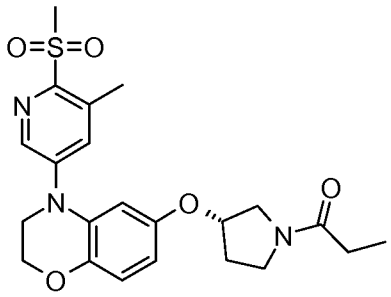
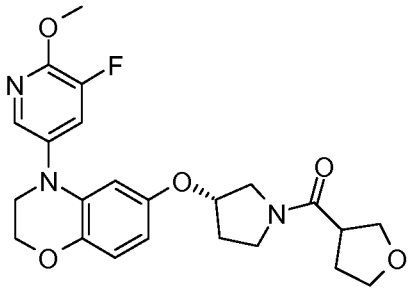
B87	 {(S)-3-[4-(6-Ethanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA13 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA58, acyl chloride 40191-32-0	1.57 (M7)	502
B88	 {(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(3-methyl-3H-imidazol-4-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA9, 41806-40-0	1.45 (M8)	450

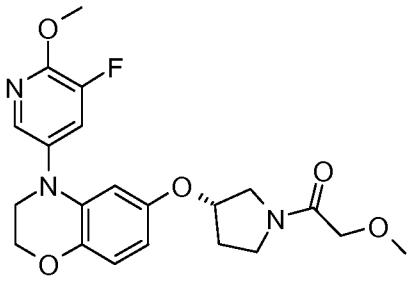
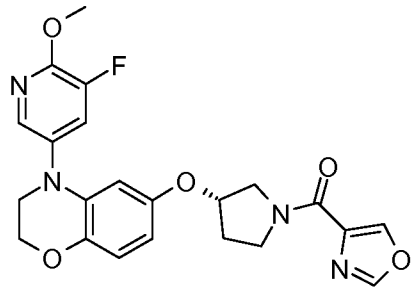
B89	 {(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA9, 41716-18-1	1.52 (M8)	450
B90	 1-(4-{(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carbonyl}-piperidin-1-yl)-ethanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA9, 25503-90-6	1.69 (M8)	495

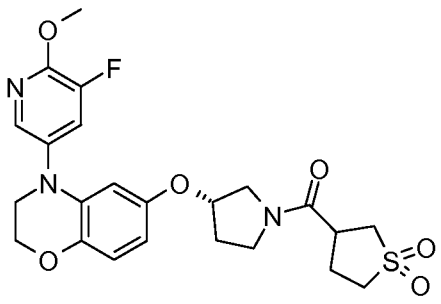
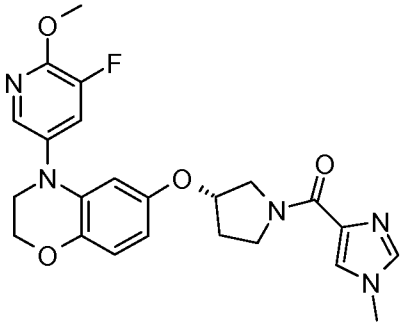
B91	 4-{(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carbonyl}-1H-pyridin-2-one Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA9, 22282-72-0	1.53 (M8)	463
B92	 5-{(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carbonyl}-1H-pyridin-2-one Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA9, 5006-66-6	1.54 (M8)	463

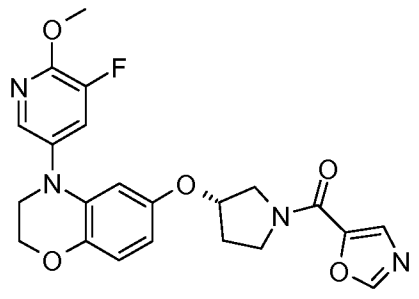
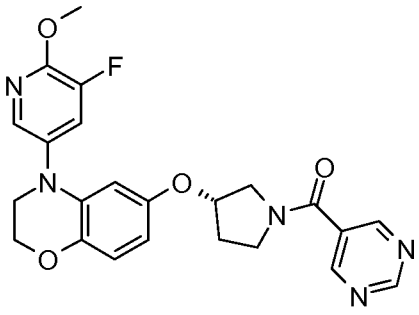
B93	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[4-(6-methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA9, 64096-87-3	1.71 (M8)	502
B94	 {(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-furan-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA9, 89364-31-8	1.88 (M8)	440

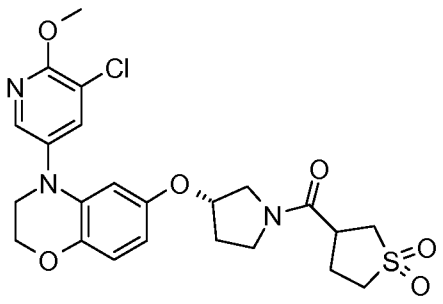
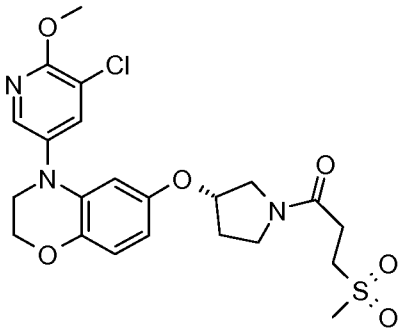
B95	 5-{(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carbonyl}-1-methyl-1H-pyridin-2-one Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA9, 3719-45-7	1.59 (M8)	477
B96	 1-{(S)-3-[4-(6-Ethanesulfonyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Buchwald amination condition: CA13 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA58, acyl chloride 79-03-8	1.50 (M7)	446

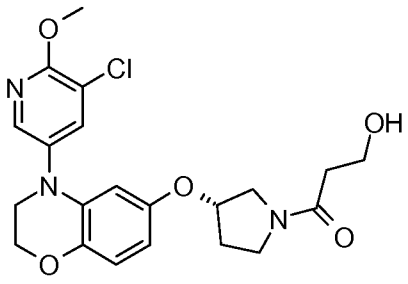
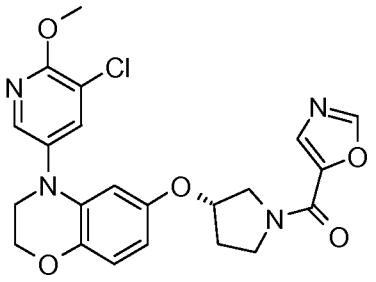
B97	 1-{(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Buchwald amination condition: CA6 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, 127423-61-4, IA1, acyl chloride 79-03-8	1.53 (M8)	446
B98	 {(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-furan-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 89364-31-8	1.83 (M7)	444

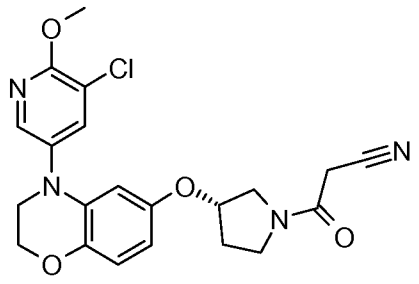
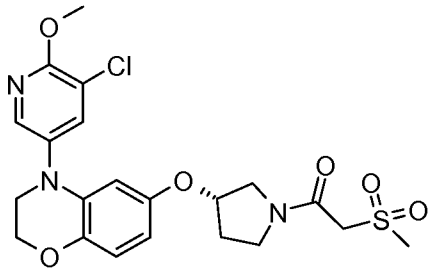
B99	 1-{(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-2-methoxy-ethanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 625-45-6	1.77 (M7)	418
B100	 {(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-oxazol-4-yl-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 23012-13-7	1.87 (M7)	441

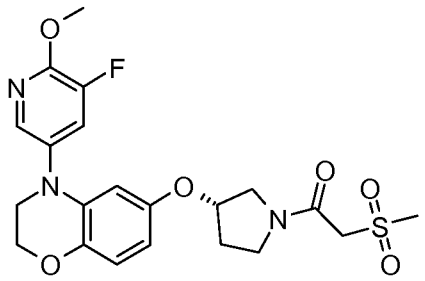
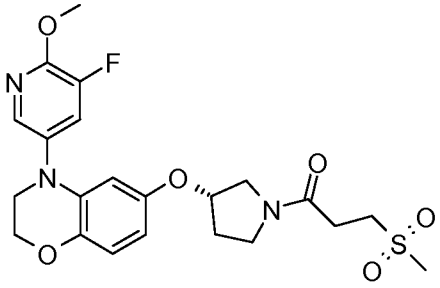
B101	 (1,1-Dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-{(S)-3-[4-(5-fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 4785-67-5	1.81 (M7)	492
B102	 {(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 41716-18-1	1.48 (M7)	453

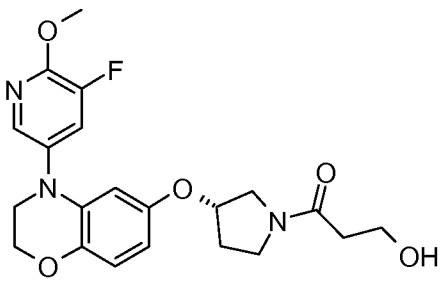
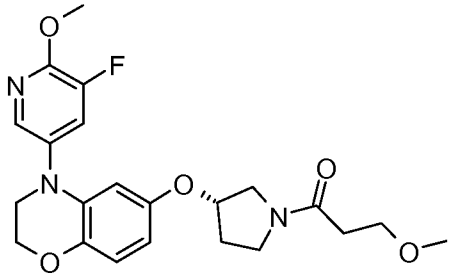
B103	 {(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-oxazol-5-yl-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 118994-90-4	1.80 (M7)	441
B104	 {(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-pyrimidin-5-yl-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 4595-61-3	1.75 (M7)	452

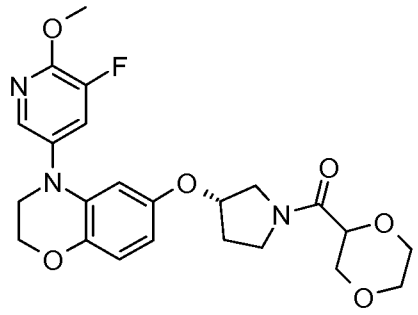
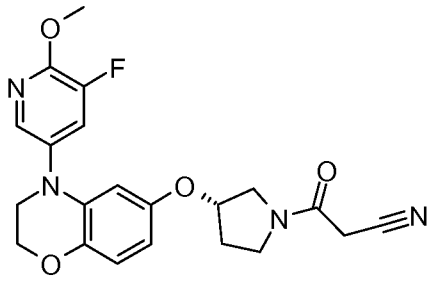
B105	 {(S)-3-[4-(5-Chloro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA11 / 4785-67-5	1.84 (M8)	508, 510
B106	 1-{(S)-3-[4-(5-Chloro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-methanesulfonyl-propan-1-one Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA11 / 645-83-0	1.78 (M8)	496, 498

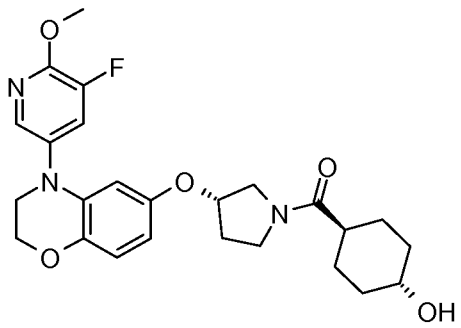
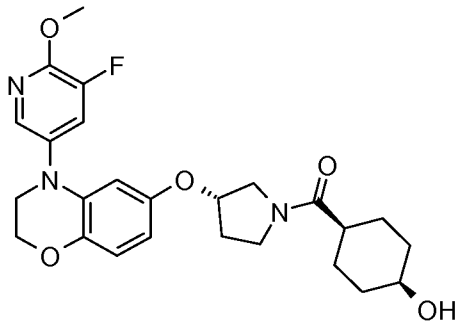
B107	 1-{(S)-3-[4-(5-Chloro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-hydroxy-propan-1-one Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA11 / 503-66-2	1.67 (M8)	434, 436
B108	 {(S)-3-[4-(5-Chloro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-oxazol-5-yl-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA11 / 118994-90-4	1.84 (M8)	457, 459

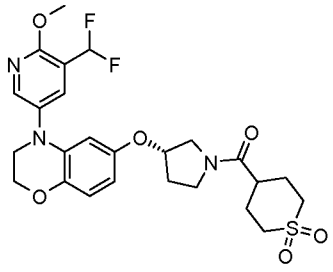
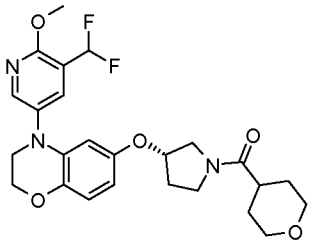
B109	 3-{(S)-3-[4-(5-Chloro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-oxo-propionitrile Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA11 / 372-09-8	1.88 (M8)	429, 431
B110	 1-{(S)-3-[4-(5-Chloro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-2-methanesulfonyl-ethanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA11 / 2516-97-4	1.90 (M8)	482

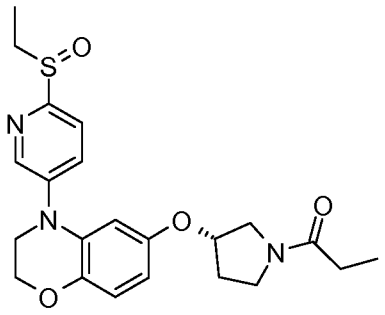
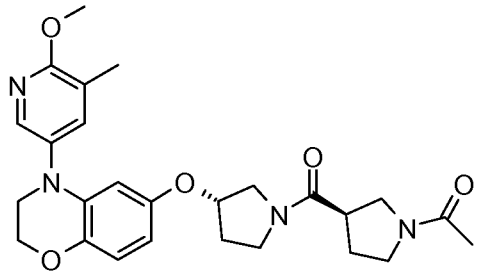
B111	 1-{(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-2-methanesulfonyl-ethanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 2516-97-4	1.70 (M8)	466
B112	 1-{(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-methanesulfonyl-propan-1-one Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 645-83-0	1.77 (M8)	480

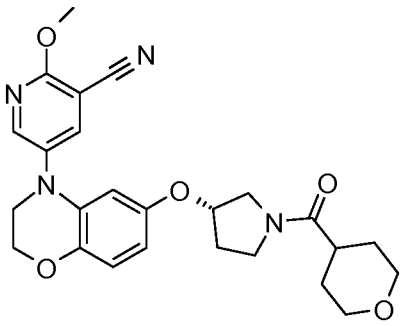
B113	 1-{(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-hydroxy-propan-1-one Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 503-66-2	1.57(M8)	418
B114	 1-{(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-methoxy-propan-1-one Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 2544-06-1	1.84 (M8)	432

B115	 [1,4]Dioxan-2-yl-{(S)-3-[4-(5-fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 89364-41-0	1.83 (M8)	459
B116	 3-{(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-3-oxo-propionitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 372-09-8	1.85 (M8)	413

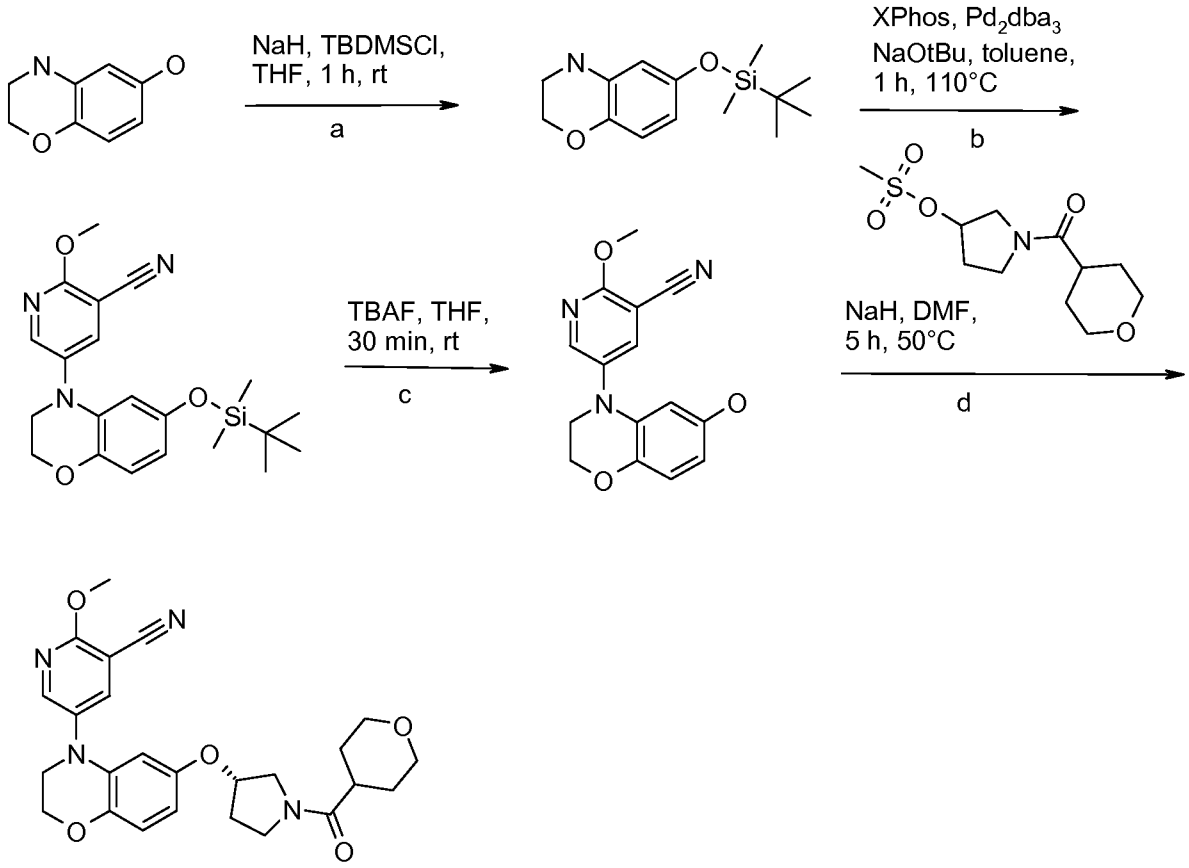
B117	 {(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(4-hydroxy-cyclohexyl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 3685-26-5	3.13 (M3)	472
B118	 {(S)-3-[4-(5-Fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(4-hydroxy-cyclohexyl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA10 / 3685-22-1	3.40 (M3)	472

B119	 {(S)-3-[4-(5-Difluoromethyl-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-hexahydro-6-thiopyran-4-yl)-methanone Buchwald amination condition: CA2 Amide bond condition: CB3 Side chain introduction condition: CC2 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA6 / 64096-87-3	0.97 (M1)	538
B120	 {(S)-3-[4-(5-Difluoromethyl-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA2 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA6 / Acyl chloride 40191-32-0	1.03 (M1)	490

B121	 1-{(S)-3-[4-(6-Ethanesulfinyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Buchwald amination condition: CA14 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4, IA44, acyl chloride CAS 79-03-8	1.42 (M8)	430
B122	 1-((R)-3-{(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carbonyl}-pyrrolidin-1-yl)-ethanone Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8 / 127423-61-4, IA9, CAS 72925-16-7, Product obtained after Deboc reaction using TFA in CH_2Cl_2 done in conventional way and final acylation in analogy to example J	1.66 (M8)	481



Example C1: 2-Methoxy-5-{6-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile (according to Scheme 3)



a) 6-(tert-Butyl-dimethyl-silanyloxy)-3,4-dihydro-2H-benzo[1,4]oxazine

Under argon, NaH (2.96 g, 74.1 mmol) was portionwise added to a solution of 3,4-dihydro-2H-benzo[1,4]oxazin-6-ol (CAS registry 26021-57-8) (5.60 g, 37.0 mmol) in THF (200 ml). After stirring at rt for 20 min, TBDMSCl (CAS registry 18162-48-6) (7.26 g, 48.2 mmol) was slowly added and stirring was continued for 1 h. The reaction mixture was diluted with Et_2O, washed with a sat. aq. $NaHCO_3$ soln. and brine. The organic phase was dried over $MgSO_4$, concentrated and the title compound was obtained after flash chromatography on silica gel (cyclohexane / EtOAc 100:0 to 60:40 over 15 min) as a yellow oil (9.20 g, 94% yield).

HPLC Rt_{M10}= 3.65 min; ESIMS: 266 [$(M+H)^+$].

^1H NMR (400 MHz, DMSO-d_6): δ 6.46 (d, 1H), 6.08 (d, 1H), 5.91 (m, 1H), 5.71 (br s, 1H), 3.91-4.12 (m, 2H), 3.12-3.28 (m, 2H), 0.87-1.01 (s, 9H), 0.03-0.21 (s, 3H).

b) 5-[6-(tert-Butyl-dimethyl-silanyloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-2-methoxy nicotinonitrile

Under argon, XPhos (CAS registry 564483-18-7) (0.79 g, 1.7 mmol) and $Pd_2(dba)_3$ (CAS registry 51364-51-3) (1.52 g, 1.7 mmol) were added to a suspension of 6-(tert-butyl-dimethyl-silanyloxy)-3,4-dihydro-2H-benzo[1,4]oxazine (9.00 g, 33.2 mmol), 5-bromo-2-methoxy-nicotinonitrile (CAS registry 941294-54-8) (7.79 g, 36.6 mmol), NaOtBu (4.79 g, 49.8 mmol) in toluene (270 ml). The reaction mixture was stirred at 110°C for 1 h and was concentrated to afford a brown solid which was washed with a mixture of DCM/MeOH (8:2) and filtered off. The filtrate was concentrated, the obtained residue was dissolved in DCM/MeOH (8:2), filtered over hyflo, the filtrate was concentrated and triturated with MeOH to afford the title compound as yellow solid (10.14 g, 77% yield).

HPLC Rt_{M11} =3.89 min; ESIMS: 398 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35-8.51 (m, 1H), 8.16-8.31 (m, 1H), 6.60-6.79 (m, 1H), 6.15-6.32 (m, 1H), 5.92-6.09 (m, 1H), 4.00 (s, 3H), 3.51-3.74 (m, 2H), 0.87 (s, 9H), 0.07 (s, 6H).

c) 5-(6-hydroxy-2,3-dihydro-benzo[1,4]oxazin-4-yl)-2-methoxy-nicotinonitrile

TBAF (1M in THF) (37.7 ml, 37.7 mmol) was added to a solution of 5-[6-(tert-butyl-dimethyl-silanyloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-2-methoxy-nicotinonitrile (10 g, 25.2 mmol) dissolved in THF (200 ml). The solution was stirred at rt for 30 min, diluted with EtOAc, washed with sat. aq. $NaHCO_3$ soln. and brine. The aqueous layers were back extracted with EtOAc, concentration of the organic phases after drying over $MgSO_4$ afforded a brown residue which was dissolved in DCM/MeOH (1:1) and filtered over hyflo. Concentration and trituration with Et_2O of the filtrate afforded the title compound as brown solid (6.63 g, 93% yield).

HPLC Rt_{M10}=2.56 min; ESIMS: 284 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (br. s, 1H), 8.44 (d, 1H), 8.28 (d, 1H), 6.62 (d, 1H), 6.12 (m, 1H), 6.01 (d, 1H), 4.11-4.32 (m, 2H), 4.01 (s, 3H), 3.54-3.68 (m, 2H).

d) 2-Methoxy-5-{6-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile

Under argon, NaH (31 mg, 0.78 mmol) was added to a solution of 5-(6-hydroxy-2,3-dihydro-benzo[1,4]oxazin-4-yl)-2-methoxy-nicotinonitrile (100 mg, 0.35 mmol) in DMF (2 ml) and stirred at rt for 5 min. Methanesulfonic acid (R)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yl ester (intermediate IC1) (98.0 mg, 0.35 mmol) was added and the reaction mixture was stirred at 50°C for 4 h. After cooling, NaH (0.5 eq., 8.47 mg, 0.21 mmol) was added, the

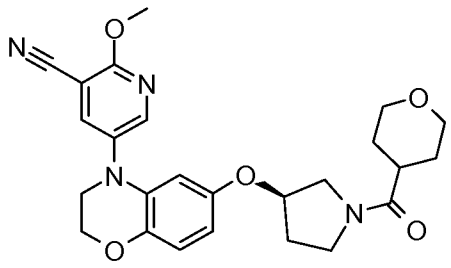
reaction mixture was stirred at rt for 5 min and methanesulfonic acid (R)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yl ester (intermediate IC1) (49.0 mg, 0.18 mmol) was added. The reaction mixture was stirred at 50°C for 1 h. Concentration and purification by prep. RP-HPLC (Sunfire PrepC18 OBD 30x100mm, 5 μm; solvent A: H_2O+0.1 Vol.-% TFA; solvent B: CH_3CN +0.1 Vol.-% TFA) afforded, after basification of the combined fractions and extraction with EtOAc, the title compound as a yellow solid (72 mg, 43% yield).

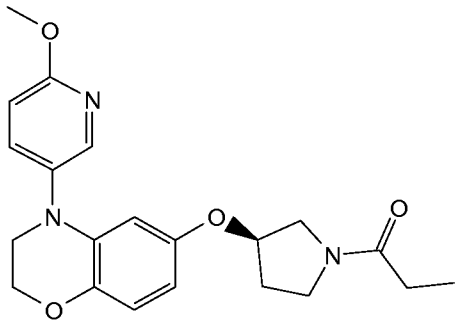
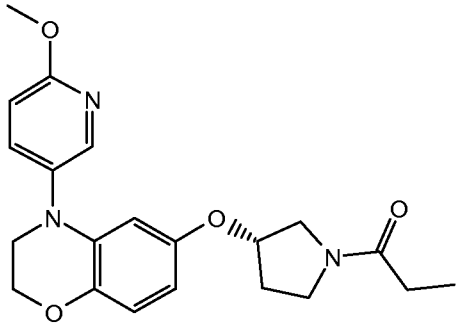
HPLC Rt_{M10}=2.72 min; ESIMS: 465 $[(M+H)^+]$.

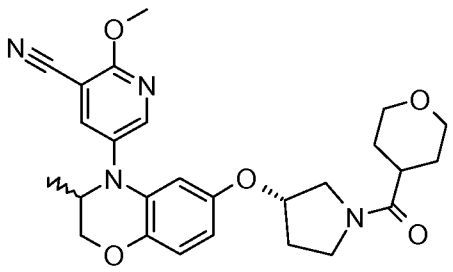
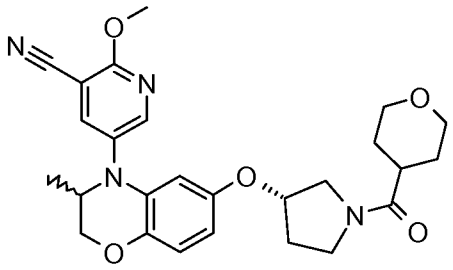
^1H NMR (400 MHz, CD_3OD): δ 8.36 (d, 1H), 8.06 (t, 1H), 6.78 (m, 1H), 6.37 (m, 1H), 6.17 (m, 1H), 4.81 (br s, 1H), 4.17-4.37 (m, 2H), 4.08 (s, 3H), 3.90-4.03 (m, 2H), 3.56-3.81 (m, 5H), 3.39-3.54 (m, 3H), 2.59-2.89 (m, 1H), 1.87-2.29 (m, 2H), 1.48-1.87 (m, 4H).

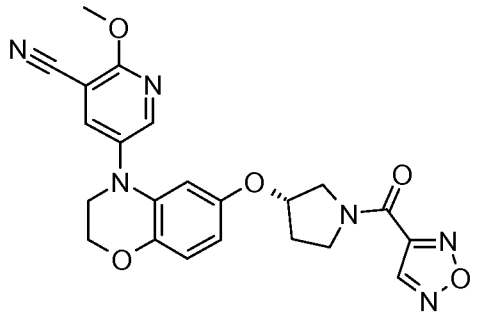
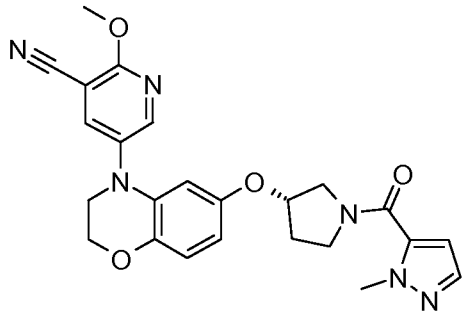
Examples C2 to C26: The compounds listed in Table 3 were prepared by a procedure analogous to that used in Example C1.

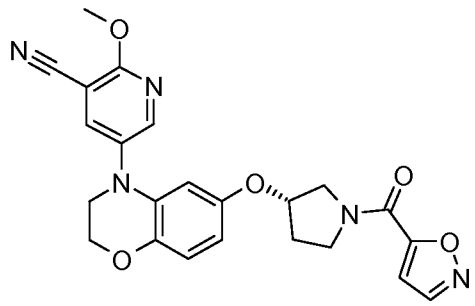
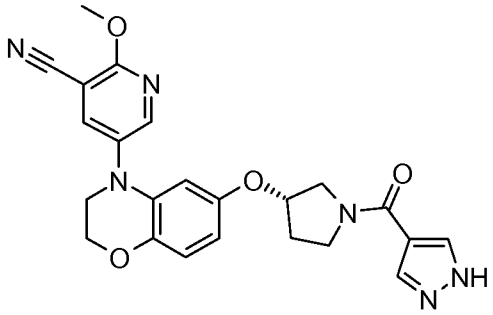
Table 3

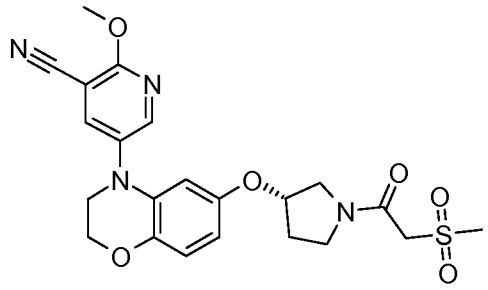
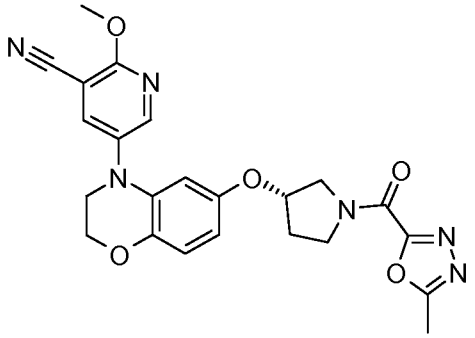
Example	Compound	UPLC Rt [min] (method)	MS [m/z; $(M+1)^+$]
C2	 2-Methoxy-5-{6-[(R)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Side chain introduction condition: CC2 Precursors used: IC2	2.71 (M10)	465

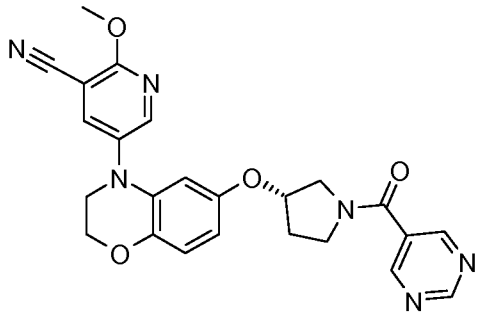
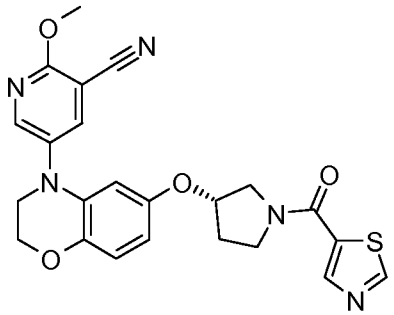
C3	 1-{(R)-3-[4-(6-Methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Buchwald amination condition: CA7 Side chain introduction condition: CC3 Precursors used: IC3	2.71 (M10)	384
C4	 1-{(S)-3-[4-(6-Methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-propan-1-one Buchwald amination condition: CA7 Side chain introduction condition: CC3 Precursors used: IC4	2.71 (M10)	384

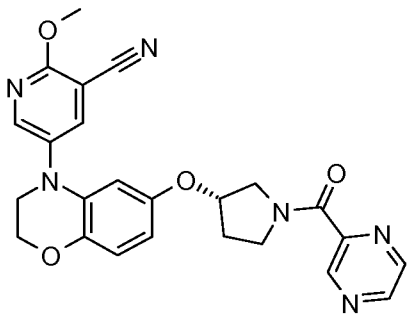
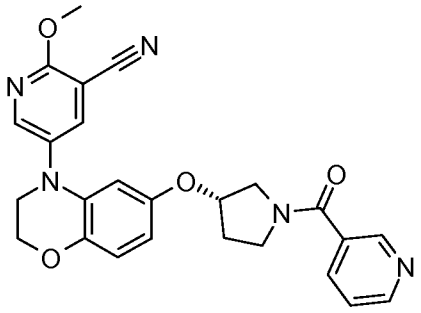
C5	 2-Methoxy-5-{3-methyl-6-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Side chain introduction condition: CC2 Precursors used: CAS 704879-75-4, IC1 Chiral separation: CD3	2.83 (M10) 16.981 (M5)	479
C6	 2-Methoxy-5-{3-methyl-6-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Side chain introduction condition: CC2 Precursors used: CAS 704879-75-4, IC1 Chiral separation : CD3	2.83 (M10) 19.957 (M5)	479

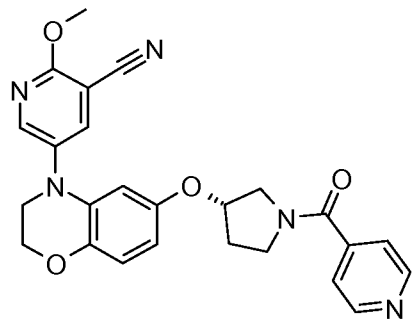
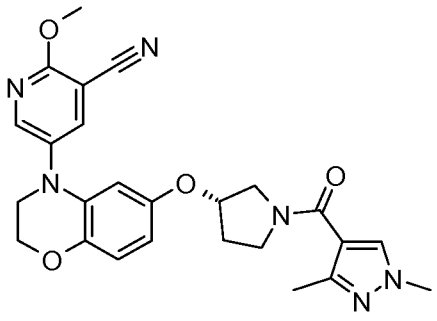
C7	 5-{6-[(S)-1-(Furazan-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA12 / 88598-08-7	4.13 (M4)	449
C8	 2-Methoxy-5-{6-[(S)-1-(2-methyl-2H-pyrazole-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-enzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA12 / 16034-46-1	4.11 (M4)	461

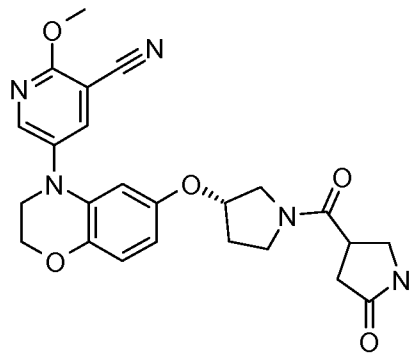
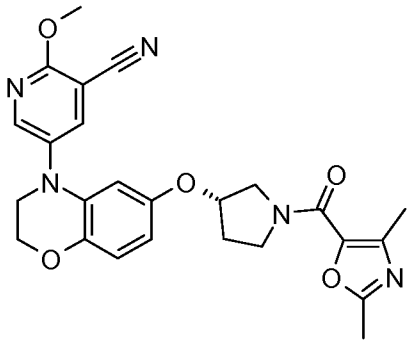
C9	 5-{6-[(S)-1-(Isoxazole-5-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA12 / 21169-71-1	4.17 (M4)	448
C10	 2-Methoxy-5-{6-[(S)-1-(1H-pyrazole-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA12 / 37718-11-9	3.60 (M4)	447

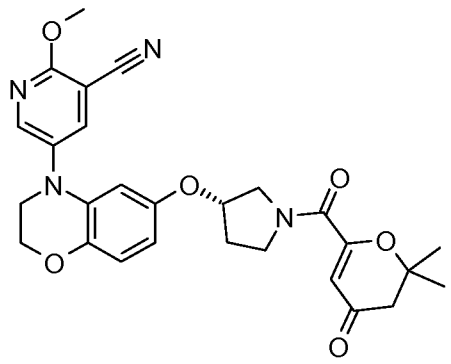
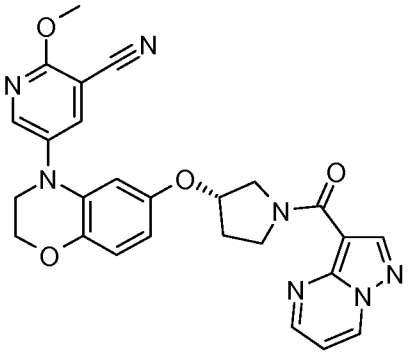
C11	 5-{6-[(S)-1-(2-Methanesulfonyl-acetyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA12 / 2516-97-4	3.73 (M4)	473
C12	 2-Methoxy-5-{6-[(S)-1-(5-methyl-[1,3,4]oxadiazole-2-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA12 / 518048-06-1	4.02 (M4)	463

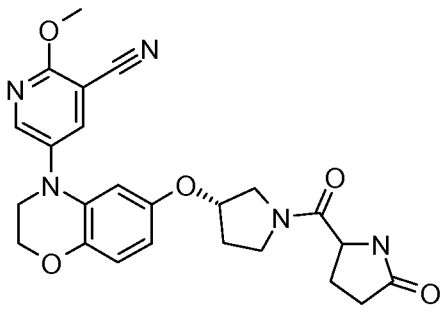
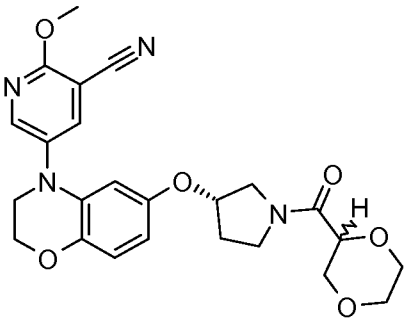
C13	 2-Methoxy-5-{6-[(S)-1-(pyrimidine-5-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8 / 127423-61-4 / IA12 / 4595-61-3	3.72 (M4)	459
C14	 2-Methoxy-5-{6-[(S)-1-(thiazole-5-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 14527-41-4	4.02 (M4)	464

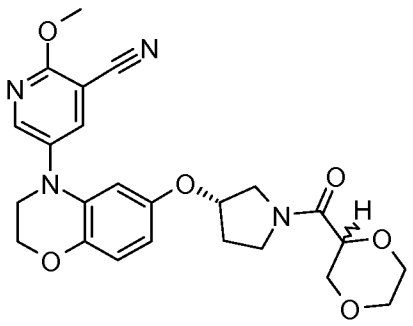
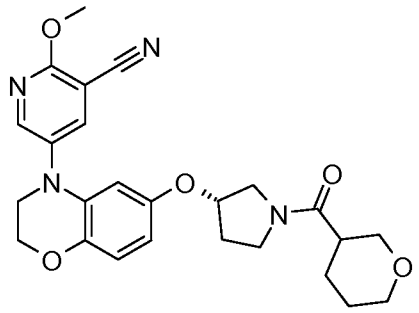
C15	 2-Methoxy-5-{6-[(S)-1-(pyrazine-2-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 1339899-95-4	4.03 (M3)	459
C16	 2-Methoxy-5-{6-[(S)-1-(pyridine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 59-67-6	3.27 (M3)	458

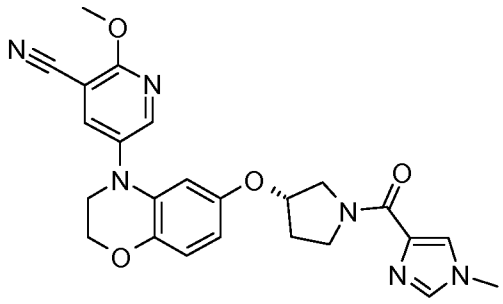
C17	 2-Methoxy-5-{6-[(S)-1-(pyridine-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrileBuchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 5-22-1	3.20 (M3)	458
C18	 5-{6-[(S)-1-(1,3-Dimethyl-1H-pyrazole-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 78703-53-4	3.91 (M3)	475

C19	 2-Methoxy-5-{6-[(S)-1-(5-oxo-pyrrolidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 7268-43-1	3.44 (M3)	464
C20	 5-{6-[(S)-1-(2,4-Dimethyl-oxazole-5-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 2510-37-4	4.27 (M3)	476

C21	 5-{6-[(S)-1-(6,6-Dimethyl-4-oxo-5,6-dihydro-4H-pyran-2-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 80866-93-9	4.33 (M3)	505
C22	 2-Methoxy-5-{6-[(S)-1-(pyrazolo[1,5-a]pyrimidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 25940-35-6	3.87 (M3)	498

C23	 2-Methoxy-5-{6-[(S)-1-(5-oxo-pyrrolidine-2-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 149-87-1	3.47 (M3)	464
C24	 5-{6-[(S)-1-([1,4]Dioxane-2-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 89364-41-0 Chiral separation : CD7	2.68 (M10) 22.58 (CD7)	467

C25	 5-{6-[(S)-1-([1,4]Dioxane-2-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 89364-41-0 Chiral separation : CD7	2.68 (M10) 33.80 (CD7)	467
C26	 2-Methoxy-5-{6-[(S)-1-(tetrahydro-pyran-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: CAS 26021-57-8, IA12, 127423-61-4, 873397-34-3	1.57 (M9)	465



Example D1: (S)-2-methoxy-5-(6-((1-(1-methyl-1H-imidazole-4-carbonyl)pyrrolidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-4(3H)-yl)nicotinonitrile (according to Scheme 4)

a1) 6-((tert-butyldimethylsilyl)oxy)-3,4-dihydro-2H-benzo[b][1,4]oxazine

A stirred solution of 3,4-dihydro-2H-1,4-benzoxazin-6-ol (CAS registry 226021-57-8) (6.00 g, 39.70 mmol) in THF (200 ml) was treated with sodium hydride (60% in mineral oil, 3.18 g, 79.00 mmol) at rt. After 20 min at rt, TBDMSCl (7.78 g, 51.6 mmol) was added, and the reaction mixture was stirred at rt for 1.5 h. After that time, diethyl ether (500 ml) and a sat. aq. $NaHCO_3$ soln. (100 ml) were added. The aq. layer was extracted with diethyl ether, and the combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (cyclohexane / EtOAc gradient) to provide the title compound as a yellow oil.

HPLC Rt_{M11} = 3.37 min; ESIMS: 266 [$(M+H)^+$].

^1H NMR (400 MHz, DMSO-d_6): δ 6.48-6.44 (m, 1H), 6.09-6.05 (m, 1H), 5.94-5.89 (m, 1H), 5.76-5.70 (m, 1H), 4.06-4.00 (m, 2H), 3.25-3.19 (m, 2H), 0.92 (s, 9H), 0.12 (s, 6H).

b1) 5-(6-((tert-butyldimethylsilyl)oxy)-2H-benzo[b][1,4]oxazin-4(3H)-yl)-2-methoxynicotinonitrile

A stirred solution of 6-((tert-butyldimethylsilyl)oxy)-3,4-dihydro-2H-benzo[b][1,4]oxazine (8.88 g, 32.80 mmol) in toluene (270 ml) was treated with 5-bromo-2-methoxynicotinonitrile (CAS registry 941294-54-8) (7.68 g, 36.10 mmol), NaOtBu (4.87 g, 49.2 mmol), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (CAS registry 564483-18-7) (0.806 g, 1.64 mmol), and Pd_2dba_3 (1.501 g, 1.64 mmol) at rt under argon. The reaction mixture was heated to 110°C for 1.5 h. After that time, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM (200 ml), filtered through a pad of celite, and concentrated under reduced pressure. The residue was dissolved in MeOH, and sonicated several times to give a yellow/orange precipitate. The residue was filtered, washed with methanol, and dried under vacuum to provide the title compound as a yellow solid.

HPLC Rt_{M11} = 3.90 min; ESIMS: 398 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45-8.42 (m, 1H), 8.28-8.24 (m, 1H), 6.72-6.68 (m, 1H), 6.24-6.19 (m, 1H), 6.06-6.03 (m, 1H), 4.24-4.18 (m, 2H), 4.00 (s, 3H), 3.66-3.61 (m, 2H), 0.87 (s, 9H), 0.07 (s, 6H).

alternative method b2: dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (CAS registry 564483-18-7) and $Pd_2(dba)_3$ were replaced with bis(tri-t-butylphosphine)palladium (CAS registry 53199-31-8)

c1) 5-(6-hydroxy-2H-benzo[b][1,4]oxazin-4(3H)-yl)-2-methoxynicotinonitrile

A stirred solution of 5-(6-((tert-butyldimethylsilyl)oxy)-2H-benzo[b][1,4]oxazin-4(3H)-yl)-2-methoxynicotinonitrile (10.85 g, 27.30 mmol) in THF (220 ml) was treated with TBAF (1.0 M in THF, 40.9 ml, 40.90 mmol) at rt. After 40 min at rt, EtOAc (300 ml) and a sat. aq. $NaHCO_3$ soln. (200 ml) were added. The organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by trituration with diethyl ether to provide the title compound as a pale brown solid.

HPLC Rt_{M11} = 2.00 min; ESIMS: 284 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 1H), 8.44 (d, 1H), 8.29 (d, 1H), 6.61 (d, 1H), 6.12 (dd, 1H), 6.01 (d, 1H), 4.21-4.16 (m, 2H), 4.01 (s, 3H), 3.64-3.59 (m, 2H).

d1) (S)-tert-butyl 3-((4-(5-cyano-6-methoxypyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)pyrrolidine-1-carboxylate

A stirred solution of 5-(6-hydroxy-2H-benzo[b][1,4]oxazin-4(3H)-yl)-2-methoxynicotinonitrile (3.70 g, 13.06 mmol) in DMF (60 ml) was treated with sodium hydride (60% in mineral oil, 1.31 g, 32.70 mmol) at rt. The reaction mixture was stirred at rt for 15 min. After that time, (R)-1-Boc-3-methanesulfonyloxypyrrolidine (CAS registry 141699-57-2) (5.36 g, 19.59 mmol) was added, and the reaction mixture was stirred at 50°C for 3 h. After that time, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (cyclohexane / acetone gradient) to provide the title compound as a yellow solid.

HPLC Rt_{M11} = 3.13 min; ESIMS: 453 [$(M+H)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, 1H), 7.81 (d, 1H), 6.82 (d, 1H), 6.32 (dd, 1H), 6.14 (d, 1H), 4.74-4.68 (m, 1H), 4.32-4.28 (m, 2H), 4.09 (s, 3H), 3.67-3.62 (m, 2H), 3.59-3.39 (m, 4H), 2.17-1.92 (m, 2H), 1.47 (s, 9H).

alternative method d2: the mesylated alcohol, sodium hydride and DMF were replaced with the corresponding hydroxy-isoxazolidine, DEAD and THF using Mitsunobu conditions described in method CC4

e1) (S)-2-methoxy-5-(6-(pyrrolidin-3-yloxy)-2H-benzo[b][1,4]oxazin-4(3H)-yl)nicotinonitrile

A stirred solution of (S)-tert-butyl 3-((4-(5-cyano-6-methoxypyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)oxy)pyrrolidine-1-carboxylate (4.35 g, 9.32 mmol) in DCM (160 ml) was treated with TFA (35.9 ml, 466 mmol) at rt. The reaction mixture was stirred at rt for 2 h. After that time, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM (500 ml), and a saturated aqueous $NaHCO_3$ solution (500 ml) was added. The organic extracts were washed with a saturated aqueous NaCl solution (50 ml), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product (title compound, yellow solid) was used in the next step without further purification.

HPLC Rt_{M10}= 2.06 min; ESIMS: 353 $[(M+H)^+]$.

^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, 1H), 7.82 (d, 1H), 6.82 (d, 1H), 6.32 (dd, 1H), 6.12 (d, 1H), 4.71-4.65 (m, 1H), 4.32-4.27 (m, 2H), 4.09 (s, 3H), 3.67-3.62 (m, 2H), 3.22-2.90 (m, 4H), 2.08-1.88 (m, 2H).

f1) (S)-2-methoxy-5-(6-((1-(1-methyl-1H-imidazole-4-carbonyl)pyrrolidin-3-yl)oxy)-2H-benzo[b][1,4]oxazin-4(3H)-yl)nicotinonitrile

A stirred solution of 1-methyl-1H-imidazole-4-carboxylic acid (CAS registry 41716-18-1) (0.578 g, 4.45 mmol) in DMF (40 ml) was treated with HOBT (0.695 g, 4.45 mmol), EDC (0.870 g, 4.45 mmol) and Et_3N (1.24 ml, 8.90 mmol) at rt. The reaction mixture was stirred at rt for 15 min. After that time, (S)-2-methoxy-5-(6-(pyrrolidin-3-yloxy)-2H-benzo[b][1,4]oxazin-4(3H)-yl)nicotinonitrile (1.10 g, 2.97 mmol) was added, and the reaction mixture was stirred for 3 h 15 min at rt. After that time, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in DCM (200 ml), and a sat. aq. $NaHCO_3$ soln. (200 ml) was added. The organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM / methanol gradient) and preparative HPLC (SunFire C18 column, CH_3CN / 1%TFA in H_2O gradient, pure fractions were treated with DCM and a saturated aqueous $NaHCO_3$ solution; the combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure) to provide the title compound as a yellow solid.

HPLC Rt_{M10}= 2.27 min; ESIMS: 461 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6): δ 8.46-8.41 (m, 1H), 8.30-8.26 (m, 1H), 7.66-7.59 (m, 2H), 6.77-6.72 (m, 1H), 6.37-6.29 (m, 1H), 6.14-6.07 (m, 1H), 4.90-4.79 (m, 1H), 4.25-4.11 (m, 3H), 3.99 (s, 3H), 3.98-3.78 (m, 1H), 3.70-3.41 (m, 7H), 2.10-1.93 (m, 2H).

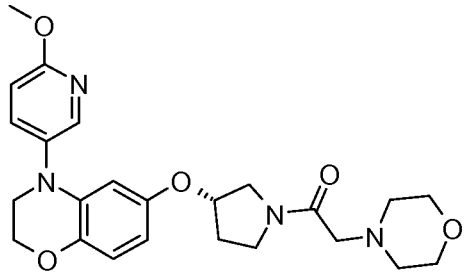
alternative method f2: the carboxylic acid, HOBT, EDC and DMF were replaced with the carboxylic acid chloride and DCM

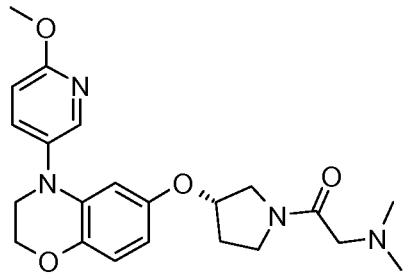
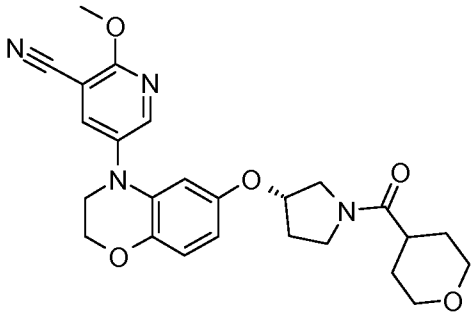
alternative method f3: the carboxylic acid, HOBT, EDC and DMF were replaced with a chloroformate and DCM

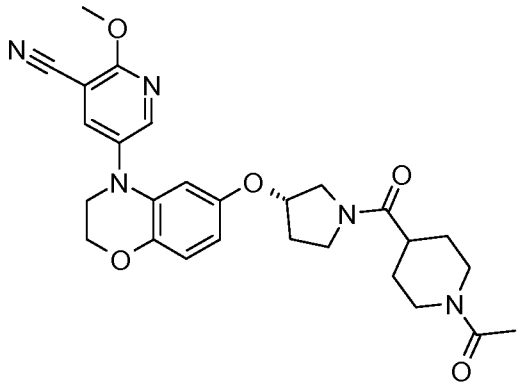
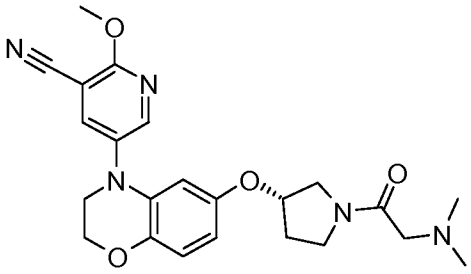
alternative method f4: the carboxylic acid, HOBT and EDC were replaced with a carbamic chloride

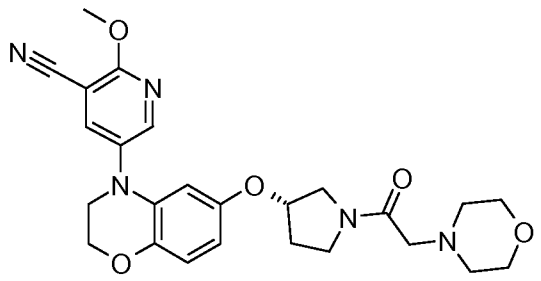
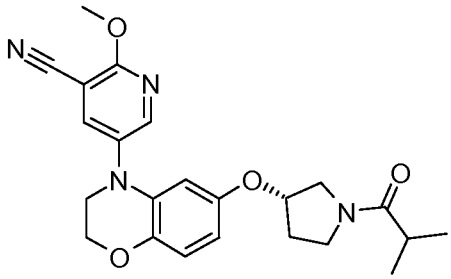
Examples D2 to D40: The compounds listed in Table 4 were prepared by a procedure analogous to that used in Example D1.

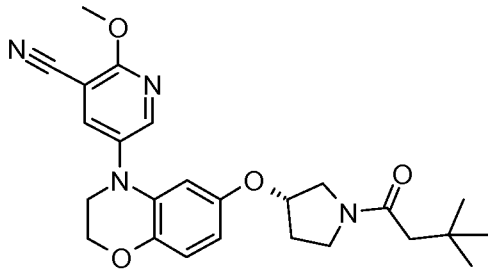
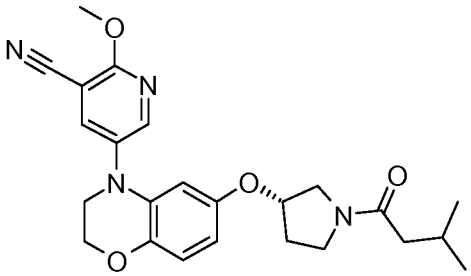
Table 4

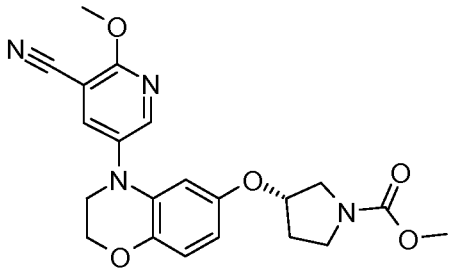
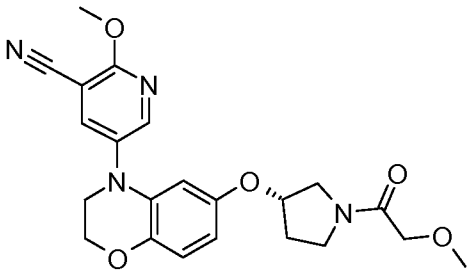
Example	Compound	HPLC Rt [min] (method)	MS [m/z; $(M+1)^+$]
D2	 1-{(S)-3-[4-(6-Methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-2-morpholin-4-yl-ethanone Synthetic route used: a1, b2 (intermediate: CAS registry 163129-79-1), c1, d1, e1, f1 (intermediate: CAS registry 89531-58-8)	2.07 (M10)	455

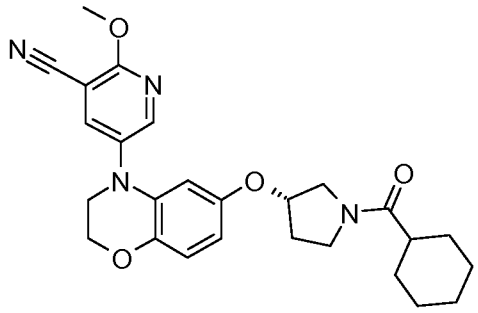
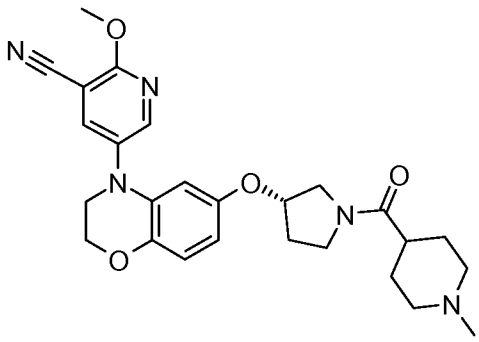
D3	 2-Dimethylamino-1-{(S)-3-[4-(6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-ethanone Synthetic route used: a1, b2 (intermediate: CAS registry 163129-79-1), c1, d1, e1, f1 (intermediate: CAS registry 1118-68-9)	2.08 (M10)	413
D4	 2-Methoxy-5-{6-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b2 (intermediate IA12), c1, d1, e1, f2 (intermediate: CAS registry 40191-32-0)	2.72 (M10)	465

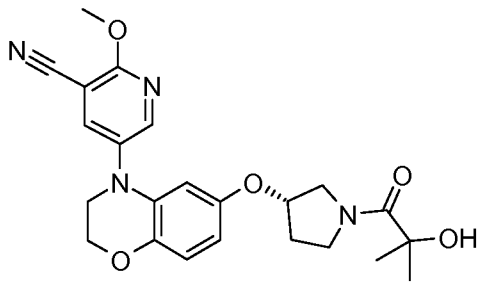
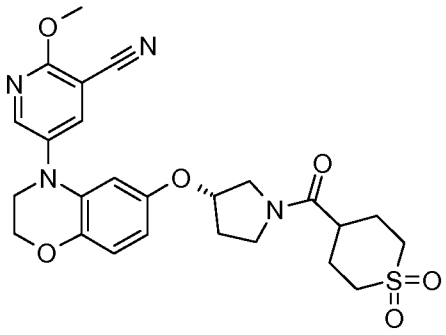
D5	 5-{6-[(S)-1-(1-Acetyl-piperidine-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 25503-90-6)	2.61 (M10)	506
D6	 5-{6-[(S)-1-(2-Dimethylamino-acetyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 1118-68-9)	2.22 (M10)	438

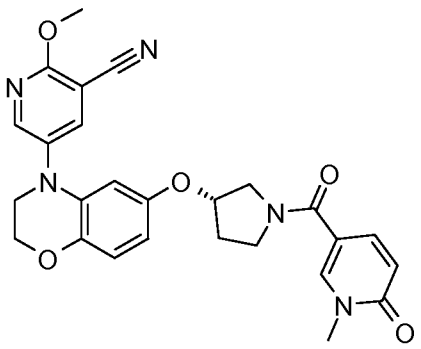
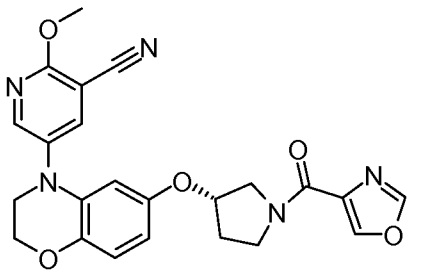
D7	 2-Methoxy-5-{6-[(S)-1-(2-morpholin-4-yl-acetyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 89531-58-8)	2.14 (M10)	480
D8	 5-[6-((S)-1-Isobutyryl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-2-methoxy-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f2 (intermediate: CAS registry 89531-58-8)	2.14 (M10)	480

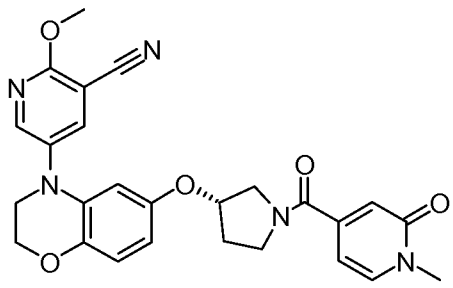
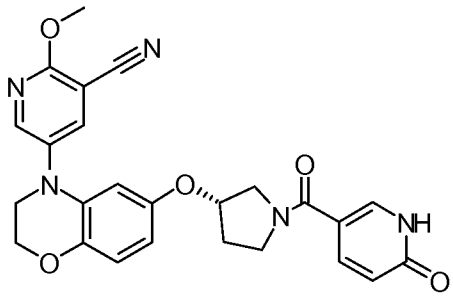
D9	 5-{6-[(S)-1-(3,3-Dimethyl-butyryl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f2 (intermediate: CAS registry 7065-46-5)	3.19 (M10)	451
D10	 2-Methoxy-5-{6-[(S)-1-(3-methyl-butyryl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f2 (intermediate: CAS registry 108-12-3)	3.06 (M10)	437

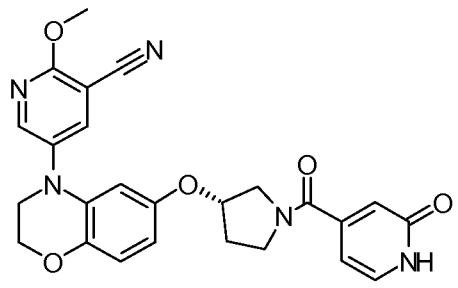
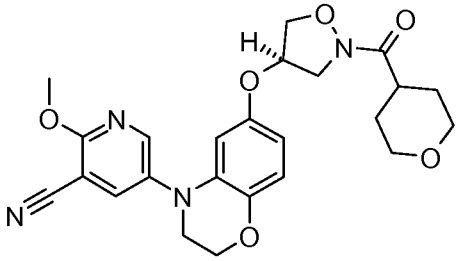
D11	 (S)-3-[4-(5-Cyano-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid methyl ester Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f3 (intermediate: CAS registry 79-22-1)	2.96 (M10)	411
D12	 2-Methoxy-5-{6-[(S)-1-(2-methoxy-acetyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f2 (intermediate: CAS registry 38870-89-2)	2.63 (M10)	425

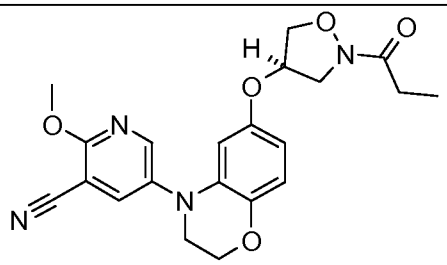
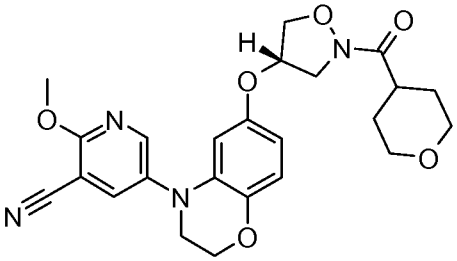
D13	 5-[6-((S)-1-Cyclohexanecarbonyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-2-methoxy-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f2 (intermediate: CAS registry 2719-27-9)	3.22 (M10)	463
D14	 2-Methoxy-5-{6-[(S)-1-(1-methyl-piperidine-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 68947-43-3)	2.23 (M10)	478

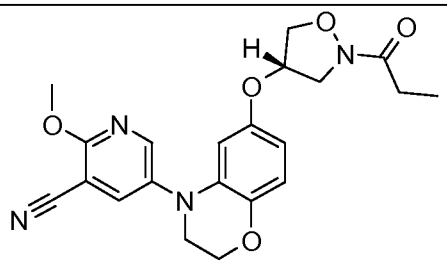
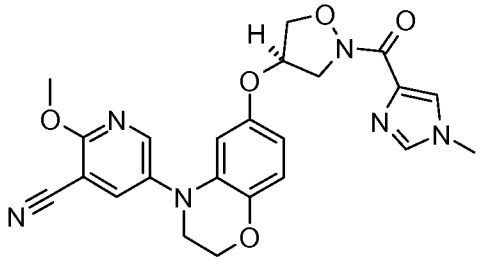
D15	 5-{6-[(S)-1-(2-Hydroxy-2-methyl-propionyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 594-61-6)	2.67 (M10)	439
D16	 5-{6-[(S)-1-(1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 64096-87-3)	1.62 (M8)	513

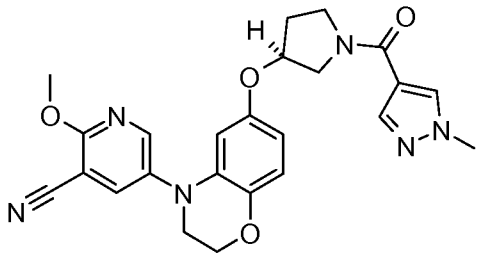
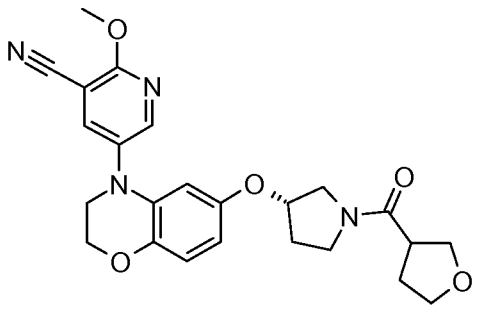
D17	 2-Methoxy-5-{6-[(S)-1-(1-methyl-6-oxo-1,6-dihydro-pyridine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 3719-45-7)	1.55 (M13)	488
D18	 2-Methoxy-5-{6-[(S)-1-(oxazole-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 23012-13-7)	1.75 (M13)	448

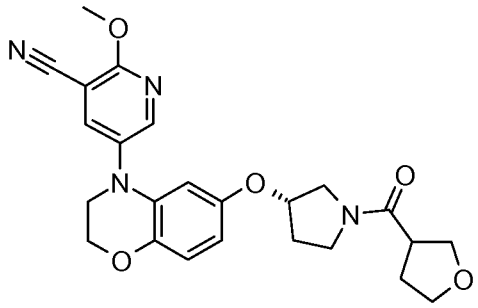
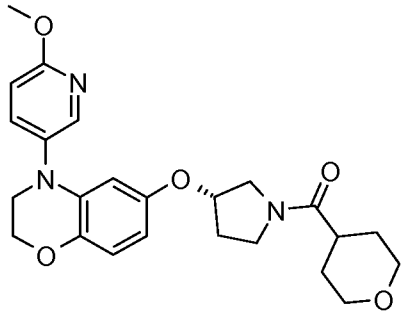
D19	 2-Methoxy-5-{6-[(S)-1-(1-methyl-2-oxo-1,2-dihydro-pyridine-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 33972-97-3)	1.56 (M13)	488
D20	 2-Methoxy-5-{6-[(S)-1-(6-oxo-1,6-dihydro-pyridine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 5006-66-6)	1.60 (M8)	474

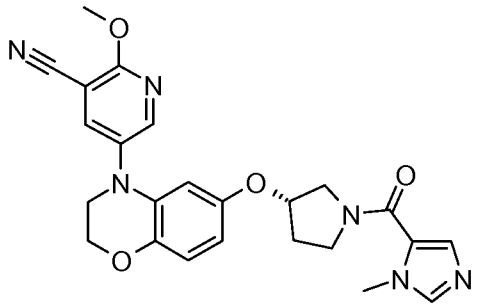
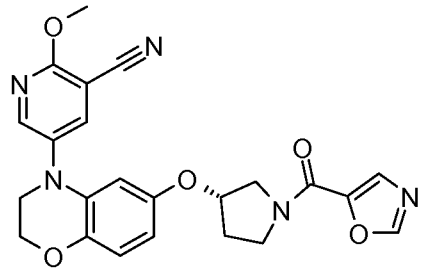
D21	 2-Methoxy-5-{6-[(S)-1-(2-oxo-1,2-dihydro-pyridine-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 22282-72-0)	1.50 (M13)	474
D22	 2-Methoxy-5-{6-[(R)-2-(tetrahydro-pyran-4-carbonyl)-isoxazolidin-4-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d2 (intermediate CAS registry 878385-72-9), e1, f2 (intermediate: CAS registry 40191-32-0)	3.01 (M10)	467

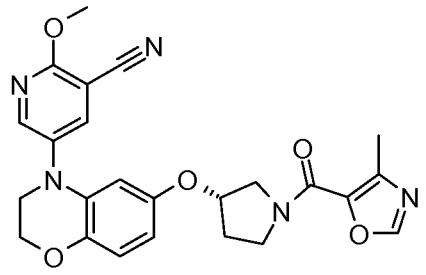
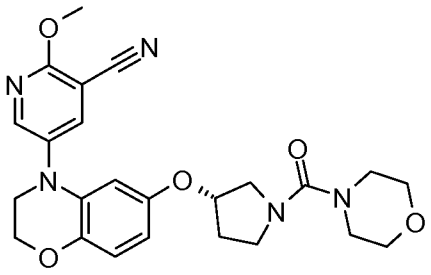
D23	 2-Methoxy-5-[6-((R)-2-propionyl-isoxazolidin-4-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d2 (intermediate CAS registry 878385-72-9), e1, f2 (intermediate: CAS registry 79-03-8)	3.11 (M10)	411
D24	 2-Methoxy-5-{6-[(S)-2-(tetrahydro-pyran-4-carbonyl)-isoxazolidin-4-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d2 (intermediate CAS registry 1092454-84-6), e1, f2 (intermediate: CAS registry 40191-32-0)	1.63 (M9)	467

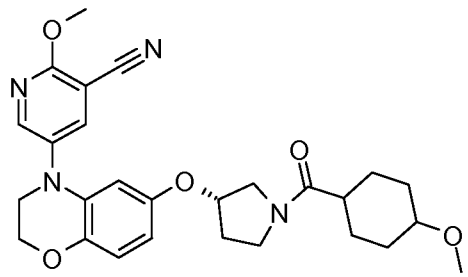
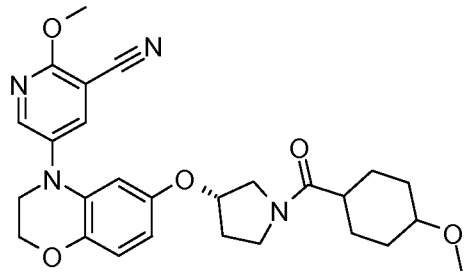
D25	 2-Methoxy-5-[6-((S)-2-propionyl-isoxazolidin-4-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d2 (intermediate CAS registry 1092454-84-6), e1, f2 (intermediate: CAS registry 79-03-8)	1.66 (M9)	411
D26	 2-Methoxy-5-{6-[(R)-2-(1-methyl-1H-imidazole-4-carbonyl)-isoxazolidin-4-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 41716-18-1)	2.31 (M10)	463

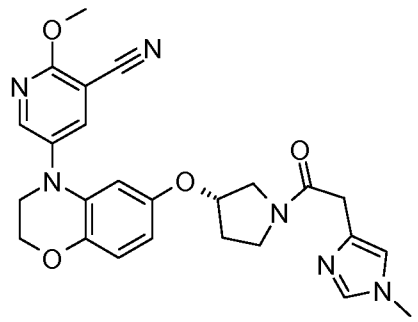
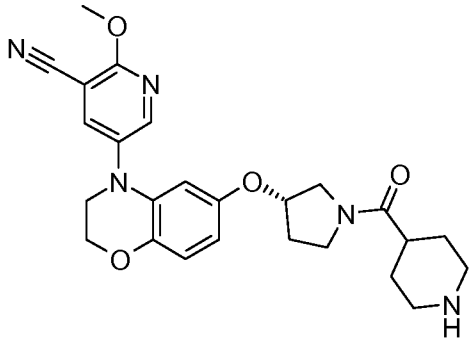
D27	 2-Methoxy-5-{6-[(S)-1-(1-methyl-1H-pyrazole-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 5952-92-1)	2.62 (M10)	461
D28	 2-Methoxy-5-{6-[(S)-1-(tetrahydro-furan-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 89364-31-8). Isomer 1	2.68 (M10)	451

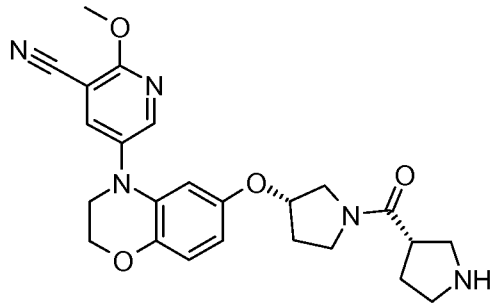
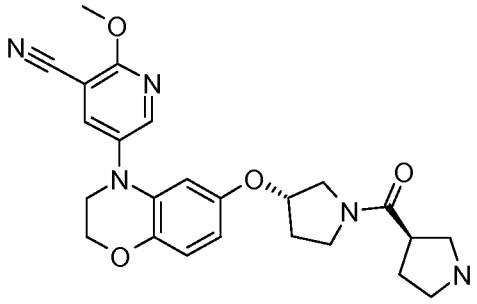
D29	 2-Methoxy-5-{6-[(S)-1-(tetrahydro-furan-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 89364-31-8). Isomer 2	2.68 (M10)	451
D30	 {(S)-3-[4-(6-Methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Synthetic route used: a1, b2 (intermediate CAS registry 163129-79-1), c1, d1, e1, f2 (intermediate: CAS registry 40191-32-0)	2.63 (M10)	440

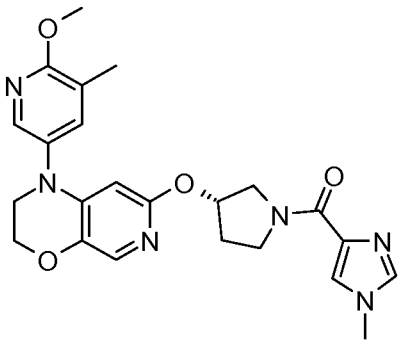
D31	 2-Methoxy-5-{6-[(S)-1-(3-methyl-3H-imidazole-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 41806-40-0)	2.24 (M10)	461
D32	 2-Methoxy-5-{6-[(S)-1-(oxazole-5-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 118994-90-4)	1.69 (M13)	448

D33	 2-Methoxy-5-{6-[(S)-1-(4-methyl-oxazole-5-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 2510-32-9)	1.80 (M13)	462
D34	 2-Methoxy-5-{6-[(S)-1-(morpholine-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f4 (intermediate: CAS registry 15159-40-7)	1.77 (M13)	466

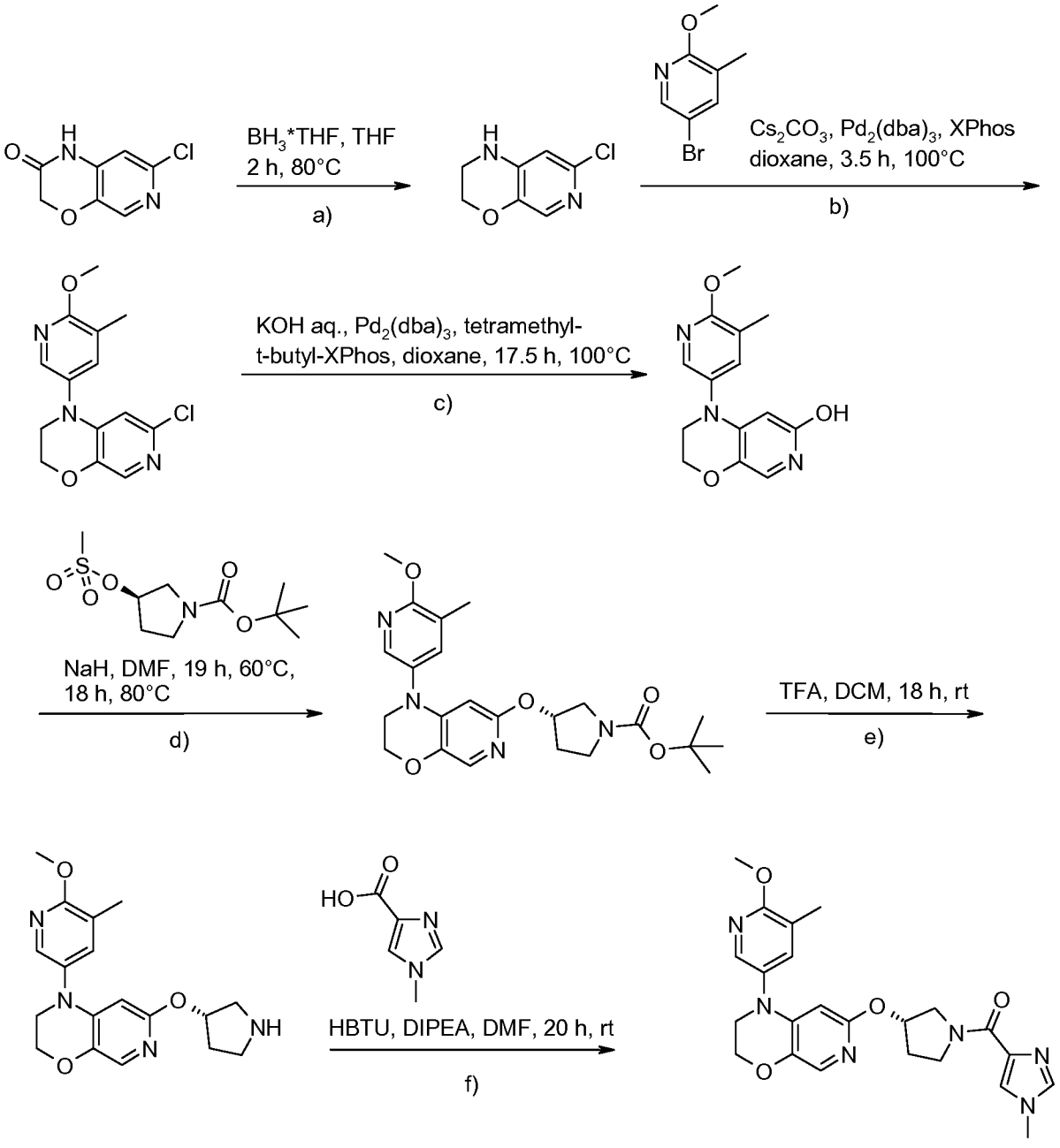
D35	 2-Methoxy-5-{6-[(S)-1-(4-methoxy-cyclohexanecarbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 95233-12-8) Isomer 1	1.90 (M13)	493
D36	 2-Methoxy-5-{6-[(S)-1-(4-methoxy-cyclohexanecarbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 95233-12-8) Isomer 2	2.01 (M13)	493

D37	 2-Methoxy-5-(6-{(S)-1-[2-(1-methyl-1H-imidazol-4-yl)-acetyl]-pyrrolidin-3-yloxy}-2,3-dihydro-benzo[1,4]oxazin-4-yl)-nicotinonitrile Synthetic route used: a1, b1 (intermediate CAS registry 941294-54-8), c1, d1, e1, f1 (intermediate: CAS registry 2625-49-2)	1.28 (M13)	475
D38	 2-Methoxy-5-{6-[(S)-1-(piperidine-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Synthetic route used: a1, b1 intermediate IA12, c1, d1 CAS registry 127423-61-4, f1 CAS registry 84358-13-4 last step : removal of Boc protecting group using TFA in a conventional way.	2.19 (M10)	464

D39	 2-Methoxy-5-{6-[(S)-1-((S)-pyrrolidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl} -nicotinonitrile Synthetic route used: a1, b1 intermediate CAS registry IA12, c1, d1 CAS registry 127423-61-4, f1 CAS registry 140148-70-5 last step : removal of Boc protecting group using TFA in a conventional way.	2.24 (M10)	450
D40	 2-Methoxy-5-{6-[(S)-1-((R)-pyrrolidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl} -nicotinonitrile Synthetic route used: a1, b1 intermediate IA12, c1, d1 CAS registry 127423-61-4, f1 CAS registry 72925-16-7, last step : removal of Boc protecting group using TFA in a conventional way.	2.24 (M10)	450



Example E1: **{(S)-3-[1-(6-Methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone (according to Scheme 5)**



5

a) 7-Chloro-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine

A mixture of 7-chloro-1H-pyrido[3,4-b][1,4]oxazin-2-one (CAS registry 928118-43-8) (630 mg, 3.41 mmol) and BH_3*THF (1 M in THF) (10.2 ml, 10.2 mmol) in THF (20 ml) was stirred for 2 h at 80°C. The reaction mixture was quenched with MeOH, NaOH aq. solution 1 M was added and the mixture was extracted with EtOAc. Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography on silica gel (heptane / EtOAc 100:0 to 50:50 in 12 min) to provide the title compound as a white solid (432 mg, 74% yield).

HPLC Rt_{M1} =0.47 min; ESIMS: 171 [$(M+H)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 6.46 (s, 1H), 4.43 (br s, 1H) 4.21-4.25 (m, 2H), 3.48-3.51 (m, 2H).

b) 7-Chloro-1-(6-methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]-oxazine

A mixture of 7-chloro-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine (127 mg, 0.74 mmol), 5-bromo-2-methoxy-3-methylpyridine (CAS registry 760207-87-2) (0.196 g, 0.986 mmol), Cs_2CO_3 (534 mg, 1.64 mmol) and XPhos (28 mg, 0.06 mmol) in dioxane (3.5 ml) was degassed with argon and $Pd_2(dba)_3$ (27 mg, 0.03 mmol) was added. After stirring for 3.5 h at 100 °C the reaction mixture was filtered over hyflo, sat. aq. $NaHCO_3$ soln. was added and the mixture was extracted with EtOAc. Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography on silica gel (heptane / EtOAc 95:5 to 40:60 in 14 min) to provide the title compound as a pale colored solid (190 mg, 87% yield).

HPLC Rt_{M1} =1.04 min; ESIMS: 292 [$(M+H)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, 1H), 7.80 (s, 1H), 7.31 (d, 1H), 6.31 (s, 1H), 4.34-4.37 (m, 2H), 4.01 (s, 3H), 3.68-3.72 (m, 2H), 2.24 (s, 3H).

c) 1-(6-Methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-ol

A mixture of 7-chloro-1-(6-methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine (190 mg, 0.65 mmol), tetramethyl-t-butyl-XPhos (13 mg, 0.03 mmol) in dioxane (3 ml) and 5M aq. KOH soln. (0.04 ml, 1.95 mmol) was degassed with argon and $Pd_2(dba)_3$ (6 mg, 0.01 mmol) was added. After stirring for 17.5 h at 100°C the reaction mixture was filtered over hyflo, the filtrate was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography on silica gel (EtOAc / MeOH 100:0 to 85:15 in 17 min) to provide the title compound as a white solid (111 mg, 62% yield).

HPLC Rt_{M1} =0.67 min; ESIMS: 274 [$(M+H)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.32 (br s, 1H), 8.02 (d, 1H), 7.62 (m, 1H), 6.89 (s, 1H), 4.84 (s, 1H), 4.17-4.21 (m, 2H), 3.91 (s, 3H), 3.61-3.66 (m, 2H), 2.17 (s, 3H).

d) (S)-3-[1-(6-Methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of 1-(6-methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-ol (111 mg, 0.41 mmol) in DMF (3 ml) was treated with NaH (33 mg, 0.81 mmol) for 10 min at 20°C. (R)-3-Methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester (CAS registry 127423-61-4) (162 mg, 0.61 mmol) was added. After stirring for 19 h at 60°C and 18 h at 80°C sat. aq. $NaHCO_3$ soln. was added and the reaction mixture was extracted with TBME. Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography on silica gel (heptane / EtOAc 93:7 to 40:60 in 13.5 min) to provide the title compound as a pale yellow oil (107 mg, 59% yield).

HPLC Rt_{M1} =1.21 min; ESIMS: 443 [$(M+H)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.61 (br s, 1H), 7.32 (br s 1H), 5.71 (s, 1H), 5.41 (br s, 1H), 4.32 (br s, 2H), 3.99 (s, 3H), 3.65-3.70 (m, 2H), 3.37-3.61 (m, 4H), 2.23 (s, 3H), 1.58 (s, 9H), 0.82-0.97 (m, 2H).

e) 1-(6-Methoxy-5-methyl-pyridin-3-yl)-7-((S)-pyrrolidin-3-yloxy)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine

A solution of (S)-3-[1-(6-methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]-oxazin-7-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (103 mg, 0.23 mmol) and TFA (0.179 ml, 2.33 mmol) in DCM (1.8 ml) was stirred for 18 h at rt. Sat. aq. Na_2CO_3 soln. was added and the reaction mixture was extracted with DCM. Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated, the title compound was as a pale yellow foam (72 mg, 90% yield).

HPLC Rt_{M1} =0.64 min; ESIMS: 343 [$(M+H)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.62 (s, 1H), 7.32 (m, 1H), 5.70 (s, 1H), 5.29-5.35 (m, 1H), 4.29-4.33 (m, 2H), 3.99 (s, 3H), 3.65-3.69 (m, 2H), 2.82-3.14 (m, 4H), 2.22 (s, 3H), 1.80-2.10 (m, 2H).

f) {(S)-3-[1-(6-Methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone

A mixture of 1-methyl-1H-imidazole-4-carboxylic acid (CAS registry 41716-18-1) (15 mg, 0.12 mmol), HBTU (53 mg, 0.14 mmol) and DIPEA (0.025 ml, 0.14 mmol) in DMF (0.6 ml) was stirred at rt for 5 min. A solution of 1-(6-methoxy-5-methyl-pyridin-3-yl)-7-((S)-pyrrolidin-

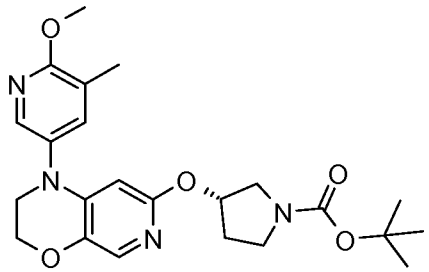
3-yloxy)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine (0.037 g, 0.11 mmol) in DMF (0.6 ml) was added. After stirring for 20 h at rt water was added and the reaction mixture and was extracted with EtOAc. Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by prep. RP-HPLC (column SunFire C18, H_2O + 0.1% TFA / ACN + 0.1% TFA 90:10 to 60:40 in 16 min) to provide the title compound as a pale yellow foam (24 mg, 49% yield).

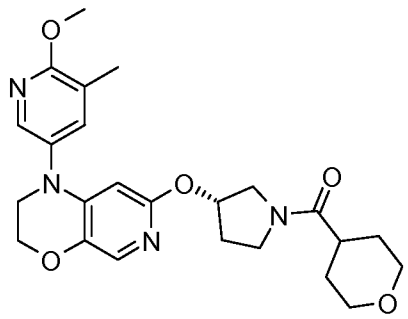
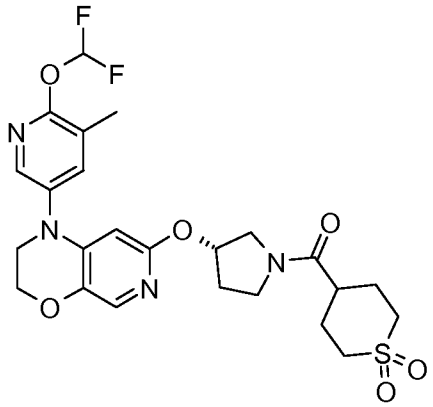
HPLC Rt_{M1} =0.74 min; ESIMS: 451 [$(M+H)^+$].

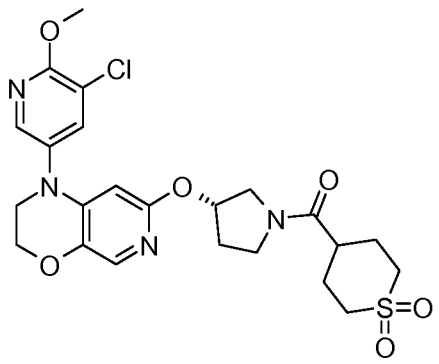
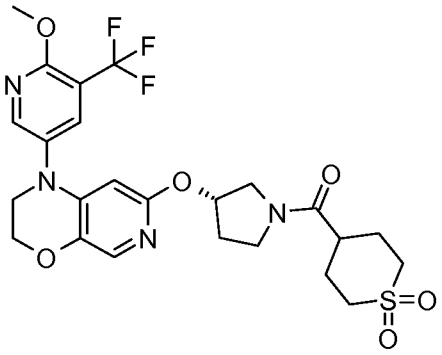
^{1}H NMR (400 MHz, DMSO): δ 8.00 (m, 1H), 7.58-7.63 (m, 3H), 7.53 (d, 1H), 5.51 (d, 1H), 5.29-5.40 (m, 1H), 4.23-4.29 (m, 2H), 3.99 (s, 3H), 3.77-4.19 (m, 2H), 3.66 (m, 5H), 3.39-3.63 (m, 2H), 2.15 (s, 3H), 1.89-2.11 (m, 2H).

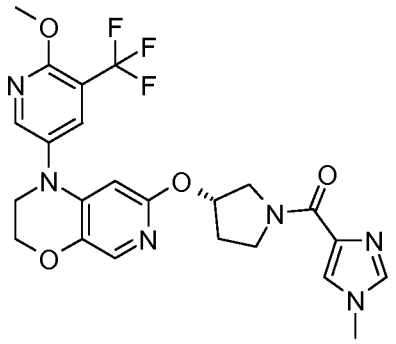
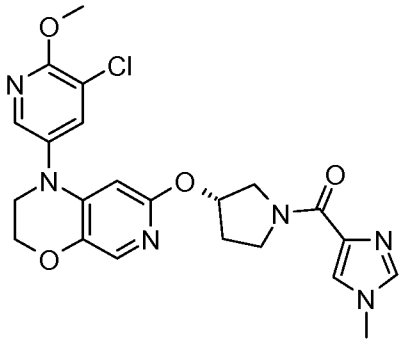
Examples E2 to 11: The compounds listed in Table 5 were prepared by a procedure analogous to that used in Example E1.

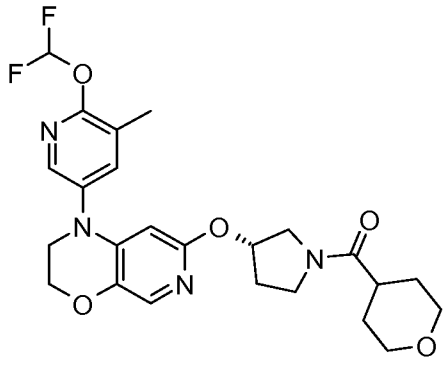
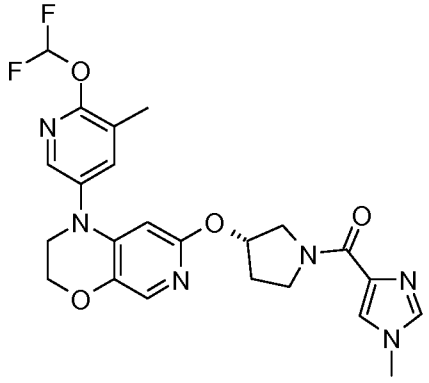
Table 5

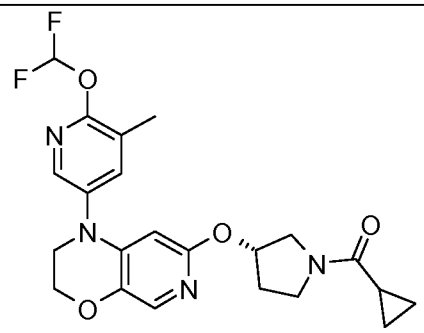
Example	Compound / Reaction Conditions	HPLC Rt [min] (method)	MS [m/z; $(M+1)^+$]
E2	 (S)-3-[1-(6-Methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester Buchwald amination condition: CA4 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8, IA9, 127423-61-4	1.19 (M1)	443

E3	 {(S)-3-[1-(6-Methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA4 Amide bond condition: CB6 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8, 127423-61-4, IA9, acyl chloride 40191-32-0	0.84 (M1)	455
E4	 {(S)-3-[1-(6-Difluoromethoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-methanone Buchwald amination condition: CA4 Amide bond condition: CB4 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8, IA8, 127423-61-4, 64096-87-3	1.09 (M1)	328

E5	 {(S)-3-[1-(5-Chloro-6-methoxy-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-methanone Buchwald amination condition: CA4 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8, 127423-61-4, IA11, 64096-87-3	0.79 (M1)	523
E6	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[1-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA4 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA21 / 64096-87-3	0.92 (M1)	557

E7	 {(S)-3-[1-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA4 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA21 / 41716-18-1	0.87 (M1)	505
E8	 {(S)-3-[1-(5-Chloro-6-methoxy-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA4 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8, 127423-61-4, IA11, 41716-18-1	0.75 (M1)	471

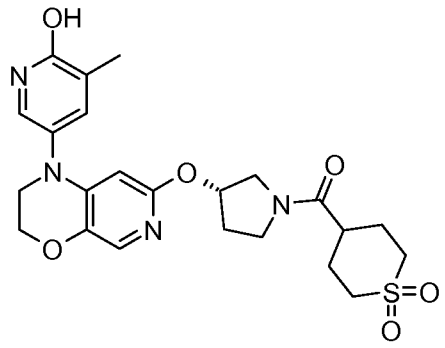
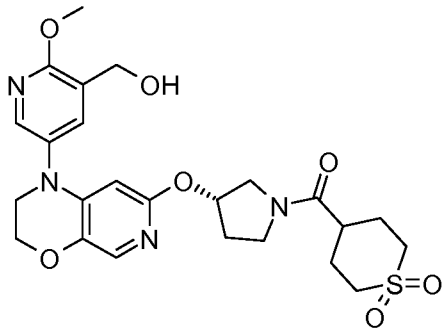
E9	 {(S)-3-[1-(6-Difluoromethoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA4 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA8 / 5337-03-1	0.95 (M1)	491
E10	 {(S)-3-[1-(6-Difluoromethoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA4 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA8 / 41716-18-1	0.84 (M1)	487

E11	 Cyclopropyl-{(S)-3-[1-(6-difluoromethoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA4 Amide bond condition: CB6 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA8 / Acyl chloride: 4023-34-1	1.01 (M1)	447

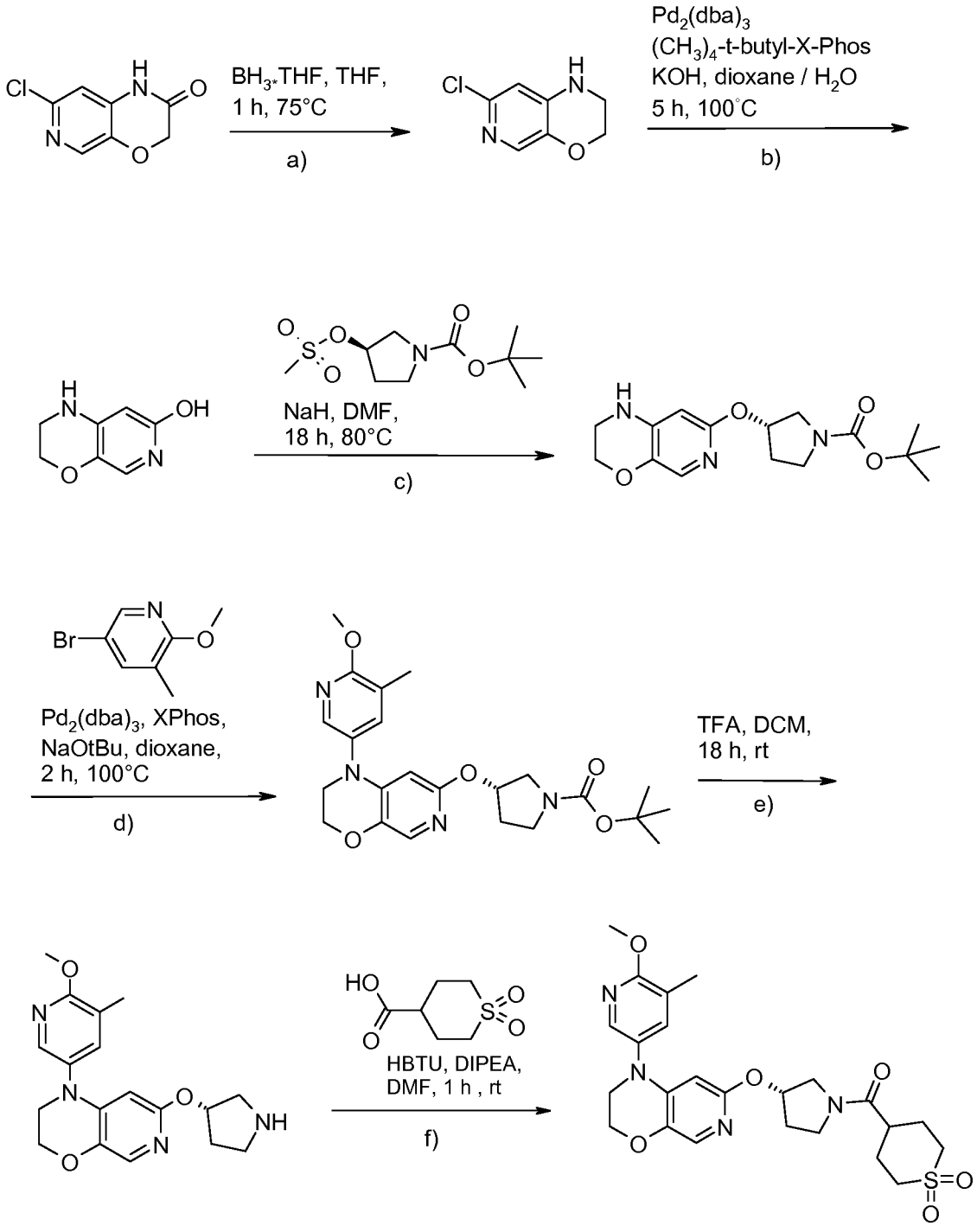
Reference Examples E12 to E13: The compounds listed in Table 5a were prepared by a procedure analogous to that used in Example E1, applying adequate protecting group strategies.

Table 5a

Reference Example	**Compound / Reaction Conditions**	**HPLC Rt [min] (method)**	**MS [m/z; $(M+1)^+$]**

E12	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[1-(6-hydroxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA2 Amide bond condition: CB7 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA69 / 64096-87-3	**0.54 (M16)**	**489**
E13	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[1-(5-hydroxymethyl-6-methoxy-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA2 Amide bond condition: CB7 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA70 / 64096-87-3	**0.63 (M16)**	**519**

Example F1: (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[1-(6-methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone (according to Scheme 6)



a) 7-Chloro-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine

A solution of 7-chloro-1H-pyrido[3,4-b][1,4]oxazin-2-one (CAS registry 928118-43-8) (3.70 g, 20 mmol) in THF (63 ml) was treated with BH_3*THF (1M in THF, 47 ml, 47 mmol). The reaction mixture was stirred at 75°C for 1 h, then cooled down to rt and quenched with methanol (24 ml, 600 mmol). The reaction mixture was concentrated under reduced pressure

and the residue was taken up with EtOAc and washed with sat. aq. $NaHCO_3$ soln. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the title product as a pale yellow solid (3.3 g, 96% yield).

UPLC Rt_{M1} =0.47 min; ESIMS: 171 [$(M+H)^+$].

^1H NMR (400 MHz, DMSO-d_6): δ 7.53 (s, 1H), 7.11 (br s, 1H), 6.47 (s, 1H), 4.09 (t, 2H), 3.17-3.38 (m, 2H).

b) 2,3-Dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-ol

A mixture of 7-chloro-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine (1.08 g, 6.33 mmol), aq. KOH soln. (1.07 g, 19 mmol KOH in 5.4 ml water), 2-di-t-butylphosphino-3,4,5,6-tetramethyl-2',4',6-tri-i-propylbiphenyl 98% (0.30 g, 0.63 mmol) and $Pd_2(dba)_3$ (0.29 g, 0.32 mmol) in dioxane (32.5 ml) was degassed three times with nitrogen, the tube was sealed and the reaction mixture was stirred at 100°C for 5 h. After cooling to rt, the reaction mixture was filtered through hyflo, rinsed with EtOAc and methanol. The filtrates were concentrated and the title compound was obtained after flash chromatography on silica gel (DCM / MeOH, 98:2 to 75:25) as an orange residue (660 mg, 69% yield)

UPLC Rt_{M1} =0.34 min; ESIMS: 153 [$(M+H)^+$].

^1H NMR (400 MHz, DMSO-d_6): δ 10.33 (br s, 1H), 7.03 (br s, 1H), 6.71 (s, 1H), 5.15 (s, 1H), 3.95 (t, 2H), 3.25 (m, 2H).

c) (S)-3-(2,3-Dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

A dry solution of 2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-ol (0.66 g, 4.34 mmol) and (R)-3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester (CAS registry 127423-61-4) (1.73 g, 6.51 mmol) in DMF (40 ml) was treated with sodium hydride (60% in mineral oil, 0.21 g, 8.68 mmol) and the reaction mixture was stirred at 80°C for 18 h. After cooling to rt, the reaction mixture was diluted with TBME and washed with sat. aq. $NaHCO_3$ soln.. The organic layer was dried over $MgSO_4$, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (cyclohexane / EtOAc, 95:5 to 30:70) as a yellow oil (1.035 g, 75% purity,, 56% yield)

UPLC Rt_{M1} =0.65 min; ESIMS: 322 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 5.86 (s, 1H), 5.42 (br s, 1H), 4.25-4.41 (m, 1H), 4.19 (t, 2H), 3.38-3.66 (m, 6H), 2.00-2.18 (m, 2H), 1.46 (d, 9H).

d) (S)-3-[1-(6-Methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (S)-3-(2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (254 mg, 0.79 mmol), 5-bromo-2-methoxy-3-methylpyridine (CAS registry 760207-87-2) (208 mg, 1.03 mmol), XPhos (30 mg, 0.06 mmol), and NaOtBu (167 mg, 1.74 mmol) in dioxane (6 ml) was degassed with argon for 5 min, then $Pd_2(dba)_3$ (29 mg, 0.03 mmol) was added. The tube was filled with argon, sealed and the reaction mixture was stirred at 100°C for 2 h. After cooling to rt, the reaction mixture was filtered through hyflo, rinsed with EtOAc and the filtrates were washed with sat. aq. $NaHCO_3$ soln.. The aq. layer was twice reextracted with EtOAc, the combined organic layers were dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (heptane / EtOAc, 100:0 to 50:50) as a clear gum (274 mg, 78% yield).UPLC Rt_{M1} =1.20 min; ESIMS: 443 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.61 (br s, 1H), 7.30-7.35 (m, 1H), 5.71 (s, 1H), 5.34-5.46 (m, 1H), 4.31 (br s, 2H), 3.99 (s, 3H), 3.68 (t, 2H), 3.34-3.62 (m, 4H), 2.23 (s, 3H), 2.01-2.09 (m, 2H), 1.44 (s, 9H).

e) 1-(6-Methoxy-5-methyl-pyridin-3-yl)-7-((S)-pyrrolidin-3-yloxy)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine

A solution of (S)-3-[1-(6-methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (364 mg, 0.82 mmol) in DCM (6 ml) was treated with TFA (0.63 ml, 8.23 mmol) and the reaction mixture was stirred at rt for 18 h, then quenched with sat. aq. $NaHCO_3$ soln. and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the title product as a red oil, which was used in the next step without further purification (313mg, 90% purity, quantitative yield).

UPLC Rt_{M1} =0.65 min; ESIMS: 343 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.62 (s, 1H), 7.32 (d, 1H), 5.70 (s, 1H), 5.26-5.36 (m, 1H), 4.31 (t, 2H), 3.99 (s, 3H), 3.67 (t, 2H), 2.95-3.15 (m, 3H), 2.81-2.92 (m, 1H), 2.22 (s, 3H), 1.98-2.10 (m, 1H), 1.79-1.90 (m, 1H).

f) (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[1-(6-methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone

A solution of 1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-carboxylic acid (CAS registry 64096-87-3) (106 mg, 0.59 mmol) in DMF (4 ml) was treated with HBTU (225 mg, 0.59 mmol) and DIPEA (0.24 ml, 1.37 mmol). The resulting orange solution was stirred at rt for 5 min, then a solution of 1-(6-methoxy-5-methyl-pyridin-3-yl)-7-((S)-pyrrolidin-3-yloxy)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine (156 mg, 0.46 mmol) in DMF (2 ml) was added. The

reaction mixture was stirred at rt for 1 h then concentrated under reduced pressure and the residue was taken up with DCM and washed with sat. aq. $NaHCO_3$ soln.. The organic layer was dried by passing it through a phase separating cartridge, concentrated and the title compound was obtained after SFC chromatography (column DEAP (250mm x 30mm, 60A, 5µm) Princeton, gradient 11 - 16% of methanol in supercritical CO_2 in 6 min) as a slightly coloured solid (112 mg, 49% yield).

UPLC Rt_{M1} =0.81 min; ESIMS: 503 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (s, 1H), 7.61 (m, 1H), 7.52 (d, 1H), 5.52 (d, 1H), 5.24-5.43 (m, 1H), 4.26 (br s, 2H), 3.89 (s, 3H), 3.59-3.79 (m, 3H), 3.41-3.56 (m, 2H), 3.21-3.39 (m, 1H), 2.98-3.21 (m, 4H), 2.67-2.83 (m, 1H), 1.84-2.20 (m, 9H).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.01 (s, 1H), 7.63-7.59 (m, 1H), 7.55-7.51 (m, 1H), 5.55-5.51 (m, 1H), 5.43-5.24 (m, 1H), 4.29-4.22 (m, 2H), 3.90 (s, 3H), 3.80-3.60 (m, 2H), 3.56-3.37 (m, 3H), 3.28-2.99 (m, 5H), 2.89-2.66 (m, 1H), 2.19-2.09 (m, 4H), 2.08-1.98 (m, 2H), 1.98-1.86 (m, 3H).

Crystallization of Example F1 by heating and cooling in isopropanol / diethyl ether

474mg of amorphous Example F1 was suspended in 1.4mL of isopropanol. The mixture was heated to 70°C and stirredat 70°C to allow complete dissolution of Example F1. The solution was cooled down to RT, a glue residue was formed. 2mL of diethyl ether was added and the slurry was stirred for 48h. A white suspension was formed. The suspension was filtered and the solid was dried at 40°C, 15mbar. A fine, white powder was obtained. The material contains only slight residual solvent (<0.5%). A crystalline anhydrous form of Example F1 with an onset melting of 148.77°C was obtained.

List of most significant 2-Theta peaks from X-ray Powder Diffraction Pattern with tolerances ±0.5 of Example F1 anhydrous form (Method M1) (including low/weak peaks for information). Note: This list of peaks is not exhaustive but are only “inter alia”.

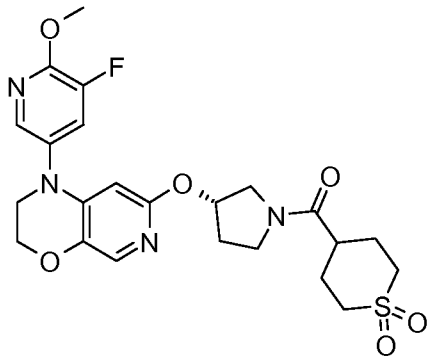
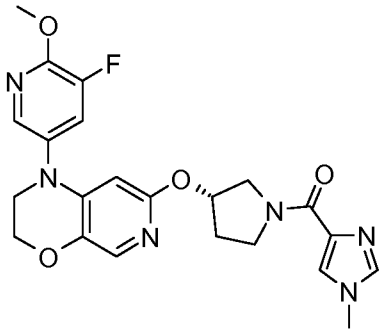
2-Theta in deg	Intensity
9.1	Low
10.2	Medium
11.9	Medium
13.0	Low
17.1	Strong
17.7	Medium, unresolved

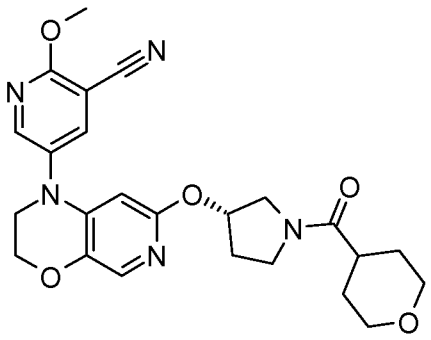
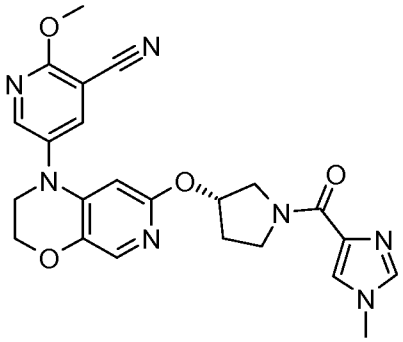
18.7	Medium
20.3	Medium, unresolved
20.8	Medium, unresolved
26.0	Medium/low
26.7	Medium
23.2	Medium/low
24.1	Medium/low
24.8	Medium/low
29.3	Medium/low
27.4	Medium/low
21.4	Medium/low

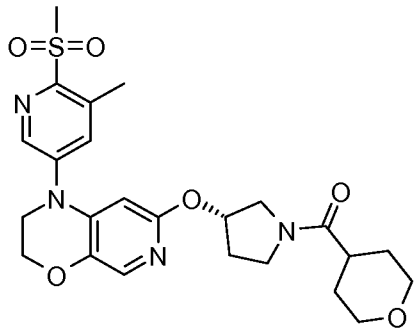
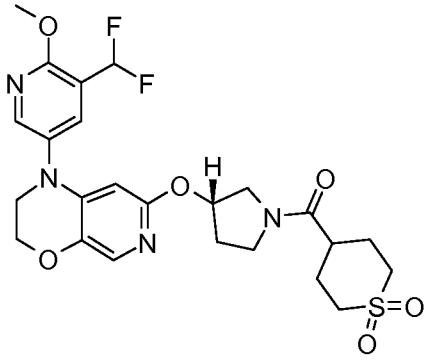
Examples F2 to F15: The compounds listed in Table 6 were prepared by a procedure analogous to that used in Example F1.

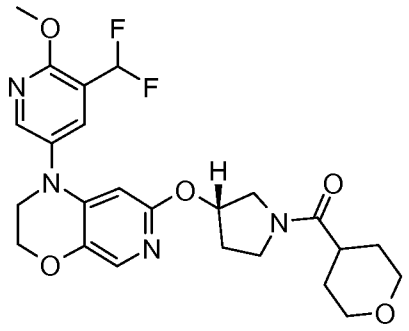
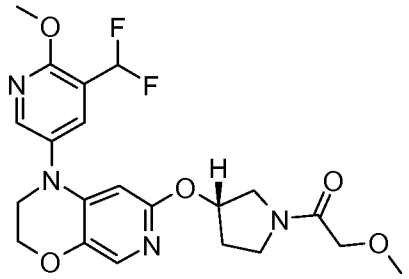
Table 6

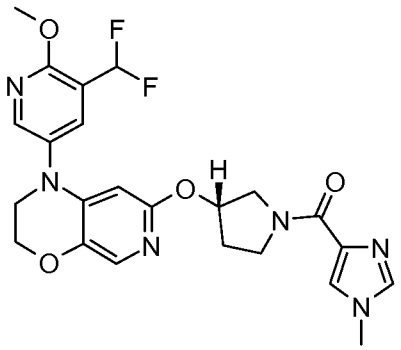
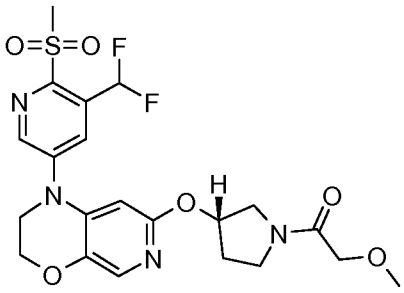
Example	Compound / Reaction Conditions	HPLC Rt [min] (method)	MS [m/z; $(M+1)^+$]

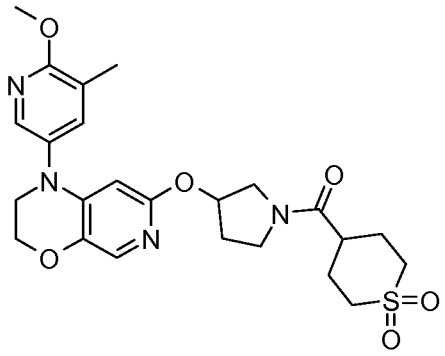
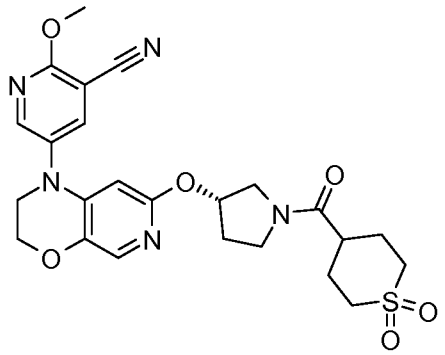
F2	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[1-(5-fluoro-6-methoxy-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA2 Amide bond condition: CB2 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA10 / 64096-87-3	0.79 (M1)	507
F3	 {(S)-3-[1-(5-Fluoro-6-methoxy-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA2 Amide bond condition: CB2 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA10 / 41716-18-1	0.73 (M1)	455

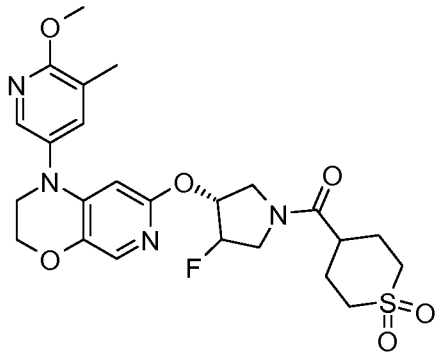
F4	 2-Methoxy-5-{7-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-pyrido[3,4-b][1,4]oxazin-1-yl}-nicotinonitrile Buchwald amination condition: CA2 Amide bond condition: CB6 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8, 127423-61-4, IA12, acyl chloride 40191-32-0	0.83 (M1)	466
F5	 2-Methoxy-5-{7-[(S)-1-(1-methyl-1H-imidazole-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-pyrido[3,4-b][1,4]oxazin-1-yl}-nicotinonitrile Buchwald amination condition: CA2 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8, 127423-61-4, IA12, 41716-18-1	0.73 (M1)	462

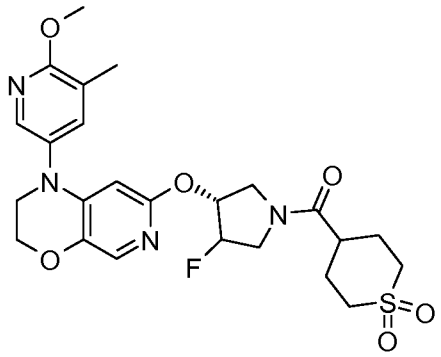
F6	 {(S)-3-[1-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA4 Amide bond condition: CB6 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8, 127423-61-4, IA1, acyl chloride 40191-32-0	0.76 (M1)	503
F7	 {(S)-3-[1-(5-Difluoromethyl-6-methoxy-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-methanone Buchwald amination condition: CA2 Amide bond condition: CB2 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA6 / 64096-87-3	0.82 (M1)	539

F8	 {(S)-3-[1-(5-Difluoromethyl-6-methoxy-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA2 Amide bond condition: CB6 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA6 / Acyl chloride 40191-32-0	0.88 (M1)	491
F9	 1-{(S)-3-[1-(5-Difluoromethyl-6-methoxy-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-2-methoxy-ethanone Buchwald amination condition: CA2 Amide bond condition: CB6 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA6 / Acyl chloride: 38870-89-2	0.83 (M1)	451

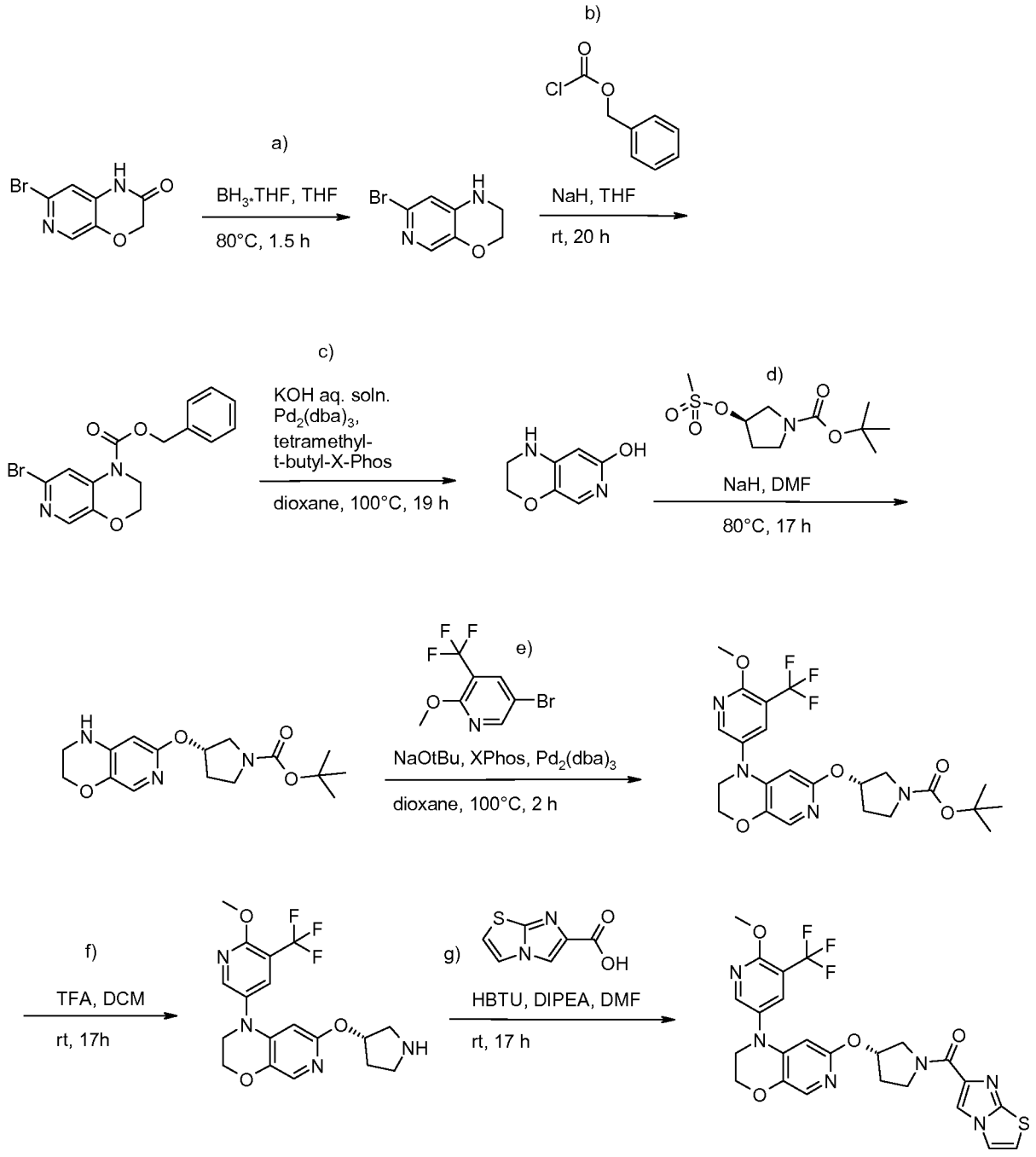
F10	 {(S)-3-[1-(5-Difluoromethyl-6-methoxy-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone Buchwald amination condition: CA2 Amide bond condition: CB3 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA6 / 41716-18-1	0.77 (M1)	487
F11	 1-{(S)-3-[1-(5-Difluoromethyl-6-methanesulfonyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-2-methoxy-ethanone Buchwald amination condition: CA1 Amide bond condition: CB6 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 127423-61-4 / IA4 / Acyl chloride: 38870-89-2	0.76 (M1)	499

F12	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{3-[1-(6-methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA4 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8 / 141699-57-2 / IA9 / 64096-87-3	0.81 (M1)	503
F13	 5-{7-[(S)-1-(1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-pyrido[3,4-b][1,4]oxazin-1-yl}-2-methoxy-nicotinonitrile Buchwald amination condition: CA2 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 928118-43-8, 127423-61-4, IA12,64096-87-3	1.12 (M1)	454

F14	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(R)-3-fluoro-4-[1-(6-methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA2 Amide bond condition: CB4 Side chain introduction condition: CC1 Precursors used: CAS 869481-93-6 / 1174020-51-9 Chiral separation method: CD12	0.89 (M1) 35.9 (CD12)	521

F15	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(R)-3-fluoro-4-[1-(6-methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA2 Amide bond condition: CB4 Side chain introduction condition: CC1 Precursors used: CAS 869481-93-6 / 1174020-51-9 Chiral separation method: CD12	0.89 (M1) 45.8 (CD12)	521

Example G1: Imidazo[2,1-b]thiazol-6-yl-{(S)-3-[1-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone



a) 7-Bromo-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine

A solution of 7-bromo-1H-pyrido[3,4-b][1,4]oxazin-2-one (CAS registry 943995-72-0) (2.93 g, 12.79 mmol) in THF (40 ml) was treated with BH_3*THF (1M in THF, 30 ml, 30 mmol). The reaction mixture was stirred at 80°C for 1.5 h, then cooled down to rt and quenched with methanol. The reaction mixture was concentrated under reduced pressure and the residue was taken up with EtOAc and washed with aq. 1M NaOH soln. The organic layer was dried

over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title product as a white solid. (2.48 g, 90% yield).

UPLC Rt_{M1} =0.49 min; ESIMS: 217 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 6.60 (s, 1H), 4.42 (br s, 1H), 4.20-4.24 (m, 2H), 3.49 (m, 2H).

b) 7-Bromo-2,3-dihydro-pyrido[3,4-b][1,4]oxazine-1-carboxylic acid benzyl ester

A dry solution of 7-bromo-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine (1.85 g, 8.60 mmol) in THF (50 ml) was portionwise treated at 0°C with 60% NaH in mineral oil (0.52 g, 12.90 mmol) and the reaction mixture was stirred at 0°C for 1 h. Benzyl chloroformate (CAS registry 501-53-1) (1.40 ml, 9.85 mmol) was dropwise added and the reaction mixture was allowed to warm to rt and to stir for 20 h, finally quenched with methanol and then diluted with sat. aq. $NaHCO_3$ soln. and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after after flash chromatography on silica gel (heptane / EtOAc, 100:0 to 60:40) as a white solid (2.06 g, 68% yield).

UPLC Rt_{M1} =1.14 min; ESIMS: 349 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (br s, 1H), 7.98 (s, 1H), 7.35-7.46 (m, 5H), 5.30 (s, 2H), 4.20-4.27 (m, 2H), 3.92-4.01 (m, 2H).

c) 2,3-Dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-ol

A mixture of 7-bromo-2,3-dihydro-pyrido[3,4-b][1,4]oxazine-1-carboxylic acid benzyl ester (1.27 g, 3.63 mmol), aq. KOH soln. (0.90 g, 16 mmol KOH in 3.2 ml water), 2-di-t-butylphosphino-3,4,5,6-tetramethyl-2',4',6-tri-i-propylbiphenyl 98% (0.26 g, 0.54 mmol) in dioxane (16 ml) was degassed with argon for 5 min, then $Pd_2(dba)_3$ (0.25 g, 0.27 mmol) was added. The tube was filled with argon, then sealed and the reaction mixture was stirred at 100°C for 19 h. After cooling to rt, the reaction mixture was filtered through hyflo, rinsed with EtOAc and methanol. The filtrates were dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (DCM / MeOH, 95:5 to 60:40) as an orange residue (262 mg, 47% yield).

UPLC Rt_{M1} =0.32 min; ESIMS: 153 [$(M+H)^+$]

^1H NMR (400 MHz, DMSO-d_6): δ 10.33 (br.s, 1H), 7.03 (br.s, 1H), 6.71 (s, 1H), 5.15 (s, 1H), 3.95 (t, 2H), 3.25 (td, 2H).

d) (S)-3-(2,3-Dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

A dry solution of 2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-ol (200 mg, 0.66 mmol) and (R)-3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester (CAS registry 127423-61-4)

(262 mg, 0.99 mmol) in DMF (6 ml) was treated with sodium hydride 60% in mineral oil (53 mg, 1.33 mmol) and the reaction mixture was stirred at 80°C for 17 h. After cooling to rt, the reaction mixture was diluted with TBME and washed with sat. aq. $NaHCO_3$ soln.. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (heptane / EtOAc, 88:12 to 0:100) as an oil (140 mg, 66% yield).

UPLC Rt_{M1} =0.66 min; ESIMS: 322 $[(M+H)^+]$.

^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 5.86 (s, 1H), 5.42 (br.s, 1H), 4.25-4.41 (m, 1H), 4.19 (t, 2H), 3.38-3.66 (m, 6H), 2.00-2.18 (m, 2H), 1.46 (d, 9H).

e) (S)-3-[1-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (S)-3-(2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (115 mg, 0.36 mmol), 5-bromo-2-methoxy-3-trifluoromethylpyridine (CAS registry 1214377-42-0) (119 mg, 0.47 mmol), XPhos (14 mg, 0.03 mmol), and NaOtBu (76 mg, 0.79 mmol) in dioxane (2.5 ml) was degassed with argon for 5 min, then $Pd_2(dba)_3$ (13 mg, 0.01 mmol) was added. The tube was filled with argon, then sealed and the reaction mixture was stirred at 100°C for 2 h. After cooling to rt, the reaction mixture was filtered through hyflo, rinsed with EtOAc and the filtrates were washed with sat. aq. $NaHCO_3$ soln.. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (heptane / EtOAc, 93:7 to 40:60) as a clear gum. (91 mg, 51% yield).

UPLC Rt_{M1} =1.27 min; ESIMS: 497 $[(M+H)^+]$.

^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, 1H), 7.79 (d, 1H), 7.64 (d, 1H), 5.70 (s, 1H), 5.36-5.46 (m, 1H), 4.34 (br s, 2H), 4.09 (s, 3H), 3.70 (t, 2H), 3.34-3.62 (m, 4H), 2.02-2.11 (m, 2H), 1.44 (s, 9H).

f) 1-(6-Methoxy-5-trifluoromethyl-pyridin-3-yl)-7-((S)-pyrrolidin-3-yloxy)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine

A solution of (S)-3-[1-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (88 mg, 0.18 mmol) in DCM (1.3 ml) was treated with TFA (0.14 ml, 1.77 mmol) and the reaction mixture was stirred at rt for 17 h, then quenched with sat. aq. Na_2CO_3 soln. and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (66 mg, 94% yield).

UPLC Rt_{M1} =0.72 min; ESIMS: 397 $[(M+H)^+]$.

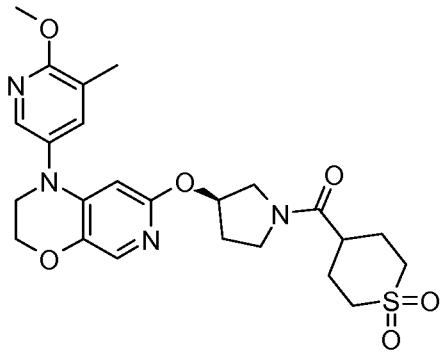
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, 1H), 7.79 (d, 1H), 7.65 (s, 1H), 5.68 (s, 1H), 5.31-5.39 (m, 1H), 4.31-4.37 (m, 2H), 4.08 (s, 3H), 3.67-3.72 (m, 2H), 3.01-3.18 (m, 3H), 2.85-2.97 (m, 1H), 2.01-2.13 (m, 1H), 1.82-1.95 (m, 1H).

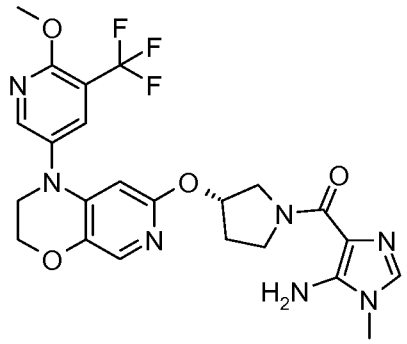
g) Imidazo[2,1-b]thiazol-6-yl-{(S)-3-[1-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone

A solution of imidazo[2,1-b]thiazole-6-carboxylic acid, hydrobromide (1:1) (CAS registry 725234-39-9) (25 mg, 0.10 mmol) in DMF (0.45 ml) was treated with HBTU (41 mg, 0.11 mmol) and DIPEA (0.04 ml, 0.21 mmol). The resulting orange solution was stirred at rt for 5 min, then a solution of 1-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-7-((S)-pyrrolidin-3-yloxy)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazine (32 mg, 0.08 mmol) in DMF (0.45 ml) was added. The reaction mixture was stirred at rt for 17 h, then concentrated under reduced pressure and the residue was taken up with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after RP prep. HPLC (Sunfire PrepC18 30x100 mm, 5 μm; solvent A: H_2O+0.1 Vol.-% TFA; solvent B: CH_3CN +0.1 Vol.-% TFA, gradient 15–45% B in 16 min).After filtration over an Agilent PL-HCO_3 MP SPE cartridge, the title compound was obtained as a solid (23 mg, 52% yield).
UPLC Rt_{M1} =1.00 min; ESIMS: 547 [$(M+H)^+$].
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.49 (dd, 1H), 8.16-8.20 (m, 2H), 7.92 (dd, 1H), 7.57 (d, 1H), 7.37 (dd, 1H), 5.63 (d, 1H), 5.33-5.45 (m, 1H), 4.25-4.31 (m, 2H), 3.52-4.14 (m, 9H), 1.88-2.12 (m, 2H).

Examples G2 to G3: The compounds listed in Table 7 were prepared by a procedure analogous to that used in Example G1.

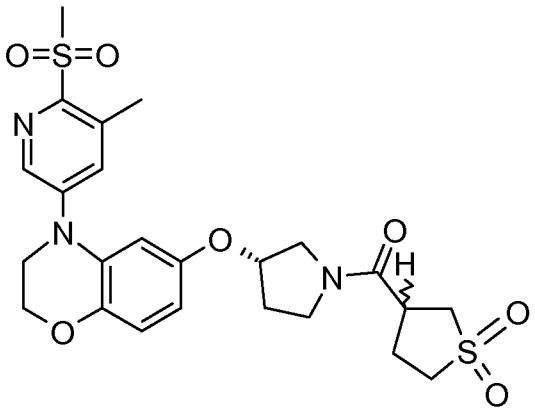
Table 7

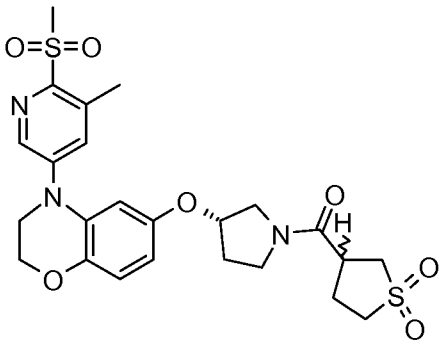
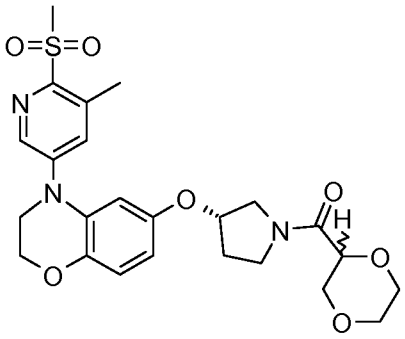
Example	Compound / Reaction Conditions	HPLC Rt [min] (method)	MS [m/z; $(M+1)^+$]
G2	 (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(R)-3-[1-(6-methoxy-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA2 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 943995-72-0 / 132945-75-6 / IA9 / 64096-87-3	0.80 (M1)	503

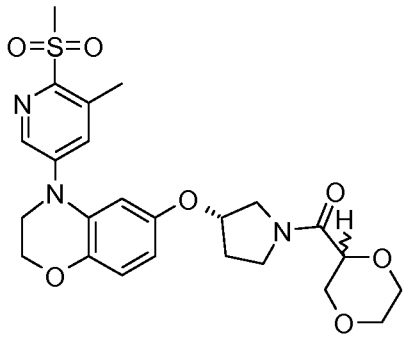
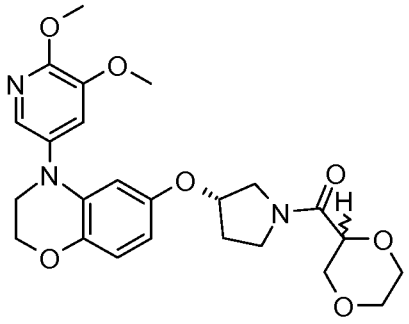
G3	 (5-Amino-1-methyl-1H-imidazol-4-yl)-{(S)-3-[1-(6-methoxy-5-trifluoromethyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA2 Amide bond condition: CB1 Side chain introduction condition: CC1 Precursors used: CAS 943995-72-0 / 127423-61-4 / IA21) / IB3) / Product obtained after Deboc reaction using TFA in CH_2Cl_2 done in conventional way	0.86 (M1M1)	520

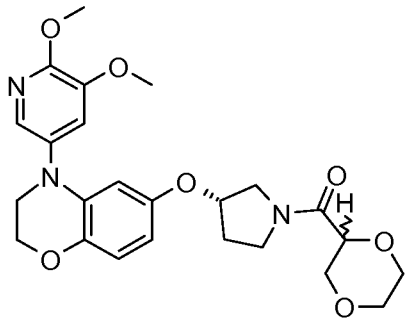
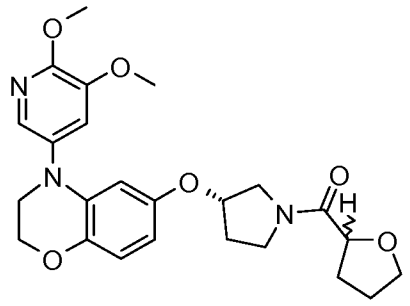
Examples H1 to H16: The compounds listed in Table 8 were prepared by chromatographic diastereomer separation.

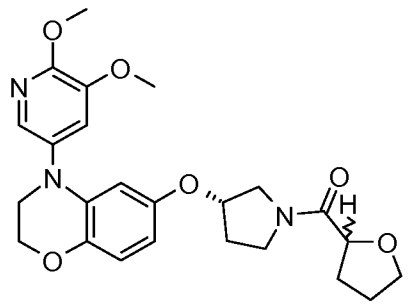
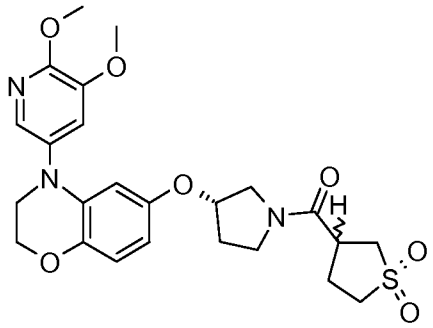
Table 8

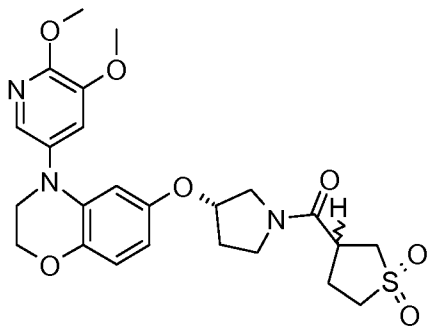
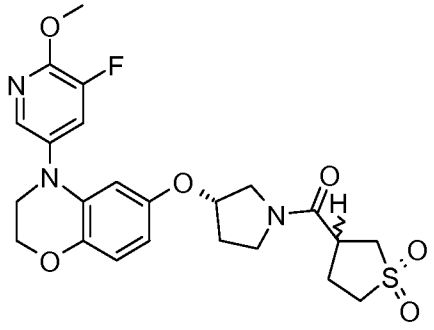
Example	Compound / Reaction Conditions	HPLC Rt [min] (method)	MS [m/z; $(M+1)^+$]
H1	 (1,1-Dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-{(S)-3-[1-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: IA1,CAS 127423-61-4 / 64096-87-3 Chiral separation method: CD5	0.87 (M2)	531

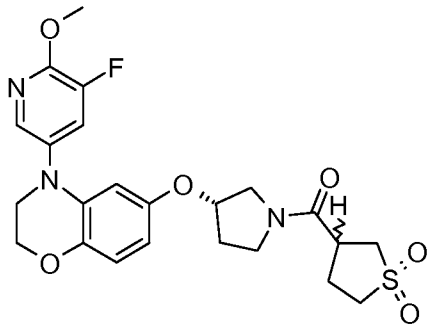
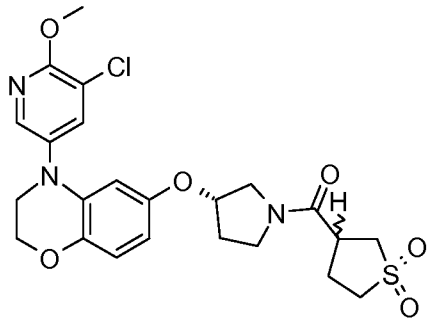
H2	 (1,1-Dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-{(S)-3-[1-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: IA1,CAS 127423-61-4 / 64096-87-3 Chiral separation method: CD5	0.87 (M2)	536
H3	 [1,4]Dioxan-2-yl-{(S)-3-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: IA1,CAS 127423-61-4 / 89364-41-0 Chiral separation method: CD6	0.88 (M2)	504

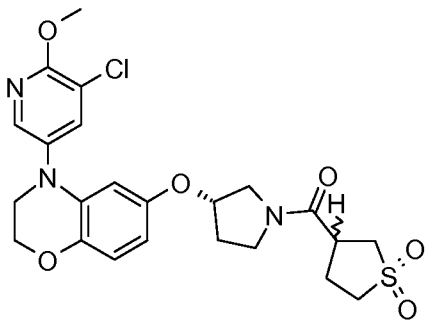
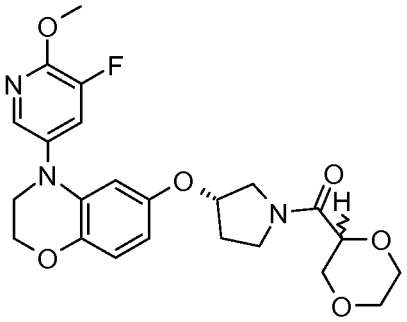
H4	 [1,4]Dioxan-2-yl-{(S)-3-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: IA1),CAS 127423-61-4 / 89364-41-0 Chiral separation method: CD6	0.88 (M2)	504
H5	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-[1,4]dioxan-2-yl-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: IA31, CAS 52605-98-8, 127423-61-4 / 89364-41-0 Chiral separation method: CD1	0.91 (M2)	472

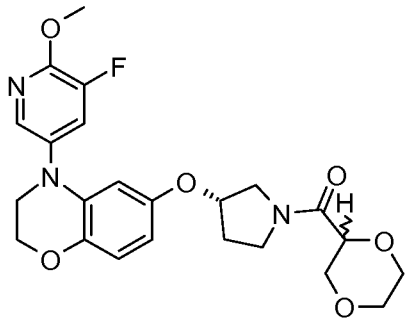
H6	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-[1,4]dioxan-2-yl-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: IA31,CAS 52605-98-8, 127423-61-4 / 89364-41-0 Chiral separation method: CD1	0.91 (M2)	472
H7	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-furan-2-yl)-methanone Buchwald amination condition: CA9 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: IA29, CAS 52605-98-8, 127423-61-4 / 1264293-76-6 Chiral separation method: CD1	0.91 (M2)	472

H8	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-furan-2-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: IA29, CAS 52605-98-8, 127423-61-4 / 1264293-76-6 Chiral separation method: CD1	0.91 (M2)	472
H9	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: IA29, CAS 52605-98-8, 127423-61-4 / 64096-87-3 Chiral separation method: CD1	0.91 (M2)	504

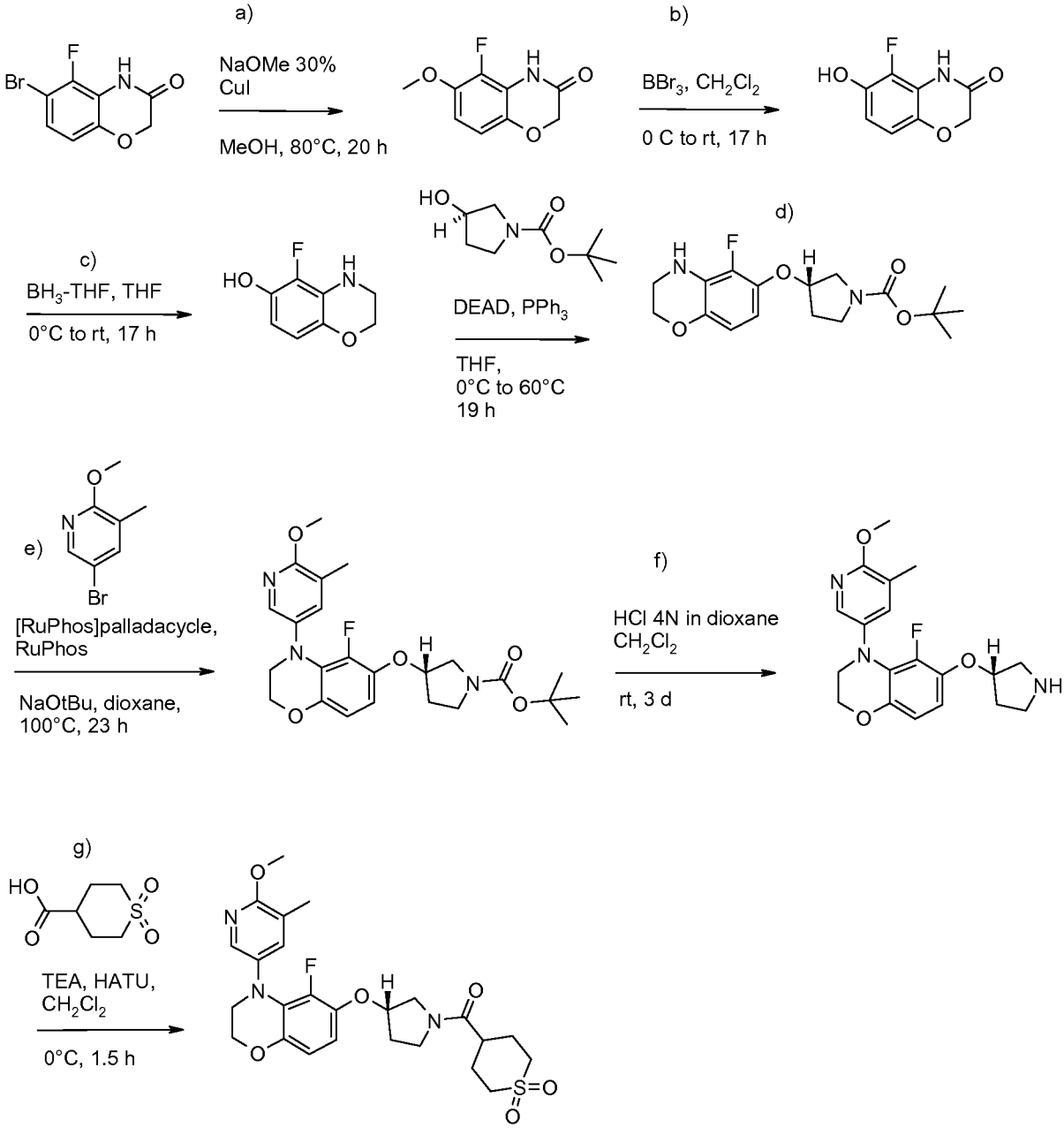
H10	 {(S)-3-[4-(5,6-Dimethoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB4 Side chain introduction condition: CC2 Precursors used: IA29, CAS 52605-98-8, 127423-61-4 / 64096-87-3 Chiral separation method: CD1	0.91 (M2)	504
H11	 (1,1-Dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-{(S)-3-[4-(5-fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: IA10,CAS 124432-70-8, 127423-61-4 / 64096-87-3 Chiral separation method: CD1	3.26 (M2)	492

H12	 (1,1-Dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-{(S)-3-[4-(5-fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: IA10,CAS 124432-70-8, 127423-61-4 / 64096-87-3 Chiral separation method: CD1	3.25 (M2)	492
H13	 {(S)-3-[4-(5-Chloro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: IA11,CAS 848366-28-9, 127423-61-4 / 64096-87-3 Chiral separation method: CD2	3.52 (M2)	508

H14	 {(S)-3-[4-(5-Chloro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-tetrahydro-1lambda*6*-thiophen-3-yl)-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: IA11,CAS 848366-28-9, 127423-61-4 / 64096-87-3 Chiral separation method: CD2	3.52 (M2)	508
H15	 [1,4]Dioxan-2-yl-{(S)-3-[4-(5-fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: IA10,CAS 124432-70-8, 127423-61-4 / 89364-41-0 Chiral separation method: CD1	3.28 (M2)	460

H16	 [1,4]Dioxan-2-yl-{(S)-3-[4-(5-fluoro-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone Buchwald amination condition: CA6 Amide bond condition: CB5 Side chain introduction condition: CC2 Precursors used: IA10,CAS 124432-70-8, 127423-61-4 / 89364-41-0 Chiral separation method: CD1	3.32 (M2)	460

Example I1: (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[5-fluoro-4-(6-methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone



a) 5-Fluoro-6-methoxy-4H-benzo[1,4]oxazin-3-one

A solution of 6-bromo-5-fluoro-4H-benzo[1,4]oxazin-3-one (CAS registry 1029421-36-0) (5.0 g, 20 mmol) in MeOH (10 ml) was treated with sodium methoxide solution (30% in MeOH, 11.3 ml, 61 mmol) and CuI (0.4 g, 2 mmol). After stirring for 20 h at 80°C, the reaction was quenched with sat. aq. $NaHCO_3$ soln and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain a pale yellow solid. (2.2 g, 92% yield).

UPLC Rt_{M1} =0.64 min.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.74 (m, 2H), 4.53 (s, 2H), 3.79 (s, 3H).

b) 5-Fluoro-6-hydroxy-4H-benzo[1,4]oxazin-3-one

A solution of 5-fluoro-6-methoxy-4H-benzo[1,4]oxazin-3-one (2.0 g, 10 mmol) in DCM (50 ml) was treated at 0°C with boron tribromide (9.6 ml, 101 mmol). The reaction mixture was stirred at rt for 17 h, then cooled down to 0°C and quenched with methanol. The mixture was concentrated under reduced pressure and the residue was taken up with EtOAc and washed with sat. aq. $NaHCO_3$ soln.. The organic layer was washed with 10% aq. $Na_2S_2O_4$ soln, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The title compound was obtained after flash chromatography on silica gel (hexane / EtOAc, 100:0 to 60:40) as a brown solid (780 mg, 42% yield).

UPLC Rt_{M1} =0.49 min; ESIMS: 228 [$(M+HCOO)^-$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 6.65 (d, 1H), 6.45 (t, 1H), 4.50 (s, 2H).

c) 5-Fluoro-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol

A solution of 5-fluoro-6-hydroxy-4H-benzo[1,4]oxazin-3-one (780 mg, 4.2 mmol) in THF (10 ml) was treated with BH_3*THF (1M in THF, 12.8 ml, 12.8 mmol). The reaction mixture was stirred at rt for 17 h, then cooled down to 0°C and quenched with methanol (30 ml). The reaction mixture was concentrated under reduced pressure to obtain a brown oil (720 mg, quantitative yield).

UPLC Rt_{M1} =0.54 min; ESIMS: 170 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 6.45 (d, 1H), 6.00 (t, 1H), 4.09 (m, 2H), 3.45 (m, 2H).

d) (S)-3-(5-Fluoro-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of triphenylphosphine (1.5 g, 5.7 mmol) in THF (20 ml) was treated at 0°C with DEAD (0.900 ml, 5.69). The orange solution was stirred over 10 min at rt, then 5-fluoro-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol (740 mg, 4.37 mmol) and (R)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate (1065 mg, 5.69 mmol) were added. The reaction mixture was stirred for 19 h at 60°C and then concentrated under reduced pressure. The title compound was obtained after flash chromatography on silica gel (Hexane / EtOAc, 100:0 to 70:30) as a colourless oil (1.1 g, 74% yield).

UPLC Rt_{M1} =1.07 min; ESIMS: 339 [$(M+H)^+$]

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.45 (d, 1H), 6.00 (t, 1H), 5.42 (br.s, 1H), 4.25-4.41 (m, 1H), 4.19 (t, 2H), 3.38-3.66 (m, 6H), 2.00-2.18 (m, 2H), 1.46 (d, 9H)

e) (S)-3-[5-fluoro-4-(6-methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (S)-3-(5-fluoro-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (100 mg, 0.296 mmol), 5-bromo-2-methoxy-3-methylpyridine (CAS registry 760207-87-2, 179 mg, 0.887 mmol), RuPhos (6.90 mg, 0.015 mmol), NaOtBu (85 mg, 0.887 mmol) and (2-dicyclohylphosphino-2' 6'-diisopropyl-1 1'-biphenyl)(2-(2-aminoethyl)phenyl)palladium(II) (12.07 mg, 0.015 mmol) in dioxane (2 ml) were degassed with argon then sealed and the reaction mixture was stirred at 100°C for 23 h. After cooling to r.t., the reaction mixture was filtered through hyflo, rinsed with EtOAc and the filtrates were washed with sat. aq. $NaHCO_3$ soln.. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (Hexane / EtOAc, 100:0 to 70:30) as a yellow oil(123 mg, 63% yield).

UPLC Rt_{M1} =1.29 min; ESIMS: 460 [$(M+H)^+$].

^1H NMR (400 MHz, DMSO-d_6): δ 7.75 (d, 1H),7.45 (d, 1H), 6.55 (t, 1H), 6.35 (d, 1H), 4.75 (m, 1H), 4.15 (t, 2H), 3.84 (s, 3H), 3.60 (t, 2H), 3.38-3.66 (m, 4H), 2.12 (s, 3H), 2.00-2.18 (m, 2H), 1.46 (d, 9H).

f) 5-Fluoro-4-(6-methoxy-5-methyl-pyridin-3-yl)-6-((S)-pyrrolidin-3-yloxy)-3,4-dihydro-2H-benzo[1,4]oxazine

A solution of (S)-3-[5-fluoro-4-(6-methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (123 mg, 0.185 mmol) in DCM (2 ml) was treated with 4N HCl/dioxane (0.046 ml, 0.185 mmol). The reaction mixture was stirred at rt for 3 d, then concentrated under reduced pressure to obtain a black oil (100 mg, 79% yield).

UPLC Rt_{M1} =0.73 min; ESIMS: 360 [$(M+H)^+$].

^1H NMR (400 MHz, DMSO-d_6): δ 7.75 (d, 1H),7.45 (d, 1H), 6.80 (m, 1H), 6.75 (m, 1H), 5.20 (m, 1H), 4.15 (t, 2H), 3.84 (s, 3H), 3.60 (t, 2H), 3.38-3.66 (m, 4H), 2.12 (s, 3H), 2.00-2.18 (m, 2H).

g) (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[5-fluoro-4-(6-methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone

A solution of 1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-carboxylic acid (CAS registry 64096-87-3) (33.9 mg, 0.15 mmol) in DCM (2 ml) was treated at rt with Et_3N (0.061 ml, 0.440 mmol) and HATU (55.7 mg, 0.147 mmol). The resulting orange solution was stirred at rt for 20 min, then a solution of 5-fluoro-4-(6-methoxy-5-methyl-pyridin-3-yl)-6-((S)-pyrrolidin-3-

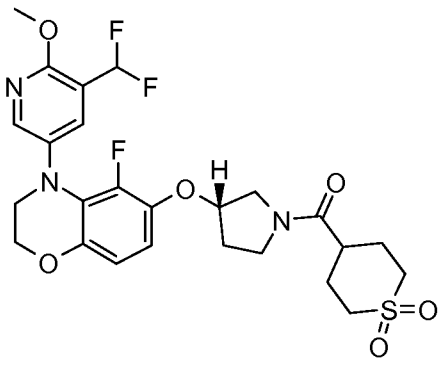
yloxy)-3,4-dihydro-2H-benzo[1,4]oxazine (100 mg, 0.147 mmol) in DCM (2 ml) was added. The reaction mixture was stirred at rt for 1.5 h, then diluted with EtOAc and washed with sat. aq. $NaHCO_3$ soln. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after prep. RP-HPLC (SunFire C18 column OBD 5 mm 30x100mm, gradient 25% to 45% ACN in 16 min). The fractions were lyophilized and filtered over a PL-HCO_3 MP SPE cartdrige to give a brown solid (54 mg, 71% yield).

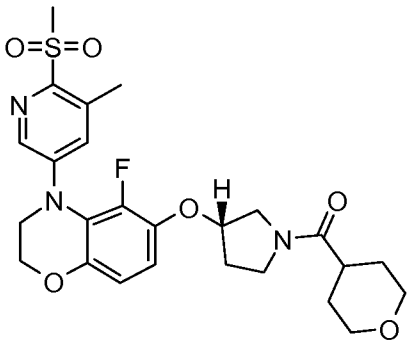
UPLC Rt_{M1} =0.94 min; ESIMS: 520 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (d, 1H),7.45 (d, 1H), 6.55 (t, 1H), 6.35 (d, 1H), 4.75 (m, 1H), 4.15 (t, 2H), 3.84 (s, 3H), 3.59-3.79 (m, 3H), 3.41-3.56 (m, 2H), 3.21-3.39 (m, 1H), 2.98-3.21 (m, 4H), 2.67-2.83 (m, 1H), 1.84-2.20 (m, 9H).

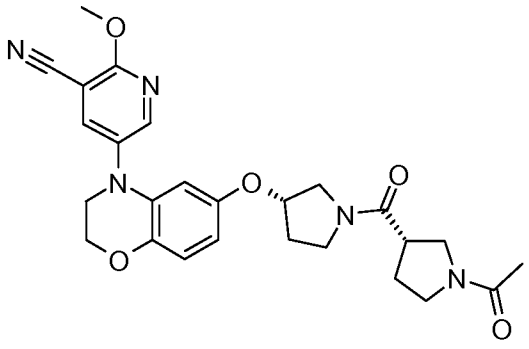
Examples I2 to I3: The compounds listed in Table 9 were prepared by a procedure analogous to that used in Example I1.

Table 9

Example	Compound / Reaction Conditions	HPLC Rt [min] (method)	MS [m/z; $(M+1)^+$]
I2	 {(S)-3-[4-(5-Difluoromethyl-6-methoxy-pyridin-3-yl)-5-fluoro-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-methanone Buchwald amination condition: CA11 Amide bond condition: CB3 Side chain introduction condition: CC4 Precursors used: IA6,CAS 1254123-51-7 / 127423-61-4, / 64096-87-3	0.97 (M2)	556

I3	 {(S)-3-[5-Fluoro-4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone Buchwald amination condition: CA11 Amide bond condition: CB3 Side chain introduction condition: Precursors used:IA1,CAS 127423-61-4 / Acyl chloride 40191-32-0	0.85 (M2)	520

Example J: 5-{6-[(S)-1-((S)-1-Acetyl-pyrrolidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]-oxazin-4-yl}-2-methoxy-nicotinonitrile

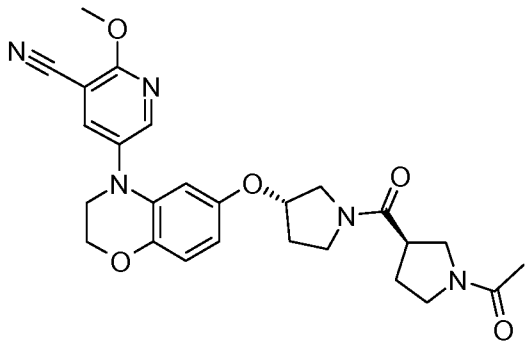


A solution of 2-methoxy-5-{6-[(S)-1-((S)-pyrrolidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile (Example D39; 23 mg, 0.051 mmol) in DCM (1 ml) was treated with Et_3N (0.014 ml, 10.4 mg, 0.102 mmol). The solution was stirred at rt for 10 min, then acetyl chloride (0.0044 ml, 4.87 mg, 0.061 mmol) was added. The reaction mixture was stirred at rt for 1.5 h. Another 2 eq. of Et_3N (0.014 ml, 10.4 mg, 0.102 mmol). and 1 eq. of acetyl chloride ((0.0037 ml, 4.06 mg, 0.051 mmol) were added, stirring was continued at rt for 1.5 h. The reaction mixture was diluted with DCM and sat. aq. $NaHCO_3$ soln., then passed through a phase separator, the aq. layer was twice extracted with DCM,

the combined org. layers were concentrated to give the title compound as a yellow oil which was purified by prep. RP-HPLC (column SunFire C18, 10-85% ACN in 20 min). The fractions were extracted with DCM/$NaHCO_3$, dried over $MgSO_4$, concentrated and lyophilized to give the title compound as a yellow foam (14 mg, 53% yield).

HPLC Rt_{M10}=2.55 min; ESIMS: 492 $[(M+H)^+]$.

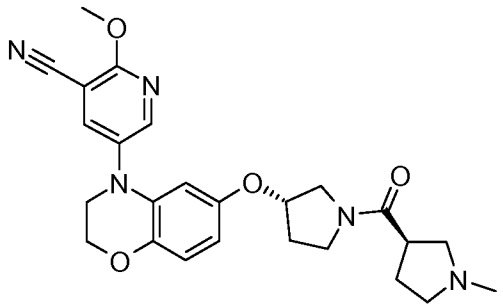
Example K: 5-{6-[(S)-1-((R)-1-Acetyl-pyrrolidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile



This example was prepared in analogy to **Example J,** starting from 2-methoxy-5-{6-[(S)-1-((R)-pyrrolidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile (Example D40).

HPLC Rt_{M10}=2.55 min; ESIMS: 492 $[(M+H)^+]$.

Example L: 2-Methoxy-5-{6-[(S)-1-((R)-1-methyl-pyrrolidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile

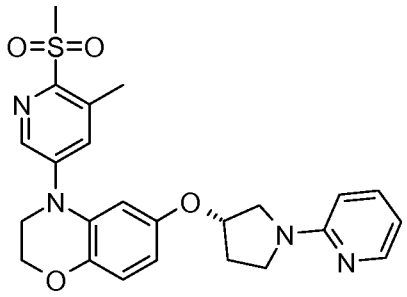


A solution of 2-methoxy-5-{6-[(S)-1-((R)-pyrrolidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile (Example D40, 26 mg, 0.058 mmol) in MeOH (1 ml) was treated with a 37% aq. formaldehyde soln. (0.043 ml, 46.9 mg, 0.578 mmol) and acetic acid (0.004 ml, 4.17 mg, 0.0069 mmol). The solution was stirred under argon at rt for 45 min, then $NaBH_3CN$ (5.65 mg of a 90% solid, 0.081 mmol) was added. The resulting mixture was stirred at rt for 45 min, diluted with DCM and sat. aq. $NaHCO_3$ soln.. The aq. layer was twice reextracted with DCM, the combined org. layers were dried over $MgSO_4$ and concentrated to give the crude title compound that was purified by prep. RP-HPLC (column

SunFire C18, gradient 5-75% ACN in 20 min). The fractions were extracted with DCM/sat. aq. $NaHCO_3$ soln, dried over $MgSO_4$, concentrated and lyophilized to give the title compound as a yellow foam (20 mg, 72% yield).

HPLC Rt_{M11}=2.24 min; ESIMS: 464 $[(M+H)^+]$.

Example M; 4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-6-((S)-1-pyridin-2-yl-pyrrolidin-3-yloxy)-3,4-dihydro-2H-benzo[1,4]oxazine

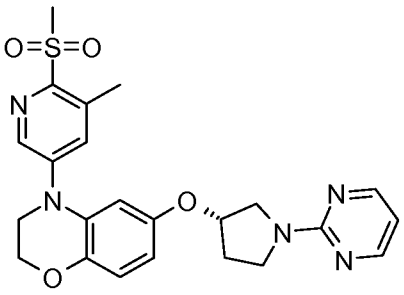


A solution of 4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-6-((S)-1-pyridin-2-yl-pyrrolidin-3-yloxy)-3,4-dihydro-2H-benzo[1,4]oxazine (prepared as described in example B1; 60 mg, 0.154 mmol), 2-chloropyridine (CAS 109-09-1, 0.017 ml, 21.0 mg, 0.185 mmol), Xphos (8.81 mg, 0.018 mmol) and Cs_2CO_3 (125 mg, 0.385 mmol) in dioxane (1 ml) was degassed with argon, then $Pd_2(dba)_3$ (7.05 mg, 0.0077 mmol) was added. The reaction mixture was heated at 80°C for 6 h, XPhos (8.81 mg, 0.018 mmol) was added, the mixture was again degassed with argon and $Pd_2(dba)_3$ (7.05 mg, 0.0077 mmol) was added. Stirring was continued over night at 80°C. The mixture was filtered through celite and concentrated to give the title compound that was purified by NP-HPLC (column Grace Grom Saphir 65 Si, gradient heptane:EtOAc:MeOH 68:30:2 to 0:65:35 in 12 min), yield 32 mg (45%).

HPLC Rt_{M1} =0.72 min; ESIMS: 467 $[(M+H)^+]$

^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, 1H), 8.14-8.12 (m, 1H), 7.49-7.39 (m, 2H), 6.86 (d, 1H), 6.61 (d, 1H), 6.57-6.46 (m, 2H), 6.37 (d, 1H), 4.92-4.85 (m, 1H), 4.26-4.24 (m, 2H), 3.76-3.74 (m, 2H), 3.71 (d, 2H), 3.63-3.55 (m, 2H), 3.32 (s, 3H), 2.67 (s, 3H), 2.35-2.27 (m, 1H), 2.26-2.15 (m, 1H).

Example N; 4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-6-((S)-1-pyrimidin-2-yl-pyrrolidin-3-yloxy)-3,4-dihydro-2H-benzo[1,4]oxazine

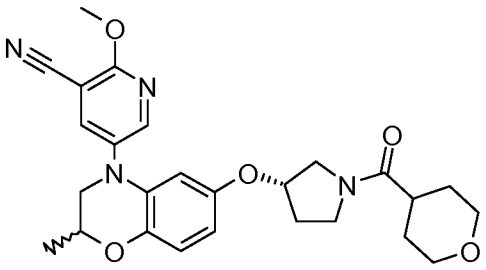


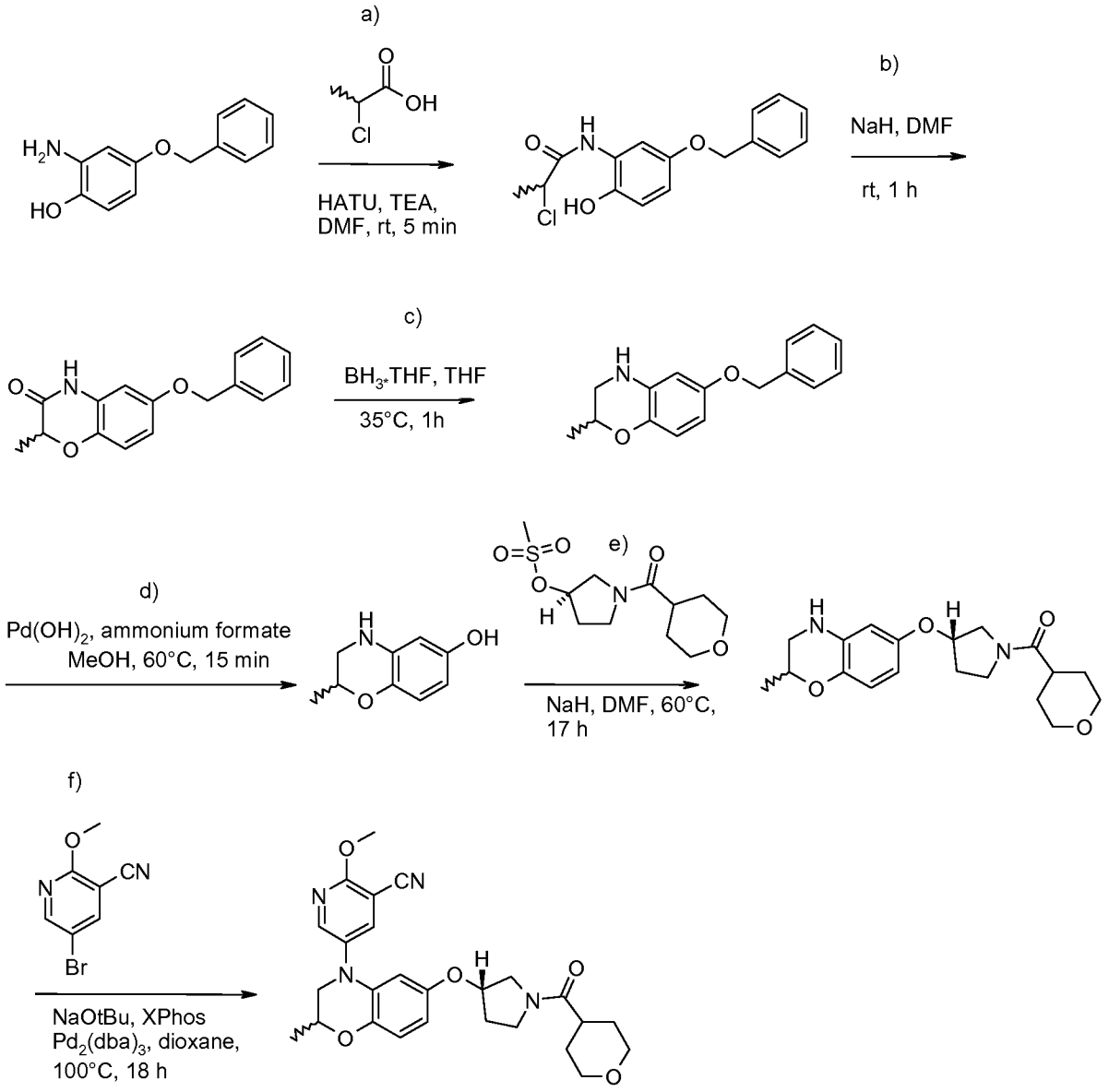
A solution of 4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-6-((S)-1-pyridin-2-yl-pyrrolidin-3-yloxy)-3,4-dihydro-2H-benzo[1,4]oxazine (prepared as described in example B1; 60 mg, 0.154 mmol), 2-chloropyrimidine (CAS 1722-12-9, 24.7 mg, 0.216 mmol) and DIPEA (0.054 ml, 39.8 mg, 0.308 mmol) in ACN (1 ml) was heated at 140 °C for 30 min in a microwave reactor. The product was extracted with sat. aq. $NaHCO_3$ soln. and EtOAc, filtered and concentrated to yield the title compound that was purified by prep. NP-HPLC (column Grace Grom Saphir 65 Si, gradient heptane:EtOAc:MeOH 68:30:2 to 0:65:35 in 12 min), yield 45 mg (63%)

HPLC Rt_{M1}=0.97 min; ESIMS: 468 [$(M+H)^+$]

^1H NMR (400 MHz, $CDCl_3$): δ 8.37-8.26 (m, 3H), 7.44 (d, 1H), 6.87 (d, 1H), 6.62 (d, 1H), 6.56-6.46 (m, 2H), 4.92-4.84 (m, 1H), 4.27-4.25 (m, 2H), 3.90-3.63 (m, 6H), 3.33 (s, 3H), 2.69 (s, 3H), 2.37-2.13 (m, 2H).

Example O1: 2-Methoxy-5-{2-methyl-6-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile





a) N-(5-Benzyloxy-2-hydroxy-phenyl)-2-chloro-propionamide

A solution of 2-chloro-propionic acid (CAS registry 598-78-7) (0.914 ml, 7.53 mmol) in DMF (20 ml) was treated with Et_3N (1.259 ml, 9.03 mmol) and HATU (3.05 g, 8.03 mmol). The resulting solution was stirred at rt for 30 min, then 2-amino-4-benzyloxy-phenol (CAS registry 102580-07-4) (1.08 g, 5.02 mmol) was added. The reaction mixture was stirred at rt for 5 min, diluted with EtOAc and concentrated. The title compound was obtained after flash chromatography on silica gel (cyclohexane / EtOAc, 100:0 to 50:50) as orange solid (617 mg, 40% yield).

UPLC Rt_{M14} =1.32 min; ESIMS: 306 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6): δ 9.50 (d, 1H), 7.70 (br,s 1H), 7.45 (m, 5H), 6.80 (d, 1H), 6.65 (dd, 1H), 5.00 (s, 2H), 2.65 (s, 3H).

b) 6-Benzyloxy-2-methyl-4H-benzo[1,4]oxazin-3-one

A dry solution of N-(5-benzyloxy-2-hydroxy-phenyl)-2-chloro-propionamide (617 mg, 2.0 mmol) in DMF (15 ml) was treated at 0°C with sodium hydride 95% (58.1 mg, 2.4 mmol). After stirring at rt for 1 h, the reaction mixture was diluted with DCM and washed with water. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (cyclohexane / EtOAc, 100:0 to 80:20) as a white solid (146 mg, 27% yield).

UPLC Rt_{M14} =1.30 min; ESIMS: 270 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6): δ 10.80 (s, 1H), 7.45 (m, 5H), 6.85 (d, 1H), 6.65 (m, 2H), 5.00 (s, 2H), 4.55 (q, 1H), 1.45 (d, 3H).

c) 6-Benzyloxy-2-methyl-3,4-dihydro-2H-benzo[1,4]oxazine

A solution of 6-benzyloxy-2-methyl-4H-benzo[1,4]oxazin-3-one (146 mg, 0.54 mmol) in THF (4 ml) was treated at 0°C with BH_3*THF (1M in THF, 0.813 ml, 0.813 mmol). After stirring at 35°C for 1 h, the reaction mixture was cooled down to 0°C, quenched with water (0.5 ml) and an aqueous NaOH 4N soln. (0.5 ml) and then diluted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained as a white solid (125 mg, 90% yield).

UPLC Rt_{M14} =1.40 min; ESIMS: 256 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6): δ 7.45 (m, 5H), 6.50 (d, 1H), 6.20 (d, 1H), 6.10 (dd, 1H), 5.35 (s, 1H), 4.90 (s, 2H), 4.00 (m, 1H), 3.25 (m, 1H), 2.90 (m, 1H), 1.35 (d, 3H).

d) 2-Methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol

A solution of 6-benzyloxy-2-methyl-3,4-dihydro-2H-benzo[1,4]oxazine (124 mg, 0.486 mmol) in MeOH (10 ml) was treated at rt with ammonium formate (276 mg, 4.37 mmol) and $Pd(OH)_2$ (68.2 mg, 0.486 mmol). The reaction mixture was stirred at 60°C for 15 min. After cooling to rt, the reaction mixture was filtered through hyflo, rinsed with DCM and MeOH and then the filtrates were concentrated. The title compound was obtained after flash chromatography on silica gel (DCM / MeOH, 100:0 to 90:10) as a brown solid. (69.4 mg, 87% yield).

UPLC Rt_{M14} =0.56 min; ESIMS: 166 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 6.45 (d, 1H), 6.00 (d, 1H), 5.85 (dd, 1H), 5.25 (s, 1H), 4.00 (m, 1H), 3.25 (m, 1H), 2.90 (m, 1H), 1.35 (d, 3H).

e) [(S)-3-(2-Methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy)-pyrrolidin-1-yl]-(tetrahydro-pyran-4-yl)-methanone

A dry solution of 2-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol (69 mg, 0.42 mmol) and (R)-1-(tetrahydro-2H-pyran-4-carbonyl)pyrrolidin-3-yl methanesulfonate (intermediate C1, 209 mg, 0.75 mmol) in DMF (1.4 ml) was treated with sodium hydride 60% in mineral oil (15.8 mg, 0.63 mmol) and the reaction mixture was stirred at 50°C for 18 h. The reaction mixture was diluted with EtOAc and washed with sat. aq. $NaHCO_3$ soln.. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (DCM / MeOH, 100:0 to 95:5) as a red orange sticky solid (128 mg, 88% yield).

UPLC Rt_{M14}=1.01 min; ESIMS: 347 $[(M+H)^+]$

^1H NMR (400 MHz, DMSO-d_6): δ 6.50 (d, 1H), 6.25 (d, 1H), 6.00 (d, 1H), 6.05 (m, 1H), 5.65 (m, 2H), 5.35 (d, 2H), 4.45 (d, 2H), 3.00-4.00 (m, 6H), 2.00-2.40 (m, 4H), 1.5 (m, 4H)

f) 2-Methoxy-5-{2-methyl-6-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile

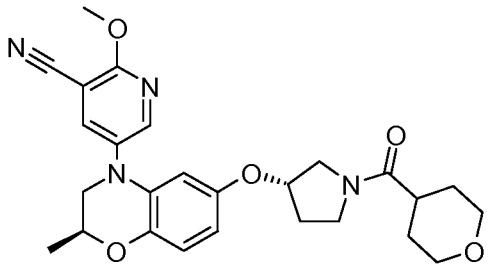
A mixture of (S)-(3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yloxy)pyrrolidin-1-yl)(tetrahydro-2H-pyran-4-yl)methanone (128 mg, 0.369 mmol), 5-bromo-2-methoxynicotinonitrile (CAS registry 941294-54-8, IA12), (94 mg, 0.443 mmol), XPhos (8.81 mg, 0.018 mmol), NaOtBu (53.3 mg, 0.554 mmol) and $Pd_2(dba)_3$ (16.92 mg, 0.018 mmol) in toluene (2.5 ml) was degassed with argon.The reaction mixture was stirred at 80°C for 20 min. After cooling to rt, the reaction mixture was filtered through hyflo, rinsed with EtOAc and the filtrates were washed with sat. aq. $NaHCO_3$ soln.. The organic layer was dried over Na_2SO_4, filtered and concentrated. The title compound was obtained after prep. RP-HPLC (SunFire C18 column OBD 5 mm 30x100mm, gradient 32% to 67% ACN in 15 min). The fractions were lyophilized and filtered over a PL-HCO_3 MP SPE cartridge to give a brown solid (39.1 mg, 22% yield).

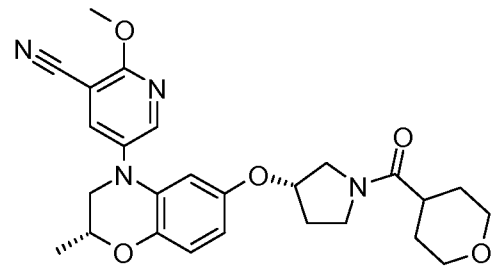
UPLC Rt_{M14} =1.10 min; ESIMS: 479 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6, 394 K): δ 8.40-8.30 (m, 1H), 8.10-8.00 (m, 1H), 6.75 (d, 1H), 6.35 (m, 1H), 6.15 (m, 1H), 4.75 (m, 1H), 4.00 (s, 3H), 3.85 (m, 1H), 3.75-3.00 (m, 5H), 2.65 (m, 1H), 2.00 (m, 1H), 1.65 (m, 2H), 1.44 (d, 3H).

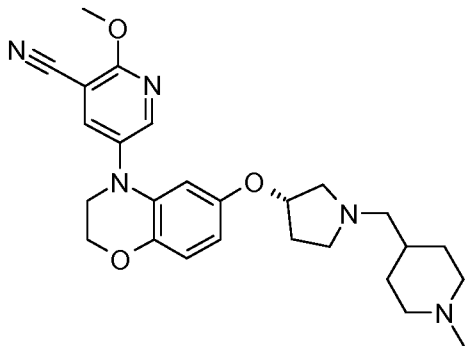
Examples O2 to O3: The compounds listed in Table 10 were prepared by chromatographic diastereomer separation.

Table 10

Example	Compound / Reaction Conditions	HPLC Rt [min] (method)	MS [m/z; $(M+1)^+$]
O2	 Peak 1 diastereomer separation 2-Methoxy-5-{(S)-2-methyl-6-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: IO, IA12, CAS 104706-47-0/ acyl chloride 40191-32-0 Chromatographic diasteroemer separation: CD11	19.89 (M15)	

O3	 Peak 2 diastereomer separation 2-Methoxy-5-{(R)-2-methyl-6-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile Buchwald amination condition: CA6 Amide bond condition: CB6 Side chain introduction condition: CC2 Precursors used: IO, IA12, CAS 104706-47-0/ Acyl chloride 40191-32-0 Chromatograhic diastereomer separation: CD11	27.33 (M15)	

Example P: 2-Methoxy-5-{6-[(S)-1-(1-methyl-piperidin-4-ylmethyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile



a) (S)-tert-butyl 4-((3-(4-(5-cyano-6-methoxypyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yloxy)pyrrolidin-1-yl)methyl)piperidine-1-carboxylate

A solution of 2-methoxy-5-[6-((S)-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-nicotinonitrile (see analogue B1, c), 95 mg, 0.270 mmol) in DCE (4.5 ml) was treated with tert-butyl 4-formylpiperidine-1-carboxylate (60 mg, 0.281 mmol). After stirring for 2 d at rt, the reaction mixture was diluted with DCM and sat. aq. $NaHCO_3$ soln. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (cyclohexane / EtOAc, 100:0 to 0:100), yield 66 mg, (40%) .

UPLC Rt_{M1} =1.66 min; ESIMS: 550 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, 1H), 7.75 (d, 1H), 7.35 (s, 1H), 7.85 (d, 1H), 6.35 (dd, 1H), 6.10 (d, 1H), 4.65 (m, 1H), 4.45 (m, 2H), 3.60 (m, 2H), 2.75-2.15 (m, 4H), 1.50 (s, 9H).

b) (S)-2-methoxy-5-(6-(1-(piperidin-4-ylmethyl)pyrrolidin-3-yloxy)-2H-benzo[b][1,4]oxazin-4(3H)-yl)nicotinonitrile

A solution of (S)-tert-butyl 4-((3-(4-(5-cyano-6-methoxypyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yloxy)pyrrolidin-1-yl)methyl)piperidine-1-carboxylate) (66 mg, 0.120 mmol) in DCM (2 ml) was treated with TFA (0.093 ml, 1.20 mmol). The reaction mixture was stirred at rt for 17 h, then quenched with sat. aq. Na_2CO_3 soln. and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title product (36 mg, 67% yield).

UPLC Rt_{M1} =1.03 min; ESIMS: 450 [$(M+H)^+$].

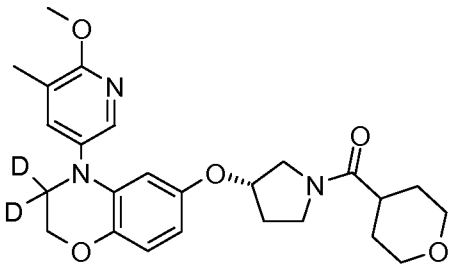
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (d, 1H), 7.80 (d, 1H), 7.25 (s, 1H), 6.80 (d, 1H), 6.25 (m, 1H), 6.15 (d, 1H), 4.65 (m, 1H), 4.45 (m, 2H), 3.60 (m, 2H), 2.75-2.15 (m, 4H).

c) (S)-2-methoxy-5-(6-(1-((1-methylpiperidin-4-yl)methyl)pyrrolidin-3-yloxy)-2H-benzo[b][1,4]oxazin-4(3H)-yl)nicotinonitrile

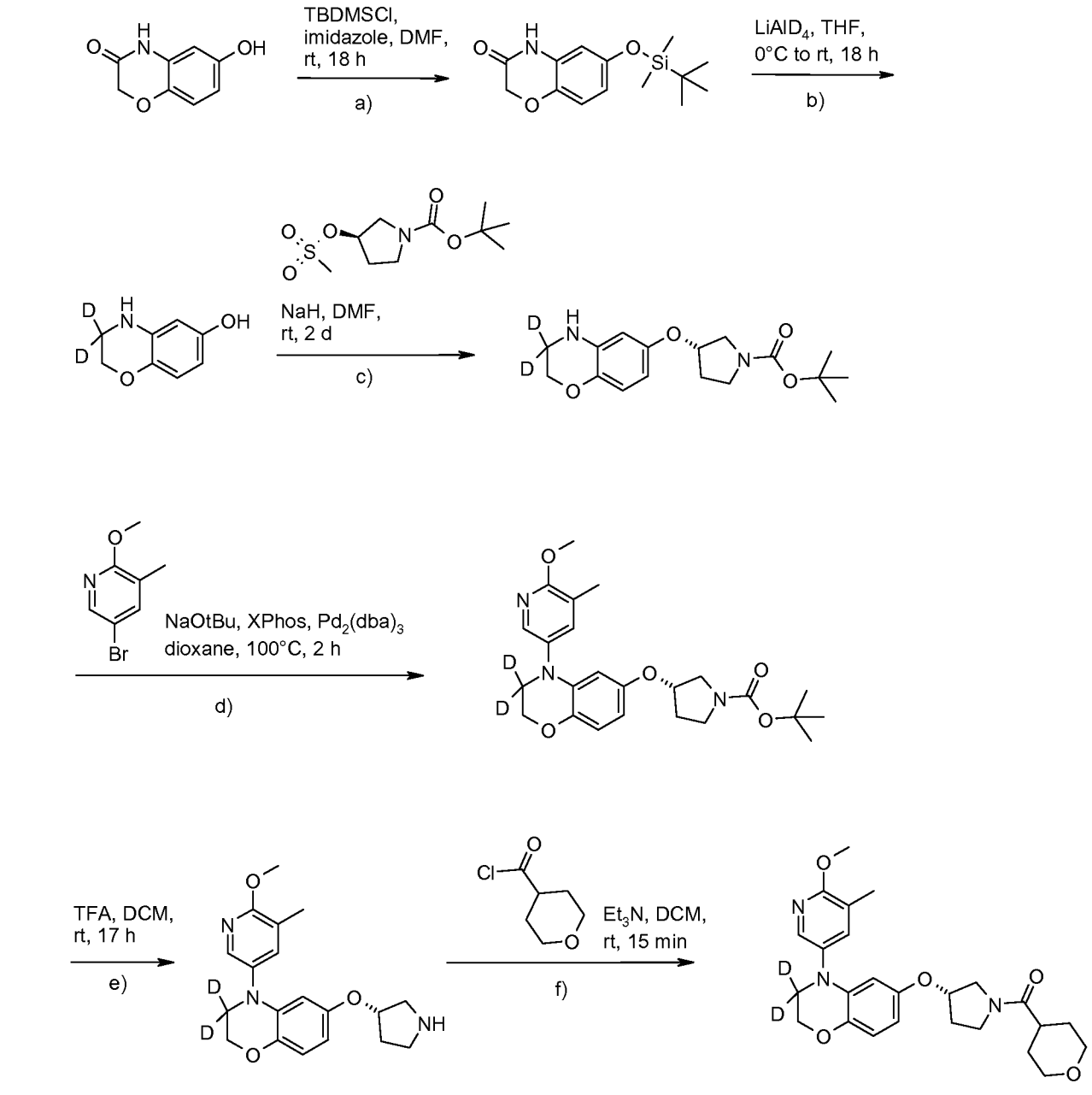
A solution of (S)-2-methoxy-5-(6-(1-(piperidin-4-ylmethyl)pyrrolidin-3-yloxy)-2H-benzo[b][1,4]oxazin-4(3H)-yl)nicotinonitrile (36 mg, 0.080 mmol) in DCE (2 ml) was treated with a 37% aq. formaldehyde soln. (8.94 µl, 0.120 mmol). The solution was stirred under argon at rt for 15 min, then $NaBH_3CN$ (50.9 mg, 0.240 mmol) was added. The resulting mixture was stirred at rt for 30 min, diluted with DCM and sat. aq. $NaHCO_3$ soln.. The organic layer was dried over Na_2SO_4 and concentrated. The title compound was obtained after purification by prep. RP-HPLC (column SunFire C18, gradient 15-50% ACN in 15 min). The fractions were extracted with DCM/sat. aq. $NaHCO_3$ soln, dried over Na_2SO_4, concentrated and lyophilized to give the title compound (18 mg, 48% yield).

UPLC Rt_{M1} =1.04 min; ESIMS: 464 [$(M+H)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, 1H), 7.85 (d, 1H), 7.45 (s, 1H), 6.75 (d, 1H), 6.35 (dd, 1H), 6.15 (d, 1H), 4.65 (m, 1H), 4.45 (m, 2H), 3.25 (m, 2H), 2.75-2.15 (m, 4H), 2.65 (s, 3H), 1.95 (m, 2H), 1.65 (m, 2H).



Example Q: {(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone



a) 6-(tert-Butyl-dimethyl-silanyloxy)-4H-benzo[1,4]oxazin-3-one

A solution of 6-hydroxy-2H-benzo[b][1,4]oxazin-3(4H)-one (CAS registry 53412-38-7) (1076 mg, 6.52 mmol) in DMF (8 ml) was treated at rt with TBDMSCl (1080 mg, 7.17 mmol) and imidazole (532 mg, 7.82 mmol). After stirring for 18 h at rt, the reaction mixture was diluted with DCM and washed with water. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (cyclohexane / EtOAc, 100:0 to 50:50) as a white solid (1.18 g, 65% yield).

UPLC Rt_{M2} =1.91 min; ESIMS: 280 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (br,s 1H), 7.35 (s, 1H), 6.85 (d, 1H), 6.45 (m, 1H), 6.30 (d, 1H), 4.50 (s, 2H), 1.00 (s, 9H), 0.25 (s, 6H).

b) 3,3-Dideutero-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol

A solution of 6-(tert-butyl-dimethyl-silanyloxy)-4H-benzo[1,4]oxazin-3-one (8.34 g, 29.8 mmol) in THF (100 ml) was treated at 0°C with lithium aluminium deuteride (2.26 g, 59.7 mmol). After stirring for 18 h at rt the reaction mixture was added to a cold aqueous 1 M Rochelle's salt soln. and was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (cyclohexane / EtOAc, 100:0 to 0:100) as a white solid (1.40 g, 31% yield).

UPLC Rt_{M9} =0.69 min; ESIMS: 154 [$(M+H)^+$].

^1H NMR (400 MHz, DMSO-d_6): δ 8.50 (s 1H), 6.45 (d, 1H), 6.00 (d, 1H), 5.85 (m, 1H), 5.15 (s, 1H), 4.00 (s, 2H).

c) (S)-3-(3,3-Dideutero-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

A dry solution of 3,3-dideutero-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol (1.44 g, 9.40 mmol) and (R)-3-methanesulfonyloxy-pyrrolidine-1-carboxylic acid tert-butyl ester (CAS registry 127423-61-4) (5.49 g, 20.68 mmol) in DMF (10 ml) was treated with sodium hydride 60% in mineral oil (0.752 g, 18.80 mmol) and the reaction mixture was stirred at rt for 2 d. The reaction mixture was diluted with EtOAc and washed with sat. aq. $NaHCO_3$ soln.. The organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc, 100:0 to 0:100), to yield 4.12 g, (quantitative yield) of the title compound.

UPLC Rt_{M1} =1.07 min; ESIMS: 323 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 6.65 (m, 1H), 6.15 (m, 2H), 5.35 (m, 1H), 4.85 (m, 2H), 3.50 (m, 4H), 2.15 (m, 2H), 1.50 (s, 9H).

d) (S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,3-dideutero-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

This example was prepared in analogy to **Example G1, e).**

UPLC Rt_{M1} =2.00 min; ESIMS: 444 $[(M+H)^+]$.

^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (br.s, 1H), 7.45 (br.s, 1H), 6.80 (m, 1H), 6.25 (m, 1H), 4.75 (m, 1H), 4.35 (s, 2H), 4.00 (s, 3H), 3.50 (m, 4H), 2.25 (m, 2H), 1.50 (s, 9H).

e) 4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,3-dideutero-6-((S)-pyrrolidin-3-yloxy)-3,4-dihydro-2H-benzo-[1,4]oxazine

This example was prepared in analogy to **Example G1, f).**

UPLC Rt_{M1} =1.26 min; ESIMS: 342 $[(M+H)^+]$.

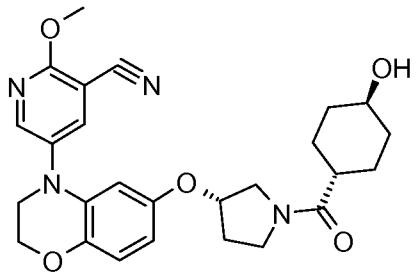
^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (br.s, 1H), 7.45 (br.s, 1H), 6.80 (m, 1H), 6.25 (m, 1H), 4.75 (m, 1H), 4.35 (s, 2H), 4.00 (s, 3H), 3.15 (m, 2H), 2.75 (m, 2H), 2.25 (m, 2H).

f) {(S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone

This example was prepared in analogy to **Example B1, d).** UPLC Rt_{M1} =1.65 min; ESIMS: 456 $[(M+H)^+]$.

^1H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.45 (m, 1H), 8.29 (s, 1H), 7.21 (t, 1H), 6.20 (t, 1H), 6.10 (s, 1H), 5.00 (d, 1H), 4.37 (t, 2H), 4.00 (m, 3H), 3.39-3.74 (m, 4H), 2.50 (m, 2H), 2.35 (s, 3H), 1.09-2.10 (m, 5H).

Example R: 5-{6-[(S)-1-(4-Hydroxy-cyclohexanecarbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-2-methoxy-nicotinonitrile

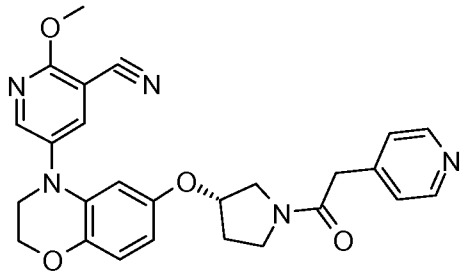


This example was prepared in analogy to **Example J,** starting from 2-methoxy-5-{6-[(S)-1-((S)-pyrrolidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile.

UPLC Rt_{M14} =0.91 min; ESIMS: 478 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d6): δ 8.43 (d, 1H), 8.28 (d, 1H), 6.73 (m, 1H), 6.34 (m, 1H), 6.08 (dd, 1H), 4.76 (d, 1H), 4.51 (m, 1H), 4.22 (s, 2H), 4.00 (s, 3H), 3.20-3.71 (m, 9H), 1.09-2.10 (m, 10H).

Example S: 2-Methoxy-5-{6-[(S)-1-(2-pyridin-4-yl-acetyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile



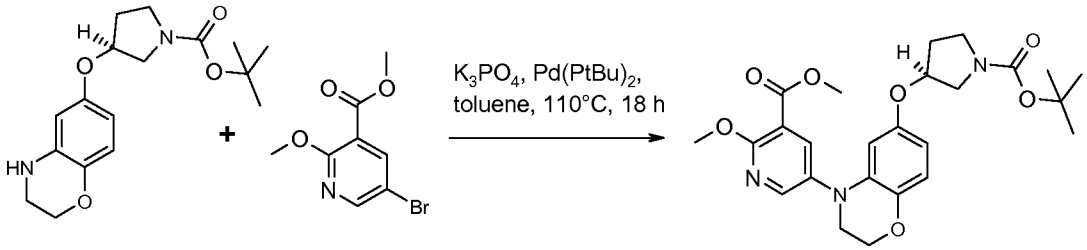
This example was prepared in analogy to **Example J**, starting from 2-methoxy-5-{6-[(S)-1-((S)-pyrrolidine-3-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile.

UPLC Rt_{M14} =0.82 min; ESIMS: 471 $[(M+H)^+]$

^1H NMR (400 MHz, DMSO-d6): δ 8.45 (m, 3H), 8.29 (s, 1H), 7.21 (m, 2H), 6.74 (m, 1H), 6.33 (m, 1H), 6.10 (m, 1H), 4.87 (d, 1H), 4.22 (s, 2H), 4.00 (s, 3H), 3.39-3.74 (m, 8H), 1.09-2.10 (m, 2H).

Example T: {(S)-3-[4-(5-Amino-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone

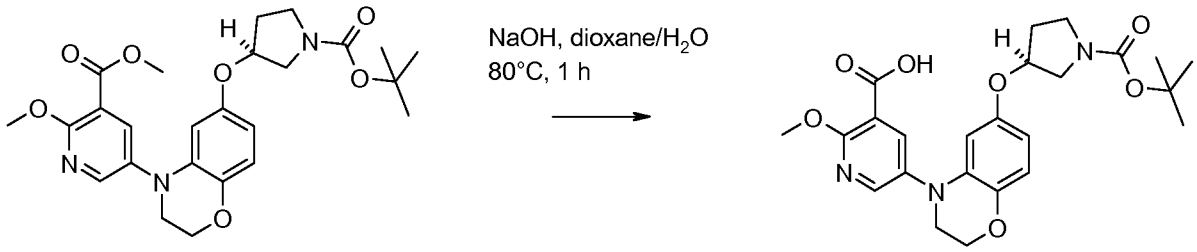
a)5-[6-((S)-1-tert-Butoxycarbonyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-2-methoxy-nicotinic acid methyl ester



Under argon, K_3PO_4 (815 mg, 2.00 mmol) and bis-(t-butylphosphine)palladium (29.4 mg. 0.06 mmol) were added to a solution of (S)-3-(3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared as described in step a) example B) (615 mg, 1.92 mmol) and 5-bromo-2-methoxy-nicotinic acid methyl ester (IA 22, CAS registry 122433-41-4) (614 mg, 1.30 mmol) in toluene (6 ml). The reaction mixture was degassed with argon for 15 min, then stirred at 110°C for 18 h, diluted with EtOAc and washed with a sat. aq. $NaHCO_3$ soln.. The organic layer was dried over $MgSO_4$ and concentrated to afford the crude title compound that was purified by flash chromatography on silica gel (heptane / EtOAc 90:10 to 0:100) to give a yellow gum (474 mg, 51% yield).

UPLC Rt_{M2} =1.36 min; ESIMS: 486 [$(M+H)^+$].

b)5-[6-((S)-1-tert-Butoxycarbonyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-2-methoxy-nicotinic acid

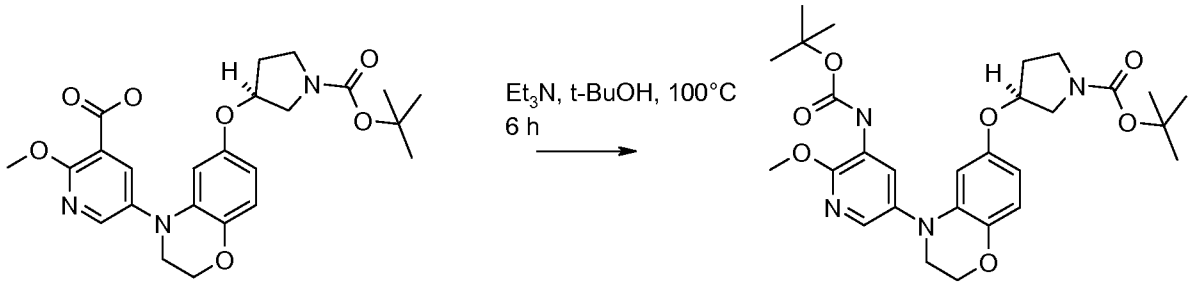


A solution of 5-[6-((S)-1-tert-butoxycarbonyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-2-methoxy-nicotinic acid methyl ester (483 mg, 0.99 mmol) in dioxane (5 ml) was treated with a solution of sodium hydroxide pellets (119mg, 2.98 mmol) in water (2 ml). The solution was stirred at 80°C for 1 h. The reaction mixture was acidified to pH3 with aq. 1N HCl soln. and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated to afford the title compound after flash chromatography on silica gel (heptane / EtOAc 100:0 to 0:100 then EtOAc/MeOH 90:10 to 80:20) as a solid (370mg, 79% yield).

UPLC Rt_{M6} =1.79 min; ESIMS: 372 [$(M+H-100)^+$]

^1H NMR (400 MHz, $CDCl_3$): δ 8.22-8.48 (m, 2H), 6.82 (d, 1H), 6.33 (m,1H), 6.21 (d, 1H), 4.60-4.76 (m, 1H), 4.27-4.41 (m, 2H), 4.15-4.27 (m, 3H), 3.62-3.77 (m, 2H), 3.31-3.58 (m, 5H), 1.85-2.19 (m, 2H), 1.34-1.56 (m, 9H)

c)(S)-3-[4-(5-tert-Butoxycarbonylamino-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester



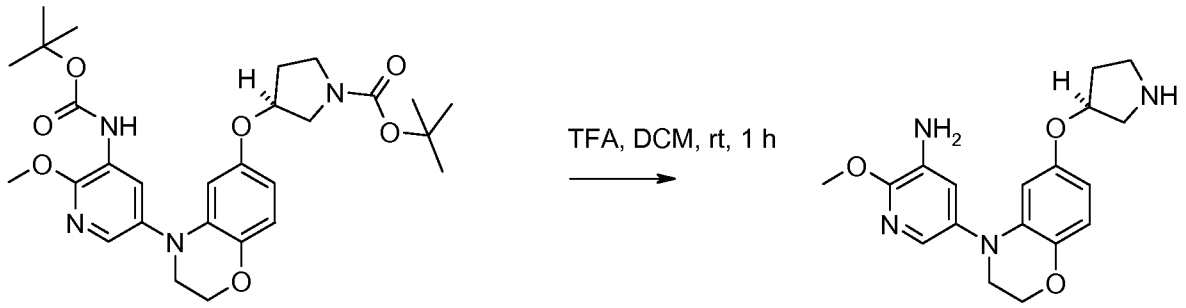
A solution of 5-[6-((S)-1-tert-butoxycarbonyl-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-2-methoxy-nicotinic acid (370 mg, 0.78 mmol) and Et_3N (0.28 ml, 1.96 mmol) in tBuOH (5 ml) was treated with DPPA (CAS registry 26386-88-9) (0.17 ml, 0.78 mmol) and stirred at 100°C for 6 h. DCM and sat. aq. $NaHCO_3$ soln. were added,the organic layer was separated by elution through a separating phase cartridge and concentrated to afford the title

compound after flash chromatography on silica gel (heptane / EtOAc 100:0 to 50:50) as a pink gum (114 mg, 24%).

UPLC Rt_{M2} =1.36 min; ESIMS: 486 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (br s, 1H), 7.75 (d, 1H), 7.02 (s, 1H), 6.78 (d, 1H), 6.15-6.41 (m, 1H), 4.71 (br s, 1H), 4.23-4.39 (m, 2H), 4.09-4.22 (m, 3H), 3.62-3.75 (m, 2H), 3.31-3.58 (m, 4H), 1.86-2.26 (m, 2H), 1.40-1.60 (m, 18H).

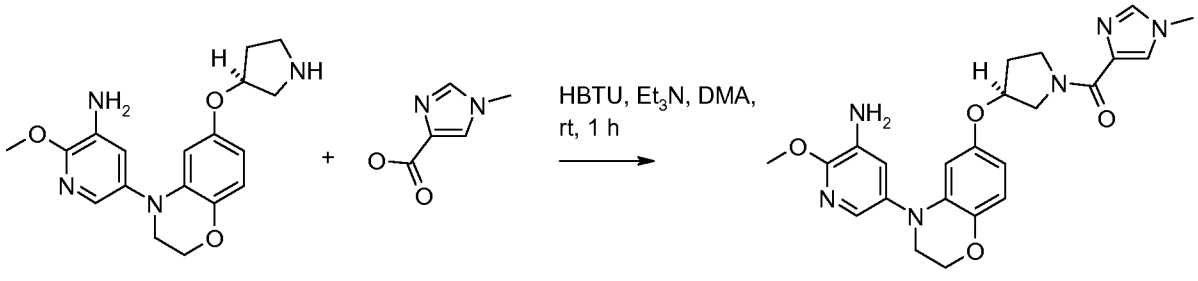
d) 2-Methoxy-5-[6-((S)-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-pyridin-3-ylamine



A solution of (S)-3-[4-(5-tert-butoxycarbonylamino-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (130 mg, 0.24 mmol) in DCM (2 ml) was treated with TFA (CAS registry 76-05-1) and stirred at rt for 1 h. The reaction mixture was concentrated to afford the title compound after elution from a 2 g Isolute SCX-2 cartridge (eluent MeOH, then 2M NH_3/MeOH) as a yellow gum (88 mg, quant. crude).

UPLC Rt_{M2} =1.25 min; ESIMS: 343 [$(M+H)^+$].

e) {(S)-3-[4-(5-Amino-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone



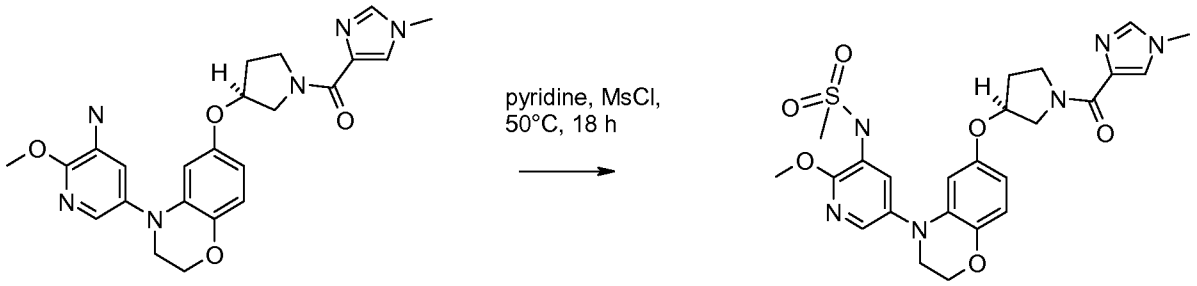
A solution of 1-methyl-1H-imidazole-4-carboxylic acid (CAS registry 41716-18-1) (36.0 mg, 0.26 mmol) and Et_3N (0.11 ml, 0.78 mmol) in DMF (1 ml) was treated with HBTU (CAS registry 94790-37) (107 mg, 0.28 mmol). After stirring at rt for 20 min, the reaction mixture was cooled down to 5°C and a solution of 2-methoxy-5-[6-((S)-pyrrolidin-3-yloxy)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-pyridin-3-ylamine (88 mg, 0.26 mmol) in DMF (3 ml) was

added. The reaction mixture was stirred at rt for 1 h, concentrated and the residue was taken up in DCM (10 ml), washed with a sat. aq. $NaHCO_3$ soln. (5 ml), the organic layer was separated by elution through a separating phase cartridge and concentrated. The residue was purifed by flash chromatography on silica gel (heptane / EtOAc 100:0 to 0:100), the combined fractions were concentrated, dissolved in tBuOH/H_2O and lyophilized to afford the title compound as a colourless solid (21 mg, 37% yield).

UPLC Rt_{M2} =0.85 min; ESIMS: 451 [$(M+H)^+$].

^1H NMR (400 MHz, CD_3OD): δ 7.64 (s, 1H), 7.62 (s, 1H), 7.65 m, 1H), 6.93 (m, 1H), 6.70 (m, 1H), 6.20-6.34 (m, 1H), 6.15 (m, 1H), 4.81 (m, 1H), 4.19-4.31 (m, 2H), 3.90-4.05 (m, 4H), 3.55-3.83 (m, 8H), 2.04-2.28 (m, 2H).

Example U: N-(2-Methoxy-5-{6-[(S)-1-(1-methyl-1H-imidazole-4-carbonyl)-pyrrolidin-3-yloxy]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-pyridin-3-yl)-methanesulfonamide

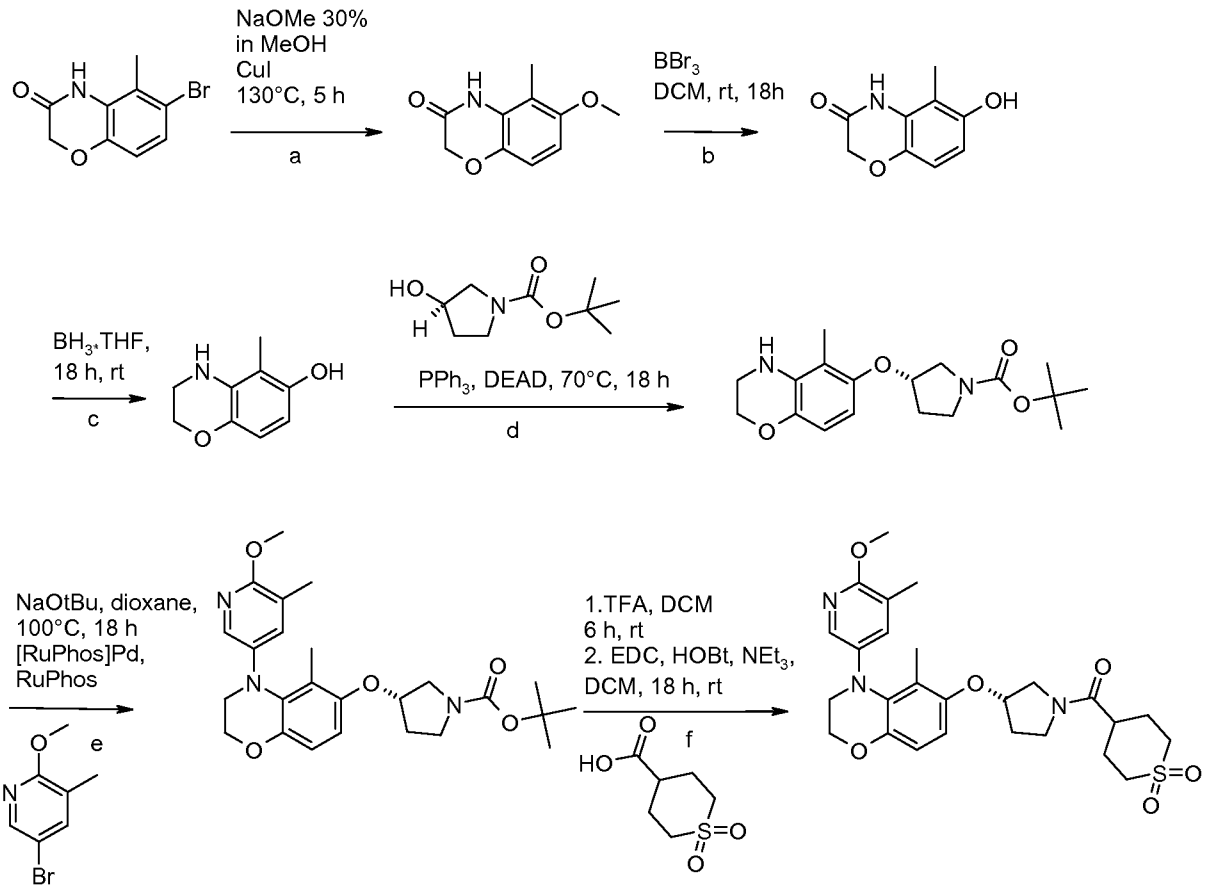


A solution of {(S)-3-[4-(5-Amino-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]-oxazinyloxy]-pyrrolidin-1-yl}-(1-methyl-1H-imidazol-4-yl)-methanone (22.9 mg, 0.05 mmol) in pyridine (1ml) was treated with methanesulfonyl chloride (CAS registry 124-63-0) (0.08 ml, 0.97 mmol) and stirred at 50°C for 18 h. The reaction mixture was diluted with DCM and H_2O, the organic layer was separated by elution through a separating phase cartridge and concentrated. The residue was purifed by flash chromatography on silica gel (heptane / EtOAc 100:0 to 0:100 then EtOAc/MeOH 90:10 to 80:20), the combined fractions were concentrated, dissolved in tBuOH/H_2O and lyophilized to afford the title compound as a colourless solid (14 mg, 49%).

UPLC Rt_{M2} =1.39 min; ESIMS: 529 [$(M+H)^+$].

^1H NMR (400 MHz, CD_3OD): δ 7.87 (d, 1H), 7.41-7.76 (m, 3H), 6.73 (m, 1H), 6.02-6.44 (m, 2H), 4.14-4.39 (m, 2H), 3.87-4.12 (m, 5H), 3.55-3.84 (m, 8H), 2.85-3.08 (m, 3H), 1.75-2.40 (m, 2H).

Example V: (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[4-(6-methoxy-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone



a) 6-Methoxy-5-methyl-4H-benzo[1,4]oxazin-3-one

A solution of 6-bromo-5-methyl-4H-benzo[1,4]oxazin-3-one (CAS registry 1154740-47-2) (1000 mg, 4.13 mmol) and CuI (79 mg, 0.41 mmol) in NaOMe 30% in MeOH (8.1 ml) was stirred at 130°C for 5 h. The orange/brown mixture was cooled to rt, diluted with EtOAc and washed with a sat. aq. $NaHCO_3$ soln. The combined organic layers were dried over $MgSO_4$, and concentrated to afford an orange solid. Trituration with cyclohexane afforded the title compound as a pink solid (647 mg, 70% yield).

HPLC Rt_{M1} =0.73 min.

^1H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 6.76 (d, 1H), 6.53 (d, 1H), 4.42 (s, 2H), 3.71 (s, 3H), 2.05 (s, 3H).

b) 6-Hydroxy-5-methyl-4H-benzo[1,4]oxazin-3-one

A suspension of 6-methoxy-5-methyl-4H-benzo[1,4]oxazin-3-one (647 mg, 3.35 mmol) in DCM (30 ml) was treated under argon at rt with BBr_3 (3.16 ml, 33.5 mmol) and stirred for 18

h at rt. The reaction mixture was quenched by dropwise addition of MeOH at 0°C until obtention of a clear solution. After removal of the solvents, the residue was poured onto ice/ sat. aq. $NaHCO_3$ soln. and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to afford the title compound as a brown solid (647 mg, crude), which was used in the next step without further purification.

HPLC Rt_{M1} =0.49 min.

^1H NMR (400 MHz, DMSO-d_6): δ 10.11 (s, 1H), 6.43 (d, 1H), 5.98 (d, 1H), 4.57 (s, 2H), 1.89 (s, 3H).

c) 5-Methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol

A solution of 6-hydroxy-5-methyl-4H-benzo[1,4]oxazin-3-one (647 mg, 3.61 mmol) in THF (20 ml) was treated under argon at 0°C with BH_3*THF (1M in THF, 10.83 ml, 10.83 mmol) and stirred for 18 h at rt. MeOH was added and the solution was stirred at rt for 1 h, concentrated to afford a residue which was dissolved in THF (20 ml), treated with BH_3*THF (1M in THF, 10.83 ml, 10.83 mmol) and stirred at rt for 18 h. MeOH was added, the solution was stirred at rt for 4 h, concentrated to dryness to afford the title compound as a brown solid (600 mg, crude), which was used in the next step without further purification.

HPLC Rt_{M1} =0.49 min; ESIMS: 166 [$(M+H)^+$].

d) (S)-3-(5-Methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of triphenylphosphine (1.33 g, 5.09 mmol) in THF (10 ml) was treated with DEAD (0.8 ml, 5.09 mmol) followed by (R)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (CAS registry 127423-61-4) (1 g, 5.45 mmol) and 5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol (600 mg, 3.63 mmol). The resulting red/brown solution was stirred at 70°C for 18 h. The brown mixture was cooled down, diluted with EtOAc and washed with sat. aq. $NaHCO_3$ soln. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a brown oil. The crude product was three times purified by flash chromatography on silica gel (cyclohexane / EtOAc 90:10 to 40:60) to afford the title compound as a colourless oil (130 mg, 11% yield)

HPLC Rt_{M1} =1.09 min; ESIMS: 335 [$(M+H)^+$].

^1H NMR (400 MHz, DMSO-d_6): δ 6.44 (d, 1H), 6.22-6.04 (m, 1H), 5.24 (br s, 1H), 4.75 (br s, 1H), 4.07-3.93 (m, 2H), 3.45-3.33 (m, 3H), 3.28 (d, 7H), 2.00 (d, 2H), 1.83 (d, 3H), 1.46-1.32 (m, 9H).

e) (S)-3-[4-(6-Methoxy-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (S)-3-(5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (120 mg, 0.36 mmol), 5-bromo-2-methoxy-3-methylpyridine (CAS registry 760207-87-2) (145 mg, 0.72 mmol), NaOtBu (103 mg, 1.08 mmol), RuPhos (CAS registry 787618-22-8) (8 mg, 0.02 mmol) and[RuPhos]palladacycle (CAS registry 787618-22-8) (15 mg, 0.02 mmol) in dioxane (2 ml) was stirred at 100°C for 18 h. The orange/brown mixture was cooled , diluted with EtOAc and washed with water. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a brown oil. The crude product was three times purified by flash chromatography on silica gel (cyclohexane / EtOAc 95:05 to 60:40) to afford the title compound as a yellow oil (97 mg, 60% yield)

HPLC Rt_{M1} =1.37 min; ESIMS: 456 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6): δ 7.40 (d, 1H), 7.28-7.07 (m, 1H), 6.74 (s, 2H), 4.84 (br s, 1H), 3.96 (br s, 2H), 3.80 (s, 2H), 3.57 (br s, 2H), 3.44-3.19 (m, 10H), 2.08 (s, 3H), 2.05-1.92 (m, 2H), 1.60 (d, 3H), 1.34 (d, 9H).

f) (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[4-(6-methoxy-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone

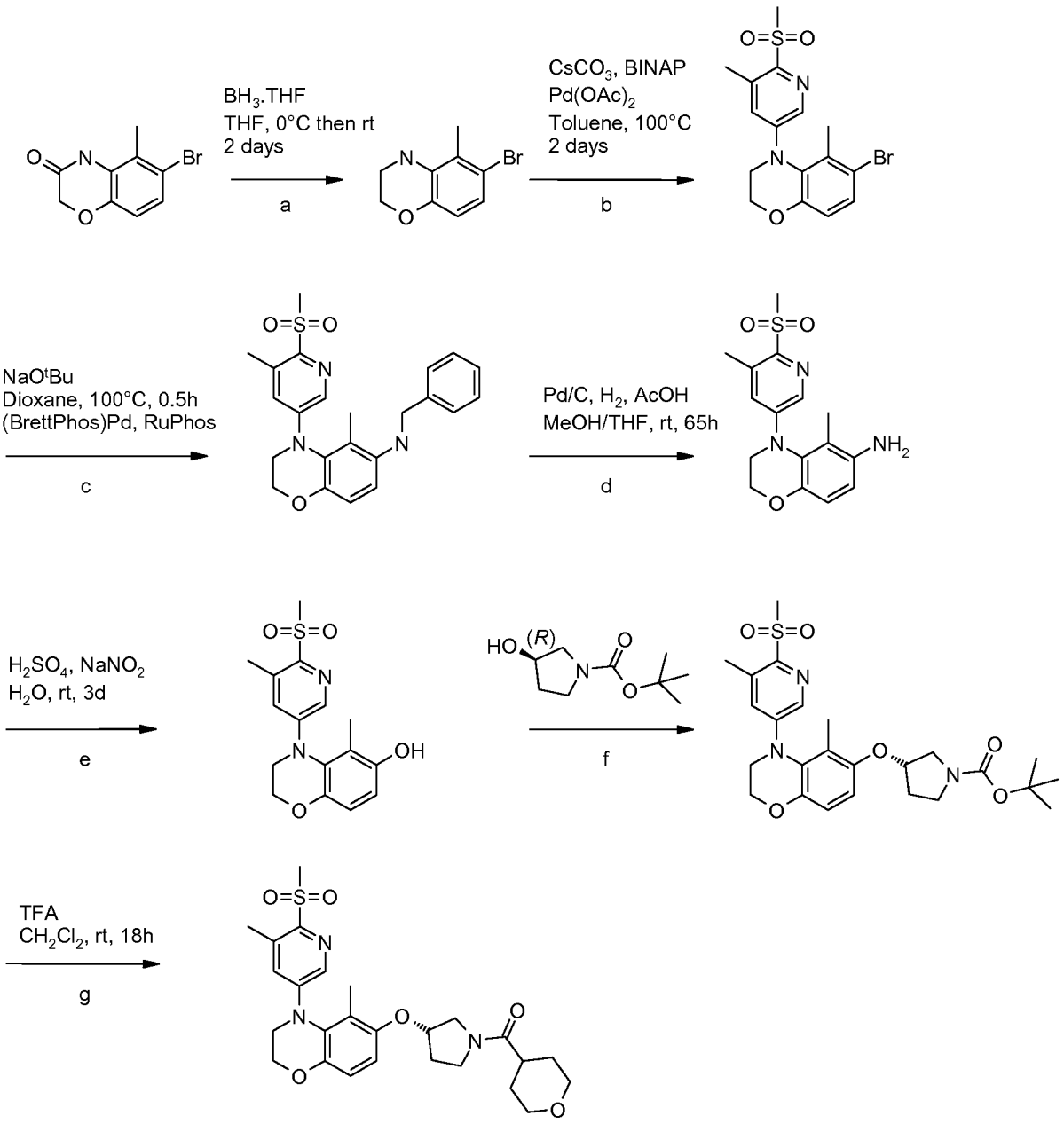
A solution of (S)-3-[4-(6-methoxy-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (97 mg, 0.21 mmol) in DCM (3 ml) was treated under argon at rt with TFA (0.16 ml, 2.13 mmol) and stirred for 6 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ soln. and the organic solution was separated through a phase separating cartridge affording a yellow solution. 1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-carboxylic acid (CAS registry 64096-87-3) (49 mg, 0.28 mmol), Et_3N (0.09 ml, 0.64 mmol), EDC (62 mg, 0.32 mmol), HOBT (49 mg, 0.32 mmol) were added to the yellow solution and stirred at rt for 18 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ soln. and the organic layer was separated by passing through a phase separating cartridge, then concentrated and purified by prep. RP-HPLC (column SunFire C18 OBD 5 mm 30x100mm, Solvent A: H_2O (0.1% TFA) Solvent B: CH_3CN (0.1% TFA) afforded the title compound as white solid (76 mg, 70% yield)

HPLC Rt_{M1} =0.98 min; ESIMS: 516 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6, 375K): δ 7.44 (br s, 1H), 7.18 (br s, 1H), 6.75 (s, 2H), 4.88 (br s, 1 H), 4.02 (t, 2H), 3.86 (s, 3H), 3.81-3.33 (m, 6H), 3.24-3.06 (m, 4H), 2.83 (br s, 1H), 1.66 (s, 3H). Rotamers.

Example W: {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone

Le



a) 6-Bromo-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazine

A solution of 6-bromo-5-methyl-4H-benzo[1,4]oxazin-3-one (CAS registry 1154740-47-2) (425 mg, 1.56 mmol) in THF (9 ml) was treated under argon at 0°C with BH_3*THF (1M in THF, 4.7 ml, 4.69 mmol) and stirred for 18 h at rt. BH_3.THF 1M (2 ml) was added and stirring was continued for another 24 h. The reaction mixture was concentrated and purified by flash

chromatography on silica gel (cyclohexane / EtOAc 100:0 to 80:20) to afford the title compound as an orange solid (324 mg, 86% yield)

HPLC Rt_{M1} =1.04 min; ESIMS: 228, 230 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.68 (d, 1H), 6.48 (d, 1H), 5.54 (br s, 1H), 4.04 (t, 2H), 3.36-3.26 (m, 2H), 2.11(s, 3H).

b) 6-Bromo-4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazine

A solution of 6-bromo-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazine (324 mg, 1.42 mmol), Intermediate IA1 (391 mg, 1.56 mmol), Cs_2CO_3 (1018 mg, 3.13 mmol), BINAP (CAS registry 98327-87-8) (44 mg, 0.07 mmol), $Pd(OAc)_2$ (CAS registry 3375-31-3) (32 mg, 0.14 mmol) in toluene (13 ml) was stirred at 100°C for 18 h. Catalyst and ligand were reloaded and stirring was continued for another 24 h at 100°c. The reaction mixture was cooled to rt, diluted with EtOAc and washed with water. Concentration of the organic layer and purification by flash chromatography on silica gel (cyclohexane / EtOAc 97:03 to 40:60) afforded the title compound as an orange solid (345 mg, 58% yield).

HPLC Rt_{M1} =1.13 min; ESIMS: 397,399 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (br. s, 1H), 7.37 (d, 1H), 7.24 (br. s, 1H), 6.83 (d, 1H), 4.13 (t, 2H), 3.97-3.86 (m, 2H), 3.30 (s, 3H), 2.52 (s, 3H), 1.93 (s, 3H).

c) Benzyl-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-amine

A solution of 6-bromo-4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazine (324 mg, 0.82 mmol), benzylamine (350 mg, 3.26 mmol), NaOtBu (157 mg, 1.63 mmol), RuPhos (CAS registry 787618-22-8) (30 mg, 0.06mmol) and [BrettPhos]palladacycle (CAS registry 1148148-01-9) (52 mg, 0.06 mmol) in dioxane (16 ml) was stirred at 80°C for 0.5 h. Filtration, concentration of the filtrate and purification by flash chromatography on silica gel (cyclohexane / EtOAc 88:12 to 35:65) afforded the title compound as a yellow oil (228 mg, 66% yield).

HPLC Rt_{M1} =1.13 min; ESIMS: 424 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 (br s, 1H), 7.40-7.33 (m, 2H), 7.30 (t, 2H), 7.19 (t, 2H), 6.58 (d, 1H), 6.30 (d, 1H), 5.25 (t, 1H), 4.30 (d, 2H), 4.04-3.97 (m, 2H), 3.90 (d, 2H), 3.29 (s, 3H), 2.51 (br s, 3H), 1.76 (s, 3H).

d) 4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylamine

A solution of benzyl-[4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl]-amine (228 mg, 0.53 mmol), acetic acid (0.21 ml, 3.70 mmol), Pd/C in MeOH/THF (2.5/2.5 ml) was hydrogenated with H_2 at rt for 65 h. Filtration and concentration of the filtrate afforded the title compound as a green oil (200 mg, crude, including remaining AcOH).

HPLC Rt_{M1} =0.64 min; ESIMS: 334 [$(M+H)^+$].

^1H NMR (400 MHz, DMSO-d_6): δ 7.96 (br s, 1H), 7.17 (br s, 1H), 6.62-6.54 (d, 1H), 6.54-6.45(d, 1H), 4.48 (br s, 2H), 4.01 (t, 2H), 3.88 (br s, 2H), 3.28 (s, 3H), 1.88 (d, 3H), 1.63 (s, 3H).

e) 4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol

A solution of 4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylamine (200 mg, 0.60 mmol) in water (3.5 ml) and H_2SO_4 (0.32 ml) was added dropwise to a solution of sodium nitrite (49.7 mg, 0.72 mmol) in water (10 ml) at 0°C. The mixture was stirred at rt for 3 d. The reaction mixture was filtered and the filtrate was quenched with sat. aq. $NaHCO_3$ soln. and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford a brown oil. Purification by flash chromatography on silica gel (DCM / MeOH 88:12 to 80:20) afforded the title compound as a brown oil (50 mg, 25% yield).

HPLC Rt_{M1} =0.78 min; ESIMS: 335 [$(M+H)^+$].

f) (1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[4-(6-methoxy-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone

A solution of triphenylphosphine (55 mg, 0.21 mmol) in THF (2.5 ml) was treated with DEAD (0.03 ml, 0.21 mmol), followed by (R)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (CAS registry 127423-61-4) (33 mg, 0.18 mmol) and 4-(6-methanesulfonyl-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol (50 mg, 0.15 mmol). The resulting red/brown solution was stirred at 70°C for 18 h. The reaction mixture was cooled down to rt, diluted with EtOAc and washed with sat. aq. $NaHCO_3$ soln.. The organic layer was dried over $MgSO_4$. concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc 90:10 to 40:60) to afford the title compound as an orange solid (44 mg, 58% yield)

HPLC Rt_{M1} =1.16 min; ESIMS: 504 [$(M+H)^+$].

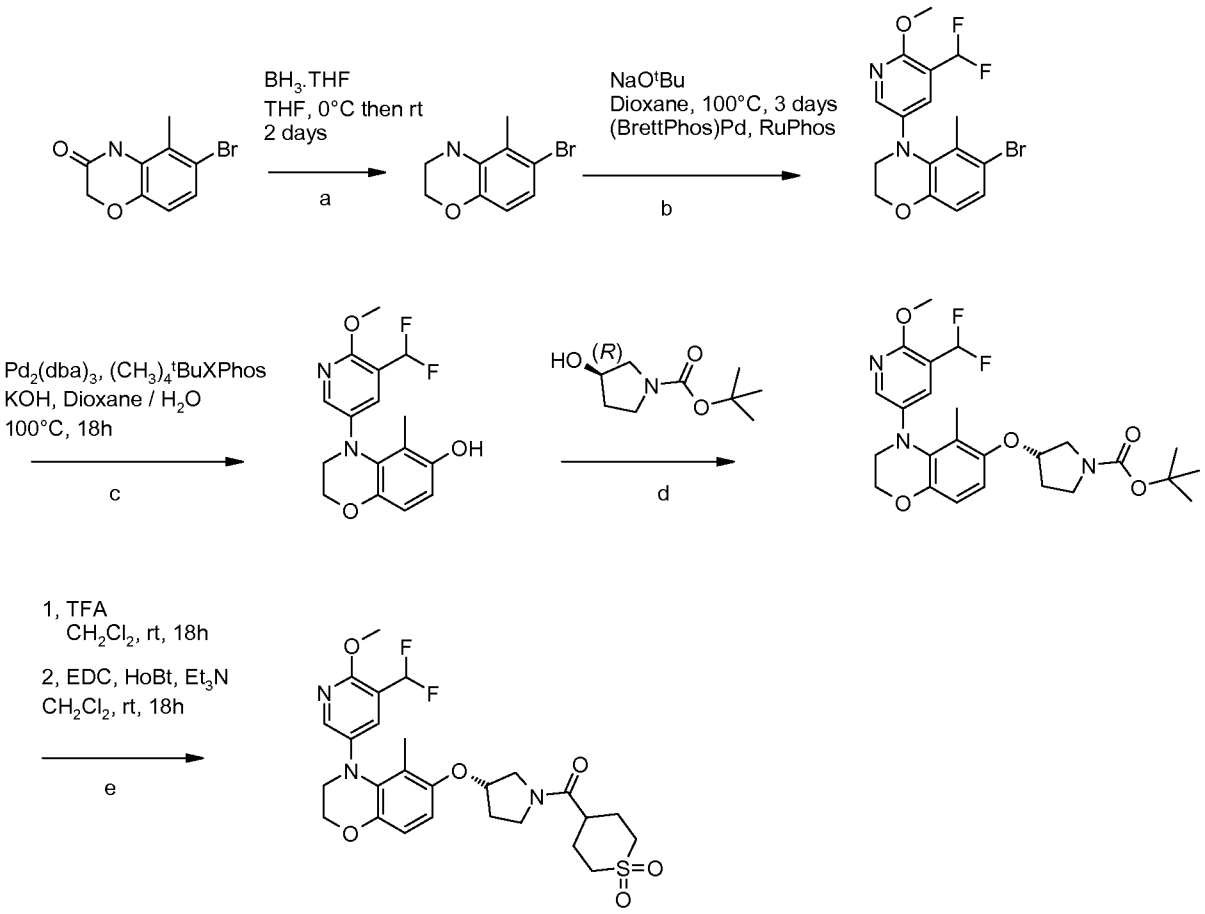
g) {(S)-3-[4-(6-Methanesulfonyl-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(tetrahydro-pyran-4-yl)-methanone

A solution of (1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-{(S)-3-[4-(6-methoxy-5-methyl-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-methanone (44 mg, 0.09 mmol) in DCM (4 ml) was treated under argon at rt with TFA (0.07 ml, 0.17 mmol) and stirred for 18 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ soln. and the organic solution was separated through a phase separating cartridge, concentrated and purified by flash chromatography on silica gel (DCM / MeOH 100:0 to 90:10).The obtained product was dissolved in DCM (4 ml) and Et_3N was added. Tetrahydro-pyran-4-carbonyl chloride (CAS registry 40191-32-0) (15 mg, 0.10 mmol) was added to the reaction mixture at 0°C and the resulting orange solution was stirred at rt for 4 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ soln. and the organic layer was separated by elution through a phase separating cartridge, concentrated and purified by SFC (column NH_2 (250 x 30mm (l x w), 60A, 5µm, Princeton, gradient of methanol in supercritical CO_2) to afford the title compound as a yellow oil (15 mg, 32% yield)

HPLC Rt_{M1} =0.88 min; ESIMS: 516 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6, 375K): δ 7.98 (br s, 1 H), 7.19 (br s, 1 H), 6.92 - 6.85 (m, 1 H), 6.85 - 6.77 (m, 1 H), 4.95 (br s, 1 H), 4.12 (t, 2 H), 3.92 (t, 2 H), 3.88 (br s, 2 H), 3.61 (br s, 3 H), 3.38 (td, 2 H), 3.27 (s, 3 H), 2.68 (d, 1 H), 2.56 (s, 3 H), 2.17 (br s, 2 H), 1.73 (s, 3 H), 1.58 (br s, 4 H). Rotamers.

Example X: {(S)-3-[4-(5-Difluoromethyl-6-methoxy-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-methanone



a) 6-Bromo-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazine

A solution of 6-bromo-5-methyl-4H-benzo[1,4]oxazin-3-one (CAS registry 1154740-47-2) (2.8 g, 11.56 mmol) in THF (50 ml) was treated under argon with BH_3*THF (1M in THF, 34.7 ml, 34.70 mmol) and heated under reflux for 2 h. MeOH was added and the solution was stirred at rt for 1 h, concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc 100:0 to 80:20) to afford the title compound as an orange solid (1.8 g, 68% yield).

HPLC Rt_{M1} =1.04 min; ESIMS: 228, 230 $[(M+H)^+]$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.68 (d, 1H), 6.48 (d, 1H), 5.54 (br s, 1H), 4.04 (t, 2H), 3.36-3.26 (m, 2H), 2.11 (s, 3H).

b) 6-Bromo-4-(5-difluoromethyl-6-methoxy-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazine

A solution of 6-bromo-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazine (500 mg, 2.19 mmol), Intermediate IA6 (574 mg, 2.41 mmol), NaOtBu (421 mg, 4.38 mmol), BrettPhos (CAS registry 1070663-78-3) (59 mg, 0.11 mmol) and [BrettPhos]palladacycle (CAS registry 1148148-01-9) (88 mg, 0.11 mmol) in dioxane (11 ml) was stirred at 100°C for 18 h. Catalyst and ligand were reloaded and stirring was continued at 100°C for 48 h. The reaction mixture was cooled down to rt, diluted with EtOAc and washed with sat. aq. $NaHCO_3$ soln. The organic layer was dried over $MgSO_4$, concentrated to afford a brown oil. Purification by flash chromatography on silica gel (cyclohexane / EtOAc 100:0 to 80:20) afforded the title compound as a brown oil (150 mg, 18% yield).

HPLC Rt_{M1} =1.34 min; ESIMS: 385, 387 $[(M+H)^+]$.

c) 4-(5-Difluoromethyl-6-methoxy-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol

A mixture of 6-bromo-4-(5-difluoromethyl-6-methoxy-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazine (150 mg, 0.39 mmol), KOH (65 mg, 1.17 mmol) in water (0.33 ml), tetramethyl-t-butyl-XPhos (CAS registry 857356-94-6) (18.72 mg, 0.04 mmol) and $Pd_2(dba)_3$ (17.83 mg, 0.02 mmol) in dioxane (2 ml) was degassed with nitrogen and heated at 100°C for 18 h. Filtration, concentration and purification by flash chromatography on silica gel (cyclohexane / EtOAc 100:0 to 70:30) afforded the title compound as an orange oil (65 mg, 52% yield).

HPLC Rt_{M1} =1.01 min; ESIMS: 323 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6): δ 8.83 (s, 1H), 7.89 (d, 1H), 7.36 (d, 1H), 7.00 (t, 1H), 6.61 (d, 1H), 6.55 (d, 1H), 3.93 (t, 2H), 3.88 (s, 3H), 3.65 (t, 2H), 1.60 (s, 3H).

d) (S)-3-[4-(5-Difluoromethyl-6-methoxy-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of triphenylphosphine (74 mg, 0.28 mmol) in THF (2 ml) was treated with DEAD (0.04 ml, 0.28 mmol) followed by (R)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (CAS registry 127423-61-4) (45 mg, 0.24 mmol) and 4-(5-difluoromethyl-6-methoxy-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol (65 mg, 0.20 mmol). The resulting red/brown solution was stirred at 70°C for 18 h, cooled down to rt, diluted with EtOAc and washed with sat. aq. $NaHCO_3$ soln. The organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc 100:0 to 70:30) to afford the title compound as a yellow solid (51 mg, 42% yield).

HPLC Rt_{M1} =1.36 min; ESIMS: 492 $[(M+H)^+]$.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92-7.75 (m, 1H), 7.46-7.33 (m, 1H), 7.19-6.84 (t, 1H), 6.77 (s, 2H), 4.86 (br s, 1H), 3.98 (br s, 2H), 3.88 (s, 3H), 3.73-3.55 (m, 2H), 3.46-3.33 (m, 2H), 2.12-1.95 (m, 2H), 1.65-1.55 (m, 3H), 1.34 (br s, 9H). Rotamers.

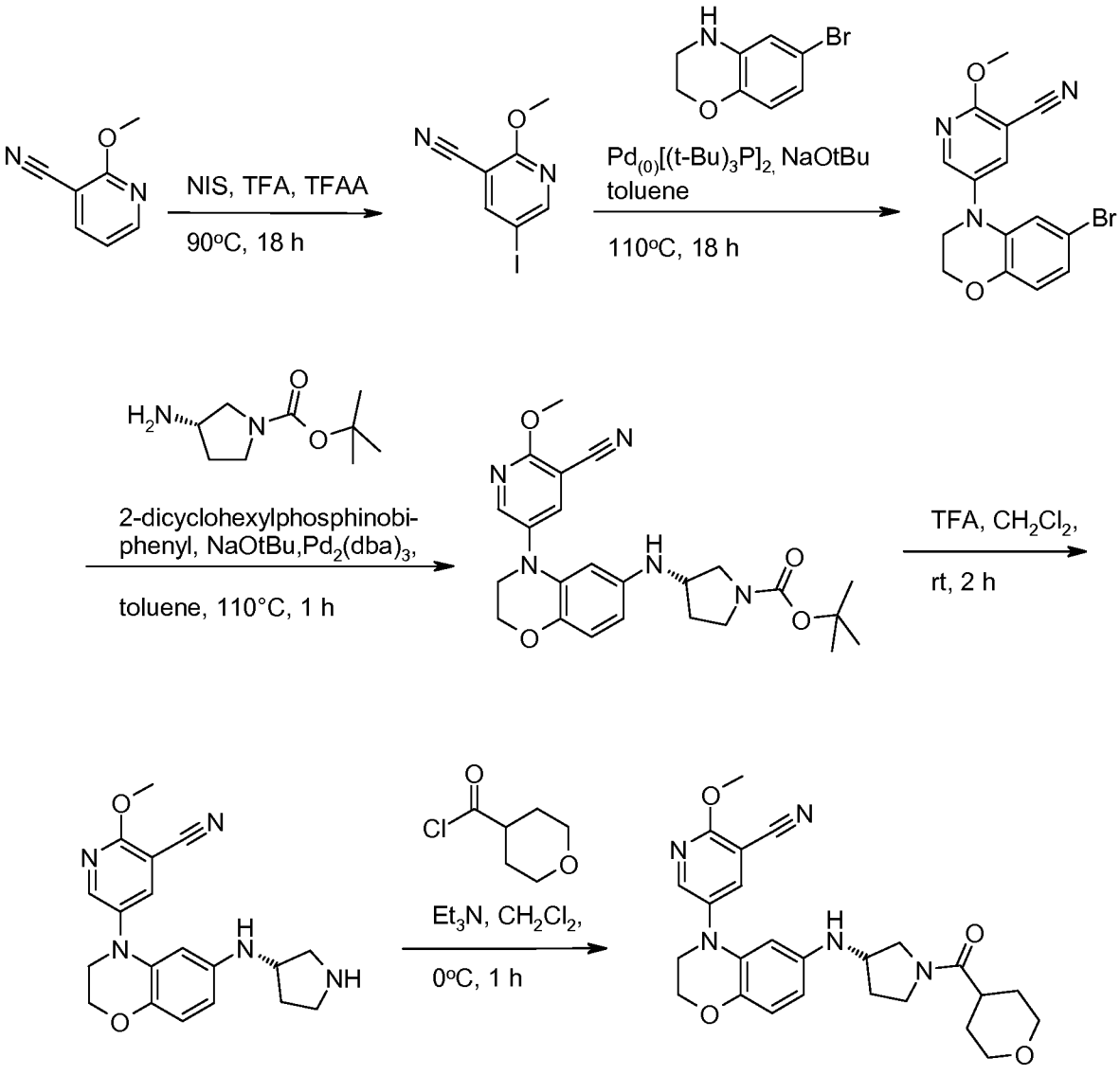
e) {(S)-3-[4-(5-Difluoromethyl-6-methoxy-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidin-1-yl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-yl)-methanone

A solution of (S)-3-[4-(5-difluoromethyl-6-methoxy-pyridin-3-yl)-5-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-yloxy]-pyrrolidine-1-carboxylic acid tert-butyl ester (51 mg, 0.10 mmol) in DCM (3 ml) was treated under argon at rt with TFA (0.08 ml, 1.10 mmol) and stirred for 18 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ soln. and the organic solution was separated through a phase separating affording a yellow solution. 1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-carboxylic acid (CAS registry 64096-87-3) (25 mg, 0.14 mmol), Et_3N (0.05 ml, 0.33 mmol), EDC (31 mg, 0.16 mmol) and HOBT (25 mg, 0.16 mmol) were added and the reaction mixture was stirred at rt for 3 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ soln. The organic layer was separated by elution through a phase separating cartridge, the crude product was purified over SFC (column Reprosil NH_2 (250 x 30mm (l x w), 60A, 5µm, Princeton, gradient of methanol in supercritical CO_2) to afford the title compound as a yellow oil (19 mg, 30% yield)

HPLC Rt_{M1} =1.00 min; ESIMS: 552 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6, 375K): δ 7.85 (br s, 1 H), 7.43 (br s, 1H), 6.96 (t, 1H), 6.80 (s, 2H), 5.11-4.71 (m, 1H), 4.04 (t, 2 H), 3.94 (s, 3H), 3.70 (d, 2 H), 3.63 (br s, 2 H), 3.52 (br s, 2 H), 3.23-3.04 (m, 4H), 2.92-2.73 (m, 1H), 2.16 (br s, 2 H), 2.06 (br s, 4H), 1.67 (s, 3 H), Rotamers.

Example Y: 2-Methoxy-5-{6-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-ylamino]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile



a) 5-Iodo-2-methoxy-nicotinonitrile

A mixture of 2-methoxy-nicotinonitrile (CAS registry 7254-34-4) (10 g, 74.6 mmol) and N-iodosuccinimide (CAS registry 516-12-1) (25.2 g, 112 mmol) was treated with trifluoroacetic acid (CAS registry 76-05-1) (68.9 ml, 895 mmol) and trifluoroacetic anhydride (CAS registry 407-25-0) (31.6 ml, 224 mmol) and the reaction mixture was heated at 90°C for 18 h then cooled to rt and poured onto ice. The mixture was slowly basified using 30% aq. NaOH soln., diluted with water and extracted with EtOAc. The organic layer was successively washed with 20% aq. sodium thiosulfate soln., and sat. aq. $NaHCO_3$ soln., dried over Na_2SO_4, filtered

and concentrated. The title compound was obtained after flash chromatography on silica gel (cyclohexane / EtOAc, 100:0 to 20:80) as a solid (12.2 g, 63% yield)

UPLC Rt_{M14} =1.30 min; ESIMS: 261 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, 1H), 8.11 (d, 1H), 4.06 (s, 3H).

b) 5-(6-Bromo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-2-methoxy-nicotinonitrile

A mixture of 6-bromo-3,4-dihydro-2H-benzo[1,4]oxazine (CAS registry 105655-01-4) (5.0 g, 23.36 mmol), 5-iodo-2-methoxy-nicotinonitrile (12.2 g, 46.7 mmol) and NaOtBu (2.69 g, 28.0 mmol) in toluene (50 ml) was degassed with argon for 10 min, then bis(tri-tert-butylphosphine)-palladium(0) (0.36 g, 0.70 mmol) was added. The reaction mixture stirred at 110°C for 18 h under argon. After cooling to rt, the reaction mixture was filtered through celite, rinsed with EtOAc and the filtrates were washed with sat. aq. $NaHCO_3$ soln.. The organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc, 100:0 to 50:50) to yield the title compound (4.2 g, 52% yield).

UPLC Rt_{M14} =1.55 min; ESIMS: 348 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, 1H), 7.80 (d, 1H), 6.89 (dd, 1H), 6.78 (d, 1H), 6.67 (d, 1H), 4.30-4.35 (m, 2H), 4.10 (s, 3H), 3.61-3.66 (m, 2H).

c) (S)-3-[4-(5-Cyano-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of 5-(6-bromo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-2-methoxy-nicotinonitrile (300 mg, 0.87 mmol), (S)-3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (CAS registry 147081-44-5) (0.26 ml, 1.47 mmol), 2-(dicyclohexylphosphino)biphenyl (CAS registry 247940-06-3) (18.2 mg, 0.05 mmol) and NaOtBu (100 mg, 1.04 mmol) in toluene (10 ml) was degassed with argon for 10 min, then $Pd_2(dba)_3$ (23.8 mg, 0.03 mmol) was added. The reaction mixture was stirred at 110°C for 1 h under argon. After cooling to rt, the reaction mixture was filtered through celite, rinsed with EtOAc and the filtrates were concentrated. The title compound was obtained after flash chromatography on silica gel (cyclohexane / EtOAc, 100:0 to 70:30) as a yellow foam (150 mg, 37% yield).

UPLC Rt_{M11} = 2.73 min; ESIMS: 452 [$(M+H)^+$].

^1H NMR (400 MHz, CD_3OD): δ 8.36 (d, 1H), 8.04 (d, 1H), 6.68 (s, 1H), 6.19 (dd, 1H), 6.03 (s, 1H), 4.19-4.24 (m, 2H), 4.06 (s, 3H), 3.81-3.89 (m, 1H), 3.62-3.68 (m, 2H), 3.48-3.56 (m, 1H), 3.35-3.48 (m, 2H), 3.08-3.18 (m, 1H), 2.05-2.18 (m, 1H), 1.75-1.87 (m, 1H), 1.46 (s, 9H).

d) 2-Methoxy-5-[6-((S)-pyrrolidin-3-ylamino)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-nicotinonitrile

A solution of (S)-3-[4-(5-cyano-6-methoxy-pyridin-3-yl)-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester (144 mg, 0.32 mmol) in CH_2Cl_2 (4 ml) was treated with TFA (0.49 ml, 6.38 mmol). The reaction mixture was stirred at rt for 2 h, quenched with sat. aq. $NaHCO_3$ soln. and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title product as a yellow foam (120 mg, 100% yield).

UPLC Rt_{M11} = 2.06 min; ESIMS: 352 $[(M+H)^+]$.

^1H NMR (400 MHz, CD_3OD): δ 8.36 (d, 1H), 8.04 (d, 1H), 6.69 (d, 1H), 6.17 (dd, 1H), 6.00 (d, 1H), 4.19-4.26 (m, 2H), 4.06 (s, 3H), 3.80-3.90 (m, 1H), 3.62-3.69 (m, 2H), 3.10-3.20 (m, 2H), 2.98-3.09 (m, 1H), 2.82-2.90 (m, 1H), 2.06-2.18 (m, 1H), 1.70-1.81 (m, 1H).

e) 2-Methoxy-5-{6-[(S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-ylamino]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-nicotinonitrile

At 0°C, a solution of 2-methoxy-5-[6-((S)-pyrrolidin-3-ylamino)-2,3-dihydro-benzo[1,4]oxazin-4-yl]-nicotinonitrile (27 mg, 0.08 mmol) in CH_2Cl_2 (1 ml) was treated with Et_3N (0.02 ml, 0.12 mmol) and tetrahydro-pyran-4-carbonyl chloride (CAS registry 40191-32-0) (11 µl, 0.09 mmol).The reaction mixture was stirred at 0°C for 1 h, then quenched with sat. aq. $NaHCO_3$ soln. and extracted with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated and the title compound was obtained after prep. RP-HPLC (column Sunfire PrepC18 OBD 30x100 mm, 5 µm; solvent A: H_2O+0.1 Vol.-% TFA; solvent B: CH_3CN +0.1 Vol.-% TFA, gradient 5–60% B in 20 min) and filtration over Agilent PL-HCO_3 MP SPE cartridgeas a yellow solid (9 mg, 25% yield).

UPLC Rt_{M2} = 1.19 min; ESIMS: 464 $[(M+H)^+]$.

^1H NMR (400 MHz, CD_3OD): δ 8.36 (d, 1H), 8.05 (m, 1H), 6.69 (dd, 1H), 6.15-6.23 (m, 1H), 5.97-6.07 (m, 1H), 4.15-4.29 (m, 2H), 4.06 (s, 3H), 3.82-4.03 (m, 3H), 3.35-3.80 (m, 8H), 2.65-2.84 (m, 1H), 2.03-2.28 (m, 1H), 1.49-2.03 (m, 5H).

Coupling conditions

A) Buchwald aminations or hydroxylations

Condition #	Pd source	Ligand	Base	Solvents used	Typical temperature	Typical reaction time
CA1	$Pd_2(dba)_3$	Rac-BINAP	Cs_2CO_3	toluene	60-100°C	16 h
CA2	$Pd_2(dba)_3$	XPhos	NaO^tBu	dioxane	100°C	1-18 h
CA3	$Pd_2(dba)_3$	XPhos	Cs_2CO_3	toluene	100°C	
CA4	$Pd_2(dba)_3$	XPhos	Cs_2CO_3	dioxane	100°C	1-18 h
CA5	$Pd_2(dba)_3$	tetramethyl-t-butyl-XPhos	KOH	dioxane /H_2O	100°C	18-72 h
CA6	$Pd_2(dba)_3$	XPhos	NaO^tBu	toluene	80-110°C	20 min-18 h
CA7	$Pd(P(tBu_3)_2$		NaO^tBu	toluene	140°C (mw)	30 min
CA8	$Pd(P(tBu_3)_2$		NaO^tBu	toluene	120°C	18 h
CA9	$Pd_2(dba)_3$	XPhos	NaO^tBu	toluene	125°C (mw)	25 min
CA10	$Pd(OAc)_2$	Rac-BINAP	Cs_2CO_3	toluene	60-100°C	21 h
CA11	Pd[Ruphos]	RuPhos	NaO^tBu	dioxane	100°C	18 h
CA12	$Pd(P(tBu_3)_2$		K_3PO_4	toluene	120°C	18 h
CA13	$Pd_2(dba)_3$	XPhos	K_3PO_4	toluene	100°C	12 h
CA14	$Pd_2(dba)_3$	XPhos	K_3PO_4	toluene	110-120°C	12 h
CA15	$Pd(P(tBu_3)_2$		NaO^tBu	THF	110°C	18 h
CA16	$Pd_2(dba)_3$	XPhos	NaO^tBu	THF	110°C	1 h-18 h

B) Amide bond formation conditions

Condition#	Coupling reagents	Solvents used	Typical temperature	Typical reaction time
CB1	HBTU	DMF or DMA	rt	1 h - 18 h
CB2	HOBT, EDC	DMF	rt	1 h - 18h
CB3	HATU	CH_2Cl_2	0°C to rt	30 min
CB4	HOBT, EDC	CH_2Cl_2	rt	18 h
CB5	COMU, DIPEA	DMF	rt	12 h
CB6	none	CH_2Cl_2	rt	1 h – 18 h
CB7	HBTU	CH_2Cl_2	rt	30 min

C) Side chain introduction conditions

CC1) Using mesylate

At rt, a dry solution of pyridin-2-ol intermediate (1 eq.) and mesylate intermediate (1.1 - 2 eq.) in DMF (0.17 M) was treated with NaH in mineral oil (2 - 3 eq.) and the reaction mixture was stirred at 20-80°C for 4 to 72 h.

CC2) Using mesylate

At rt, a dry solution aryl-6-ol intermediate (1 eq.) and mesylate intermediate (1.1 - 2 eq.) in DMF (0.17M) was treated with NaH in mineral oil (2 - 3 eq.) and the reaction mixture was stirred at 50-80°C for 4 to 72 h.

CC3) Using mesylate

At rt, a dry solution of aryl-6-ol intermediate (1 eq.) and mesylate intermediate (2.5 eq.) in DMF (0.06M) was treated with K_2CO_3 (4 eq.) and the reaction mixture was stirred at 85°ZC to 100°C for 4 to 50 h.

CC4) Using Mitsunobu

At rt, DEAD (1.4 eq.), (R)-3-Hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (1.5 eq.) and aryl-6-ol intermediate (1 eq.) were added to a solution of triphenylphosphine (1.4 eq.) in THF (0.30M) . The red/brown solution was stirred at 70 °C for 18 h.

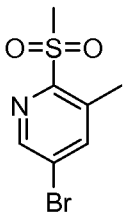
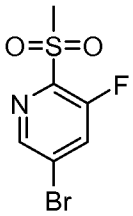
D) Conditions for chiral separation chromatography

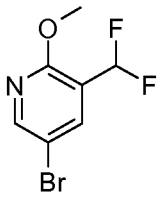
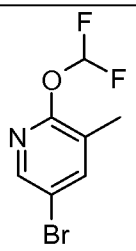
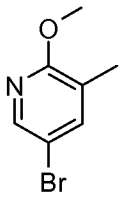
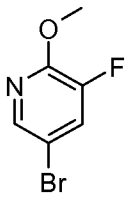
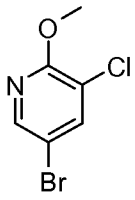
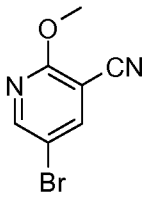
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CD2	Chiralpak IC 250x30 mm, 5µm	ACN 100%	230 nm
CD3	Chiralcel ODH 250x30 mm, 5 µm	EtOH/MeOH 60:40	220 nm
CD4	Chiralpak IC 250x30 mm, 5µm	DMME/IPA/MeOH/DEA 70:25:5:0.05,	230 nm
CD5	Chiralpak IC 250x30 mm, 5µm	ACN 100%	220 nm
CD6	Chiralpak IC 250x30 mm, 5µm	MeOH 100%	220 nm
CD7	Chiralpak IC 250x46 mm, 5µm	n-Heptane/DMME/EtOH/DEA 40:50:10:0.05	240 nm
CD8	Chiralcel OD-H,	CO_2/IPA 70:30 (isocratic	215 nm

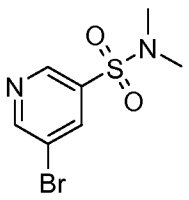
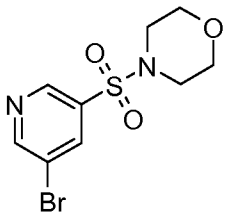
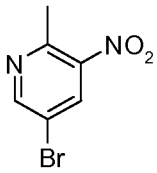
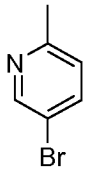
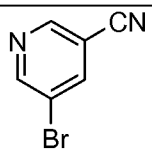
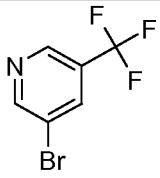
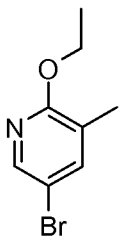
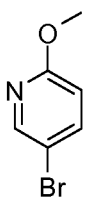
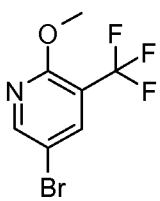
	4.6 x 250 mm		
CD9	Chiralpak AD-H, 5µm	Heptane/EtOH 60:40	
CD10	Chiralpak IC 250x46 mm, 5µm	DMME/IPA/MeOH/DEA 70:25:5:0.05,	230 nm
CD11	Chiralcel ODH 250x20 mm, 5 µm	EtOH/MeOH 60:40	220 nm
CD12	Chiralpak IC 765x37.5 cm, 20 µm	EtOH/MeOH 50:50	210 nm

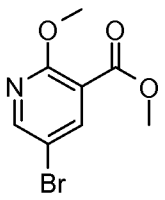
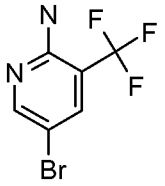
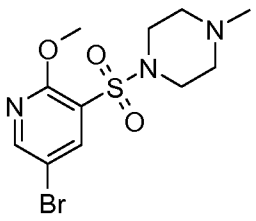
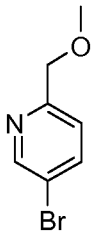
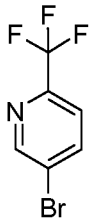
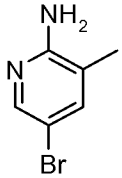
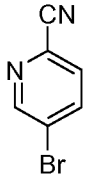
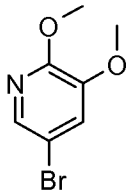
Preparation of Intermediates

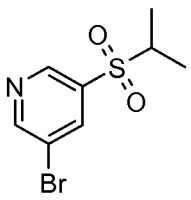
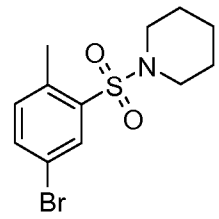
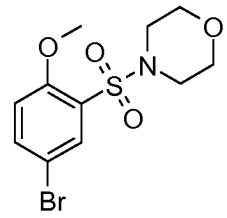
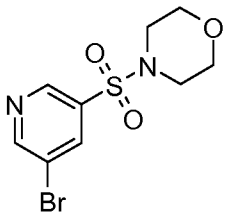
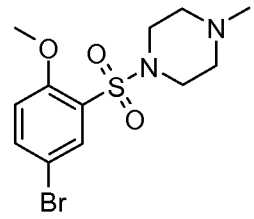
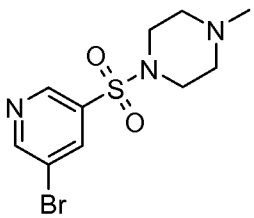
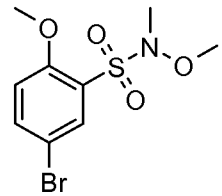
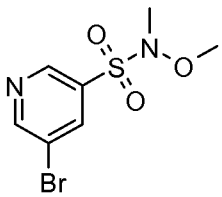
IA) Aromatic bromides

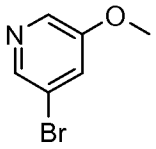
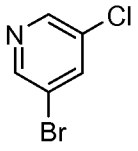
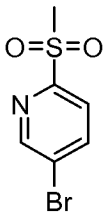
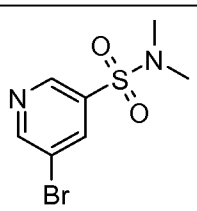
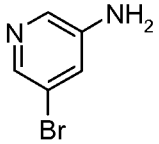
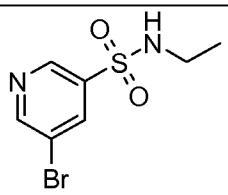
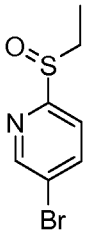
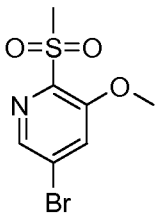
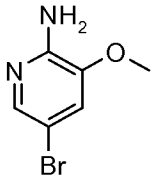
Intermediate #	IA) Aromatic Bromides Structure	Autonom name	Comment on synthesis
IA1		5-Bromo-2-methanesulfonyl-3-methyl-pyridine	1 step from CAS 1289270-74-1
IA2		5-Bromo-3-fluoro-2-methanesulfonyl-pyridine	1 step from CAS 1289007-85-7
IA3		5-Bromo-2-methanesulfonyl-3-trifluoromethyl-pyridine	1 step from CAS 211122-42-8
IA4		5-Bromo-3-difluoromethyl-2-methanesulfonyl-pyridine	2 steps from CAS 852181-11-4

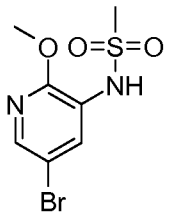
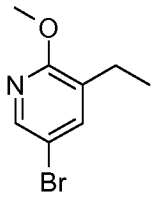
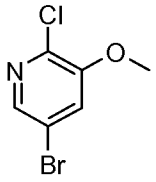
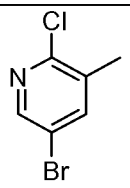
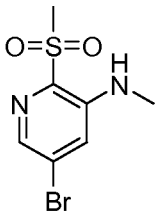
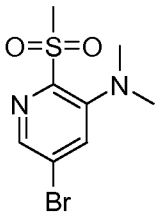
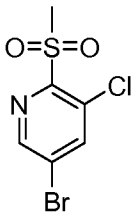
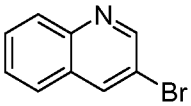
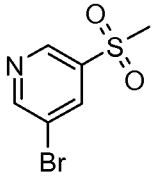
IA5		5-Bromo-3-fluoromethyl-2-methanesulfonyl-pyridine	2 steps from CAS 742100-75-0
IA6		5-Bromo-3-difluoromethyl-2-methoxy-pyridine	CAS 1254123-51-7
IA7		5-Bromo-3-fluoromethyl-2-methoxy-pyridine	1 step from CAS 351410-47-4
IA8		5-Bromo-2-difluoromethoxy-3-methyl-pyridine	CAS 1214337-94-6
IA9		5-Bromo-2-methoxy-3-methyl-pyridine	CAS 760207-87-2
IA10		5-Bromo-3-fluoro-2-methoxy-pyridine	CAS 124432-70-8
IA11		5-Bromo-3-chloro-2-methoxy-pyridine	CAS 848366-28-9
IA12		5-Bromo-2-methoxy-nicotinonitrile	CAS 941294-54-8

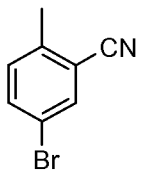
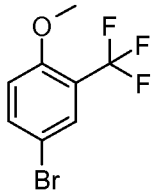
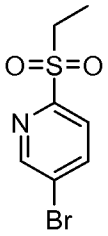
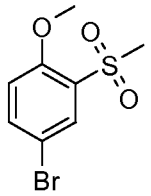
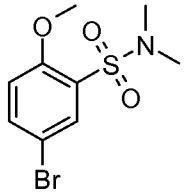
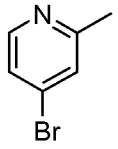
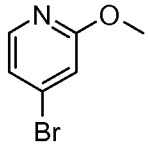
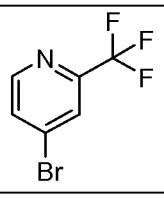
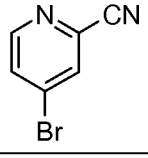
IA13		5-Bromo-pyridine-3-sulfonic acid dimethylamide	CAS 896160-99-9
IA14		4-(5-Bromo-pyridine-3-sulfonyl)-morpholine	CAS 889676-35-1
IA15		5-Bromo-2-methyl-3-nitro-pyridine	CAS 911434-05-4
IA16		5-Bromo-2-methyl-pyridine	CAS 3430-13-5
IA17		5-Bromo-nicotinonitrile	CAS 35590-37-5
IA18		5-bromo-trifluoromethylpyridine	CAS 436799-33-6
IA19		5-Bromo-2-ethoxy-3-methyl-pyridine	CAS 610279-03-3
IA20		5-bromo-2-methoxypyridine	CAS 13472-85-0
IA21		5-bromo-2-methoxy-3-trifluoromethylpyridine	CAS 1214377-42-0

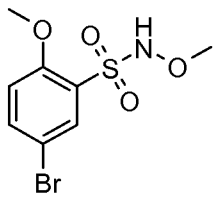
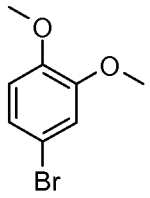
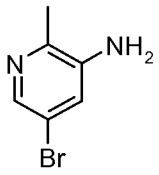
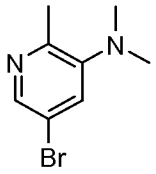
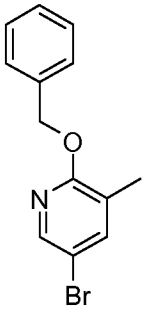
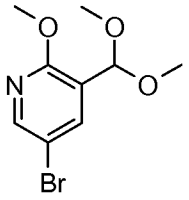
IA22		5-Bromo-2-methoxy-nicotinic acid me thyl ester	CAS 122433-41-4
IA23		2-amino-5-bromo-3-trifluoromethylpyridine	CAS 79456-34-1
IA24		1-(5-Bromo-2-methoxy-pyridine-3-sulfonyl)-4-methyl-piperazine	
IA25		5-Bromo-2-methoxymethyl-pyridine	CAS 1000787-43-8
IA26		5-bromo-2-trifluromethylpyridine	CAS 436799-32-5
IA27		5-Bromo-3-methyl-pyridin-2-ylamine	CAS 3430-21-5
IA28		5-Bromo-pyridine-2-carbonitrile	CAS 97483-77-7
IA29		5-Bromo-2,3-dimethoxy-pyridine	CAS 52605-98-8

IA30		3-Bromo-5-(propane-2-sulfonyl)-pyridine	
IA31		1-(5-Bromo-2-methyl-benzenesulfonyl)-piperidine	CAS 364736-61-8
IA32		4-(5-Bromo-2-methoxy-benzenesulfonyl)-morpholine	CAS 325809-68-5
IA33		4-(5-Bromo-pyridine-3-sulfonyl)-morpholine	CAS 889676-35-1
IA34		1-(5-Bromo-2-methoxy-benzenesulfonyl)-4-methyl-piperazine	CAS 325809-71-0
IA35		1-(5-Bromo-pyridine-3-sulfonyl)-4-methyl-piperazine	CAS 1007212-08-9
IA36		5-Bromo-2,N-dimethoxy-N-methyl-benzenesulfonamide	CAS 1247891-51-5
IA37		5-Bromo-pyridine-3-sulfonic acid methoxy-methyl-amide	CAS 1248282-54-3

IA38		3-Bromo-5-methoxy-pyridine	CAS 50720-12-2
IA39		3-Bromo-5-chloro-pyridine	CAS 73583-39-8
IA40		5-Bromo-2-methanesulfonyl-pyridine	CAS 98626-95-0
IA41		5-Bromo-pyridine-3-sulfonic acid dimethylamide	CAS 896160-99-9
IA42		5-Bromo-pyridin-3-ylamine	CAS 13535-01-8
IA43		5-Bromo-pyridine-3-sulfonic acid ethylamide	CAS 1065074-78-3
IA44		5-Bromo-2-ethanesulfinyl-pyridine	
IA45		5-Bromo-2-methanesulfonyl-3-methoxy-pyridine	
IA46		5-Bromo-3-methoxy-pyridin-2-ylamine	CAS 42409-58-5

IA47		N-(5-Bromo-2-methoxy-pyridin-3-yl)-methanesulfonamide	CAS 1083327-58-5
IA48		5-Bromo-3-ethyl-2-methoxy-pyridine	CAS 1256788-92-7
IA49		5-Bromo-2-chloro-3-methoxy-pyridine	CAS 286947-03-3
IA50		5-Bromo-2-chloro-3-methyl-pyridine	CAS 29241-60-9
IA51		(5-Bromo-2-methanesulfonyl-pyridin-3-yl)-methyl-amine	
IA52		(5-Bromo-2-methanesulfonyl-pyridin-3-yl)-dimethyl-amine	
IA53		5-Bromo-3-chloro-2-methanesulfonyl-pyridine	1335052-54-4
IA54		3-Bromo-quinoline	CAS 5332-24-1
IA55		3-Bromo-5-methanesulfonyl-pyridine	CAS 445491-71-4

IA56		5-Bromo-2-methyl-benzonitrile	CAS 156001-51-3
IA57		4-Bromo-1-methoxy-2-trifluoromethyl-benzene	CAS 1514-11-0
IA58		5-Bromo-2-ethanesulfonyl-pyridine	CAS 223556-06-7
IA59		4-Bromo-2-methanesulfonyl-1-methoxy-benzene	CAS 90531-99-0
IA60		5-Bromo-2-methoxy-N,N-dimethyl-benzenesulfonamide	CAS 871269-16-8
IA61		4-Bromo-2-methyl-pyridine	CAS 22282-99-1
IA62		4-Bromo-2-methoxy-pyridine	CAS 100367-39-3
IA63		4-Bromo-2-trifluoromethyl-pyridine	CAS 887583-90-6
IA64		4-Bromo-pyridine-2-carbonitrile	CAS 62150-45-2

IA65		5-Bromo-2,N-dimethoxy-benzenesulfonamide	
IA66		4-Bromo-1,2-dimethoxy-benzene	CAS 2859-78-1
IA67		5-Bromo-2-methyl-pyridin-3-ylamine	CAS 914358-73-9
IA68		(5-Bromo-2-methyl-pyridin-3-yl)-dimethyl-amine	CAS 1280592-37-1
IA69		2-(Benzyloxy)-5-bromo-3-methylpyridine	CAS 1289270-73-0
IA70		5-Bromo-3-(dimethoxymethyl)-2-methoxypyridine	CAS 351410-59-8

Intermediate IA1: 5-bromo-2-methanesulfonyl-3-methyl-pyridine

A solution of 5-bromo-2-methylsulfanyl-3-methyl-pyridine (9.04 g, 41.4 mmol) in DCM (83 ml) was treated at 0°C with mCPBA (21.46 g, 124 mmol). After stirring for 18 h at rt, the reaction mixture was added to 2N aq. NaOH soln. and was extracted with DCM. The organic layer was dried over Na_2SO_4, concentrated and the title compound was obtained after trituration with cyclohexane to afford a white solid (9.25 g, 89% yield).

UPLC Rt_{M1} =0.81 min; MS (ESI, m/z): 250.1 [$(M+H^+]$]

^1H NMR (400 MHz, DMSO-d_6): δ 8.68 (d, 1H), 8.30 (d, 1H), 3.37 (s, 3H), 2.58 (s, 3H).

Intermediate IA2: 5-bromo-3-fluoro2-methanesulfonyl-pyridine

A solution of 5-bromo-3-fluoro-2-methylsulfanyl-pyridine (222 mg, 1.0 mmol) in DCM (5 ml) was treated at 0 °C with mCPBA (518 mg, 3.0 mmol). After stirring for 1.5 h at rt the reaction mixture was added to 2N aq. NaOH soln. and was extracted with DCM. The organic layer was dried over Na_2SO_4, concentrated and the title compound was obtained as a white solid (241 mg, 95% yield) which was used without further purification.

UPLC Rt_{M1} =0.63 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.75 (d, 1H), 8.60 (d, 1H), 3.40 (s, 3H).

Intermediate IA3: 5-Bromo-2-methanesulfonyl-3-trifluoromethyl-pyridine

A solution of 5-bromo-2-methylsulfanyl-3-trifluoromethyl-pyridine (1.40 g, 1.16 mmol) in DCM (30 ml) was treated at 0°C with mCPBA (2.67 g, 15.48 mmol). After stirring for 18 h at rt the reaction mixture was added to a 4N aq. NaOH soln. and was extracted with DCM. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (hexane / EtOAc, 100:0 to 70:30) as a white solid (940 mg, 60% yield).

UPLC Rt_{M1} =0.87 min; MS (ESI, m/z): 323.0 [$(M+NH_4)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (d, 1H), 8.76 (d, 1H), 3.57 (s, 3H).

.

Intermediate IA4: 5-Bromo-3-difluoromethyl-2-methanesulfonyl-pyridine

a) 2,5-Dibromo-3-difluoromethyl-pyridine

A solution of Et_3N trifluoride (1.80 ml, 11.3 mmol) in DCM (40ml) was treated at 0 °C with Xtalfluor-E (2.67 g, 15.5 mmol) and 2,5-dibromo-pyridine-3-carbaldehyde (1.0 g, 3.77 mmol). After stirring for 19 h at rt the reaction mixture was diluted with TBME and washed with sat. aq. $NaHCO_3$ soln. The organic layer was dried over Na_2SO_4, concentrated to leave a yellow oil (950 mg, 88% yield) which was used without further purification.

UPLC Rt_{M1} =1.05 min;

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (d, 1H), 8.48 (d, 1H), 7.14 (t, 1H), 3.35 (s, 3H).

b) 5-Bromo-3-difluoromethyl-2-methanesulfonyl-pyridine

A solution of 2,5-dibromo-3-difluoromethyl-pyridine (1400 mg, 1.16 mmol) in DMF (10ml) was treated at 0°C with sodium methanethiolate (348 mg, 4.97 mmol). After stirring for 1,5 h at rt, the reaction was cooled at 0°C and mCPBA (2857 mg, 16.56 mmol) was added to the reaction mixture. After stirring for 1 h at rt the reaction mixture was added to a 4N aq. NaOH soln. and was extracted with TBME. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (hexane / EtOAc, 100/0 to 80/20) as a white solid (498 mg, 53% yield).

UPLC Rt_{M1} =0.86 min;

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, 1H), 8.45 (d, 1H), 7.37 (t, 1H), 3.37 (s, 3H).

Intermediate IA5: 5-Bromo-3-fluoromethyl-2-methanesulfonyl-pyridine

a) 5-Bromo-2-chloro-3-fluoromethyl-pyridine

A solution of Et_3N trifluoride (1.76 ml, 10.79 mmol) in DCM (20 ml) was treated at 0°C with Xtalfluor-E (1.65 g, 7.19 mmol) and (5-bromo-2-chloro-pyridin-3-yl)-methanol (0.80 g, 3.60 mmol). After stirring for 18 h at rt the reaction mixture was diluted with TBME and washed with sat. aq. $NaHCO_3$ soln. The organic layer was dried over Na_2SO_4, concentrated and the title compound was obtained after flash chromatography on silica gel (hexane / EtOAc, 100/0 to 90/10) as a colourless oil (286 mg, 35% yield).

UPLC Rt_{M1} =0.98 min;

^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H), 8.45 (d, 1H), 5.52 (d, 1H)

b) 5-Bromo-3-fluoromethyl-2-methanesulfonyl-pyridine

A solution of 2,5-dibromo-3-difluoromethyl-pyridine (1.4 g, 1.16 mmol) in DMF (10 ml) was treated at 0°C with sodium methanethiolate (348 mg, 4.97 mmol). After stirring at rt for 1.5 h, the reaction was cooled down to 0°C and mCPBA (2857 mg, 16.56 mmol) was introduced to the reaction mixture. After stirring for 1 h at rt the reaction mixture was added to an 4N aq. NaOH soln. and was extracted with TBME. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after flash chromatography on silica gel (hexane / EtOAc, 100/0 to 80/20) as a white solid (498 mg, 53%yield)

UPLC Rt_{M1} =0.86 min;

^1H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, 1H), 8.45 (d, 1H), 7.37 (t, 1H), 3.37 (s, 3H).

Intermediate IA7: 5-Bromo-3-fluoromethyl-2-methoxy-pyridine

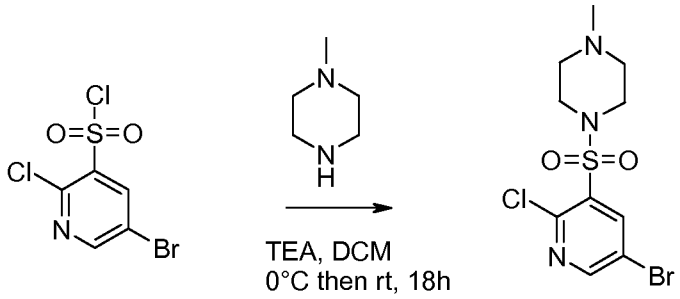
A solution of (5-bromo-2-methoxy-pyridin-3-yl)-methanol (343 mg, 1.57 mmol) in DCM (7 ml) was treated at 0°C with deoxofluor (1.5 ml, 3.46 mmol) and EtOH (27.6 µl, 0.47 mmol). The reaction mixture was stirred at rt, quenched with sat. aq. $NaHCO_3$ soln. and was extracted with DCM. The organic layer was dried over Na_2SO_4, concentrated to afford the title compound after flash chromatography on silica gel (hexane/EtOAc 80:20) as a yellow oil (80 mg, 23%yield).

UPLC Rt_{M1} =1.07 min;

^1H NMR (400 MHz, DMSO-d_6): δ 8.32 (t, 1H), 8.00 (t, 1H), 5.37 (d, 2H), 3.89 (s, 3H).

Intermediate IA24: 1-(5-Bromo-2-methoxy-pyridine-3-sulfonyl)-4-methyl-piperazine

a)(5-Bromo-2-methanesulfonyl-pyridin-3-yl)-methyl-amine

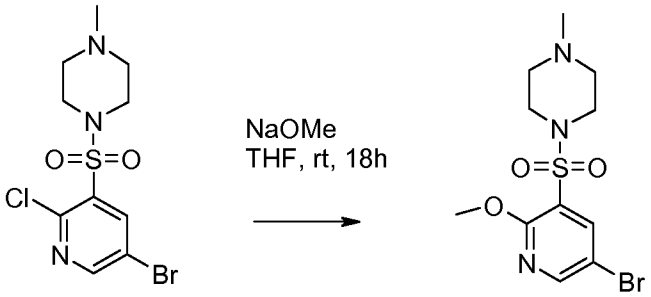


A solution of 5-bromo-2-chloro-pyridine-3-sulfonyl chloride (CAS registry 1146290-19-8) (580 mg, 1.99 mmol) and Et_3N (0.55 ml, 3.99 mmol) in DCM (20 ml) at 0°C was treated with 1-methyl-piperazine (0.33 ml, 2.99 mmol), the resulting mixture was stirred at 0°C for 20 min and at rt for 18 h. The mixture was diluted with DCM (30 ml) and washed with sat.aq. $NaHCO_3$ soln. The organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (DCM / MeOH 100:0 to 90:10) to afford the title compound as an orange solid (420 mg, 59% yield).

HPLC Rt_{M2} =1.49 min; ESIMS: 356 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, 1H), 8.50 (d, 1H), 3.57-3.29 (t, 4H), 2.50 (t, 4H), 2.33(s, 3H).

b)1-(5-Bromo-2-methoxy-pyridine-3-sulfonyl)-4-methyl-piperazine

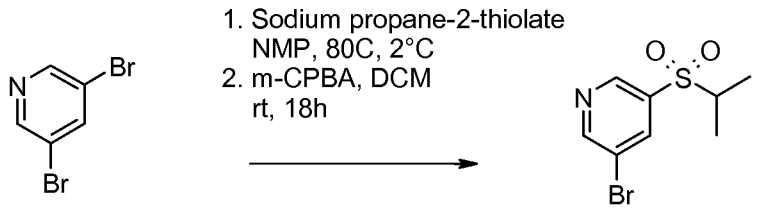


A solution of 1-(5-bromo-2-chloro-pyridine-3-sulfonyl)-4-methyl-piperazine (420 mg, 1.18 mmol) in THF (10 ml) was treated portionwise with sodium methoxide (192 mg, 3.55 mmol). The resulting mixture was stirred at rt for 18 h. The mixture was quenched by addition of water and extracted with EtOAc. The combined organic layers were washed with sat. aq. $NaHCO_3$ soln. and dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (DCM / MeOH 100:0 to 90:10) to afford the title compound (358 mg, 85% yield).

HPLC Rt_{M2} =1.47 min; ESIMS: 350, 352 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, 1H), 8.28 (d, 1H), 4.05 (s, 3H), 3.35 (br s, 4 H), 2.49 (br s, 4 H), 2.33 (s, 3H).

<u>Intermediate IA30:</u> 3-Bromo-5-(propane-2-sulfonyl)-pyridine



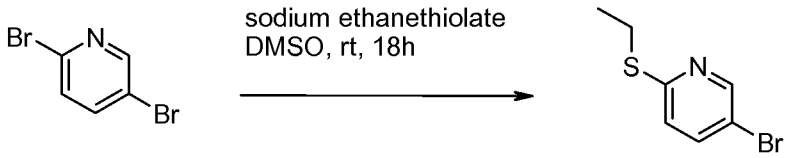
A solution of 3,5-dibromo-pyridine (CAS registry 625-92-3) (495 mg, 2.09 mmol) in NMP (5 ml) was treated with sodium propane-2-thiolate (CAS registry 20607-43-6) (205 mg, 2.09 mmol), the resulting mixture was stirred at 80°C for 2 h. The mixture was cooled down and diluted with EtOAc, washed with water (2x), then brine. The organic layer was dried over $MgSO_4$ and concentrated. The obtained residue was dissolved in DCM (10 ml), treated with mCPBA (1083 mg, 6.27 mmol) and stirred at rt for 18 h.10% aq. sodium sulfite soln. was added and the mixture was stirred at rt for 1 h. The phases were separated and the organic layer was washed with sat. aq. $NaHCO_3$ soln., dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc 100:0 to 00:100) to afford the title compound (364 mg, 59% yield).

HPLC Rt_{M2} =0.77 min; ESIMS: 264, 266 $[(M+H)^+]$.

^1H NMR (400 MHz, $CDCl_3$): δ 8.98 (dd, 2H), 8.33 (t, 1H),3.34-3.17 (m, 1H), 1.37 (d, 6H).

<u>Intermediate IA44:</u> 5-Bromo-2-ethanesulfinyl-pyridine

a)5-Bromo-2-ethylsulfanyl-pyridine



A mixture of 2,5-dibromo-pyridine (CAS registry 588729-99-1) (1.15 g, 4.85 mmol) and sodium ethanthiolate (CAS registry 811-51-8)(2.04 g, 24.27 mmol) in DMSO (15 ml) was stirred at rt for 18 h. Water was added and the mixture was extracted with DCM. The organic layer was dried by passing it through a phase separating cartridge, was concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc 100:0 to 70:30) to afford the title compound as an orange oil (1.09 g, 92% yield).

HPLC Rt_{M2} =1.25 min; ESIMS: 218, 220 $[(M+H)^+]$.

b) 5-Bromo-2-ethanesulfinyl-pyridine



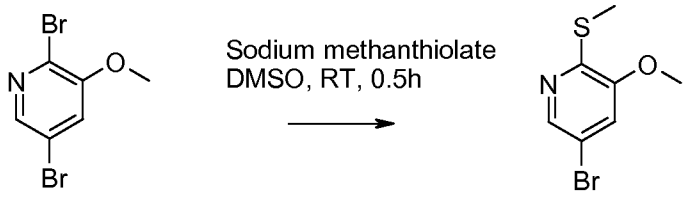
A solution of 5-Bromo-2-ethylsulfanyl-pyridine (1.09 g, 4.49 mmol) in DCM (15 ml) was treated with mCPBA (1.55 g, 8.98 mmol). The resulting solution was stirred at rt for 15 min. The mixture was quenched by addition of aq. 2M NaOH soln., and extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. The compound was purified by prep. RP-HPLC (column SunFire C18 OBD, gradient 5-60% ACN in 15 min) to afford the title compound as a colourless oil (490 mg, 45% yield).

HPLC Rt_{M2} =0.65 min; ESIMS: 234, 236 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6): δ 8.85 (d, 1H), 8.37 (dd, 1H), 7.80 (d, 1H), 3.33 (s, 2H), 3.27-3.10 (m, 1H), 2.94-2.72 (m, 1 H), 1.01 (t, 3 H).

Intermediate IA45: 5-Bromo-2-methanesulfonyl-3-methoxypyridine

a)5-Bromo-3-methoxy-2-methylsulfanyl-pyridine



A mixture of 2,5-dibromo-3-methoxy-pyridine (CAS registry 1142191-57-8) (550 mg, 2.06 mmol) and sodium methanethiolate (CAS registry 5188-07-8)(722 mg, 10.30 mmol) in DMSO (1.5 ml) was stirred at rt for 0.5 h. Water was added and the mixture was extracted with DCM. The organic layer was dried by passing it through a phase separating cartridge and was concentrated to afford the title compound as a colourless oil (1.50 g, 93% yield, crude).

^1H NMR (400 MHz, DMSO-d_6): δ 8.19 (d, 1H), 7.53 (d, 1H), 3.89 (s, 3H), 3.32 (s, 3H).

b) 5-Bromo-2-methanesulfonyl-3-methoxypyridine



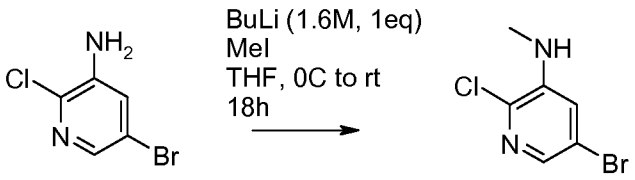
A solution of 5-bromo-3-methoxy-2-methylsulfanyl-pyridine (1.50 g, 2.24 mmol) in DCM (10 ml) was treated with mCPBA (1.55 g, 8.97 mmol). The resulting mixture was stirred at rt for 18 h .The mixture was quenched by addition of aq. 2M NaOH soln., and extracted with DCM. The organic layer was dried by passing through a phase separating cartridge and concentrated to afford the title compound (400 mg, 33% yield as crude).

HPLC Rt_{M2} =0.75 min; ESIMS: 268$[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6): δ 8.41 (d, 1H), 8.17 (s, 1H), 4.01 (s, 3H), 3.30 (s, 3H).

Intermediate IA51: (5-Bromo-2-methanesulfonyl-pyridin-3-yl)-methyl-amine

a) (5-Bromo-2-chloro-pyridin-3-yl)-methyl-amine

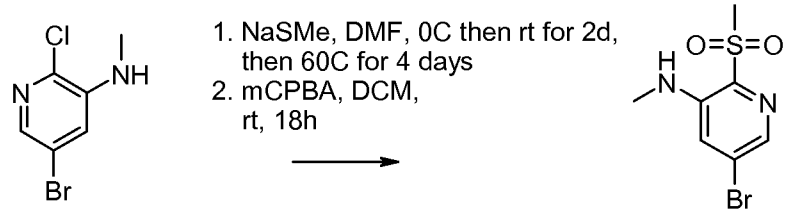


A solution of 5-bromo-2-chloro-pyridin-3-ylamine (CAS registry 588729-99-1) (565 mg, 2.72 mmol) in THF (4 ml) at 0°C was treated with BuLi 1.6M in hexane (0.17 ml, 0.17 mmol), the resulting mixture was stirred at 0°C for 0.5 h, then methyl iodide (0.17 ml, 2.72 mmol) was slowly added. The reaction mixture was allowed to warm to rt and was stirred for 18 h. The orange/brown mixture was poured into sat. aq. $NaHCO_3$ soln., and extracted with EtOAc. The organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc 95:5 to 60:40) to afford the title compound as an orange solid (354 mg, 59% yield).

HPLC Rt_{M1} =0.94 min; ESIMS: 221, 223, 225 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6): δ 7.65 (d, 1H), 7.14 (d, 1H), 6.11 (d, 1H), 2.74 (d, 3H).

b) (5-Bromo-2-methanesulfonyl-pyridin-3-yl)-methyl-amine



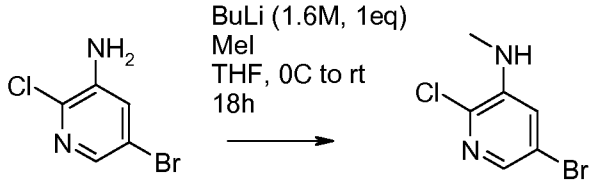
A solution of (5-bromo-2-chloro-pyridin-3-yl)-methyl-amine (354 mg, 1.60 mmol) in DMF (2.6 ml) was treated with sodium methanethiolate (168 mg, 2.40 mmol) at 0°C. The resulting solution was stirred at rt for 2 d and heated at 60°C for 4 d. The mixture was quenched at 0°C by addition of aq. 2M NaOH soln., and extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated to afford an orange oil which was dissolved in DCM (5 ml) and treated at 0°C with mCPBA (CAS registry 937-14-4) (827 mg, 4.79 mmol) and stirred for 18 h at rt. The mixture was quenched at 0°C by addition of aq. NaOH 2M soln. andextracted with DCM. Combined organics were dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc 92:8 to 32:68) to afford the title compound as an orange solid (174 mg, 41% yield).

HPLC Rt_{M1} =0.78 min; ESIMS: 265, 267 $[(M+H)^+]$.

^1H NMR (400 MHz, DMSO-d_6): δ 7.95 (d, 1H), 7.50 (d, 1H), 6.70-6.59 (m, 1H), 3.26 (s, 3H), 2.82 (d, 3H).

Intermediate IA52: (5-Bromo-2-methanesulfonyl-pyridin-3-yl)-dimethyl-amine

a) (5-Bromo-2-chloro-pyridin-3-yl)-methyl-amine

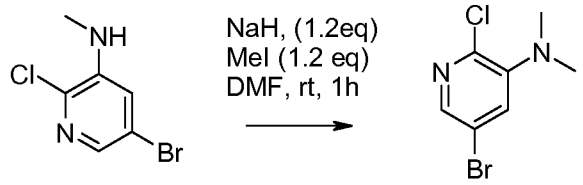


A solution of 5-bromo-2-chloro-pyridin-3-ylamine (CAS registry 588729-99-1) (1 g, 4.82 mmol) in THF (7 ml) at 0°C was treated with BuLi 1.6M in hexane (6 ml, 9.64 mmol), the resulting mixture was stirred at 0°C for 0.5 h, then methyl iodide (0.60 ml, 9.64 mmol) was slowly added. The reaction mixture was allowed to warm at rt and was stirred for 18 h. The orange/brown mixture was poured onto sat. aq. $NaHCO_3$ soln., and extracted with EtOAc, the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc 95:05 to 70:30) to afford the title compound as an orange solid (182 mg, 17% yield).

HPLC Rt_{M1} =0.94 min; ESIMS: 221, 223[$(M+H)^+$].

^1H NMR (400 MHz, DMSO-d_6): δ 7.65 (d, 1H), 7.14 (d, 1H), 6.11 (d, 1H), 2.74 (d, 3H).

b) (5-Bromo-2-chloro-pyridin-3-yl)-dimethyl-amine



A solution of (5-bromo-2-chloro-pyridin-3-yl)-methyl-amine (182 mg, 0.82 mmol) in DMF (4 ml) was treated with NaH (23 mg, 0.99 mmol) at rt, and the mixture was stirred at rt for 0.5 h, methyl iodide (0.06 ml, 0.99 mmol) was added and the resulting mixture was stirred at rt for 1 h. The mixture was diluted with TBME and washed with a sat. aq. $NaHCO_3$ soln., the organic layer was dried over $MgSO_4$ and concentrated to afford the title compound as an orange oil (174 mg, 90% yield). It was used without further purification.

HPLC Rt_{M1} =1.03 min; ESIMS: 235, 237 [$(M+H)^+$].

^1H NMR (400 MHz, DMSO-d_6): δ 8.10 (d, 1H), 7.70 (d, 1H), 2.78 (s, 6H).

c) (5-Bromo-2-methanesulfonyl-pyridin-3-yl)-methyl-amine

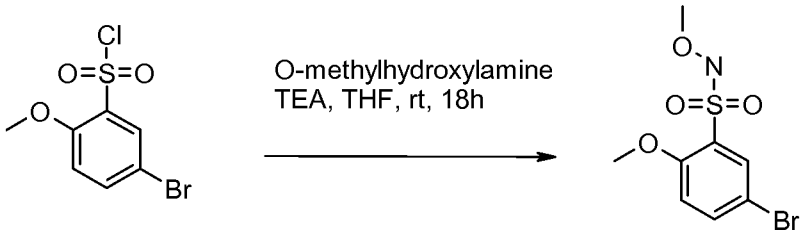


A solution of (5-bromo-2-chloro-pyridin-3-yl)-dimethyl-amine (174 mg, 0.74 mmol) in DMF (5 ml) was treated with sodium methanethiolate (104 mg, 1.48 mmol) at rt, the resulting solution was stirred at 80°C for 18 h. At 0°C, the mixture was quenched by addition of aq. 2M NaOH soln. then extracted with TBME. The combined organic layers were dried over $MgSO_4$ and concentrated to afford an orange oil which was dissolved in DCM (5 ml), treated at 0°C with mCPBA (CAS registry 937-14-4) (382 mg, 2.21 mmol) and stirred for 18 h at rt. At 0°C, the mixture was quenched by addition of aq. 2M NaOH soln., then extracted with DCM. The combined organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc 88:12 to 00:100) to afford the title compound as an orange solid (50 mg, 24% yield).

HPLC Rt_{M1} =0.83 min; ESIMS: 279, 281 [$(M+H)^+$].

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (d, 1H), 7.90 (d, 1H), 3.29 (s, 3H), 2.91 (s, 6H).

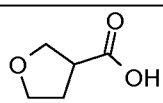
Intermediate IA65: 5-Bromo-2,N-dimethoxy-benzenesulfonamide

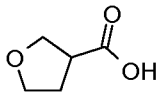
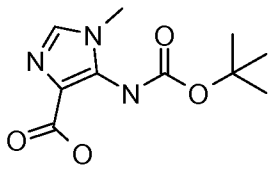


A solution of 5-bromo-2-methoxy-benzenesulfonyl chloride (CAS registry 23095-05-8) (218 mg, 0.76 mmol) and Et_3N (0.55 ml, 3.99 mmol) in DCM (20 ml) at 0°C was stirred for 15 min and treated with O-methylhydroxylamine (36 mg, 0.76 mmol), the resulting mixture was stirred at rt for 18 h. The mixture was partitioned between EtOAc and water. The organic layer was washed with sat.aq. $NaHCO_3$ soln., dried over $MgSO_4$ concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc 100:0 to 0:100) to afford the title compound (189 mg, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, 1 H), 7.78 (s, 1 H), 7.72 (dd, 1 H), 6.97 (d, 1 H), 4.01 (s, 3 H), 3.81 (s, 3 H).

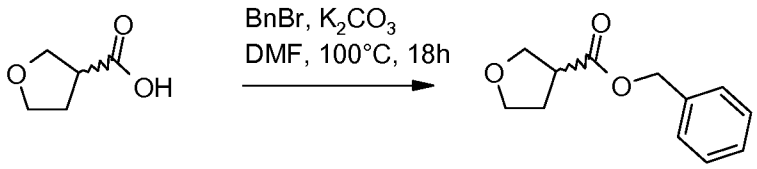
IB) Carboxylic acids or acid chlorides

Intermediate #	IB) Carboxylic acids or acid chlorides Structure	Autonom name
IB1	 enantiomer 1	Tetrahydro-furan-3-carboxylic acid (pure enantiomer)

IB2	 enantiomer 2	Tetrahydro-furan-3-carboxylic acid (pure enantiomer)
IB3		5-tert-butoxycarbonylamino-1-methyl-1H-imidazole-4-carboxylic acid

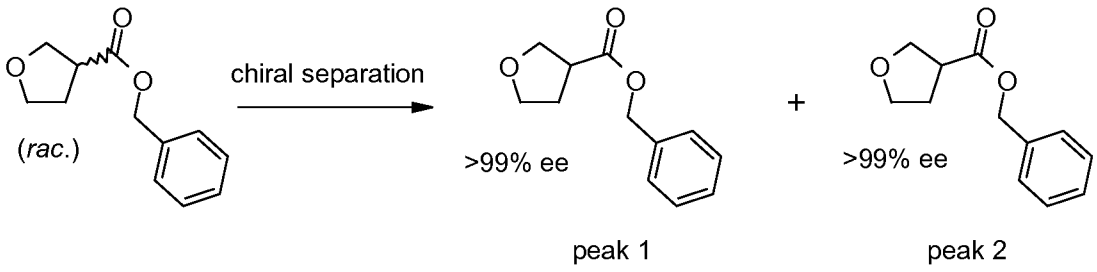
Example IB1/IB2: (S)-Tetrahydro-furan-3-carboxylic acid / (R)-Tetrahydro-furan-3-carboxylic acid

a) Tetrahydro-furan-3-carboxylic acid benzyl ester



A solution of tetrahydro-furan-3-carboxylic acid (CAS registry 89364-31-8) (4.00 g, 34.40 mmol) in DMF (20 ml) was treated with K_2CO_3 (9.52 g, 68.9 mmol) and benzyl bromide (CAS registry 100-39-0) (8.18 ml, 68.9 mmol) at 100°C for 18 h. The mixture was cooled down to rt, diluted with EtOAc, washed with water and brine. Combined organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (cyclohexane / EtOAc 92:8 to 34:66) to afford the title compound as colourless oil (6.93 g, 98% yield)
HPLC Rt_{M2} =0.94 min; ESIMS: 207 [$(M+H)^+$].
^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.26 (m, 5H), 5.17 (m, 2H), 4.05-3.75 (m, 4H), 3.29-3.05(m, 1H), 2.36-2.09 (m, 2H).

b) Enantiomer separation of tetrahydro-furan-3-carboxylic acid benzyl ester



Method information:
Column: Chiralpak AD-PREP
Solvent: HEPTANE/ETOH/MEOH 95/2.5/2.5
Flow: 1.0 ml/min
Long onde: 210 nm
Engine: Agilent 1200 DAD Magellan
Solution EtOH

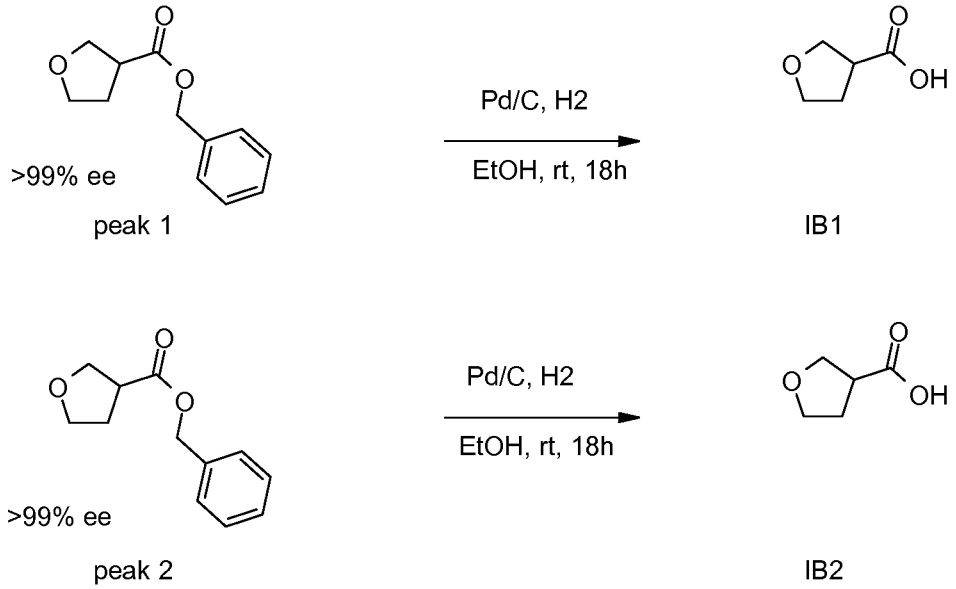
After separation of 6.347 g of racemic, 2 peaks were obtained: peak 1 at 9.086 min (2.43 g, ee>99%) and peak 2 at 10.584 min (2.19 g, ee>99%).

HPLC (peak 1 or 2) Rt_{M2} =0.92 min; ESIMS: 207 [$(M+H)^+$].

^{1}H NMR (peak 1) (400 MHz, $CDCl_3$): δ 7.48-7.29 (m, 5H), 5.23-5.07 (m, 2H), 4.05-3.77 (m, 4H), 3.23-3.10(m, 1H), 2.35-2.06 (m, 2H).

^{1}H NMR (peak 2) (400 MHz, $CDCl_3$): δ 7.51-7.31 (m, 5H), 5.23-5.09 (m, 2H), 4.07-3.77 (m, 4H), 3.24-3.07 (m, 1H), 2.35-2.06 (m, 2H).

c) (S)-Tetrahydro-furan-3-carboxylic acid / (R)-Tetrahydro-furan-3-carboxylic acid

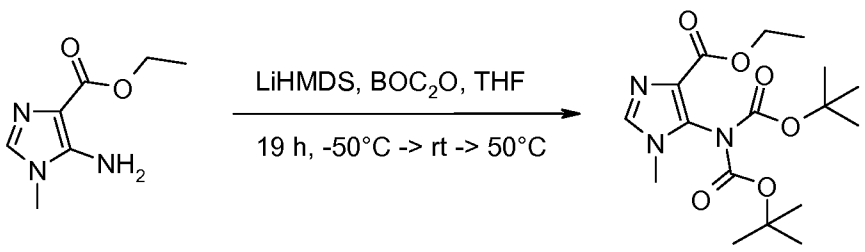


A solution of an enantiomerically pure tetrahydro-furan-3-carboxylic acid benzyl ester (peak 1 or peak 2, 200 mg, 0.97 mmol), Pd/C (103 mg, 0.97 mmol) in EtOH (2 ml) was hydrogenated with H_2 at rt for 18 h. Filtration of the reaction mixture and concentration of the filtrate afforded the title compound as colourless oil (125 mg (Peak 1), 111mg (Peak 2), crude).

^{1}H NMR (both enantiomers) (400 MHz, DMSO-d_6): δ 12.40 (br s, 1H), 3.84-3.59 (m, 4H), 3.00 (m, 1H), 2.08-1.92(m, 1H).

<u>Example IB3):</u> 5-tert-Butoxycarbonylamino-1-methyl-1H-imidazole-4-carboxylic acid

a) 5-di(tert-Butoxycarbonyl)amino-1-methyl-1H-imidazole-4-carboxylic acid ethyl ester



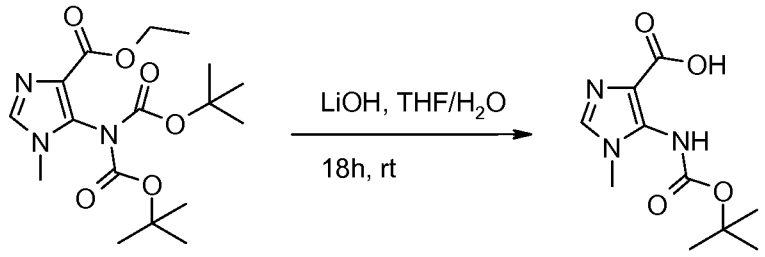
A solution of 5-amino-1-methyl-1H-imidazole-4-carboxylic acid ethyl ester (CAS registry 54147-04-5) (82 mg, 0.49 mmol) in THF (4 ml) was treated at - 50°C with 1M LiHMDS in THF

soln. (0.97 ml, 0.97 mmol) and the reaction mixture was stirred at - 50°C for 10 min, then a solution of Boc_2O (237 mg, 1.07 mmol) in THF (1.5 ml) was added. The reaction mixture was allowed to warm slowly to rt, then to 50°C and to stir for 15 h at 50°C. The reaction mixture was cooled to rt, diluted with EtOAc and quenched with H_2O. The organic layer was dried over Na_2SO_4, filtered, concentrated and the title compound was obtained after after flash chromatography on silica gel (heptane / EtOAc, 85:15 to 0:100) as a white solid (140 mg, 78% yield).

UPLC Rt_{M1} =0.96 min; ESIMS: 370 [$(M+H)^+$]

^1H NMR (400 MHz, $CDCl_3$, 298 K): δ 4.33 (q, 2H), 3.50 (s, 3H), 1.41 (s, 18H), 1.35 (t, 3H).

b) 5-tert-Butoxycarbonylamino-1-methyl-1H-imidazole-4-carboxylic acid



A solution of 5-di(tert-butoxycarbonyl)amino-1-methyl-1H-imidazole-4-carboxylic acid ethyl ester (167 mg, 0.452 mmol) in THF (2.2 ml) and H_2O (2.2 ml) was treated with LiOH (54.1 mg, 2.26 mmol) and the reaction mixture was stirred at rt for 18 h, then quenched with 1M aq. HCl soln. to reach pH 2 and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, concentrated to afford the title compound. (70 mg, 65% yield).

UPLC Rt_{M1} =0.47 min; ESIMS: 242 [$(M+H)^+$]

^1H NMR (400 MHz, DMSO-d_6): δ 12.42 (br.s., 1H), 8.98 (br.s., 1H), 7.82 (s, 1H), 3.45 (s, 3H), 1.41 (s, 9H).

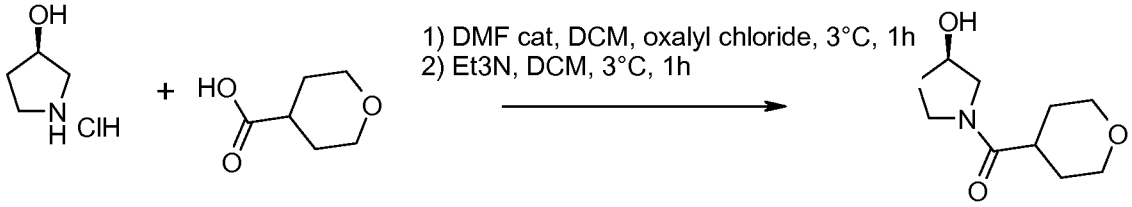
IC) Pyrrolidinol derivatives or analogues

Intermediate #	Autonom name	Used for example #	Comment on synthesis
IC1	Methanesulfonic acid (R) -(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yl ester	**C1**	2 steps from CAS 104706-47-0
IC2	Methanesulfonic acid (S)-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yl ester	**C2**	2 steps from CAS 100243-39-8

IC3	Methanesulfonic acid (S)-1-propionyl-pyrrolidin-3-yl ester	**C3**	2 steps from CAS 100243-39-8
IC4	Methanesulfonic acid (R)-1-propionyl-pyrrolidin-3-yl ester	**C4**	2 steps from CAS 2799-21-5

Intermediate IC1: Methanesulfonic acid (R)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yl ester

a) ((R)-3-Hydroxy-pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone

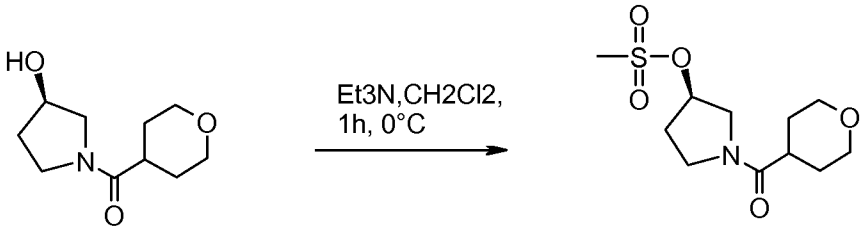


Oxalyl chloride (0.20 ml, 3.84 mmol) was added to a solution of tetrahydro-pyran-4-carboxylic acid (CAS registry 5337-03-1) and DMF (0.012 ml, 0.15 mmol). The reaction mixture was stirred at 3°C for 1 h. Concentration of the reaction mixture under reduced pressure (170 mbar) at 40°C (water bath) afforded the acyl intermediate as a colourless oil. The intermediate was dissolved in DCM (2ml) and added to a solution of (R)-pyrrolidin-3-ol hydrochloride (CAS registry 104706-47-0) (190 mg, 1.54 mmol) in DCM (3 ml), cooled down to 3°C, the formed white suspension was stirred at 3°C for 1 h. The reaction mixture was concentrated; EtOAc was added to the residue which was filtered off and washed with EtOAc. Concentration and purification of the filtrate by flash chromatography on silica gel (DCM /DCM: MeOH (9:1), 100:0 to 60:40 over 11 min) afforded the title compound as white solid (250 mg, 82% yield).

ESIMS: 200 $[(M+H)^+]$.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.43 - 4.65 (m, 1H), 3.95-4.16 (m, 2H), 3.30-3.82 (m, 6H), 2.45-2.75 (m, 1H), 1.83-2.30 (m, 4H), 1.54-1.78 (m, 3H).

b) Methanesulfonic acid (R)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yl ester



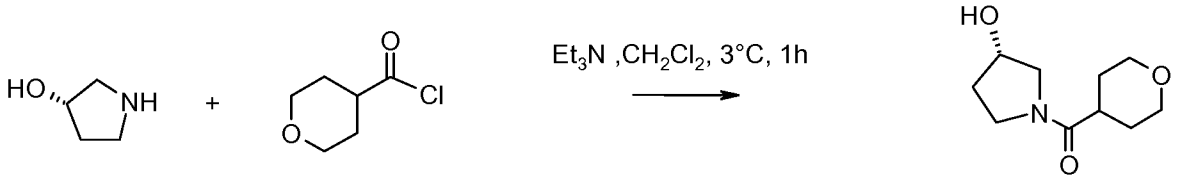
Under argon, methanesulfonyl chloride (CAS registry 124-63-0) (3.52ml, 45.2 mmol) was added to a solution of ((R)-3-hydroxy-pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone (6 g, 22.6 mmol) and Et_3N (6.30 ml, 45.2 mmol) in DCM (100 ml) at -10°C. The solution was stirred at 0°C for 1 h, diluted with H_2O and DCM, the organic layer was washed twice with H_2O and brine and dried over $MgSO_4$. Concentration and trituration of the resulting oil with diethyl ether afforded the title compound as an off-white solid (5.3 g, 84%).

ESIMS: 278 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 5.22-5.44 (m, 1H), 3.96-4.13 (m, 2H), 3.85-3.96 (m, 1H), 3.56-3.83 (m, 3H), 3.36-3.53 (m, 2H), 3.08 (d, 3H), 2.07-2.75 (m, 3H), 1.93 (m, 2H), 1.51-1.75 (m, 3H).

<u>Intermediate IC2</u>: Methanesulfonic acid (S)-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yl ester

a) ((S)-3-Hydroxy-pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone

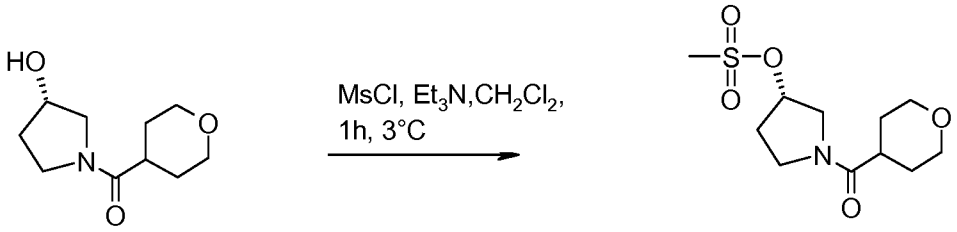


A solution of tetrahydro-pyran-4-carbonyl chloride (CAS registry 40191-32-0) (316 mg, 2.02 mmol) in DCM (2ml) was dropwise added (0°C <T <10°C) to a solution of (S)-pyrrolidin-3-ol (CAS registry 100243-39-8) (250 mg, 2.02 mmol) and Et_3N (0.62 ml, 4.45 mmol) in DCM (5 ml). The reaction mixture was stirred at 3°C for 1 h. The volatiles were concentrated and EtOAc was added to the residue, remaining solid was filtered off and washed with EtOAc, concentration of the filtrate afforded the title compound as a white solid (390 mg, 97% yield).

ESIMS: 200 [$(M+H)^+$].

^1H NMR (400 MHz, $CDCl_3$): δ 4.55 (d, 1H), 3.96-4.11 (m, 2H), 3.36-3.80 (m, 6H), 2.48-2.74 (m, 1H), 1.52-2.20 (m, 7H).

b) Methanesulfonic acid (S)-1-(tetrahydro-pyran-4-carbonyl)-pyrrolidin-3-yl ester



Under argon, methanesulfonyl chloride (CAS registry 124-63-0) (0.23 ml, 2.94 mmol) was added to a solution of ((S)-3-hydroxy-pyrrolidin-1-yl)-(tetrahydro-pyran-4-yl)-methanone (0.39 g, 1.96 mmol) and Et_3N (0.55 ml, 3.91 mmol) in DCM (10 ml) at -10°C. The solution was stirred at 3°C for 1 h, diluted with H_2O and DCM, the organic layer was washed twice with H_2O and brine, then dried over $MgSO_4$. Concentration and trituration of the resulting oil with diethyl ether afforded the title compound as white solid (0.45 g, 83% yield).

ESIMS: 278 [$(M+H)^+$].

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.25-5.44 (m, 1H), 3.99-4.16 (m, 2H), 3.85-3.95 (m, 1H), 3.56-3.83 (m, 3H), 3.37-3.54 (m, 2H), 3.08 (d, 3H), 2.09-2.78 (m, 3H), 1.93 (m, 2H), 1.51-1.76 (m, 2H)

<u>Intermediate IC3</u>: Methanesulfonic acid (S)-1-propionyl-pyrrolidin-3-yl ester

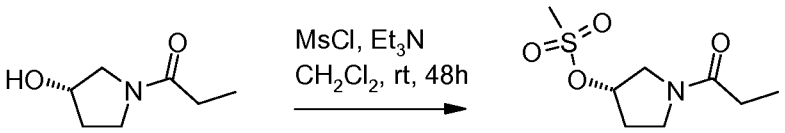
a) 1-((S)-3-Hydroxy-pyrrolidin-1-yl)-propan-1-one



Propionyl chloride (CAS registry 79-03-8) (4.78 ml, 54.8 mmol) was dropwise added over a period of 15 min to a solution of (S)-pyrrolidin-3-ol (CAS registry 100243-39-8) (4.8 g, 55.9 mmol) and Et_3N (8.74 ml, 63.1 mmol) at 5°C, the solution was allowed to warm to rt and was stirred for 1 h. H_2O (10ml) and sat. aq. $NaHCO_3$ soln (10 ml) were added to the solution, the organic phase was washed with brine (10 ml) and a 0.25M aq. HCl soln (20 ml). The combined aqueous layers were concentrated and extracted with EtOAc (2x 100ml), the combined organic phases were dried over $MgSO_4$ and concentrated to afford the title compound as a pale yellow oil (4.80 g, 54% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.54 (d, 1H), 3.31-3.73 (m, 3H), 3.12 (m, 1H), 1.82-2.46 (m, 5H), 1.17 (t, 3H)

b) Methanesulfonic acid (S)-1-propionyl-pyrrolidin-3-yl ester



Under argon, methanesulfonyl chloride (CAS registry 124-63-0) (1.36 ml, 17.46 mmol) was added over a period of 10 min to a solution of 1-((S)-3-hydroxy-pyrrolidin-1-yl)-propan-1-one (2.5 g, 17.4 mmol) and Et_3N (2.43 ml, 17.4 mmol) in DCM (50 ml) at 5°C. The solution was allowed to warm to rt and was stirred for 18 h, methanesulfonyl chloride (CAS registry 124-63-0) (1.36 ml, 17.46 mmol) and Et_3N (2.43 ml, 17.4 mmol) were then added to the reaction mixture which was stirred for 48 h at rt. DCM and H_2O were added to the solution and the organic phase was separated through a phase separation cartridge, concentrated and the title compound was obtained after flash chromatography on silica gel (EtOAc / MeOH 100:0 to 95:5 over 40 min) as a colourless oil (2.7 g, 66% yield).

^1H NMR (400 MHz, $CDCl_3$): δ 5.19-5.42 (m, 1H), 3.48-3.99 (m, 4H), 3.06 (d, 3H). 2.04-2.54 (m, 4H), 1.16 (t, 3H).

<u>Intermediate IC4</u>: Methanesulfonic acid (R)-1-propionyl-pyrrolidin-3-yl ester

a) 1-((R)-3-Hydroxy-pyrrolidin-1-yl)-propan-1-one

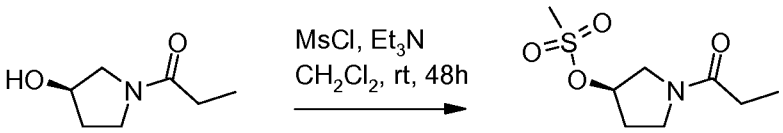


Propionyl chloride (CAS registry 79-03-8) (7.06 ml, 81 mmol) was added (0°C <T <10°C) over a period of 15 min to a suspension of (R)-pyrrolidin-3-ol (CAS registry 2799-21-5) (10 g, 81 mmol) and Et_3N (23.6 ml, 170 mmol) in DCM (150 ml) that was precooled at -10°C. The off-white suspension was stirred at 0°C for 2 h, MeOH (9.82 ml, 243 mmol) was added and the mixture was allowed to stir at rt for 1 h. Concentration and dilution of the residue with Et_2O (200 ml) afforded, after filtration and concentration of the filtrate, the title compound as a yellow oil (11.2 g, 95%).

ESIMS: 144 [$(M+H)^+$].

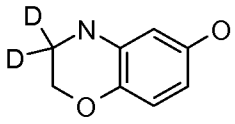
^1H NMR (400 MHz, DMSO-d_6): δ 4.81-5.04 (m, 1H), 4.15-4.38 (m, 1H), 3.35-3.59 (m, 2H), 3.16-3.29 (m, 2H), 2.11-2.33 (m, 2H), 1.65-2.00 (m, 2H), 0.98 (td, 3H).

b) Methanesulfonic acid (R)-1-propionyl-pyrrolidin-3-yl ester



Under argon, methanesulfonyl chloride (CAS registry 124-63-0) (0.16 ml, 2.09 mmol) was dropwise added over a period of 5 min to a solution of 1-((R)-3-hydroxy-pyrrolidin-1-yl)-propan-1-one (300 mg, 2.09 mmol) and Et_3N (0.29 ml, 2.09 mmol) in DCM (10ml) at 5°C, the reaction mixture was allowed to stir at rt for 18 h. Methanesulfonyl chloride (CAS registry 124-63-0) (0.16 ml, 2.09 mmol) and Et_3N (0.29 ml, 2.09 mmol) were then added to the reaction mixture which was stirred at rt for 48 h. DCM and H_2O were added to the solution and the organic phase was separated through a phase separation cartridge and concentrated. The title compound was obtained after flash chromatography on silica gel (EtOAc / MeOH 100:0 to 95:5 over 25 min) as a colourless oil (420 mg, 86%).
^1H NMR (400 MHz, $CDCl_3$): δ 5.21-5.44 (m, 1H). 3.49-4.03 (m, 4H), 2.98-3.12 (m, 3H), 1.97-2.54 (m, 4H), 1.18 (t, 3H).

ID) DBO derivatives or analogues

Intermediate #	ID) DBO derivative or analogue Structure	Autonom name	Comment on synthesis
ID1		3,3-Dideutero-3,4-dihydro-2H-benzo[1,4]oxazin-6-ol	2 steps from CAS 53412-38-7, see Example Q steps a), b)

Biological evaluation

The activity of a compound according to the present invention can be assessed by the following *in vitro & in vivo* methods.

Biological assays

1 Determination of enzymatic PI3K alpha and PI3K delta isoform inhibition

1.1 Test of lipid kinase activity

The efficacy of the compounds of examples 1-117 as PI3 kinase inhibitors can be demonstrated as follows:

The kinase reaction is performed in a final volume of 50 μl per well of a half area COSTAR, 96 well plate. The final concentrations of ATP and phosphatidyl inositol in the assay are 5 μM and 6 μg/mL, respectively. The reaction is started by the addition of PI3 kinase, e.g. PI3 kinase δ.

p110δ. The components of the assay are added per well as follows:

- 10 μl test compound in 5% DMSO per well in columns 2-1.
- Total activity is determined by addition 10 μl of 5% vol/vol DMSO in the first 4 wells of column 1 and the last 4 wells of column 12.
- The background is determined by addition of 10 μM control compound to the last 4 wells of column 1 and the first 4 wells of column 12.
- 2 mL 'Assay mix' are prepared per plate:

  1.912 mL of HEPES assay buffer

  8.33 μl of 3 mM stock of ATP giving a final concentration of 5 μM per well

  1 μl of [^{33}P]ATP on the activity date giving 0.05 μCi per well

  30 μl of 1 mg/mL PI stock giving a final concentration of 6 μg/mL per well

  5 μl of 1 M stock $MgCl_2$ giving a final concentration of 1 mM per well
- 20 μl of the assay mix are added per well.
- 2 mL 'Enzyme mix' are prepared per plate (x* μl PI3 kinase p110β in 2 mL of kinase buffer). The 'Enzyme mix' is kept on ice during addition to the assay plates.
- 20 μl 'Enzyme mix' are added/well to start the reaction.
- The plate is then incubated at room temperature for 90 minutes.

- The reaction is terminated by the addition of 50 μl WGA-SPA bead (wheat germ agglutinin-coated Scintillation Proximity Assay beads) suspension per well.
- The assay plate is sealed using TopSeal-S (heat seal for polystyrene microplates, PerkinElmer LAS [Deutschland] GmbH, Rodgau, Germany) and incubated at room temperature for at least 60 minutes.
- The assay plate is then centrifuged at 1500 rpm for 2 minutes using the Jouan bench top centrifuge (Jouan Inc., Nantes, France).
- The assay plate is counted using a Packard TopCount, each well being counted for 20 seconds.

* The volume of enzyme is dependent on the enzymatic activity of the batch in use.

In a more preferred assay, the kinase reaction is performed in a final volume of 10 μl per well of a low volume non-binding CORNING, 384 well black plate (Cat. No. #3676). The final concentrations of ATP and phosphatidyl inositol (PI) in the assay are 1 μM and 10 μg/mL, respectively. The reaction is started by the addition of ATP.

The components of the assay are added per well as follows:

50 nl test compounds in 90% DMSO per well, in columns 1-20, 8 concentrations (1/3 and 1/3.33 serial dilution step) in single.

- Low control: 50 nl of 90% DMSO in half the wells of columns 23-24 (0.45% in final).
- High control: 50 nl of reference compound (e.g. compound of Example 7 in WO 2006/122806) in the other half of columns 23-24 (2.5 μM in final).
- Standard: 50 nl of reference compound as just mentioned diluted as the test compounds in columns 21-22.
- 20 mL 'buffer' are prepared per assay :

  200 μl of 1M TRIS HCl pH7.5 (10 mM in final)
  60 μl of 1M $MgCl_2$ (3 mM in final)
  500 μl of 2M NaCl (50 mM in final)
  100 μl of 10% CHAPS (0.05% in final)
  200 μl of 100mM DTT (1mM in final)
  18.94 mL of nanopure water

- 10 mL 'PI' are prepared per assay :

  200 μl of 1 mg/mL l-alpha-Phosphatidylinositol (Liver Bovine, Avanti Polar Lipids Cat. No. 840042C MW=909.12) prepared in 3% OctylGlucoside (10 μg/mL in final)

9.8 mL of 'buffer'

- 10 mL 'ATP' are prepared per assay :

  6.7 μl of 3 mM stock of ATP giving a final concentration of 1 μM per well
  10 mL of 'buffer'

- 2.5 mL of each PI3K construct are prepared per assay in 'PI' with the following final concentration :

  10 nM PI3K alfa EMV B1075

  25 nM beta EMV BV949

  10 nM delta EMV BV1060

  150 nM gamma EMV BV950

- 5 μl of 'PI/PI3K' are added per well.
- 5 μl 'ATP' are added per well to start the reaction.
- The plates are then incubated at room temperature for 60 minutes (alfa, beta, delta) or 120 minutes (gamma).
- The reaction is terminated by the addition of 10 μl Kinase-Glo (Promega Cat. No. #6714).
- The assay plates are read after 10 minutes in Synergy 2 reader (BioTek, Vermont USA) with an integration time of 100 milliseconds and sensitivity set to 191.
- Output : The High control is around 60'000 counts and the Low control is 30'000 or lower
- This luminescence assay gives a useful Z' ratio between 0.4 and 0.7

The Z' value is a universal measurement of the robustness of an assay. A Z' between 0.5 and 1.0 is considered an excellent assay.

For this assay, the PI3K constructs mentioned are prepared as follows:

1.2 Generation of gene constructs

Two different constructs, BV 1052 and BV 1075, are used to generate the PI3 Kinase α proteins for compound screening.

PI3Kα BV-1052 p85(iSH2)-Gly linker-p110a(D20aa)-C-term His tag

PCR products for the inter SH2 domain (iSH2) of the p85 subunit and for the p110-a subunit (with a deletion of the first 20 amino acids) are generated and fused by overlapping PCR.

The iSH2 PCR product is generated from first strand cDNA using initially primers gwG130-p01 (5'-CGAGAATATGATAGATTATATGAAGAAT-3') (SEQ ID NO: 1) and gwG130-p02 (5'-TGGTTT-AATGCTGTTCATACGTTTGTCAAT-3') (SEQ ID NO: 2). Subsequently in a secondary PCR reaction, Gateway (Invitrogen AG, Basel, Switzerland) recombination AttB1 sites and linker sequences are added at the 5'end and 3'end of the p85 iSH2 fragment respectively, using primers gwG130-p03 (5'-GGGACAAGTTTGTACAAAAAAGCAGGCTACGAAGGAGATATACATAT-GCGAGAATATGATAGATTATATGAAGAAT -3') (SEQ ID NO: 3) and gwG152-p04 (5'- TACCATAATTCCACCACCACCACCGGAAATTCCCCCTGGTTT-AATGCTGTTCATACGTTTGTCAAT-3') (SEQ ID NO: 4).

The p110-a fragment is also generated from first strand cDNA, initially using primers gwG152-p01 (5'- CTAGTGGAATGTTTACTACCAAATGG-3') (SEQ ID NO: 5) and gwG152-p02 (5'- GTTCAATG-CATGCTGTTTAATTGTGT -3') (SEQ ID NO: 6).

In a subsequent PCR reaction, linker sequence and a Histidine tag are added at the 5'end and 3'end of the p110-a fragment respectively, using primers gw152-p03 (5'-GGGGGAATTTCCGGTGGTGGTGGTGGAATTATGGTAC-TAGTGGAATGTTTACTACC-AAATGGA-3') (SEQ ID NO: 7) and gwG152-p06 (5'-AGCTCCGTGATGGTGATGGTGATGTGCTCCGTTCAATG-CATGCTGTTTAATTGTGT-3') (SEQ ID NO: 8).

The p85-iSH2/p110-a fusion protein is assembled in a third PCR reaction by the overlapping linkers at the 3'end of the iSH2 fragment and the 5'end of the p110-a fragment, using the above mentioned gwG130-p03 primer and a primer containing an overlapping Histidine tag and the AttB2 recombination sequences (5'-GGGACCACTTTGTACAAGAAAGCTGGGTTTAAGCTCCGTGATGGTGATGGTGAT-GTGCTCC-3') (SEQ ID NO: 9).

This final product is recombined in a (Invitrogen) OR reaction into the donor vector pDONR201 to generate the ORF318 entry clone. This clone is verified by sequencing and used in a Gateway LR reaction to transfer the insert into the Gateway adapted pBlueBac4.5 (Invitrogen) vector for generation of the baculovirus expression vector LR410.

PI3Kα BV-1075 p85(iSH2)-12 XGly linker-p110a(D20aa)-C-term His tag

The construct for Baculovirus BV-1075 is generated by a three-part ligation comprised of a p85 fragment and a p110-a fragment cloned into vector pBlueBac4.5. The p85 fragment is derived from plasmid p1661-2 digested with Nhe/Spe. The p110-a fragment

derived from LR410 (see above) as a SpeI/HindIII fragment. The cloning vector pBlueBac4.5 (Invitrogen) is digested with Nhe/HindIII. This results in the construct PED 153.8

The p85 component (iSH2) is generated by PCR using ORF 318 (described above) as a template and one forward primer

KAC1028 (5'- GCTAGCATGCGAGAATATGATAGATTATATGAAGAATATACC) (SEQ ID NO: 10) and two reverse primers,

KAC1029 (5'- GCCTCCACCACCTCCGCCTGGTTTAATGCTGTTCATACGTTTGTC) (SEQ ID NO: 11) and

KAC1039 (5'-TACTAGTCCGCCTCCACCACCTCCGCCTCCACCACCTCCGCC) (SEQ ID NO: 12).

The two reverse primers overlap and incorporate the 12x Gly linker and the N-terminal sequence of the p110a gene to the SpeI site. The 12x Gly linker replaces the linker in the BV1052 construct. The PCR fragment is cloned into pCR2.1 TOPO (Invitrogen). Of the resulting clones, p1661-2 is determined to be correct. This plasmid is digested with Nhe and SpeI and the resulting fragment is gel-isolated and purified for sub-cloning.

The p110-a cloning fragment is generated by enzymatic digest of clone LR410 (see above) with Spe I and HindIII. The SpeI site is in the coding region of the p110a gene. The resulting fragment is gel-isolated and purified for sub-cloning.

The cloning vector, pBlueBac4.5 (Invitrogen) is prepared by enzymatic digestion with Nhe and HindIII. The cut vector is purified with Qiagen (Quiagen N.V, Venlo, Netherlands) column and then dephosphorylated with Calf Intestine alkaline phosphatase (CIP) (New England BioLabs, Ipswich, MA). After completion of the CIP reaction the cut vector is again column purified to generate the final vector. A 3 part ligation is performed using Roche Rapid ligase and the vendor specifications.

<u>PI3Kβ BV-949 p85(iSH2)-Gly linker-p110b(full-length)-C-term His tag</u>

PCR products for the inter SH2 domain (iSH2) of the p85 subunit and for the full-length p110-b subunit are generated and fused by overlapping PCR.

The iSH2 PCR product is generated from first strand cDNA initially using primers gwG130-p01 (5'-CGAGAATATGATAGATTATATGAAGAAT-3') (SEQ ID NO: 1) and gwG130-p02 (5'-TGGTTT-AATGCTGTTCATACGTTTGTCAAT-3') (SEQ ID NO: 2). Subsequently, in a secondary PCR reaction Gateway (Invitrogen) recombination AttB1 sites and linker sequences are added at the 5'end and 3'end of the p85 iSH2 fragment respectively, using primers

gwG130-p03 (5'- GGGACAAGTTTGTACAAAAAAGCAGGCTACGAAGGAGATA-TACATATGCGAGAATATGATAGATTATATGAAGAAT -3') (SEQ ID NO: 3) and

gwG130-p05 (5'-ACTGAAGCATCCTCCTCCTCCTCCTGGTTTAAT-GCTGTTCATACGTTTGTC-3') (SEQ ID NO: 13).

The p110-b fragment is also generated from first strand cDNA initially using primers gwG130-p04 (5'-ATTAAACCAGGAGGAGGAGGAGGAGGATGCTTCAGTTTCATAATGCC-TCCTGCT -3') (SEQ ID NO: 4)

which contains linker sequences and the 5'end of p110-b and gwG130-p06 (5'-AGCTCCGTGATGGTGATGGTGATGTGCTCCAGATCTGTAGTCTTT-CCGAACTGTGTG -3') (SEQ ID NO: 14)

which contains sequences of the 3'end of p110-b fused to a Histidine tag.

The p85-iSH2/p110-b fusion protein is assembled by an overlapping PCR a reaction of the linkers at the 3'end of the iSH2 fragment and the 5'end of the p110-b fragment, using the above mentioned gwG130-p03 primer and a primer containing an overlapping Histidine tag and the AttB2 recombination sequences (5'-GGGACCACTTTGTACAAGAAAGCTGGGTTT-AAGCTCCGTGATGGTGATGGTGATGTGCTCC-3') (SEQ ID NO: 15).

This final product is recombined in a Gateway (Invitrogen) OR reaction into the donor vector pDONR201 to generate the ORF253 entry clone. This clone is verified by sequencing and used in a Gateway LR reaction to transfer the insert into the Gateway adapted pBlueBac4.5 (Invitrogen) vector for generation of the baculovirus expression vector LR280.

<u>PI3Kδ BV-1060 p85(iSH2)-Gly linker-p110d(full-length)-C-term His tag</u>

PCR products for the inter SH2 domain (iSH2) of the p85 subunit and for the full-length p110-d subunit are generated and fused by overlapping PCR.

The iSH2 PCR product is generated from first strand cDNA using initially primers gwG130-p01 (5'-CGAGAATATGATAGATTATATGAAGAAT-3') (SEQ ID NO: 1) and gwG130-p02 (5'-TGGTTT-AATGCTGTTCATACGTTTGTCAAT-3') (SEQ ID NO: 2).

Subsequently, in a secondary PCR reaction Gateway (Invitrogen) recombination AttB1 sites and linker sequences are added at the 5'end and 3'end of the p85 iSH2 fragment respectively, using primers

gwG130-p03 (5'- GGGACAAGTTTGTACAAAAAAGCAGGCTACGAAGGAGATATACAT-ATGCGAGAATATGATAGATTATATGAAGAAT -3') (SEQ ID NO: 3) and gwG154-p04 (5'- TCCTCCTCCTCCTCCTCCTGGTTTAATGCTGTTCATACGTTTGTC -3') (SEQ ID NO: 16).

The p110-a fragment is also generated from first strand cDNA using initially primers gwG154-p01 (5'- ATGCCCCCTGGGGTGGACTGCCCCAT -3') (SEQ ID NO: 17) and gwG154-p02 (5'- CTACTG-CCTGTTGTCTTTGGACACGT -3') (SEQ ID NO: 18).
In a subsequent PCR reaction linker sequences and a Histidine tag is added at the 5'end and 3'end of the p110-d fragment respectively, using primers gw154-p03 (5'- ATTAAACCAGGAGGAGGAGGAGGAGGACCCCCTGGGGTGGAC-TGCCCCATGGA -3') (SEQ ID NO: 19) and gwG154-p06 (5'-AGCTCCGTGATGGTGAT-GGTGATGTGCT-CCCTGCCTGTTGTCTTTGGACACGTTGT -3') (SEQ ID NO: 20).
The p85-iSH2/p110-d fusion protein is assembled in a third PCR reaction by the overlapping linkers at the 3'end of the iSH2 fragment and the 5'end of the p110-d fragment, using the above mentioned gwG130-p03 primer and a primer containing an overlapping Histidine tag and the Gateway (Invitrogen) AttB2 recombination sequences (5'-GGGACCACTTTGTA-CAAGAAAGCTGGGTTT-AAGCTCCGTGATGGTGATGGTGATGTGCTCC-3') (SEQ ID NO: 21).
This final product is recombined in a Gateway (Invitrogen) OR reaction into the donor vector pDONR201 to generate the ORF319 entry clone. This clone is verified by sequencing and used in a Gateway LR reaction to transfer the insert into the Gateway adapted pBlueBac4.5 (Invitrogen) vector for generation of the baculovirus expression vector LR415.

PI3Kγ BV-950 p110g(D144aa)-C-term His tag

This construct is obtained from Roger Williams lab, MRC Laboratory of Molecular Biology, Cambridge, UK (November, 2003). Description of the construct in: Pacold M. E. et al. (2000) Cell 103, 931-943.

1.3 Protein expression and purification

Methods to generate recombinant baculovirus and protein for PI3K isoforms:
The pBlue-Bac4.5 (for a, b, and d isoforms) or pVL1393 (for g) plasmids containing the different PI3 kinase genes are co-transfected with BaculoGold WT genomic DNA (BD Biosciences, Franklin Lakes, NJ, USA) using methods recommended by the vendor. Subsequently, the recombinant baculovirus obtained from the transfection is plaque-purified on Sf9 insect cells to yield several isolates expressing recombinant protein. Positive clones are selected by anti-HIS or anti-isoform antibody western. For PI3K alpha and delta isoforms, a secondary plaque-purification is performed on the first clonal virus stocks of PI3K. Amplification of all baculovirus isolates is performed at low multiplicity of infection (moi) to generate high-titer, low passage stock for protein

production. The baculoviruses are designated BV1052 (α) and BV1075 (α), BV949 (β), BV1060 (δ) and BV950 (γ).

Protein production involves infection (passage 3 or lower) of suspended Tn5 (Trichoplusia ni) or TiniPro (Expression Systems, LLC, Woodland, CA, USA) cells in protein-free media at moi of 2-10 for 39-48 hours in 2 l glass Erlenmyer flasks (110 rpm) or wave-bioreactors (22-25 rpm). Initially, 10 l working volume wave-bioreactors are seeded at a density of 3e5 cells/mL at half capacity (5L). The reactor is rocked at 15 rpm during the cell growth phase for 72 hours, supplemented with 5% oxygen mixed with air (0.2 l per minute). Immediately prior to infection, the wave-reactor cultures are analyzed for density, viability and diluted to approximately 1.5e6 cell/mL. 100-500 mL of high titer, low passage virus is added following 2-4 hours of additional culture. Oxygen is increased to 35% for the 39-48 hour infection period and rocking platform rpm increased to 25. During infection, cells are monitored by Vicell viability analyzer (Beckman Coulter, Inc, Fullerton, CA, USA) bioprocess for viability, diameter and density. Nova Bioanalyzer (NOVA Biomedical Corp., Waltham, MA, USA) readings of various parameters and metabolites (pH, O_2 saturation, glucose, etc.) are taken every 12-18 hours until harvest. The wave-bioreactor cells are collected within 40 hours post infection. Cells are collected by centrifugation (4 degrees C at 1500 rpm), and subsequently maintained on ice during pooling of pellets for lysis and purification. Pellet pools are made with small amounts of cold, un-supplemented Grace's media (w/o protease inhibitors).

PI3K alpha Purification Protocol For HTS (BV1052)

PI3K alpha is purified in three chromatographic steps: immobilized metal affinity chromatography on a Ni Sepharose resin (GE Healthcare, belonging to General Electric Company, Fairfield, CT, USA), gel filtration utilizing a Superdex 200 26/60 column (GE Healthcare), and finally a cation exchange step on a SP-XL column (GE Healthcare). All buffers are chilled to 4ºC and lysis is performed chilled on ice. Column fractionation is performed rapidly at room temperature.

Typically frozen insect cells are lysed in a hypertonic lysis buffer and applied to a prepared IMAC column. The resin is washed with 3-5 column volumes of lysis buffer, followed by 3-5 column volumes wash buffer containing 45 mM imidazole, and the target protein is then eluted with a buffer containing 250 mM imidazole. Fractions are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled and applied to a prepared GFC column. Fractions from the GFC column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled. The pool from the GFC column is diluted into a low salt buffer and applied to a prepared SP-XL column. The column is washed with low salt buffer until a stable A280

baseline absorbance is achieved, and eluted using a 20 column volume gradient from 0 mM NaCl to 500 mM NaCl. Again, fractions from the SP-XL column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing the target protein are pooled. The final pool is dialyzed into a storage buffer containing 50% glycerol and stored at -20°C. The final pool is assayed for activity in a phosphoinosititol kinase assay.

PI3K beta Purification Protocol For HTS (BV949)

PI3K beta is purified in two chromatographic steps: immobilized metal affinity chromatography (IMAC) on a Ni Sepharose resin (GE Healthcare) and gel filtration (GFC) utilizing a Superdex 200 26/60 column (GE Healthcare). All buffers are chilled to 4°C and lysis is performed chilled on ice. Column fractionation is performed rapidly at room temperature.

Typically frozen insect cells are lysed in a hypertonic lysis buffer and applied to a prepared IMAC column. The resin is washed with 3-5 column volumes of lysis buffer, followed by 3-5 column volumes wash buffer containing 45 mM imidazole, and the target protein is then eluted with a buffer containing 250 mM imidazole. Fractions are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled and applied to a prepared GFC column. Fractions from the GFC column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled. The final pool is dialyzed into a storage buffer containing 50% glycerol and stored at -20°C. The final pool is assayed for activity in the phosphoinostitol kinase assay.

PI3K gamma Purification Protocol For HTS (BV950)

PI3K gamma is purified in two chromatographic steps: immobilized metal affinity chromatography (IMAC) on a Ni Sepharose resin (GE Healthcare) and gel filtration (GFC) utilizing a Superdex 200 26/60 column (GE Healthcare). All buffers are chilled to 4°C and lysis is performed chilled on ice. Column fractionation is performed rapidly at room temperature. Typically frozen insect cells are lysed in a hypertonic lysis buffer and applied to a prepared IMAC column. The resin is washed with 3-5 column volumes of lysis buffer, followed by 3-5 column volumes wash buffer containing 45 mM imidazole, and the target protein is then eluted with a buffer containing 250 mM imidazole. Fractions are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled and applied to a prepared GFC column. Fractions from the GFC column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing target protein are pooled. The final pool is dialyzed into a storage buffer

containing 50% glycerol and stored at -20°C. The final pool is assayed for activity in the phosphoinostitol kinase assay.

PI3K delta Purification Protocol For HTS (BV1060)

PI3K delta is purified in three chromatographic steps: immobilized metal affinity chromatography on a Ni Sepharose resin (GE Healthcare), gel filtration utilizing a Superdex 200 26/60 column (GE Healthcare), and finally a anion exchange step on a Q-HP column (GE Healthcare). All buffers are chilled to 4°C and lysis is performed chilled on ice. Column fractionation is performed rapidly at room temperature. Typically frozen insect cells are lysed in a hypertonic lysis buffer and applied to a prepared IMAC column. The resin is washed with 3-5 column volumes of lysis buffer, followed by 3-5 column volumes wash buffer containing 45 mM imidazole, and the target protein is then eluted with a buffer containing 250 mM imidazole. Fractions are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing the target protein are pooled and applied to a prepared GFC column. Fractions from the GFC column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing the target protein are pooled. The pool from the GFC column is diluted into a low salt buffer and applied to a prepared Q-HP column. The column is washed with low salt buffer until a stable A280 baseline absorbance is achieved, and eluted using a 20 column volume gradient from 0 mM NaCl to 500 mM NaCl. Again, fractions from the Q-HP column are analyzed by Coomassie stained SDS-PAGE gels, and fractions containing the target protein are pooled. The final pool is dialyzed into a storage buffer containing 50% glycerol and stored at -20°C. The final pool is assayed for activity in the phosphoinostitol kinase assay.

IC_{50} is determined by a four parameter curve fitting routine that comes along with "excel fit". A four parameter logistic equation is used to calculate IC_{50} values (IDBS XLfit) of the percentage inhibition of each compound at 8 concentrations (usually 10, 3.0, 1.0, 0.3, 0.1, 0.030, 0.010 and 0.003 µM). Alternatively, IC_{50} values are calculated using idbsXLfit model 204, which is a 4 parameter logistic model.

Yet alternatively, for an ATP depletion assay, compounds of the formula I to be tested are dissolved in DMSO and directly distributed into a white 384-well plate at 0.5 µl per well. To start the reaction, 10 µl of 10 nM PI3 kinase and 5 µg/mL 1-alpha-phosphatidylinositol (PI) are added into each well followed by 10 µl of 2 µM ATP. The reaction is performed until approx 50% of the ATP is depleted, and then stopped by the addition of 20 µl of Kinase-Glo solution (Promega Corp., Madison, WI, USA). The

stopped reaction is incubated for 5 minutes and the remaining ATP is then detected via luminescence. IC_{50} values are then determined.

In one embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, wherein the range of activity, expressed as IC_{50}, in the enzymatic PI3K delta assay is from is between 1 nM and 500 nM.

In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, wherein the range of activity, expressed as IC_{50}, in the enzymatic PI3K delta assay is from is between 1 nM and 100 nM.

In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, wherein the range of activity, expressed as IC_{50}, in the enzymatic PI3K delta assay is from is between 0.5nM and 10 nM.

In one embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, wherein the range of activity, expressed as IC_{50}, in the cellular PI3K delta assay is from is between 1 nM and 1000 nM.

In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, wherein the range of activity, expressed as IC_{50}, in the cellular PI3K delta assay is from is between 1 nM and 500 nM.

In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta where the inhibitor shows a selectivity for the PI3K isoform delta over one or more of the other isoforms wherein this selectivity is at least 10 fold.

In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta where the inhibitor shows a selectivity for the PI3K isoform delta over one or more of the other isoforms wherein this selectivity is at least 20 fold.

In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta where the inhibitor shows a selectivity for the PI3K isoform delta over the different paralogs PI3K α and β, wherein this selectivity is at least 10 fold.

In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta where the inhibitor shows a selectivity for the PI3K isoform delta over the different paralogs PI3K α and β, wherein this selectivity is at least 20 fold.

In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, wherein the range of activity, expressed as IC_{50}, in the cellular PI3K delta assay is from is between 1 nM and 500 nM and wherein said inhibitor has an inhibitory action on the PI3K isoform delta where the inhibitor shows a selectivity for the PI3K isoform delta over the different paralogs PI3K α and β, wherein this selectivity is at least 10 fold.

In another embodiment of the present invention, the PI3K inhibitor, wherein said inhibitor has an inhibitory action on the PI3K isoform delta, wherein the range of activity, expressed as IC_{50}, in the cellular PI3K delta assay is from is between 1 nM and 500 nM and wherein said inhibitor has an inhibitory action on the PI3K isoform delta where the inhibitor shows a selectivity for the PI3K isoform delta over the different paralogs PI3K α and β, wherein this selectivity is at least 20 fold.

2. Cellular assays

2.1 Phosphoinositide-3 kinase (PI3K)-mediated Akt 1/2 (S473) phosphorylation in Rat-1 cells

Rat-1 cells stably overexpressing a myristoylated form of the catalytic subunit of human phosphoinositide-3 kinase (PI3K) alpha, beta or delta were plated in 384-well plates at a density of 7500 (PI3K alpha), 6200 (PI3K beta), or 4000 (PI3K delta) cells in 30ul complete growth medium (Dulbecco's modified Eagle's medium (DMEM high glucose) supplemented with 10% (v/v) fetal bovine serum, 1% (v/v) MEM non essential amino acids, 10mM HEPES, 2mM L-glutamine, 10 µg/mL puromycin and 1% (v/v) Penicillin/Streptomycin) and were incubated at 37%C / 5%CO_2 / 95% humidity for 24h. Compounds were diluted in 384-well compound plates to obtain 8-point serial dilutions for 40 test compounds in 90% DMSO, as well as 4 reference compounds plus 16 high controls and 16 low (inhibited) controls. Predilution plates were prepared by dispensing pipetting 250 nl of compound solutions into 384-well polypropylen plates using a Hummingwell nanoliter dispensor . Compounds were prediluted by the addition of 49.75 ul complete growth medium. 10ul of prediluted compound solution were transferred to the cell plate using a 384-well pipettor, resulting in a final DMSO concentration of 0.11%.

Cells were incubated for 1 h at 37%C / 5%CO_2 / 95% humidity. The supernatant was removed, the cells were lysed in 20ul of lysis buffer for AlphaScreen® *SureFire*® detection.

For detection of p-AKT(Ser473), the *SureFire*® p-Akt 1/2 (Ser473) Assay Kit (PerkinElmer, U.S.A) was used. 5ul of cell lysate was transferred to 384-well low volume Proxiplates for detection using a 384-well pipettor. Addition of AlphaScreen® *SureFire*® reagents was done according to the manufacturer's protocol. First, 5ul of reaction buffer plus activation buffer mix containing AlphaScreen® acceptor beads was added, the plate was sealed, and incubated on a plate shaker for 2 hours at room temperature. Second, 2ul of dilution buffer containing AlphaScreen® donor beads was added, and the plate was incubated on plate shaker as above for a further 2 hours. The plate was read on an AlphaScreen® compatible plate reader, using standard AlphaScreen® settings.

2.2 Determination of murine B cell activation

PI3Kδ has been recognized to modulate B cell function when cells are stimulated through the B cell receptor (BCR) (Okkenhaug et al. Science 297:1031 (2002). For assessing the inhibitory property of compounds on B cell activation, the upregulation of activation markers CD86 and CD69 on murine B cells derived from mouse spleen antibody is measured after stimulation with anti-IgM. CD69 is a well known activation marker for B and T cells (Sancho et al. Trends Immunol. 26:136 (2005). CD86 (also known as B7-2) is primarily expressed on antigen-presenting cells, including B cells . Resting B cells express CD86 at low levels, but upregulate it following stimulation of e.g. the BCR or IL-4 receptor. CD86 on a B cell interacts with CD28 on T cells. This interaction is required for optimal T cell activation and for the generation of an optimal IgG1 response (Carreno et al. Annu Rev Immunol. 20:29 (2002)).

Spleens from Balb/c mice are collected, splenocytes are isolated and washed twice with RPMI containing 10% foetal bovine serum (FBS), 10 mM HEPES, 100 Units/mL penicilline/streptomycine. RPMI supplemented in this way is subsequently referred to as medium. The cells are adjusted to 2.5 X 10^6 cells/mL in medium and 200 µl cell suspension (5 x10^6cells) are added to the appropriate wells of 96 well plates.

Then the cells are stimulated by adding 50 µl anti-IgM mAb in medium (final concentration: 30 µg/mL). After incubation for 24 hours at 37°C, the cells are stained with the following antibody cocktails: anti-mouse CD86-FITC, anti-mouse CD69-PerCP-Cy5.5, anti-mouse CD19-PerCP for the assessment of B cells, and anti-mouse CD3-FITC, anti-mouse CD69-PE for the assessment of T cells (2 µl of each antibody/well). After one hour at room temperature (rt) in the dark the cells are transferred to 96

Deepwell plates. The cells are washed once with 1 mL PBS containing 2% FBS and after re-suspension in 200 µl the samples are analyzed on a FACS Calibur flow cytometer. Lymphocytes are gated in the FSC/SSC dot plot according to size and granularity and further analyzed for expression of CD19, CD3 and activation markers (CD86, CD69). Data are calculated from dot blots as percentage of cells positively stained for activation markers within the CD19+ or CD3+ population using BD CellQest Software.

For assessing the inhibitory property of compounds, compounds are first dissolved and diluted in DMSO followed by a 1:50 dilution in medium. Splenocytes from Balb/c mice are isolated, re-suspended and transfered to 96 well plates as described above (200 µl/well). The diluted compounds or solvent are added to the plates (25 µl) and incubated at 37°C for 1 hour. Then the cultures are stimulated with 25 µl anti-IgM mAb/well (final concentration 30 µg/mL) for 24 hours at 37°C and stained with anti-mouse CD86-FITC and anti-mouse CD19-PerCP (2 µl of each antibody/well). CD86 expression on CD19 positive B cells is quantified by flow cytometry as described above.

2.3 Determination of rat B cell activation

PI3Kδ has been recognized to modulate B cell function when cells are stimulated through the B cell receptor (BCR) (Okkenhaug et al. Science 297:1031 (2002). For assessing the inhibitory property of compounds on B cell activation, the upregulation of activation markers CD86 on rat B cells derived from whole blood is measured after stimulation with anti-IgM and recombinant IL-4. The CD86 molecule (also known as B7-2) is primarily expressed on antigen-presenting cells, including B cells. Resting B cells express CD86 at low levels, but upregulate it following stimulation of e.g. the BCR or IL-4 receptor. CD86 on a B cell interacts with CD28 on T cells. This interaction is required for optimal T cell activation and for the generation of an optimal IgG1 response (Carreno et al. Annu Rev Immunol. 20:29 (2002)).

Collection of rat blood

Whole blood was collected from the abdominal aorta adult male Lewis rats (LEW/HanHsd) oby using a 10 ml syringe with hypodermic needle pre-coated with sodium heparin. Blood was transferred into 50 ml Falcon tubes and the anticoagulant concentration was adjusted to 100 U/ml.

Stimulation of rat B cells and treatment with specific inhibitor

For assessment of the *in vitro* effects of immunosuppressive drugs, heparinized blood was prediluted to 50% with medium. As medium served DMEM high glucose (Animed cat# 1-26F01-I) supplemented with 100 U/ml penicillin, 100 mg/ml streptomycin, 2 mM L-glutamin,

50 mg/ml dextran 40 and 5% fetal calf serum (FCS, Fetaclone I, Gibco #10270-106). Then, 190 µl prediluted blood was spiked with 10 µl of pre-diluted test compound in 96 well U-bottomed microtiter plates (Nunc) resulting in a 3-fold serial dilution with a concentration range from 20 to 0.0003 µM. Control wells were pretreated with DMSO to obtain a final concentration of 0.5% DMSO. Cultures were set up in duplicates, mixed well by agitation on a plate shaker (Heidolph Titramax 101; 30 sec, speed 900), pipetting up and down and agitated on the plate shaker again. Cultures were incubated at 37°C, 5% CO_2 for 1 hr. Then, 20 µl of polyclonal goat anti-rat IgM Ab (Serotec, cat# 302001) and 10 µl of diluted recombinant rIL-4 (Immunotools # 340085) were added to obtain final concentrations of 30 µg/ml and 5 ng/ml, respectively. Plates were mixed by agitation on a plate shaker as above and incubated for 24 hrs at 37°C, 5% CO_2.

Determination of B cell activation by flow cytometry

After incubation, 15 µl of a 25 mM EDTA solution was added per well and shaken for 15 min to detach adherent cells. For analysis of surface activation markers, samples were then stained with PE-Cy5-labeled anti-ratCD45RA (BD cat# 557015) to allow gating on B cells in FACS analysis. In addition, samples were stained with PE-labeled anti-rat CD86 (BD cat# 551396). All staining procedures were performed at rt for 30 min in the dark. After incubation, samples were transferred to 96-deep well V-bottomed microtiter plates (Corning # 396096) containing 2 ml/well of BD Lysing Solution (BD # 349202). After lysis of erythrocytes samples were washed with 2 ml of CellWASH (BD # 349524). Data was acquired on an LSRII or FACScalibur flow cytometer (BD Biosciences) using Cellquest Plus or DIVA (version 6.1.1) software, respectively. Lymphocytes were gated in the FSC/SSC dot blot according to size and granularity and further analyzed for expression of CD45RA and activation markers. Data were calculated from dot blots or histograms as percentage of cells positively stained for activation markers within the CD45RA+ population.

Statistical evaluation

The percentage inhibition of B cell activation after exposure to drug was calculated by the following formula:

$$\% \text{ Inhibition} = 100 \text{ x } \frac{\text{stimulation without drug} - \text{stimulation with drug}}{\text{stimulation without drug} - \text{unstimulated}}$$

ORIGIN 7 software (OriginLab Corporation, Northampton, MA) was used for non-linear regression curve fitting. The drug concentration resulting in 50% inhibition (IC_{50}) was obtained by fitting the Hill equation to inhibition data.

2.4 Determination of TLR9-induced IL-6 in mouse splenocytes

Preparation of single cell suspension from mouse spleen

Spleens were dissected from C57BL/6 mice immediately following euthanasia. Excess fat was trimmed from the spleens prior to mashing the spleen through a 0.4 µM cell strainer using a plunger from a 5 ml syringe. A single cell suspension was prepared and the volume was adjusted to 15 ml in a 50 ml Falcon tube using cold PBS. Cells were centrifuged at 1500 rpm for 5 minutes at 4°C degrees prior to removal of supernatant and re-suspension in 5 ml of red blood cell lysis buffer per spleen and incubation for 5 minutes at room temperature. Ice cold PBS (30 ml) was added to the cells prior to centrifugation at 1500 rpm for 5 minutes at 4°C. The supernatant was removed and the cells were washed twice with 40 ml of murine splenocyte culture media (MSCM). MSCM consisted of RPMI supplemented with 100 units/ml Penicillin and 100 µg/ml Streptomycin, 1 x nonessential amino acids, 1 mM Sodium Pyruvate, 0.05 mM β-mercaptoethanol, and 10% heatinactivated Fetal Bovine Serum (FBS). Cells were re-suspended in 10-20 ml of MSCM and counted using a Countess cell counter. Approximately $60x10^6$ splenocytes were obtained from a single C57BL/6 mouse spleen.

Stimulation of murine splenocytes and treatment with specific inhibitor

Splenocytes were plated at a final density of $2x10^5$ cells/well in a volume of 100 µl in 96 well flat bottomed plates and incubated in a humidified 37°C incubator for 2-4 hours. Afterwards, compounds to be tested were dispensed using an automated liquid handling machine using previously prepared compound stock plates. Stock plates consisted of compounds (in 90%/10% DMSO/ddH_20) arrayed in 8-10 point using 2- or 3-fold dilutions. The liquid handling machine dispensed 1 µl of each dilution from the previously prepared compound source plate into the appropriate destination well in the 96-well plate. The final starting concentration of the compounds in the cell culture was 10 µM. The final concentration of DMSO in the cell cultures was 0.5%. Cells were incubated with compounds for 1 hour prior to addition of TLR ligand. Then, a 10x EC_{80} concentration of CpG1826 was added in a volume of 20 µl (for a final culture volume of 200 µl) whereupon cultures were incubated overnight in a humidified 37°C incubator.

Determination of Interleukin-6 by ELISA

After overnight culture, plates were centrifugated at 2000 rpm for 5 minutes at room temperature. Subsequently 150 µl of each culture was transferred to 96-well V-bottomed plates and IL-6 levels were measured using commercially available mouse IL-6 sandwich ELISA kit. Briefly, plates were coated overnight with the capture antibody prior to blocking for 1 hour with PBS/0.1% BSA. Samples and standards were added in a volume of 50 µl and the plate was incubated for 2 hours at room temperature. After removal of the standards/samples, the plate was washed using PBS/0.05% Tween prior to addition of 50 µl of the biotinylated detection antibody whereupon the plate was incubated for 2 hours at room temperature with agitation. Plates were washed again prior to addition of 50 µl streptavidin-horseradish peroxidase per well for 20 minutes. Following additional plate washes 50 µl TMB

substrate was added to each well and plates were incubated for 20 minutes prior addition of 25 µl/well stop solution. IL-6 levels were measured using a SpectraMax 190 Plate Reader (450 nm) and analyzed using SoftMax Pro and GraphPad Prism software.

2.5 Determination of TLR9-induced IFNalpha in human peripheral blood mononuclear cells (PBMC)

Preparation of PBMC from fresh human blood

Human blood (ca. 75 ml) was collected in 10 S-Monovette tubes containing Heparin (S-Monovette 7.5 mL NH Heparin 16 IU/mL blood; Starstedt). Leucosep™ tubes (30 mL #227290; Greiner Bio-one) were prepared by addition of 15 ml lymphocyte separation medium LSM1077™ per tube (#J15-004; PAA Laboratories) and centrifugation for 30 sec at 1000g. Some 25 ml blood was transferred to Leucosep™ tubes following dilution with equal parts of PBS (without Ca2+/Mg2+; #14190-094). Samples were centrifuged at 800g for 20 min at 22 °C using an Eppendorf 5810R centrifuge without brake. The PBMC layer was carefully removed from plasma:separation medium interface and transferred into clean 50 ml tube. Cells were washed once by addition of PBS (up to 45 ml) and centrifuged (1400rpm, 10 min at 22 °C) with brake (set at speed 9) using an Eppendorf 5810R. Pelleted cells were carefully resuspended in Media (RPMI 1640+GlutaMAX-I, 0.05 mM 2-mercaptoethanol, 10 mM HEPES and 5% v/v FCS) and samples pooled. The medium components 2-mercaptoethanol (#31350-010; 50 mM), Hepes (#15630-056, 1M) and RPMI 1640 (1x) + GlutaMAX-I (#61870-010) were obtained from Gibco. FCS (#2-01F36-1) was obtained from Amimed. The PBMC were counted using a Countess® Automated cell counter (sample was pre-diluted 1:10 in Media, prior to the addition of equal volume (10 µl) of Trypan Blue). Cells were diluted to 4 x 10^6 cells/ml and seeded in 384-well plates (#353962; Becton Dickinson AG) to give a final volume of 25 µl (i.e. 1 x 10^5 cells/well).

Stimulation of PBMC and treatment with specific inhibitor

Compounds were pre-diluted in 100% v/v DMSO (#41640-100mL; Sigma-Aldrich), followed by transfer in Media (to achieve a final DMSO concentration of 0.25%). Cells were treated with appropriate compound dilution (5 µl) or vehicle control (5 µl) and incubated for 30 min at 37 °C in a humidified incubator in air with 5% (v/v) CO_2. Cells were stimulated with CpG2216 (0.3 µM; #tlrl-hodna; Invivogen) or vehicle control (10 µl/well) and incubated for 20 h. Plates were briefly centrifuged (200 x g for 2 min at 22 °C) and supernatant samples (30 µl) removed for quantification of IFNα levels.

Quantification of IFNα using AlphaLisa technology

For quantification of IFNalpha the human interferon AlphaLISA Kit (#AL264F) from PerkinElmer was used. An antibody mix containing anti-IFNα acceptor beads (5 µg/ml final) and biotinylated antibody anti-IFNα (0.5 nM final) is prepared fresh and dispensed (5 µl) into 384-well Optiplates™ (#6007299; PerkinElmer). Dilution of known IFNα standards (human

IFNα B (2b)) were prepared and together with cell supernatants (5 µl) were added to plates above. Plates were briefly centrifuged (pulse at 200g), covered with adhesive sealing film, vortexed and incubated 1 h at room temperature in the dark. Streptavidin-coated donor beads (20 µg/ml final) was prepared and added to each well (5 µl) in a dark lit area (light sensitive mix). Plates were incubated 30 min at room temperature (Pates must not be centrifuged or covered). After incubation, the plates were read with an EnVision™ multiplate reader equipped with the ALPHA option using the instrument's own "AlphaScreen standard settings" (e.g. total measurement time: 550 ms, Laser 680 nm excitation time: 180 ms, mirror: D640 as, emission filter: M570w, center wavelength 570 nm, bandwidth 100 nm, transmittance 75%). Data were collected for analysis and quantification of IFNα levels.

Data evaluation and analysis

Data were analysed using Excel XL fit 4.0 (Microsoft) with XLfit add-in (IDBS; version 4.3.2). Specific IFNα concentrations were determined following extrapolation to standard curves using human IFNα B (2b). Individual IC_{50} values of compounds were determined by nonlinear regression after fitting of curves to the experimental data.

3 Determination of antibody production to sheep red blood cells (SRBC).

In brief, OFA rats were injected i.v. with sheep erythrocytes on d0 and treated orally on four consecutive days (d0 to d3) with the compounds under investigation. Spleen cell suspensions were prepared on d4 and lymphocytes were plated onto soft agar in presence of indicator cells (SRBC) and complement. Lysis of the indicator cells due to secretion of SRBC-specific antibody (predominantly of the IgM subclass) and presence of complement yielded plaques. The number of plaques per plate were counted and expressed as number of plaques per spleen.

Immunization: Groups of five female OFA rats were immunized on day 0 with $2x10^8$/ml SRBC (obtained from Laboratory Animal Services LAS, Novartis Pharma AG) in a volume of 0.5ml per rat by i.v. injection.

Compound treatment: Animals were treated with compound suspended in 0.5% CMC, 0.5%Tween80 in for 4 consecutive days (days 0, 1, 2 and 3) starting on the day of immunization. Compound was administered orally twice daily with 12 hours intervalls between doses in an application volume of 5 ml/kg body weight.

Preparation of spleen cell suspensions:

On day 4, animals were euthanized with CO_2. Spleens were removed, weighed, and deposited in plastic tubes containing 10 ml of cold (4 °C) Hank's balanced salt solution (HBSS; Gibco, pH 7.3, containing 1mg Phenolred/100ml) for each rat spleen. Spleens were homogenized with a glass potter, left on ice for 5 minutes and 1 ml supernatant

was transferred into a new tube. Cells were washed once in 4 ml HBSS then supernatants were discarded and pellets re-suspended in 1 ml of HBSS. Lymphocyte numbers per spleen were determined by automated cell counter and spleen cell suspensions were adjusted to a cell concentration of $30x10^6$/ml.

Plaque forming assay:

Soft agar petri dishes were prepared with 0.7% agarose (SERVA) in HBSS.

In addition, one ml of 0.7% agarose was prepared in plastic tubes and kept at 48°C in a water bath. Some 50 µl of a $30x10^6$/ml spleen cell suspension and 50 µl of SRBC at 40 x 10^8/ml were added, mixed rapidly (Vortex) and poured onto the prepared agarose dishes. Petri dishes were slightly tilted to achieve even distribution of cell mixture on agarose layer. The dishes were left at room temperature for 15 minutes and were then incubated at 37°C for 60 minutes. Then, 1.4ml guinea pig complement (Harlan; 10%) was added and the incubation continued for another 60 minutes at 37 °C. SRBC-specific antibodies released by the plated-out B cells bound to the antigen (SRBC) in their vicinity. These antigen-antibody complexes activated complement and led to the lysis of the SRBC leaving a bright spot (plaque) within the red erythrocyte layer. Plaques were counted with a microscope.

The following formula for determination of inhibition of plaque formation was used:

%Inhibition = C*100/V-100

with: V= mean number of plaques/spleen for vehicle group; C= mean number of plaques/spleen for compound treated group

References:

N.K. Jerne & A.A. Nordin (1963) Plaque formation in agar by single antibody-producing cells. Science 140:405.

N.K. Jerne, A.A. Nordin & C. Henry (1963) The agar plaque technique for recognizing antibody-producing cells. In: "Cell Bound Antibodies", B. Amos & H. Koprowski, Eds., Wistar Inst. Press, Philadelphia pp.109-125.

Biological data

Enzymatic Assay

Example	PI3K alpha (uM)	PI3K delta (uM)
A1	0.322	0.006
A2	0.047	0.006
A3	0.313	0.003
A4	> 9.1	
A5	4.663	0.037
A6	0.377	0.009

A7	1.915	0.031
A8	5.928	0.04
A9	0.410	0.014
A10	0.220	0.018
A11	2.279	0.069
A12	0.182	0.003
A13	0.292	0.005
A14	> 9.1	5.399
A15	4.892	0.184
A16	> 9.1	0.323
A17	0.104	0.014
A18	0.895	0.011
A19	7.547	0.38
A20	> 9.1	
A21	8.429	
A22	0.757	0.021
A23	1.573	0.17
A24	6.878	0.317
A25	5.755	
A26	0.152	0.022
A27	> 9.1	
A28	0.531	0.016
A29	2.730	0.042
A30	0.260	0.031
A31	6.022	0.088
A32	3.195	0.074
A33	1.702	0.085
A34	0.773	0.009
A35	5.589	1.419
A36	1.269	0.078
A37	0.370	0.078
A38	0.343	0.064
A39	0.071	0.009
A40	5.361	0.462
A41	2.794	0.296
A42	1.141	0.03

A43	4.689	0.054
B1	0.390	0.014
B2	1.641	0.026
B3	> 9.1	
B4	1.234	0.083
B5	0.236	0.025
B6	2.242	0.11
B7	3.544	0.114
B8	0.188	0.025
B9	1.770	0.078
B10	0.870	0.035
B11	0.823	0.014
B12	0.365	0.011
B13	0.862	0.062
B14	0.244	0.006
B15	2.647	0.031
B16	4.117	0.037
B17	2.087	0.023
B18	0.723	0.012
B19	1.158	0.033
B20	0.339	0.047
B21	0.666	0.013
B22	0.589	0.005
B23	1.004	0.028
B24	0.212	0.008
B25	0.665	0.04
B26	0.281	< 0.009
B27	2.507	0.055
B28	0.788	0.012
B29	0.558	0.041
B30	0.216	0.0155
B31	0.977	0.003
B32	0.369	0.036
B33	0.610	< 0.009
B34	0.795	0.046
B35	1.387	0.027

B36	0.801	< 0.003
B37	1.104	0.103
B38	0.166	0.003
B39	0.176	0.011
B40	0.249	0.012
B41	0.421	0.025
B42	0.502	0.033
B43	0.514	0.057
B44	0.071	0.022
B45	0.574	0.0745
B46	2.076	0.2265
B47	0.241	0.0106667
B48	0.109	0.007
B49	0.450	0.007
B50	0.933	0.013
B51	1.026	0.01
B52	0.556	< 0.003
B53	0.343	0.0045
B54	0.756	0.011
B55	3.850	0.065
B56	1.415	0.023
B57	2.270	0.095
B58	0.366	0.004
B59	0.461	0.017
B60	0.463	0.011
B61	0.732	0.037
B62	0.496	0.041
B63	1.518	0.068
B64	0.193	0.032
B65	0.795	0.035
B66	0.446	0.011
B67	0.804	0.025
B68	0.840	0.039
B69	0.189	0.005
B70	0.134	0.003
B71	0.360	0.0055

B72	2.057	0.032
B73	1.771	0.03
B74	0.054	0.009
B75	0.211	0.011
B76	0.399	0.061
B77	0.897	0.032
B78	0.243	0.023
B79	0.661	0.003
B80	0.295	0.004
B81	0.482	0.081
B82	0.353	0.066
B83	0.214	0.029
B84	0.346	0.08
B85		
B86	6.626	0.061
B87	7.092	0.029
B88	0.234	0.008
B89	0.133	0.009
B90	1.456	0.011
B91	0.353	0.012
B92	0.346	0.008
B93	0.525	0.004
B94	0.416	0.005
B95	0.438	0.009
B96	> 9.1	0.118
B97	0.476	0.0215
B98	0.910	0.013
B99	0.302	0.057
B100	0.567	0.014
B101	0.471	0.015
B102	0.209	0.01025
B103	0.241	0.046
B104	1.374	0.162
B105	0.762	0.02
B106	0.247	0.017
B107	0.239	0.004

B108	0.094	< 0.003
B109	0.118	< 0.003
B110	0.148	0.003
B111	0.685	0.06
B112	0.38	0.026
B113	2.73	0.109
B114	1.440	0.071
B115	0.468	0.023
B116	0.304	0.022
B117	1.212	0.008
B118	0.498	0.01
B119	0.124	0.006
B120	0.088	0.006
B121	3.357	0.075
B122	0.425	0.024
C1	0.300	0.0190
C2	1.218	0.243
C3	3.377	1.207
C4	3.001	0.028
C5	5.510	0.095
C6	4.259	0.181
C7	> 9.1	
C8	0.374	0.013
C9	0.185	0.006
C10	0.147	0.015
C11	0.353	0.023
C12	0.303	0.116
C13	0.667	0.077
C14	0.250	0.005
C15	0.383	0.017
C16	0.478	0.015
C17	0.358	0.008
C18	0.425	0.012
C19	0.488	0.021
C20	0.193	0.006
C21	0.698	0.028

C22	0.202	0.02
C23	0.658	0.032
C24	0.560	0.003
C25	0.474	0.0125
C26	6.946	3.219
D1	0.424	0.005
D2	2.743	0.149
D3	4.418	0.219
D4	0.236	
D5	0.802	0.042
D6	0.650	0.009
D7	0.234	
D8	0.463	0.011
D9	0.494	0.015
D10	0.385	0.062
D11	0.442	0.019
D12	0.142	< 0.003
D13	0.5225	0.005
D14	0.415	
D15	0.711	0.058
D16	0.503	0.007
D17	0.705	0.012
D18	0.281	0.019
D19	0.273	0.013
D20	0.206	0.007
D21	0.519	0.041
D22	1.018	0.024
D23	2.534	0.214
D24	> 9.1	7.085
D25	> 9.1	2.693
D26	1.236	0.028
D27	1.574	0.064
D28	0.411	0.005
D29	0.534	0.003
D30	5.150	0.127
D31	0.135	0.009

D32	0.094	0.009
D33	0.117	0.008
D34	0.273	0.009
D35	0.414	< 0.003
D36	0.346	
D37	0.298	0.127
D38	0.516	0.018
D39	0.987	0.036
D40	0.7045	0.025
E1	0.098	0.004
E2		
E3	0.494	< 0.003
E4	0.870	0.010
E5		
E6	0.341	0.009
E7	0.133	0.022
E8		
E9	0.593	0.007
E10	0.229	0.013
E11	0.377	< 0.003
F1	0.109	0.003
F2	0.725	0.005
F3	0.337	0.006
F4	0.577	0.003
F5	0.444	0.025
F6	0.783	0.003
F7	0.071	< 0.003
F8	0.038	0.005
F9	0.028	< 0.003
F10	0.039	< 0.003
F11	0.078	0.076
F12	0.440	< 0.003
F13	0.704	0.024
G1	0.049	0.017
G2	1.195	0.207
G3	0.372	0.056

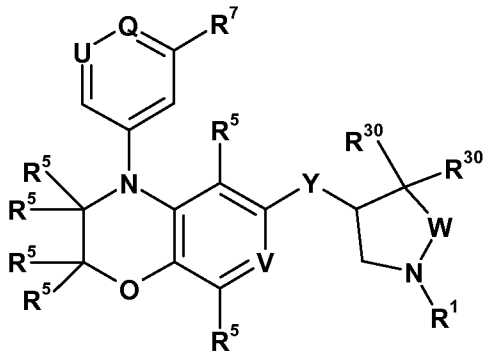
H1	0.850	0.008
H2	0.913	0.013
H3	0.559	0.008
H4	0.8475	0.011
H5	0.477	0.011
H6	0.846	0.053
H7	0.703	0.005
H8	0.521	0.007
H9	0.616	0.011
H10	0.727	0.018
H11	0.299	0.008
H12	0.530	0.007
H13	0.387	0.009
H14	0.103	0.005
H15	0.724	0.008
H16	0.871	0.016
I1	0.842	0.018
I2	0.308	0.005
I3	0.836	0.006
J	0.998	0.065
K	0.393	< 0.003
L	0.538	0.013
M	0.304	0.006
N	0.838	0.012
O1	4.574	0.053
O2	5.692	0.049
P	0.954	0.072
Q	1.144	0.014
R	0.602	0.011
S	0.612	0.036
T	1.876	0.076
U	0.192	0.015
V	3.196	0.079
W	2.979	0.056
X	3.575	0.061
Y	1.925	

Cellular Assays

Example	Cell PI3Kδ / IC50 [umol l-1]	RWB/ IC50 CD86 [nmol l-1]
A1	0.043	37
B1	0.154	29
C1	0.081	68
D1	0.147	84
E1	0.007	78
E3	0.018	14
F1	0.011	7
F3	0.050	
F7	0.018	40
Q	0.145	37

Claims:

1. A compound of formula (I)



(I)

or a salt thereof, wherein

Y is selected from O or NH;

V is selected from CR^5 or N;

W is selected from CH_2, or O;

U is selected from N or CH;

Q is selected from N or CR_6;

wherein U and Q are not both N;

R^1 is selected from phenyl, pyridyl, pyrimininyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl,

or

-X-R^4

wherein X is selected from C(O), $S(O)_2$ or CH_2

and

R^4 is selected from C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, cyano-C_1-C_8-alkyl, N,N-di-C_1-C_4-alkyl-amino-C_1-C_8-alkyl, C_1-C_4-alkyl-sulfonyl-C_1-C_8-alkyl, phenyl, heterocyclyl, heterocyclyl-oxy, heterocyclyl-C_1-C_8-alkyl, C_3-C_{12}-cycloalkyl, C_3-C_{12}-cycloalkyl-oxy, C_3-C_{12}-cycloalkyl-C_1-C_8-alkyl, heteroaryl, heteroaryl-oxy, heteroaryl-C_1-C_8-alkyl, hydroxy, C_1-C_8-alkoxy, amino, N-C_1-C_8-alkyl-amino or N,N-di-C_1-C_8-alkyl-amino,

wherein C_1-C_8-alkyl in N-C_1-C_8-alkyl-amino and in N,N-di-C_1-C_8-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy,

wherein C_3-C_{12}-cycloalkyl in C_3-C_{12}-cycloalkyl and in C_3-C_{12}-cycloalkyl-C_1-C_8-alkyl may be unsubstituted or substituted by by 1-5 substituents selected from halogen, hydroxy or C_1-C_4-alkoxy;

wherein 'heterocyclyl' is a 3 to 7 membered saturated or partially unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, each of which is unsubstituted or substituted by 1-5 substituents selected from oxo, halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states,

wherein 'heteroaryl' is a 3 to 7 membered fully unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, or pyrazolo[1,5-a]pyrimidine or imidazo[2,1-b]thiazole, each of which is unsubstituted or substituted by 1-5 substituents selected from halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;

R^6 is selected from hydrogen, halogen, C_1-C_4-alkyl, halo-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkyl-sulfonyl, C_1-C_4-alkyl-sulfinyl, C_1-C_4-alkyl-sulfanyl, halo-C_1-C_4-alkoxy, C_1-C_4-alkoxy-C_1-C_4-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino;

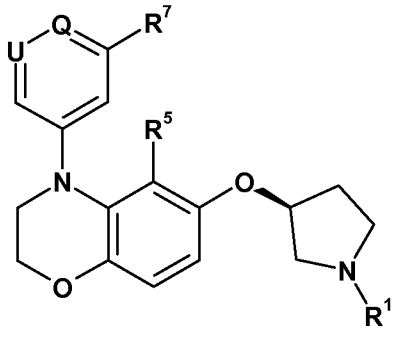
R^7 is selected from hydrogen, halogen, cyano, nitro, C_1-C_4-alkyl, halo-C_1-C_4-alkyl, C_1-C_4-alkoxy, N(R^8)$_2$-sulfonyl, C_1-C_4-alkyl-sulfonyl, C_1-C_4-alkyl-sulfonyl-amino, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, or N,N-di-C_1-C_8-alkyl-amino;
or R^6 and R^7, together are CH=CH-CH=CH,

wherein R^8 is independently selected from hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or two R^8 together with the nitrogen they are attached to form a 4 to 7 membered heterocyclic ring containing 1-2 heteroatoms selected from N, O, S, which is unsubstituted or substituted by 1-3 substituents selected from C_1-C_4-alkyl;

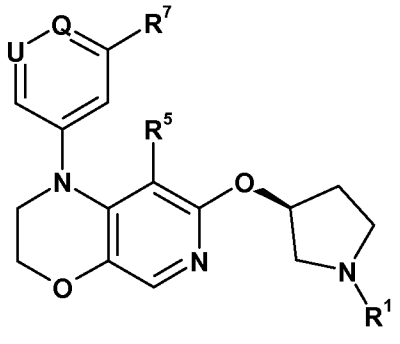
R^5 is independently selected from H, D, F or C_1-C_2-alkyl;

R^{30} is independently selected from H, D or F.

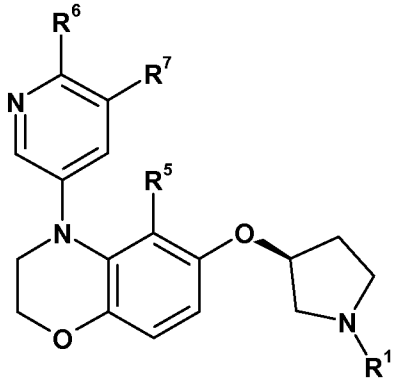
2. A compound according to claim 1 or a salt thereof, of the formula (Ic')


(Ic').

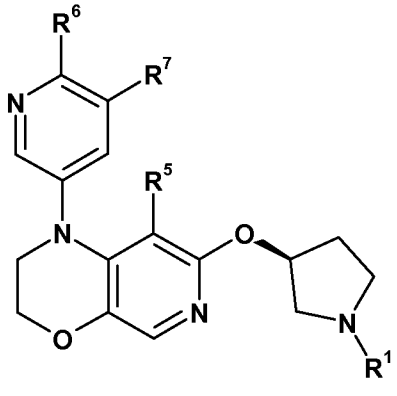
3. A compound according to claim 1 or a salt thereof, of the formula (Id')


(Id').

4. A compound according to any one of claim 1 or 2 or a salt thereof, of the formula (Ie')


(Ie').

5. A compound according to claim 1 or 3 or a salt thereof, of the formula (If')



(If').

6. A compound according to any one of claims 1 to 5 or a salt thereof, wherein

R^1 is selected from phenyl, pyridyl, pyrimininyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl,

or

-X-R^4, wherein

R^4 is selected from C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, cyano-C_1-C_8-alkyl, N,N-di-C_1-C_4-alkyl-amino-C_1-C_8-alkyl, C_1-C_4-alkyl-sulfonyl-C_1-C_8-alkyl, phenyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, C_3-C_{12}-cycloalkyl, heteroaryl, heteroaryl-C_1-C_8-alkyl, C_1-C_8-alkoxy, wherein C_1-C_8-alkyl in N-C_1-C_8-alkyl-amino and in N,N-di-C_1-C_8-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy,

wherein C_3-C_{12}-cycloalkyl in C_3-C_{12}-cycloalkyl and in C_3-C_{12}-cycloalkyl-C_1-C_8-alkyl may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy;

wherein 'heterocyclyl' is a 3 to 7 membered saturated or partially unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, which is unsubstituted or substituted by 1-5 substituents selected from oxo, halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states,

wherein 'heteroaryl' is a 3 to 7 membered fully unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, or pyrazolo[1,5-a]pyrimidine or imidazo[2,1-b]thiazole, each of which is unsubstituted or substituted by 1-5 substituents selected from halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl,

amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states.

7. A compound according to any one of claims 1 to 6 or a salt thereof, wherein

R^1 is selected from

-X-R^4, wherein

R^4 is selected from C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, cyano-C_1-C_8-alkyl, N,N-di-C_1-C_4-alkyl-amino-C_1-C_8-alkyl, C_1-C_4-alkyl-sulfonyl-C_1-C_8-alkyl, phenyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, C_3-C_{12}-cycloalkyl, heteroaryl, heteroaryl-C_1-C_8-alkyl, C_1-C_8-alkoxy, wherein C_1-C_8-alkyl in N-C_1-C_8-alkyl-amino and in N,N-di-C_1-C_8-alkyl-amino may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy,

wherein C_3-C_{12}-cycloalkyl in C_3-C_{12}-cycloalkyl and in C_3-C_{12}-cycloalkyl-C_1-C_8-alkyl may be unsubstituted or substituted by halogen, hydroxy or C_1-C_4-alkoxy;

wherein 'heterocyclyl' is a 3 to 7 membered saturated or partially unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, which is unsubstituted or substituted by 1-5 substituents selected from oxo, halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heterocyclyl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states,

wherein 'heteroaryl' is a 3 to 7 membered fully unsaturated monocyclic ring system containing 1 to 3 heteroatoms selected from N, O or S, or pyrazolo[1,5-a]pyrimidine or imidazo[2,1-b]thiazole, each of which is unsubstituted or substituted by 1-5 substituents selected from halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, hydroxy-C_1-C_8-alkyl, hydroxyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino, N-C_1-C_8-alkyl-amino, N,N-di-C_1-C_8-alkyl-amino, C_1-C_8-alkyl-carbonyl, halo-C_1-C_8-alkyl-carbonyl, hydroxy-C_1-C_8-alkyl-carbonyl or C_1-C_8-alkoxy-C_1-C_8-alkyl-carbonyl; wherein 'heteroaryl' can be attached at a heteroatom or a carbon atom and where the N and/or S heteroatoms can also optionally be oxidized to various oxidation states;

R^6 is selected from halogen, C_1-C_4-alkoxy, C_1-C_4-alkyl-sulfonyl or halo-C_1-C_4-alkoxy and R^7 is selected from hydrogen, halogen, cyano, C_1-C_4-alkyl, halo-C_1-C_4-alkyl or C_1-C_4-alkoxy.

8. A compound of claim 1 in crystalline form.

9. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use as a medicament.

10. A combination comprising a therapeutically effective amount of a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, and one or more therapeutically active co-agents.

11. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder or a disease selected from rheumatoid arthritis (RA), pemphigus vulgaris (PV), endemic form of Brazilian pemphigus (Fogo selvagem), idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune hemolytic anemia (AIHA), acquired hemophilia type A (AHA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis (MG), Sjögren‘s syndrome (SS), ANCA-associated vasculitides, cryoglobulinemia, chronic autoimmune urticaria (CAU), allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, transplant rejection, cancers of haematopoietic origin, severe and cerebral malaria, trypanosomiasis, leishmaniasis, toxoplasmosis and neurocysticercosis.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

13. A method of modulating the activity of the PI3K enzymes, preferably of the PI3Kδ isoform , in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof.

14. A method of treating a disorder or a disease selected from rheumatoid arthritis (RA), pemphigus vulgaris (PV), endemic form of Brazilian pemphigus (Fogo selvagem),idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune hemolytic anemia (AIHA), acquired hemophilia type A (AHA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis (MG), Sjögren's syndrome (SS), ANCA-associated vasculitides, cryoglobulinemia, chronic autoimmune urticaria (CAU), allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, transplant rejection, cancers of haematopoietic origin, severe and cerebral malaria, trypanosomiasis, leishmaniasis, toxoplasmosis and neurocysticercosis comprising administering to a subject a therapeutically effective amount of a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof.

15. Use of a compound according to anyone of claims 1 to 8, or a pharmeceutically acceptable salt therof, in the manufacture of a medicament for the treatment of a disorder or a disease selected from rheumatoid arthritis (RA), pemphigus vulgaris (PV), endemic form of Brazilian pemphigus (Fogo selvagem), idiopathic thrombocytopenia purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune hemolytic anemia (AIHA), acquired hemophilia type A (AHA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis (MG), Sjögren's syndrome (SS), ANCA-associated vasculitides, cryoglobulinemia, chronic autoimmune urticaria (CAU), allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), goodpasture's syndrome, transplant rejection, cancers of haematopoietic origin, severe and cerebral malaria, trypanosomiasis, leishmaniasis, toxoplasmosis and neurocysticercosis.

Figure 1

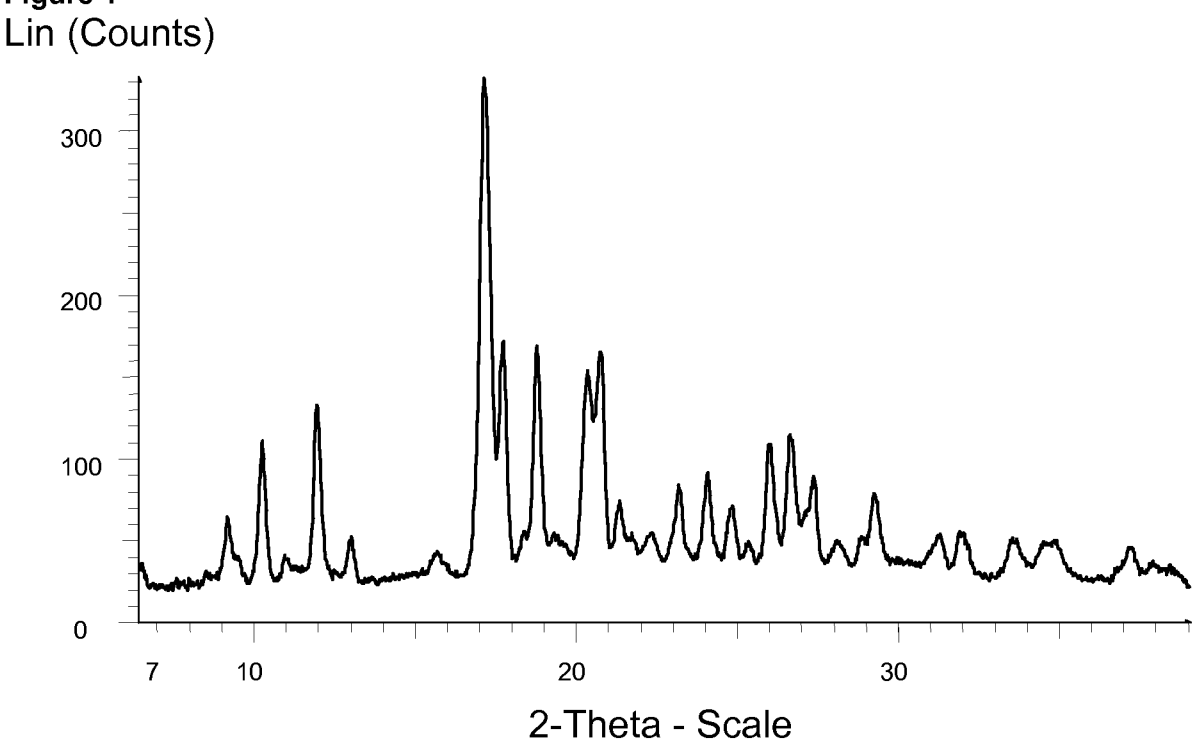
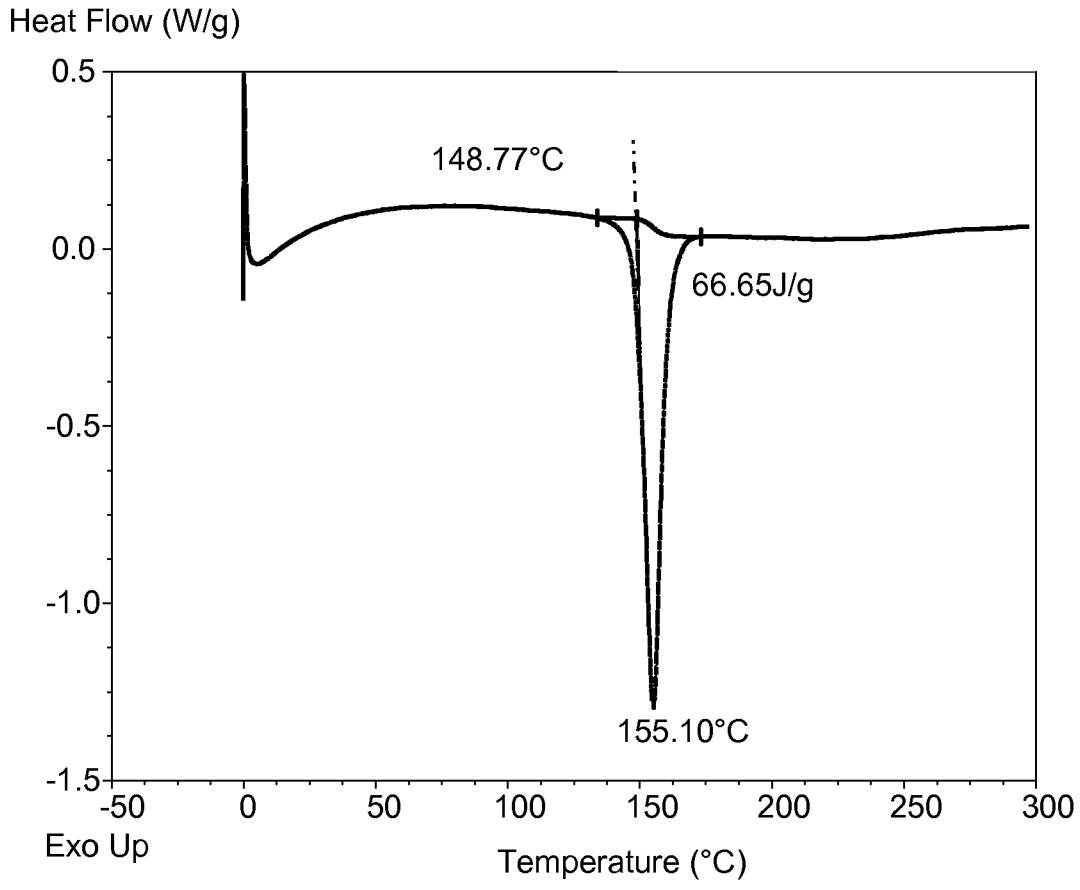


Figure 2



5

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/057554

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 C07D498/04 A61K31/536 A61K31/5365
ADD. A61P19/02 A61P37/08 A61P35/00 A61P33/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/044022 A1 (UCB PHARMA SA [BE]) 17 April 2008 (2008-04-17) claims 1,10 -----	1-15

☐ 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
11 April 2013	18/04/2013

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	Cortés, José

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/057554

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008044022 A1	17-04-2008	EP 2076512 A1	08-07-2009
		US 2010069361 A1	18-03-2010
		WO 2008044022 A1	17-04-2008

(12) SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (TCP)

(19) Organización Mundial de la Propiedad Intelectual
Oficina Internacional

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(10) Número de Publicación Internacional
PCT **WO 2013/093849 A1**

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C07D 498/04 (2006.01) ***A61P 37/08*** (2006.01)
A61K 31/536 (2006.01) ***A61P 35/00*** (2006.01)
A61K 31/5365 (2006.01) ***A61P 33/06*** (2006.01)

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20 de diciembre de 2012 (20.12.2012)

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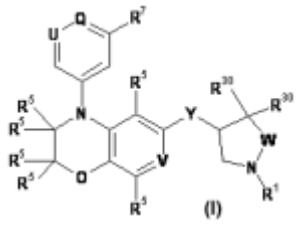
(81) Estados (Países) Designados (*a menos que se indique de otra manera, para cada tipo de protección nacional disponible*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declaraciones de acuerdo con la Regla 4.17:
-- *con respecto al derecho de la solicitante de solicitar y que le sea otorgada una patente (Regla 4.17(ii))*

Publicada:
-- *con reporte de búsqueda internacional (Art. 21(3))*
-- *antes del vencimiento del límite de tiempo para enmendar las reivindicaciones, y para volverse a publicar en el caso de recibirse las enmiendas (Regla 48.2(h))*
-- *con la parte del listado de secuencias de la descripción (Regla 5.2(a))*

(54) Título : DERIVADOS DE DIHIDRO-BENZO-OXAZINA Y DIHIDRO-PIRIDO-OXAZINA



(I)

(57) Resumen: La invención se refiere a los compuestos de dihidro-benzo-oxazina y dihidro-pirido-oxazina de la fórmula (I) y/o a las sales farmacéuticamente aceptables y/o solvatos de los mismos, en donde Y, V, W, U, Q, R^1, R^5, R^7 y R^{30} son como se definen en la descripción. Estos compuestos son adecuados para el tratamiento de un trastorno o de una enfermedad que sea mediada por la actividad de las enzimas de PI3K.

DERIVADOS DE DIHIDRO-BENZO-OXAZINA Y DIHIDRO-PIRIDO-OXAZINA

CAMPO DE LA INVENCIÓN

La invención se refiere a la preparación y uso de nuevos derivados de dihidro-benzo-oxazina y dihidro-pirido-oxazina como fármacos candidatos en forma libre o en forma de sal farmacéuticamente aceptable con valiosas propiedades de tipo fármaco, tales como, por ejemplo, una forma con estabilidad metabólica y farmacocinética adecuada, para la modulación, notoriamente la inhibición de la actividad o función de la familia de cinasa de fosfoinositida-3'-OH (posteriormente en la presente PI3K).

ANTECEDENTES DE LA INVENCIÓN

Los miembros de la familia de cinasa de fosfoinositida-3 (PI3K) están involucrados en el crecimiento, diferenciación, y sobrevivencia celular, en la remodelación citoesquelética, y en el tráfico de los organelos intracelulares en muchos tipos diferentes de células (Okkenhaug y Wymann, Nature Rev. Immunol., 3: 317 (2003).

Hasta la fecha, se han identificado ocho PI3Ks de mamífero, divididas en tres clases principales (I, II y III) con base en su secuencia genética, estructura, moléculas adaptadoras, expresión, modo de activación, y sustrato preferido.

PI3Kδ es una cinasa de lípido que pertenece a la familia de

PI3K clase I (PI3K α, ß, γ y δ) que genera señales de segundo mensajero corriente abajo de los receptores enlazados a la cinasa de tirosina.

PI3Kδ es un heterodímero compuesto de una proteína adaptadora y una subunidad catalítica p110δ que convierte el fosfatidil-inositol-4,5-bis-fosfato (PtdInsP2) hasta el fosfatidil-inositol-3,4,5-tri-fosfato (PtdInsP3). Las proteínas efectoras interactúan con el PtdInsP3 y desencadenan sendas de señalización específicas involucradas en la activación, diferenciación, migración, y sobrevivencia celular.

La expresión de las subunidades catalíticas p110δ y p110γ es preferencial para los leucocitos. La expresión también se observa en las células de músculo liso, en los miocitos, y en las células endoteliales. En contraste, p110α y p110ß son expresadas por todos los tipos de células (Marone y colaboradores, Biochimica et Biophysica Acta 1784: 159 (2008)).

PI3Kδ está asociada con el desarrollo y la función de las células-B (Okkenhaug y colaboradores, Science 297: 1031 (2002)).

Las células-B también tienen una función crítica en la patogénesis de un número de enfermedades autoinmunes y alérgicas, así como en el proceso de rechazo de trasplante (Martin y Chan, Annu. Rev. Immunol. 24: 467 (2006)).

La quimiotaxis está involucrada en muchas enfermedades autoinmunes o inflamatorias, en la angiogénesis, invasión/ metástasis, neurodegeneración, o en el sanado de heridas (Gerard y

colaboradores, Nat. Immunol. 2: 108 (2001)). Los sucesos temporalmente distintos en la migración de los leucocitos en respuesta a las quimiocinas dependen completamente de PI3Kδ y PI3Kγ (Liu y colaboradores, Blood 110: 1191 (2007)).

PI3Kα y PI3Kß tienen una función esencial en el mantenimiento de la homeostasia, y la inhibición farmacológica de estos objetivos moleculares se ha asociado con la terapia de cáncer (Maira y colaboradores, Expert Opin. Ther. Targets 12: 223 (2008)).

PI3Kα está involucrada en las sendas de señalización de insulina y de crecimiento celular (Foukas y colaboradores, Nature 441: 366 (2006)). Se espera que la inhibición selectiva de la isoforma PI3Kδ evite los efectos secundarios potenciales, tales como hiperglicemia, y mala regulación metabólica o del crecimiento.

Las infecciones parasitarias todavía representan una de las causas más importantes de patología y mortalidad en todo el mundo. Entre los parásitos que provocan patología humana y animal el filo *apicomplexa* comprende un grupo de parásitos que surgen del vector que es responsable de una amplia variedad de enfermedades serias incluyendo, pero no limitándose a, malaria, Leishmaniasis y tripanosomiasis. Solamente la malaria infecta al 5-10 por ciento de la humanidad y provoca alrededor de dos millones de muertes por año. *[Schofield y colaboradores, "Immunological processes in malaria pathogenesis", Nat Rev Imm 2005], [Schofield L, "Intravascular infiltrates and organ-specific inflammation in malaria pathogenesis], [Mishra y colaboradores, "TLRs in CNS Parasitic infections", Curr*

Top Micro Imm 2009], [Bottieau y colaboradores, "Therapy of vector-borne protozoan infections in nonendemic settings", Expert Rev. Anti infect. Ther., 2011].

Los receptores tipo Toll (TLRs) son moléculas filogenéticamente antiguas codificadas por la línea germinal que reconocen moléculas estructuralmente relevantes evolutivamente conservadas (conocidas como patrones moleculares asociados con patógenos (PAMPs)) dentro de los patógenos microbianos. Varios tipos diferentes de células, incluyendo células, incluyendo las células del sistema inmunológico, expresan los receptores tipo Toll (TLRs) y, de esta manera, son capaces de detectar la presencia de los patrones moleculares asociados con patógenos (PAMPs). Hasta ahora se han descrito 10 miembros funcionales de la familia TLR (TLR1-10) en los seres humanos, todos los cuales reconocen moléculas PAMP específicas. En seguida del reconocimiento de estos PAMPs específicos, los receptores tipo Toll (TLRs) inducen y orquestan la respuesta inmunitaria del huésped a las infecciones con bacterias, virus, hongos y parásitos. *[Hedíaat y colaboradores, "Targeting of TLRs: a decade of progress in combating infectious disease", reseña, Lancet infectious disease 2011], [Kwai y colaboradores, "TLRs and their crosstalk with other innate receptors in infection and immunity", reseña, Immunity Mayo-2011].*

El sistema inmunológico del huésped infectado responde a la infección con la producción inducida por TLR de citoquinas pro-inflamatorias principalmente del tipo auxiliar-T 1 (Th1). Aunque son

benéficas las cantidades adecuadas de estas citoquinas y se requieren para eliminar la infección, una sobreproducción de estos mediadores es dañina para el huésped, y está asociada con una patología inmunológicamente mediada, incluyendo neuropatología y daño al tejido con consecuencias graves y con frecuencia fatales. Un ejemplo prominente y altamente relevante de esta patología inmunológicamente mediada es la malaria aguda y cerebral (CM) que provoca síntomas clínicos graves y con frecuencia es fatal. *[Schofield y colaboradores, "Immunological processes in malaria pathogenesis", Nat Rev Imm 2005], [Schofield L, "Intravascular infiltrates and organ-specific inflammation in malaria pathogenesis], [Mishra y colaboradores, "TLRs in CNS Parasitic infections", Curr Top Micro Imm 2009], [Bottieau y colaboradores, "Therapy of vector-borne protozoan infections in nonendemic settings", Expert Rev. Anti infect. Ther., 2011] [Hedíaat y colaboradores, "Targeting of TLRs: a decade of progress in combating infectious disease", reseña, Lancet Infectious Disease 2011]. A* pesar del progreso hecho en el tratamiento y la erradicación de la malaria, la tasa de mortalidad que está asociada con una malaria grave, incluyendo la malaria cerebral (CM), sigue siendo inaceptablemente alta. Las estrategias dirigidas exclusivamente a la erradicación del parásito en el huésped, por consiguiente, podrían no ser suficientes para prevenir las complicaciones neurológicas y la muerte en todos los casos de malaria cerebral (CM). El desarrollo de nuevas estrategias terapéuticas complementarias innovadoras para reducir de una

manera eficiente la mortalidad y patología asociada con la malaria cerebral (CM) que es causada, en parte, por la inmunopatología mediada por el huésped, por consiguiente, sigue siendo una necesidad médica urgente. *[Higgins y colaboradores, "Immunopathogenesis of falciparum malaria: implications for adjunctive therapy in the management of severe and cerebral malaria", Expert Rev. Anti Infect. Ther. 2011].*

Recientemente se ha proporcionado evidencia adicional de que el TLR9 tiene una función clave en el reconocimiento y la respuesta a los parásitos, incluyendo, pero no limitándose a, Plasmodium, Leishmania, Tripanosoma y Toxoplasma *[Gowda y colaboradores, "The Nucleosome is the TLR9-specific Immunostimulatory component plasmodium falciparum that activates DCs", PLoS ONE, Junio 2011], [Peixoto-Rangel y colaboradores, "Candidate gene analysis of ocular toxoplasmosis in Brazil: evidence for a role for TLR9", Mem Inst Oswaldo Cruz 2009], [Pellegrini y colaboradores, "The role of TLRs and adoptive immunity in the development of protective or pathological immune response triggered by the Tripanosoma cruzi protozoan", Future Microbiol 2011],* y de que la interferencia con la activación de TLRs, incluyendo el TLR9, representa una estrategia prometedora para prevenir las respuestas inflamatorias perjudiciales en la malaria grave y cerebral *[Franklin y colaboradores, "Therapeutical targeting of nucleic acid-sensing TLRs prevents experimental cerebral malaria", PNAS 2011].*

La malaria es una enfermedad infecciosa causada por cuatro

parásitos protozoarios: *Plasmodium falciparum; Plasmodium vivax; Plasmodium ovale*; y *Plasmodium malaria*. Estos cuatro parásitos típicamente son transmitidos por la mordida de un mosquito Anopheles hembra infectado. La malaria es un problema en muchas partes del mundo y durante las últimas décadas, el problema de la malaria ha aumentado continuamente. Se estima que cada año mueren de 1 a 3 millones de personas de malaria – en su mayor parte niños de menos de 5 años de edad. Este aumento en la mortalidad por malaria se debe en parte al hecho de que el *Plasmodium falciparum*, el parásito de malaria más letal, ha adquirido resistencia contra casi todos los fármacos contra la malaria disponibles, con la excepción de los derivados de artemisinina.

La Leishmaniasis es causada por una o más de 20 variedades de protozoarios parasitarios que pertenecen al género Leishmania, y es transmitida por la mordida de moscas de arena hembras. La Leishmaniasis es endémica en aproximadamente 88 países, incluyendo muchas áreas tropicales y sub-tropicales. Existen cuatro formas principales de Leishmaniasis. Leishmaniasis visceral, también denominada como kala-azar, es la forma más grave y es causada por el parásito *Leishmania donovani*. Los pacientes que desarrollan Leishmaniasis visceral pueden morir en meses a menos que reciban tratamiento. Las dos terapias principales para Leishmaniasis visceral son los derivados de antimonio de estibogluconato de sodio (Pentostam®), y antimoniato de meglumina (Glucantim®). El estibogluconato de sodio se ha utilizado durante aproximadamente

70 años, y la resistencia a este fármaco es un problema creciente. En adición, el tratamiento es relativamente largo y doloroso, y puede provocar efectos secundarios indeseables.

La Tripanosomiasis Africana Humana, también conocida como enfermedad del sueño, es una enfermedad parasitaria que surge del vector. Los parásitos concernidos son protozoarios pertenecientes al Género *Tripanosoma*. Son transmitidos a los seres humanos por las mordidas de la mosca tse-tsé (Género *Glossina*) que ha adquirido su infección a partir de seres humanos o a partir de animales que alojan a los parásitos patogénicos humanos.

La enfermedad de Chagas (también denominada como Tripanosomiasis Americana) es otra enfermedad parasitaria humana que es endémica entre las poblaciones pobres del Continente Americano. La enfermedad es causada por el protozoario parásito *Tripanosoma cruzi*, el cual es transmitido a los seres humanos por los insectos succionadores de sangre. La enfermedad humana se presenta en dos etapas: La etapa aguda, que se presenta poco tiempo después de la infección, y la etapa crónica, la cual puede desarrollarse durante muchos años. Las infecciones crónicas dan como resultado diferentes trastornos neurológicos, incluyendo demencia, daño al músculo cardíaco, y algunas veces dilatación del tracto digestivo, así como pérdida de peso. La enfermedad crónica no tratada con frecuencia es fatal. Los fármacos actualmente disponibles para el tratamiento de la enfermedad de Chagas son nifurtimox y benzonidazol. Sin embargo, los problemas con estas

terapias actuales incluyen sus diversos efectos secundarios, la duración del tratamiento, y el requerimiento de supervisión médica durante el tratamiento. Adicionalmente, el tratamiento es en realidad solamente efectivo cuando se da durante la etapa aguda de la enfermedad. Ya se ha presentado resistencia a los dos fármacos de la línea frontal. Se ha propuesto el agente antifúngico de anfotericina b como un fármaco de segunda línea, pero este fármaco es costoso y relativamente tóxico.

La toxoplasmosis es endémica a través de la mayor parte del mundo, la cual puede infectar a una gran proporción de la población adulta. Sin embargo, su prevalencia difiere en diferentes países. Se estima que infecta a cuando menos el 10 por ciento de los adultos en los países templados del norte, y a más de la mitad de los adultos en los países del Mediterráneo y tropicales. *Toxoplasma gondii* es un protozoario intracelular obligado ubicuito y se considera que es la causa más común de retinitis infecciosa en los seres humanos, la cual depende de una variedad de factores, incluyendo el clima, la higiene, y los hábitos dietéticos. El curso de la enfermedad en los adultos inmunocompetentes es usualmente asintomático y auto-limitante. Tan pronto como se ha presentado la infección, el parásito forma quistes latentes en la retina y en otros órganos del cuerpo, los cuales pueden reactivarse años después de la infección inicial, dando lugar a una retinocoroiditis aguda y a la formación de nuevas lesiones retinocoroidales. *[Arevalo y colaboradores, "Ocular Toxoplasmosis in the developing world", Internat. Oftal. Clin 2010].*

La neurocisticercosis es la enfermedad parasitaria más común del sistema nervioso central (CNS) (incidencia de aproximadamente 2.5 millones en todo el mundo) causada por las larvas de *Taenia solium*. La enfermedad tiene una larga fase asintomática en los seres humanos caracterizada por la ausencia de una respuesta inflamatoria detectable alrededor del parásito. La respuesta inmunitaria global durante la fase asintomática es del fenotipo Th2. Sin embargo, la destrucción de las larvas mediante el tratamiento terapéutico o por el desgaste normal del parásito provoca una fuerte respuesta inflamatoria, que consiste con frecuencia en una reacción granulomatosa crónica y la manifestación de los síntomas típicos de la enfermedad. La respuesta inmunitaria en el sistema nervioso central (CNS) de los pacientes sintomáticos consiste en un fenotipo Th1 evidente o una respuesta mixta de Th1, Th2, y Th3, dependiendo de la ausencia o presencia de granulomas. La respuesta híper-inflamatoria prevaleciente durante la fase sintomática en el sistema nervioso central (CNS) es responsable de la severa neuropatología y mortalidad asociada con la neurocisticercosis. *[Mishra y colaboradores, "TLRs in CNS Parasitic Infections", Curr Top Micro Imm 2009].*

Existe una necesidad de proporcionar nuevos inhibidores de PI3K que sean buenos fármacos candidatos. En particular, los compuestos de la invención deben enlazarse potentemente a PI3K mientras que muestren poca afinidad por otros receptores y muestren la actividad funcional como inhibidores. Deben ser bien absorbidos

desde el tracto gastrointestinal, deben ser metabólicamente estables, y deben poseer propiedades farmacocinéticas favorables. Cuando se dirijan contra los receptores del sistema nervioso central, deben cruzar la barrera hematoencefálica libremente, y cuando se dirijan selectivamente contra los receptores del sistema nervioso periférico, no deben cruzar la barrera hematoencefálica. No deben ser tóxicos, y deben demostrar pocos efectos secundarios. Adicionalmente, el fármaco candidato ideal existirá en una forma física que sea estable, no higroscópica y fácilmente formulada.

Los compuestos de la invención muestran cierto nivel de selectividad contra los diferentes parálogos de PI3K α, ß, γ, y δ. En particular, muestran cierto nivel de selectividad para la isoforma PI3Kδ.

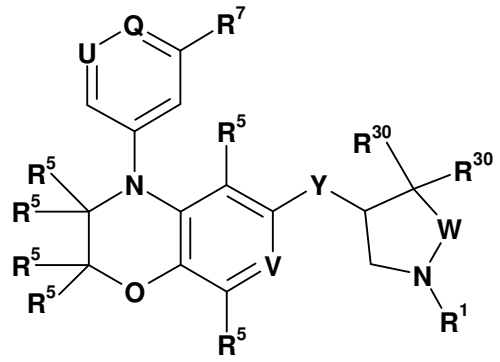
Los compuestos de la presente invención, por consiguiente, son potencialmente útiles en el tratamiento de una amplia gama de trastornos, en particular los trastornos que incluyen, pero no se limitan a, trastornos autoinmunitarios, enfermedades inflamatorias, enfermedades alérgicas, inmunopatologías asociadas con enfermedades o infecciones, enfermedades de las vías respiratorias, tales como asma y enfermedad pulmonar obstructiva crónica (COPD), rechazo de trasplante, cánceres, por ejemplo, de origen hematopoiético, o tumores sólidos.

La invención también se refiere al tratamiento, ya sea solo o bien en combinación, con uno o más compuestos farmacológicamente activos diferentes, incluyendo los métodos para

el tratamiento de condiciones, enfermedades o trastornos en donde una o más de las funciones de las células-B, tales como la producción de anticuerpos, la presentación de antígeno, la producción de citoquinas o la organogénesis linfoide, sean anormales o sean indeseables, incluyendo artritis reumatoide, pénfigo vulgar y las enfermedades relacionadas, púrpura trombocitopénica idiopática, lupus eritematoso sistémico, esclerosis múltiple, miastenia grave, síndrome de Sjögren, anemia hemolítica autoinmune, vasculitidas asociadas con ANCA, crioglobulinemia, púrpura trombocitopénica trombótica, urticaria autoinmune crónica, alergia (dermatitis atópica, dermatitis por contacto, rinitis alérgica), síndrome de Goodpasture, AMR (rechazo de trasplante mediado por anticuerpos), rechazo de trasplante híper-agudo, agudo y crónico mediado por células-B, y cánceres de origen hematopoiético, incluyendo, pero no limitándose a, mieloma múltiple; leucemia mielógena aguda; leucemia mielógena crónica; leucemia linfocítica; leucemia mieloide; linfoma no de Hodgkin; linfomas; policitemia vera; trombocitemia esencial; mielofibrosis con metaplasia mieloide; y enfermedad de Walden Ströem, así como en la inmunopatología asociada con enfermedades o infecciones.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

La invención se refiere a los compuestos de dihidro-benzo-oxazina y dihidro-pirido-oxazina de la fórmula (I) y/o a las sales farmacéuticamente aceptables y/o solvatos de los mismos:



(I)

en donde:

Y se selecciona a partir de O o NH;

V se selecciona a partir de CR^5 ó N;

W se selecciona a partir de CH_2, u O;

U se selecciona a partir de N o CH;

Q se selecciona a partir de N o CR^6;

en donde U y Q no son ambos N;

R^1 se selecciona a partir de fenilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, 1,2,3-triazinilo, 1,2,4-triazinilo, 1,3,5-triazinilo,

o

$-X-R^4$

en donde X se selecciona a partir de C(O), $S(O)_2$ ó CH_2

y

R^4 se selecciona a partir de alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, ciano-alquilo de 1 a 8 átomos de carbono, N,N-di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de

1 a 8 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonil-alquilo de 1 a 8 átomos de carbono, fenilo, heterociclilo, heterociclil-oxilo, heterociclil-alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, cicloalquiloxilo de 3 a 12 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono-alquilo de 1 a 8 átomos de carbono, heteroarilo, heteroaril-oxilo, heteroaril-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, o N,N-di-alquilo de 1 a 8 átomos de carbono-amino,

en donde el alquilo de 1 a 8 átomos de carbono en N-alquilo de 1 a 8 átomos de carbono-amino y en N,N-di-alquilo de 1 a 8 átomos de carbono-amino puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono,

en donde el cicloalquilo de 3 a 12 átomos de carbono en cicloalquilo de 3 a 12 átomos de carbono y en cicloalquilo de 3 a 12 átomos de carbono-alquilo de 1 a 8 átomos de carbono puede estar insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono;

en donde el 'heterociclilo' es un sistema de anillo monocíclico de 3 a 7 miembros saturado o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, cada uno de los cuales está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de oxo, halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de

carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heterociclilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación,

en donde el 'heteroarilo' es un sistema de anillo monocíclico de 3 a 7 miembros completamente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, o pirazolo-[1,5-a]-pirimidina o imidazo-[2,1-b]-tiazol, cada uno de los cuales está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heteroarilo' se puede unir en un heteroátomo o en un

átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación;

R^6 se selecciona a partir de hidrógeno, halógeno, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonilo, alquilo de 1 a 4 átomos de carbono-sulfinilo, alquilo de 1 a 4 átomos de carbono-sulfanilo, halo-alcoxilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono-alquilo de 1 a 4 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino;

R^7 se selecciona a partir de hidrógeno, halógeno, ciano, nitro, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, $N(R^8)_2$-sulfonilo, alquilo de 1 a 4 átomos de carbono-sulfonilo, alquilo de 1 a 4 átomos de carbono-sulfonil-amino, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, o N,N-di-alquilo de 1 a 8 átomos de carbono-amino;

o R^6 y R^7, son juntos CH=CH-CH=CH,

en donde R^8 se selecciona independientemente a partir de hidrógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, o dos R^8 junto con el nitrógeno con el que están unidos, forman un anillo heterocíclico de 4 a 7 miembros que contiene de 1 a 2 heteroátomos seleccionados a partir de N, O, S,

que está insustituido o sustituido por 1 a 3 sustituyentes seleccionados a partir de alquilo de 1 a 4 átomos de carbono;

R^5 se selecciona independientemente a partir de H, D, F o alquilo de 1 a 2 átomos de carbono;

R^{30} se selecciona independientemente a partir de H, D o F.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

La Figura **1** es el patrón de difracción en polvo de rayos-X del Ejemplo F1, forma cristalina anhidra.

La Figura **2** es la gráfica de calorimetría de exploración diferencial del Ejemplo F1, forma cristalina anhidra.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

A menos que se especifique de otra manera, el término “compuestos de la presente invención” se refiere a los compuestos de la fórmula (I), y de las sub-fórmulas de la misma, a las sales del compuesto, a los hidratos o solvatos de los compuestos y/o sales, así como a todos los estereoisómeros (incluyendo diaestereoisómeros y enantiómeros), tautómeros y compuestos isotópicamente marcados (incluyendo las sustituciones con deuterio). Los compuestos de la presente invención comprenden además los polimorfos de los compuestos de la fórmula (I) (o de las subfórmulas de la misma), y las sales de los mismos. Cuando se mencionan los compuestos de la fórmula (I), esto pretende incluir también los tautómeros y N-óxidos de los compuestos de la fórmula (I).

La invención se puede apreciar más completamente haciendo referencia a la siguiente descripción, incluyendo el siguiente glosario

de términos y los ejemplos concluyentes. Como se utilizan en la presente, los términos "incluyendo", "conteniendo" y "comprendiendo" se utilizan en la presente en su sentido abierto, no limitante.

Los tautómeros, tales como los tautómeros entre la forma de ceto- y enol, la forma de lactama y lactima, la forma de amida y la forma de ácido imídico o la forma de enamina y la forma de imina, pueden estar presentes, por ejemplo, en la porción R^1 de los compuestos de la fórmula (I). Los residuos de heterociclilo y heteroarilo que contienen nitrógeno pueden formar N-óxidos.

Cuando se utiliza la forma plural para los compuestos, sales, y similares, esto también significa un solo compuesto, sal, o similar.

Los términos generales utilizados anteriormente en la presente y más adelante en la presente, de preferencia tienen, dentro del contexto de esta divulgación, los siguientes significados, a menos que se indique de otra manera:

Como se utiliza en la presente, el término “alquilo” se refiere a una fracción de hidrocarburo ramificado, incluyendo una sola o múltiples ramificaciones, o no ramificado, completamente saturado, que tiene hasta 20 átomos de carbono. A menos que se disponga de otra manera, alquilo se refiere a fracciones de hidrocarburo que tienen 1 a 16 átomos de carbono, de 1 a 10 átomos de carbono, de 1 a 7 átomos de carbono, o de 1 a 4 átomos de carbono. Los ejemplos representativos de alquilo incluyen, pero no se limitan a, metilo, etilo, propilo normal, isopropilo, butilo normal, butilo secundario,

isobutilo, butilo terciario, pentilo normal, isopentilo, neopentilo, hexilo normal, 3-metil-hexilo, 2,2- dimetil-pentilo, 2,3-dimetil-pentilo, heptilo normal, octilo normal, nonilo normal, decilo normal, y similares. Típicamente, los grupos alquilo tienen de 1 a 7, más preferiblemente de 1 a 4 átomos de carbono.

Como se utiliza en la presente, el término “halo-alquilo” se refiere a un alquilo como se define en la presente, que está sustituido por uno o más grupos halógeno como se definen en la presente. El halo-alquilo puede ser mono-halo-alquilo, di-halo-alquilo o poli-halo-alquilo incluyendo per-halo-alquilo. Un mono-halo-alquilo puede tener un átomo de yodo, bromo, cloro o flúor dentro del grupo alquilo. Los grupos di-halo-alquilo y poli-halo-alquilo pueden tener dos o más de los mismos átomos de halógeno o una combinación de diferentes grupos halógeno dentro del alquilo. Típicamente, el poli-halo-alquilo contiene hasta 12, o 10, u 8, o 6, o 4, o 3, o 2 grupos halógeno. Los ejemplos no limitantes de halo-alquilo incluyen fluoro-metilo, di-fluoro-metilo, tri-fluoro-metilo, cloro-metilo, di-cloro-metilo, tri-cloro-metilo, penta-fluoro-etilo, hepta-fluoro-propilo, di-fluoro-cloro-metilo, di-cloro-fluoro-metilo, di-fluoro-etilo, di-fluoro-propilo, di-cloro-etilo y dicloro-propilo. Un per-halo-alquilo se refiere a un alquilo que tiene todos los átomos de hidrógeno reemplazados con átomos de halógeno.

Como se utiliza en la presente, el término “heterociclilo" o "heterocíclico” se refiere a un anillo o sistema de anillos monocíclico de 3 a 7 miembros o de 7 a 10 miembros, saturado o parcialmente

saturado, que contiene cuando menos un heteroátomo seleccionado a partir de N, O, y S, en donde los átomos de N y S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación. 'Heterociclilo' se puede unir en un heteroátomo o en un átomo de carbono. 'Heterociclilo' puede incluir anillos fusionados o puenteados, así como anillos espirocíclicos.

En el contexto de R^4, los ejemplos de los heterociclos incluyen oxiranilo, aziridinilo, oxetanilo, tietanilo, acetitinilo, pirrolidinilo, tetrahidro-furanilo, tetrahidro-tiofenilo, 2,3-dihidro-furanilo, 2,5-dihidro-furanilo, 2,3-dihidro-tiofenilo, 1-pirrolinilo, 2-pirrolinilo, 3-pirrolinilo, tetrahidro-piranilo, piperidinilo, tetrahidro-tiopiranilo, morfolinilo, tiomorfolinilo, oxatianilo, dioxanilo, piperazinilo, dihidro-piranilo, tetrahidro-piridinilo, dihidro-tiopiranilo, azepanilo, tiepanilo y oxepanilo.

En el contexto de R^8, los ejemplos de los heterociclos incluyen pirrolinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, tetrahidro-piridinilo y azepanilo.

Como se utiliza en la presente, el término "heteroarilo" o "heteroarílico" se refiere a un anillo o sistema de anillos insaturado monocíclico de 4, 5, 6, ó 7 miembros, bicíclico de 7, 8, 9, 10, 11, ó 12 miembros, o tricíclico de 10, 11, 12, 13, 14, ó 15 miembros - que lleva el número más alto posible de dobles enlaces conjugados en el(los) anillo(s), que contiene cuando menos un heteroátomo seleccionado a partir de N, O, y S, en donde los átomos de N y S también se pueden oxidar opcionalmente hasta diferentes estados de

oxidación. ‘Heteroarilo’ se puede unir en un heteroátomo o en un átomo de carbono. ‘Heteroarilo’ pueden incluir anillos fusionados o puenteados, así como anillos espirocíclicos. Los ejemplos de heteroarilo incluyen furanilo, tiofenilo, pirrolilo, imidazolilo, pirazolilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, 1,2,5-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,3-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2,5-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,3-tiadiazolilo, 1,3,4-tiadiazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, 1,2,3-triazinilo, 1,2,4-triazinilo y 1,3,5-triazinilo.

Como se utiliza en la presente, el término "cicloalquilo" se refiere a los grupos hidrocarburo monocíclicos, bicíclicos o tricíclicos, saturados o parcialmente insaturados de 3 a 12 átomos de carbono. A menos que se disponga de otra manera, cicloalquilo se refiere a los grupos hidrocarburo cíclicos que tienen entre 3 y 10 átomos de carbono del anillo, o entre 3 y 7 átomos de carbono del anillo. Los grupos hidrocarburo bicíclicos de ejemplo incluyen octahidro-indilo, decahidro-naftilo. Los grupos hidrocarburo tricíclicos de ejemplo incluyen biciclo-[2.1.1]-hexilo, biciclo-[2.2.1]-heptilo, biciclo-[2.2.1]-heptenilo, 6,6-dimetil-biciclo-[3.1.1]-heptilo, 2,6,6-trimetil-biciclo-[3.1.1]-heptilo, biciclo-[2.2.2]-octilo. Los grupos hidrocarburo tetracíclicos de ejemplo incluyen adamantilo.

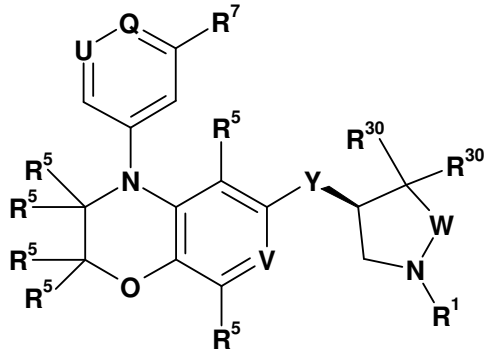
Como se utiliza en la presente, el término “oxilo" se refiere a un grupo de enlace -O-.

Como se utiliza en la presente, el término “carboxilo" o "carboxi” es –COOH.

Como se utiliza en la presente, todos los sustituyentes se escriben de una manera para mostrar el orden de los grupos funcionales (grupos) de los que se componen. Los grupos funcionales se definen anteriormente en la presente.

En la presente se describen diferentes modalidades enumeradas de la invención. Se reconocerá que las características especificadas en cada modalidad se pueden combinar con otras características especificadas para proporcionar otras modalidades de la presente invención.

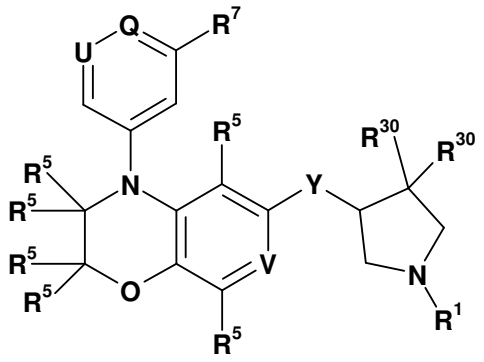
En una modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (I'):



(I'),

en donde R^1, R^5, R^7, R^{30}, Y, V, W, U y Q son como se definen anteriormente.

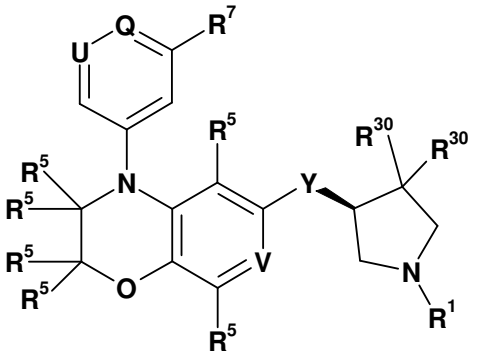
En una modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ia):



(Ia),

en donde R^1, R^5, R^7, R^{30}, Y, V, U y Q son como se definen anteriormente.

En una modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ia'):

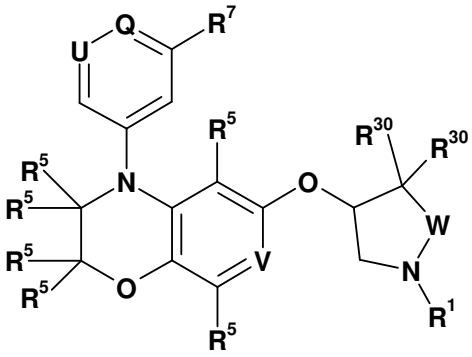


(Ia'),

en donde R^1, R^5, R^7, R^{30} Y, V, U y Q son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato

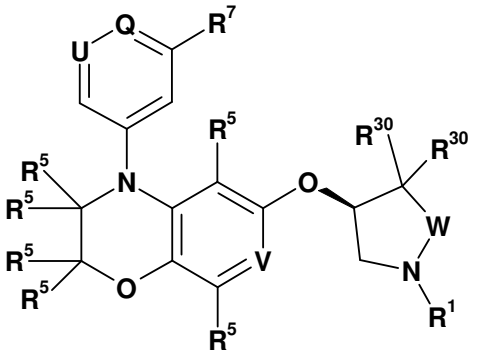
del mismo, seleccionado a partir de un compuesto de la fórmula (Ib):



(Ib),

en donde R^1, R^5, R^7, R^{30}, V, W, U y Q son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ib'):

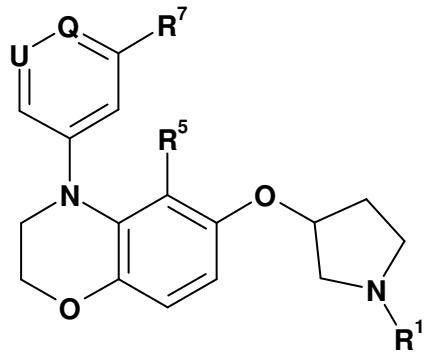


(Ib'),

en donde R^1, R^5, R^7, R^{30}, V, W, U y Q son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de

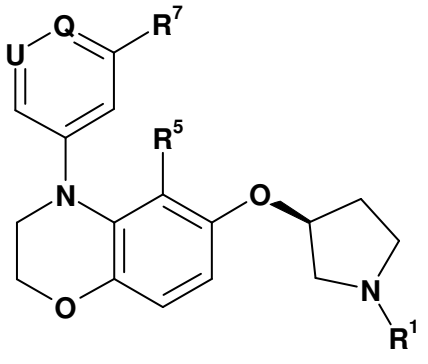
la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ic):



(Ic),

en donde R^1, R^5, R^7, U y Q son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ic'):

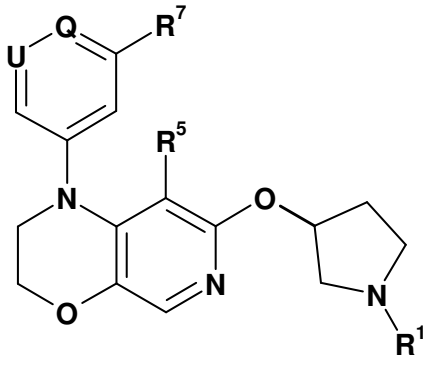


(Ic'),

en donde R^1, R^5, R^7, U y Q son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato

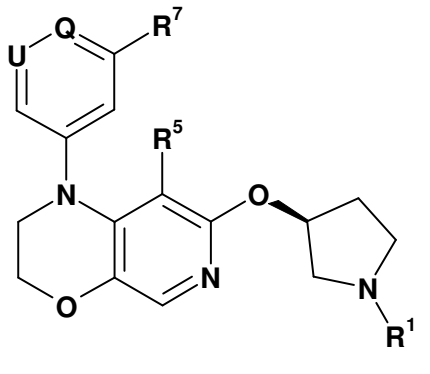
del mismo, seleccionado a partir de un compuesto de la fórmula (Id):



(Id),

en donde R^1, R^5, R^7, U y Q son como se definen anteriormente.

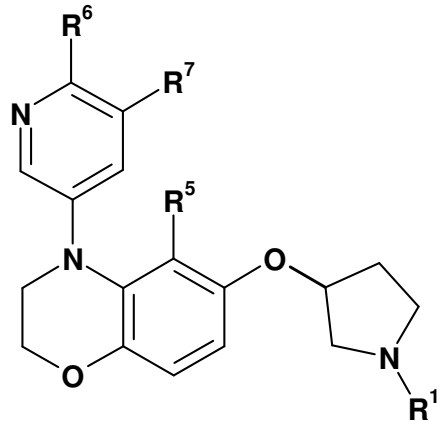
En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Id'):



(Id'),

en donde R^1, R^5, R^7, U y Q son como se definen anteriormente.

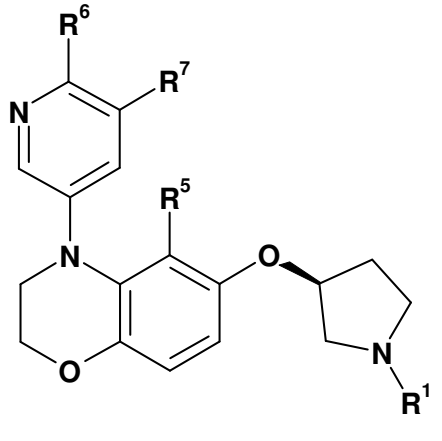
En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ie):



(Ie),

en donde R^1, R^5, R^6 y R^7 son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ie'):

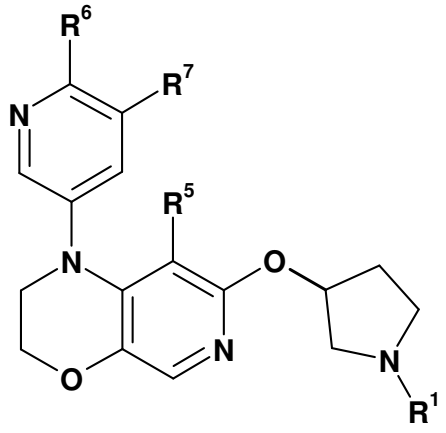


(Ie'),

en donde R^1, R^5, R^6 y R^7 son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato

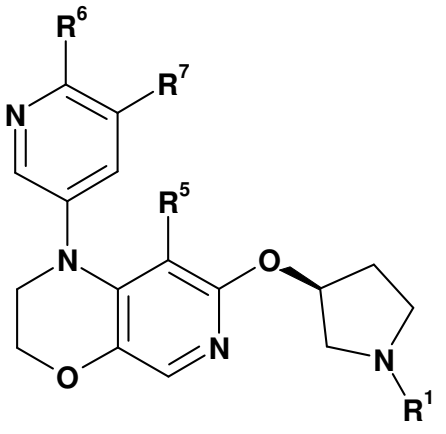
del mismo, seleccionado a partir de un compuesto de la fórmula (If):



(If),

en donde R^1, R^5, R^6 y R^7 son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (If'):

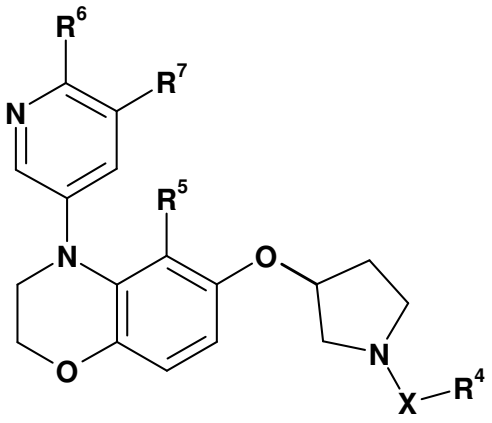


(If'),

en donde R^1, R^5, R^6 y R^7 son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de

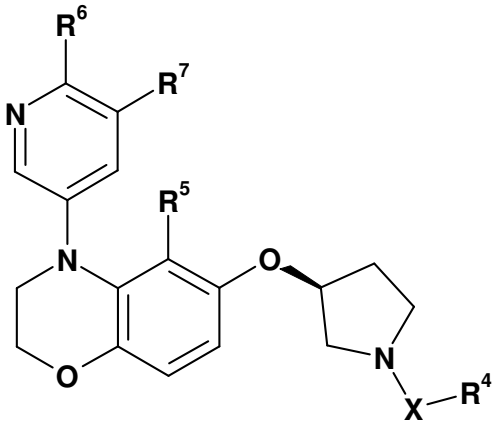
la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ig):



(Ig),

en donde X, R^4, R^5, R^6 y R^7 son como se definen anteriormente.

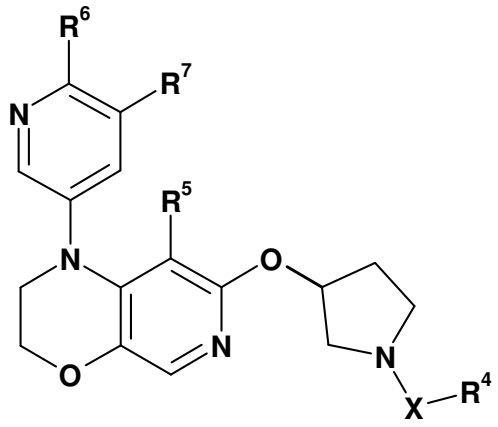
En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ig'):



(Ig'),

en donde X, R^4, R^5, R^6 y R^7 son como se definen anteriormente.

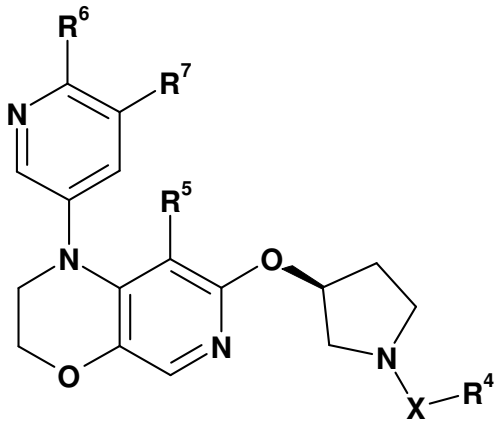
En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ih):



(Ih),

en donde X, R^4, R^5, R^6 y R^7 son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ih'):

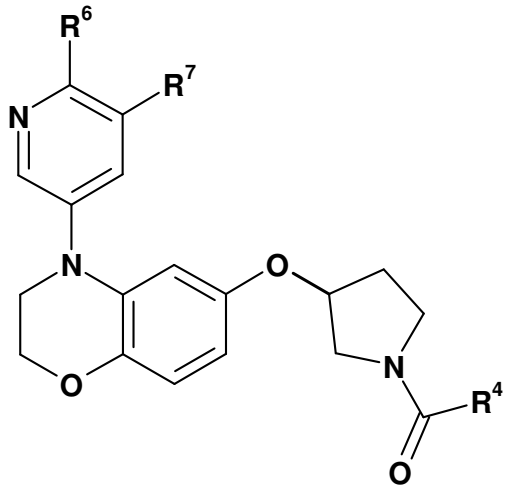


(Ih'),

en donde X, R^4, R^5, R^6 y R^7 son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de

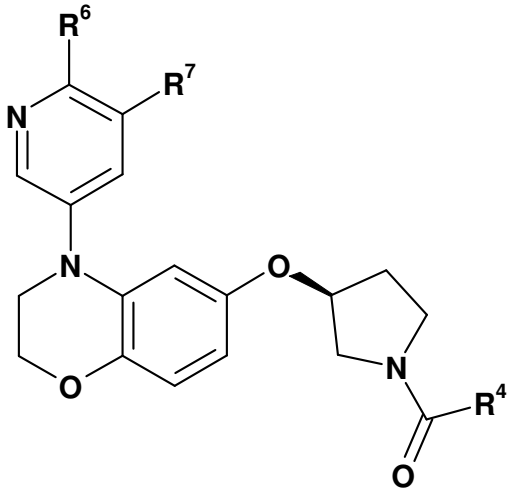
la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ii):



(Ii),

en donde R^4, R^5, R^6 y R^7 son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ii'):

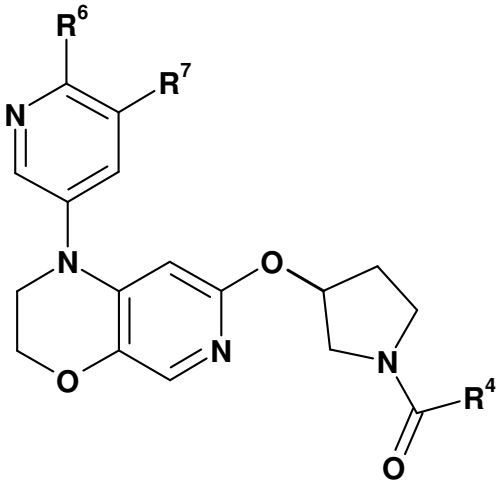


(Ii'),

en donde R^4, R^5, R^6 y R^7 son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato

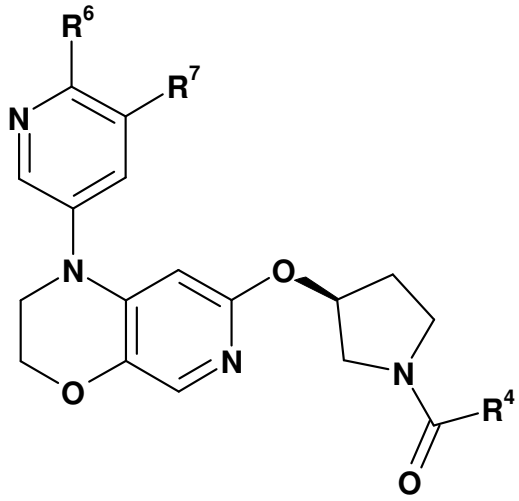
del mismo, seleccionado a partir de un compuesto de la fórmula (Ij):



(Ij),

en donde R^4, R^5, R^6 y R^7 son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de la fórmula (I) y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, seleccionado a partir de un compuesto de la fórmula (Ij'):



(Ij'),

en donde R^4, R^5, R^6 y R^7 son como se definen anteriormente.

En otra modalidad, la invención proporciona un compuesto de las fórmulas (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) o (Ij') y/o una sal

farmacéuticamente aceptable y/o un solvato del mismo, en donde:

R^4 se selecciona a partir de alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, ciano-alquilo de 1 a 8 átomos de carbono, N,N-di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonil-alquilo de 1 a 8 átomos de carbono, fenilo, heterociclilo, heterociclil-alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heteroarilo, heteroaril-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono en N-alquilo de 1 a 8 átomos de carbono-amino y en N,N-di-alquilo de 1 a 8 átomos de carbono-amino puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono,

en donde el cicloalquilo de 3 a 12 átomos de carbono en cicloalquilo de 3 a 12 átomos de carbono y en cicloalquilo de 3 a 12 átomos de carbono-alquilo de 1 a 8 átomos de carbono puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono;

en donde el 'heterociclilo' es un sistema de anillo monocíclico de 3 a 7 miembros saturado o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, que está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de oxo, halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos

de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heterociclilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación,

en donde el 'heteroarilo' es un sistema de anillo monocíclico de 3 a 7 miembros completamente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, o pirazolo-[1,5-a]-pirimidina o imidazo-[2,1-b]-tiazol, cada uno de los cuales está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en

donde el 'heteroarilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación.

En otra modalidad, la invención proporciona un compuesto de las fórmulas (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) o (Ij') y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, en donde:

R^4 se selecciona a partir de alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, ciano-alquilo de 1 a 8 átomos de carbono, N,N-di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonil-alquilo de 1 a 8 átomos de carbono, fenilo, heterociclilo, heterociclil-alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heteroarilo, heteroaril-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono en N-alquilo de 1 a 8 átomos de carbono-amino y en N,N-di-alquilo de 1 a 8 átomos de carbono-amino puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono,

en donde el cicloalquilo de 3 a 12 átomos de carbono en cicloalquilo de 3 a 12 átomos de carbono y en cicloalquilo de 3 a 12 átomos de carbono-alquilo de 1 a 8 átomos de carbono puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4

átomos de carbono;

en donde el 'heterociclilo' se selecciona a partir de pirrolidinilo, tetrahidro-furanilo, tetrahidro-tiofenilo, tetrahidro-piranilo, piperidinilo, tetrahidro-tiopiranilo, morfolinilo, dioxanilo o dihidro-piranilo, cada uno de los cuales está insustituido o sustituido por 1 a 3 sustituyentes seleccionados a partir de oxo, alquilo de 1 a 8 átomos de carbono, o alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heterociclilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación,

en donde el 'heteroarilo' se selecciona a partir de imidazolilo, pirazolilo, tiazolilo, oxazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, piridilo, pirimidinilo, pirazinilo, pirazolo-[1,5-a]-pirimidina o imidazo-[2,1-b]-tiazol, cada uno de los cuales está insustituido o sustituido por 1 a 3 sustituyentes seleccionados a partir de alquilo de 1 a 8 átomos de carbono, hidroxilo o amino; en donde el 'heteroarilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación.

En otra modalidad, la invención proporciona un compuesto de las fórmulas (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) o (Ij') y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, en donde:

R^6 se selecciona a partir de halógeno, alcoxilo de 1 a 4 átomos

de carbono, alquilo de 1 a 4 átomos de carbono-sulfonilo, o halo-alcoxilo de 1 a 4 átomos de carbono.

En otra modalidad, la invención proporciona un compuesto de las fórmulas (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) o (Ij') y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, en donde:

R^7 se selecciona a partir de hidrógeno, halógeno, ciano, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, o alcoxilo de 1 a 4 átomos de carbono.

En otra modalidad, la invención proporciona un compuesto de las fórmulas (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) o (Ij') y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, en donde:

R^4 se selecciona a partir de alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, ciano-alquilo de 1 a 8 átomos de carbono, N,N-di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonil-alquilo de 1 a 8 átomos de carbono, fenilo, heterociclilo, heterociclil-alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heteroarilo, heteroaril-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono en N-alquilo de 1 a 8 átomos de carbono-amino y en N,N-di-alquilo de 1 a 8 átomos de carbono-amino puede estar insustituido o sustituido por

halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono,

en donde el cicloalquilo de 3 a 12 átomos de carbono en cicloalquilo de 3 a 12 átomos de carbono y en cicloalquilo de 3 a 12 átomos de carbono-alquilo de 1 a 8 átomos de carbono puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono;

en donde el 'heterociclilo' es un sistema de anillo monocíclico de 3 a 7 miembros saturado o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, que está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de oxo, halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heterociclilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación,

en donde el 'heteroarilo' es un sistema de anillo monocíclico de 3 a 7 miembros completamente insaturado que contiene de 1 a 3

heteroátomos seleccionados a partir de N, O o S, o pirazolo-[1,5-a]-pirimidina o imidazo-[2,1-b]-tiazol, cada uno de los cuales está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heteroarilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación;

y R^6 se selecciona a partir de halógeno, alcoxilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonilo, o halo-alcoxilo de 1 a 4 átomos de carbono.

En otra modalidad, la invención proporciona un compuesto de las fórmulas (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) o (Ij') y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, en donde:

R^4 se selecciona a partir de alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a

8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, ciano-alquilo de 1 a 8 átomos de carbono, N,N-di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonil-alquilo de 1 a 8 átomos de carbono, fenilo, heterociclilo, heterociclil-alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heteroarilo, heteroaril-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono en N-alquilo de 1 a 8 átomos de carbono-amino y en N,N-di-alquilo de 1 a 8 átomos de carbono-amino puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono,

en donde el cicloalquilo de 3 a 12 átomos de carbono en cicloalquilo de 3 a 12 átomos de carbono y en cicloalquilo de 3 a 12 átomos de carbono-alquilo de 1 a 8 átomos de carbono puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono;

en donde el 'heterociclilo' es un sistema de anillo monocíclico de 3 a 7 miembros saturado o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, que está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de oxo, halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo

de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heterociclilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación,

en donde el 'heteroarilo' es un sistema de anillo monocíclico de 3 a 7 miembros completamente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, o pirazolo-[1,5-a]-pirimidina o imidazo-[2,1-b]-tiazol, cada uno de los cuales está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heteroarilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de

oxidación;

y R^7 se selecciona a partir de hidrógeno, halógeno, ciano, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, o alcoxilo de 1 a 4 átomos de carbono.

En otra modalidad, la invención proporciona un compuesto de las fórmulas (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) o (Ij') y/o una sal farmacéuticamente aceptable y/o un solvato del mismo, en donde:

R^4 se selecciona a partir de alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, ciano-alquilo de 1 a 8 átomos de carbono, N,N-di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonil-alquilo de 1 a 8 átomos de carbono, fenilo, heterociclilo, heterociclil-alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heteroarilo, heteroaril-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono en N-alquilo de 1 a 8 átomos de carbono-amino y en N,N-di-alquilo de 1 a 8 átomos de carbono-amino puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono,

en donde el cicloalquilo de 3 a 12 átomos de carbono en cicloalquilo de 3 a 12 átomos de carbono y en cicloalquilo de 3 a 12 átomos de carbono-alquilo de 1 a 8 átomos de carbono puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4

átomos de carbono;

en donde el 'heterociclilo' es un sistema de anillo monocíclico de 3 a 7 miembros saturado o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, que está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de oxo, halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heterociclilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación,

en donde el 'heteroarilo' es un sistema de anillo monocíclico de 3 a 7 miembros completamente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, o pirazolo-[1,5-a]-pirimidina o imidazo-[2,1-b]-tiazol, cada uno de los cuales está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de

carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heteroarilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación;

R^6 se selecciona a partir de halógeno, alcoxilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonilo, o halo-alcoxilo de 1 a 4 átomos de carbono;

y R^7 se selecciona a partir de hidrógeno, halógeno, ciano, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, o alcoxilo de 1 a 4 átomos de carbono.

En otra modalidad, los compuestos individuales de acuerdo con la invención son aquéllos enlistados en la sección de Ejemplos más adelante.

Como se utiliza en la presente, el término "un isómero óptico" o "un estereoisómero" se refiere a cualquiera de las diferentes configuraciones estereoisoméricas, las cuales pueden existir para un compuesto dado de la presente invención, e incluyen los isómeros geométricos. Se entiende que un sustituyente se puede unir en un

centro quiral de un átomo de carbono. El término "quiral" se refiere a las moléculas que tienen la propiedad de no poderse sobreponer en su compañera de imagen de espejo, mientras que el término "aquiral" se refiere a las moléculas que se pueden sobreponer en su compañera de imagen de espejo. Por consiguiente, la invención incluye los enantiómeros, diaestereómeros o racematos del compuesto. “Enantiómeros” son un par de estereoisómeros que son imágenes de espejo que no se pueden sobreponer una en la otra. Una mezcla de 1:1 de un par de enantiómeros es una mezcla "racémica”. El término se utiliza para designar una mezcla racémica donde sea apropiado. "Diaestereoisómeros” son estereoisómeros que tienen cuando menos dos átomos asimétricos, pero que no son imágenes de espejo uno del otro. La estereoquímica absoluta se especifica de acuerdo con el sistema de Cahn-Ingold-Prelog R-S. Cuando un compuesto es un enantiómero puro, la estereoquímica en cada átomo de carbono quiral se puede especificar mediante cualquiera de *R* o *S*. Los compuestos resueltos cuya configuración absoluta se desconoce, se pueden designar como (+) o (-) dependiendo de la dirección (dextrógira o levógira) en que roten la luz polarizada en el plano a la longitud de onda de la línea de sodio D. Algunos de los compuestos descritos en la presente contienen uno o más centros o ejes asimétricos y, por consiguiente, pueden dar lugar a enantiómeros, diaestereómeros, y otras formas estereoisoméricas que se puedan definir en términos de estereoquímica absoluta, como (*R*) o (*S*).

Dependiendo de la elección de los materiales de partida y de los procedimientos, los compuestos pueden estar presentes en la forma de uno de los posibles isómeros o como mezclas de los mismos, por ejemplo, como los isómeros ópticos puros, o como mezclas de isómeros, tales como racematos y mezclas de diaestereoisómeros, dependiendo del número de átomos de carbono asimétricos. La presente invención pretende incluir todos los posibles isómeros, incluyendo las mezclas racémicas, las mezclas diaestereoméricas, y las formas ópticamente puras. Los isómeros (R) y (S) ópticamente activos se pueden preparar utilizando sintones quirales o reactivos quirales, o se pueden resolver empleando técnicas convencionales. Si el compuesto contiene un doble enlace, el sustituyente puede estar en la configuración E o Z. Si el compuesto contiene a dicicloalquilo sustituido, el sustituyente de cicloalquilo puede tener una configuración *cis* o *trans*. También se pretende incluir a todas las formas tautoméricas.

Como se utilizan en la presente, los términos “sal" o "sales” se refieren a una sal de adición de ácido o de base de un compuesto de la invención. Las “sales” incluyen en particular las “sales farmacéuticas aceptables”. El término “sales farmacéuticamente aceptables” se refiere a las sales que retienen la efectividad biológica y las propiedades de los compuestos de esta invención, y que típicamente no sean biológicamente o de otra manera indeseables. En muchos casos, los compuestos de la presente invención son capaces de formar sales de ácido y/o de base en

virtud de la presencia de los grupos amino y/o carboxilo, o grupos similares a los mismos.

Las sales de adición de ácido farmacéuticamente aceptables se pueden formar con ácidos inorgánicos y ácidos orgánicos, por ejemplo, las sales de acetato, aspartato, benzoato, besilato, bromuro/bromhidrato, bicarbonato/carbonato, bisulfato/sulfato, canforsulfonato, cloruro/clorhidrato, clorteofilonato, citrato, etan-disulfonato, fumarato, gluceptato, gluconato, glucuronato, hipurato, yodhidrato/yoduro, isetionato, lactato, lactobionato, lauril-sulfato, malato, maleato, malonato, mandelato, mesilato, metil-sulfato, naftoato, napsilato, nicotinato, nitrato, octadecanoato, oleato, oxalato, palmitato, pamoato, fosfato / fosfato ácido / fosfato diácido, poligalacturonato, propionato, estearato, succinato, sulfosalicilato, tartrato, tosilato, y trifluoro-acetato.

Los ácidos inorgánicos a partir de los cuales se pueden derivar las sales incluyen, por ejemplo, ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y similares.

Los ácidos orgánicos a partir de los cuales se pueden derivar las sales incluyen, por ejemplo, ácido acético, ácido propiónico, ácido glicólico, ácido oxálico, ácido maleico, ácido malónico, ácido succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido mandélico, ácido metan-sulfónico, ácido etan-sulfónico, ácido p-toluen-sulfónico, ácido sulfosalicílico, y similares. Las sales de adición de base farmacéuticamente aceptables se pueden formar con bases inorgánicas y orgánicas.

Las bases inorgánicas a partir de las cuales se pueden derivar las sales incluyen, por ejemplo, las sales de amonio y de los metales a partir de las columnas I a XII de la Tabla Periódica. En ciertas modalidades, las sales se derivan a partir de sodio, potasio, amonio, calcio, magnesio, hierro, plata, zinc, y cobre; las sales particularmente adecuadas incluyen las sales de amonio, potasio, sodio, calcio, y magnesio.

Las bases orgánicas a partir de las cuales se pueden derivar las sales incluyen, por ejemplo, aminas primarias, secundarias, y terciarias, aminas sustituidas, incluyendo las aminas sustituidas que se presentan naturalmente, aminas cíclicas, resinas básicas de intercambio de iones, y similares. Ciertas aminas orgánicas incluyen isopropil-amina, benzatina, colinato, dietanolamina, dietil-amina, lisina, meglumina, piperazina, y trometamina.

Las sales farmacéuticamente aceptables de la presente invención se pueden sintetizar a partir de una fracción básica o ácida, mediante métodos químicos convencionales. En términos generales, estas sales se pueden preparar mediante la reacción de las formas del ácido libre de estos compuestos con una cantidad estequiométrica de la base apropiada (tales como hidróxido, carbonato, bicarbonato de Na, Ca, Mg, o K, o similares), o mediante la reacción de las formas de base libre de estos compuestos con una cantidad estequiométrica del ácido apropiado. Estas reacciones típicamente se llevan a cabo en agua o en un solvente orgánico, o en una mezcla de los dos. En términos generales, es deseable el uso de

un medio no acuoso como éter, acetato de etilo, etanol, isopropanol, o acetonitrilo, en donde sea practicable. Se pueden encontrar listas de sales adecuadas adicionales, por ejemplo, en “Remington's Pharmaceutical Sciences”, 20ª Edición, Mack Publishing Company, Easton, Pa., (1985); y en “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” por Stahl y Wermuth (Wiley-VCH, Weinheim, Alemania, 2002).

Cualquier fórmula dada en la presente también pretende representar las formas no marcadas así como las formas isotópicamente marcadas de los compuestos. Los compuestos isotópicamente marcados tienen las estructuras ilustradas por las fórmulas dadas en la presente, excepto que uno o más átomos son reemplazados por un átomo que tiene una masa atómica o número de masa seleccionados. Los ejemplos de los isótopos que se pueden incorporar en los compuestos de la invención incluyen los isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor, y cloro, tales como ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I, respectivamente. La invención incluye diferentes compuestos isotópicamente marcados como se definen en la presente, por ejemplo, aquéllos en donde están presentes los isótopos radioactivos, tales como ^{3}H y ^{14}C, o aquéllos en donde están presentes los isótopos no radioactivos, tales como ^{2}H y ^{13}C. Estos compuestos isotópicamente marcados son útiles en los estudios metabólicos (con ^{14}C), en los estudios de cinética de reacción (con, por ejemplo ^{2}H ó ^{3}H), en las técnicas de detección o de formación de

imágenes, tales como tomografía por emisión de positrones (PET) o tomografía computarizada con emisión de un solo fotón (SPECT), incluyendo los ensayos de distribución del fármaco o del sustrato en el tejido, o en el tratamiento radioactivo de los pacientes. En particular, puede ser particularmente deseable un compuesto de ^{18}F o marcado para los estudios de PET o SPECT. Los compuestos isotópicamente marcados de la fórmula (I) se pueden preparar en términos generales mediante las técnicas convencionales conocidas por los expertos en este campo o mediante procesos análogos a aquéllos descritos en los ejemplos y preparaciones acompañantes, utilizando un reactivo isotópicamente marcado apropiado en lugar del reactivo no marcado previamente empleado.

Además, la sustitución con isótopos más pesados, en particular deuterio (es decir, ^{2}H o D) puede proporcionar ciertas ventajas terapéuticas resultantes de la mayor estabilidad metabólica, por ejemplo un aumento de la vida media *in vivo* o requerimientos de dosificación reducida o una mejora en el índice terapéutico. Se entiende que el deuterio en este contexto se considera como un sustituyente de un compuesto de la fórmula (I). La concentración de este isótopo más pesado, específicamente deuterio, se puede definir por el factor de enriquecimiento isotópico. El término "factor de enriquecimiento isotópico", como se utiliza en la presente, significa la proporción entre la abundancia isotópica y la abundancia natural de un isótopo especificado. Si un sustituyente en un compuesto de esta invención es denotado como deuterio, este compuesto tiene un

factor de enriquecimiento isotópico para cada átomo de deuterio designado de cuando menos 3500 (52.5 por ciento de incorporación de deuterio en cada átomo de deuterio designado), de cuando menos 4000 (60 por ciento de incorporación de deuterio), de cuando menos 4500 (67.5 por ciento de incorporación de deuterio), de cuando menos 5000 (75 por ciento de incorporación de deuterio), de cuando menos 5500 (82.5 por ciento de incorporación de deuterio), de cuando menos 6000 (90 por ciento de incorporación de deuterio), de cuando menos 6333.3 (95 por ciento de incorporación de deuterio), de cuando menos 6466.7 (97 por ciento de incorporación de deuterio), de cuando menos 6600 (99 por ciento de incorporación de deuterio), o de cuando menos 6633.3 (99.5 por ciento de incorporación de deuterio).

Los solvatos farmacéuticamente aceptables de acuerdo con la invención incluyen aquéllos en donde el solvente de cristalización puede ser isotópicamente sustituido, por ejemplo, D_2O, d_6-acetona, DMSO-d_6.

Los compuestos de la invención, es decir, los compuestos de la fórmula (I), que contienen grupos capaces de actuar como donadores y/o aceptores para los enlaces de hidrógeno, pueden ser capaces de formar co-cristales con formadores de co-cristales adecuados. Estos co-cristales se pueden preparar a partir de los compuestos de la fórmula (I) mediante los procedimientos de formación de co-cristales conocidos. Estos procedimientos incluyen molienda, calentamiento, co-sublimación, co-fusión, o contacto en solución de los compuestos

de la fórmula (I) con el formador de co-cristales bajo condiciones de cristalización, y el aislamiento de los co-cristales formados de esta manera. Los formadores de co-cristales adecuados incluyen aquéllos descritos en la Publicación Internacional Número WO 2004/078163. Por consiguiente, la invención proporciona además co-cristales, los cuales comprenden un compuesto de la fórmula (I).

Como se utiliza en la presente, el término "vehículo farmacéuticamente aceptable" incluye cualquiera y todos los solventes, medios de dispersión, recubrimientos, tensoactivos, antioxidantes, conservadores (por ejemplo, agentes antibacterianos, agentes antifúngicos), agentes isotónicos, agentes retardantes de absorción, sales, conservadores, estabilizantes de fármacos, aglutinantes, excipientes, agentes de desintegración, lubricantes, agentes edulcorantes, agentes saborizantes, tintes, y similares, y combinaciones de los mismos, como serían conocidos por los expertos en este campo (véase, por ejemplo, Remington's Pharmaceutical Sciences, 18ª Edición, Mack Printing Company, 1990, páginas 1289-1329). Excepto hasta donde cualquier vehículo convencional sea incompatible con el ingrediente activo, se contempla su uso en las composiciones terapéuticas o farmacéuticas.

El término "una cantidad terapéuticamente efectiva" de un compuesto de la presente invención se refiere a una cantidad del compuesto de la presente invención que provocará la respuesta biológica o médica de un sujeto, por ejemplo, la reducción o

inhibición de la actividad de una enzima o de una proteína, o que mitigará los síntomas, aliviará las condiciones, hará más lento o retardará el progreso de la enfermedad, o prevendrá una enfermedad, etc. En una modalidad no limitante, el término “una cantidad terapéuticamente efectiva” se refiere a la cantidad del compuesto de la presente invención que, cuando se administra a un sujeto, es efectiva para: (1) cuando menos parcialmente aliviar, inhibir, impedir y/o mitigar una condición, o un trastorno, o una enfermedad (i) mediada por PI3K, o (ii) asociada con la actividad de PI3K, o (iii) caracterizada por una actividad (normal o anormal) de PI3K, o (2) reducir o inhibir la actividad de PI3K, o (3) reducir o inhibir la expresión de PI3K. En otra modalidad no limitante, el término “una cantidad terapéuticamente efectiva” se refiere a la cantidad del compuesto de la presente invención que, cuando se administra a una célula, o a un tejido, o a un material biológico no celular, o a un medio, es efectiva para reducir o inhibir cuando menos parcialmente la actividad de PI3K; o para reducir o inhibir cuando menos parcialmente la expresión de PI3K. El significado del término “una cantidad terapéuticamente efectiva” como se ilustra en la modalidad anterior para PI3K también se aplica por el mismo medio a cualesquiera otras proteínas/péptidos/enzimas relevantes.

Como se utiliza en la presente, el término “sujeto” se refiere a un animal. Típicamente, el animal es un mamífero. Un sujeto también se refiere, por ejemplo, a primates (por ejemplo, a seres humanos, masculinos o femeninos), reses, ovejas, cabras, caballos, perros,

gatos, conejos, ratas, ratones, peces, aves y similares. En ciertas modalidades, el sujeto es un primate. En todavía otras modalidades, el sujeto es un ser humano.

Como se utiliza en la presente, el término “inhibir”, "inhibición", o "inhibiendo” se refiere a la reducción o supresión de una condición, síntoma, o trastorno, o enfermedad dados, o a una disminución significativa en la actividad de la línea base de una actividad o proceso biológico.

Como se utiliza en la presente, el término “tratar”, “tratando", o "tratamiento" de cualquiera enfermedad o trastorno, se refiere, en una modalidad, a mitigar la enfermedad o el trastorno (es decir, hacer más lento o detener o reducir el desarrollo de la enfermedad, o de cuando menos uno de los síntomas clínicos de la misma). En otra modalidad, “tratar”, "tratando", o "tratamiento" se refiere a aliviar o mitigar cuando menos un parámetro físico, incluyendo aquéllos que no puedan ser discernibles por parte del paciente. En todavía otra modalidad, “tratar”, "tratando", o "tratamiento" se refiere a modular la enfermedad o el trastorno, ya sea físicamente (por ejemplo, la estabilización de un síntoma discernible), fisiológicamente (por ejemplo, la estabilización de un parámetro físico), o ambas. En todavía otra modalidad, “tratar”, "tratando", o "tratamiento" se refiere a prevenir o retardar el establecimiento o desarrollo o progreso de la enfermedad o del trastorno.

Como se utiliza en la presente, un sujeto está “en necesidad de” tratamiento, si este sujeto se beneficiaría biológicamente,

médicamente, o en su calidad de vida, a partir de dicho tratamiento.

Como se utiliza en la presente, el término "un", "uno", "el", y términos similares utilizados en el contexto de la presente invención (en especial en el contexto de las reivindicaciones), se deben interpretar para cubrir tanto el singular como el plural, a menos que se indique de otra manera en la presente o que sea claramente contradicho por el contexto.

Todos los métodos descritos en la presente se pueden llevar a cabo en cualquier orden adecuado, a menos que se indique de otra manera en la presente o que sea claramente contradicho de otra manera por el contexto. El uso de cualquiera y todos los ejemplos, o del lenguaje de ejemplo (por ejemplo, "tal como") proporcionados en la presente, pretende meramente iluminar mejor la invención, y no presenta una limitación sobre el alcance de la invención reivindicada de otra manera.

Cualquier átomo asimétrico (por ejemplo, carbono, o similares) de los compuestos de la presente invención, puede estar presente en una configuración racémica o enantioméricamente enriquecida, por ejemplo en la configuración (R), (S) o (R,S). En ciertas modalidades, cada átomo asimétrico tiene un exceso enantiomérico de cuando menos el 50 por ciento, un exceso enantiomérico de cuando menos el 60 por ciento, un exceso enantiomérico de cuando menos el 70 por ciento, un exceso enantiomérico de cuando menos el 80 por ciento, un exceso enantiomérico de cuando menos el 90 por ciento, un exceso enantiomérico de cuando menos el 95 por ciento, o un exceso

enantiomérico de cuando menos el 99 por ciento en la configuración (R) o (S). Los sustituyentes en los átomos con dobles enlaces insaturados, si es posible, pueden estar presentes en la forma *cis* (Z) o *trans* (E).

De conformidad con lo anterior, como se utiliza en la presente, un compuesto de la presente invención puede estar en la forma de uno de los posibles isómeros, rotámeros, atropisómeros, tautómeros, o mezclas de los mismos, por ejemplo, como isómeros geométricos (*cis* o *trans*), diaestereómeros, isómeros ópticos (antípodas), o racematos sustancialmente puros, o mezclas de los mismos.

Cualesquiera mezclas de isómeros resultantes se pueden separar con base en las diferencias fisicoquímicas de los constituyentes, en los isómeros geométricos u ópticos diaestereómeros, racematos puros o sustancialmente puros, por ejemplo, mediante cromatografía y/o cristalización fraccionaria.

Cualesquiera racematos resultantes de los productos finales o intermediarios se pueden resolver en los antípodas ópticos mediante los métodos conocidos, por ejemplo, mediante la separación de las sales diaestereoméricas de los mismos, obtenidas con un ácido o base ópticamente activos, y liberando el compuesto ácido o básico ópticamente activo. En particular, por consiguiente, se puede emplear una fracción básica para resolver los compuestos de la presente invención en sus antípodas ópticos, por ejemplo, mediante la cristalización fraccionaria de una sal formada con un ácido ópticamente activo, por ejemplo, ácido tartárico, ácido dibenzoil-

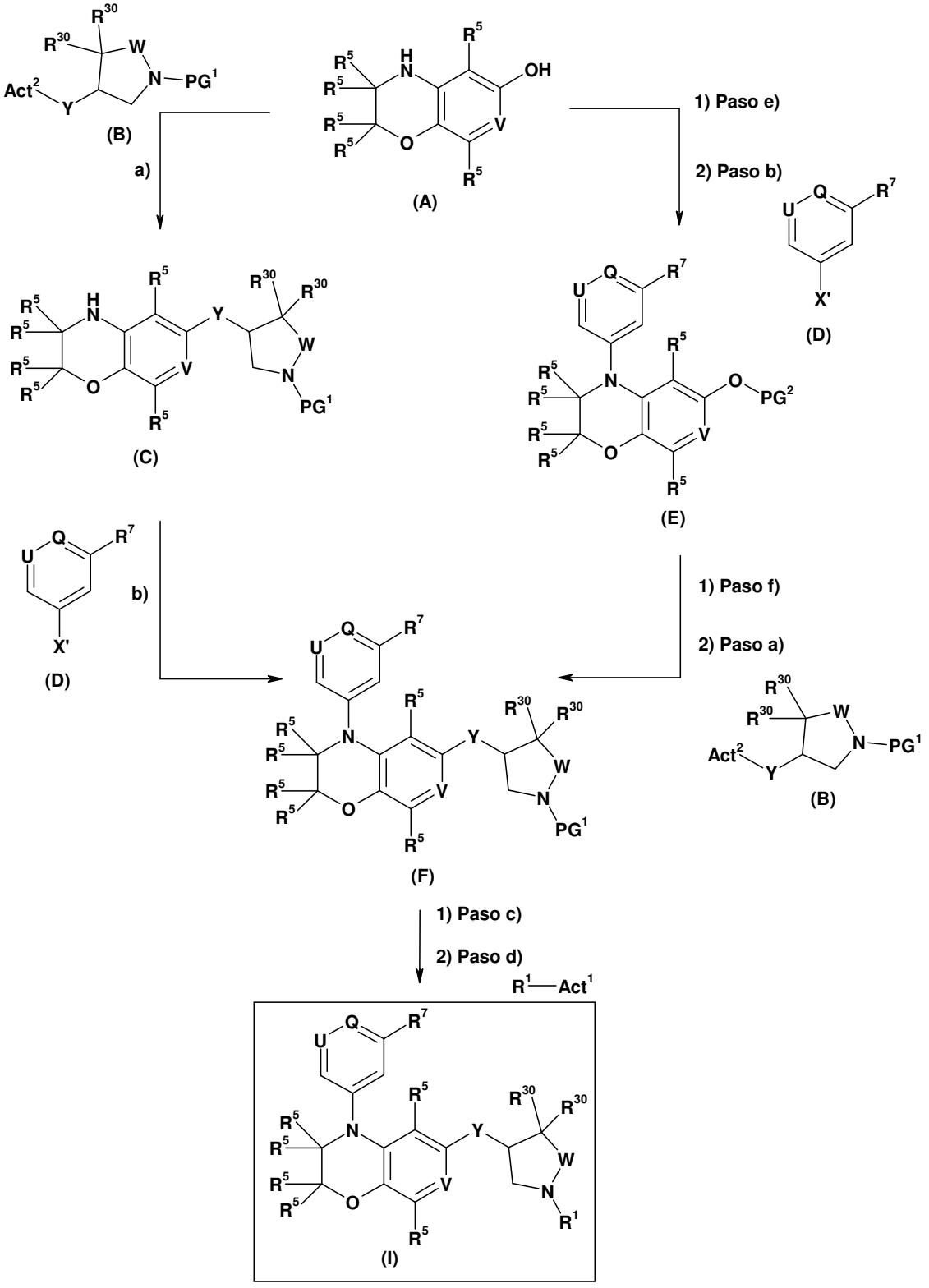
tartárico, ácido diacetil-tartárico, ácido di-*O,O'*-*p*-toluoil-tartárico, ácido mandélico, ácido málico, o ácido canfor-10-sulfónico. Los productos racémicos también se pueden resolver mediante cromatografía quiral, por ejemplo, cromatografía de líquidos a alta presión (HPLC), utilizando un adsorbente quiral.

Adicionalmente, los compuestos de la presente invención, incluyendo sus sales, también se pueden obtener en la forma de sus hidratos, o pueden incluir otros solventes utilizados para su cristalización. Los compuestos de la presente invención pueden formar, inherentemente o por diseño, solvatos, con los solventes farmacéuticamente aceptables (incluyendo agua); por consiguiente, se pretende que la invención abarque las formas tanto solvatadas como no solvatadas. El término "solvato" se refiere a un complejo molecular de un compuesto de la presente invención (incluyendo las sales farmacéuticamente aceptables del mismo) con una o más moléculas de solvente. Estas moléculas de solvente son aquéllas comúnmente utilizadas en la técnica farmacéutica que sean conocidas como inocuas para el receptor, por ejemplo, agua, etanol, y similares. El término "hidrato" se refiere al complejo en donde la molécula de solvente es agua.

Los compuestos de la presente invención, incluyendo las sales, hidratos y solvatos de los mismos, pueden formar, inherentemente o por diseño, polimorfos.

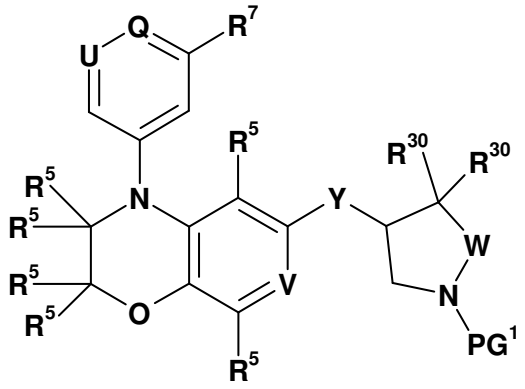
Típicamente, los compuestos de la fórmula (I) se pueden preparar de acuerdo con los métodos proporcionados a continuación.

Esquema A



En una modalidad, la invención se refiere a un proceso para la elaboración de un compuesto de la fórmula (I) (Método A), el cual comprende los pasos a, b, c, d.

El compuesto de la fórmula (I) se obtiene por medio del paso c de desproteger PG^1 a partir del compuesto de la fórmula (F), en donde PG^1 representa un grupo protector adecuado, tal como un grupo Boc, y los otros sustituyentes son como se definen anteriormente,



(F)

seguido por el paso de reacción de acoplamiento d con

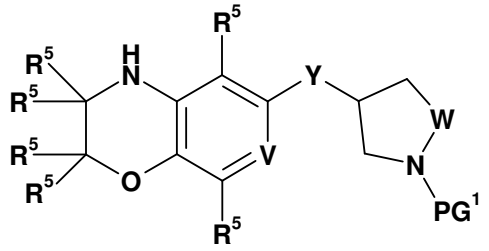
R^1-Act^1,

Paso c1: en donde R^1 es -C(O)-R^4 o -$S(O)_2$-R^4, en donde R^4 se define anteriormente, y Act^1 representa un grupo activador o un grupo hidroxilo: La reacción de acoplamiento es la formación de una amida, urea, éster carbámico o sulfonamida. Hay muchas maneras conocidas de preparar amidas, urea, ésteres carbámicos o sulfonamidas. El paso de reacción de acoplamiento se puede llevar a cabo con Act^1 que representa un grupo activador, de preferencia en un procedimiento de un paso o con Act^1 que representa un grupo

hidroxilo involucrando un procedimiento ya sea de uno o de dos pasos. Para los ejemplos de las formaciones de enlaces de amida, véase Mantalbetti, C.A.G.N y Falque, V., Amide bond formation and peptide coupling, Tetrahedron, 2005, 61(46), páginas 10827-10852 y las referencias citadas en el mismo. Para los ejemplos de la síntesis de urea, véase Sartori, G.; Maggi, R. Acyclic and cyclic ureas, Science of Synthesis (2005), 18, 665-758; Gallou, Isabelle. Unsymmetrical ureas Synthetic methodologies and application in drug design, Organic Preparations and Procedures International (2007), 39(4), 355-383. Para los ejemplos de la síntesis de carbamato, véase Adams, Philip; Baron, Frank A. Esters of carbamic acid, Chemical Reviews (1965), 65(5), 567-602. Los ejemplos proporcionados en la presente, por consiguiente, no pretenden ser exhaustivos, sino meramente ilustrativos;

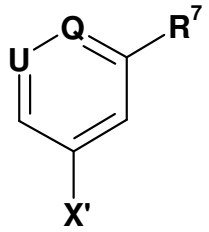
Paso c2: en donde R^1 se selecciona a partir de fenilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, 1,2,3-triazinilo, 1,2,4-triazinilo o 1,3,5-triazinilo, y Act^1 representa halógeno, en particular yodo o bromo: La reacción de acoplamiento se lleva a cabo en la presencia de una base de amina, tal como N,N-di-isopropil-etil-amina. La reacción se lleva a cabo en la presencia de un solvente orgánico o sin un solvente, bajo calentamiento con microondas. De una manera alternativa, la reacción se lleva a cabo bajo las condiciones de Buchwald-Hartwig acostumbradas, tales como las condiciones descritas anteriormente. La reacción de preferencia se lleva a cabo bajo un gas inerte, tal como nitrógeno o argón.

El compuesto de la fórmula (F) se obtiene por medio del paso b de acoplamiento del compuesto de la fórmula (C), en donde PG^1 representa un grupo protector adecuado, tal como un Boc, y los otros sustituyentes son como se definen anteriormente,



(C)

con un compuesto de la fórmula (D), en donde X' representa halógeno, tal como yodo o bromo, y los otros sustituyentes son como se definen anteriormente,

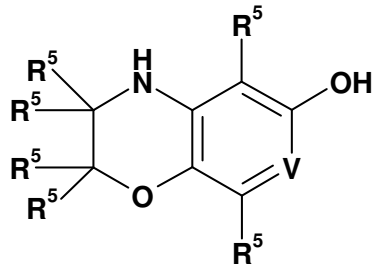


(D)

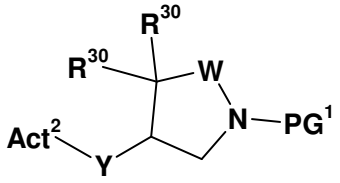
bajo las condiciones de Buchwald-Hartwig acostumbradas, utilizando una combinación adecuada de catalizador de Pd / ligando, tal como $Pd_2(dba)_3$/2-(diciclohexil-fosfino)-bifenilo o $Pd_2(dba)_3$/2-diciclohexil-fosfino-2',4',6'-tri-isopropil-bifenilo, $Pd_2(dba)_3$/X-Phos, $Pd_2(dba)_3$/(rac)-BINAP, $Pd(OAc)_2$/(rac)-BINAP o bis-(tri-terbutil-fosfina)-paladio, y una base adecuada, tal como NaOtBu, Cs_2CO_3 ó K_3PO_4 y un solvente orgánico, tal como tolueno, dioxano o tetrahidrofurano (THF). La reacción se agita a una temperatura de

aproximadamente 60°C a 140°C, por ejemplo, de 100°C a 110°C, y opcionalmente se lleva a cabo en un reactor de microondas. La reacción de preferencia se lleva a cabo bajo un gas inerte, tal como nitrógeno o argón.

El compuesto de la fórmula (C) se obtiene por medio del paso a de acoplamiento del compuesto de la fórmula (A), en donde los sustituyentes son como se definen anteriormente, con un compuesto de la fórmula (B), en donde PG^1 representa un grupo protector adecuado, tal como un grupo Boc, y Act^2 es un grupo activador o H, y los otros sustituyentes son como se definen anteriormente,



(A)



(B)

Paso a1: en donde Y es O, y Act^2 representa un grupo activador, tal como un mesilato: La reacción tiene lugar en la presencia de una base adecuada, tal como hidróxido de sodio (NaH), K_2CO_3 ó terbutóxido de potasio (tBuOK), en un solvente orgánico polar adecuado, tal como dimetil-formamida, tetrahidrofurano (THF), 2-metil-tetrahidrofurano (THF) o Dioxano, a una temperatura

adecuada, tal como desde la temperatura ambiente hasta 100°C;

Paso a2: en donde Y es O, y Act^2 representa H: La reacción tiene lugar utilizando las condiciones de Mitsunobu acostumbradas, por ejemplo, utilizando Ph_3P y DEAD, en un solvente orgánico, tal como tetrahidrofurano (THF), bajo condiciones de gas inerte, a una temperatura elevada, tal como a 70°C.

Paso a3: en donde Y es NH, y Act^2 representa H: se emplea una reacción de acoplamiento de fosfonio promovida por una base, en donde un compuesto de la fórmula (A), en un solvente adecuado, tal como acetonitrilo, se hace reaccionar con una sal de fosfonio, tal como hexafluoro-fosfato de benzotriazol-1-iloxi-tris-(dimetil-amino)-fosfonio (BOP), en la presencia de una base, tal como 1,8-diaza-7-biciclo-[5.4.0]-undeceno (DBU), seguida por la adición de un compuesto de la fórmula (B). La mezcla de reacción se agita a una temperatura de 20°C a 100°C.

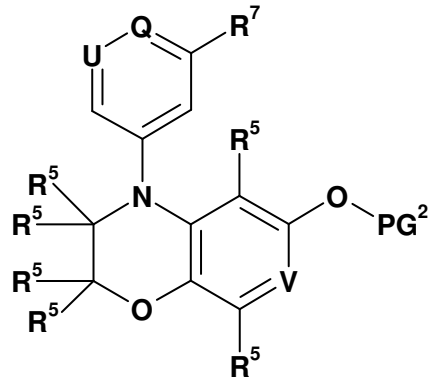
En otra modalidad, la invención se refiere a un proceso para la elaboración de un compuesto de la fórmula (I) (Método A-a), el cual comprende los pasos a y b como se definen anteriormente para el Método A, utilizando un compuesto de la fórmula (B), en donde PG^1 representa R^1.

En otra modalidad, la invención se refiere a un proceso para la elaboración de un compuesto de la fórmula (I) (Método B), el cual comprende los pasos e, b, f, a, c, y d.

El compuesto de la fórmula (I) se obtiene por medio de los pasos c y d como se describen anteriormente para el Método A, a

partir del compuesto de la fórmula (F).

El compuesto de la fórmula (F) se obtiene por medio del paso f de desproteger PG^2 a partir del compuesto de la fórmula (E), en donde PG^2 es un grupo protector adecuado, tal como un grupo protector de sililo, y los otros sustituyentes son como se definen anteriormente,



(E)

,

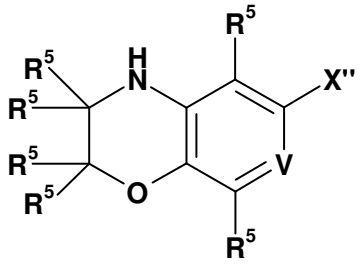
seguido por el paso de reacción de acoplamiento a, como se describe anteriormente para el Método A, con el compuesto de la fórmula (B).

El compuesto de la fórmula (E) se obtiene por medio del paso e de proteger el compuesto de la fórmula (A) con un grupo protector adecuado PG^2, seguido por el compuesto de la fórmula (E), en donde PG^2 es un grupo protector adecuado, tal como un grupo protector de sililo, seguido por el paso de reacción de acoplamiento b, como se describe anteriormente para el Método A, con el compuesto de la fórmula (D).

En otra modalidad, la invención se refiere a un proceso para la elaboración de un compuesto de la fórmula (I) (Método B-a), el cual

comprende los pasos e, b, y f como se definen anteriormente para el Método B, utilizando un compuesto de la fórmula (B), en donde PG^1 representa R^1.

En otra modalidad, la invención se refiere a un proceso para la elaboración de un compuesto de la fórmula (I) (Método C), utilizando un compuesto de la fórmula (A'), en donde X'' representa halógeno, y los otros sustituyentes son como se definen anteriormente,



(A')

el cual comprende los pasos b, c, y d como se definen anteriormente para el Método B, utilizando un compuesto de la fórmula (B), y un paso modificado a4:

Paso a4: en donde Y es NH, y Act^2 es H: La reacción tiene lugar en la presencia de una base adecuada, tal como, por ejemplo, carbonato de potasio o una base de amina adecuada, tal como trietil-amina o N,N-di-isopropil-etil-amina, a una temperatura elevada, tal como de 100°C a 140°C. De una manera alternativa, la reacción se lleva a cabo bajo las condiciones de Buchwald-Hartwig acostumbradas, tales como las condiciones descritas anteriormente. La reacción de preferencia se lleva a cabo bajo un gas inerte, tal como nitrógeno o argón.

En otra modalidad, la invención se refiere a un proceso para la

elaboración de un compuesto de la fórmula (I) (Método C-a), el cual comprende los pasos b, a4, c, y d como se definen anteriormente para el método B^1, utilizando un compuesto de la fórmula (B), en donde PG^1 representa R^1.

El término “grupo activador", como se utiliza en la presente, se refiere a un grupo que puede activar un ácido carboxílico, un ácido carbónico, o un derivado de ácido carbónico, para acoplarse con una fracción de amina para formar una fracción de amida, urea o éster carbámico, respectivamente, (Act^1), o con un grupo que pueda activar un grupo hidroxilo para acoplarse con otra fracción de hidroxilo para formar un éter (Act^2).

Los grupos que pueden activar un ácido carboxílico, un ácido carbónico, o un derivado de ácido carbónico, para acoplarse con una fracción de amina para formar una fracción de amida, urea o éster carbámico, son los cloruros, o los grupos resultantes de la reacción del derivado de ácido con un agente activador. Los agentes activadores adecuados son conocidos por la persona experta, y los ejemplos de tales reactivos activadores son los derivados de carbodi-imida, los derivados de pentafluoro-fenil-éster, los derivados de triazol, y los derivados de imidazol.

Los grupos que pueden activar un grupo hidroxilo para acoplarse con otra fracción de hidroxilo para formar un éter son los grupos conocidos por la persona experta, y los ejemplos de tales grupos activadores son los mesilatos y tosilatos.

El término “grupo protector", como se utiliza en la presente, se

refiere a un grupo que protege a un grupo funcional que está presente en los materiales de partida y no se pretende que tome parte en la reacción. En los pasos adicionales del proceso, llevados a cabo como se desee, los grupos funcionales de los compuestos de partida que no deban tomar parte en la reacción pueden estar presentes en una forma desprotegida, o se pueden proteger, por ejemplo, mediante uno o más grupos protectores. Los grupos protectores entonces se remueven total o parcialmente de acuerdo con uno de los métodos conocidos. Los grupos protectores, y la manera en la que se introducen y se remueven, se describen, por ejemplo, en "Protective Groups in Organic Chemistry", Plenum Press, Londres, Nueva York 1973, y en "Methoden der organischen Chemie", Houben-Weyl, 4a. Edición, Volumen 15/1, Georg-Thieme-Verlag, Stuttgart 1974, y en Theodora W. Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons, Nueva York 1981. Una característica de los grupos protectores es que se pueden remover fácilmente, es decir, sin la presentación de reacciones secundarias indeseadas, por ejemplo, mediante solvólisis, reducción, fotólisis, o de una manera alternativa, bajo condiciones fisiológicas.

La invención incluye además cualquier variante de los presentes procesos, en donde se utiliza un producto intermediario que se pueda obtener en cualquier etapa de los mismos como material de partida y se llevan a cabo los pasos restantes, o en donde los materiales de partida se forman *in situ* bajo las condiciones de reacción, o en donde los componentes de la reacción

se utilizan en la forma de sus sales o de un material ópticamente puro.

Los compuestos de la invención e intermediarios también se pueden convertir unos en otros de acuerdo con los métodos conocidos generalmente por los expertos en este campo.

Los intermediarios y los productos finales se pueden procesar y/o purificar de acuerdo con los métodos convencionales, por ejemplo, empleando métodos cromatográficos, métodos de distribución, (re-)cristalización, y similares.

Lo siguiente se aplica en general a todos los procesos mencionados anteriormente en la presente y más adelante en la presente.

Todos los pasos de proceso anteriormente mencionados se pueden llevar a cabo en condiciones de reacción que son conocidas por los expertos en este campo, incluyendo aquéllas mencionadas de una manera específica, en ausencia, o, por costumbre, en la presencia de solventes o diluyentes, incluyendo, por ejemplo, solventes o diluyentes que sean inertes hacia los reactivos utilizados y los disuelvan, en ausencia o en la presencia de catalizadores, agentes de condensación o neutralizantes, por ejemplo intercambiadores de iones, tales como intercambiadores de cationes, por ejemplo, en la forma de H+, dependiendo de la naturaleza de la reacción y/o de los reactivos, a temperatura reducida, normal, o elevada, por ejemplo en un intervalo de temperatura de aproximadamente -100°C a aproximadamente 190°C, incluyendo, por

ejemplo, de aproximadamente -80 °C a aproximadamente 150 °C, por ejemplo de -80 °C a -60 °C, a temperatura ambiente, de -20 °C a 40 °C, o a la temperatura de reflujo, bajo presión atmosférica o en un recipiente cerrado, en donde sea apropiado bajo presión, y/o en una atmósfera inerte, por ejemplo bajo una atmósfera de argón o de nitrógeno.

En todas las etapas de las reacciones, las mezclas de isómeros que se formen se pueden separar en los isómeros individuales, por ejemplo en los diaestereoisómeros o enantiómeros, o en cualesquiera mezclas de isómeros deseadas, por ejemplo racematos, o mezclas de diaestereoisómeros, por ejemplo de una manera análoga a los métodos descritos anteriormente en la presente.

Los solventes a partir de los cuales se pueden seleccionar aquellos solventes que sean adecuados para cualquier reacción particular, incluyen aquéllos mencionados específicamente o, por ejemplo, agua, ésteres, tales como alcanoatos inferiores de alquilo inferior, por ejemplo acetato de etilo, éteres, tales como éteres alifáticos, por ejemplo dietil-éter, o éteres cíclicos, por ejemplo tetrahidrofurano (THF) o dioxano, hidrocarburos aromáticos líquidos, tales como benceno o tolueno, alcoholes, tales como metanol, etanol o 1- ó 2-propanol, nitrilos, tales como acetonitrilo, hidrocarburos halogenados, tal como cloruro de metileno o cloroformo, amidas de ácido, tales como dimetil-formamida (DMF) o dimetil-acetamida, bases, tales como bases de nitrógeno heterocíclicas, por ejemplo

piridina o *N*-metil-pirrolidin-2-ona, anhídridos de ácido carboxílico, tales como anhídridos del ácido alcanoico inferior, por ejemplo anhídrido acético, hidrocarburos cíclicos, lineales o ramificados, tales como ciclohexano, hexano o isopentano, metil-ciclohexano, o las mezclas de estos solventes, por ejemplo soluciones acuosas, a menos que se indique de otra manera en la descripción de los procesos. Estas mezclas de solventes también se pueden utilizar en el procesamiento, por ejemplo mediante cromatografía o división.

Los compuestos, incluyendo sus sales, también se pueden obtener en la forma de hidratos, o sus cristales, por ejemplo, pueden incluir al solvente utilizado para la cristalización. Puede haber diferentes formas cristalinas presentes.

La invención se refiere también a las formas del proceso en donde se utiliza un compuesto que se pueda obtener como un intermediario en cualquier etapa del proceso como material de partida y se llevan a cabo los pasos restantes del proceso, o en donde se forma un material de partida bajo las condiciones de reacción o se utiliza en la forma de un derivado, por ejemplo en una forma protegida o en la forma de una sal, o se produce un compuesto que se pueda obtener mediante el proceso de acuerdo con la invención bajo las condiciones del proceso y se procesa adicionalmente *in situ*.

En otro aspecto, la presente invención proporciona una composición farmacéutica, la cual comprende un compuesto de la presente invención, o una sal farmacéuticamente aceptable del

mismo, y un vehículo farmacéuticamente aceptable. La composición farmacéutica se puede formular para vías de administración particulares, tales como administración oral, administración parenteral, y administración rectal, etc. En adición, las composiciones farmacéuticas de la presente invención, se pueden configurar en una forma sólida (incluyendo, sin limitación, cápsulas, tabletas, píldoras, gránulos, polvos o supositorios), o en una forma líquida (incluyendo, sin limitación, soluciones, suspensiones o emulsiones). Las composiciones farmacéuticas se pueden someter a las operaciones farmacéuticas convencionales, tales como esterilización y/o pueden contener diluyentes inertes, agentes lubricantes, o agentes reguladores convencionales, así como adyuvantes, tales como conservadores, estabilizantes, agentes humectantes, emulsionantes y reguladores del pH, etc.

Típicamente, las composiciones farmacéuticas son tabletas o cápsulas de gelatina, las cuales comprenden el ingrediente activo junto con:

a) diluyentes, por ejemplo, lactosa, dextrosa, sacarosa, manitol, sorbitol, celulosa y/o glicina;

b) lubricantes, por ejemplo, sílice, talco, ácido esteárico, su sal de magnesio o de calcio y/o polietilenglicol; para tabletas también,

c) aglutinantes, por ejemplo, silicato de magnesio y aluminio, pasta de almidón, gelatina, tragacanto, metil-celulosa, carboxi-metil-celulosa de sodio y/o polivinil-pirrolidona; si se desea,

d) desintegrantes, por ejemplo, almidones, agar, ácido algínico o su sal sódica, o mezclas efervescentes; y/o

e) absorbentes, colorantes, saborizantes y edulcorantes.

Las tabletas se pueden recubrir con película o se pueden recubrir entéricamente de acuerdo con los métodos conocidos en la técnica.

Las composiciones adecuadas para administración oral incluyen una cantidad efectiva de un compuesto de la invención en la forma de tabletas, grageas, suspensiones acuosas u oleosos, polvos o gránulos dispersables, emulsiones, cápsulas duras o blandas, o jarabes o elíxires. Las composiciones pretendidas para uso oral se preparan de acuerdo con cualquier método conocido en la materia para la elaboración de composiciones farmacéuticas, y estas composiciones pueden contener uno o más agentes seleccionados a partir del grupo que consiste en agentes edulcorantes, agentes saborizantes, agentes colorantes, y agentes conservadores, con el objeto de proporcionar preparaciones farmacéuticamente elegantes y sabrosas. Las tabletas pueden contener al ingrediente activo mezclado con excipientes farmacéuticamente aceptables no tóxicos que sean adecuados para la elaboración de tabletas. Estos excipientes son, por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio, o fosfato de sodio; agentes de granulación y desintegrantes, por ejemplo almidón de maíz, o ácido algínico; agentes aglutinantes, por ejemplo almidón, gelatina, o acacia; y agentes lubricantes, por

ejemplo estearato de magnesio, ácido esteárico, o talco. Las tabletas son no recubiertas o son recubiertas mediante técnicas conocidas para demorar la desintegración y absorción en el tracto gastrointestinal y de esta manera proporcionar una acción sostenida durante un período más largo. Por ejemplo, se puede emplear un material de demora de tiempo, tal como monoestearato de glicerilo o diestearato de glicerilo. Las formulaciones para uso oral se pueden presentar como cápsulas de gelatina dura, en donde el ingrediente activo se mezcla con un diluyente sólido inerte, por ejemplo carbonato de calcio, fosfato de calcio, o caolín, o como cápsulas de gelatina blanda, en donde el ingrediente activo se mezcla con agua o un medio oleoso, por ejemplo aceite de cacahuate, parafina líquida, o aceite de oliva.

Ciertas composiciones inyectables son soluciones o suspensiones isotónicas acuosas, y los supositorios convenientemente se preparan a partir de emulsiones o suspensiones grasas. Estas composiciones se pueden esterilizar y/o pueden contener adyuvantes, tales como agentes conservadores, estabilizantes, humectantes, o emulsionantes, promotores de solución, sales para regular la presión osmótica, y/o reguladores del pH. En adición, también pueden contener otras sustancias terapéuticamente valiosas. Estas composiciones se preparan de acuerdo con los métodos convencionales de mezcla, granulación, o recubrimiento, respectivamente, y contienen de aproximadamente el 0.1 al 75 por ciento, o contienen de aproximadamente el 1 al 50 por ciento del

ingrediente activo.

Las composiciones adecuadas para aplicación transdérmica incluyen una cantidad efectiva de un compuesto de la invención con un vehículo adecuado. Los vehículos adecuados para suministro transdérmico incluyen solventes farmacéuticamente aceptables absorbibles para ayudar al paso a través de la piel del huésped. Por ejemplo, los dispositivos transdérmicos están en la forma de un parche que comprende un miembro de respaldo, un depósito que contiene al compuesto opcionalmente con vehículos, opcionalmente una barrera de control de velocidad para suministrar el compuesto de la piel del huésped a una velocidad controlada y previamente determinada durante un período de tiempo prolongado, y elementos para asegurar el dispositivo a la piel.

Las composiciones adecuadas para aplicación tópica, por ejemplo, a la piel y a los ojos, incluyen soluciones acuosas, suspensiones, ungüentos, cremas, geles, o formulaciones en rociables, por ejemplo para el suministro mediante aerosol o similar. Estos sistemas de suministro tópico serán en particular apropiados para aplicación dérmica, por ejemplo para el tratamiento de cáncer de piel, por ejemplo para uso profiláctico en cremas solares, lociones, aerosoles, y similares. Por consiguiente, son particularmente adecuados para utilizarse en formulaciones tópicas, incluyendo cosméticas, bien conocidas en este campo. Pueden contener solubilizantes, estabilizantes, agentes potenciadores de tonicidad, reguladores del pH, y conservadores.

Como se utiliza en la presente, una aplicación tópica también puede pertenecer a una inhalación o a una aplicación intranasal. De una manera conveniente se pueden suministrar en la forma de un polvo seco (ya sea solo, como una mezcla, por ejemplo una mezcla seca con lactosa, o bien como una partícula componente mezclada, por ejemplo con fosfolípidos) a partir de un inhalador de polvo seco, o como una presentación de aspersión en aerosol a partir de un recipiente presurizado, bomba, aspersor, atomizador o nebulizador, con o sin el uso de un propelente adecuado.

La presente invención proporciona además composiciones farmacéuticas y formas de dosificación anhidras, las cuales comprenden los compuestos de la presente invención como ingredientes activos, debido a que el agua puede facilitar la degradación de ciertos compuestos.

Las composiciones farmacéuticas y formas de dosificación anhidras de la invención se pueden preparar utilizando ingredientes anhidros o que contengan una baja humedad, y condiciones de baja humedad. Una composición farmacéutica anhidra se puede preparar y almacenar de tal manera que se mantenga su naturaleza anhidra. De conformidad con lo anterior, las composiciones anhidras de preferencia se empacan utilizando materiales que se sepa que impiden la exposición al agua, de tal modo que se puedan incluir en kits de formulación adecuados. Los ejemplos del empaque adecuado incluyen, pero no se limitan a, láminas herméticamente selladas, plásticos, recipientes de dosis unitaria (por ejemplo, frascos),

paquetes de burbujas, y paquetes de tiras.

La invención proporciona además composiciones farmacéuticas y formas de dosificación que comprenden uno o más agentes que reducen la velocidad a la cual se descompondrá el compuesto de la presente invención como un ingrediente activo. Estos agentes, que son referidos en la presente como “estabilizantes”, incluyen, pero no se limitan a, antioxidantes, tales como ácido ascórbico, reguladores del pH, o reguladores de sales, etc.

Los compuestos de la fórmula I, en forma libre o en forma de sal, exhiben valiosas propiedades farmacológicas, por ejemplo, propiedades moduladoras de PI3K, por ejemplo, como se indica en las pruebas *in vitro* e *in vivo* proporcionadas en las siguientes secciones y, por consiguiente, se indican para terapia o para utilizarse como productos químicos de investigación, por ejemplo, como compuestos de herramienta.

Los compuestos de la invención pueden ser útiles en el tratamiento de condiciones, enfermedades o trastornos, incluyendo la inmunopatología asociada con enfermedades o infecciones en donde una o más de las funciones de las células-B, tales como la producción de anticuerpos, la presentación de antígeno, la producción de citoquinas o la organogénesis linfoide, sean anormales o sean indeseables, incluyendo artritis reumatoide, pénfigo vulgar y las enfermedades relacionadas, púrpura trombocitopénica idiopática, lupus eritematoso sistémico, esclerosis múltiple, miastenia grave, síndrome de Sjögren, anemia hemolítica

autoinmune, vasculitidas asociadas con ANCA, crioglobulinemia, púrpura trombocitopénica trombótica, urticaria autoinmune crónica, alergia (dermatitis atópica, dermatitis por contacto, rinitis alérgica), síndrome de Goodpasture, AMR (rechazo de trasplante mediado por anticuerpos), rechazo de trasplante híper-agudo, agudo y crónico mediado por células-B, y cánceres de origen hematopoiético, incluyendo, pero no limitándose a, mieloma múltiple; leucemia mielógena aguda; leucemia mielógena crónica; leucemia linfocítica; leucemia mieloide; linfoma no de Hodgkin; linfomas; policitemia vera; trombocitemia esencial; mielofibrosis con metaplasia mieloide; y enfermedad de Walden Ströem.

La invención incluye métodos para el tratamiento de condiciones, enfermedades o trastornos en donde una o más de las funciones de los neutrófilos, tales como la liberación de superóxido, la exocitosis estimulada, o la migración quimioatráctica sean anormales o sean indeseables, incluyendo artritis reumatoide, sepsis, trastornos pulmonares o respiratorios, tales como asma, dermatosis inflamatorias, tales como soriasis, así como en la inmunopatología asociada con enfermedades o infecciones y otras.

La invención incluye métodos para el tratamiento de condiciones, enfermedades o trastornos en donde una o más de las funciones de los basófilos y mastocitos, tales como la migración quimioatráctica o la desgranulación mediada por IgE-alergeno sean anormales o sean indeseables, incluyendo las enfermedades alérgicas (dermatitis atópica, dermatitis por contacto, rinitis

alérgica), así como otros trastornos, tales como enfermedad pulmonar obstructiva crónica (COPD), asma o enfisema.

La invención incluye métodos para el tratamiento de condiciones, enfermedades o trastornos en donde una o más de las funciones de las células-T, tales como la producción de citoquinas o la citotoxicidad mediada por células sean anormales o sean indeseables, incluyendo artritis reumatoide, esclerosis múltiple, rechazo agudo o crónico de injertos de células, tejidos u órganos, o cánceres de origen hematopoiético, así como en la inmunopatología asociada con enfermedades o infecciones.

Además, la invención incluye métodos para el tratamiento de las enfermedades neurodegenerativas, las enfermedades cardiovasculares y la acumulación de plaquetas.

Además, la invención incluye los métodos para el tratamiento de enfermedades de la piel, tales como porfiria cutánea tardía, erupción ligera polimorfa, dermatomiositis, urticaria solar, liquen plano oral, paniculitis, esclerodermia, vasculitis con urticaria.

Además, la invención incluye los métodos para el tratamiento de las enfermedades inflamatorias crónicas, tales como sarcoidosis, granuloma anular.

En otras modalidades, la condición o el trastorno (por ejemplo, mediado por PI3K) se selecciona a partir del grupo que consiste en: policitemia vera, trombocitemia esencial, mielofibrosis con metaplasia mieloide, asma, enfermedad pulmonar obstructiva crónica (COPD), síndrome de insuficiencia respiratoria de adultos (ARDS),

síndrome de Loffler, neumonía eosinofílica, infestación parasitaria (en particular de metazoarios) (incluyendo eosinofilia tropical), aspergilosis broncopulmonar, poliarteritis nodosa (incluyendo síndrome de Churg-Strauss), granuloma eosinofílico, trastornos relacionados con los eosinófilos que afecten a las vías respiratorias, ocasionados por reacción a fármacos, soriasis, dermatitis por contacto, dermatitis atópica, alopecia areata, eritema multiforme, dermatitis herpetiforme, esclerodermia, vitiligo, angitis por hipersensibilidad, urticaria, penfigoide bulloso, lupus eritematoso, pénfigo, epidermólisis bullosa adquirida, trastornos hematológicos autoinmunes (por ejemplo, anemia hemolítica, anemia aplásica, anemia de glóbulos rojos puros, y trombocitopenia idiopática), lupus eritematoso sistémico, policondritis, esclerodermia, granulomatosis de Wegener, dermatomiositis, hepatitis activa crónica, miastenia grave, síndrome de Steven-Johnson, prurito idiopático, enfermedad inflamatoria autoinmune del intestino (por ejemplo, colitis ulcerativa y enfermedad de Crohn), oftalmopatía endocrina, enfermedad de Graves, sarcoidosis, alveolitis, neumonitis por hipersensibilidad crónica, esclerosis múltiple, cirrosis biliar primaria, uveítis (anterior y posterior), fibrosis pulmonar intersticial, artritis soriática, glomerulonefritis, enfermedades cardiovasculares, ateroesclerosis, hipertensión, trombosis venosa profunda, embolia, infarto de miocardio, angina inestable, tromboembolismo, embolia pulmonar, enfermedades trombolíticas, isquemia arterial aguda, oclusiones trombóticas periféricas, y enfermedad de arterias coronarias,

lesiones por reperfusión, retinopatía, tal como retinopatía diabética o retinopatía inducida por oxígeno hiperbárico, y condiciones caracterizadas por una presión intraocular elevada o por secreción del humor acuoso ocular, tales como glaucoma.

En otra modalidad, los compuestos de la presente invención son útiles en el tratamiento, prevención, o mitigación de enfermedades autoinmunes y de condiciones inflamatorias, en particular condiciones inflamatorias con una etiología que incluye un componente autoinmune, tal como artritis (por ejemplo, artritis reumatoide, artritis crónica progrediente, y artritis deformante), y enfermedades reumáticas, incluyendo condiciones inflamatorias y enfermedades reumáticas que involucran pérdida ósea, dolor inflamatorio, espondiloartropatías, incluyendo espondilitis anquilosante, síndrome de Reiter, artritis reactiva, artritis soriática, y artritis enterofática, hipersensibilidad (incluyendo tanto hipersensibilidad de las vías respiratorias como hipersensibilidad dérmica), y alergias. Las enfermedades autoinmunes específicas para las cuales se pueden emplear los anticuerpos de la invención incluyen trastornos hematológicos autoinmunes (incluyendo, por ejemplo, anemia hemolítica, anemia aplásica, anemia de glóbulos rojos puros, y trombocitopenia idiopática), hemofilia adquirida A, enfermedad de aglutinina fría, crioglobulinemia, púrpura trombocitopénica trombótica, síndrome de Sjögren, lupus eritematoso sistémico, trastornos inflamatorios musculares, policondritis, esclerodoma, vasculitis asociada con anticuerpos citoplásmicos anti-

neutrófilos, neuropatía mediada por IgM, síndrome de opsoclonus mioclonus, granulomatosis de Wegener, dermatomiositis, hepatitis activa crónica, miastenia grave, soriasis, síndrome de Steven-Johnson, pénfigo vulgar, pénfigo foliacius, prurito idiopático, enfermedad inflamatoria autoinmune del intestino (incluyendo, por ejemplo, colitis ulcerativa, enfermedad de Crohn y Síndrome de intestino irritable), oftalmopatía endocrina, enfermedad de Graves, sarcoidosis, esclerosis múltiple, neuromielitis óptica, cirrosis biliar primaria, diabetes juvenil (diabetes mellitus tipo I), uveítis (anterior, intermedia y posterior, así como panuveítis), queratoconjuntivitis sicca y queratoconjuntivitis vernal, fibrosis pulmonar intersticial, artritis soriática, y glomerulonefritis (con y sin síndrome nefrótico, por ejemplo, incluyendo síndrome nefrótico idiopático o nefropatía de cambios mínimos), tumores, enfermedad inflamatoria de la piel y de la córnea, miositis, aflojamiento de implantes óseos, trastornos metabólicos, tales como ateroesclerosis, diabetes, y dislipidemia.

En otra modalidad, los compuestos de la presente invención son útiles en el tratamiento de condiciones o trastornos seleccionados a partir del grupo que consiste en linfoma de células-B cutáneo primario, enfermedad inmunoampollar, pénfigo vulgar, pénfigo foliáceo, la forma endémica de pénfigo brasileño (*Fogo selvagem*), pénfigo paraneoplásico, penfigoide bulloso, penfigoide de la membrana mucosa, epidermólisis bullosa adquirida, enfermedad crónica del injerto contra el huésped, dermatomiositis, lupus eritematoso sistémico, vasculitis, vasculitis de vasos pequeños,

vasculitis por urticaria hipocomplementémica, vasculitis por anticuerpos citoplásmicos anti-neutrófilos, crioglobulinemia, síndrome de Schnitzler, macroglobulinemia de Waldenstrom, angioedema, vitiligo, lupus eritematoso sistémico, púrpura trombocitopénica idiopática, esclerosis múltiple, enfermedad por aglutinina de resfriado, anemia hemolítica autoinmune, vasculitis asociada con anticuerpos citoplásmicos anti-neutrófilos, enfermedad del injerto contra el huésped, crioglobulinemia, y trombocitopenia trombótica.

Por consiguiente, como una modalidad adicional, la presente invención proporciona el uso de un compuesto de las fórmulas (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) o (Ij') en terapia. En una modalidad adicional, la terapia se selecciona a partir de una enfermedad que se puede tratar mediante la inhibición de PI3K. En otra modalidad, la enfermedad se selecciona a partir de la lista anteriormente mencionada, de una manera adecuada a partir de trastornos autoinmunitarios, enfermedades inflamatorias, enfermedades alérgicas, enfermedades de las vías respiratorias, tales como asma y enfermedad pulmonar obstructiva crónica (COPD), rechazo de trasplante; la producción de anticuerpos, la presentación de antígeno, la producción de citoquinas o la organogénesis linfoide son anormales o son indeseables, incluyendo artritis reumatoide, pénfigo vulgar, púrpura trombocitopénica idiopática, lupus eritematoso sistémico, esclerosis múltiple, miastenia grave, síndrome de Sjögren,

anemia hemolítica autoinmune, vasculitidas asociadas con ANCA, crioglobulinemia, púrpura trombocitopénica trombótica, urticaria autoinmune crónica, alergia (dermatitis atópica, dermatitis por contacto, rinitis alérgica), síndrome de Goodpasture, AMR (rechazo de trasplante mediado por anticuerpos), rechazo de trasplante híper-agudo, agudo y crónico mediado por células-B, y cánceres de origen hematopoiético, incluyendo, pero no limitándose a, mieloma múltiple; una leucemia; leucemia mielógena aguda; leucemia mielógena crónica; leucemia linfocítica; leucemia mieloide; linfoma no de Hodgkin; linfomas; policitemia vera; trombocitemia esencial; mielofibrosis con metaplasia mieloide; y enfermedad de Walden Ströem; de una manera más adecuada, a partir de artritis reumatoide (RA), pénfigo vulgar (PV), púrpura trombocitopénica idiopática (ITP), púrpura trombocitopénica trombótica (TTP), anemia hemolítica autoinmune (AIHA), hemofilia adquirida tipo A (AHA), lupus eritematoso sistémico (SLE), esclerosis múltiple (MS), miastenia grave (MG), síndrome de Sjögren (SS), vasculitidas asociadas con ANCA, crioglobulinemia, urticaria autoinmune crónica (CAU), alergia (dermatitis atópica, dermatitis por contacto, rinitis alérgica), síndrome de Goodpasture, rechazo de trasplante y cánceres de origen hematopoiético, así como en la inmunopatología asociada con enfermedades o infecciones, por ejemplo, en malaria grave y cerebral, tripanosomiasis, Leishmaniasis, toxoplasmosis y neurocisticercosis.

En otra modalidad, la invención proporciona un método para el

tratamiento de una enfermedad que se trato mediante la inhibición de PI3K, el cual comprende la administración de una cantidad terapéuticamente aceptable de un compuesto de las fórmulas (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) o (Ij'). En una modalidad adicional, la enfermedad se selecciona a partir de la lista anteriormente mencionada, de una manera adecuada a partir de trastornos autoinmunitarios, enfermedades inflamatorias, enfermedades alérgicas, enfermedades de las vías respiratorias, tales como asma y enfermedad pulmonar obstructiva crónica (COPD), rechazo de trasplante; la producción de anticuerpos, la presentación de antígeno, la producción de citoquinas o la organogénesis linfoide son anormales o son indeseables, incluyendo artritis reumatoide, pénfigo vulgar, púrpura trombocitopénica idiopática, lupus eritematoso sistémico, esclerosis múltiple, miastenia grave, síndrome de Sjögren, anemia hemolítica autoinmune, vasculitidas asociadas con ANCA, crioglobulinemia, púrpura trombocitopénica trombótica, urticaria autoinmune crónica, alergia (dermatitis atópica, dermatitis por contacto, rinitis alérgica), síndrome de Goodpasture, AMR (rechazo de trasplante mediado por anticuerpos), rechazo de trasplante híper-agudo, agudo y crónico mediado por células-B, y cánceres de origen hematopoiético, incluyendo, pero no limitándose a, mieloma múltiple; una leucemia; leucemia mielógena aguda; leucemia mielógena crónica; leucemia linfocítica; leucemia mieloide; linfoma no de Hodgkin; linfomas; policitemia vera; trombocitemia esencial;

mielofibrosis con metaplasia mieloide; y enfermedad de Walden Ströem; de una manera más adecuada, a partir de artritis reumatoide (RA), pénfigo vulgar (PV), púrpura trombocitopénica idiopática (ITP), púrpura trombocitopénica trombótica (TTP), anemia hemolítica autoinmune (AIHA), hemofilia adquirida tipo A (AHA), lupus eritematoso sistémico (SLE), esclerosis múltiple (MS), miastenia grave (MG), síndrome de Sjögren (SS), vasculitidas asociadas con ANCA, crioglobulinemia, urticaria autoinmune crónica (CAU), alergia (dermatitis atópica, dermatitis por contacto, rinitis alérgica), síndrome de Goodpasture, rechazo de trasplante y cánceres de origen hematopoiético, así como en la inmunopatología asociada con enfermedades o infecciones, por ejemplo, en malaria grave y cerebral, tripanosomiasis, Leishmaniasis, toxoplasmosis y neurocisticercosis.

Por consiguiente, como una modalidad adicional, la presente invención proporciona el uso de un compuesto de las fórmulas (I), (I'), (Ia), (Ia'), (Ib), (Ib') (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If), (If'), (Ig), (Ig'), (Ih), (Ih'), (Ii), (Ii'), (Ij) o (Ij') para la elaboración de un medicamento. En una modalidad adicional, el medicamento es para el tratamiento de una enfermedad que se pueda tratar mediante la inhibición de PI3K. En otra modalidad, la enfermedad se selecciona a partir de la lista anteriormente mencionada, de una manera adecuada a partir de trastornos autoinmunitarios, enfermedades inflamatorias, enfermedades alérgicas, enfermedades de las vías respiratorias, tales como asma y enfermedad pulmonar obstructiva crónica

(COPD), rechazo de trasplante; la producción de anticuerpos, la presentación de antígeno, la producción de citoquinas o la organogénesis linfoide son anormales o son indeseables, incluyendo artritis reumatoide, pénfigo vulgar, púrpura trombocitopénica idiopática, lupus eritematoso sistémico, esclerosis múltiple, miastenia grave, síndrome de Sjögren, anemia hemolítica autoinmune, vasculitidas asociadas con ANCA, crioglobulinemia, púrpura trombocitopénica trombótica, urticaria autoinmune crónica, alergia (dermatitis atópica, dermatitis por contacto, rinitis alérgica), síndrome de Goodpasture, AMR (rechazo de trasplante mediado por anticuerpos), rechazo de trasplante híper-agudo, agudo y crónico mediado por células-B, y cánceres de origen hematopoiético, incluyendo, pero no limitándose a, mieloma múltiple; una leucemia; leucemia mielógena aguda; leucemia mielógena crónica; leucemia linfocítica; leucemia mieloide; linfoma no de Hodgkin; linfomas; policitemia vera; trombocitemia esencial; mielofibrosis con metaplasia mieloide; y enfermedad de Walden Ströem; de una manera más adecuada, a partir de artritis reumatoide (RA), pénfigo vulgar (PV), púrpura trombocitopénica idiopática (ITP), púrpura trombocitopénica trombótica (TTP), anemia hemolítica autoinmune (AIHA), hemofilia adquirida tipo A (AHA), lupus eritematoso sistémico (SLE), esclerosis múltiple (MS), miastenia grave (MG), síndrome de Sjögren (SS), vasculitidas asociadas con ANCA, crioglobulinemia, urticaria autoinmune crónica (CAU), alergia (dermatitis atópica, dermatitis por contacto, rinitis alérgica), síndrome de Goodpasture,

rechazo de trasplante y cánceres de origen hematopoiético, así como en la inmunopatología asociada con enfermedades o infecciones, por ejemplo, en malaria grave y cerebral, tripanosomiasis, Leishmaniasis, toxoplasmosis y neurocisticercosis.

La composición o una combinación farmacéutica de la presente invención puede estar en una dosificación unitaria de aproximadamente 1 a 1,000 miligramos de ingrediente(s) activo(s) para un sujeto de aproximadamente 50 a 70 kilogramos, o de aproximadamente 1 a 500 miligramos, o de aproximadamente 1 a 250 miligramos, o de aproximadamente 1 a 150 miligramos, o de aproximadamente 0.5 a 100 miligramos, o de aproximadamente 1 a 50 miligramos de ingredientes activos. La dosificación terapéuticamente efectiva de un compuesto, de la composición farmacéutica, o de las combinaciones de los mismos, depende de la especie del sujeto, del peso corporal, de la edad y condición individual, del trastorno o enfermedad que se esté tratando, o de la gravedad de la misma. Un médico, clínico, o veterinario de una experiencia ordinaria puede determinar fácilmente la cantidad efectiva de cada uno de los ingredientes activos necesaria para prevenir, tratar, o inhibir el progreso del trastorno o de la enfermedad.

Las propiedades de dosificación anteriormente citadas se pueden demostrar en pruebas *in vitro* e *in vivo* utilizando convenientemente mamíferos, por ejemplo, ratones, ratas, perros, monos u órganos aislados, tejidos y preparaciones de los mismos.

Los compuestos de la presente invención se pueden aplicar *in vitro* en la forma de soluciones, por ejemplo, soluciones acuosas, e *in vivo* ya sea enteralmente, parenteralmente, de una manera conveniente intravenosamente, por ejemplo, como una suspensión o en solución acuosa. La dosificación *in vitro* puede estar en el intervalo de concentraciones de entre aproximadamente 10^{-3} molar y 10^{-9} molar. Una cantidad terapéuticamente efectiva *in vivo,* dependiendo de la vía de administración, puede estar en el intervalo de entre aproximadamente 0.1 y 500 miligramos/kilogramo, o de entre aproximadamente 1 y 100 miligramos/kilogramo.

El compuesto de la presente invención se puede administrar ya sea de una manera simultánea con, o antes o después de, uno o más agentes terapéuticos diferentes. El compuesto de la presente invención se puede administrar por separado, por la misma o diferente vía de administración, o juntos en la misma composición farmacéutica que los otros agentes.

En una modalidad, la invención proporciona un producto que comprende un compuesto de la fórmula (I), y cuando menos otro agente terapéutico, como una preparación combinada para su uso simultáneo, separado, o en secuencia, en terapia. En una modalidad, la terapia es el tratamiento de una enfermedad o condición mediada por la actividad de las enzimas de PI3K. Los productos proporcionados como una preparación combinada incluyen una composición que comprende el compuesto de la fórmula (I), y el (los) otro(s) agente(s) terapéutico(s) juntos en la misma composición

farmacéutica, o el compuesto de la fórmula (I), y el (los) otro(s) agente(s) terapéutico(s) en una forma separada, por ejemplo, en la forma de un kit.

En una modalidad, la invención proporciona una composición farmacéutica, la cual comprende un compuesto de la fórmula (I), y otro(s) agente(s) terapéutico(s). Opcionalmente, la composición farmacéutica puede comprender un vehículo farmacéuticamente aceptable, como se describe anteriormente.

En una modalidad, la invención proporciona un kit, el cual comprende dos o más composiciones farmacéuticas separadas, cuando menos una de las cuales conteniendo un compuesto de la fórmula (I). En una modalidad, el kit comprende medios para conservar por separado estas composiciones, tales como un recipiente, un frasco dividido, o un paquete de lámina dividido. Un ejemplo de este kit e un paquete de burbuja, como se utiliza típicamente para el empaque de tabletas, cápsulas, y similares.

El kit de la invención se puede utilizar para administrar diferentes formas de dosificación, por ejemplo, oral y parenteral, para administrar las composiciones separadas a diferentes intervalos de dosificación, o para titular las composiciones separadas una contra la otra. Para ayudar al cumplimiento, el kit de la invención típicamente comprende instrucciones para su administración.

En las terapias de combinación de la invención, el compuesto de la invención y el otro agente terapéutico pueden ser elaborados y/o formulados por los mismos o diferentes fabricantes. Más aún, el

compuesto de la invención y el otro agente terapéutico se pueden juntar en una terapia de combinación: (i) antes de liberar el producto de combinación a los médicos (por ejemplo, en el caso de un kit que comprenda el compuesto de la invención y el otro agente terapéutico); (ii) por los médicos mismos (o bajo la guía del médico) poco antes de la administración; (iii) en los pacientes mismos, por ejemplo, durante la administración en secuencia del compuesto de la invención y el otro agente terapéutico.

De conformidad con lo anterior, la invención proporciona el uso de un compuesto de la fórmula (I) para el tratamiento de una enfermedad o condición mediada por la actividad de las enzimas de PI3K, en donde el medicamento se prepara para su administración con otro agente terapéutico. La invención también proporciona el uso de otro agente terapéutico para el tratamiento de una enfermedad o condición mediada por la actividad de las enzimas de PI3K, en donde el medicamento se administra con un compuesto de la fórmula (I).

La invención también proporciona un compuesto de la fórmula (I) para utilizarse en un método para el tratamiento de una enfermedad o condición mediada por la actividad de las enzimas de PI3K, en donde el compuesto de la fórmula (I) se prepara para su administración con otro agente terapéutico. La invención también proporciona otro agente terapéutico para utilizarse en un método para el tratamiento de una enfermedad o condición mediada por la actividad de las enzimas de PI3K, en donde el otro agente terapéutico se prepara para su administración con un compuesto de

la fórmula (I). La invención también proporciona un compuesto de la fórmula (I) para utilizarse en un método para el tratamiento de una enfermedad o condición mediada por la actividad de las enzimas de PI3K en donde el compuesto de la fórmula (I) se administra con otro agente terapéutico. La invención también proporciona otro agente terapéutico para utilizarse en un método para el tratamiento de una enfermedad o condición mediada por la actividad de las enzimas de PI3K en donde el otro agente terapéutico se administra con un compuesto de la fórmula (I).

La invención también proporciona el uso de un compuesto de la fórmula (I) para el tratamiento de una enfermedad o condición mediada por la actividad de las enzimas de PI3K, en donde el paciente ha sido tratado previamente (por ejemplo, dentro de 24 horas) con otro agente terapéutico. La invención también proporciona el uso de otro agente terapéutico para el tratamiento de una enfermedad o condición mediada por la actividad de las enzimas de PI3K, en donde el paciente ha sido tratado previamente (por ejemplo, dentro de 24 horas) con un compuesto de la fórmula (I).

Los compuestos de la fórmula I se pueden administrar como el único ingrediente activo, o en conjunto con, por ejemplo, como un adyuvante para, otros fármacos, por ejemplo, agentes inmunosupresores o inmunomoduladores u otros agentes anti-inflamatorios, por ejemplo, para el tratamiento o la prevención de rechazo agudo o crónico de alo- o xeno-injerto, o de los trastornos inflamatorios o autoinmunes, o un agente quimioterapéutico, por

ejemplo, un agente anti-proliferativo de las células malignas. Por ejemplo, los compuestos de la fórmula I se pueden utilizar en combinación con un inhibidor de calcineurina, por ejemplo, ciclosporina A o FK 506; un inhibidor de mTOR, por ejemplo, rapamicina, 40-O-(2-hidroxi-etil)-rapamicina, CCI779, ABT578, AP23573, TAFA-93, biolimus-7 o biolimus-9; una ascomicina con propiedades inmunosupresoras, por ejemplo, ABT-281, ASM981, etc.; corticosteroides; ciclofosfamida; azatiopreno; metotrexato; leflunomida; mizoribina; ácido micofenólico o su sal; micofenolato-mofetil; 15-desoxi-espergualina o un homólogo, análogo o derivado inmunosupresor de la misma; un inhibidor de PKC, por ejemplo, como se da a conocer en las Publicaciones Internacionales Números WO 02/38561 o WO 03/82859, por ejemplo, el compuesto del Ejemplo 56 ó 70; un inhibidor de cinasa JAK3, por ejemplo, N-bencil-3,4-dihidroxi-benciliden-ciano-acetamida / α-ciano-(3,4-dihidroxi)-]N-bencil-cinamamida (Tirfostina AG 490), prodigiosina 25-C (PNU156804), [4-(4'-hidroxi-fenil)-amino-6,7-dimetoxi-quinazolina] (WHI-P131), [4-(3'-bromo-4'-hidroxil-fenil)-amino-6,7-dimetoxi-quinazolina] (WHI-P154), [4-(3',5'-dibromo-4'-hidroxil-fenil)-amino-6,7-dimetoxi-quinazolina] WHI-P97, KRX-211, 3-{(3R,4R)-4-metil-3-[metil-(7H-pirrolo-[2,3-d]-pirimidin-4-il)-amino]-piperidin-1-il}-3-oxo-propionitrilo, en forma libre o en una forma de sal farmacéuticamente aceptable, por ejemplo, el mono-citrato (también denominado como CP-690,550), o un compuesto como se da a conocer en las Publicaciones Internacionales Números WO 04/052359 o WO

05/066156; anticuerpos monoclonales inmunosupresores, por ejemplo, los anticuerpos monoclonales para los receptores de leucocitos, por ejemplo, MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD40, CD45, CD52, CD58, CD80, CD86 o sus ligandos; otros compuestos inmunomoduladores, por ejemplo, una molécula de enlace recombinante que tenga cuando menos una porción del dominio extracelular de CTLA4 o un mutante de la misma, por ejemplo, cuando menos una porción extracelular de CTLA4 o un mutante de la misma unida a una secuencia de proteína que no es CTLA4, por ejemplo, CTLA4Ig (por ejemplo, designada como ATCC 68629) o un mutante de la misma, por ejemplo, LEA29Y; inhibidores de moléculas de adhesión, por ejemplo, antagonistas de LFA-1, antagonistas de ICAM-1 ó -3, antagonistas de VCAM-4 o antagonistas de VLA-4; o antihistaminas; o antitusivos, o un agente broncodilatador; o un bloqueador de los receptores de angiotensinas; o un agente anti-infeccioso.

Cuando los compuestos de la fórmula I se administran en conjunto con otra terapia inmunosupresora / inmunomoduladora, anti-inflamatoria, quimioterapéutica o anti-infecciosa, las dosificaciones del compuesto inmunosupresor, inmunomodulador, anti-inflamatorio, quimioterapéutico o anti-infeccioso co-administrado, desde luego, variarán dependiendo del tipo de co-fármaco empleado, por ejemplo, si es un esteroide o un inhibidor de calcineurina, del fármaco específico empleado, de la condición que se esté tratando, etc.

Un compuesto de la fórmula (I) también se puede utilizar con

ventaja uno en combinación con otro, o en combinación con otros agentes terapéuticos, en especial otros agentes anti-proliferativos. Estos agentes anti-proliferativos incluyen, pero no se limitan a, los inhibidores de aromatasa; anti-estrógenos; inhibidores de topoisomerasa I; inhibidores de topoisomerasa II; agentes activos en microtúbulos; agentes alquilantes; inhibidores de desacetilasa de histona; compuestos que inducen los procesos de diferenciación celular; inhibidores de ciclo-oxigenasa; inhibidores de MMP; inhibidores de mTOR; anti-metabolitos anti-neoplásicos; compuestos de platina; compuestos que dirigen/reducen una actividad de cinasa de proteína o de lípido, y otros compuestos anti-angiogénicos; compuestos que dirigen, reducen, o inhiben la actividad de una fosfatasa de proteína o de lípido; agonistas de gonadorelina; anti-andrógenos; inhibidores de amino-peptidasa de metionina; bisfosfonatos; modificadores de la respuesta biológica; anticuerpos anti-proliferativos; inhibidores de heparanasa; inhibidores de las isoformas oncogénicas Ras; inhibidores de telomerasa; inhibidores de proteasoma; agentes utilizados en el tratamiento de malignidades hematológicas; compuestos que dirigen, reducen, o inhiben la actividad de Flt-3; inhibidores de Hsp90; temozolomida (TEMODAL®); y leucovorina.

El término "inhibidor de aromatasa", como se utiliza en la presente, se refiere a un compuesto que inhibe la producción de estrógeno, es decir, la conversión de los sustratos androstenodiona y testosterona hasta estrona y estradiol, respectivamente. El término

incluye, pero no se limita a, esteroides, en especial atamestano, exemestano y formestano; y, en particular, no esteroides, en especial amino-glutetimida, rogletimida, pirido-glutetimida, trilostano, testolactona, quetoconazol, vorozol, fadrozol, anastrozol y letrozol. El exemestano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada AROMASIN. El formestano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada LENTARON. El fadrozol se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada AFEMA. El anastrozol se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ARIMIDEX. El letrozol se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FEMARA o FEMAR. La amino-glutetimida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ORIMETEN. Una combinación de la invención que comprenda un agente quimioterapéutico que sea un inhibidor de aromatasa, es en particular útil para el tratamiento de los tumores positivos para el receptor de hormonas, por ejemplo, tumores de mama.

El término "anti-estrógeno", como se utiliza en la presente, se refiere a un compuesto que antagoniza el efecto de los estrógenos al nivel del receptor de estrógeno. El término incluye, pero no se limita a, tamoxifeno, fulvestrant, raloxifeno, y clorhidrato de raloxifeno. El

tamoxifeno se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada NOLVADEX. El clorhidrato de raloxifeno se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada EVISTA. El fulvestrant se puede formular como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número 4,659,516, o se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FASLODEX. Una combinación de la invención que comprenda un agente quimioterapéutico que sea un anti-estrógeno es en particular útil para el tratamiento de los tumores positivos para el receptor de estrógeno, por ejemplo, tumores de mama.

El término "anti-andrógeno", como se utiliza en la presente, se refiere a cualquier sustancia que sea capaz de inhibir los efectos biológicos de las hormonas androgénicas e incluye, pero no se limita a, bicalutamida (CASODEX), que se puede formular, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número 4,636,505.

El término "agonista de gonadorelina", como se utiliza en la presente, incluye, pero no se limita a, abarelix, goserelina, y acetato de goserelina. La goserelina se da a conocer en la Patente de los Estados Unidos de Norteamérica Número 4,100,274, y se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ZOLADEX. El abarelix se puede

formular, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número 5,843,901.

El término "inhibidor de topoisomerasa I", como se utiliza en la presente, incluye, pero no se limita a, topotecano, gimatecano, irinotecano, camptotecina y sus análogos, 9-nitro-camptotecina, y el conjugado de camptotecina macromolecular PNU-166148 (compuesto A1 de la Publicación Internacional Número WO 99/17804). El irinotecano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada CAMPTOSAR. El topotecano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada HYCAMTIN.

El término "inhibidor de topoisomerasa II", como se utiliza en la presente, incluye, pero no se limita a, las antraciclinas, tales como doxorrubicina, incluyendo la formulación liposomal, por ejemplo, CAELYX; daunorrubicina; epirrubicina; idarrubicina; nemorrubicina; las antraquinonas mitoxantrona y losoxantrona; y las podofilotoxinas etoposida y teniposida. La etoposida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ETOPOPHOS. La teniposida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada VM 26-BRISTOL. La doxorrubicina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ADRIBLASTIN o ADRIAMYCIN. La epirrubicina se puede administrar, por ejemplo, en

la forma como se comercia, por ejemplo, bajo la marca comercial registrada FARMORUBICIN. La idarrubicina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ZAVEDOS. La mitoxantrona se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada NOVANTRON.

El término "agente activo en microtúbulos" se refiere a los agentes estabilizantes de microtúbulos, agentes desestabilizantes de microtúbulos, y a los inhibidores de la polimerización de microtubulina, incluyendo, pero no limitándose a, taxanos, por ejemplo, paclitaxel y docetaxel; alcaloides vinca, por ejemplo, vinblastina, en especial sulfato de vinblastina; vincristina, en especial sulfato de vincristina, y vinorelbina; discodermolidas; colquicina; y epotilonas y derivados de las mismas, por ejemplo, epotilona B o D o derivados de las mismas. El paclitaxel se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, TAXOL. El docetaxel se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada TAXOTERE. El sulfato de vinblastina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada VINBLASTIN R.P. El sulfato de vincristina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FARMISTIN. La discodermolida se puede obtener, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número

5,010,099. También se incluyen los derivados de epotilona que se dan a conocer en la Publicación Internacional Número WO 98/10121, en la Patente de los Estados Unidos de Norteamérica Número 6,194,181, en la Publicación Internacional Número WO 98/25929, en la Publicación Internacional Número WO 98/08849, en la Publicación Internacional Número WO 99/43653, en la Publicación Internacional Número WO 98/22461, y en la Publicación Internacional Número WO 00/31247. Se prefieren en especial epotilona A y/o B.

El término "agente alquilante", como se utiliza en la presente, incluye, pero no se limita a, ciclofosfamida, ifosfamida, melfalano o nitrosourea (BCNU o Gliadel). La ciclofosfamida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada CICLOSTIN. La ifosfamida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada HOLOXAN.

El término "inhibidores de desacetilasa de histona" o "inhibidores de HDAC", se refiere a los compuestos que inhiben la desacetilasa de histona, y que poseen una actividad anti-proliferativa. Esto incluye a los compuestos que se dan a conocer en la Publicación Internacional Número WO 02/22577, en especial *N*-hidroxi-3-[4-[[(2-hidroxi-etil)[2-(1*H*-indol-3-il)-etil]-amino]-metil]-fenil]-2*E*-2-propenamida, N-hidroxi-3-[4-[[[2-(2-metil-1H-indol-3-il)-etil]-amino]-metil]-fenil]-2E-2-propenamida, y las sales farmacéuticamente aceptables de las mismas. Además incluye en especial el ácido hidroxámico de suberoil-anilida (SAHA).

El término "antimetabolito anti-neoplásico" incluye, pero no se limita a, 5-fluoro-uracilo o 5-FU; capecitabina; gemcitabina; agentes desmetilantes del ADN, tales como 5-azacitidina y decitabina; metotrexato y edatrexato; y antagonistas de ácido fólico, tales como pemetrexed. La capecitabina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada XELODA. La gemcitabina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada GEMZAR. También se incluye el anticuerpo monoclonal trastuzumab, el cual se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada HERCEPTIN.

El término "compuesto de platina", como se utiliza en la presente, incluye, pero no se limita a, carboplatina, *cis*-platina, cisplatino, y oxaliplatina. La carboplatina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada CARBOPLAT. La oxaliplatina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ELOXATIN.

El término "compuestos que dirigen/reducen una actividad de cinasa de proteína o de lípido; o una actividad de fosfatasa de proteína o de lípido; u otros compuestos anti-angiogénicos", como se utiliza en la presente, incluye, pero no se limita a, los inhibidores de cinasa de proteína tirosina y/o de cinasa de serina y/o treonina, o los inhibidores de cinasa de lípido, por ejemplo:

a) compuestos que dirigen, reducen, o inhiben la actividad de los receptores del factor de crecimiento derivado de plaquetas (PDGFR), tales como los compuestos que dirigen, reducen, o inhiben la actividad de PDGFR, en especial los compuestos que inhiben al receptor del factor de crecimiento derivado de plaquetas, por ejemplo, un derivado de N-fenil-2-pirimidin-amina, por ejemplo, imatinib, SU101, SU6668 y GFB-111;

b) compuestos que dirigen, reducen, o inhiben la actividad de los receptores del factor de crecimiento de fibroblastos (FGFR);

c) compuestos que dirigen, reducen, o inhiben la actividad del receptor del factor de crecimiento tipo insulina I (IGF-IR), tales como los compuestos que dirigen, reducen, o inhiben la actividad de IGF-IR, en especial los compuestos que inhiben el receptor IGF-IR, tales como los compuestos que se dan a conocer en la Publicación Internacional Número WO 02/092599;

d) compuestos que dirigen, reducen, o inhiben la actividad de la familia de la cinasa de tirosina receptora Trk;

e) compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasa de tirosina receptora Axl;

f) compuestos que dirigen, reducen, o inhiben la actividad del receptor c-Met;

g) compuestos que dirigen, reducen, o inhiben la actividad de la cinasa de tirosina receptora Kit/SCFR;

h) compuestos que dirigen, reducen, o inhiben la actividad de las cinasas de tirosina receptoras C-kit - (parte de la familia

PDGFR), tales como los compuestos que dirigen, reducen, o inhiben la actividad de la familia de la cinasa de tirosina receptora c-Kit, en especial los compuestos que inhiben al receptor c-Kit, por ejemplo, imatinib;

i) compuestos que dirigen, reducen, o inhiben la actividad de los miembros de la familia c-Abl y sus productos de fusión genética, por ejemplo, cinasa BCR-Abl, tales como los compuestos que dirigen la disminución o inhiben la actividad de los miembros de la familia c-Abl y sus productos de fusión genética, por ejemplo, un derivado de N-fenil-2-pirimidin-amina, por ejemplo, imatinib, PD180970, AG957, NSC 680410, ó PD173955 de ParkeDavis;

j) compuestos que dirigen, reducen, o inhiben la actividad de los miembros de la cinasa C de proteína (PKC), y la familia de cinasas de serina/treonina Raf, los miembros de la familia de MEK, SRC, JAK, FAK, PDK, y los miembros de la familia de Ras/MAPK, o de la familia de la cinasa PI(3), o de la familia de cinasa relacionada con cinasa PI(3), y/o los miembros de la familia de cinasa dependiente de ciclina (CDK), y son en especial los derivados de estaurosporina que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número 5,093,330, por ejemplo, midostaurina; los ejemplos de compuestos adicionales incluyen, por ejemplo, UCN-01; safingol; BAY 43-9006; Briostatina 1; Perifosina; Ilmofosina; RO 318220 y RO 320432; GO 6976; Isis 3521; LY333531/LY379196; los compuestos de isoquinolina, tales como aquéllos que se dan a conocer en la Publicación Internacional

Número WO 00/09495; FTIs; PD184352; o QAN697 (un inhibidor de P13K);

k) compuestos que dirigen, reducen, o inhiben la actividad de los inhibidores de cinasa de proteína tirosina, tales como los compuestos que dirigen, reducen, o inhiben la actividad de los inhibidores de cinasa de proteína tirosina, que incluyen mesilato de Imatinib (GLEEVEC) o tirfostina. Una tirfostina es de preferencia un compuesto de bajo peso molecular (Mr < 1500), o una sal farmacéuticamente aceptable del mismo, en especial un compuesto seleccionado a partir de la clase de benciliden-malonitrilo o la clase de compuestos de S-aril-bencen-malonitrilo o de quinolina del bisustrato, más especialmente cualquier compuesto seleccionado a partir del grupo que consiste en Tirfostina A23/RG-50810, AG 99, Tirfostina AG 213, Tirfostina AG 1748, Tirfostina AG 490, Tirfostina B44, enantiómero de Tirfostina B44 (+), Tirfostina AG 555, AG 494, Tirfostina AG 556, AG957, y adafostina (adamantil-éster del ácido 4-{[(2,5-dihidroxi-fenil)-metil]-amino}-benzoico, NSC 680410, adafostina; y

l) compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasas de tirosina receptoras del factor de crecimiento epidérmico (EGFR, ErbB2, ErbB3, ErbB4 como homo- o hetero-dímeros), tales como los compuestos que dirigen, reducen, o inhiben la actividad de la familia de receptores del factor de crecimiento epidérmico, y son en especial los compuestos, proteínas o anticuerpos que inhiben a los miembros de la familia de cinasa de

tirosina receptora del factor de crecimiento epidérmico, por ejemplo, el receptor de EGF, ErbB2, ErbB3 y ErbB4, o que se enlazan con el factor de crecimiento epidérmico o con los ligandos relacionados con el factor de crecimiento epidérmico, y son en particular los compuestos, proteínas, o anticuerpos monoclonales genérica y específicamente dados a conocer en la Publicación Internacional Número WO 97/02266, por ejemplo, el compuesto del Ejemplo 39, o en las Patentes Números EP 0 564 409; WO 99/03854; EP 0520722; EP 0 566 226; EP 0 787 722; EP 0 837 063; US 5,747,498; WO 98/10767; WO 97/30034; WO 97/49688; WO 97/38983 y, en especial, la Publicación Internacional Número WO 96/30347, por ejemplo, el compuesto conocido como CP 358774; la Publicación Internacional Número WO 96/33980, por ejemplo, el compuesto ZD 1839; y la Publicación Internacional Número WO 95/03283, por ejemplo, el compuesto ZM105180, por ejemplo, trastuzumab (HERCEPTIN), cetuximab, Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 o E7.6.3; y los derivados de 7H-pirrolo-[2,3-d]-pirimidina, los cuales se dan a conocer en la Publicación Internacional Número WO 03/013541.

Otros compuestos anti-angiogénicos incluyen los compuestos que tienen otro mecanismo para su actividad, por ejemplo, no relacionado con la inhibición de la cinasa de proteína o de lípido, por ejemplo, talidomida (THALOMID), y TNP-470.

Los compuestos que dirigen, reducen, o inhiben la actividad de una fosfatasa de proteína o de lípido son, por ejemplo, los

inhibidores de fosfatasa 1, fosfatasa 2A, PTEN o CDC25, por ejemplo, ácido ocadaico o un derivado del mismo.

Los compuestos que inducen los procesos de diferenciación celular son, por ejemplo, ácido retinoico, α-, γ-, ó δ-tocoferol, o α-, γ-, ó δ-tocotrienol.

El término "inhibidor de ciclo-oxigenasa", como se utiliza en la presente, incluye, pero no se limita a, por ejemplo, los inhibidores de Cox-2, ácido 2-aril-amino-fenil-acético sustituido por 5-alquilo y sus derivados, tales como celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib, o un ácido 5-alquil-2-aril-amino-fenil-acético, por ejemplo, ácido 5-metil-2-(2'-cloro-6'-fluoro-anilino)-fenil-acético, o lumiracoxib.

El término "bisfosfonatos", como se utiliza en la presente, incluye, pero no se limita a, ácido etridónico, clodrónico, tiludrónico, pamidrónico, alendrónico, ibandrónico, risedrónico, y zoledrónico. El "ácido etridónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada DIDRONEL. El “ácido clodrónico” se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada BONEFOS. El “ácido tiludrónico” se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada SKELID. El “ácido pamidrónico” se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada AREDIA^{MR}. El “ácido alendrónico” se puede administrar, por ejemplo, en la forma como se comercia,

por ejemplo, bajo la marca comercial registrada FOSAMAX. El “ácido ibandrónico” se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada BONDRANAT. El “ácido risedrónico” se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ACTONEL. El “ácido zoledrónico” se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ZOMETA.

El término “inhibidores de mTOR” se refiere a compuestos que inhiben el objetivo de mamífero de rapamicina (mTOR), y que poseen una actividad anti-proliferativa, tal como sirolimus (Rapamune®), everolimus (Certican^{MR}), CCI-779 y ABT578.

El término “inhibidor de heparanasa", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la degradación del sulfato de heparina. El término incluye, pero no se limita a, PI-88.

El término “modificador de la respuesta biológica", como se utiliza en la presente, se refiere a una linfocina o interferones, por ejemplo, interferón γ.

El término “inhibidor de las isoformas oncogénicas Ras”, por ejemplo, H-Ras, K-Ras, o N-Ras, como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad oncogénica de Ras, por ejemplo, un “inhibidor de farnesil-transferasa” por ejemplo, L-744832, DK8G557 o R115777 (Zarnestra).

El término “inhibidor de telomerasa", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad de la telomerasa. Los compuestos que dirigen, reducen, o inhiben la actividad de telomerasa, son en especial los compuestos que inhiben al receptor de telomerasa, por ejemplo, telomestatina.

El término “inhibidor de amino-peptidasa de metionina", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad de la amino-peptidasa de metionina. Los compuestos que dirigen, reducen, o inhiben la actividad de la amino-peptidasa de metionina son, por ejemplo, bengamida o un derivado de la misma.

El término “inhibidor de proteasoma", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad del proteasoma. Los compuestos que dirigen, reducen, o inhiben la actividad del proteasoma incluyen, por ejemplo, PS-341 y MLN 341.

El término “inhibidor de metaloproteinasa de matriz” o (“inhibidor de MMP”), como se utiliza en la presente, incluye, pero no se limita a, inhibidores peptidomiméticos y no peptidomiméticos de colágeno, derivados de tetraciclina, por ejemplo, el inhibidor peptidomimético de hidroxamato batimastato y su análogo oralmente biodisponible marimastato (BB-2516), prinomastato (AG3340), metastato (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B o AAJ996.

El término “agentes utilizados en el tratamiento de

malignidades hematológicas", como se utiliza en la presente, incluye, pero no se limita a, inhibidores de cinasa de tirosina tipo FMS, por ejemplo, los compuestos que dirigen, reducen, o inhiben la actividad de los receptores de cinasa de tirosina tipo FMS (Flt-3R); interferón, 1-b-D-arabino-furanosil-citosina (ara-c) y bisulfano; e inhibidores de ALK, por ejemplo, los compuestos que dirigen, reducen, o inhiben la cinasa de linfoma anaplásico.

Los compuestos que dirigen, reducen, o inhiben la actividad de los receptores de cinasa de tirosina tipo FMS (Flt-3R) son en especial los compuestos, proteínas o anticuerpos que inhiben a los miembros de la familia de la cinasa receptora Flt-3R, por ejemplo, PKC412, midostaurina, un derivado de estaurosporina, SU11248 y MLN518.

El término “inhibidores de HSP90", como se utiliza en la presente, incluye, pero no se limita a, los compuestos que dirigen, reducen, o inhiben la actividad intrínseca de la ATPasa de HSP90; que degradan, dirigen, reducen, o inhiben las proteínas clientes de HSP90 por medio de la senda de proteasoma de ubiquitina. Los compuestos que dirigen, reducen, o inhiben la actividad intrínseca de la ATPasa de HSP90 son en especial los compuestos, proteínas o anticuerpos que inhiben la actividad de ATPasa de HSP90, por ejemplo, 17-alil-amino,17-desmetoxi-geldanamicina (17AAG), un derivado de geldanamicina; otros compuestos relacionados con geldanamicina; radicicol, e inhibidores de desacetilasa de histona (HDAC).

El término “anticuerpos anti-proliferativos", como se utiliza en la presente, incluye, pero no se limita a, trastuzumab (Herceptin^{MR}), trastuzumab-DM1, erlotinib (Tarceva^{MR}), bevacizumab (Avastin^{MR}), rituximab (Rituxan®), PRO64553 (anti-CD40) y Anticuerpo 2C4. Anticuerpos significan, por ejemplo, los anticuerpos monoclonales intactos, anticuerpos policlonales, anticuerpos multiespecíficos formados a partir de cuando menos 2 anticuerpos intactos, y fragmentos de anticuerpos, siempre que éstos exhiban la actividad biológica deseada.

Para el tratamiento de leucemia mieloide aguda (AML), los compuestos de la fórmula (I) se pueden utilizar en combinación con las terapias convencionales de leucemia, en especial en combinación con las terapias empleadas para el tratamiento de leucemia mieloide aguda. En particular, los compuestos de la fórmula (I) se pueden administrar en combinación con, por ejemplo, los inhibidores de farnesil-transferasa y/u otros fármacos útiles para el tratamiento de leucemia mieloide aguda (AML), tales como Daunorrubicina, Adriamicina, Ara-C, VP-16, Teniposida, Mitoxantrona, Idarrubicina, Carboplatino, y PKC412.

Un compuesto de la fórmula (I) también se puede utilizar con ventaja en combinación uno con otro o en combinación con otros agentes terapéuticos, en especial otros agentes contra la malaria. Estos agentes contra la malaria incluyen, pero no se limitan a, proguanil, clorproguanil, trimetoprim, cloroquina, mefloquina, lumefantrina, atovacuona, pirimetamina-sulfadoxina, pirimetamina-

dapsona, halofantrina, quinina, quinidina, amodiaquina, amopiroquina, sulfonamidas, artemisinina, artefleno, artemeter, artesunato, primaquina, NO inhalado, L-arginina, Dipropilen-tri-amina NONOato (donador de NO), Rosiglitazona (agonista de PPARγ), carbón activado, Eritropoietina, Levamisol, y pironaridina.

Un compuesto de la fórmula (I) también se puede utilizar con ventaja en combinación uno con otro o en combinación con otros agentes terapéuticos, tales como los utilizados para el tratamiento de Leishmaniasis, Tripanosomiasis, Toxoplasmosis y Neurocisticercosis. Estos agentes incluyen, pero no se limitan a, sulfato de cloroquina, atovacuona-proguanil, artemeter-lumefantrina, sulfato de quinina, artesunato, quinina, doxiciclina, clindamicina, antimoniato de meglumina, estibogluconato de sodio, miltefosina, quetoconazol, pentamidina, anfotericina B (AmB), AmB liposomal, paromomicina, eflornitina, nifurtimox, suramina, melarsoprol, prednisolona, benzonidazol, sulfadiazina, pirimetamina, clindamicina, trimetropim, sulfametoxazol, azitromicina, atovacuona, dexametasona, prazicuantel, albendazol, beta-lactamas, fluoro-quinolonas, macrolidas, amino-glicósidos, sulfadiazina y pirimetamina.

La estructura de los agentes activos identificados por números de código, nombres genéricos o comerciales, se puede tomar de la edición actual del compendio estándar "The Merck Index" o de las bases de datos, por ejemplo, Patents International, por ejemplo, IMS World Publications.

Los compuestos anteriormente mencionados, los cuales se

pueden utilizar en combinación con un compuesto de la fórmula (I), se pueden preparar y administrar como se describe en la técnica, tal como en los documentos citados anteriormente.

Un compuesto de la fórmula (I) también se puede utilizar con ventaja en combinación con los procesos terapéuticos conocidos, por ejemplo, la administración de hormonas o en especial radiación.

Un compuesto de la fórmula (I) se puede utilizar en particular como un radiosensibilizante, en especial para el tratamiento de tumores que exhiban una pobre sensibilidad a la radioterapia.

"Combinación" se refiere a ya sea una combinación fija en una forma unitaria de dosificación, o bien a un kit de partes para la administración combinada, en donde un compuesto de la fórmula (I), y un componente de combinación (por ejemplo, otro fármaco como se explica más adelante, también referido como "agente terapéutico" o "co-agente") se pueden administrar independientemente al mismo tiempo o por separado dentro de intervalos de tiempo, en especial en donde estos intervalos de tiempo permitan que los componentes de la combinación muestren un efecto cooperativo, por ejemplo, sinérgico. Los términos "co-administración" o "administración combinada" o similares, como se utilizan en la presente, pretenden abarcar la administración del componente de combinación seleccionado a un solo sujeto que lo necesite, por ejemplo, un paciente, y se pretende que incluyan los regímenes de tratamiento en donde los agentes no necesariamente se administren por la misma vía de administración o al mismo tiempo. El término

“combinación farmacéutica", como se utiliza en la presente, significa un producto que resulta de la mezcla o combinación de más de un ingrediente activo, e incluye tanto las combinaciones fijas como no fijas de los ingredientes activos. El término “combinación fija” significa que los ingredientes activos, por ejemplo, un compuesto de la fórmula (I), y un componente de combinación, se administran ambos a un paciente de una manera simultánea en la forma de una sola entidad o dosificación. El término “combinación no fija” significa que los ingredientes activos, por ejemplo, un compuesto de la fórmula (I), y un componente de combinación, se administran ambos a un paciente como entidades separadas, ya sea de una manera simultánea, concurrente, o en secuencia, sin límites de tiempo específicos, en donde esta administración proporcione niveles terapéuticamente efectivos de los dos compuestos en el cuerpo del paciente. Esto último también se aplica a la terapia de cóctel, por ejemplo, la administración de tres o más ingredientes activos.

EJEMPLOS

Detalles experimentales:

Los siguientes ejemplos pretenden ilustrar la invención y no deben interpretarse como limitaciones sobre la misma. Las temperaturas se dan en grados Celsius. Si no se menciona de otra manera, todas las evaporaciones se llevan a cabo bajo presión reducida, típicamente entre aproximadamente 15 mm Hg y 100 mm Hg (= de 20 a 133 mbar). La estructura de los productos finales, intermediarios y materiales de partida se confirma mediante los

métodos analíticos convencionales, por ejemplo, microanálisis y características espectroscópicas, por ejemplo, MS, IR, RMN. Las abreviaturas empleadas son aquéllas convencionales en la materia.

Todos los materiales de partida, bloques de construcción, reactivos, ácidos, bases, agentes deshidratantes, solventes, y catalizadores utilizados para sintetizar los compuestos de la presente invención son cualquiera de aquéllos comercialmente disponibles, o se pueden producir mediante los métodos de síntesis orgánica conocidos por un experto ordinario en este campo (Houben-Weyl, 4ª Edición 1952, Methods of Organic Synthesis, Thieme, Volumen 21). Además, los compuestos de la presente invención se pueden producir mediante los métodos de síntesis orgánica conocidos por un experto ordinario en este campo, como se muestra en los siguientes ejemplos.

Abreviaturas

ACN	acetonitrilo
AcOH	ácido acético
aq.	acuoso
Boc	terbutoxi-carbonilo
Boc_2O	dicarbonato de diterbutilo
tBu	terbutilo
tBuOH	terbutanol
BrettPhos	2-(diciclohexil-fosfino)-3,6-dimetoxi-2'-4'-6'-tri-isopropil-1,1'-bifenilo
br s	singulete amplio

COMU	hexafluorofosfato de (1-ciano-2-etoxi-2-oxo-etiliden-amino-oxi)-dimetil-amino-morfolino-carbenio
conc.	concentrado
d	día(s)
d	doblete
dd	doblete de dobletes
dba	dibenciliden-acetona
DCM	dicloro-metano
DEA	dietil-amina
DEAD	azodicarboxilato de dietilo
DEAP	dietil-amino-piridina
DIPEA	di-isopropil-etil-amina
DMF	dimetil-formamida
DMME	dimetoxi-metano
DMSO	sulfóxido de dimetilo
DPPA	difenil-fosforil-azida
DPPF	1,1'-bis-(difenil-fosfino)-ferroceno
EDC	clorhidrato de 1-(3-dimetil-amino-propil)-3-etil-carbodi-imida
eq.	equivalente(s)
ESI	ionización por electroaspersión
Et_3N	trietil-amina
Et_2O	dietil-éter
EtOAc	acetato de etilo

EtOH	etanol
h	hora(s)
HATU	hexafluorofosfato de O-(7-aza-benzotriazol-1-il)-N,N,N′,N′-tetrametil-uronio
HBTU	hexafluorofosfato de O-(1H-benzotriazol-1-il)-N,N,N’,N’-tetrametil-uronio
HMDS	hexametil-disilazano
HOBT	1-hidroxi-benzotriazol
HPLC	cromatografía de líquidos de alto rendimiento
IPA	isopropanol
LCMS	cromatografía de líquidos con espectrometría de masas
mCPBA	ácido meta-cloroperoxi-benzoico
MeOH	metanol
m	multiplete
min	minuto(s)
MS	espectrometría de masas
mw	microondas
RMN	espectrometría de resonancia magnética nuclear
NaOtBu	terbutóxido de sodio
NP	fase normal

OBD	densidad de lecho óptima
$Pd_2(dba)_3$	tris-(dibenciliden-acetona)-dipaladio
SPE PL-HCO_3 MP	cartucho de bicarbonato soportado por polímero para la remoción de ácido
prep.	preparación
PPh_3	trifenil-fosfina
q	cuarteto
Rac-BINAP	2,2′-bis-(di-*p*-tolil-fosfino)-1,1′-binaftilo racémico
RP	fase inversa
Rt	tiempo de retención
rt	temperatura ambiente
RuPhos	2-diciclohexil-fosfino-2',6'-di-isopropoxi-1,1'-bifenilo
sat.	saturado
SCX-2	poliestireno macroporoso de ácido sulfónico soportado por polímero
soln.	solución
t	triplete
TBME	terbutil-metil-éter
TBAF	fluoruro de tetrabutil-amonio
TBDMSCl	cloruro de terbutil-dimetil-sililo
TMTB	tetrametil-terbutilo
-XPhos	2-diterbutil-fosfino-3,4,5,6-tetrametil-2’,4’,6’-tri-isopropil-bifenilo

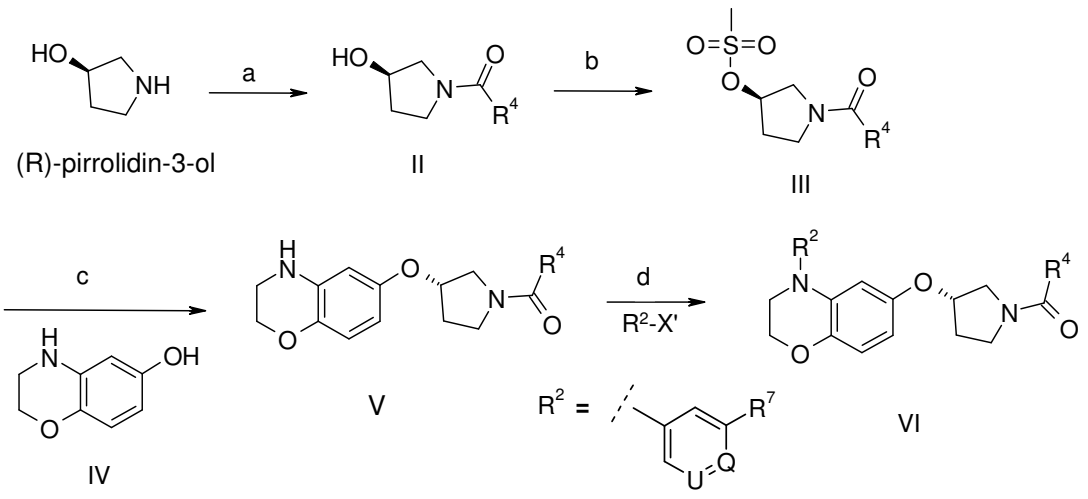
TFA	ácido trifluoro-acético
THF	tetrahidrofurano
TLC	cromatografía de capa delgada
UPLC	cromatografía de líquidos de ultra-alto rendimiento
XPhos	2-diciclohexil-fosfino-2',4',6'-tri-isopropil-bifenilo
Pd[RuPhos]	(2-diciclohexil-fosfino-2'6'-di-isopropil-11'-bifenil)-(2-(2-amino-etil)-fenil)-paladio(II)

El equipo de microondas utilizado es un Biotage Initiator®.

Todos los compuestos se nombran utilizando AutoNom.

Preparación de Ejemplos – Procedimientos Generales

Esquema 1



a) El (R)-pirrolidin-3-ol y un cloruro de ácido de la fórmula $R^4C(O)Cl$ o ácido carboxílico de la fórmula $R^4C(O)OH$ se hicieron reaccionar para preparar una amida de la fórmula general **II**. Los

expertos en este campo apreciarán que hay muchas maneras conocidas de preparar amidas. Por ejemplo, véase Mantalbetti, C.A.G.N y Falque, V., Amide bond formation and peptide coupling, Tetrahedron, 2005, 61(46), páginas 10827-10852 y las referencias citadas en el mismo. Se han empleado los siguientes métodos generales i – ii.

i. Una solución del ácido carboxílico y dimetil-formamida (DMF) (1 equivalente) en dicloro-metano (DCM) se trató con cloruro de oxalilo (1.5 equivalentes) durante 1 hora a 3°C. La mezcla de reacción se concentró bajo presión reducida, se disolvió en dicloro-metano (DCM), y se agregó a una solución de clorhidrato de (R)-pirrolidin-3-ol (1.0 equivalentes), y Et_3N (2.5 equivalentes) en dicloro-metano (DCM) a 3°C. La mezcla resultante se agitó vigorosamente a 3°C durante 1 hora, y entonces se concentró bajo presión reducida. El residuo se trató con EtOAc y se filtró. El residuo se lavó con EtOAc, y los filtrados combinados se concentraron bajo presión reducida y se purificaron mediante cromatografía por evaporación instantánea.

ii. Una solución de un cloruro de ácido comercial (1.0 equivalentes) en dicloro-metano (DCM) se agregó a una solución de clorhidrato de (R)-pirrolidin-3-ol (1.0 equivalentes), y Et_3N (2.5 equivalentes) en dicloro-metano (DCM) a 3°C. La mezcla resultante se agitó vigorosamente a 3°C durante 1 hora, y entonces se concentró bajo presión reducida. El residuo se trató con EtOAc y se filtró. El residuo se lavó con EtOAc, y los filtrados combinados se

concentraron bajo presión reducida y se purificaron mediante cromatografía por evaporación instantánea.

Las condiciones típicas para las reacciones de formación de enlace de amida se ejemplifican en la sección B) Condiciones de formación de enlace de amida, más adelante.

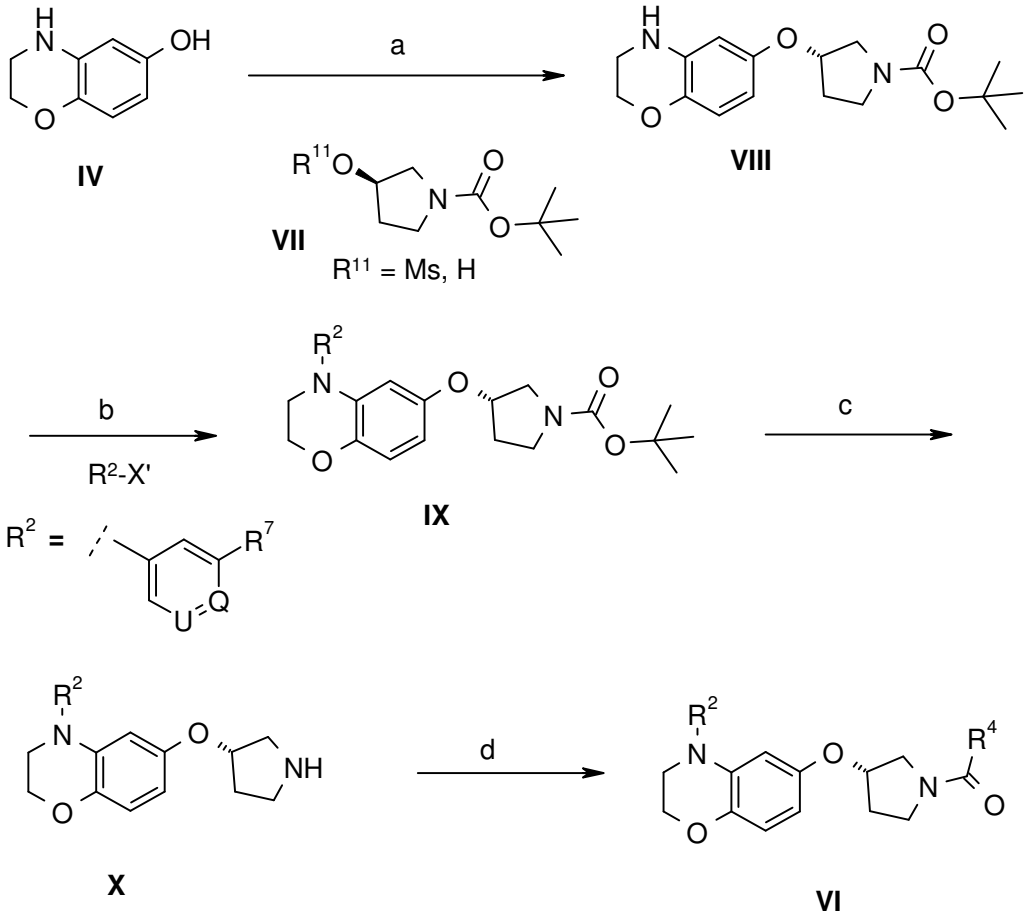
b) Los mesilatos de los compuestos de la fórmula general **II** se prepararon mediante las condiciones acostumbradas, de preferencia mediante la reacción del **II** con cloruro de metan-sulfonilo (2 equivalentes), y Et_3N (2 equivalentes) en dicloro-metano (DCM) a 0°C.

c) Los compuestos de la fórmula general **V** se prepararon mediante la reacción del 3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol **IV** con los compuestos de la fórmula general **III** en la presencia de una base adecuada, tal como hidruro de sodio (NaH), y un solvente orgánico polar, tal como dimetil-formamida (DMF), bajo condiciones de gas inerte a 50°C. Las condiciones típicas para estas reacciones se ejemplifican en la sección C) Condiciones de introducción de cadena lateral, más adelante.

d) Acoplamiento cruzado de Buchwald-Hartwig entre el **V** y un haluro de arilo de la fórmula general R^2-X', en donde X' = bromo o yodo, se llevó a cabo bajo las condiciones de Buchwald-Hartwig acostumbradas, utilizando una combinación de catalizador de Pd / ligando, tal como de preferencia $Pd_2(dba)_3$/2-(diciclohexil-fosfino)-bifenilo o $Pd_2(dba)_3$/2-diciclohexil-fosfino-2′,4′,6′-tri-isopropil-bifenilo o bis-(tri-terbutil-fosfina)-paladio, y una base, tal como de

preferencia NaOtBu, y un solvente orgánico, tal como de preferencia tolueno. La reacción de preferencia se agitó a una temperatura de aproximadamente 80°C a 120°C, de preferencia de 110°C, y de preferencia se llevó a cabo en un reactor de microondas. La reacción de preferencia se llevó a cabo bajo un gas inerte, tal como nitrógeno o argón. Los compuestos finales se purificaron mediante cromatografía normal o en fase inversa. Las condiciones típicas para las reacciones de acoplamiento cruzado de Buchwald-Hartwig se ejemplifican en la sección A) Aminaciones o hidroxilaciones de Buchwald, más adelante.

Esquema 2



a) El (S)-3-((3,4-dihidro-2H-benzo-[b][1,4]-oxazin-6-il)-oxi)-pirrolidin-1-carboxilato de terbutilo (compuesto **VIII**) se preparó mediante la reacción del 3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol **IV** con un compuesto de la fórmula general **VII** mediante uno de los siguientes métodos: i) para X = mesilato, los compuestos **IV** y **VII** se hicieron reaccionar en la presencia de una base adecuada, tal como hidruro de sodio (NaH), y un solvente orgánico polar, tal como dimetil-formamida (DMF), bajo condiciones de gas inerte, a temperatura ambiente; ii) para X = H, los compuestos de la fórmula general **IV** y **VII** se hicieron reaccionar utilizando las condiciones de Mitsunobu acostumbradas, de preferencia utilizando Ph_3P (1.4 equivalentes), y azodicarboxilato de dietilo (1.4 equivalentes) en un solvente orgánico, tal como tetrahidrofurano (THF), bajo condiciones de gas inerte, a una temperatura de preferencia de 70°C. Las condiciones típicas para estas reacciones se ejemplifican en la sección C) Condiciones de introducción de cadena lateral, más adelante.

b) El acoplamiento cruzado de Buchwald-Hartwig entre el **VIII** y un haluro de arilo de la fórmula general R^2-X', en donde X' = bromo o yodo, se llevó a cabo bajo las condiciones de Buchwald-Hartwig acostumbradas, utilizando una combinación de catalizador de Pd / ligando, tal como de preferencia $Pd_2(dba)_3$/X-Phos, $Pd_2(dba)_3$/(rac)-BINAP, $Pd(OAc)_2$/(rac)-BINAP o bis-(tri-terbutil-fosfina)-paladio, y una base, tal como de preferencia NaOtBu, Cs_2CO_3 ó K_3PO_4 y un solvente orgánico, tal como de preferencia

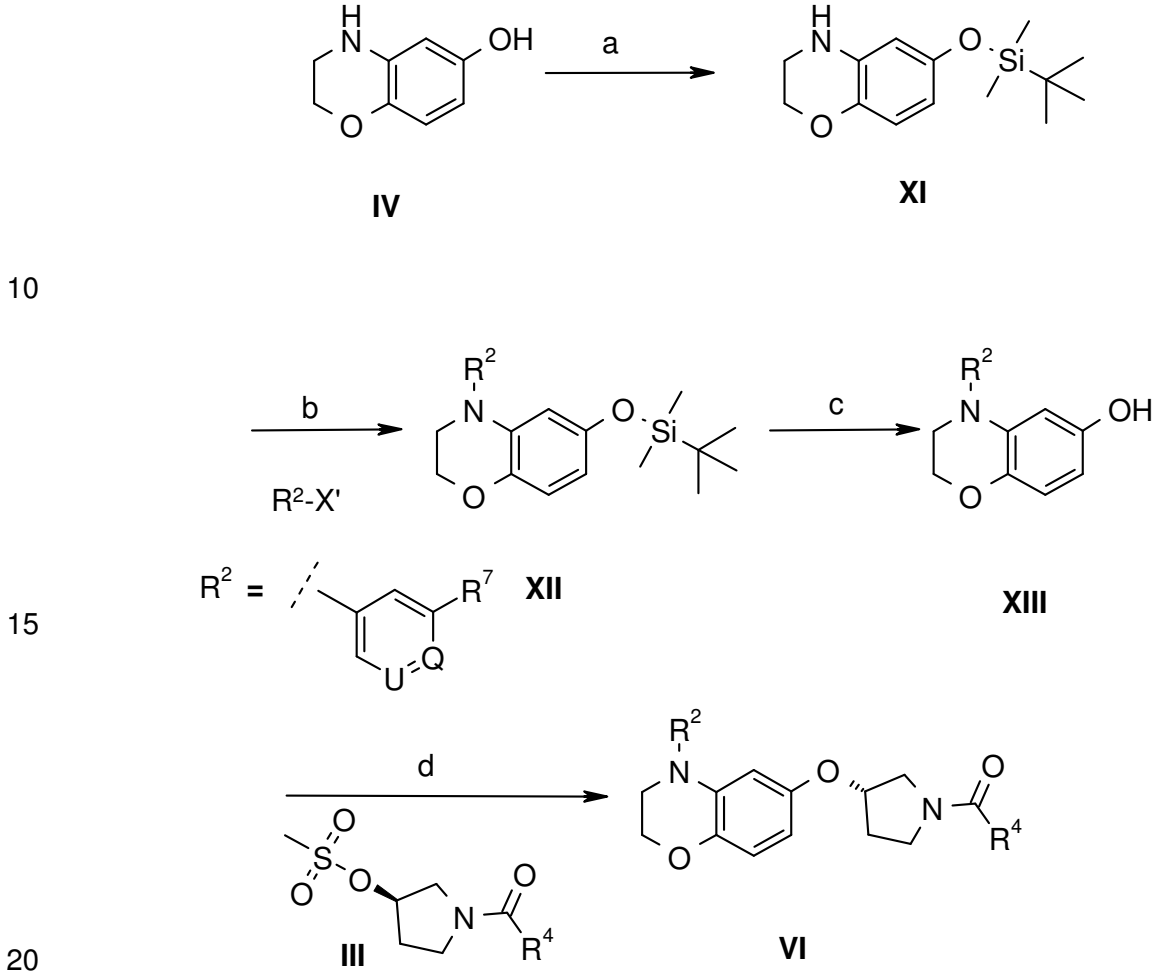
tolueno, dioxano o tetrahidrofurano (THF). La reacción de preferencia se agitó a una temperatura de aproximadamente 60°C a 120°C, y de preferencia se llevó a cabo en un reactor de microondas. La reacción de preferencia se llevó a cabo bajo un gas inerte, tal como nitrógeno o argón. Las condiciones típicas para las reacciones de acoplamiento cruzado de Buchwald-Hartwig se ejemplifican en la sección A) Aminaciones o hidroxilaciones de Buchwald, más adelante.

c) La desprotección de N-BOC de los compuestos de la fórmula general **IX** se llevó a cabo bajo las condiciones de desprotección de BOC acostumbradas, utilizando entre los posibles ácidos, de preferencia ácido trifluoro-acético (TFA) y un solvente orgánico, de preferencia dicloro-metano (DCM). La reacción de preferencia se llevó a cabo a temperatura ambiente.

d) Un compuesto de la fórmula general **X** y un cloruro de ácido de la fórmula $R^4C(O)Cl$ o un ácido carboxílico de la fórmula $R^4C(O)OH$ se hicieron reaccionar para preparar una amida de la fórmula general **VI** utilizando las condiciones de acoplamiento de amida acostumbradas: en adición a los métodos descritos en el esquema 1, paso a), los reactivos de acoplamiento preferidos fueron HBTU, HOBt/EDC, COMU/DIPEA. Los acoplamientos se llevaron a cabo en un solvente orgánico, tal como de preferencia dimetil-formamida (DMF) o dicloro-metano (DCM), y los compuestos finales se purificaron mediante cromatografía normal o en fase inversa. Las condiciones típicas para las reacciones de formación de enlace de

amida se ejemplifican en la sección B) Condiciones de formación de enlace de amida, más adelante.

Esquema 3



a) El 3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol **IV** se O-protegió empleando los procedimientos de sililación convencionales, utilizando un reactivo de sililación, de preferencia TBDMSCl, y una base, de preferencia NaH, en un solvente orgánico, de preferencia

tetrahidrofurano (THF), a temperatura ambiente.

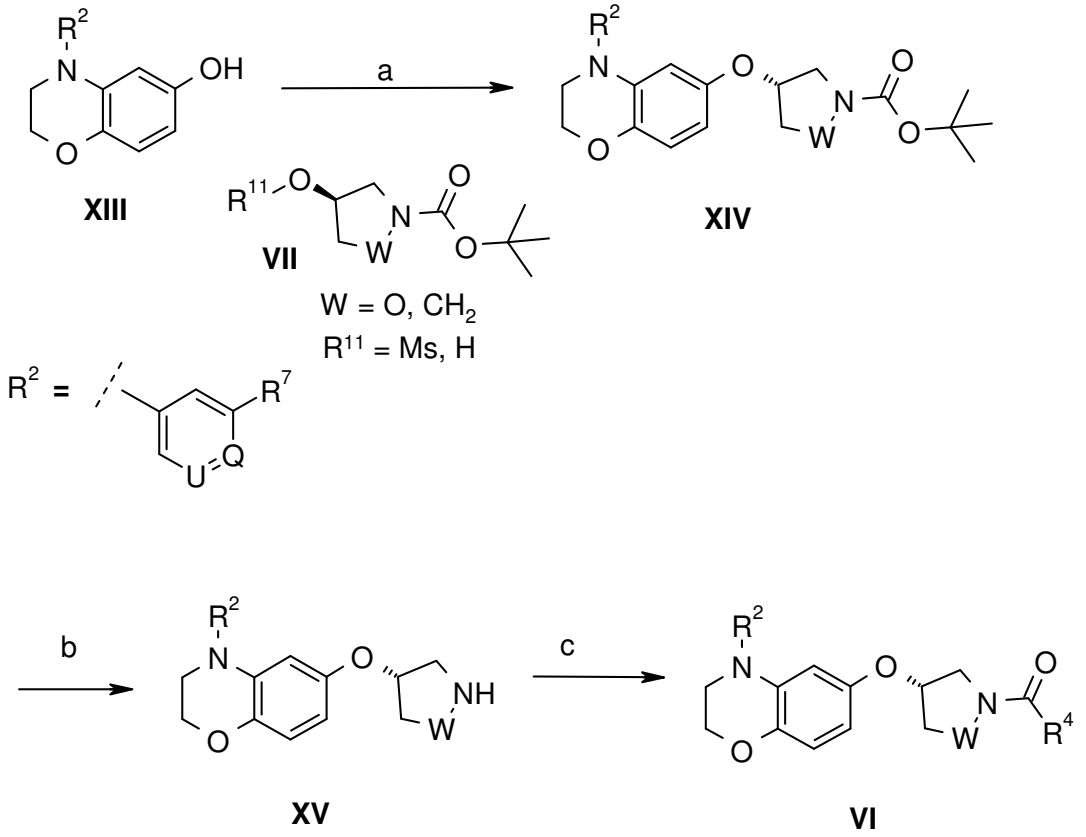
b) El acoplamiento cruzado de Buchwald-Hartwig entre el **XI** y un haluro de arilo de la fórmula general R^2-X', en donde X' = bromo o yodo, se llevó a cabo bajo las condiciones de Buchwald-Hartwig acostumbradas, utilizando una combinación de catalizador de Pd / ligando, tal como de preferencia $Pd_2(dba)_3$/X-Phos, $Pd_2(dba)_3$/ diciclohexil-fosfino-2',4',6'-tri-isopropil-bifenilo o bis-(tri-terbutil-fosfina)-paladio, y una base, tal como de preferencia NaOtBu, y un solvente orgánico, tal como de preferencia tolueno. La reacción de preferencia se agitó a una temperatura de aproximadamente 110°C a 140°C, y de preferencia se llevó a cabo en un reactor de microondas. La reacción de preferencia se llevó a cabo bajo un gas inerte, tal como nitrógeno o argón. Las condiciones típicas para las reacciones de acoplamiento cruzado de Buchwald-Hartwig se ejemplifican en la sección A) Aminaciones o hidroxilaciones de Buchwald, más adelante.

c) La desprotección de *O*-TBDMS de los compuestos de la fórmula general **XII** se llevó a cabo bajo las condiciones de desprotección acostumbradas, utilizando de preferencia TBAF y un solvente orgánico, de preferencia tetrahidrofurano (THF). La reacción de preferencia se llevó a cabo a temperatura ambiente

d) Los compuestos de la fórmula general **XIII** se acoplaron con los mesilatos de la fórmula general **III,** utilizando una base adecuada, tal como de preferencia hidruro de sodio (NaH) o K_2CO_3 y un solvente orgánico polar, tal como dimetil-formamida (DMF), bajo

condiciones de gas inerte, a temperatura ambiente o a temperaturas elevadas de hasta 100°C. Los compuestos finales se purificaron mediante cromatografía normal o en fase inversa. Las condiciones típicas para estas reacciones se ejemplifican en la sección C) Condiciones de introducción de cadena lateral, más adelante.

Esquema 4



a) Los compuestos de la fórmula general **XIII** (preparados como se describe en el esquema 3) se hicieron reaccionar con los compuestos de la fórmula general **VII** mediante uno de los siguientes

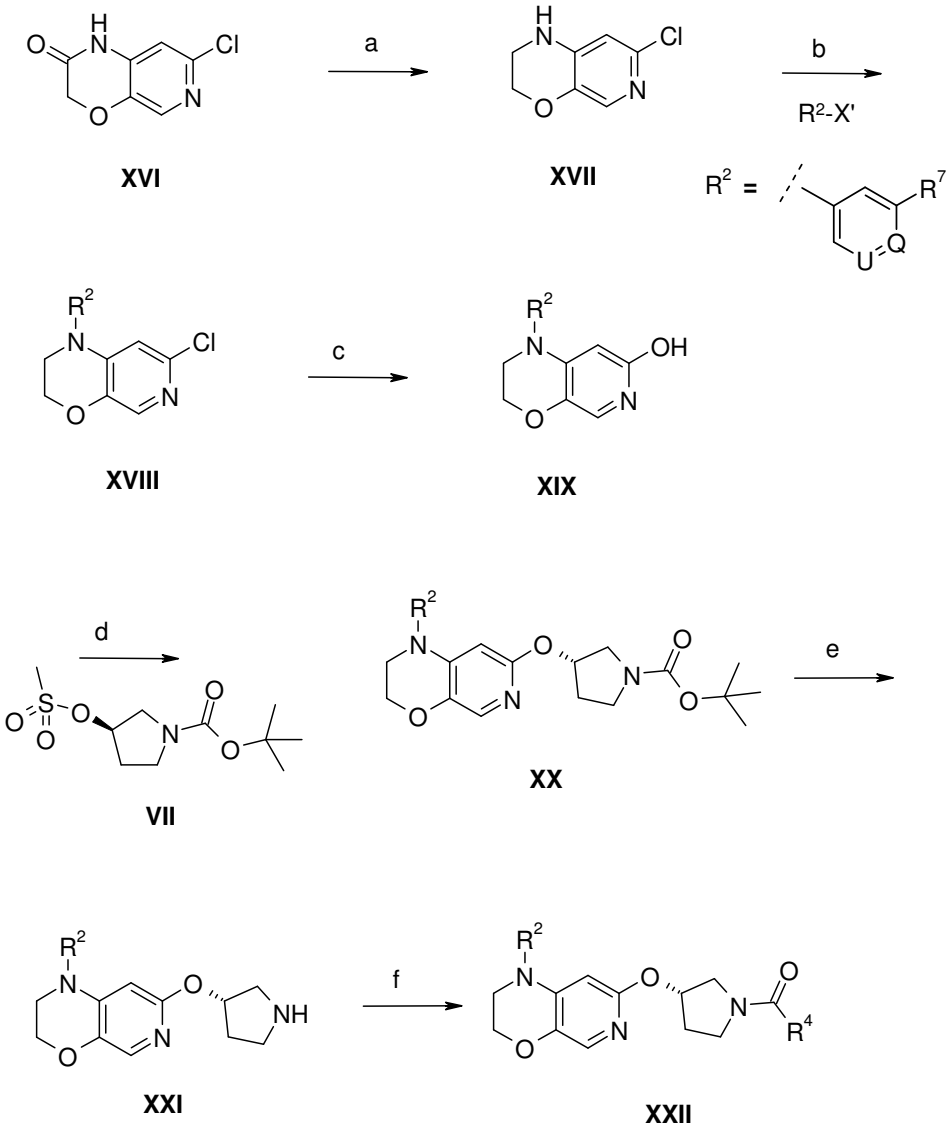
métodos: 1) para X = mesilato, los compuestos **XIII** y **VII** se hicieron reaccionar en la presencia de una base adecuada, tal como hidruro de sodio (NaH), y un solvente orgánico polar, tal como dimetil-formamida (DMF), bajo condiciones de gas inerte, a temperatura ambiente; ii) para X = H, los compuestos de la fórmula general **XIII** y **VII** se hicieron reaccionar utilizando las condiciones de Mitsunobu acostumbradas, de preferencia utilizando Ph_3P (1.4 equivalentes), y azodicarboxilato de dietilo (1.4 equivalentes) en un solvente orgánico, tal como tetrahidrofurano (THF), bajo condiciones de gas inerte, a una temperatura de preferencia de 70°C. Las condiciones típicas para estas reacciones se ejemplifican en la sección C) Condiciones de introducción de cadena lateral, más adelante.

b) La desprotección de N-BOC se llevó a cabo bajo las condiciones de desprotección de BOC acostumbradas, utilizando entre los posibles ácidos, de preferencia ácido trifluoro-acético, y un solvente orgánico, de preferencia CH_2Cl_2. La reacción de preferencia se llevó a cabo a temperatura ambiente.

c) La formación de enlace de amida se llevó a cabo utilizando los compuestos de la fórmula general **XV** y un cloruro de ácido de la fórmula $R^4C(O)Cl$ o ácido carboxílico de la fórmula $R^4C(O)OH$, para preparar una amida de la fórmula general **VI**; se utilizaron las condiciones de acoplamiento de enlace de amida acostumbradas, como se describen en el esquema 1, paso a). En adición a los métodos descritos en el esquema 1, paso a), se utilizó el acoplamiento de ácidos carboxílicos utilizando HOBt/EDC o el

acoplamiento utilizando cloroformatos o cloruros carbámicos. Los acoplamientos se llevaron a cabo en un solvente orgánico, tal como de preferencia dimetil-formamida (DMF) o dicloro-metano (DCM), y los compuestos finales se purificaron mediante cromatografía normal o en fase inversa. Las condiciones típicas para las reacciones de formación de enlace de amida se ejemplifican en la sección B) Condiciones de formación de enlace de amida, más adelante.

Esquema 5



XVI **XVII** **XVIII** **XIX** **VII** **XX** **XXI** **XXII**

a) La 7-cloro-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina **XVII** se preparó a partir de la 7-cloro-1H-pirido-[3,4-b][1,4]-oxazin-2-ona **XVI** mediante los métodos de reducción acostumbrados, utilizando como el agente de reducción, de preferencia BH_3*THF, y como el solvente de preferencia tetrahidrofurano (THF). El **XVI** está disponible por medio de nitración de flujo del 2-cloro-5-(2-metoxi-2-oxoetoxi)-piridin-1-óxido, seguida por reducción y ciclación.

b) El acoplamiento cruzado entre el **XVII** y un haluro de arilo de la fórmula general R^2-X', en donde X' = bromo o yodo, se llevó a cabo bajo las condiciones de Buchwald-Hartwig acostumbradas, utilizando una combinación de catalizador de Pd / ligando, tal como de preferencia $Pd_2(dba)_3$/X-Phos, y una base, tal como de preferencia Cs_2CO_3, y un solvente orgánico, tal como de preferencia dioxano. La reacción de preferencia se agitó a una temperatura de aproximadamente 100°C y se pudo llevar a cabo en un reactor de microondas. La reacción de preferencia se llevó a cabo bajo un gas inerte, tal como nitrógeno o argón. Las condiciones típicas para las reacciones de acoplamiento cruzado de Buchwald-Hartwig se ejemplifican en la sección A) Aminaciones o hidroxilaciones de Buchwald, más adelante.

c) La hidroxilación del **XVIII** se llevó a cabo utilizando KOH acuoso y una combinación de catalizador de Pd / ligando, tal como de preferencia $Pd_2(dba)_3$/tetrametil-terbutil-Xphos, y un solvente orgánico, tal como de preferencia dioxano. La reacción de preferencia se agitó a una temperatura de aproximadamente 100°C.

La reacción de preferencia se llevó a cabo bajo un gas inerte, tal como nitrógeno o argón.

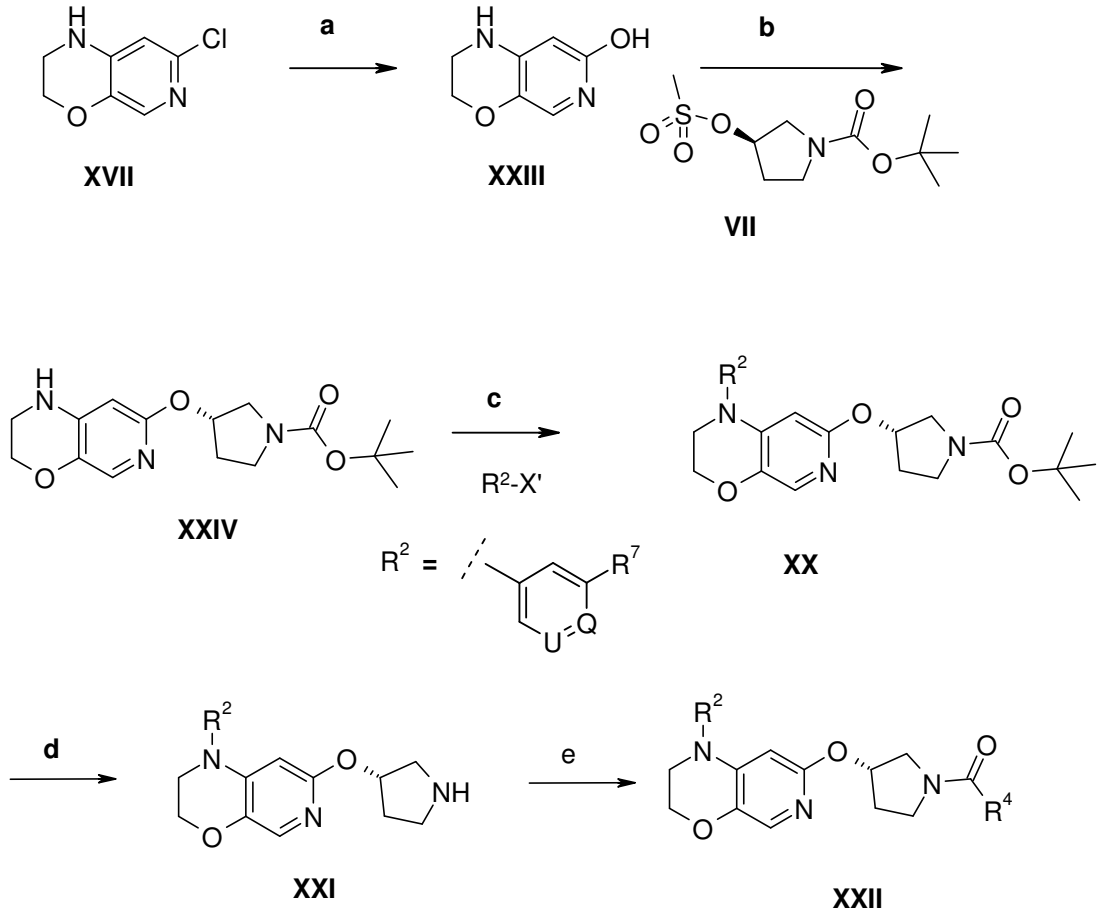
d) El acoplamiento de un compuesto de la fórmula general **XIX** con un compuesto de la fórmula general **VII** se llevó a cabo utilizando una base adecuada, tal como hidruro de sodio (NaH, Cs_2CO_3, K_2CO_3), y un solvente orgánico polar, tal como dimetil-formamida (DMF), bajo condiciones de gas inerte, a una temperatura de preferencia de 60°C a 80°C. Las condiciones típicas para estas reacciones se ejemplifican en la sección C) Condiciones de introducción de cadena lateral, más adelante.

e) La desprotección de N-BOC se llevó a cabo bajo las condiciones de desprotección de BOC acostumbradas, utilizando entre los posibles ácidos, de preferencia ácido trifluoro-acético, y un solvente orgánico, de preferencia CH_2Cl_2. La reacción de preferencia se llevó a cabo a temperatura ambiente.

f) La formación de enlace de amida se llevó a cabo utilizando los compuestos de la fórmula general **XXI** y un cloruro de ácido de la fórmula $R^4C(O)Cl$ o ácido carboxílico de la fórmula $R^4C(O)OH$, para preparar una amida de la fórmula general **XXII**; se utilizaron las condiciones de acoplamiento de enlace de amida acostumbradas, como se describen en el esquema 1, paso a), en adición, se aplicó el acoplamiento de ácidos carboxílicos utilizando HOBt/EDC. Los acoplamientos se llevaron a cabo en un solvente orgánico, tal como de preferencia dimetil-formamida (DMF) o dicloro-metano (DCM), y los compuestos finales se purificaron mediante

cromatografía normal o en fase inversa. Las condiciones típicas para las reacciones de formación de enlace de amida se ejemplifican en la sección B) Condiciones de formación de enlace de amida, más adelante.

Esquema 6



a) La hidroxilación de la 7-cloro-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina **XVII** para dar el 2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-ol **XXIII** se llevó a cabo utilizando KOH acuoso y una combinación de catalizador de Pd / ligando, tal como de preferencia

$Pd_2(dba)_3$/tetrametil-terbutil-Xphos, y un solvente orgánico, tal como de preferencia dioxano. La reacción de preferencia se agitó a una temperatura de aproximadamente 100°C. La reacción de preferencia se llevó a cabo bajo un gas inerte, tal como nitrógeno o argón.

b) El acoplamiento del compuesto **XXIII** con el mesilato **VII** se efectuó utilizando una base adecuada, tal como hidruro de sodio (NaH), y un solvente orgánico polar, tal como dimetil-formamida (DMF), bajo condiciones de gas inerte, a una temperatura de preferencia de 80°C. Las condiciones típicas para estas reacciones se ejemplifican en la sección C) Condiciones de introducción de cadena lateral, más adelante.

c) El acoplamiento cruzado entre el **XXIV** y un haluro de arilo de la fórmula general R^2-X', en donde X' = bromo o yodo, se llevó a cabo bajo las condiciones de Buchwald-Hartwig acostumbradas, utilizando una combinación de catalizador de Pd / ligando, tal como de preferencia $Pd_2(dba)_3$/X-Phos o $Pd_2(dba)_3$/(rac)-BINAP, y una base, tal como de preferencia Cs_2CO_3 ó NaOtBu, y un solvente orgánico, tal como de preferencia dioxano o tolueno. La reacción de preferencia se agitó a una temperatura de aproximadamente 100°C y se pudo llevar a cabo en un reactor de microondas. La reacción de preferencia se llevó a cabo bajo un gas inerte, tal como nitrógeno o argón. Las condiciones típicas para las reacciones de acoplamiento cruzado de Buchwald-Hartwig se ejemplifican en la sección A) Aminaciones o hidroxilaciones de Buchwald, más adelante.

d) La desprotección de N-BOC se llevó a cabo bajo las condiciones de desprotección de BOC acostumbradas, utilizando entre los posibles ácidos, de preferencia ácido trifluoro-acético, y un solvente orgánico, de preferencia CH_2Cl_2. La reacción de preferencia se llevó a cabo a temperatura ambiente

e) La formación de enlace de amida se llevó a cabo utilizando los compuestos de la fórmula general **XXI** y un cloruro de ácido de la fórmula $R^4C(O)Cl$ o ácido carboxílico de la fórmula $R^4C(O)OH$, para preparar una amida de la fórmula general **XXII**; se utilizaron las condiciones de acoplamiento de enlace de amida acostumbradas, como se describen en el esquema 1, paso a), o se aplicó el acoplamiento de ácidos carboxílicos utilizando HBTU, HOBt/EDC o HATU. Los acoplamientos se llevaron a cabo en un solvente orgánico, tal como de preferencia dimetil-formamida (DMF) o dicloro-metano (DCM), y los compuestos finales se purificaron mediante cromatografía normal o en fase inversa. Las condiciones típicas para las reacciones de formación de enlace de amida se ejemplifican en la sección B) Condiciones de formación de enlace de amida, más adelante.

Información general de cromatografía

LCMS método M1 (Rt_{M1})

HPLC-dimensiones de la columna: 2.1 x 50 milímetros.

HPLC-tipo de columna: Acquity UPLC HSS T3, 1.8 micras.

HPLC-eluyente: A) agua + ácido fórmico al 0.05 por ciento por volumen + acetato

de amonio 3.75 mM, B) acetonitrilo (ACN) + ácido fórmico al 0.04 por ciento por volumen.

HPLC-gradiente: Del 2 al 98 por ciento de B en 1.4 minutos, 98 por ciento de B en 0.45 minutos, flujo = 1.2 mililitros / minuto.

HPLC-temperatura de la columna: 50°C.

LCMS método M2 (Rt_{M2})

HPLC-dimensiones de la columna: 2.1 x 30 milímetros.

HPLC-tipo de columna: Ascentis Express C18, 2.7 micras.

HPLC-eluyente: A) agua + ácido fórmico al 0.05 por ciento por volumen + acetato de amonio 3.75 mM, B) acetonitrilo (ACN) + ácido fórmico al 0.04 por ciento por volumen.

HPLC-gradiente: Del 2 al 98 por ciento de B en 1.4 minutos, 0.75 minutos con el 98 por ciento de B, flujo = 1.2 mililitros / minuto.

HPLC-temperatura de la columna: 50°C.

LCMS método M3 (Rt_{M3})

HPLC-dimensiones de la columna: 2.1 x 30 milímetros.

HPLC-tipo de columna: Ascentis Express C18, 2.7 micras.

HPLC-eluyente: A) agua + ácido fórmico al 0.05

por ciento por volumen + acetato de amonio 3.75 mM, B) acetonitrilo (ACN) + ácido fórmico al 0.04 por ciento por volumen.

HPLC-gradiente: Del 2 al 98 por ciento de B en 8.5 minutos, 1 minuto con el 98 por ciento de B, flujo = 1.2 mililitros / minuto.

HPLC-temperatura de la columna: 50ºC.

LCMS método M4 (Rt_{M4})

HPLC-dimensiones de la columna: 4.6 x 50 milímetros.

HPLC-tipo de columna: SunFire C18, 5 micras.

HPLC-eluyente: A) agua + ácido trifluoro-acético (TFA) al 0.1 por ciento por volumen, B) acetonitrilo (ACN) + ácido trifluoro-acético (TFA) al 0.1 por ciento por volumen.

HPLC-gradiente: Del 5 al 100 por ciento de B en 8.0 minutos B, flujo = 2 mililitros / minuto.

HPLC-temperatura de la columna: 40ºC.

LCMS método M5 (Rt_{M5})

HPLC-dimensiones de la columna: 0.46 x 25 centímetros.

HPLC-tipo de columna: Chiralcel OJ-H (1189).

HPLC-eluyente: EtOH/MeOH, 60:40.

HPLC-gradiente: Isocrática, flujo = 0.5 mililitros / minuto.

Detector: UV 220 nanómetros.

LCMS método M6 (Rt_{M6})

HPLC-dimensiones de la columna: 2.1 x 30 milímetros.

HPLC-tipo de columna: Ascentis Express C18, 2.7 micras.

HPLC-eluyente: A) agua + ácido trifluoro-acético (TFA) al 0.05 por ciento, B) acetonitrilo (ACN) + ácido trifluoro-acético (TFA) al 0.04 por ciento.

HPLC-gradiente: Del 2 al 98 por ciento de B en 1.4 minutos, 0.75 minutos con el 98 por ciento de B, flujo = 1.2 mililitros / minuto.

HPLC-temperatura de la columna: 50°C.

LCMS método M7 (Rt_{M7})

HPLC-dimensiones de la columna: 2.1 x 30 milímetros.

HPLC-tipo de columna: Ascentis Express C18, 2.7 micras.

HPLC-eluyente: A) agua + ácido trifluoro-acético (TFA) al 0.05 por ciento, B) acetonitrilo (ACN) + ácido trifluoro-acético (TFA) al 0.04 por ciento.

HPLC-gradiente: Del 10 al 95 por ciento de B en 3.0

minutos, 1 minuto con el 95 por ciento de B, flujo = 1.2 mililitros / minuto.

HPLC-temperatura de la columna: 50ºC.

LCMS método M8 (Rt_{M8})

HPLC-dimensiones de la columna: 2.1 x 30 milímetros.

HPLC-tipo de columna: Ascentis Express C18 2.7 micras.

HPLC-eluyente: A) agua + ácido fórmico al 0.05 por ciento + acetato de amonio 3.75 mM, B) acetonitrilo + ácido fórmico al 0.04 por ciento.

HPLC-gradiente: Del 10 al 95 por ciento de B en 3.0 minutos, flujo = 1.2 mililitros / minuto.

LCMS método M9 (Rt_{M9})

HPLC-dimensiones de la columna: 2.1 x 30 milímetros.

HPLC-tipo de columna: Ascentis Express C18 2.7 micras.

HPLC-eluyente: A) agua + ácido fórmico al 0.05 por ciento + acetato de amonio 3.75 mM, B) acetonitrilo + ácido fórmico al 0.04 por ciento.

HPLC-gradiente: 10 por ciento de B en 0.0 a 0.5 minutos, entonces de 0.5 minutos a 3.0 minutos con gradiente del 10 al 95 por ciento de B, flujo = 1.2

mililitros / minuto.

LCMS método M10 (Rt_{M10})

HPLC-dimensiones de la columna:	2.1 x 50 milímetros.
HPLC-tipo de columna:	Acquity UPLC BEH C18 1.7 micras.
HPLC-eluyente:	A) agua + ácido fórmico al 0.1 por ciento por volumen, B) acetonitrilo.
HPLC-gradiente:	Del 20 al 25 por ciento de B en 1.00 minutos, entonces del 25 al 95 por ciento de B en 3.20 minutos, entonces del 95 al 100 por ciento de B en 0.10 minutos, entonces 100 por ciento durante 0.20 minutos, flujo = 0.7 mililitros / minuto.

LCMS método M11 (Rt_{M11})

HPLC-dimensiones de la columna:	2.1 x 50 milímetros.
HPLC-tipo de columna:	Acquity UPLC BEH C18, 1.7 micras.
HPLC-eluyente:	A) agua + ácido fórmico al 0.1 por ciento por volumen, B) acetonitrilo.
HPLC-gradiente:	Del 5 al 10 por ciento de B en 1.00 minutos, entonces del 10 al 90 por

ciento de B en 3.00 minutos, entonces del 90 al 100 por ciento de B en 0.10 minutos, entonces 100 por ciento durante 0.40 minutos, flujo = 0.7 mililitros / minuto.

LCMS método M12 (Rt_{M12})

HPLC-dimensiones de la columna: 2.1 x 30 milímetros.

HPLC-tipo de columna: Ascentis Express C18, 2.7 micras.

HPLC-eluyente: A) agua + ácido trifluoro-acético (TFA) al 0.1 por ciento por volumen, B) acetonitrilo.

HPLC-gradiente: Del 10 al 95 por ciento de B durante 1.7 minutos, y 1.2 mililitros / minuto como el flujo de solvente, y entonces el 95 por ciento de B durante 0.7 minutos, flujo = 1.4 mililitros / minuto.

LCMS método M13 (Rt_{M13})

HPLC-dimensiones de la columna: 2.1 x 30 milímetros.

HPLC-tipo de columna: Ascentis Express C18, 2.7 micras.

HPLC-eluyente: A) agua + ácido fórmico al 0.05 por ciento + acetato de amonio 3.75 mM, B) acetonitrilo + ácido fórmico al 0.04 por ciento.

HPLC-gradiente: Del 10 al 95 por ciento de B en 3.7 minutos, flujo = 1.2 mililitros / minuto.

LCMS método M14 (Rt_{M14})

HPLC-dimensiones de la columna: 2.1 x 30 milímetros.

HPLC-tipo de columna: Ascentis Express C18, 2.7 micras.

HPLC-eluyente: A) agua + ácido fórmico al 0.05 por ciento + acetato de amonio 3.75 mM, B) acetonitrilo + ácido fórmico al 0.04 por ciento.

HPLC-gradiente: Del 10 al 95 por ciento de B en 1.5 minutos, 1 minuto con el 95 por ciento de B, flujo = 1.2 mililitros / minuto.

LCMS método M15 (Rt_{M15})

HPLC-dimensiones de la columna: 0.46 x 25 centímetros.

HPLC-tipo de columna: Chiralcel OD-H (1194).

HPLC-eluyente: Hexano/EtOH, 50:50 + DEA al 0.05 por ciento.

HPLC-gradiente: Isocrática, flujo = 0.5 mililitros / minuto.

Detector: UV 220 nanómetros.

LCMS método M16 (Rt_{M16})

HPLC-dimensiones de la columna: 2.1 x 50 milímetros.

HPLC-tipo de columna: Acquity UPLC HSS T3, 1.8 micras.

HPLC-eluyente:	A) agua + ácido fórmico al 0.05 por ciento por volumen + acetato de amonio 3.75 mM, B) acetonitrilo (ACN) + ácido fórmico al 0.04 por ciento por volumen.
HPLC-gradiente:	Del 5 al 98 por ciento de B en 1.4 minutos, 98 por ciento de B en 0.4 minutos, flujo = 1.0 mililitros / minuto.

HPLC-temperatura de la columna: 60°C.

Difracción en polvo de rayos-X

Instrumentación:

Método X1

Instrumento:	Bruker D8 GADDS Discover
Irradiación:	CuKα (40 kV, 40 mA)
Detector:	HI-STAR Detector de área
Rango de exploración:	6°-39° (valor 2-Theta)

Determinación del punto de fusión:

El punto de fusión se determinó mediante calorimetría de exploración diferencial (DSC), la calorimetría de exploración diferencial (DSC) fue como se registró en un TA Instruments DSC Q2000 utilizando una velocidad de calentamiento de 10°C/minuto. Una muestra de 0.6 miligramos se pesó en una bandeja de aluminio estándar (bandeja + tapa, TA 900786.901, 900779.901). El

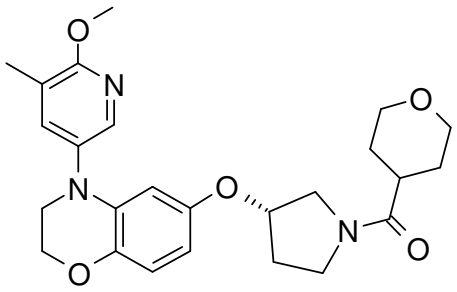
instrumento se operó utilizando el software Thermal Advantage Q-Series V.2.6.0.367 y el software Thermal Advantage V4.6.9. Los eventos térmicos se caracterizaron utilizando el Universal Analysis V4.3A Construcción 4.3.0.6. Las muestras se midieron contra la bandeja de muestra sin orificio. La muestra se trató de acuerdo con el siguiente protocolo:

Paso 1: EQUILIBRAR a 0°C.

Paso 2: Rampa a 10°C/minuto hasta 300°C.

Preparación de ejemplos

Cuando se menciona que los compuestos se prepararon de la manera descrita para un ejemplo anterior, la persona experta apreciará que los tiempos de reacción, el número de equivalentes de reactivos, y las temperaturas de reacción se pueden modificar para cada reacción específica, y que, no obstante, puede ser necesario o recomendable emplear condiciones de procesamiento o de purificación diferentes.



<u>Ejemplo A1:</u> (S)-(3-((4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[b][1,4]-oxazin-6-il)-oxi)-pirrolidin-1-il)-(tetrahidro-2H-piran-4-il)-metanona

(de acuerdo con el esquema 1)

a1) (R)-(3-hidroxi-pirrolidin-1-il)-(tetrahidro-2H-piran-4-il)-metanona

Una solución agitada de ácido tetrahidro-2H-piran-4-carboxílico (CAS registro 5337-03-1) (0.200 gramos, 1.537 milimoles), y dimetil-formamida (DMF) (0.012 mililitros, 0.154 milimoles) en dicloro-metano (DCM) (3 mililitros) se trató con cloruro de oxalilo (0.202 mililitros, 2.305 milimoles) a 3°C. Después de 1 hora a 3°C, la mezcla de reacción se concentró bajo presión reducida. El residuo entonces se disolvió en dicloro-metano (DCM) (2 mililitros), y se agregó a una solución agitada de clorhidrato de (R)-pirrolidin-3-ol (CAS registro 104706-47-0) (0.190 gramos, 1.537 milimoles), y Et_3N (0.535 mililitros, 3.84 milimoles) en dicloro-metano (DCM) (3 mililitros) a 3°C. Después de 1 hora a 3°C, la mezcla de reacción se concentró bajo presión reducida. El residuo se trató con EtOAc (10 mililitros), y se filtró. El residuo se lavó con EtOAc, y los filtrados combinados se concentraron bajo presión reducida. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (gradiente de dicloro-metano (DCM) / metanol), para proporcionar el compuesto del título como un sólido blanco.

ESIMS: 200 [$(M+H)^+$].

^1H RMN (400 MHz, $CDCl_3$): δ 4.61-4.50 (m, 1H), 4.10-4.02 (m, 2H), 3.77-3.40 (m, 6H), 2.70-2.53 (m, 1H), 2.20-1.85 (m, 4H), 1.75-

1.69 (m, 3H).

Método alternativo a2: en lugar de preparar el cloruro de ácido *in situ*, se utilizó un cloruro de ácido comercialmente disponible como el cloruro de propanoílo (CAS registro 79-03-8).

b1) Metan-sulfonato de (R)-1-(tetrahidro-2H-piran-4-carbonil)-pirrolidin-3-ilo

Una solución agitada de la (R)-(3-hidroxi-pirrolidin-1-il)-(tetrahidro-2H-piran-4-il)-metanona (0.245 gramos, 1.230 milimoles) en dicloro-metano (DCM) (10 mililitros) se trató con Et_3N (0.343 mililitros, 2.459 milimoles), y cloruro de metan-sulfonilo (0.192 mililitros, 2.459 milimoles) a 0°C. Después de 1 hora a 0°C, se agregó agua (20 mililitros). La capa orgánica se lavó con una solución saturada de NaCl (20 mililitros), se secó con $MgSO_4$, se filtró, y se concentró bajo presión reducida. El producto crudo se purificó mediante trituración con dietil-éter para proporcionar el compuesto del título como un sólido blanco.

ESIMS: 278 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 5.40-.5.29 (m, 1H), 4.10-4.02 (m, 2H), 3.94-3.87 (m, 1H), 3.82-3.56 (m. 3H), 3.52-3.41 (m, 2H), 3.11-3.04 (m, 3H), 2.70-2.10 (m, 3H), 2.02-2.87 (m, 2H), 1.72-1.57 (m, 2H).

c1) (S)-(3-((3,4-dihidro-2H-benzo-[b][1,4]-oxazin-6-il)-oxi)-pirrolidin-1-il)-(tetrahidro-2H-piran-4-il)-metanona

Una solución agitada del 3,4-dihidro-2H-benzoxazin-6-ol (CAS registro 26021-57-8) (0.140 gramos, 0.926 milimoles) en dimetil-

formamida (DMF) (3 mililitros) se trató con hidruro de sodio (al 60 por ciento en aceite mineral, 0.445 gramos, 1.111 milimoles), a temperatura ambiente. Después de 10 minutos a temperatura ambiente, se agregó metan-sulfonato de (R)-1-(tetrahidro-2H-piran-4-carbonil)-pirrolidin-3-ilo (0.283 gramos, 1.019 milimoles). El frasco se tapó y se calentó a 50°C durante 3 horas. Después de este tiempo, la mezcla de reacción se concentró bajo presión reducida. El residuo se disolvió en EtOAc (50 mililitros), y se agregó agua (50 mililitros). La capa orgánica se lavó con una solución saturada de NaCl (20 mililitros), se secó con $MgSO_4$, se filtró, y se concentró bajo presión reducida. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (gradiente de dicloro-metano (DCM) / metanol), para proporcionar el compuesto del título como un sólido amorfo color gris.

HPLC Rt_{M10}= 2.07 minutos; ESIMS: 333 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 6.55-6.50 (m, 1H), 6.15-6.11 (m, 1H), 6.07-6.00 (m, 1H), 5.77 (br s, 1H), 4.88-4.74 (m, 1H), 4.06-4.01 (m, 2H), 3.90-3.22 (m, 10H), 2.75-2.58 (m, 1H), 2.15-1.95 (m, 2H), 1.65-1.45 (m, 4H).

d1) (S)-(3-((4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[b][1,4]-oxazin-6-il)-oxi)-pirrolidin-1-il)-(tetrahidro-2H-piran-4-il)-metanona

Una solución agitada de la (S)-(3-((3,4-dihidro-2H-benzo-[b][1,4]-oxazin-6-il)-oxi)-pirrolidin-1-il)-(tetrahidro-2H-piran-4-il)-metanona (0.050 gramos, 0.150 milimoles) en tolueno (1 mililitro) se

trató con 5-bromo-2-metoxi-3-metil-piridina (CAS registro 760207-87-2) (0.030 gramos, 0.150 milimoles), NaOtBu (0.022 gramos, 0.226 milimoles), 2-(diciclohexil-fosfino)-bifenilo (CAS registro 247940-06-3), y $Pd_2(dba)_3$ (0.004 gramos, 0.005 milimoles), a temperatura ambiente bajo argón. El frasco de reacción se tapó y se calentó a 110°C en un reactor de microondas durante 3 horas. Después de este tiempo, la mezcla de reacción se concentró bajo presión reducida. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (gradiente de ciclohexano / EtOAc), para proporcionar el compuesto del título como un sólido grisáceo.

HPLC Rt_{M10}= 2.85 minutos; ESIMS: 454 [$(M+H)^+$].

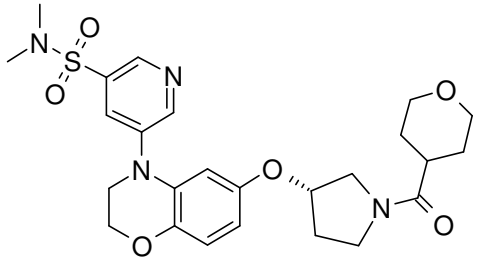
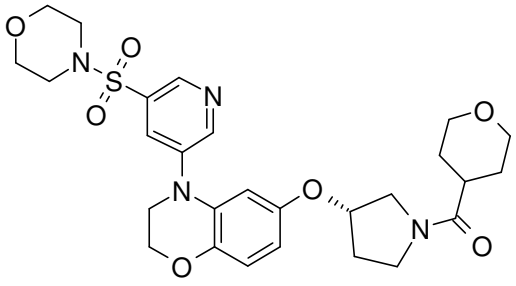
^{1}H RMN (400 MHz, CD_3OD): δ 7.90-7.85 (m, 1H), 7.49-7.44 (m, 1H), 6.76-6.69 (m, 1H), 6.32-6.24 (m, 1H), 6.07-6.02 (m, 1H), 4.86-4.73 (m, 1H), 4.29-4.23 (m, 2H), 4.02-3.92 (m, 5H), 3.80-3.40 (m, 8H), 2.85-2.60 (m, 1H), 2.25-1.91 (m, 5H), 1.85-1.50 (m, 4H).

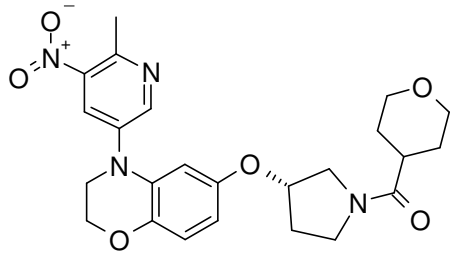
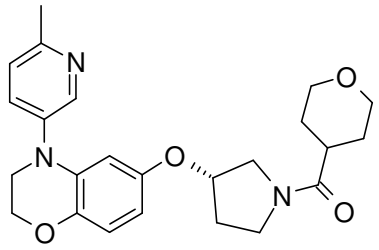
Método alternativo d2: El 2-(diciclohexil-fosfino)-bifenilo (CAS registro 247940-06-3) fue reemplazado con el 2-diciclohexil-fosfino-2′,4′,6′-tri-isopropil-bifenilo (CAS registro 564483-18-7).

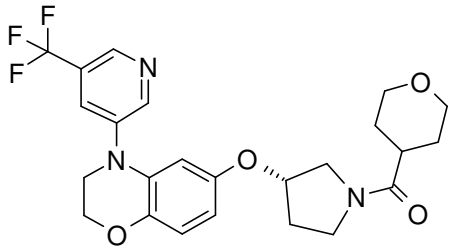
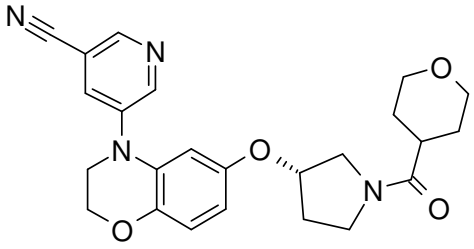
Método alternativo d3: El 2-(diciclohexil-fosfino)-bifenilo (CAS registro 247940-06-3), y el $Pd_2(dba)_3$ fueron reemplazados con bis-(tri-terbutil-fosfina)-paladio (CAS registro 53199-31-8).

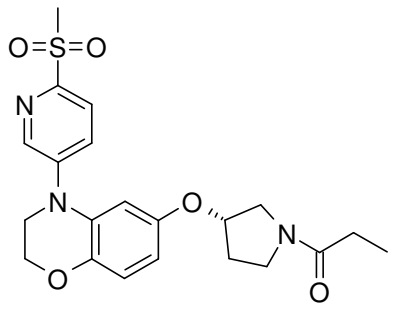
Ejemplos A2 a A43: Los compuestos enlistados en la Tabla 1 se prepararon mediante un procedimiento análogo a aquél empleado en el Ejemplo A1.

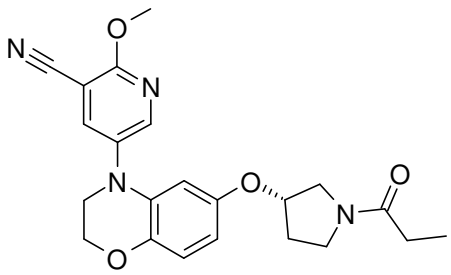
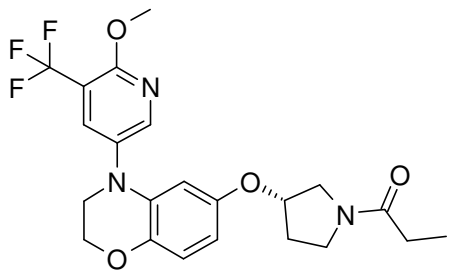
Tabla 1

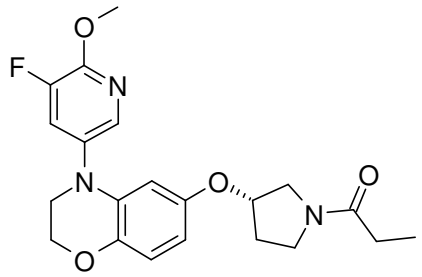
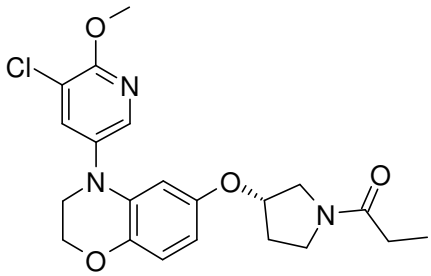
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
A2	 Dimetil-amida del ácido 5-{6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-piridin-3-sulfónico Ruta sintética utilizada: a1, b1, c1, d1 (intermediario IA13)	2.50 (M10)	517
A3	 ((S)-3-{4-[5-(morfolin-4-sulfonil)-piridin-3-il]-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi}-pirrolidin-1-il)-(tetrahidro-piran-4-il)-metanona	1.10 (M12)	560

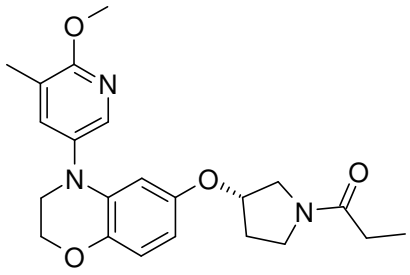
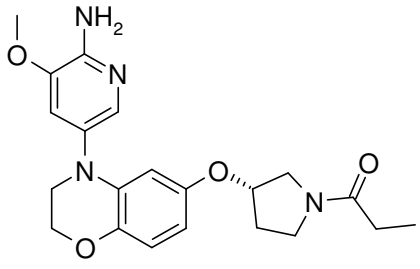
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Ruta sintética utilizada: a1, b1, c1, d1 (intermediario IA14)		
A4	 {(S)-3-[4-(6-metil-5-nitro-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Ruta sintética utilizada: a1, b1, c1, d1 (intermediario IA15)	1.78 (M10)	469
A5	 {(S)-3-[4-(6-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-	1.03 (M10)	425

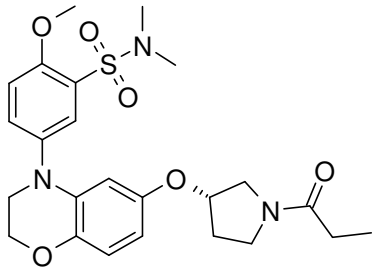
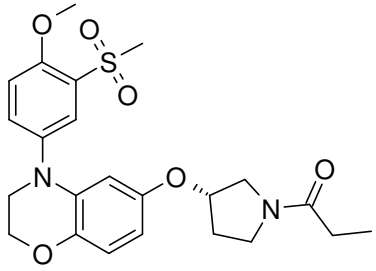
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	4-il)-metanona Ruta sintética utilizada: a1, b1, c1, d1 (intermediario IA16)		
A6	 (Tetrahidro-piran-4-il)-{(S)-3-[4-(5-trifluoro-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Ruta sintética utilizada: a1, b1, c1, d1 (intermediario IA18)	1.21 (M12)	479
A7	 5-{6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-iloxi]-2,3-	2.44 (M10)	435

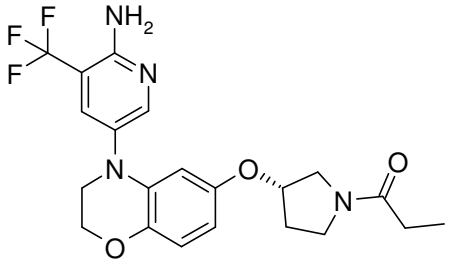
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1, c1, d2 (intermediario IA17)		
A8	 1-{(S)-3-[4-(6-metan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Ruta sintética utilizada: a2, b1, c1, d2 (intermediario IA40)	1.46 (M8)	432

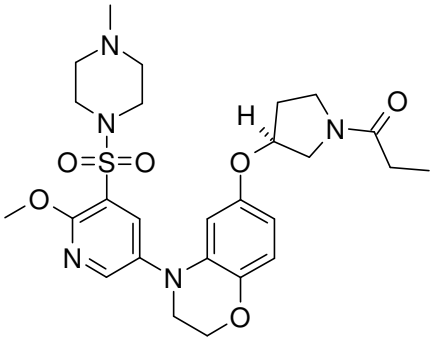
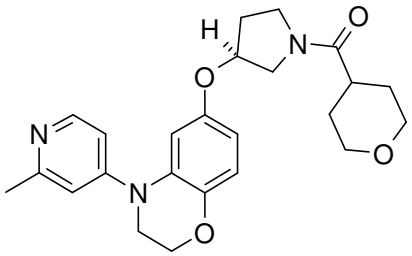
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
A9	 2-metoxi-5-[6-((S)-1-propionil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-nicotinonitrilo Ruta sintética utilizada: a2, b1, c1, d2 (intermediario IA12)	2.80 (M10)	409
A10	 1-{(S)-3-[4-(6-metoxi-5-trifluoro-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Ruta sintética utilizada: a2, b1, c1, d2 (intermediario IA21)	2.74 (M11)	452

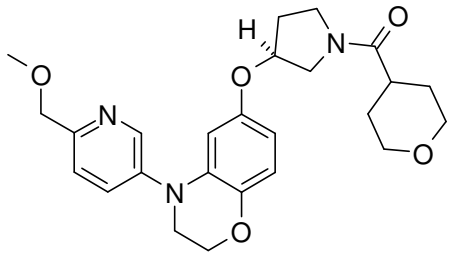
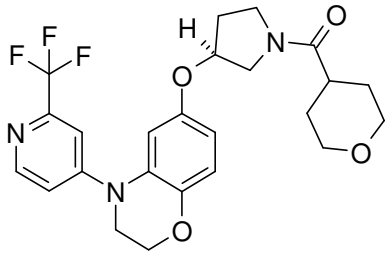
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
A11	 1-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Ruta sintética utilizada: a2, b1, c1, d2 (intermediario IA10)	2.86 (M10)	402
A12	 1-{(S)-3-[4-(5-cloro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Ruta sintética utilizada: a2, b1, c1,	3.00 (M10)	418

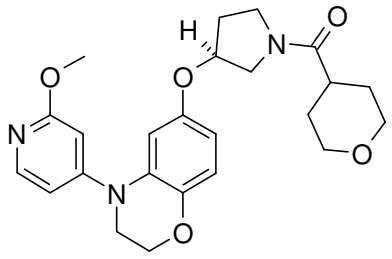
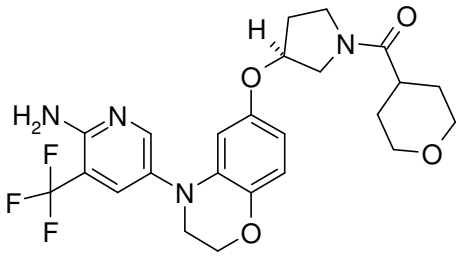
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	d2 (intermediario IA11)		
A13	 1-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Ruta sintética utilizada: a2, b1, c1, d2 (intermediario IA9)	2.93 (M10)	398
A14	 1-{(S)-3-[4-(6-amino-5-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona	1.98 (M10)	399

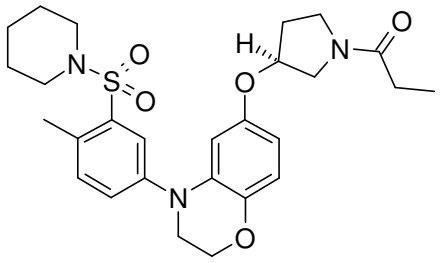
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Ruta sintética utilizada: a2, b1, c1, d2 (intermediario IA46)		
A15	 2-metoxi-N,N-dimetil-5-[6-((S)-1-propionil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-bencen-sulfonamida Ruta sintética utilizada: a2, b1, c1, d2 (intermediario IA60)	2.76 (M10)	490
A16	 1-{(S)-3-[4-(3-metan-sulfonil-4-metoxi-fenil)-3,4-dihidro-2H-benzo-	2.56 (M10)	461

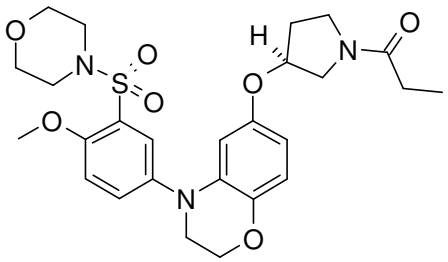
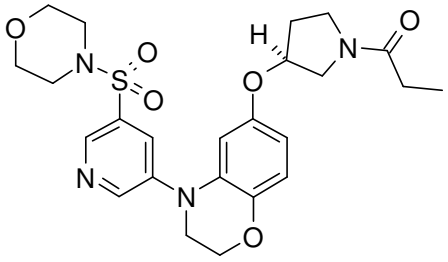
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Ruta sintética utilizada: a2, b1, c1, d2 (intermediario IA59)		
A17	 1-{(S)-3-[4-(6-amino-5-trifluoro-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Ruta sintética utilizada: a2, b1, c1, d2 (intermediario IA23)	2.67 (M10)	437

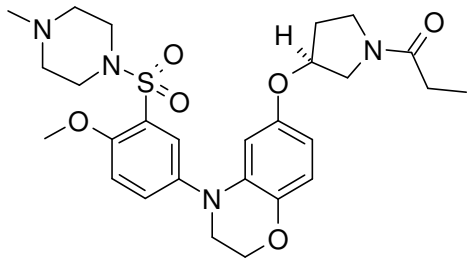
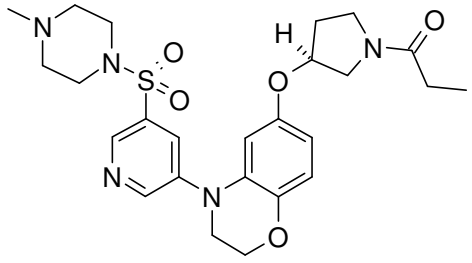
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
A18	 1-((S)-3-{4-[6-metoxi-5-(4-metil-piperazin-1-sulfonil)-piridin-3-il]-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi}-pirrolidin-1-il)-propan-1-ona Ruta sintética utilizada: a2, b1, c1, d3 (intermediario IA24)	1.60 (M9)	546
A19	 {(S)-3-[4-(2-metil-piridin-4-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona	1.32 (M9)	424

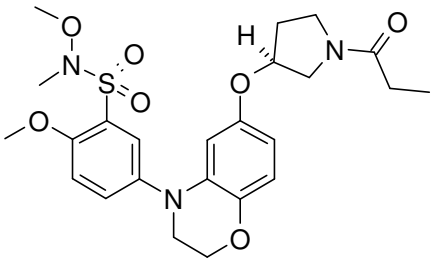
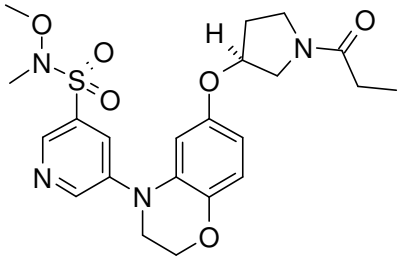
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA61)		
A20	 {(S)-3-[4-(6-metoxi-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA25)	1.47 (M9)	454
A21	 (Tetrahidro-piran-4-il)-{(S)-3-[4-(2-trifluoro-metil-piridin-4-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-	1.61 (M9)	478

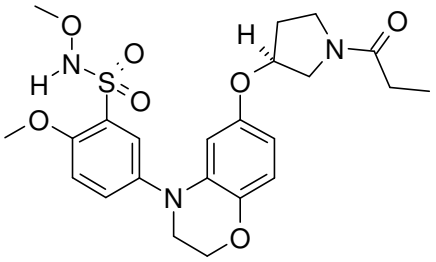
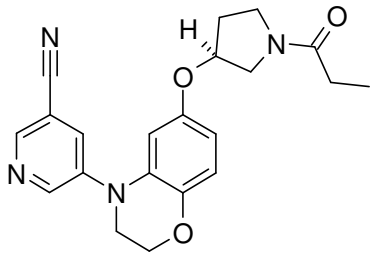
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
	iloxi]-pirrolidin-1-il}-metanona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA63)		
A22	 {(S)-3-[4-(2-metoxi-piridin-4-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA62)	1.43 (M9)	440
A23	 {(S)-3-[4-(6-amino-5-trifluoro-metil-piridin-3-il)-3,4-dihidro-2H-benzo-	1.57 (M9)	493

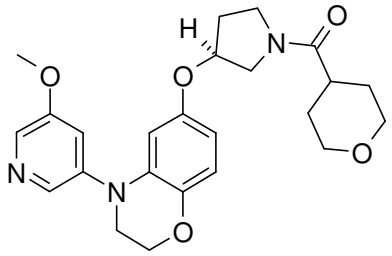
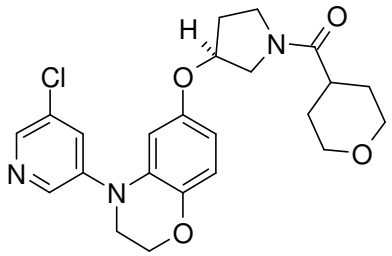
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA23)		
A24	 1-((S)-3-{4-[4-metil-3-(piperidin-1-sulfonil)-fenil]-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi}-pirrolidin-1-il)-propan-1-ona Ruta sintética utilizada: a2, b1, c1, d3 (intermediario IA31)	2.04 (M9)	514

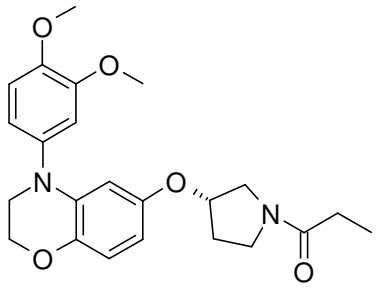
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
A25	 1-((S)-3-{4-[4-metoxi-3-(morfolin-4-sulfonil)-fenil]-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi}-pirrolidin-1-il)-propan-1-ona Ruta sintética utilizada: a2, b1, c1, d3 (intermediario IA32)	1.83 (M9)	532
A26	 1-((S)-3-{4-[5-(morfolin-4-sulfonil)-piridin-3-il]-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi}-pirrolidin-1-il)-propan-1-ona Ruta sintética utilizada: a2, b1, c1,	1.83 (M9)	503

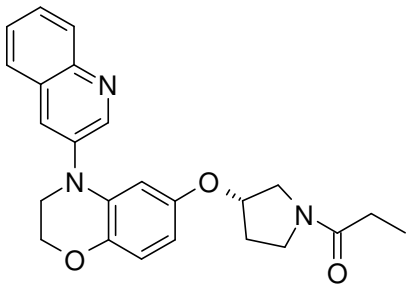
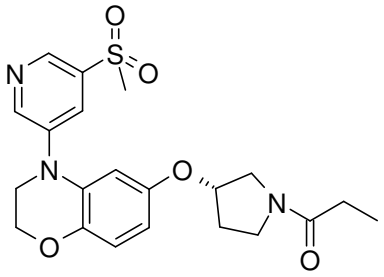
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	d3 (intermediario IA33)		
A27	 1-((S)-3-{4-[4-metoxi-3-(4-metil-piperazin-1-sulfonil)-fenil]-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi}-pirrolidin-1-il)-propan-1-ona Ruta sintética utilizada: a2, b1, c1, d3 (intermediario IA34)	2.22 (M9)	545
A28	 1-((S)-3-{4-[5-(4-metil-piperazin-1-sulfonil)-piridin-3-il]-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi}-pirrolidin-	2.08 (M9)	516

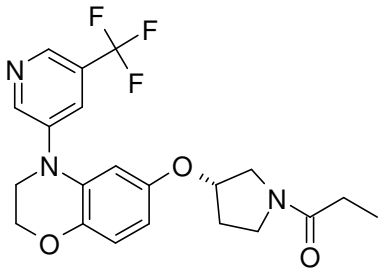
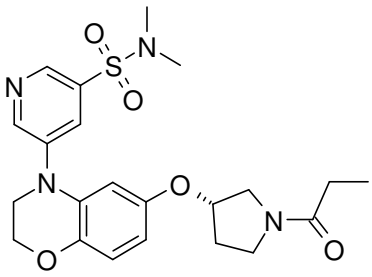
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
	1-il)-propan-1-ona Ruta sintética utilizada: a2, b1, c1, d3 (intermediario IA35)		
A29	 2,N-dimetoxi-N-metil-5-[6-((S)-1-propionil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-bencen-sulfonamida Ruta sintética utilizada: a2, b1, c1, d3 (intermediario IA36)	2.82 (M9)	506
A30	 Metoxi-metil-amida del ácido 5-[6-	2.69 (M9)	477

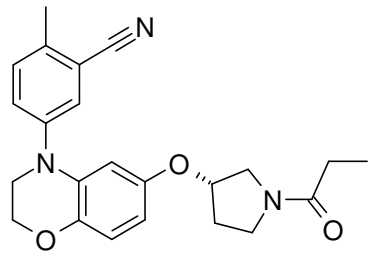
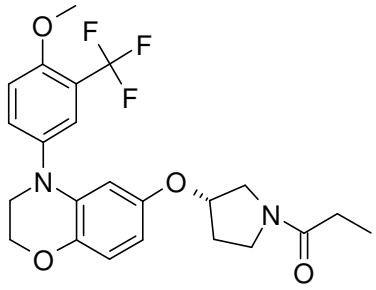
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	((S)-1-Propionil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-piridin-3-sulfónico Ruta sintética utilizada: a2, b1, c1, d3 (intermediario IA37)		
A31	 2,N-dimetoxi-5-[6-((S)-1-propionil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-bencen-sulfonamida Ruta sintética utilizada: a2, b1, c1, d3 (intermediario IA65)	2.72 (M9)	492
A32		2.49 (M9)	379

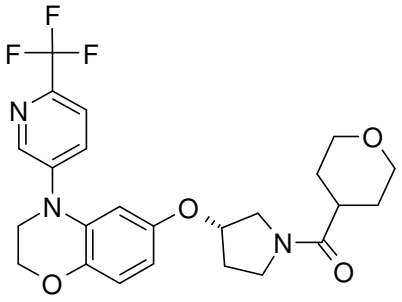
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	5-[6-((S)-1-Propionil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-nicotinonitrilo Ruta sintética utilizada: a2, b1, c1, d3 (intermediario IA17)		
A33	 {(S)-3-[4-(5-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA38)	1.54 (M9)	440
A34		1.76 (M9)	444

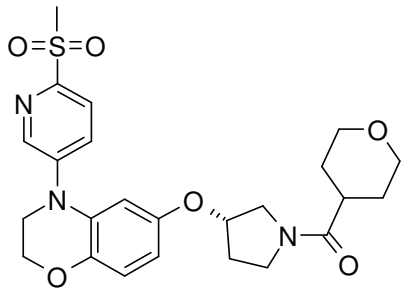
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	{(S)-3-[4-(5-cloro-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA39)		
A35	 1-{(S)-3-[4-(3,4-dimetoxi-fenil)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA66)	1.24 (M6)	413

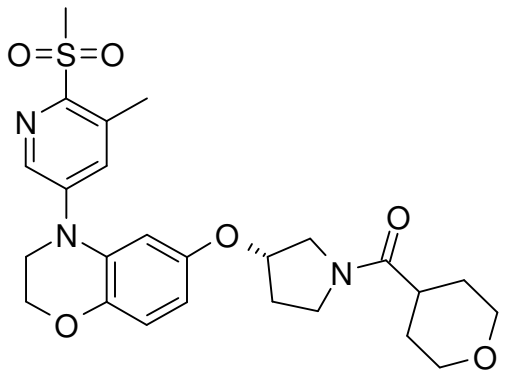
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
A36	 1-[(S)-3-(4-quinolin-3-il-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi)-pirrolidin-1-il]-propan-1-ona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA54)	1.02(M6)	404
A37	 1-{(S)-3-[4-(5-metan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA55)	1.03 (M6)	432

Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
A38	 1-{(S)-3-[4-(5-trifluoro-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA18)	1.24 (M6)	422
A39	 Dimetil-amida del ácido 5-[6-((S)-1-Propionil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-piridin-3-sulfónico Ruta sintética utilizada: a1, b1, c1,	1.13 (M6)	461

Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	d3 (intermediario IA13)		
A40	 2-metil-5-[6-((S)-1-propionil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-benzonitrilo Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA56)	1.33 (M6)	392
A41	 1-{(S)-3-[4-(4-metoxi-3-trifluoro-metil-fenil)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona	1.44 (M6)	451

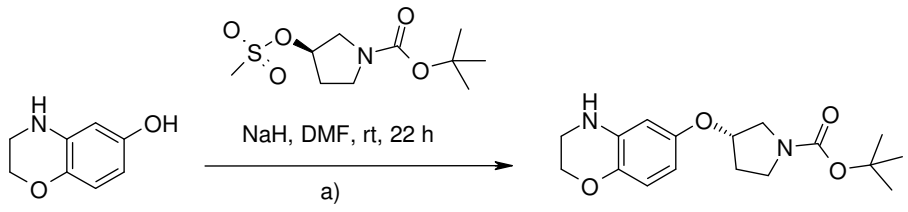
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA57)		
A42	 (Tetrahidro-piran-4-il)-{(S)-3-[4-(6-trifluoro-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA26)	1.82 (M6)	478

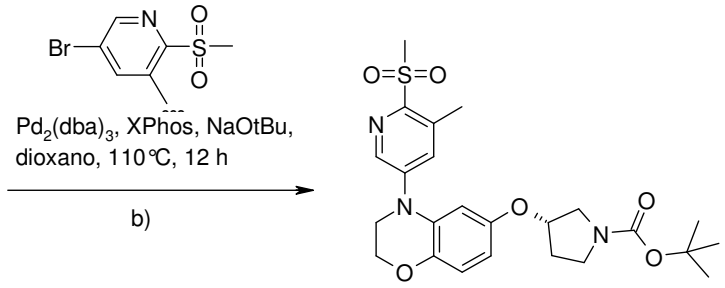
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
A43	 {(S)-3-[4-(6-metan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Ruta sintética utilizada: a1, b1, c1, d3 (intermediario IA40)	1.44 (M6)	488

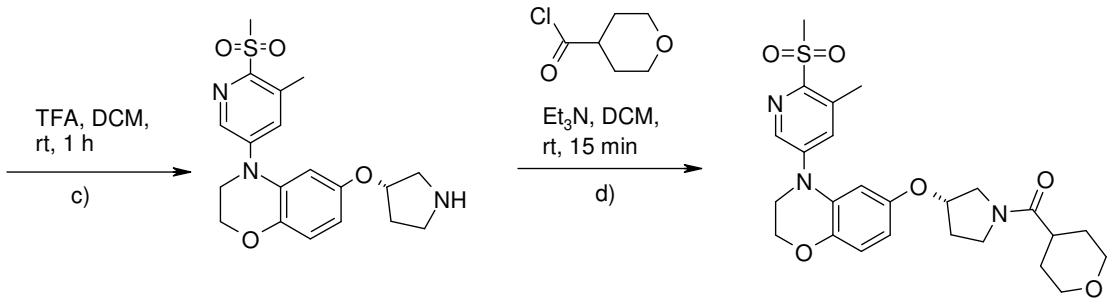


Ejemplo B1: **{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-**

dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona (de acuerdo con el esquema 2)







a) Terbutil-éster del ácido (S)-3-(3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi)-pirrolidin-1-carboxílico

Una solución del 3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol (CAS registro 26021-57-8) (4.0 gramos, 26.5 milimoles) en dimetil-formamida (DMF) (150 mililitros) se trató con NaH (2.117 gramos, 52.9 milimoles) durante 20 minutos a 20°C. Se agregó el terbutil-éster del ácido (R)-3-metan-sulfoniloxi-pirrolidin-1-carboxílico (CAS

registro 127423-61-4) (9.13 gramos, 34.4 milimoles). Después de agitar durante 22 horas a temperatura ambiente, la mezcla de reacción se concentró a sequedad, entonces se absorbió con EtOAc, se filtró a través de Hyflo, y el filtrado se lavó con una solución acuosa saturada de Na_2CO_3. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se evaporaron. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / isopropanol, de 100:0 a 85:15, en 40 minutos), para proporcionar el compuesto del título como un aceite color amarillo.

HPLC Rt_{M8} =1.84 minutos; ESIMS: 321 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO): 6.52 (d, 1H), 6.12 (d, 1H), 6.02 (m, 1H), 5.76 (m, 1H), 4.75 (br s, 1H), 4.01-40.5 (m, 2H), 3.27-3.50 (m, 4H), 3.22-3.26 (m, 2H), 1.95-2.08 (m, 2H), 1.39 (m, 9H).

b) Terbutil-éster del ácido (S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carboxílico

Una mezcla del terbutil-éster del ácido (S)-3-(3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi)-pirrolidin-1-carboxílico (2.12 gramos, 6.62 milimoles), 5-bromo-2-metan-sulfonil-3-metil-piridina (Intermediario IA1) (2.091 gramos, 7.94 milimoles), NaOtBu (1.272 gramos, 13.23 milimoles), ligando de XPhos (0.158 gramos, 0.331 milimoles), y $Pd_2(dba)_3$ (0.303 gramos, 0.331 milimoles) en dioxano (3.5 mililitros) se desgasificó y se agitó durante 12 horas a 110°C. Se agregó una solución acuosa saturada de $NaHCO_3$, y la mezcla de reacción se

extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se evaporaron. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 50:50), para proporcionar el compuesto del título.

HPLC Rt_{M14} =1.25 minutos; ESIMS: 490 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.33 (d, 1H), 7.43 (d, 1H), 6.86 (d, 1H), 6.59 (d, 1H), 6.47 (m, 1H), 4.69-4.73 (m,12H), 4.23-4.28 (m, 2H), 3.73-3.78 (m, 2H), 3.41-3.58 (m, 4H), 3.34 (s, 3H), 2.69 (s, 3H), 1.96-2.17 (m, 2H), 1.46 (s, 9H).

c) 4-(6-metan-sulfonil-5-metil-piridin-3-il)-6-((S)-pirrolidin-3-iloxi)-3,4-dihidro-2H-benzo-[1,4]-oxazina

Una solución del terbutil-éster del ácido (S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carboxílico (1.5 gramos, 3.06 milimoles), y ácido trifluoro-acético (TFA) (0.236 mililitros, 3.06 milimoles) en dicloro-metano (DCM) (15 mililitros) se agitó durante 1 hora a temperatura ambiente. La mezcla de reacción se enfrió a 0°C, se agregó una solución saturada de Na_2CO_3, y la mezcla de reacción se extrajo con dicloro-metano (DCM). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron, y se evaporaron, para proporcionar el compuesto del título.

HPLC Rt_{M2} =0.66 minutos; ESIMS: 390 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.33 (d, 1H), 7.43 (d, 1H), 6.86 (d, 1H), 6.58 (d, 1H), 6.47 (m, 1H), 4.68 (m, 1H), 4.22-4.27 (m, 2H),

3.73-3.78 (m, 2H), 3.33 (s, 3H), 3.12-3.22 (m, 2H), 2.86-3.04 (m, 2H), 2.68 (s, 3H), 1.88-2.08 (m, 2H).

d) {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona

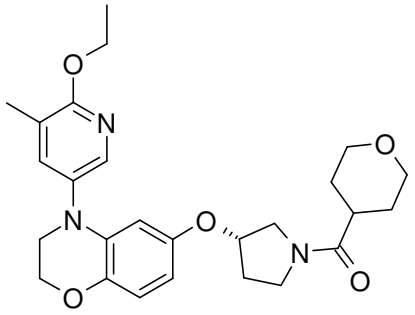
Una mezcla de la 4-(6-metan-sulfonil-5-metil-piridin-3-il)-6-((S)-pirrolidin-3-iloxi)-3,4-dihidro-2H-benzo-[1,4]-oxazina (0.085 gramos, 0.218 milimoles), cloruro de tetrahidro-2H-piran-4-carbonilo (CAS registro 40191-32-0) (0.049 miligramos, 0.327 milimoles), y Et_3N (0.046 mililitros, 0.327 milimoles) en dicloro-metano (DCM) (4 mililitros) se agitó a temperatura ambiente durante 15 minutos. La mezcla de reacción se concentró a sequedad. El producto crudo se purificó mediante RP-HPLC de preparación (columna SunFire C18, H_2O + ácido trifluoro-acético (TFA) al 0.1 por ciento / acetonitrilo (ACN) + ácido trifluoro-acético (TFA) al 0.1 por ciento, de 90:10 a 30:70 en 12 minutos), para proporcionar el compuesto del título como un sólido blanco.

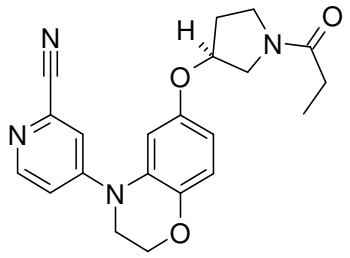
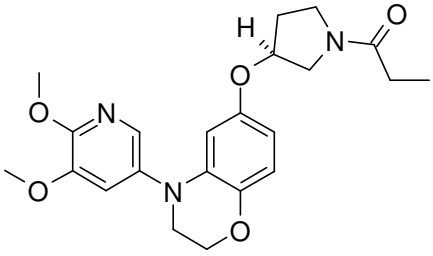
HPLC Rt_{M7} =1.62 minutos; ESIMS: 502 [$(M+H)^+$].

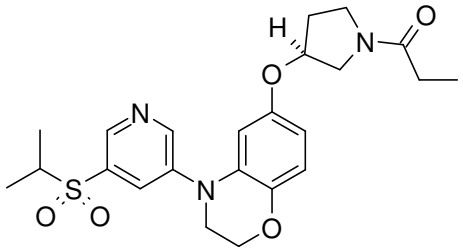
^{1}H RMN (400 MHz, DMSO): δ 8.38-8.42 (m, 1H), 7.72 (m, 1H), 6.84 (d, 1H), 6.67 (m, 1H), 6.50-6.57 (m, 1H), 4.82-4.94 (m, 1H), 4.20 (m, 2H), 3.31 (s, 3H), 3.28-3.88 (m, 10H), 2.59-2.73 (m, 1H), 2.56 (s, 3H), 1.95-2.13 (m, 2H), 1.44-1.62 (m, 4H).

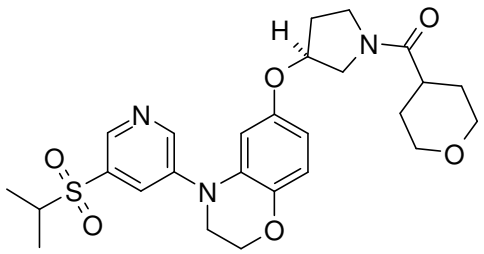
Ejemplos B2 a B122: Los compuestos enlistados en la Tabla 2 se prepararon mediante un procedimiento análogo a aquél empleado en el Ejemplo B1.

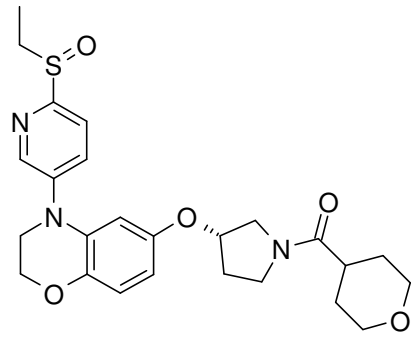
Tabla 2

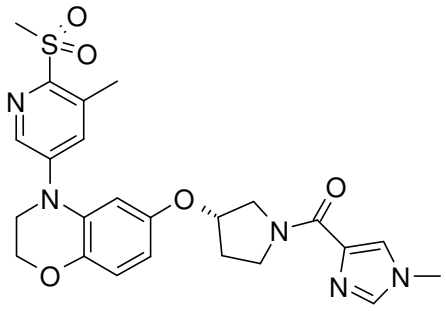
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B2	 {(S)-3-[4-(6-etoxi-5-metil-piridin-3-il)-3,4dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8,127423-61-4, IA19, 40191-32-0	2.00 (M8)	**468**

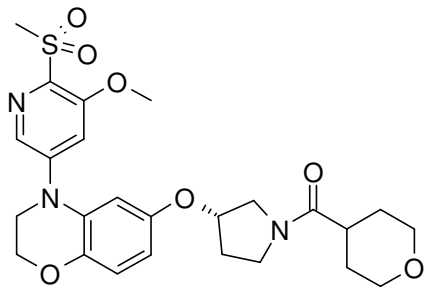
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B3	 4-[6-((S)-1-Propionil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-piridin-2-carbonitrilo Condición de aminación de Buchwald: CA12 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: Precursores utilizados: CAS 26021-57-8,127423-61-4, IA30, 79-03-8	1.53 (M8)	**379**
B4	 1-{(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-	1.58 (M9)	**414**

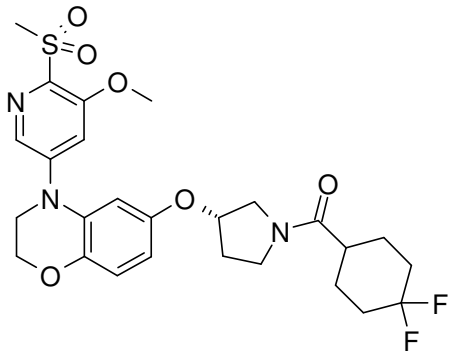
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8,127423-61-4, IA31, 79-03-8		
B5	 1-((S)-3-{4-[5-(Propan-2-sulfonil)-piridin-3-il]-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi}-pirrolidin-1-il)-propan-1-ona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB6	2.61 (M10)	**460**

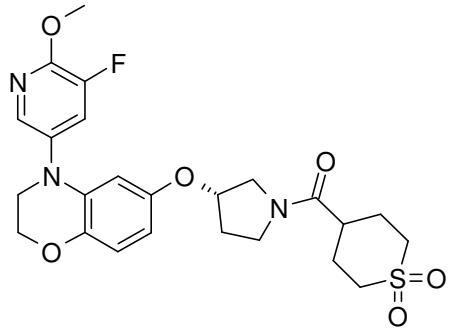
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8,127423-61-4, IA30, 79-03-8		
B6	 ((S)-3-{4-[5-(Propan-2-sulfonil)-piridin-3-il]-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi}-pirrolidin-1-il)-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8,127423-61-4, IA30, 40191-32-0	1.50 (M9)	**560**

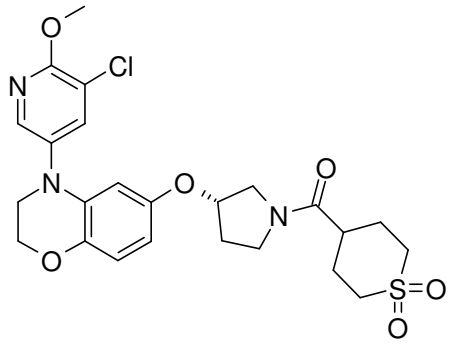
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B7	 {(S)-3-[4-(6-etan-sulfinil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA13 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8,127423-61-4, IA58, 40191-32-0	1.37 (M8)	**486**

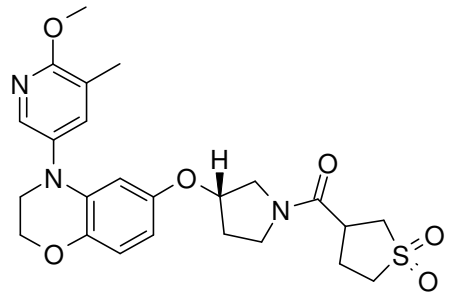
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B8	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA14 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8,127423-61-4, IA1, 41716-18-1	1.27 (M8)	**498**

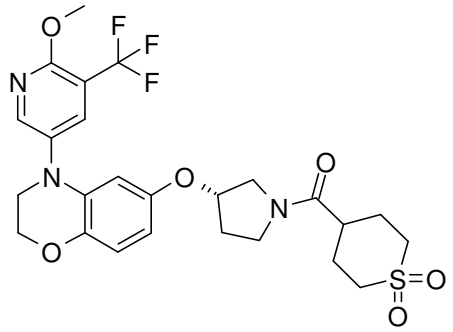
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B9	 {(S)-3-[4-(6-metan-sulfonil-5-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA14 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8,127423-61-4, IA45, 40191-32-0	1.34 (M8)	**518**

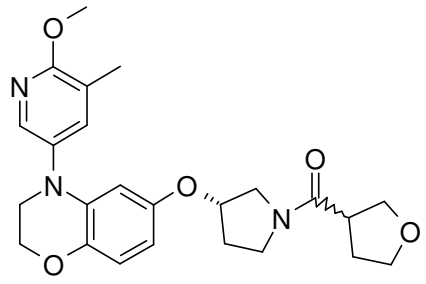
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B10	 (4,4-difluoro-ciclohexil)-{(S)-3-[4-(6-metan-sulfonil-5-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA14 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8,127423-61-4, IA45, 122665-97-8	1.68 (M8)	**522**

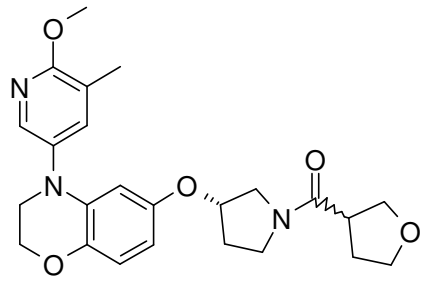
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B11	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2 H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10/ 64096-87-3	1.67 (M8)	506

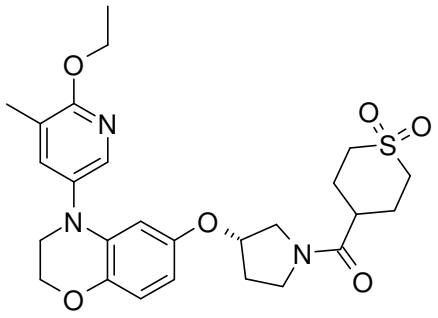
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B12	 {(S)-3-[4-(5-cloro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1, 1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA11/ 64096-87-3	1.80 (M8)	522, 524

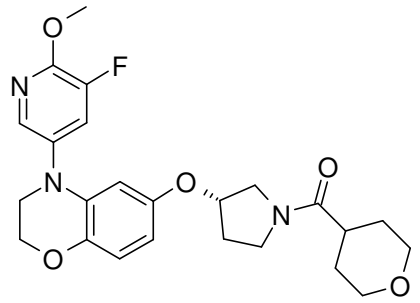
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B13	 (1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2 H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA16 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA9 /4785-67-5	1.74 (M8)	488

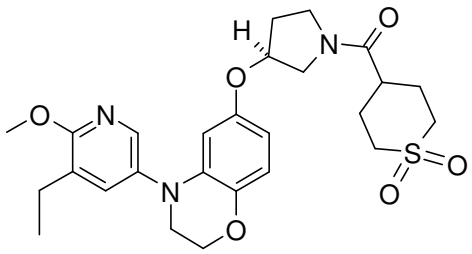
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B14	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[4-(6-metoxi-5-trifluoro-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA21/ 64096-87-3	1.95 (M8)	556

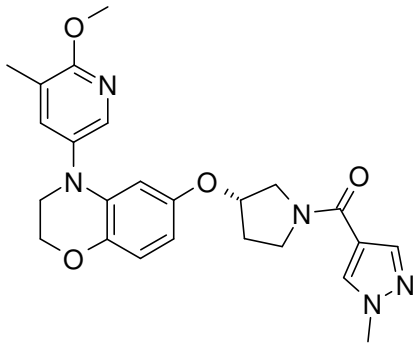
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B15	 {(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidrofuran-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA9 / 89364-31-8 Separación quiral: CD9	1.89 (M7)	440

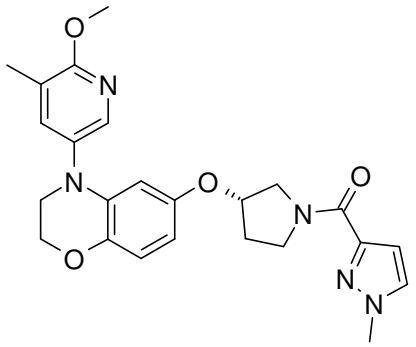
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B16	 {(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidrofuran-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-614 / IA9 / 89364-31-8 Separación quiral: CD9	1.89 (M7)	440

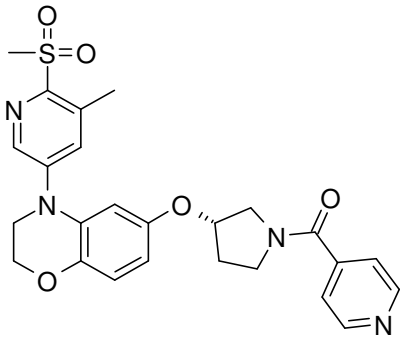
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B17	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[4-(6-etoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB7 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA19/ 64096-87-3	1.88 (M8)	516

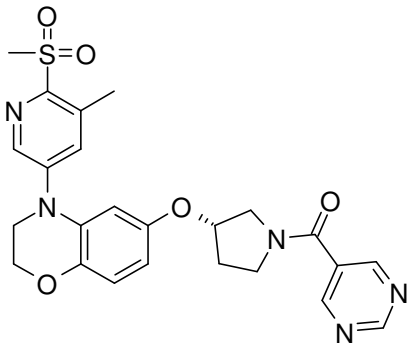
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B18	 ({(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10/ 40191-32-0	1.86 (M7)	458

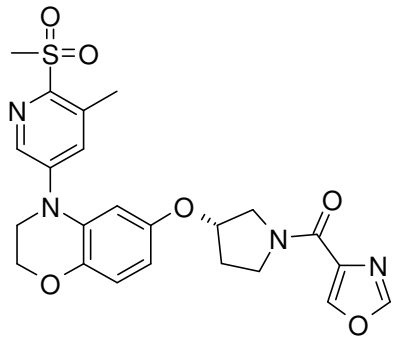
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B19	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[4-(5-etil-6-metoxi-piridin-3-il)-3,4-dihidro-2H -benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA48/ 64096-87-3	1.04 (M2)	516

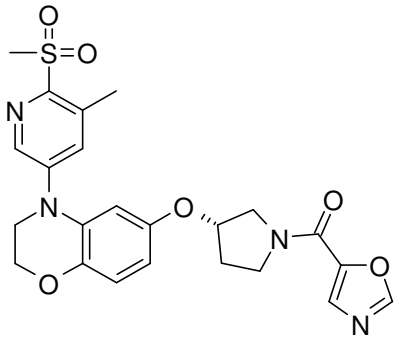
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B20	 {(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1-metil-1H-pirazol-4-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA9 / 5952-92-1	1.70 (M8)	450

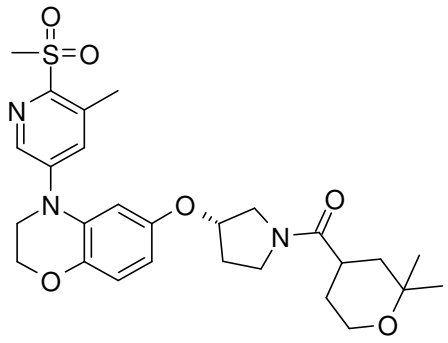
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B21	 {(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1-metil-1H-pirazol-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA9 / 25016-20-0	1.87 (M8)	450

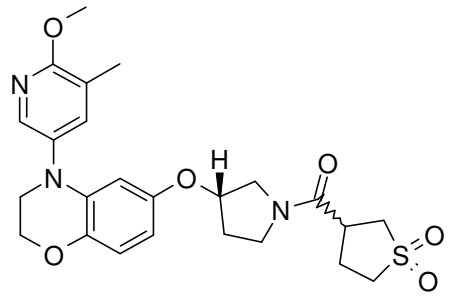
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B22	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1 -il}-piridin-4-il-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1 / 55-22-1	0.85 (M6)	495

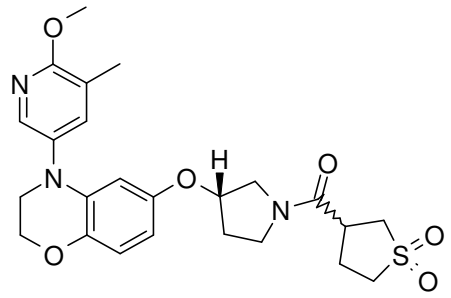
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B23	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1 -il}-pirimidin-5-il-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1 / 4595-61-3	0.92 (M6)	496

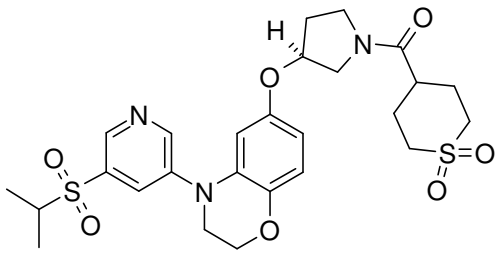
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B24	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1 -il}-oxazol-4-il-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1 / 23012-13-7	0.95 (M6)	485

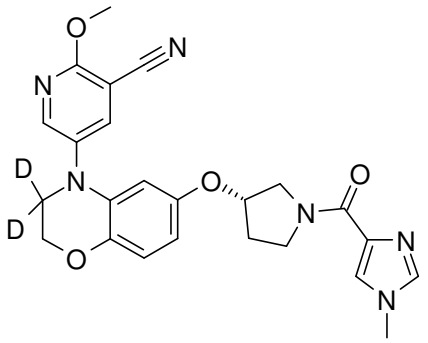
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B25	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1 -il}-oxazol-5-il-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1/ 118994-90-4	0.94 (M6)	485

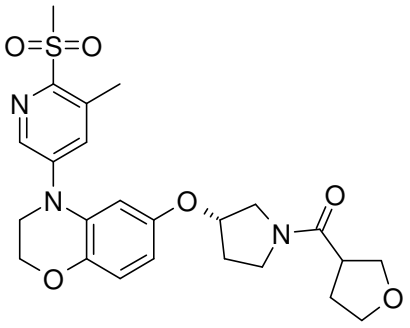
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B26	 (2,2-dimetil-tetrahidro-piran-4-il)-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1 / 52916-16-2	1.01 (M6)	530

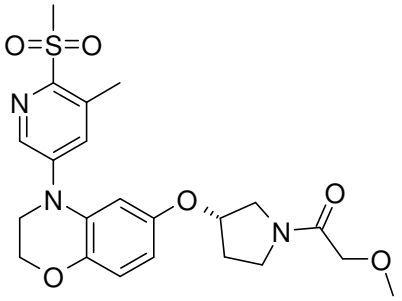
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B27	 (1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2 H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA9 /4785-67-5 Separación quiral : CD8	1.62 (M2)	488

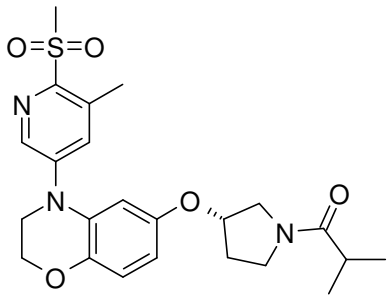
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B28	 (1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2 H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA9 / 4785-67-5 Separación quiral: CD8	1.62 (M2)	488

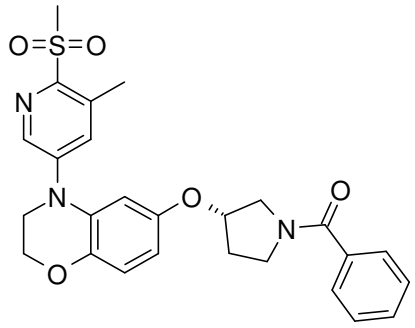
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B29	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-((S)-3-{4-[5-(propan-2-sulfonil)-piridin-3-il]-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi}-pirrolidin-1-il)-metanona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA30/ 64096-87-3	1.53 (M6)	564

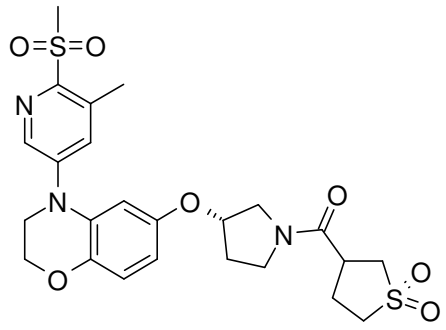
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B30	 2-metoxi-5-{6-[(S)-1-(1-metil-1H-imidazol-4-carbonil)-pirrolidin-3-iloxi]-3,3-dideutero-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA15 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: ID1, CAS 127423-61-4, IA12, CAS 41716-18-1	1.50 (M9)	464

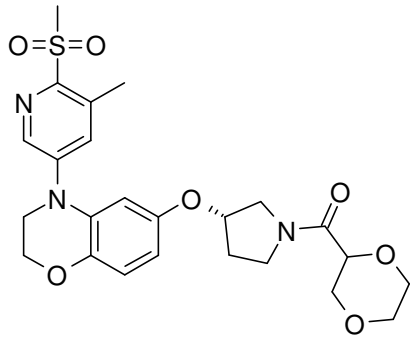
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B31	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidrofuran-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 89364-31-8	0.94 (M6)	488

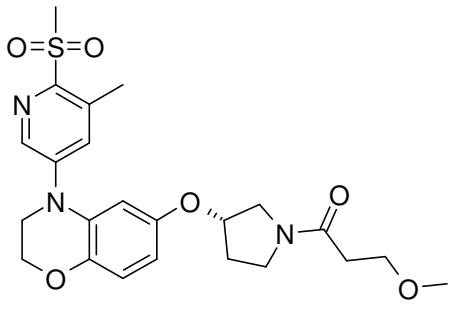
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B32	 1-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-2-metoxi-etanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 625-45-6	0.92 (M6)	462

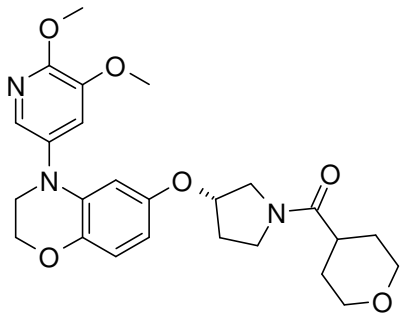
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B33	 1-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-2-metil-propan-1-ona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 79-31-2	1.01 (M6)	460

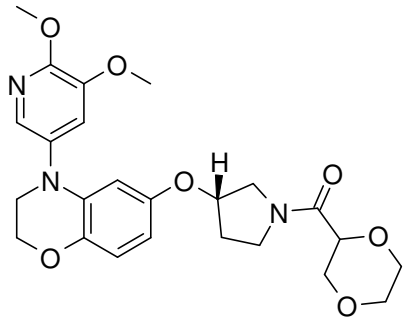
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B34	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-fenil-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 65-85-0	1.05 (M6)	494

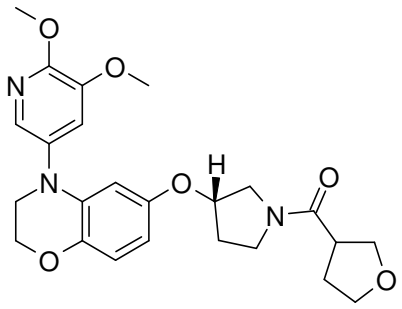
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B35	 (1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 4785-67-5	0.87 (M2)	536

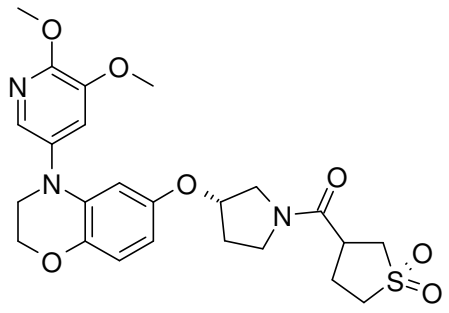
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B36	 [1,4]-dioxan-2-il-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 89364-41-0	0.88 (M2)	504

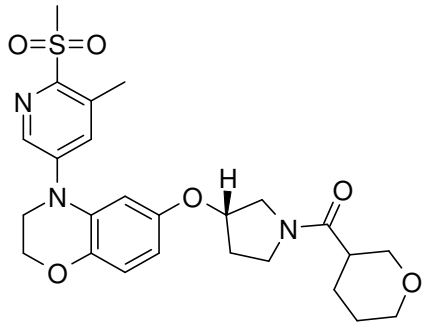
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B37	 1-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-metoxi-propan-1-ona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, CAS 127423-61-4, IA1, CAS 2544-06-1	0.88 (M2)	476

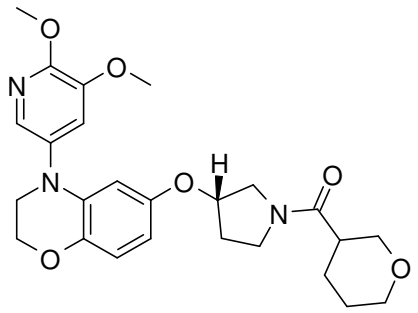
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B38	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, CAS 127423-61-4, IA29, cloruro de acilo 40191-32-0	0.93 (M2)	470

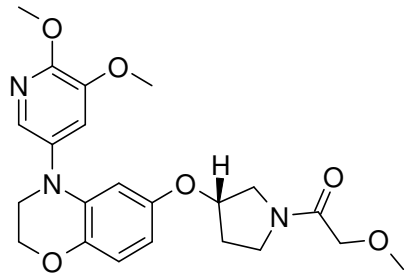
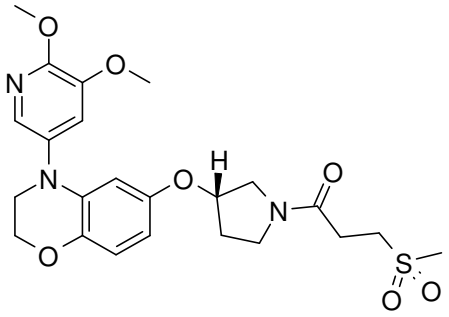
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B39	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-[1,4]-dioxan-2-il-metanona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA29/ 89364-41-0	0.91 (M2)	472

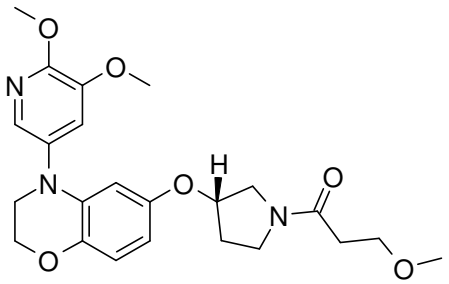
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B40	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidrofuran-3-il)-metanona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA29/ 89364-31-8	0.92 (M2)	456

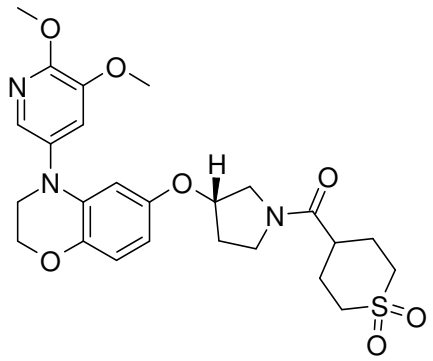
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B41	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-metanona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA29 / 4785-67-5	0.91 (M2)	504

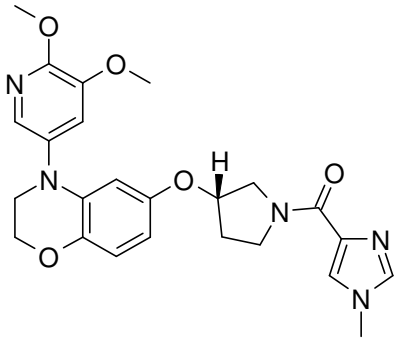
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B42	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1/ 873397-34-3	0.91 (M2)	502

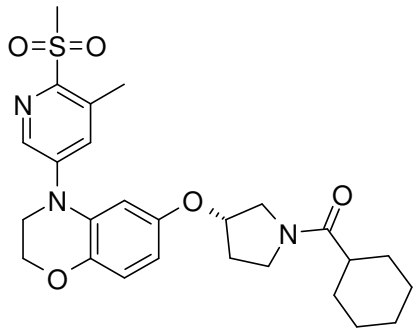
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B43	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-3-il)-metanona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA29 / 873397-34-3	0.96 (M2)	470

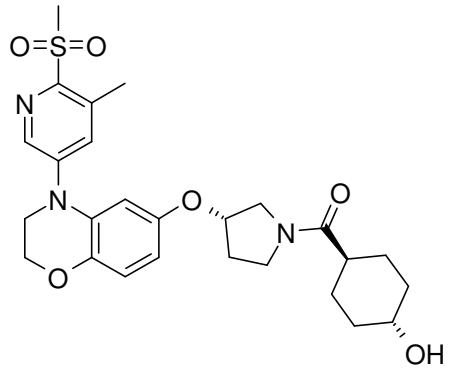
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B44	 1-{(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-2-metoxi-etanona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA29 / 625-45-6	0.90 (M2)	430
B45		0.89 (M2)	492

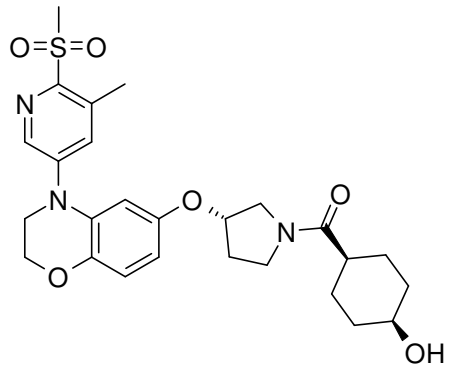
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	1-{(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-metan-sulfonil-propan-1-ona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA29 / 645-83-0		
B46	 1-{(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-metoxi-propan-1-ona	0.92 (M2)	444

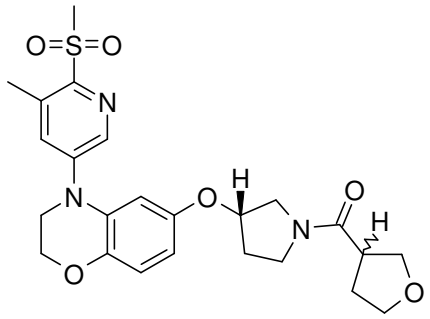
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA29 / 2544-06-1		
B47	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-metanona Condición de aminación de Buchwald: CA8	0.90 (M2)	518

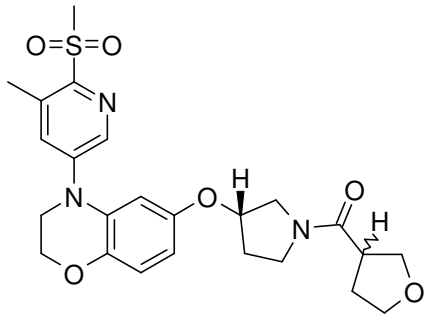
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA29/ 64096-87-3		
B48	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2	0.85 (M2)	466

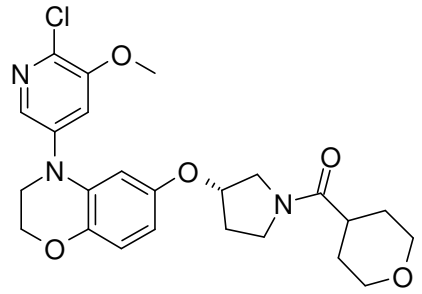
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA29/ 41716-18-1		
B49	 Ciclohexil-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1 / 98-89-5	1.06 (M2)	500

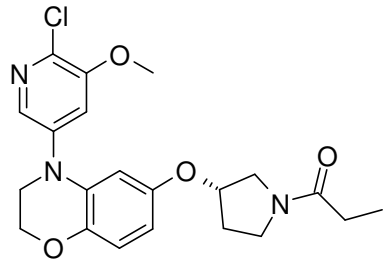
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B50	 (4-hidroxi-ciclohexil)-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1 / 3685-26-5	0.86 (M2)	516

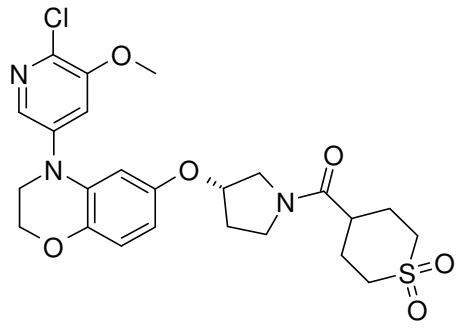
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B51	 (4-hidroxi-ciclohexil)-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1 / 3685-22-1	0.89 (M2)	516

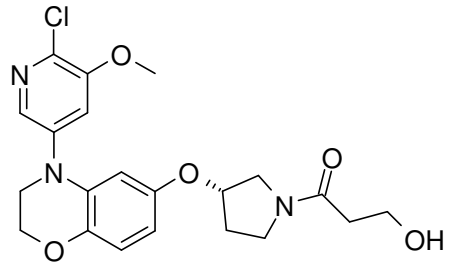
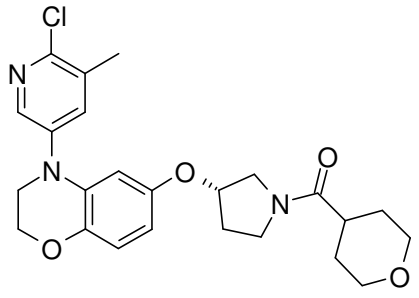
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B52	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidrofuran-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1 / 89364-31-8 Separación quiral: CD4	0.88 (M2) 15.13 (CD10)	488

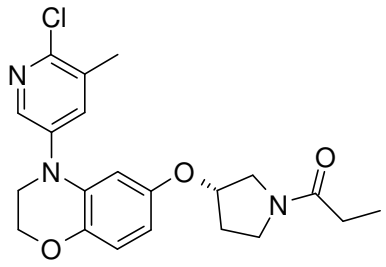
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B53	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidrofuran-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1 / 89364-31-8 Separación quiral: CD4	0.88 (M2) 18.70 (CD10)	488

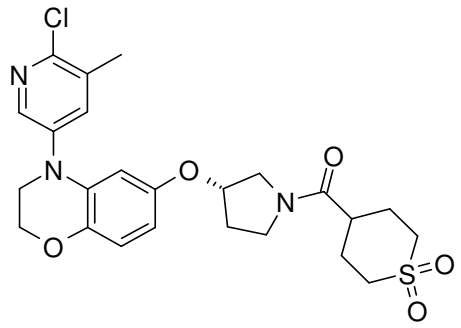
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B54	 {(S)-3-[4-(6-cloro-5-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA49 / cloruro de acilo: 40191-32-0	3.21 (M3)	474, 476

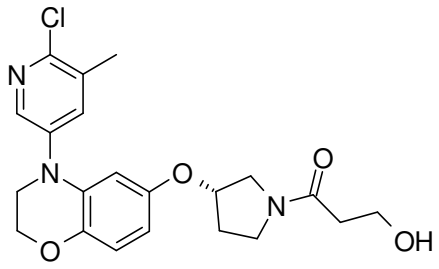
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B55	 1-{(S)-3-[4-(6-cloro-5-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA49 / cloruro de acilo: 79-03-8	3.30 (M3)	418, 420

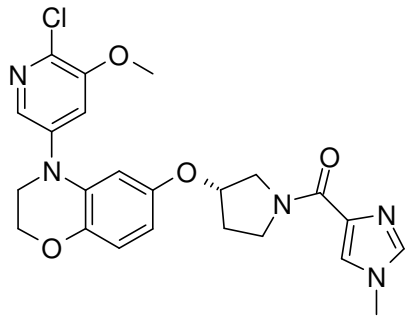
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B56	 {(S)-3-[4-(6-cloro-5-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-metanona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA49/ 64096-87-3	3.02 (M3)	522, 524

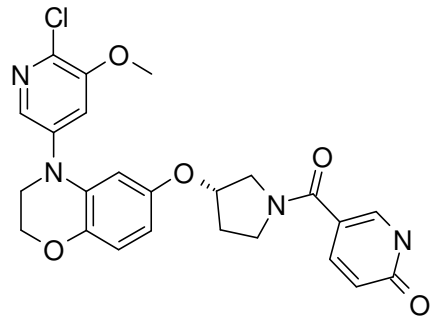
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B57	 1-{(S)-3-[4-(6-cloro-5-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-hidroxi-propan-1-ona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA49 / 503-66-2	0.88 (M2)	434, 436
B58		3.36 (M3)	458, 460

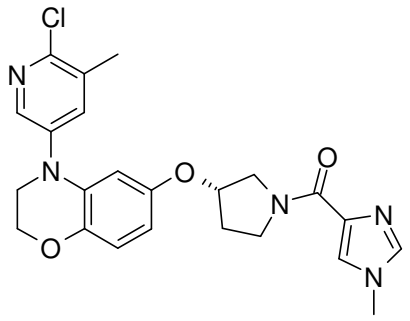
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	{(S)-3-[4-(6-cloro-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA50 / cloruro de acilo: 40191-32-0		
B59	 1-{(S)-3-[4-(6-cloro-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Condición de aminación de Buchwald:	3.47 (M3)	402, 404

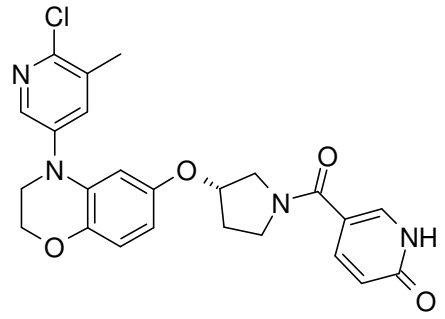
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	CA9 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA50 / cloruro de acilo: 79-03-8		
B60	 {(S)-3-[4-(6-cloro-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-metanona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB5	3.17 (M3)	506, 508

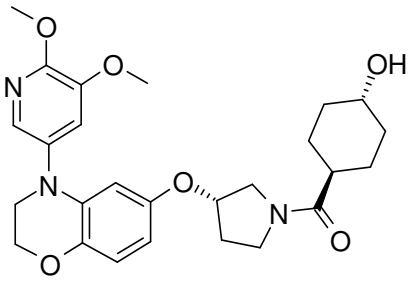
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA50/ 64096-87-3		
B61	 1-{(S)-3-[4-(6-cloro-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-hidroxi-propan-1-ona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA50 / 503-66-2	0.91 (M2)	418, 420

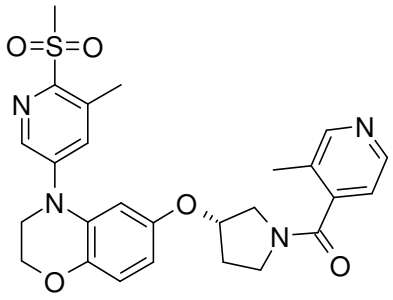
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B62	 {(S)-3-[4-(6-cloro-5-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA49/ 41716-18-1	2.59 (M3)	469

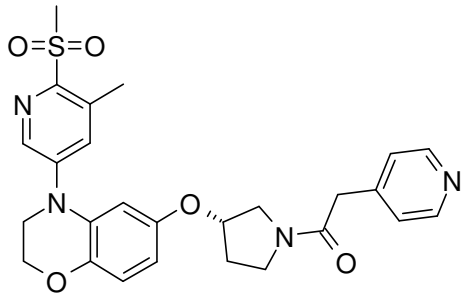
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B63	 5-{(S)-3-[4-(6-cloro-5-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carbonil}-1H-piridin-2-ona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA49 / 5006-66-6	2.85 (M3)	482, 483

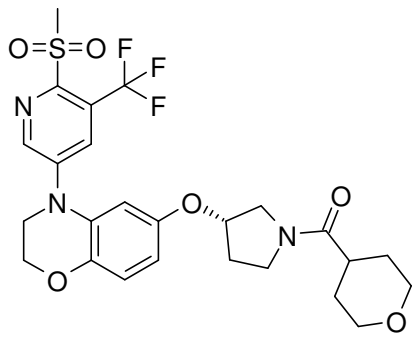
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B64	 {(S)-3-[4-(6-cloro-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA50/ 41716-18-1	2.71 (M3)	453

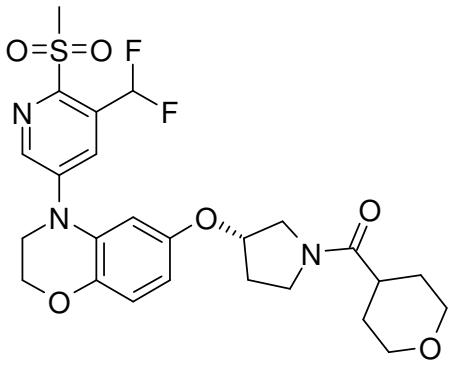
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B65	 5-{(S)-3-[4-(6-cloro-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carbonil}-1H-piridin-2-ona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA50 / 5006-66-6	2.97 (M3)	466, 468

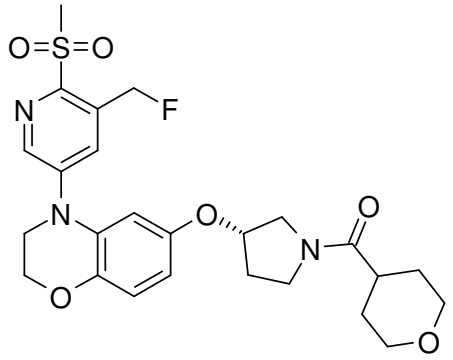
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B66	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(4-hidroxi-ciclohexil)-metanona Condición de aminación de Buchwald: CA8 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA29 / 3685-26-5	0.88 (M2)	484

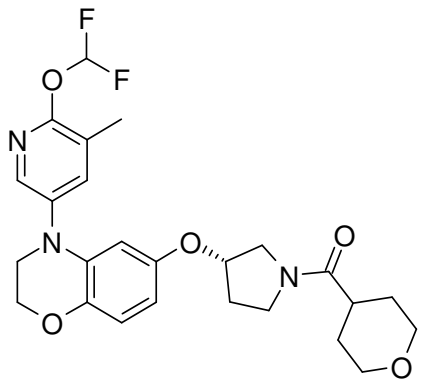
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B67	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(3-metil-piridin-4-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1 / 4021-12-9	0.86 (M2)	509

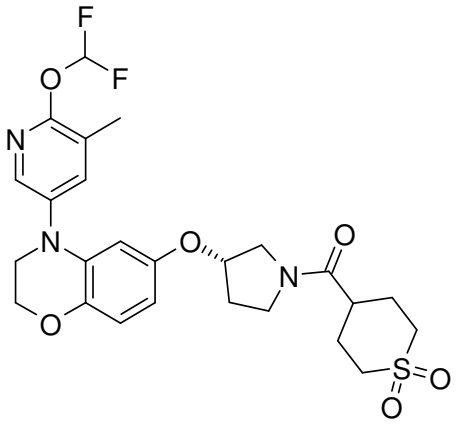
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B68	 1-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-2-piridin-4-il-etanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA1 / 6622-91-9	0.77 (M2)	509

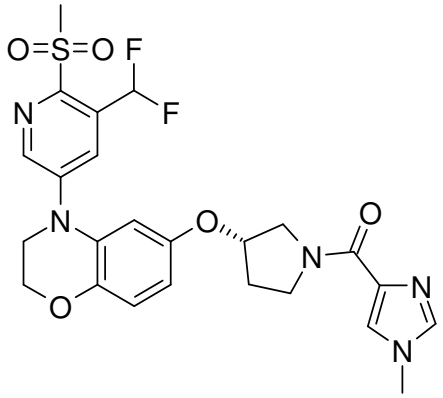
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B69	 {(S)-3-[4-(6-metan-sulfonil-5-trifluoro-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA10 Condición de enlace de amida: abreviado: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA3 / cloruro de acilo: 40191-32-0	0.93 (M1)	556

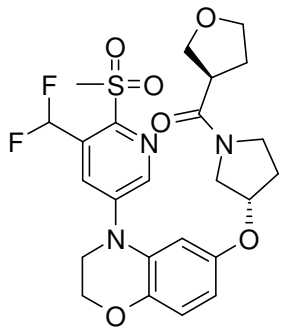
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B70	 {(S)-3-[4-(5-difluoro-metil-6-metan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA10 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA4 / cloruro de acilo: 40191-32-0	0.91 (M1)	538

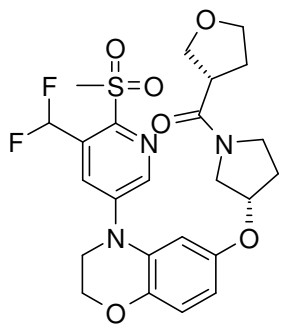
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B71	 {(S)-3-[4-(5-fluoro-metil-6-metan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA10 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA5 / cloruro de acilo: 40191-32-0	0.88 (M1)	520

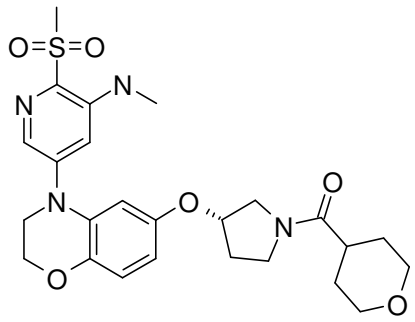
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B72	 {(S)-3-[4-(6-difluoro-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC4 Precursores utilizados: CAS 26021-57-8 / 109431-87-0 / IA8 / cloruro de acilo: 40191-32-0	1.07 (M1)	490

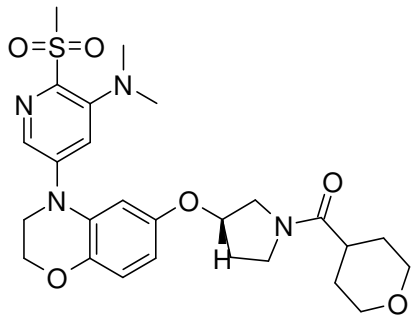
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B73	 {(S)-3-[4-(6-difluoro-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-hexahidro-6-tiopiran-4-il)-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB3 Condición de introducción de cadena lateral: CC4 Precursores utilizados: CAS 26021-57-8 / 109431-87-0 / IA8 / 64096-87-3	1.01 (M1)	538

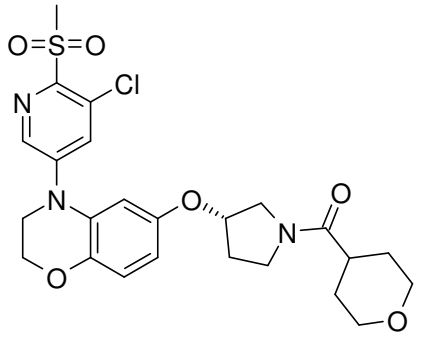
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B74	 {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA10 Condición de enlace de amida: CB3 Condición de introducción de cadena lateral: CC4 Precursores utilizados: CAS 26021-57-8 / 109431-87-0 / IA4 / 41716-18-1	0.81 (M1)	534

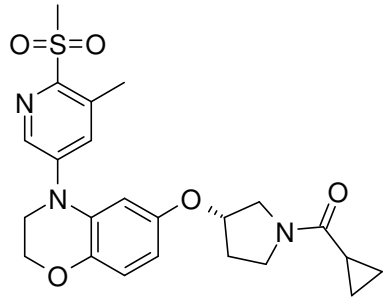
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B75	 {(S)-3-[4-(5-difluoro-metil-6-metan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(R)-tetrahidrofuran-3-il-metanona Condición de aminación de Buchwald: CA10 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC4 Precursores utilizados: CAS 26021-57-8 / 109431-87-0 / IA4 / IB1	0.88 (M1)	524

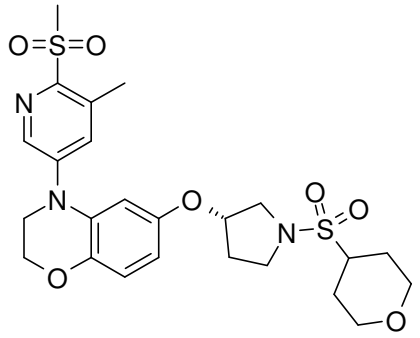
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B76	 {(S)-3-[4-(5-difluoro-metil-6-metan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(S)-tetrahidrofuran-3-il-metanona Condición de aminación de Buchwald: CA10 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC4 Precursores utilizados: CAS 26021-57-8 / 109431-87-0 / IA4 / IB2	0.88 (M1)	524

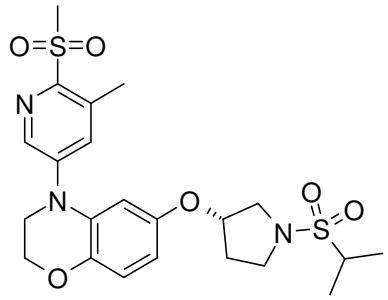
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B77	 {(S)-3-[4-(6-metan-sulfonil-5-metil-amino-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA10 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC4 Precursores utilizados: CAS 26021-57-8 / 109431-87-0 / IA51 / cloruro de acilo: 40191-32-0	0.85 (M1)	517

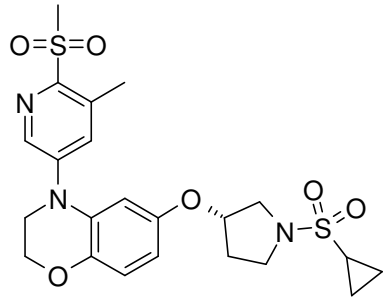
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B78	 {(S)-3-[4-(5-dimetil-amino-6-metan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA10 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC4 Precursores utilizados: CAS 26021-57-8 / 109431-87-0 / IA52 / cloruro de acilo: 40191-32-0	0.86 (M1)	531

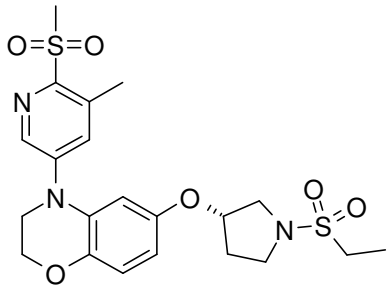
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B79	 {(S)-3-[4-(5-cloro-6-metan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA10 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA53, cloruro de acilo 40191-32-0	0.98 (M1)	522

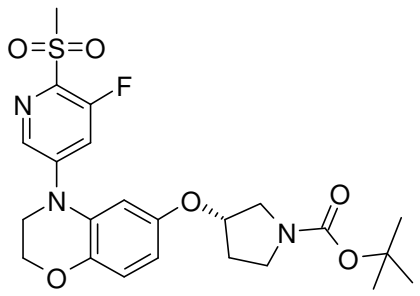
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B80	 Ciclopropil-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA1, cloruro de acilo 4023-34-1	0.94 (M1)	458

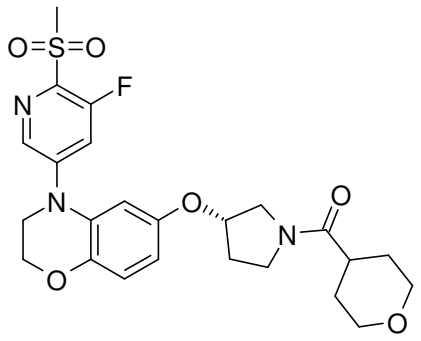
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B81	 4-(6-metan-sulfonil-5-metil-piridin-3-il)-6-[(S)-1-(tetrahidro-piran-4-sulfonil)-pirrolidin-3-iloxi]-3,4-dihidro-2H-benzo-[1,4]-oxazina Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA1, cloruro de sulfonilo 338453-21-7	0.95 (M1)	538

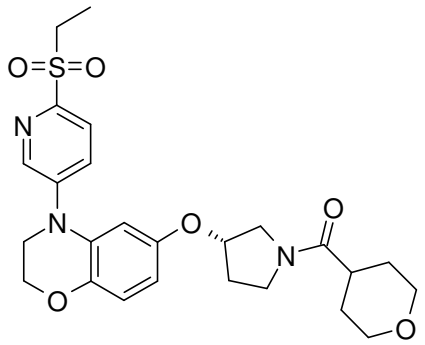
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B82	 4-(6-metan-sulfonil-5-metil-piridin-3-il)-6-[(S)-1-(propan-2-sulfonil)-pirrolidin-3-iloxi]-3,4-dihidro-2H-benzo-[1,4]-oxazina Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA1, cloruro de sulfonilo 10147-37-2	0.99 (M1)	496

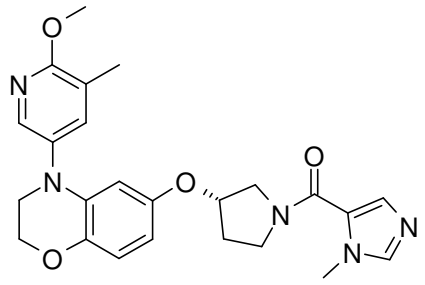
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B83	 6-((S)-1-ciclopropan-sulfonil-pirrolidin-3-iloxi)-4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazina Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA1, cloruro de sulfonilo 139631-62-2	0.96 (M1)	494

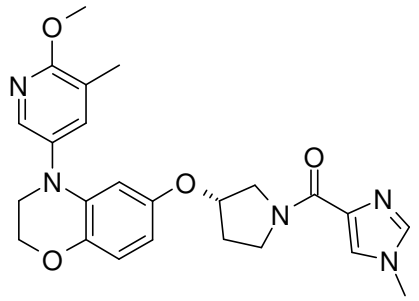
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B84	 6-((S)-1-etan-sulfonil-pirrolidin-3-iloxi)-4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazina Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA1, cloruro de sulfonilo 594-44-5	0.94 (M1)	482

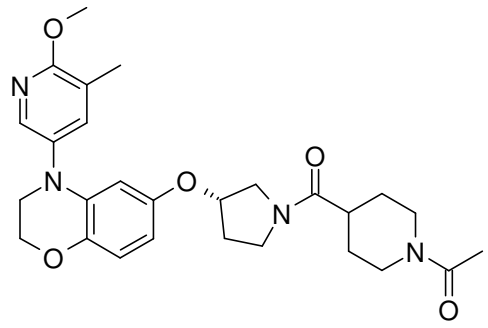
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B85	 Terbutil-éster del ácido (S)-3-[4-(5-fluoro-6-metan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carboxílico Condición de aminación de Buchwald: CA10 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA2	1.08 (M1)	494

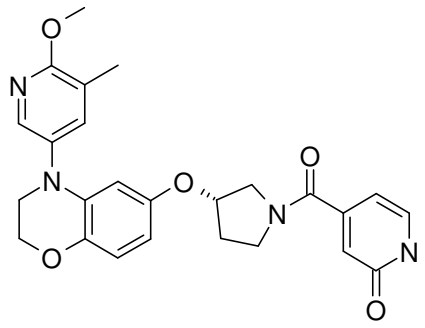
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B86	 {(S)-3-[4-(5-fluoro-6-metan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA10 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA2, cloruro de acilo 40191-32-0 Disociación de BOC con HCl en dioxano en lugar del ácido trifluoro-acético	0.80 (M1)	506

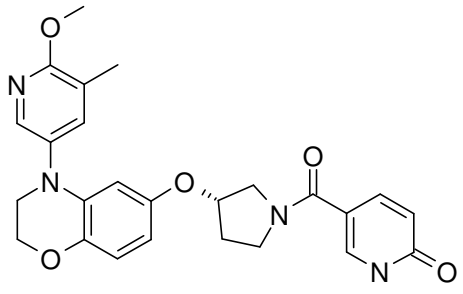
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B87	 {(S)-3-[4-(6-etan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA13 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA58, cloruro de acilo 40191-32-0	1.57 (M7)	502

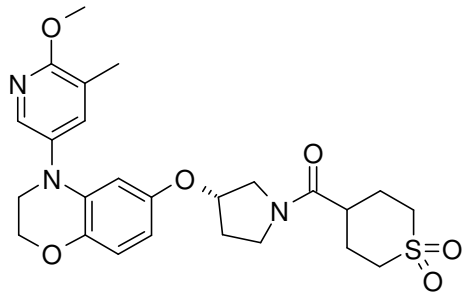
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B88	 {(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(3-metil-3H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA9, 41806-40-0	1.45 (M8)	450

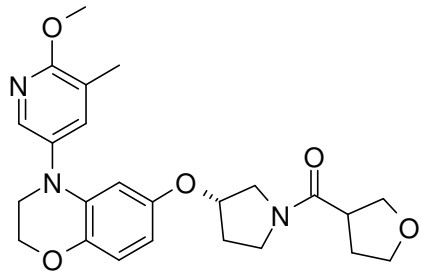
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B89	 {(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA9, 41716-18-1	1.52 (M8)	450

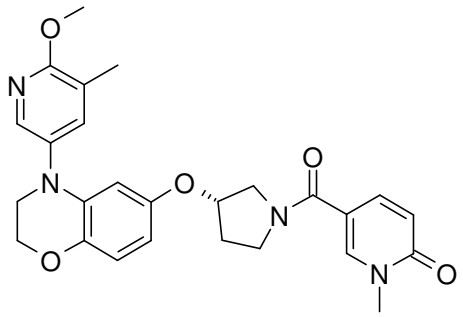
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B90	 1-(4-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carbonil}-piperidin-1-il)-etanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA9, 25503-90-6	1.69 (M8)	495

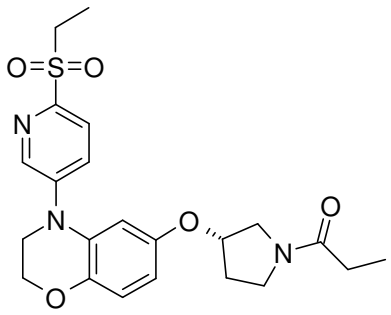
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B91	 4-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carbonil}-1H-piridin-2-ona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA9, 22282-72-0	1.53 (M8)	463

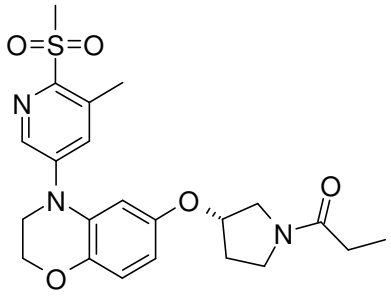
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B92	 5-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carbonil}-1H-piridin-2-ona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA9, 5006-66-6	1.54 (M8)	463

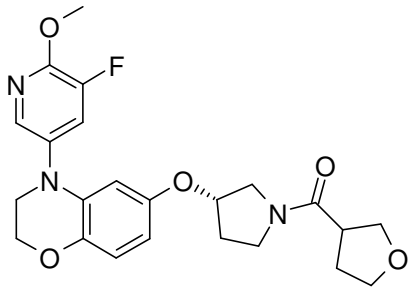
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B93	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA9, 64096-87-3	1.71 (M8)	502

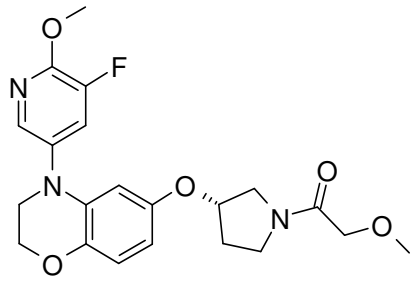
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B94	 {(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidrofuran-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA9, 89364-31-8	1.88 (M8)	440

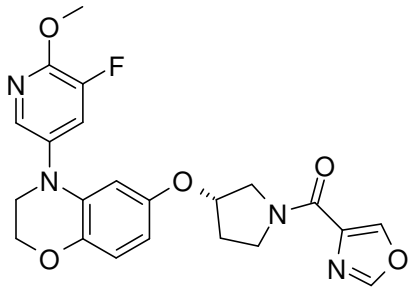
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B95	 5-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carbonil}-1-metil-1H-piridin-2-ona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA9, 3719-45-7	1.59 (M8)	477

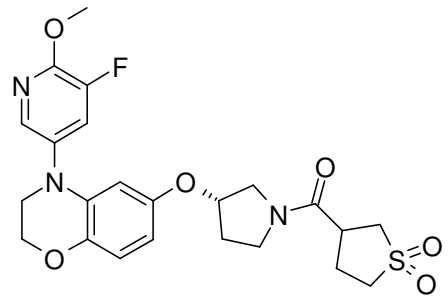
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B96	 1-{(S)-3-[4-(6-etan-sulfonil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Condición de aminación de Buchwald: CA13 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA58, cloruro de acilo 79-03-8	1.50 (M7)	446

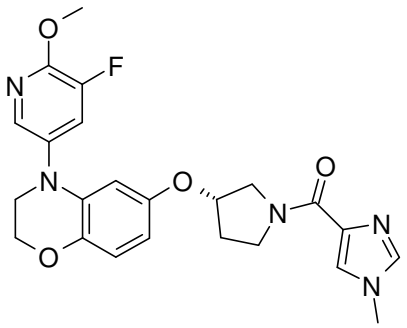
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B97	 1-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, 127423-61-4, IA1, cloruro de acilo 79-03-8	1.53 (M8)	446

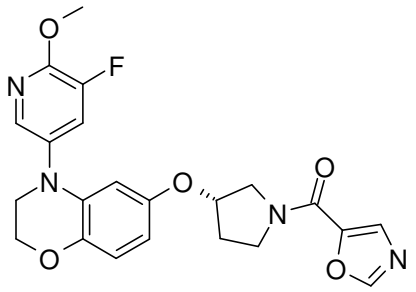
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B98	 {(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidrofuran-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10/ 89364-31-8	1.83 (M7)	444

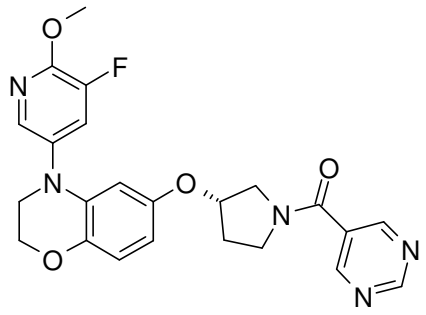
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B99	 1-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-2-metoxi-etanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10 / 625-45-6	1.77 (M7)	418

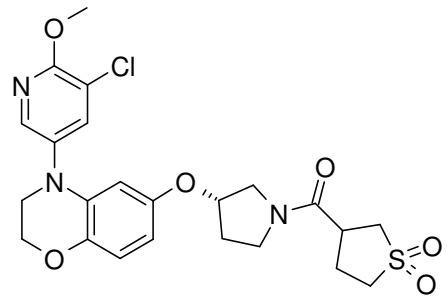
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B100	 {(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-oxazol-4-il-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10/ 23012-13-7	1.87 (M7)	441

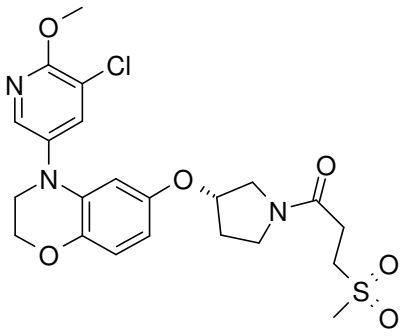
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B101	 (1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10 / 4785-67-5	1.81 (M7)	492

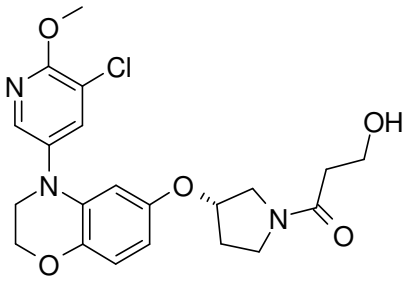
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B102	 {(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10/ 41716-18-1	1.48 (M7)	453

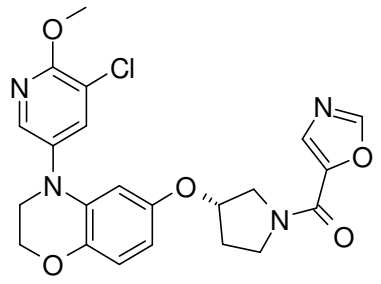
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B103	 {(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-oxazol-5-il-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10 / 118994-90-4	1.80 (M7)	441

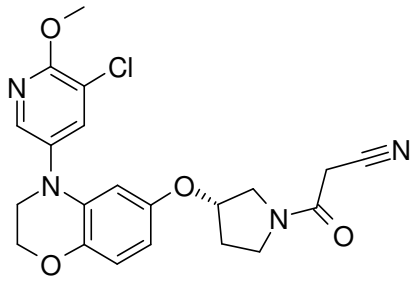
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B104	 {(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-pirimidin-5-il-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10 / 4595-61-3	1.75 (M7)	452

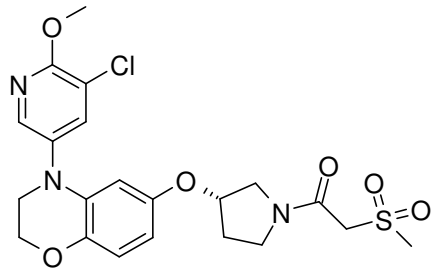
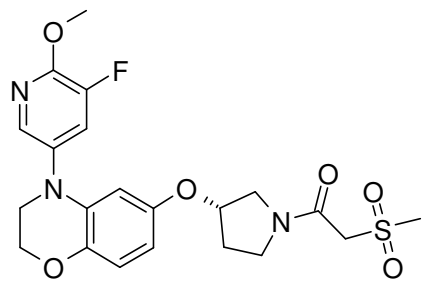
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B105	 {(S)-3-[4-(5-cloro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA11 / 4785-67-5	1.84 (M8)	508, 510

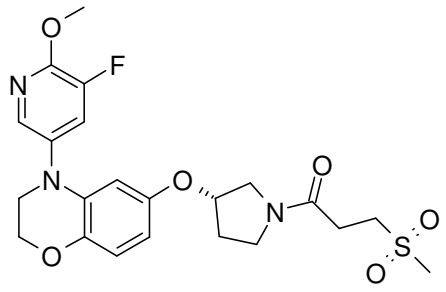
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B106	 1-{(S)-3-[4-(5-cloro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-metan-sulfonil-propan-1-ona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA11 / 645-83-0	1.78 (M8)	496, 498

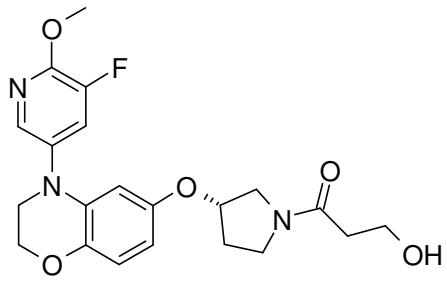
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B107	 1-{(S)-3-[4-(5-cloro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-hidroxi-propan-1-ona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA11 / 503-66-2	1.67 (M8)	434, 436

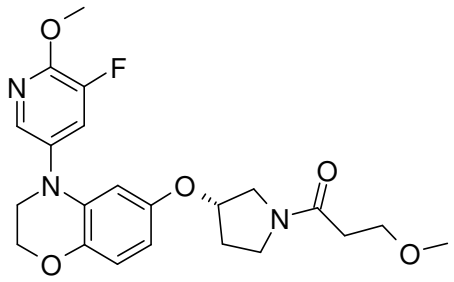
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B108	 {(S)-3-[4-(5-cloro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-oxazol-5-il-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA11 / 118994-90-4	1.84 (M8)	457, 459

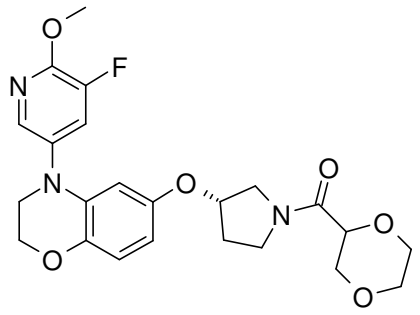
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B109	 3-{(S)-3-[4-(5-cloro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-oxo-propionitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA11 / 372-09-8	1.88 (M8)	429, 431

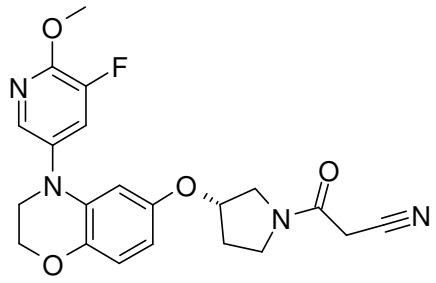
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B110	 1-{(S)-3-[4-(5-cloro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-2-metan-sulfonil-etanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA11 / 2516-97-4	1.90 (M8)	482
B111		1.70 (M8)	466

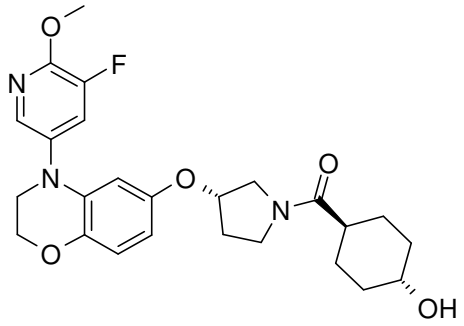
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	1-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-2-metan-sulfonil-etanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10 / 2516-97-4		
B112	 1-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-metan-sulfonil-propan-1-ona	1.77 (M8)	480

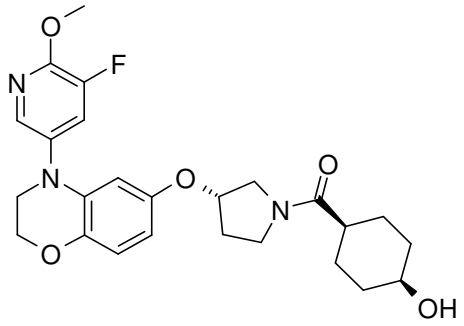
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10 / 645-83-0		
B113	 1-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-hidroxi-propan-1-ona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena	1.57(M8)	418

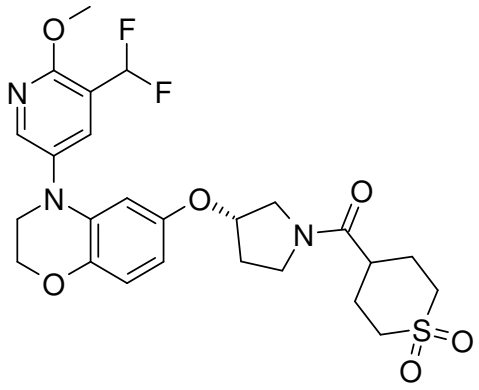
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10 / 503-66-2		
B114	 1-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-metoxi-propan-1-ona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10 / 2544-06-1	1.84 (M8)	432

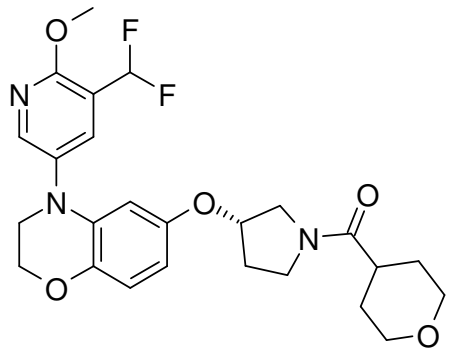
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B115	 [1,4]-dioxan-2-il-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10/ 89364-41-0	1.83 (M8)	459

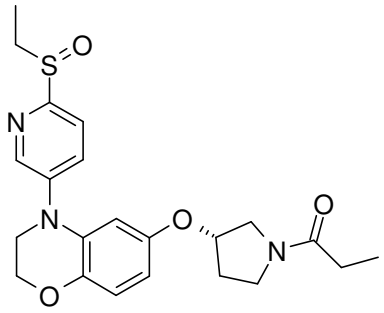
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B116	 3-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-3-oxo-propionitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10 / 372-09-8	1.85 (M8)	413

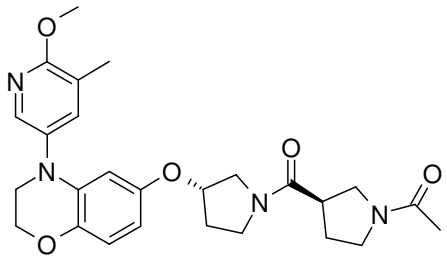
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B117	 {(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(4-hidroxi-ciclohexil)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10 / 3685-26-5	3.13 (M3)	472

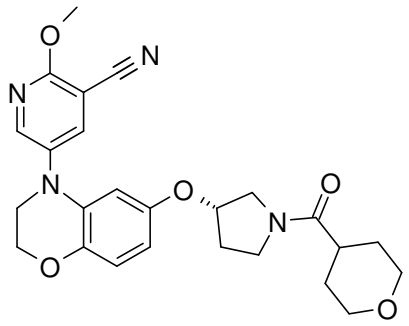
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B118	 {(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(4-hidroxi-ciclohexil)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA10 / 3685-22-1	3.40 (M3)	472

Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B119	 {(S)-3-[4-(5-difluoro-metil-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-hexahidro-6-tiopiran-4-il)-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB3 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA6 / 64096-87-3	0.97 (M1)	538

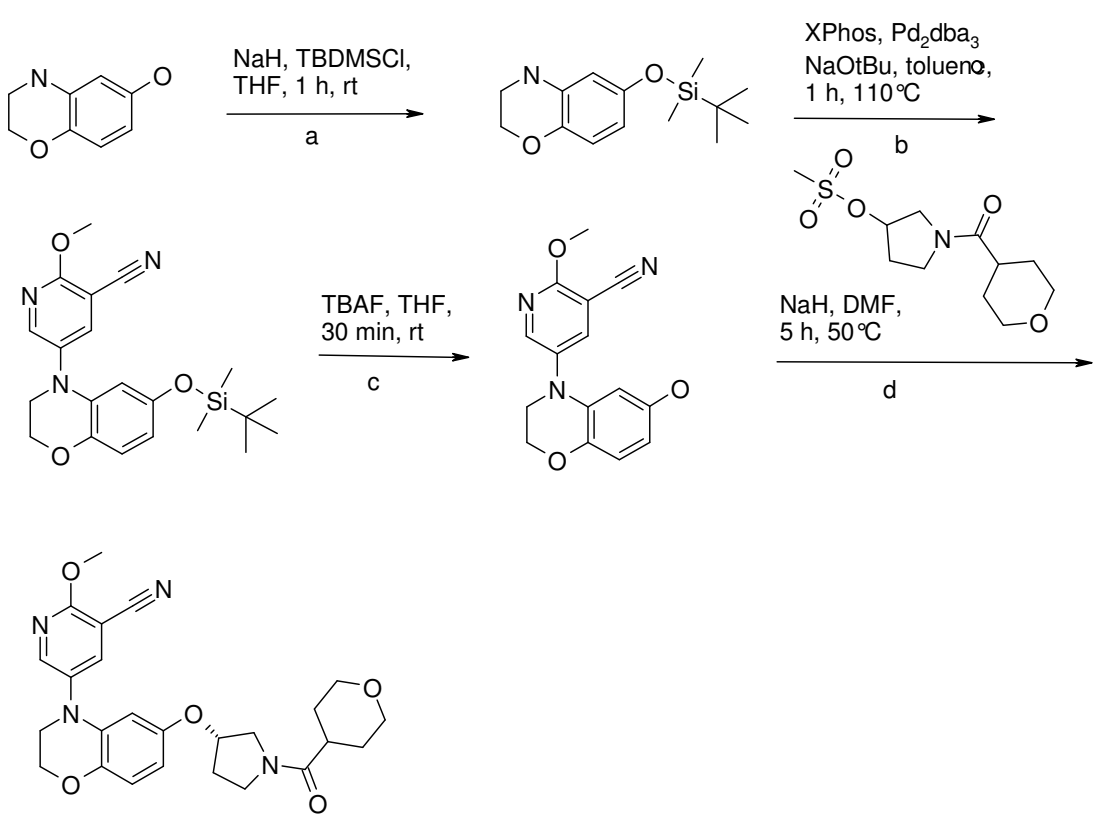
Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B120	 {(S)-3-[4-(5-difluoro-metil-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA6 / cloruro de acilo 40191-32-0	1.03 (M1)	490

Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B121	 1-{(S)-3-[4-(6-etan-sulfinil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Condición de aminación de Buchwald: CA14 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4, IA44, cloruro de acilo CAS 79-03-8	1.42 (M8)	430

Ejemplo	Compuesto / Condiciones de Reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
B122	 1-((R)-3-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carbonil}-pirrolidin-1-il)-etanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8 / 127423-61-4, IA9, CAS 72925-16-7, Producto obtenido después de la reacción de disociación de Boc utilizando ácido trifluoro-acético (TFA) en CH_2Cl_2 hecha de una manera convencional, y la acilación final en analogía al Ejemplo J	1.66 (M8)	481



Ejemplo C1: **2-metoxi-5-{6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo (de acuerdo con el esquema 3)**



a) 6-(terbutil-dimetil-silaniloxi)-3,4-dihidro-2H-benzo-[1,4]-oxazina

Bajo argón, se agregó NaH (2.96 gramos, 74.1 milimoles) en porciones a una solución del 3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol (CAS registro 26021-57-8) (5.60 gramos, 37.0 milimoles) en tetrahidrofurano (THF) (200 mililitros). Después de agitar a temperatura ambiente durante 20 minutos, se agregó lentamente TBDMSCl (CAS registro 18162-48-6) (7.26 gramos, 48.2 milimoles), y se continuó la agitación durante 1 hora. La mezcla de reacción se diluyó con Et_2O, se lavó con una solución acuosa saturada de $NaHCO_3$ y salmuera. La fase orgánica se secó sobre $MgSO_4$, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 60:40 durante 15 minutos), como un aceite amarillo (9.20 gramos, 94 por ciento de rendimiento).

HPLC Rt_{M10}= 3.65 minutos; ESIMS: 266 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 6.46 (d, 1H), 6.08 (d, 1H), 5.91 (m, 1H), 5.71 (br s, 1H), 3.91-4.12 (m, 2H), 3.12-3.28 (m, 2H), 0.87-1.01 (s, 9H), 0.03-0.21 (s, 3H).

b) 5-[6-(terbutil-dimetil-silaniloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-2-metoxi-nicotinonitrilo

Bajo argón, se agregaron XPhos (CAS registro 564483-18-7) (0.79 gramos, 1.7 milimoles), y $Pd_2(dba)_3$ (CAS registro 51364-51-3) (1.52 gramos, 1.7 milimoles) a una suspensión de 6-(terbutil-dimetil-silaniloxi)-3,4-dihidro-2H-benzo-[1,4]-oxazina (9.00 gramos, 33.2 milimoles), 5-bromo-2-metoxi-nicotinonitrilo (CAS registro 941294-54-8) (7.79 gramos, 36.6 milimoles), y NaOtBu (4.79 gramos, 49.8

milimoles) en tolueno (270 mililitros). La mezcla de reacción se agitó a 110°C durante 1 hora, y se concentró, para proporcionar un sólido color café, el cual se lavó con una mezcla de DCM/MeOH (8:2), y se filtró. El filtrado se concentró, el residuo obtenido se disolvió en DCM/MeOH (8:2), se filtró sobre Hyflo, el filtrado se concentró y se trituró con metanol, para proporcionar el compuesto del título como un sólido amarillo (10.14 gramos, 77 por ciento de rendimiento).

HPLC Rt_{M11} =3.89 minutos; ESIMS: 398 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.35-8.51 (m, 1H), 8.16-8.31 (m, 1H), 6.60-6.79 (m, 1H), 6.15-6.32 (m, 1H), 5.92-6.09 (m, 1H), 4.00 (s, 3H), 3.51-3.74 (m, 2H), 0.87 (s, 9H), 0.07 (s, 6H).

c) 5-(6-hidroxi-2,3-dihidro-benzo-[1,4]-oxazin-4-il)-2-metoxi-nicotinonitrilo

Se agregó TBAF (1M en tetrahidrofurano (THF)) (37.7 mililitros, 37.7 milimoles), a una solución de 5-[6-(terbutil-dimetil-silaniloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-2-metoxi-nicotinonitrilo (10 gramos, 25.2 milimoles) disuelto en tetrahidrofurano (THF) (200 mililitros). La solución se agitó a temperatura ambiente durante 30 minutos, se diluyó con EtOAc, se lavó con una solución acuosa saturada de $NaHCO_3$ y salmuera. Las capas acuosas se retro-extrajeron con EtOAc, y la concentración de las fases orgánicas después de secar sobre $MgSO_4$ proporcionó un residuo color café, el cual se disolvió en DCM/MeOH (1:1), y se filtró sobre Hyflo. La concentración y trituración con Et_2O del filtrado proporcionó el compuesto del título como un sólido color café (6.63 gramos, 93 por

ciento de rendimiento).

HPLC Rt_{M10}=2.56 minutos; ESIMS: 284 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.70 (br. s, 1H), 8.44 (d, 1H), 8.28 (d, 1H), 6.62 (d, 1H), 6.12 (m, 1H), 6.01 (d, 1H), 4.11-4.32 (m, 2H), 4.01 (s, 3H), 3.54-3.68 (m, 2H).

d) 2-metoxi-5-{6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo

Bajo argón, se agregó NaH (31 miligramos, 0.78 milimoles), a una solución de 5-(6-hidroxi-2,3-dihidro-benzo-[1,4]-oxazin-4-il)-2-metoxi-nicotinonitrilo (100 miligramos, 0.35 milimoles) en dimetil-formamida (DMF) (2 mililitros), y se agitó a temperatura ambiente durante 5 minutos. Se agregó el (R)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-il-éster de ácido metan-sulfónico (intermediario IC1) (98.0 miligramos, 0.35 milimoles), y la mezcla de reacción se agitó a 50°C durante 4 horas. Después de enfriarse, se agregó NaH (0.5 equivalentes, 8.47 miligramos, 0.21 milimoles), la mezcla de reacción se agitó a temperatura ambiente durante 5 minutos, y se agregó el (R)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-il-éster de ácido metan-sulfónico (intermediario IC1) (49.0 miligramos, 0.18 milimoles). La mezcla de reacción se agitó a 50°C durante 1 hora. La concentración y la purificación mediante RP-HPLC de preparación (Sunfire Prep C18 OBD 30 x 100 milímetros, 5 micras; solvente A: H_2O + ácido trifluoro-acético (TFA) al 0.1 por ciento por volumen; solvente B: CH_3CN + ácido trifluoro-acético (TFA) al 0.1 por ciento por volumen) proporcionó, después de la basificación de las

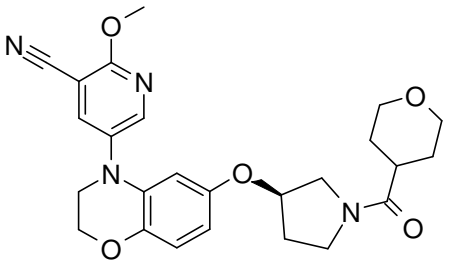
fracciones combinadas y de la extracción con EtOAc, el compuesto del título como un sólido amarillo (72 miligramos, 43 por ciento de rendimiento).

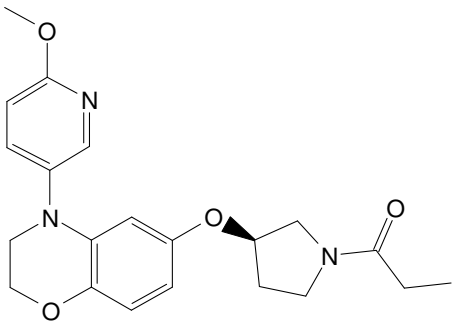
HPLC Rt_{M10}=2.72 minutos; ESIMS: 465 [$(M+H)^+$].

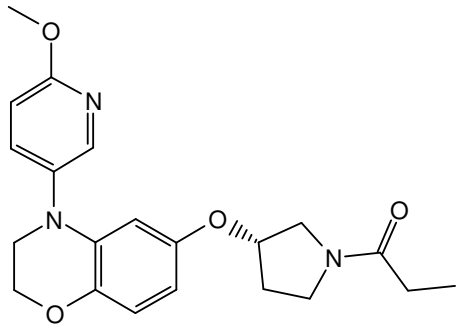
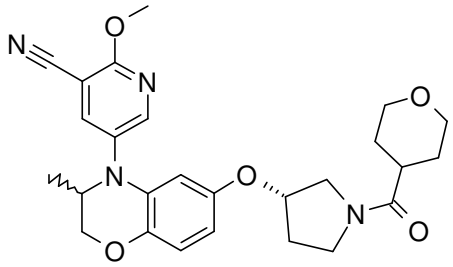
^{1}H RMN (400 MHz, CD_3OD): δ 8.36 (d, 1H), 8.06 (t, 1H), 6.78 (m, 1H), 6.37 (m, 1H), 6.17 (m, 1H), 4.81 (br s, 1H), 4.17-4.37 (m, 2H), 4.08 (s, 3H), 3.90-4.03 (m, 2H), 3.56-3.81 (m, 5H), 3.39-3.54 (m, 3H), 2.59-2.89 (m, 1H), 1.87-2.29 (m, 2H), 1.48-1.87 (m, 4H).

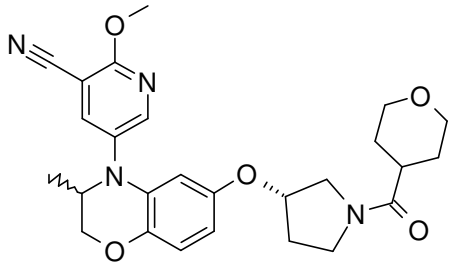
Ejemplos C2 a C26: Los compuestos enlistados en la Tabla 3 se prepararon mediante un procedimiento análogo a aquél empleado en el Ejemplo C1.

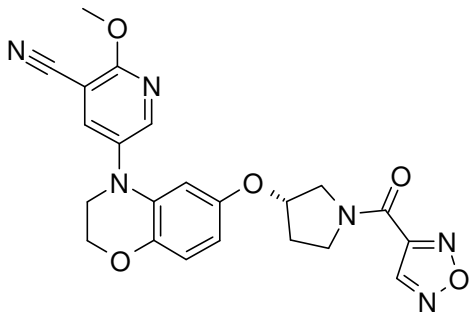
Tabla 3

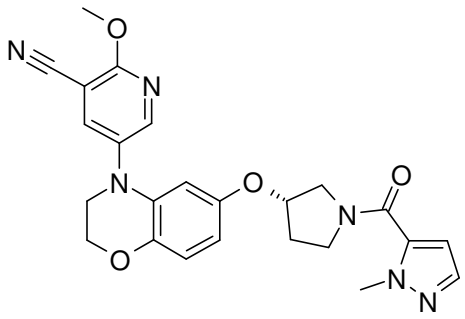
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C2	 2-metoxi-5-{6-[(R)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo	2.71 (M10)	465

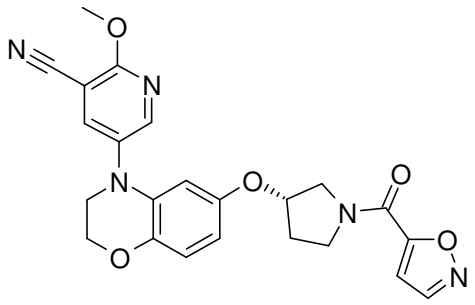
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Condición de aminación de Buchwald: CA6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IC2		
C3	 1-{(R)-3-[4-(6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Condición de aminación de Buchwald: CA7 Condición de introducción de cadena lateral: CC3 Precursores utilizados: IC3	2.71 (M10)	384

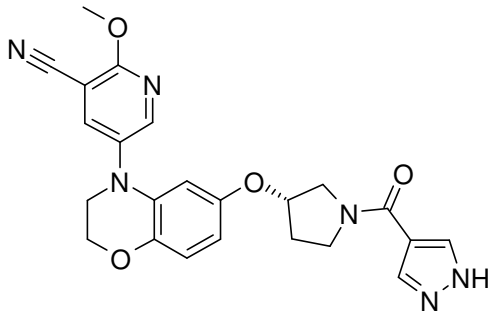
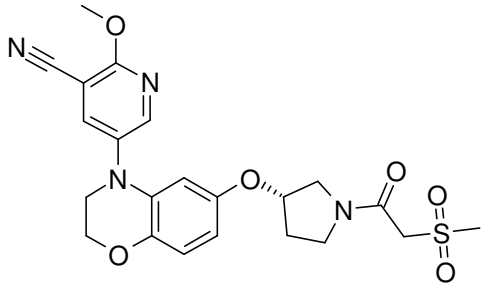
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C4	 1-{(S)-3-[4-(6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-propan-1-ona Condición de aminación de Buchwald: CA7 Condición de introducción de cadena lateral: CC3 Precursores utilizados: IC4	2.71 (M10)	384
C5	 2-metoxi-5-{3-metil-6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-	2.83 (M10) 16.981 (M5)	479

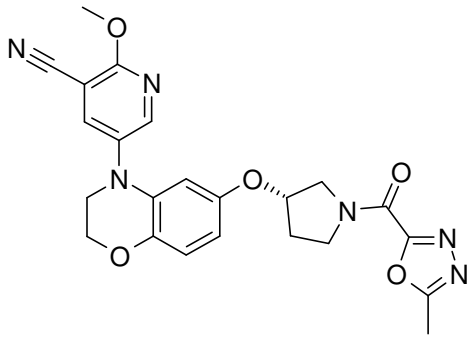
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 704879-75-4, IC1 Separación quiral: CD3		
C6	 2-metoxi-5-{3-metil-6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de introducción de cadena	2.83 (M10) 19.957 (M5)	479

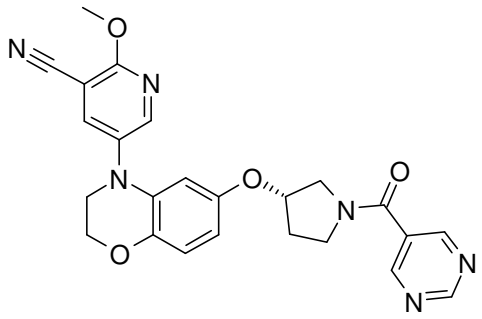
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	lateral: CC2 Precursores utilizados: CAS 704879-75-4, IC1 Separación quiral : CD3		
C7	 5-{6-[(S)-1-(Furazan-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA12/ 88598-08-7	4.13 (M4)	449

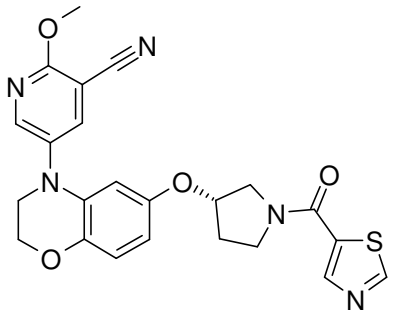
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C8	 2-metoxi-5-{6-[(S)-1-(2-metil-2H-pirazol-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-enzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA12/ 16034-46-1	4.11 (M4)	461

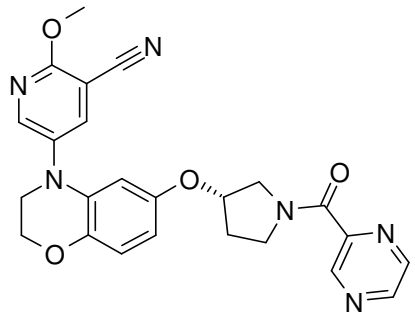
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C9	 5-{6-[(S)-1-(Isoxazol-5-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA12/ 21169-71-1	4.17 (M4)	448

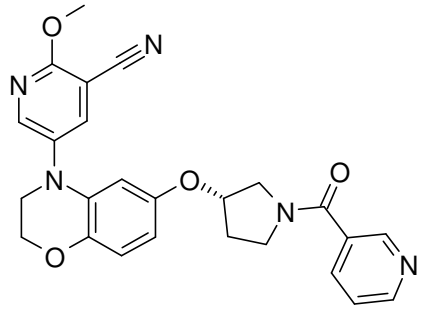
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C10	 2-metoxi-5-{6-[(S)-1-(1H-pirazol-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA12/ 37718-11-9	3.60 (M4)	447
C11		3.73 (M4)	473

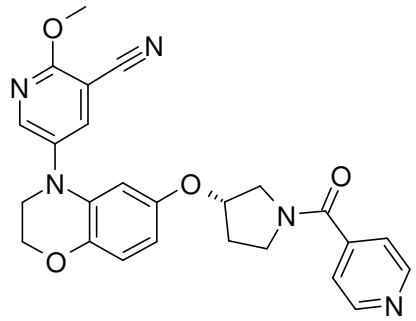
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	5-{6-[(S)-1-(2-metan-sulfonil-acetil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA12 / 2516-97-4		
C12	 2-metoxi-5-{6-[(S)-1-(5-metil-[1,3,4]-oxadiazol-2-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-	4.02 (M4)	463

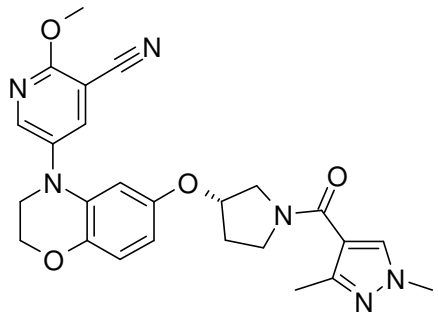
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA12 / 518048-06-1		
C13	 2-metoxi-5-{6-[(S)-1-(pirimidin-5-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1	3.72 (M4)	459

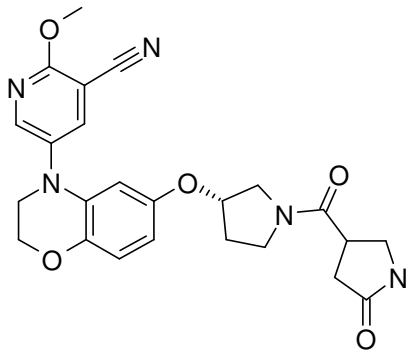
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8 / 127423-61-4 / IA12 / 4595-61-3		
C14	 2-metoxi-5-{6-[(S)-1-(tiazol-5-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4, 14527-41-4	4.02 (M4)	464

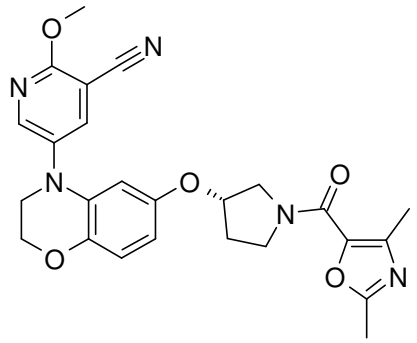
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C15	 2-metoxi-5-{6-[(S)-1-(pirazin-2-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12,127423-61-4,1339899-95-4	4.03 (M3)	459

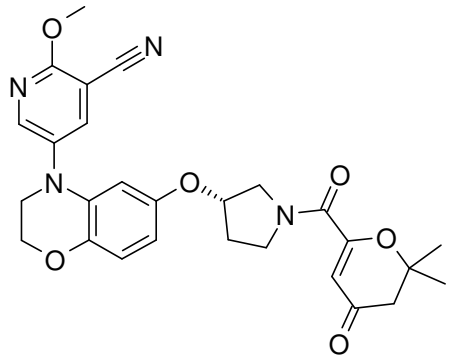
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C16	 2-metoxi-5-{6-[(S)-1-(piridin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4, 59-67-6	3.27 (M3)	458

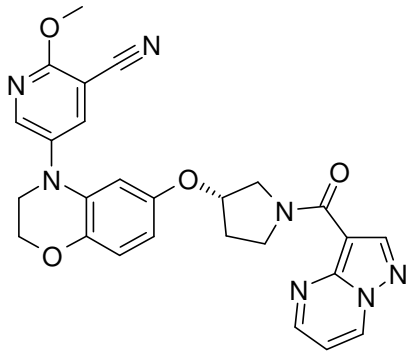
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C17	 2-metoxi-5-{6-[(S)-1-(piridin-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4,5-22-1	3.20 (M3)	458

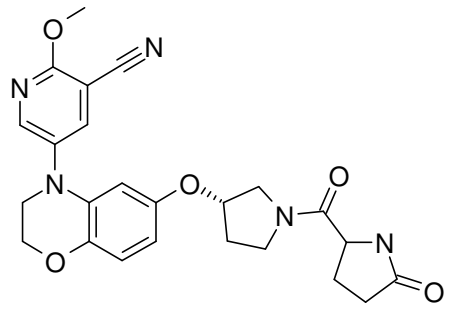
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C18	 5-{6-[(S)-1-(1,3-dimetil-1H-pirazol-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4, 78703-53-4	3.91 (M3)	475

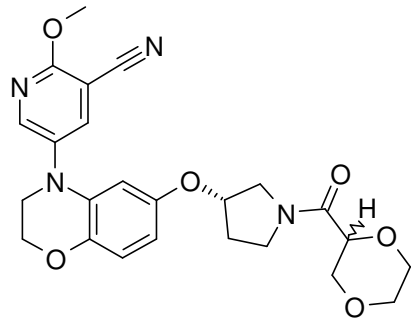
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C19	 2-metoxi-5-{6-[(S)-1-(5-oxo-pirrolidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4, 7268-43-1	3.44 (M3)	464

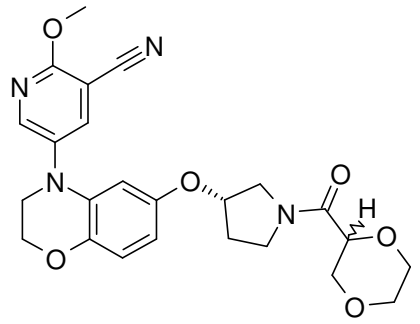
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C20	 5-{6-[(S)-1-(2,4-dimetil-oxazol-5-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4, 2510-37-4	4.27 (M3)	476

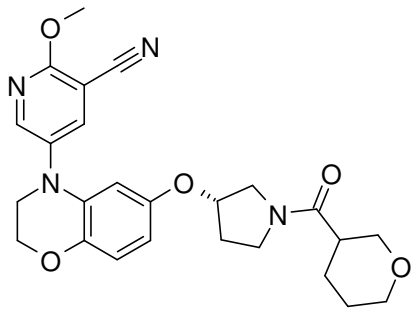
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C21	 5-{6-[(S)-1-(6,6-dimetil-4-oxo-5,6-dihidro-4H-piran-2-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4, 80866-93-9	4.33 (M3)	505

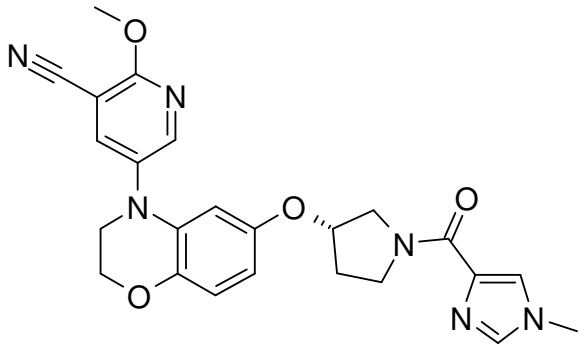
Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C22	 2-metoxi-5-{6-[(S)-1-(pirazolo-[1,5-a]-pirimidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4, 25940-35-6	3.87 (M3)	498

Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C23	 2-metoxi-5-{6-[(S)-1-(5-oxo-pirrolidin-2-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4, 149-87-1	3.47 (M3)	464

Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C24	 5-{6-[(S)-1-([1,4]-dioxan-2-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4, 89364-41-0 Separación quiral : CD7	2.68 (M10) 22.58 (CD7)	467

Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C25	 5-{6-[(S)-1-([1,4]-dioxan-2-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4, 89364-41-0 Separación quiral : CD7	2.68 (M10) 33.80 (CD7)	467

Ejemplo	Compuesto	UPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
C26	 2-metoxi-5-{6-[(S)-1-(tetrahidro-piran-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: CAS 26021-57-8, IA12, 127423-61-4, 873397-34-3	1.57 (M9)	465



<u>Ejemplo D1:</u> **(S)-2-metoxi-5-(6-((1-(1-metil-1H-imidazol-4-carbonil)-pirrolidin-3-il)-oxi)-2H-benzo-[b][1,4]-oxazin-4(3H)-il)-nicotinonitrilo (de acuerdo con el esquema 4)**

a1) 6-((terbutil-dimetil-silil)-oxi)-3,4-dihidro-2H-benzo-[b][1,4]-oxazina

Una solución agitada del 3,4-dihidro-2H-1,4-benzoxazin-6-ol (CAS registro 226021-57-8) (6.00 gramos, 39.70 milimoles) en tetrahidrofurano (THF) (200 mililitros) se trató con hidruro de sodio (al 60 por ciento en aceite mineral, 3.18 gramos, 79.00 milimoles), a temperatura ambiente. Después de 20 minutos a temperatura ambiente, se agregó TBDMSCl (7.78 gramos, 51.6 milimoles), y la mezcla de reacción se agitó a temperatura ambiente durante 1.5 horas. Después de este tiempo, se agregaron dietil-éter (500 mililitros), y una solución acuosa saturada de $NaHCO_3$ (100 mililitros). La capa acuosa se extrajo con dietil-éter, y los extractos orgánicos combinados se secaron con $MgSO_4$, se filtraron, y se

concentraron bajo presión reducida. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (gradiente de ciclohexano / EtOAc), para proporcionar el compuesto del título como un aceite color amarillo.

HPLC Rt_{M11} = 3.37 minutos; ESIMS: 266 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 6.48-6.44 (m, 1H), 6.09-6.05 (m, 1H), 5.94-5.89 (m, 1H), 5.76-5.70 (m, 1H), 4.06-4.00 (m, 2H), 3.25-3.19 (m, 2H), 0.92 (s, 9H), 0.12 (s, 6H).

b1) 5-(6-((terbutil-dimetil-silil)-oxi)-2H-benzo-[b][1,4]-oxazin-4(3H)-il)-2-metoxi-nicotinonitrilo,

Una solución agitada de la 6-((terbutil-dimetil-silil)-oxi)-3,4-dihidro-2H-benzo-[b][1,4]-oxazina (8.88 gramos, 32.80 milimoles) en tolueno (270 mililitros) se trató con 5-bromo-2-metoxi-nicotinonitrilo (CAS registro 941294-54-8) (7.68 gramos, 36.10 milimoles), NaOtBu (4.87 gramos, 49.2 milimoles), 2-diciclohexil-fosfino-2′,4′,6′-tri-isopropil-bifenilo (CAS registro 564483-18-7) (0.806 gramos, 1.64 milimoles), y Pd_2dba_3 (1.501 gramos, 1.64 milimoles), a temperatura ambiente bajo argón. La mezcla de reacción se calentó a 110°C durante 1.5 horas. Después de este tiempo, la mezcla de reacción se concentró bajo presión reducida. El residuo se disolvió en dicloro-metano (DCM) (200 mililitros), se filtró a través de un cojín de Celite, y se concentró bajo presión reducida. El residuo se disolvió en MeOH, y se sonicó varias veces para dar un precipitado color amarillo/naranja. El residuo se filtró, se lavó con metanol, y se secó

al vacío, para proporcionar el compuesto del título como un sólido amarillo.

HPLC Rt_{M11} = 3.90 minutos; ESIMS: 398 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.45-8.42 (m, 1H), 8.28-8.24 (m, 1H), 6.72-6.68 (m, 1H), 6.24-6.19 (m, 1H), 6.06-6.03 (m, 1H), 4.24-4.18 (m, 2H), 4.00 (s, 3H), 3.66-3.61 (m, 2H), 0.87 (s, 9H), 0.07 (s, 6H).

Método alternativo b2: El diciclohexil-fosfino-2′,4′,6′-tri-isopropil-bifenilo (CAS registro 564483-18-7) y el $Pd_2(dba)_3$ fueron reemplazados con bis-(tri-terbutil-fosfina)-paladio (CAS registro 53199-31-8)

c1) 5-(6-hidroxi-2H-benzo-[b][1,4]-oxazin-4(3H)-il)-2-metoxi-nicotinonitrilo,

Una solución agitada del 5-(6-((terbutil-dimetil-silil)-oxi)-2H-benzo-[b][1,4]-oxazin-4(3H)-il)-2-metoxi-nicotinonitrilo (10.85 gramos, 27.30 milimoles) en tetrahidrofurano (THF) (220 mililitros) se trató con TBAF (1.0 M en tetrahidrofurano (THF), 40.9 mililitros, 40.90 milimoles), a temperatura ambiente. Después de 40 minutos a temperatura ambiente, se agregaron EtOAc (300 mililitros), y una solución acuosa saturada de $NaHCO_3$ (200 mililitros). Los extractos orgánicos se secaron con $MgSO_4$, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó mediante trituración con dietil-éter para proporcionar el compuesto del título como un sólido color café pálido.

HPLC Rt_{M11} = 2.00 minutos; ESIMS: 284 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.71 (s, 1H), 8.44 (d, 1H), 8.29 (d, 1H), 6.61 (d, 1H), 6.12 (dd, 1H), 6.01 (d, 1H), 4.21-4.16 (m, 2H), 4.01 (s, 3H), 3.64-3.59 (m, 2H).

d1) (S)-3-((4-(5-ciano-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[b][1,4]-oxazin-6-il)-oxi)-pirrolidin-1-carboxilato de terbutilo

Una solución agitada del 5-(6-hidroxi-2H-benzo-[b][1,4]-oxazin-4(3H)-il)-2-metoxi-nicotinonitrilo (3.70 gramos, 13.06 milimoles) en dimetil-formamida (DMF) (60 mililitros) se trató con hidruro de sodio (al 60 por ciento en aceite mineral, 1.31 gramos, 32.70 milimoles), a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 15 minutos. Después de este tiempo, se agregó (R)-1-Boc-3-metan-sulfoniloxi-pirrolidina (CAS registro 141699-57-2) (5.36 gramos, 19.59 milimoles), y la mezcla de reacción se agitó a 50°C durante 3 horas. Después de este tiempo, la mezcla de reacción se concentró bajo presión reducida. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (gradiente de ciclohexano / acetona), para proporcionar el compuesto del título como un sólido amarillo.

HPLC Rt_{M11} = 3.13 minutos; ESIMS: 453 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.31 (d, 1H), 7.81 (d, 1H), 6.82 (d, 1H), 6.32 (dd, 1H), 6.14 (d, 1H), 4.74-4.68 (m, 1H), 4.32-4.28 (m,

2H), 4.09 (s, 3H), 3.67-3.62 (m, 2H), 3.59-3.39 (m, 4H), 2.17-1.92 (m, 2H), 1.47 (s, 9H).

Método alternativo d2: El alcohol mesilado, hidruro de sodio y dimetil-formamida (DMF) fueron reemplazados con la hidroxi-isoxazolidina, el azodicarboxilato de dietilo (DEAD), y el tetrahidrofurano (THF) correspondientes utilizando las condiciones de Mitsunobu descritas en el método CC4.

e1) (S)-2-metoxi-5-(6-(pirrolidin-3-iloxi)-2H-benzo-[b][1,4]-oxazin-4(3H)-il)-nicotinonitrilo

Una solución agitada del (S)-3-((4-(5-ciano-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[b][1,4]-oxazin-6-il)-oxi)-pirrolidin-1-carboxilato de terbutilo (4.35 gramos, 9.32 milimoles) en dicloro-metano (DCM) (160 mililitros) se trató con ácido trifluoro-acético (TFA) (35.9 mililitros, 466 milimoles), a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. Después de este tiempo, la mezcla de reacción se concentró bajo presión reducida. El residuo se disolvió en dicloro-metano (DCM) (500 mililitros), y se agregó una solución acuosa saturada de NaHCO3 (500 mililitros). Los extractos orgánicos se lavaron con una solución acuosa saturada de NaCl (50 mililitros), se secaron con $MgSO_4$, se filtraron, y se concentraron bajo presión reducida. El producto crudo (compuesto del título, sólido amarillo) se utilizó en el siguiente paso sin mayor purificación.

HPLC Rt_{M10}= 2.06 minutos; ESIMS: 353 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.31 (d, 1H), 7.82 (d, 1H), 6.82 (d, 1H), 6.32 (dd, 1H), 6.12 (d, 1H), 4.71-4.65 (m, 1H), 4.32-4.27 (m, 2H), 4.09 (s, 3H), 3.67-3.62 (m, 2H), 3.22-2.90 (m, 4H), 2.08-1.88 (m, 2H).

f1) (S)-2-metoxi-5-(6-((1-(1-metil-1H-imidazol-4-carbonil)-pirrolidin-3-il)-oxi)-2H-benzo-[b][1,4]-oxazin-4(3H)-il)-nicotinonitrilo,

Una solución agitada del ácido 1-metil-1H-imidazol-4-carboxílico (CAS registro 41716-18-1) (0.578 gramos, 4.45 milimoles) en dimetil-formamida (DMF) (40 mililitros) se trató con HOBT (0.695 gramos, 4.45 milimoles), EDC (0.870 gramos, 4.45 milimoles), y Et_3N (1.24 mililitros, 8.90 milimoles), a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 15 minutos. Después de este tiempo, se agregó (S)-2-metoxi-5-(6-(pirrolidin-3-iloxi)-2H-benzo-[b][1,4]-oxazin-4(3H)-il)-nicotinonitrilo (1.10 gramos, 2.97 milimoles), y la mezcla de reacción se agitó durante 3 horas 15 minutos a temperatura ambiente. Después de este tiempo, la mezcla de reacción se concentró bajo presión reducida. El residuo se disolvió en dicloro-metano (DCM) (200 mililitros), y se agregó una solución acuosa saturada de $NaHCO_3$ (200 mililitros). Los extractos orgánicos se secaron con $MgSO_4$, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice

(gradiente de dicloro-metano (DCM) / metanol), y HPLC de preparación (columna SunFire C18, CH_3CN / ácido trifluoro-acético (TFA) al 1 por ciento en un gradiente de H_2O, las fracciones puras se trataron con dicloro-metano (DCM) y una solución acuosa saturada de $NaHCO_3$; los extractos orgánicos combinados se secaron con $MgSO_4$, se filtraron, y se concentraron bajo presión reducida), para proporcionar el compuesto del título como un sólido amarillo.

HPLC Rt_{M10}= 2.27 minutos; ESIMS: 461 [$(M+H)^+$].

^1H RMN (400 MHz, DMSO-d_6): δ 8.46-8.41 (m, 1H), 8.30-8.26 (m, 1H), 7.66-7.59 (m, 2H), 6.77-6.72 (m, 1H), 6.37-6.29 (m, 1H), 6.14-6.07 (m, 1H), 4.90-4.79 (m, 1H), 4.25-4.11 (m, 3H), 3.99 (s, 3H), 3.98-3.78 (m, 1H), 3.70-3.41 (m, 7H), 2.10-1.93 (m, 2H).

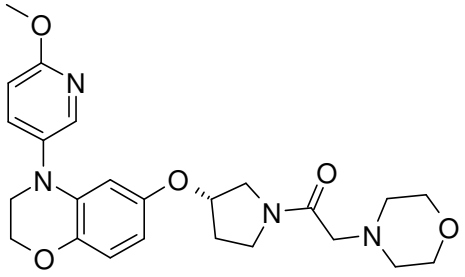
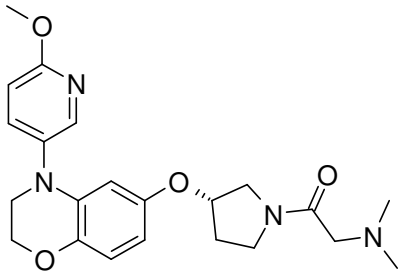
Método alternativo f2: El ácido carboxílico, HOBT, EDC y dimetil-formamida (DMF) fueron reemplazados con el cloruro de ácido carboxílico y dicloro-metano (DCM).

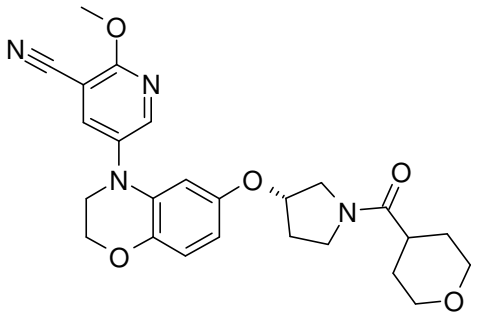
Método alternativo f3: El ácido carboxílico, HOBT, EDC y dimetil-formamida (DMF) fueron reemplazados con cloroformato y dicloro-metano (DCM).

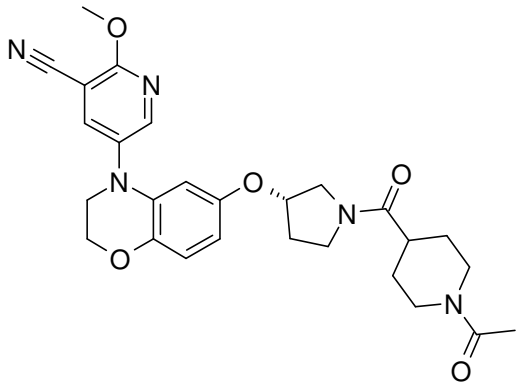
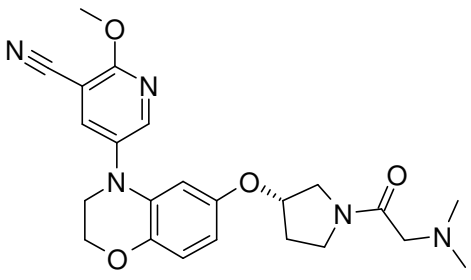
Método alternativo f4: El ácido carboxílico, HOBT y EDC fueron reemplazados con cloruro carbámico.

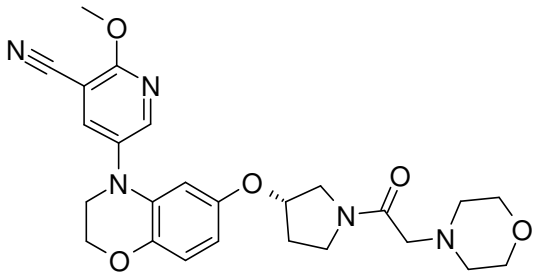
Ejemplos D2 a D40: Los compuestos enlistados en la Tabla 4 se prepararon mediante un procedimiento análogo a aquél empleado en el Ejemplo D1.

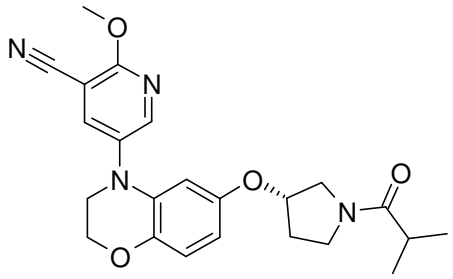
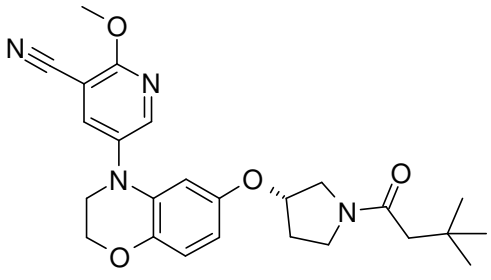
Tabla 4

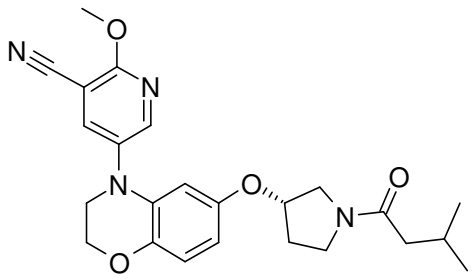
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D2	 1-{(S)-3-[4-(6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-2-morfolin-4-il-etanona Ruta sintética utilizada: a1, b2 (intermediario: CAS registro 163129-79-1), c1, d1, e1, f1 (intermediario: CAS registro 89531-58-8)	2.07 (M10)	455
D3	 2-dimetil-amino-1-{(S)-3-[4-(6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-	2.08 (M10)	413

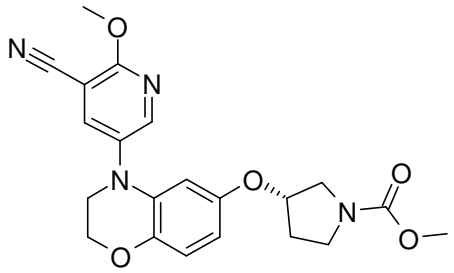
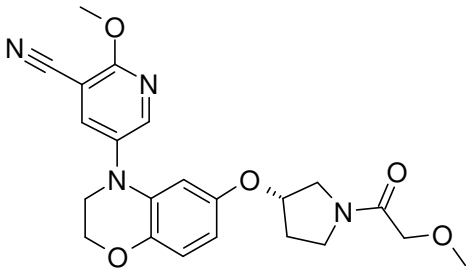
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	etanona Ruta sintética utilizada: a1, b2 (intermediario: CAS registro 163129-79-1), c1, d1, e1, f1 (intermediario: CAS registro 1118-68-9)		
D4	 2-metoxi-5-{6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b2 (intermediario IA12), c1, d1, e1, f2 (intermediario: CAS registro 40191-32-0)	2.72 (M10)	465

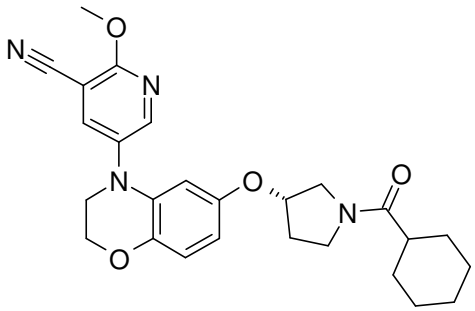
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D5	 5-{6-[(S)-1-(1-acetil-piperidin-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 25503-90-6)	2.61 (M10)	506
D6	 5-{6-[(S)-1-(2-dimetil-amino-acetil)-	2.22 (M10)	438

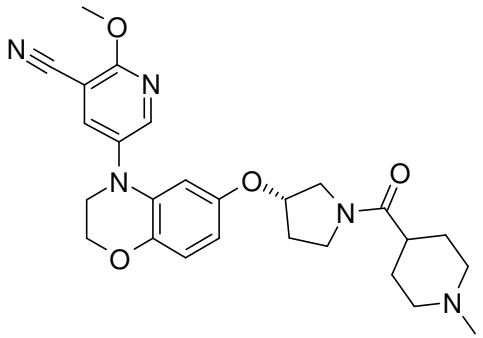
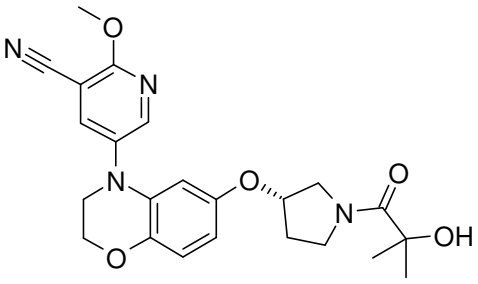
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 1118-68-9)		
D7	 2-metoxi-5-{6-[(S)-1-(2-morfolin-4-il-acetil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 89531-58-8)	2.14 (M10)	480

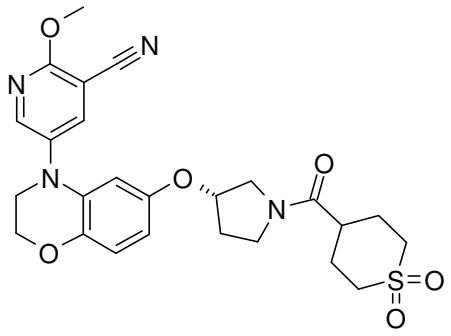
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D8	 5-[6-((S)-1-isobutiril-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-2-metoxi-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f2 (intermediario: CAS registro 89531-58-8)	2.14 (M10)	480
D9	 5-{6-[(S)-1-(3,3-dimetil-butiril)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo	3.19 (M10)	451

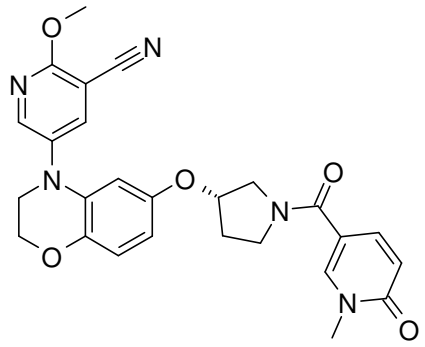
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f2 (intermediario: CAS registro 7065-46-5)		
D10	 2-metoxi-5-{6-[(S)-1-(3-metil-butiril)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f2 (intermediario: CAS registro 108-12-3)	3.06 (M10)	437

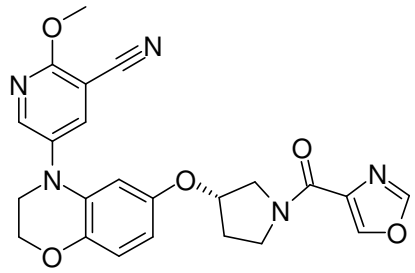
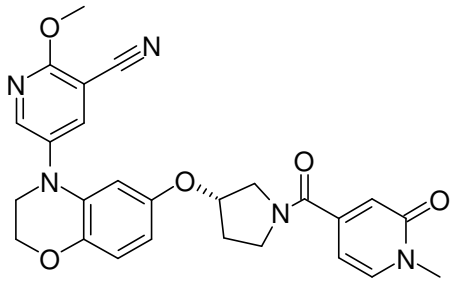
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D11	 Metil-éster del ácido (S)-3-[4-(5-ciano-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carboxílico Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f3 (intermediario: CAS registro 79-22-1)	2.96 (M10)	411
D12	 2-metoxi-5-{6-[(S)-1-(2-metoxi-acetil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo	2.63 (M10)	425

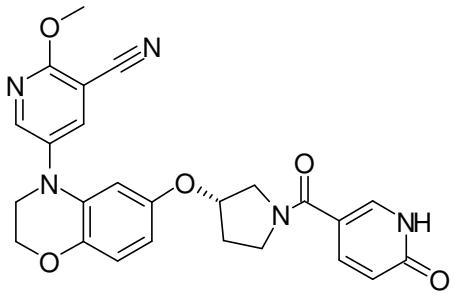
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f2 (intermediario: CAS registro 38870-89-2)		
D13	 5-[6-((S)-1-ciclohexan-carbonil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-2-metoxi-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f2 (intermediario: CAS registro 2719-27-9)	3.22 (M10)	463

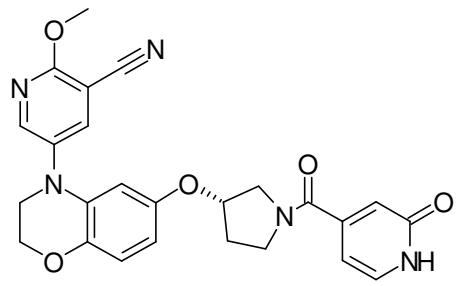
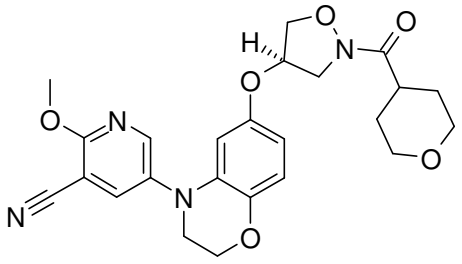
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D14	 2-metoxi-5-{6-[(S)-1-(1-metil-piperidin-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 68947-43-3)	2.23 (M10)	478
D15	 5-{6-[(S)-1-(2-hidroxi-2-metil-	2.67 (M10)	439

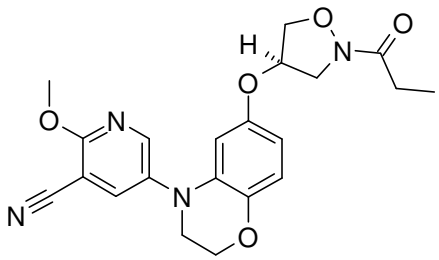
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	propionil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 594-61-6)		
D16	 5-{6-[(S)-1-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario:	1.62 (M8)	513

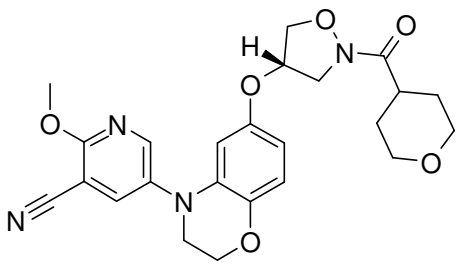
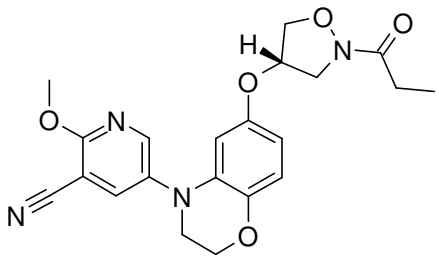
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	CAS registro 64096-87-3)		
D17	 2-metoxi-5-{6-[(S)-1-(1-metil-6-oxo-1,6-dihidro-piridin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 3719-45-7)	1.55 (M13)	488

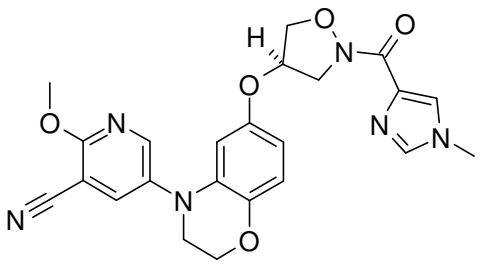
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D18	 2-metoxi-5-{6-[(S)-1-(oxazol-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 23012-13-7)	1.75 (M13)	448
D19	 2-metoxi-5-{6-[(S)-1-(1-metil-2-oxo-1,2-dihidro-piridin-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo	1.56 (M13)	488

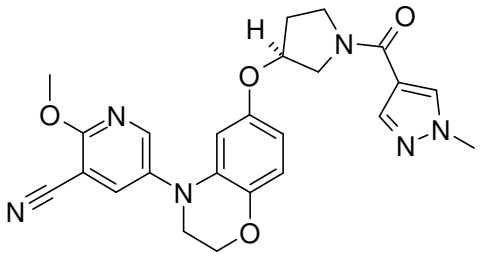
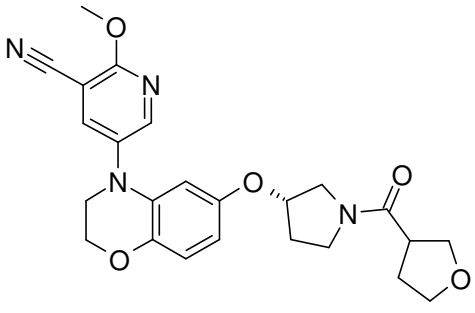
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 33972-97-3)		
D20	 2-metoxi-5-{6-[(S)-1-(6-oxo-1,6-dihidro-piridin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 5006-66-6)	1.60 (M8)	474

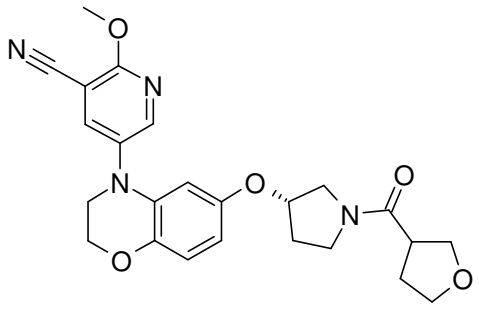
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D21	 2-metoxi-5-{6-[(S)-1-(2-oxo-1,2-dihidro-piridin-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 22282-72-0)	1.50 (M13)	474
D22	 2-metoxi-5-{6-[(R)-2-(tetrahidro-piran-4-carbonil)-isoxazolidin-4-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-	3.01 (M10)	467

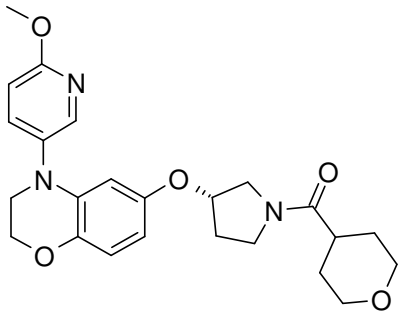
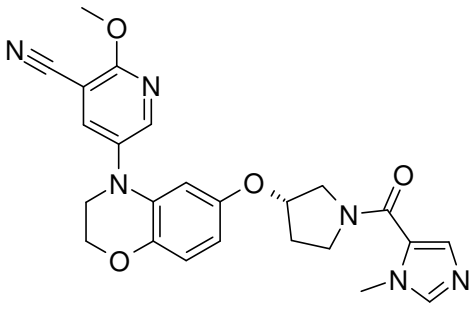
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d2 (intermediario: CAS registro 878385-72-9), e1, f2 (intermediario: CAS registro 40191-32-0)		
D23	 2-metoxi-5-[6-((R)-2-propionil-isoxazolidin-4-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d2 (intermediario: CAS registro 878385-72-9), e1, f2 (intermediario: CAS registro 79-03-8)	3.11 (M10)	411

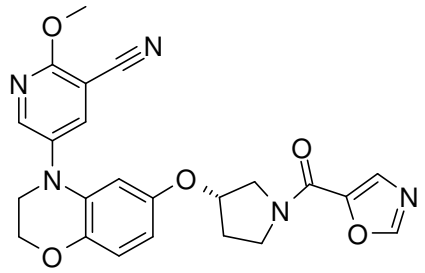
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D24	 2-metoxi-5-{6-[(S)-2-(tetrahidro-piran-4-carbonil)-isoxazolidin-4-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d2 (intermediario: CAS registro 1092454-84-6), e1, f2 (intermediario: CAS registro 40191-32-0)	1.63 (M9)	467
D25	 2-metoxi-5-[6-((S)-2-propionil-	1.66 (M9)	411

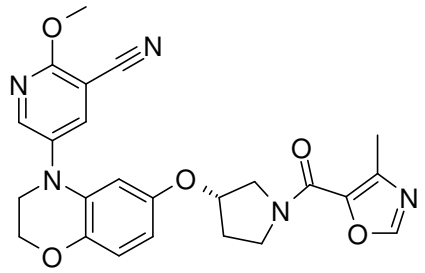
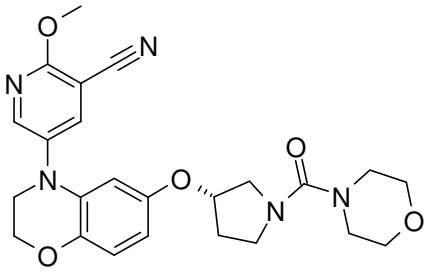
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	isoxazolidin-4-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d2 (intermediario: CAS registro 1092454-84-6), e1, f2 (intermediario: CAS registro 79-03-8)		
D26	 2-metoxi-5-{6-[(R)-2-(1-metil-1H-imidazol-4-carbonil)-isoxazolidin-4-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 41716-18-1)	2.31 (M10)	463

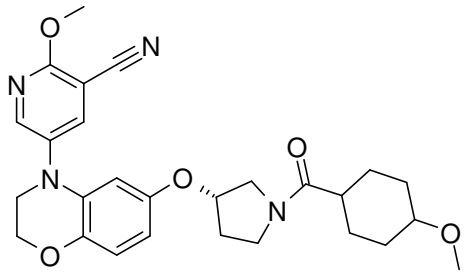
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D27	 2-metoxi-5-{6-[(S)-1-(1-metil-1H-pirazol-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 5952-92-1)	2.62 (M10)	461
D28	 2-metoxi-5-{6-[(S)-1-(tetrahidrofuran-3-carbonil)-pirrolidin-3-iloxi]-2,3-	2.68 (M10)	451

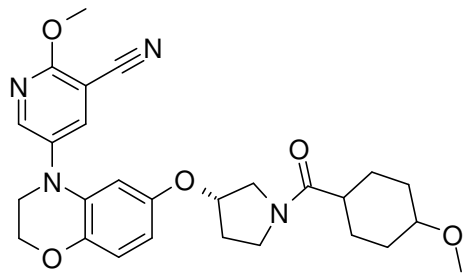
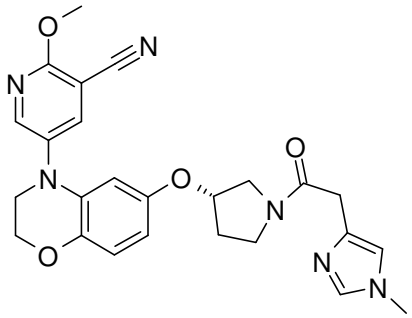
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 89364-31-8). Isómero 1		
D29	 2-metoxi-5-{6-[(S)-1-(tetrahidrofuran-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 89364-31-8).	2.68 (M10)	451

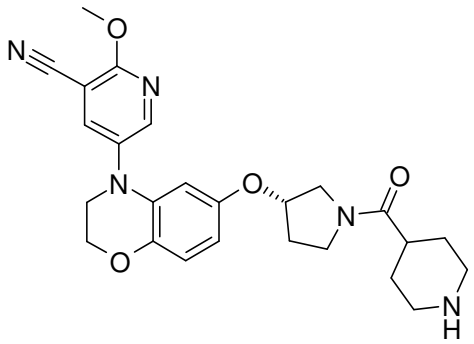
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Isómero 2		
D30	 {(S)-3-[4-(6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Ruta sintética utilizada: a1, b2 (intermediario: CAS registro 163129-79-1), c1, d1, e1, f2 (intermediario: CAS registro 40191-32-0)	2.63 (M10)	440
D31		2.24 (M10)	461

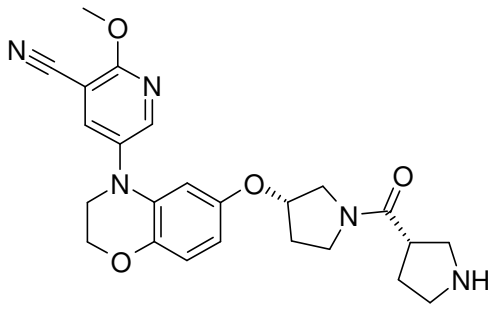
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	2-metoxi-5-{6-[(S)-1-(3-metil-3H-imidazol-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 41806-40-0)		
D32	 2-metoxi-5-{6-[(S)-1-(oxazol-5-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 118994-90-4)	1.69 (M13)	448

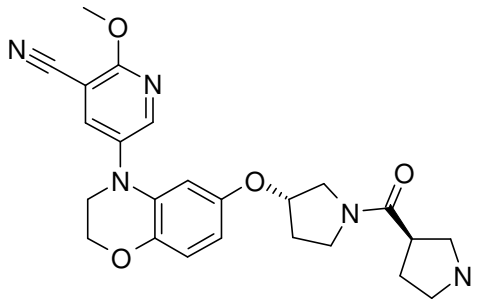
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D33	 2-metoxi-5-{6-[(S)-1-(4-metil-oxazol-5-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 2510-32-9)	1.80 (M13)	462
D34	 2-metoxi-5-{6-[(S)-1-(morfolin-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1	1.77 (M13)	466

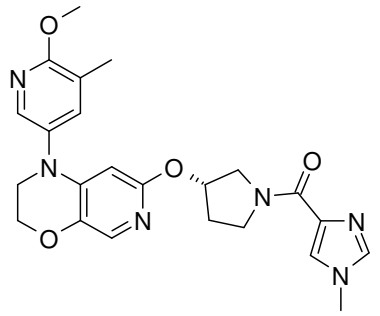
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	(intermediario: CAS registro 941294-54-8), c1, d1, e1, f4 (intermediario: CAS registro 15159-40-7)		
D35	 2-metoxi-5-{6-[(S)-1-(4-metoxi-ciclohexan-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 95233-12-8) Isómero 1	1.90 (M13)	493

Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D36	 2-metoxi-5-{6-[(S)-1-(4-metoxi-ciclohexan-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 95233-12-8) Isómero 2	2.01 (M13)	493
D37	 2-metoxi-5-(6-{(S)-1-[2-(1-metil-1H-	1.28 (M13)	475

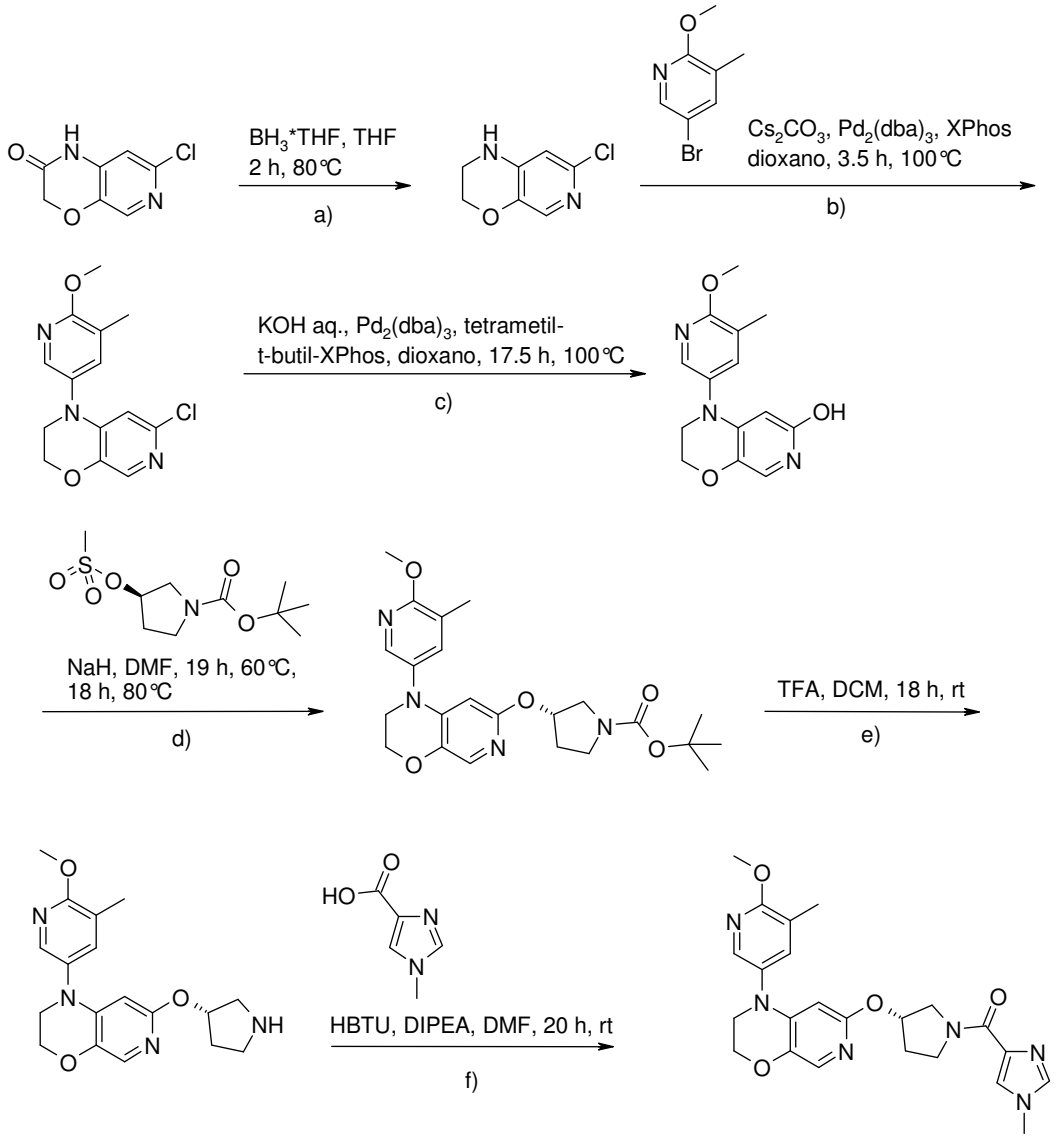
Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	imidazol-4-il)-acetil]-pirrolidin-3-iloxi}-2,3-dihidro-benzo-[1,4]-oxazin-4-il)-nicotinonitrilo Ruta sintética utilizada: a1, b1 (intermediario: CAS registro 941294-54-8), c1, d1, e1, f1 (intermediario: CAS registro 2625-49-2)		
D38	 2-metoxi-5-{6-[(S)-1-(piperidin-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 intermediario IA12, c1, d1 CAS registro 127423-61-4, f1 CAS registro 84358-13-4	2.19 (M10)	464

Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	último paso : remoción del grupo protector de Boc utilizando ácido trifluoro-acético (TFA) de una manera convencional.		
D39	 2-metoxi-5-{6-[(S)-1-((S)-pirrolidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 intermediario: CAS registro IA12, c1, d1 CAS registro 127423-61-4, f1 CAS registro 140148-70-5 último paso : remoción del grupo protector de Boc utilizando ácido trifluoro-acético (TFA) de una manera convencional.	2.24 (M10)	450

Ejemplo	Compuesto	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
D40	 2-metoxi-5-{6-[(S)-1-((R)-pirrolidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Ruta sintética utilizada: a1, b1 intermediario IA12, c1, d1 CAS registro 127423-61-4, f1 CAS registro 72925-16-7, último paso : remoción del grupo protector de Boc utilizando ácido trifluoro-acético (TFA) de una manera convencional.	2.24 (M10)	450



Ejemplo E1: **{(S)-3-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona (de acuerdo con el esquema 5)**



a) 7-cloro-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina

Una mezcla de la 7-cloro-1H-pirido-[3,4-b][1,4]-oxazin-2-ona (CAS registro 928118-43-8) (630 miligramos, 3.41 milimoles), y BH_3*THF (1 M en tetrahidrofurano (THF)) (10.2 mililitros, 10.2 milimoles) en tetrahidrofurano (THF) (20 mililitros) se agitó durante 2 horas a 80°C. La mezcla de reacción se apagó con MeOH, se agregó una solución acuosa de NaOH 1 M, y la mezcla se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se evaporaron. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 100:0 a 50:50 en 12 minutos), para proporcionar el compuesto del título como un sólido blanco (432 miligramos, 74 por ciento de rendimiento).

HPLC Rt_{M1} =0.47 minutos; ESIMS: 171 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 6.46 (s, 1H), 4.43 (br s, 1H) 4.21-4.25 (m, 2H), 3.48-3.51 (m, 2H).

b) 7-cloro-1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina

Una mezcla de la 7-cloro-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina (127 miligramos, 0.74 milimoles), 5-bromo-2-metoxi-3-metil-piridina (CAS registro 760207-87-2) (0.196 gramos, 0.986 milimoles), Cs_2CO_3 (534 miligramos, 1.64 milimoles), y XPhos (28 miligramos, 0.06 milimoles) en dioxano (3.5 mililitros) se desgasificó con argón y se agregó $Pd_2(dba)_3$ (27 miligramos, 0.03 milimoles). Después de

agitar durante 3.5 horas a 100°C, la mezcla de reacción se filtró sobre Hyflo, se agregó una solución acuosa saturada de $NaHCO_3$, y la mezcla se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se evaporaron. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 95:5 a 40:60, en 14 minutos), para proporcionar el compuesto del título como un sólido de color pálido (190 miligramos, 87 por ciento de rendimiento).

HPLC Rt_{M1} =1.04 minutos; ESIMS: 292 [$(M+H)^+$].

^1H RMN (400 MHz, $CDCl_3$): δ 7.94 (d, 1H), 7.80 (s, 1H), 7.31 (d, 1H), 6.31 (s, 1H), 4.34-4.37 (m, 2H), 4.01 (s, 3H), 3.68-3.72 (m, 2H), 2.24 (s, 3H).

c) 1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-ol

Una mezcla de la 7-cloro-1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina (190 miligramos, 0.65 milimoles), tetrametil-terbutil-XPhos (13 miligramos, 0.03 milimoles) en dioxano (3 mililitros), y una solución acuosa de KOH 5M (0.04 mililitros, 1.95 milimoles) se desgasificó con argón, y se agregó $Pd_2(dba)_3$ (6 miligramos, 0.01 milimoles). Después de agitar durante 17.5 horas a 100°C, la mezcla de reacción se filtró sobre Hyflo, el filtrado se secó sobre Na_2SO_4, se filtró, y se evaporó. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (EtOAc / metanol, de 100:0 a 85:15,

en 17 minutos), para proporcionar el compuesto del título como un sólido blanco (111 miligramos, 62 por ciento de rendimiento).

HPLC Rt_{M1} =0.67 minutos; ESIMS: 274 [$(M+H)^+$].

^1H RMN (400 MHz, $CDCl_3$): δ 10.32 (br s, 1H), 8.02 (d, 1H), 7.62 (m, 1H), 6.89 (s, 1H), 4.84 (s, 1H), 4.17-4.21 (m, 2H), 3.91 (s, 3H), 3.61-3.66 (m, 2H), 2.17 (s, 3H).

d) Terbutil-éster del ácido (S)-3-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-carboxílico

Una solución del 1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-ol (111 miligramos, 0.41 milimoles) en dimetil-formamida (DMF) (3 mililitros) se trató con NaH (33 miligramos, 0.81 milimoles) durante 10 minutos a 20°C. Se agregó el terbutil-éster del ácido (R)-3-metan-sulfoniloxi-pirrolidin-1-carboxílico (CAS registro 127423-61-4) (162 miligramos, 0.61 milimoles). Después de agitar durante 19 horas a 60°C, y durante 18 horas a 80°C, se agregó una solución acuosa saturada de $NaHCO_3$, y la mezcla de reacción se extrajo con terbutil-metil-éter (TBME). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se evaporaron. El producto crudo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 93:7 a 40:60, en 13.5 minutos), para proporcionar el compuesto del título como un aceite amarillo pálido (107 miligramos, 59 por ciento de rendimiento).

HPLC Rt_{M1} =1.21 minutos; ESIMS: 443 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.61 (br s, 1H), 7.32 (br s 1H), 5.71 (s, 1H), 5.41 (br s, 1H), 4.32 (br s, 2H), 3.99 (s, 3H), 3.65-3.70 (m, 2H), 3.37-3.61 (m, 4H), 2.23 (s, 3H), 1.58 (s, 9H), 0.82-0.97 (m, 2H).

e) 1-(6-metoxi-5-metil-piridin-3-il)-7-((S)-pirrolidin-3-iloxi)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina

Una solución del terbutil-éster del ácido (S)-3-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-carboxílico (103 miligramos, 0.23 milimoles), y ácido trifluoro-acético (TFA) (0.179 mililitros, 2.33 milimoles) en dicloro-metano (DCM) (1.8 mililitros) se agitó durante 18 horas a temperatura ambiente. Se agregó una solución acuosa saturada de Na_2CO_3, y la mezcla de reacción se extrajo con dicloro-metano (DCM). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se evaporaron; el compuesto del título se obtuvo como una espuma color amarillo pálido (72 miligramos, 90 por ciento de rendimiento).

HPLC Rt_{M1} =0.64 minutos; ESIMS: 343 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.62 (s, 1H), 7.32 (m, 1H), 5.70 (s, 1H), 5.29-5.35 (m, 1H), 4.29-4.33 (m, 2H), 3.99 (s, 3H), 3.65-3.69 (m, 2H), 2.82-3.14 (m, 4H), 2.22 (s, 3H), 1.80-2.10 (m, 2H).

f) {(S)-3-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona

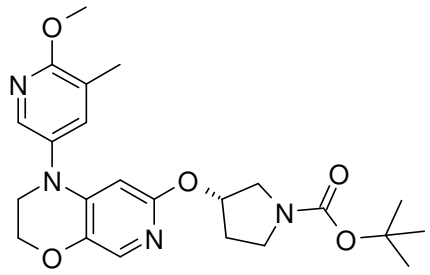
Una mezcla del ácido 1-metil-1H-imidazol-4-carboxílico (CAS registro 41716-18-1) (15 miligramos, 0.12 milimoles), HBTU (53 miligramos, 0.14 milimoles), y di-isopropil-etil-amina (DIPEA) (0.025 mililitros, 0.14 milimoles) en dimetil-formamida (DMF) (0.6 mililitros) se agitó a temperatura ambiente durante 5 minutos. Se agregó una solución de 1-(6-metoxi-5-metil-piridin-3-il)-7-((S)-pirrolidin-3-iloxi)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina (0.037 gramos, 0.11 milimoles) en dimetil-formamida (DMF) (0.6 mililitros). Después de agitar durante 20 horas a temperatura ambiente, se agregó agua, y la mezcla de reacción se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se evaporaron. El producto crudo se purificó mediante RP-HPLC de preparación (columna SunFire C18, H_2O + ácido trifluoro-acético (TFA) al 0.1 por ciento / acetonitrilo (ACN) + ácido trifluoro-acético (TFA) al 0.1 por ciento, de 90:10 a 60:40 en 16 minutos), para proporcionar el compuesto del título como una espuma color amarillo pálido (24 miligramos, 49 por ciento de rendimiento).

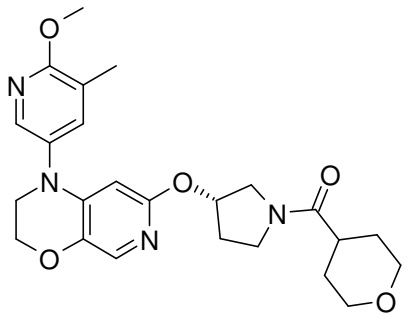
HPLC Rt_{M1} =0.74 minutos; ESIMS: 451 [$(M+H)^+$].

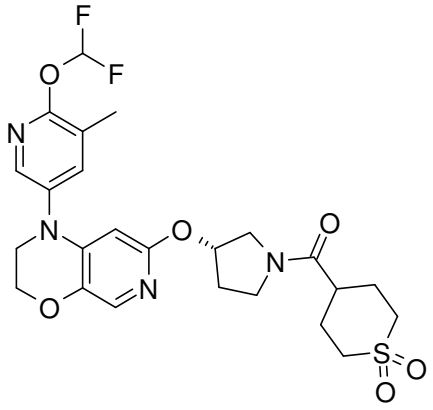
^{1}H RMN (400 MHz, DMSO): δ 8.00 (m, 1H), 7.58-7.63 (m, 3H), 7.53 (d, 1H), 5.51 (d, 1H), 5.29-5.40 (m, 1H), 4.23-4.29 (m, 2H), 3.99 (s, 3H), 3.77-4.19 (m, 2H), 3.66 (m, 5H), 3.39-3.63 (m, 2H), 2.15 (s, 3H), 1.89-2.11 (m, 2H).

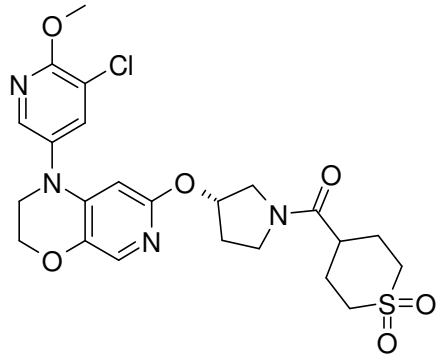
Ejemplos E2 a 11: Los compuestos enlistados en la Tabla 5 se prepararon mediante un procedimiento análogo a aquél empleado en el Ejemplo E1.

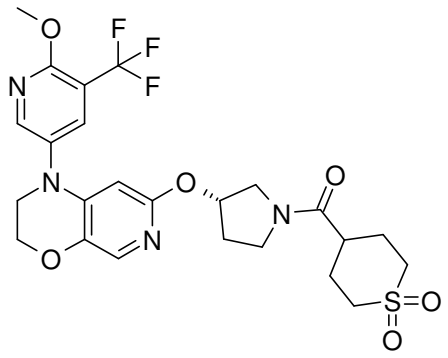
Tabla 5

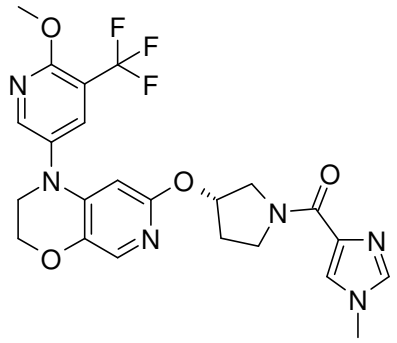
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
E2	 Terbutil-éster del ácido (S)-3-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-carboxílico Condición de aminación de Buchwald: CA4 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8, IA9, 127423-61-4	1.19 (M1)	443

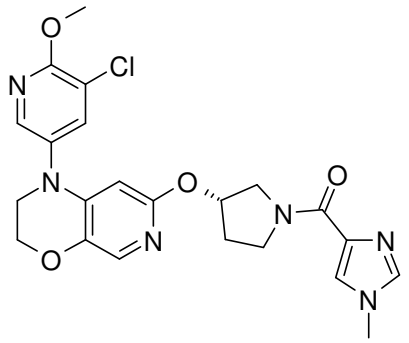
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
E3	 {(S)-3-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8, 127423-61-4, IA9, cloruro de acilo 40191-32-0	0.84 (M1)	455

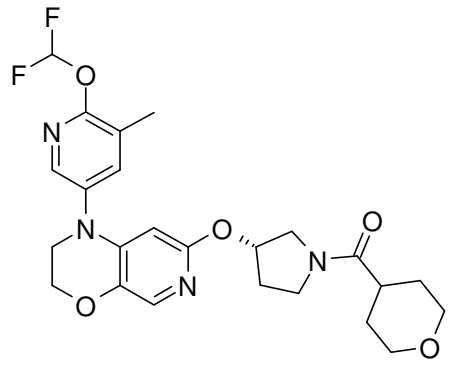
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
E4	 {(S)-3-[1-(6-difluoro-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8, IA8, 127423-61-4, 64096-87-3	1.09 (M1)	328

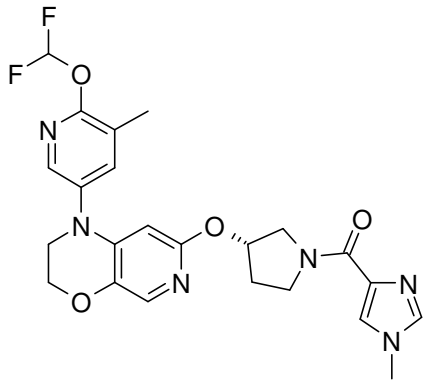
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
E5	 {(S)-3-[1-(5-cloro-6-metoxi-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8, 127423-61-4, IA11, 64096-87-3	0.79 (M1)	523

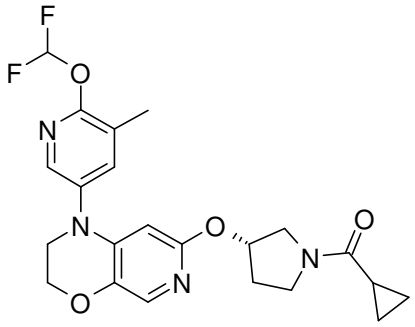
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
E6	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[1-(6-metoxi-5-trifluoro-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA21/ 64096-87-3	0.92 (M1)	557

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
E7	 {(S)-3-[1-(6-metoxi-5-trifluoro-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA21/ 41716-18-1	0.87 (M1)	505

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
E8	 {(S)-3-[1-(5-cloro-6-metoxi-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8, 127423-61-4, IA11, 41716-18-1	0.75 (M1)	471

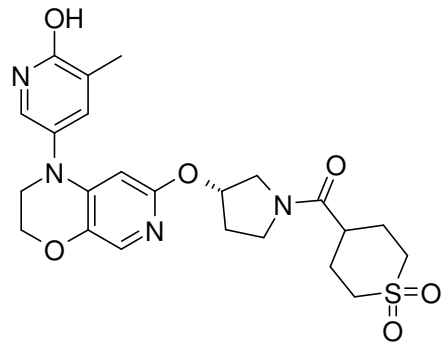
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
E9	 {(S)-3-[1-(6-difluoro-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA8 / 5337-03-1	0.95 (M1)	491

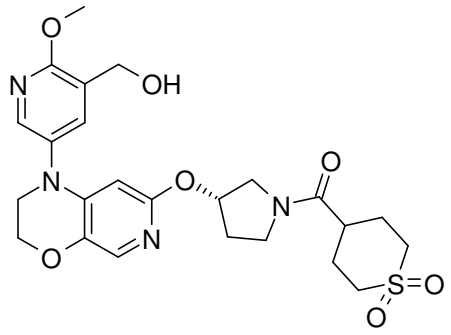
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
E10	 {(S)-3-[1-(6-difluoro-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA8 / 41716-18-1	0.84 (M1)	487

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
E11	 Ciclopropil-{(S)-3-[1-(6-difluoro-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA8 / cloruro de acilo: 4023-34-1	1.01 (M1)	447

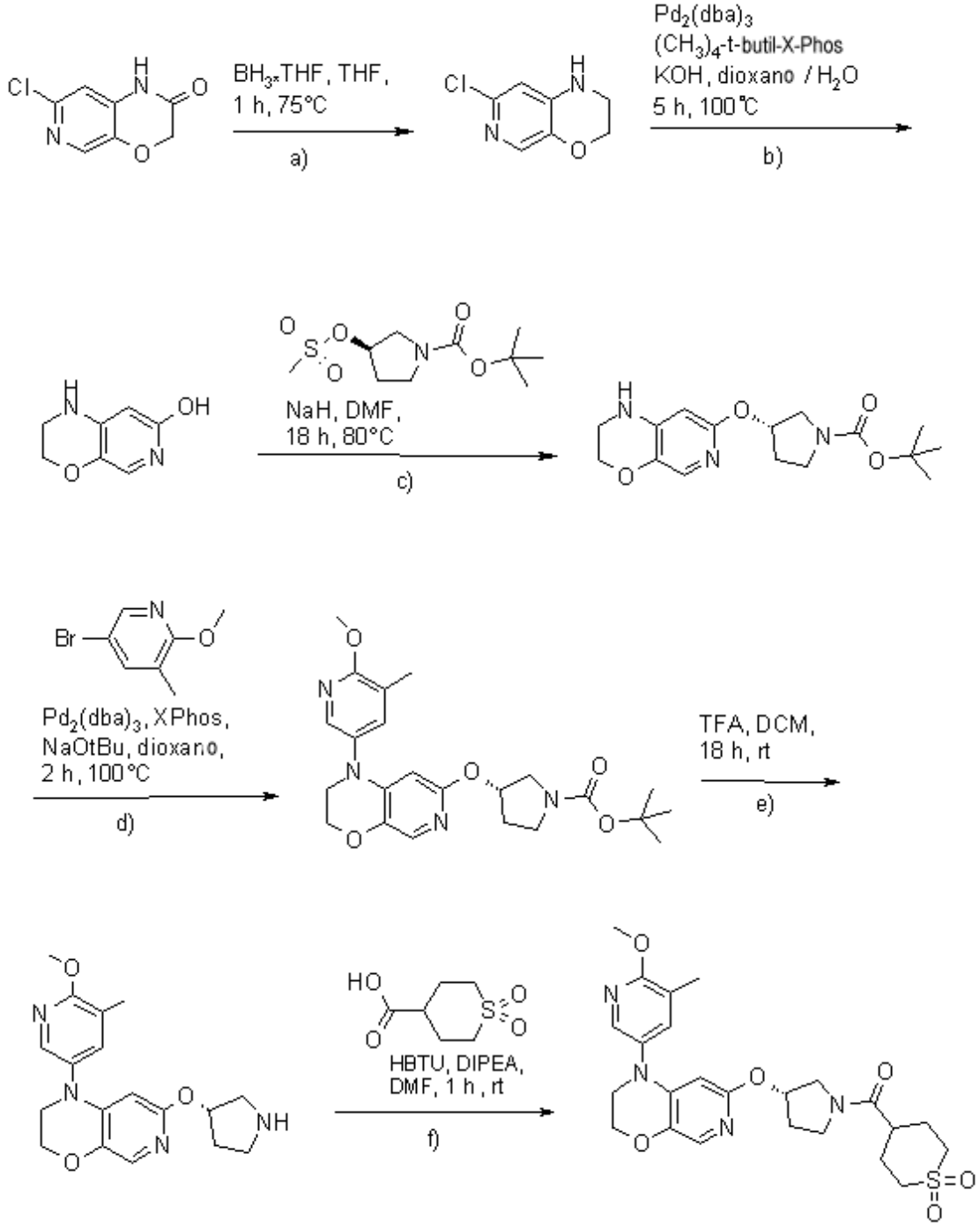
Ejemplos de Referencia E12 a E13: Los compuestos enlistados en la Tabla 5a se prepararon mediante un procedimiento análogo a aquél empleado en el Ejemplo E1, aplicando estrategias de grupos protectores adecuadas.

Tabla 5a

Ejemplo de Referencia	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
E12	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[1-(6-hidroxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB7 Condición de introducción de cadena lateral: CC1	**0.54 (M16)**	**489**

Ejemplo de Referencia	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA69 / 64096-87-3		
E13	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[1-(5-hidroxi-metil-6-metoxi-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB7 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8/127423-61-4/ IA70/ 64096-87-3	**0.63 (M16)**	**519**

<u>Ejemplo F1:</u> (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona (de acuerdo con el esquema 6)



a) 7-cloro-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina

Una solución de la 7-cloro-1H-pirido-[3,4-b][1,4]-oxazin-2-ona (CAS registro 928118-43-8) (3.70 gramos, 20 milimoles) en tetrahidrofurano (THF) (63 mililitros) se trató con BH_3*THF (1M en tetrahidrofurano (THF), 47 mililitros, 47 milimoles). La mezcla de reacción se agitó a 75°C durante 1 hora, entonces se enfrió a temperatura ambiente, y se apagó con metanol (24 mililitros, 600 milimoles). La mezcla de reacción se concentró bajo presión reducida, y el residuo se absorbió con EtOAc, y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre $MgSO_4$, se filtró, y se concentró bajo presión reducida, para proporcionar el producto del título como un sólido amarillo pálido (3.3 gramos, 96 por ciento de rendimiento).

UPLC Rt_{M1} =0.47 minutos; ESIMS: 171 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.53 (s, 1H), 7.11 (br s, 1H), 6.47 (s, 1H), 4.09 (t, 2H), 3.17-3.38 (m, 2H).

b) 2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-ol

Una mezcla de la 7-cloro-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina (1.08 gramos, 6.33 milimoles), una solución acuosa de KOH (1.07 gramos, 19 milimoles de KOH en 5.4 mililitros de agua), 2-diterbutil-fosfino-3,4,5,6-tetrametil-2',4',6-tri-i-propil-bifenilo al 98 por ciento (0.30 gramos, 0.63 milimoles), y $Pd_2(dba)_3$ (0.29 gramos, 0.32 milimoles) en dioxano (32.5 mililitros), se desgasificó tres veces con nitrógeno, el tubo se selló, y la mezcla de reacción se agitó a 100°C durante 5 horas. Después de enfriarse a temperatura ambiente, la

mezcla de reacción se filtró a través de Hyflo, y se enjuagó con EtOAc y metanol. Los filtrados se concentraron, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (dicloro-metano (DCM) / MeOH, de 98:2 a 75:25), como un residuo color naranja (660 miligramos, 69 por ciento de rendimiento).

UPLC Rt_{M1} =0.34 minutos; ESIMS: 153 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 10.33 (br s, 1H), 7.03 (br s, 1H), 6.71 (s, 1H), 5.15 (s, 1H), 3.95 (t, 2H), 3.25 (m, 2H).

c) Terbutil-éster del ácido (S)-3-(2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi)-pirrolidin-1-carboxílico

Una solución seca de 2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-ol (0.66 gramos, 4.34 milimoles), y terbutil-éster del ácido (R)-3-metan-sulfoniloxi-pirrolidin-1-carboxílico (CAS registro 127423-61-4) (1.73 gramos, 6.51 milimoles) en dimetil-formamida (DMF) (40 mililitros) se trató con hidruro de sodio (al 60 por ciento en aceite mineral, 0.21 gramos, 8.68 milimoles), y la mezcla de reacción se agitó a 80°C durante 18 horas. Después de enfriarse a temperatura ambiente, la mezcla de reacción se diluyó con el terbutil-metil-éter (TBME), y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre $MgSO_4$, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 95:5 a 30:70), como un aceite amarillo (1.035 gramos, pureza del 75 por ciento, 56 por ciento de rendimiento)

UPLC Rt_{M1} =0.65 minutos; ESIMS: 322 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 5.86 (s, 1H), 5.42 (br s, 1H), 4.25-4.41 (m, 1H), 4.19 (t, 2H), 3.38-3.66 (m, 6H), 2.00-2.18 (m, 2H), 1.46 (d, 9H).

d) Terbutil-éster del ácido (S)-3-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-carboxílico

Una mezcla del terbutil-éster del ácido (S)-3-(2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi)-pirrolidin-1-carboxílico (254 miligramos, 0.79 milimoles), 5-bromo-2-metoxi-3-metil-piridina (CAS registro 760207-87-2) (208 miligramos, 1.03 milimoles), XPhos (30 miligramos, 0.06 milimoles), y NaOtBu (167 miligramos, 1.74 milimoles) en dioxano (6 mililitros), se desgasificó con argón durante 5 minutos, y entonces se agregó $Pd_2(dba)_3$ (29 miligramos, 0.03 milimoles). El tubo se llenó con argón, se selló, y la mezcla de reacción se agitó a 100°C durante 2 horas. Después de enfriarse a temperatura ambiente, la mezcla de reacción se filtró a través de Hyflo, se enjuagó con EtOAc, y los filtrados se lavaron con una solución acuosa saturada de $NaHCO_3$. La capa acuosa se re-extrajo dos veces con EtOAc, las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron, se concentraron, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 100:0 a 50:50), como una goma transparente (274 miligramos, 78 por ciento de rendimiento).

UPLC Rt_{M1} =1.20 minutos; ESIMS: 443 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.61 (br s, 1H), 7.30-7.35 (m, 1H), 5.71 (s, 1H), 5.34-5.46 (m, 1H), 4.31 (br s, 2H), 3.99 (s, 3H), 3.68 (t, 2H), 3.34-3.62 (m, 4H), 2.23 (s, 3H), 2.01-2.09 (m, 2H), 1.44 (s, 9H).

e) 1-(6-metoxi-5-metil-piridin-3-il)-7-((S)-pirrolidin-3-iloxi)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina

Una solución del terbutil-éster del ácido (S)-3-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-carboxílico (364 miligramos, 0.82 milimoles) en dicloro-metano (DCM) (6 mililitros) se trató con ácido trifluoro-acético (TFA) (0.63 mililitros, 8.23 milimoles), y la mezcla de reacción se agitó a temperatura ambiente durante 18 horas, entonces se apagó con una solución acuosa saturada de $NaHCO_3$ y se extrajo con dicloro-metano (DCM). La capa orgánica se secó sobre $MgSO_4$, se filtró, y se concentró bajo presión reducida, para proporcionar el producto del título como un aceite color rojo, el cual se utilizó en el siguiente paso sin mayor purificación (313 miligramos, pureza del 90 por ciento, rendimiento cuantitativo).

UPLC Rt_{M1} =0.65 minutos; ESIMS: 343 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.93 (d, 1H), 7.62 (s, 1H), 7.32 (d, 1H), 5.70 (s, 1H), 5.26-5.36 (m, 1H), 4.31 (t, 2H), 3.99 (s, 3H), 3.67 (t, 2H), 2.95-3.15 (m, 3H), 2.81-2.92 (m, 1H), 2.22 (s, 3H), 1.98-2.10 (m, 1H), 1.79-1.90 (m, 1H).

f) (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[1-(6-

metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona

Una solución del ácido 1,1-dioxo-hexahidro-1lambda*6*-tio-piran-4-carboxílico (CAS registro 64096-87-3) (106 miligramos, 0.59 milimoles) en dimetil-formamida (DMF) (4 mililitros) se trató con HBTU (225 miligramos, 0.59 milimoles), y di-isopropil-etil-amina (DIPEA) (0.24 mililitros, 1.37 milimoles). La solución color naranja resultante se agitó a temperatura ambiente durante 5 minutos, y entonces se agregó una solución de la 1-(6-metoxi-5-metil-piridin-3-il)-7-((S)-pirrolidin-3-iloxi)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina (156 miligramos, 0.46 milimoles) en dimetil-formamida (DMF) (2 mililitros). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora, entonces se concentró bajo presión reducida, y el residuo se absorbió con dicloro-metano (DCM), y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó pasándola a través de un cartucho de separación de fases, se concentró, y se obtuvo el compuesto del título después de la cromatografía SFC (columna DEAP (250 milímetros x 30 milímetros, 60A, 5 micras) Princeton, gradiente del 11 al 16 por ciento de metanol en CO_2 súper-crítico en 6 minutos), como un sólido ligeramente coloreado (112 miligramos, 49 por ciento de rendimiento).

UPLC Rt_{M1} =0.81 minutos; ESIMS: 503 [$(M+H)^+$].

^1H RMN (400 MHz, DMSO-d_6): δ 8.01 (s, 1H), 7.61 (m, 1H), 7.52 (d, 1H), 5.52 (d, 1H), 5.24-5.43 (m, 1H), 4.26 (br s, 2H), 3.89 (s,

3H), 3.59-3.79 (m, 3H), 3.41-3.56 (m, 2H), 3.21-3.39 (m, 1H), 2.98-3.21 (m, 4H), 2.67-2.83 (m, 1H), 1.84-2.20 (m, 9H).

^{1}H RMN (600 MHz, DMSO-d_6): δ 8.01 (s, 1H), 7.63-7.59 (m, 1H), 7.55-7.51 (m, 1H), 5.55-5.51 (m, 1H), 5.43-5.24 (m, 1H), 4.29-4.22 (m, 2H), 3.90 (s, 3H), 3.80-3.60 (m, 2H), 3.56-3.37 (m, 3H), 3.28-2.99 (m, 5H), 2.89-2.66 (m, 1H), 2.19-2.09 (m, 4H), 2.08-1.98 (m, 2H), 1.98-1.86 (m, 3H).

Cristalización del Ejemplo F1 mediante calentamiento y enfriamiento en isopropanol / dietil-éter

474 miligramos del Ejemplo F1 amorfo se suspendieron en 1.4 mililitros de isopropanol. La mezcla se calentó a 70°C, y se agitó a 70°C para permitir la disolución completa del Ejemplo F1. La solución se enfrió a temperatura ambiente, se formó un residuo pegajoso. Se agregaron 2 mililitros de dietil-éter, y la pasta acuosa se agitó durante 48 horas. Se formó una suspensión blanca. La suspensión se filtró y el sólido se secó a 40°C, 15 mbar. Se obtuvo un polvo blanco fino. El material contuvo solamente un ligero solvente residual (<0.5 por ciento). Se obtuvo una forma cristalina anhidra del Ejemplo F1 con un punto de fusión de fraguado de 148.77°C.

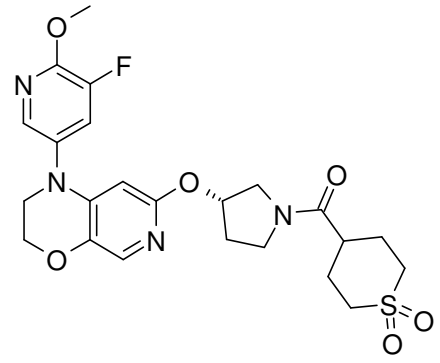
Lista de los picos 2-Theta más significativos a partir del patrón de difracción en polvo de rayos-X con tolerancias de ±0.5 de la forma anhidra del Ejemplo F1 (Método M1) (incluyendo los picos bajos/ débiles para información). Nota: Esta lista de picos no es exhaustiva sino que son solamente “entre otros”.

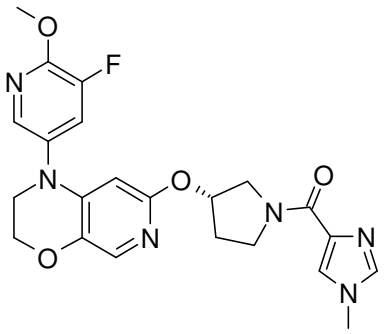
2-Theta en grados	Intensidad
9.1	Baja
10.2	Media
11.9	Media
13.0	Baja
17.1	Fuerte
17.7	Media, no resuelta
18.7	Media
20.3	Media, no resuelta
20.8	Media, no resuelta
26.0	Media/baja
26.7	Media
23.2	Media/baja
24.1	Media/baja
24.8	Media/baja
29.3	Media/baja

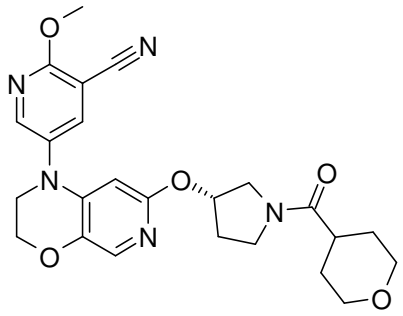
2-Theta en grados	Intensidad
27.4	Media/baja
21.4	Media/baja

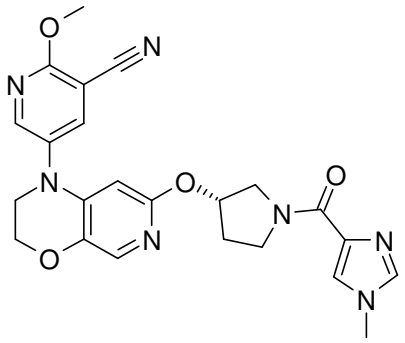
Ejemplos F2 a F15: Los compuestos enlistados en la Tabla 6 se prepararon mediante un procedimiento análogo a aquél empleado en el Ejemplo F1.

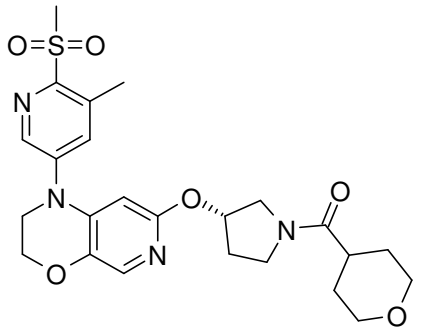
Tabla 6

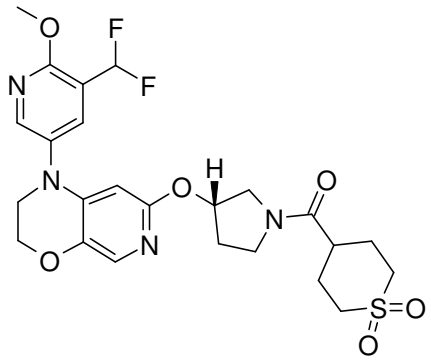
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F2	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[1-(5-fluoro-6-metoxi-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona	0.79 (M1)	507

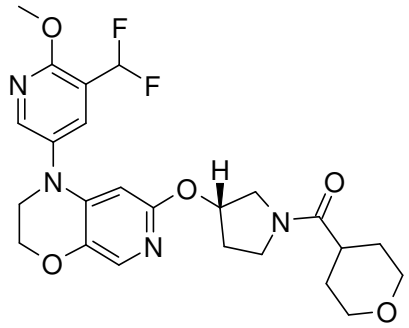
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
	Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB2 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4/IA10/ 64096-87-3		
F3	 {(S)-3-[1-(5-fluoro-6-metoxi-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB2 Condición de introducción de cadena	0.73 (M1)	455

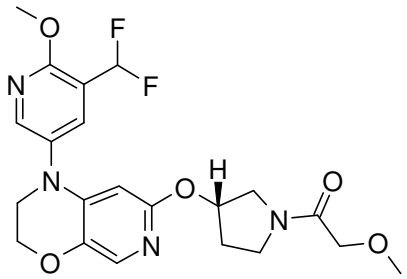
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
	lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4/IA10/ 41716-18-1		
F4	 2-metoxi-5-{7-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-pirido-[3,4-b][1,4]-oxazin-1-il}-nicotinonitrilo Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8, 127423-61-4, IA12, cloruro de acilo 40191-32-0	0.83 (M1)	466

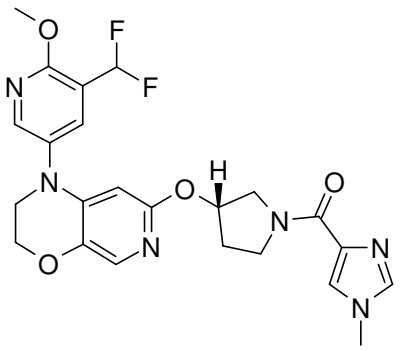
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F5	 2-metoxi-5-{7-[(S)-1-(1-metil-1H-imidazol-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-pirido-[3,4-b][1,4]-oxazin-1-il}-nicotinonitrilo Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8, 127423-61-4, IA12, 41716-18-1	0.73 (M1)	462

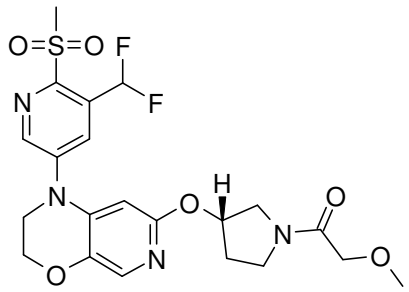
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F6	 {(S)-3-[1-(6-metan-sulfonil-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8, 127423-61-4, IA1, cloruro de acilo 40191-32-0	0.76 (M1)	503

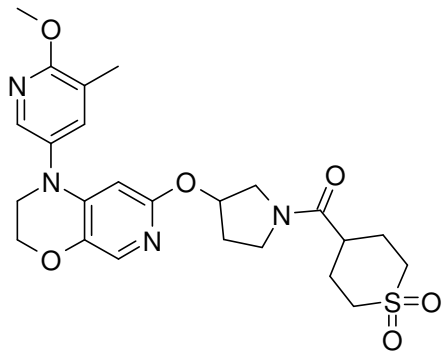
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F7	 {(S)-3-[1-(5-difluoro-metil-6-metoxi-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB2 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA6 / 64096-87-3	0.82 (M1)	539

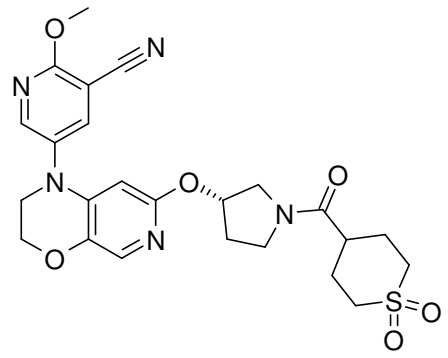
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F8	 {(S)-3-[1-(5-difluoro-metil-6-metoxi-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA6 / cloruro de acilo 40191-32-0	0.88 (M1)	491

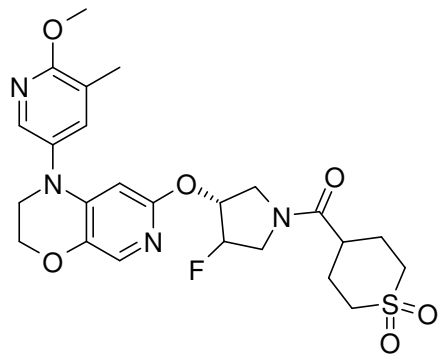
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F9	 1-{(S)-3-[1-(5-difluoro-metil-6-metoxi-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-2-metoxi-etanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA6 / cloruro de acilo: 38870-89-2	0.83 (M1)	451

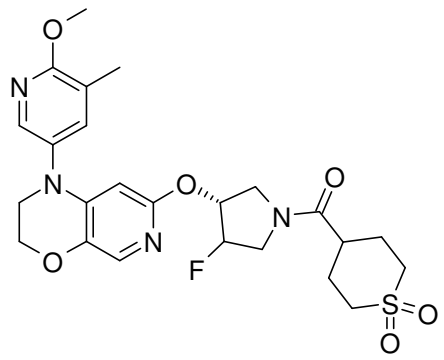
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F10	 {(S)-3-[1-(5-difluoro-metil-6-metoxi-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB3 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA6 / 41716-18-1	0.77 (M1)	487

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F11	 1-{(S)-3-[1-(5-difluoro-metil-6-metan-sulfonil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-2-metoxi-etanona Condición de aminación de Buchwald: CA1 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 127423-61-4 / IA4 / cloruro de acilo: 38870-89-2	0.76 (M1)	499

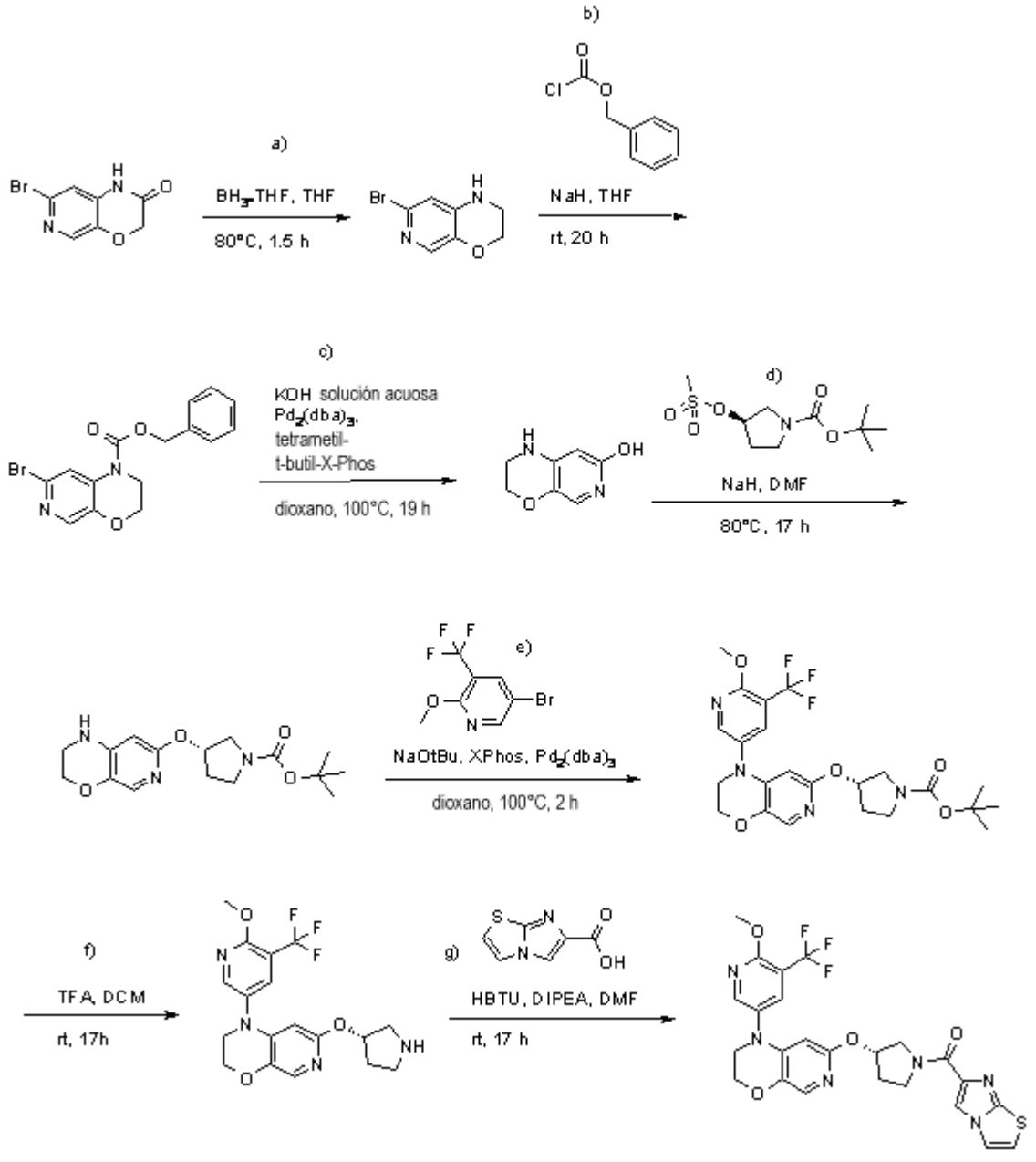
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F12	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{3-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA4 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8 / 141699-57-2 / IA9 / 64096-87-3	0.81 (M1)	503

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F13	 5-{7-[(S)-1-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-pirido-[3,4-b][1,4]-oxazin-1-il}-2-metoxi-nicotinonitrilo Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 928118-43-8, 127423-61-4, IA12,64096-87-3	1.12 (M1)	454

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F14	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(R)-3-fluoro-4-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 869481-93-6 / 1174020-51-9 Método de separación quiral: CD12	0.89 (M1) 35.9 (CD12)	521

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
F15	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(R)-3-fluoro-4-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 869481-93-6 / 1174020-51-9 Método de separación quiral: CD12	0.89 (M1) 45.8 (CD12)	521

Ejemplo G1: **Imidazo-[2,1-b]-tiazol-6-il-{(S)-3-[1-(6-metoxi-5-trifluoro-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona**



a) 7-bromo-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina

Una solución de la 7-bromo-1H-pirido-[3,4-b][1,4]-oxazin-2-ona (CAS registro 943995-72-0) (2.93 gramos, 12.79 milimoles) en tetrahidrofurano (THF) (40 mililitros) se trató con BH_3*THF (1M en tetrahidrofurano (THF), 30 mililitros, 30 milimoles). La mezcla de reacción se agitó a 80°C durante 1.5 horas, entonces se enfrió a temperatura ambiente, y se apagó con metanol. La mezcla de reacción se concentró bajo presión reducida, y el residuo se absorbió con EtOAc, y se lavó con una solución acuosa de NaOH 1M. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró bajo presión reducida, para proporcionar el producto del título como un sólido blanco. (2.48 gramos, 90 por ciento de rendimiento).

UPLC Rt_{M1} =0.49 minutos; ESIMS: 217 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 6.60 (s, 1H), 4.42 (br s, 1H), 4.20-4.24 (m, 2H), 3.49 (m, 2H).

b) Bencil-éster del ácido 7-bromo-2,3-dihidro-pirido-[3,4-b][1,4]-oxazin-1-carboxílico

Una solución seca de la 7-bromo-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina (1.85 gramos, 8.60 milimoles) en tetrahidrofurano (THF) (50 mililitros) se trató en porciones a 0°C con NaH al 60 por ciento en aceite mineral (0.52 gramos, 12.90 milimoles), y la mezcla de reacción se agitó a 0°C durante 1 hora. Se agregó por goteo cloroformato de bencilo (CAS registro 501-53-1) (1.40 mililitros, 9.85 milimoles), y la mezcla de reacción se dejó calentar a temperatura

ambiente, y se agitó durante 20 horas; finalmente se apagó con metanol, y entonces se diluyó con una solución acuosa saturada de $NaHCO_3$ y se extrajo con EtOAc. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 100:0 a 60:40), como un sólido blanco (2.06 gramos, 68 por ciento de rendimiento).

UPLC Rt_{M1} =1.14 minutos; ESIMS: 349 [$(M+H)^+$].

^1H RMN (400 MHz, $CDCl_3$): δ 8.28 (br s, 1H), 7.98 (s, 1H), 7.35-7.46 (m, 5H), 5.30 (s, 2H), 4.20-4.27 (m, 2H), 3.92-4.01 (m, 2H).

c) 2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-ol

Una mezcla del bencil-éster del ácido 7-bromo-2,3-dihidro-pirido-[3,4-b][1,4]-oxazin-1-carboxílico (1.27 gramos, 3.63 milimoles), una solución acuosa de KOH (0.90 gramos, 16 milimoles de KOH en 3.2 mililitros de agua), y 2-diterbutil-fosfino-3,4,5,6-tetrametil-2',4',6-tri-i-propil-bifenilo al 98 por ciento (0.26 gramos, 0.54 milimoles) en dioxano (16 mililitros), se desgasificó con argón durante 5 minutos, y entonces se agregó $Pd_2(dba)_3$ (0.25 gramos, 0.27 milimoles). El tubo se llenó con argón, entonces se selló, y la mezcla de reacción se agitó a 100°C durante 19 horas. Después de enfriarse a temperatura ambiente, la mezcla de reacción se filtró a través de Hyflo, y se enjuagó con EtOAc y metanol. Los filtrados se secaron sobre Na_2SO_4, se filtraron, se concentraron, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (dicloro-metano (DCM) / MeOH, de 95:5 a 60:40), como

un residuo color naranja (262 miligramos, 47 por ciento de rendimiento).

UPLC Rt_{M1} =0.32 minutos; ESIMS: 153 [$(M+H)^+$]

^{1}H RMN (400 MHz, DMSO-d_6): δ 10.33 (br.s, 1H), 7.03 (br.s, 1H), 6.71 (s, 1H), 5.15 (s, 1H), 3.95 (t, 2H), 3.25 (td, 2H).

d) Terbutil-éster del ácido (S)-3-(2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi)-pirrolidin-1-carboxílico

Una solución seca del 2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-ol (200 miligramos, 0.66 milimoles), y terbutil-éster del ácido (R)-3-metan-sulfoniloxi-pirrolidin-1-carboxílico (CAS registro 127423-61-4) (262 miligramos, 0.99 milimoles) en dimetil-formamida (DMF) (6 mililitros) se trató con hidruro de sodio al 60 por ciento en aceite mineral (53 miligramos, 1.33 milimoles), y la mezcla de reacción se agitó a 80°C durante 17 horas. Después de enfriarse a temperatura ambiente, la mezcla de reacción se diluyó con el terbutil-metil-éter (TBME), y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 88:12 a 0:100), como un aceite (140 miligramos, 66 por ciento de rendimiento).

UPLC Rt_{M1} =0.66 minutos; ESIMS: 322 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 5.86 (s, 1H), 5.42 (br.s, 1H), 4.25-4.41 (m, 1H), 4.19 (t, 2H), 3.38-3.66 (m, 6H), 2.00-2.18 (m, 2H), 1.46 (d, 9H).

e) Terbutil-éster del ácido (S)-3-[1-(6-metoxi-5-trifluoro-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-carboxílico

Una mezcla del terbutil-éster del ácido (S)-3-(2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi)-pirrolidin-1-carboxílico (115 miligramos, 0.36 milimoles), 5-bromo-2-metoxi-3-trifluoro-metil-piridina (CAS registro 1214377-42-0) (119 miligramos, 0.47 milimoles), XPhos (14 miligramos, 0.03 milimoles), y NaOtBu (76 miligramos, 0.79 milimoles) en dioxano (2.5 mililitros), se desgasificó con argón durante 5 minutos, y entonces se agregó $Pd_2(dba)_3$ (13 miligramos, 0.01 milimoles). El tubo se llenó con argón, entonces se selló, y la mezcla de reacción se agitó a 100°C durante 2 horas. Después de enfriarse a temperatura ambiente, la mezcla de reacción se filtró a través de Hyflo, se enjuagó con EtOAc, y los filtrados se lavaron con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 93:7 a 40:60), como una goma transparente. (91 miligramos, 51 por ciento de rendimiento).

UPLC Rt_{M1} =1.27 minutos; ESIMS: 497 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.29 (d, 1H), 7.79 (d, 1H), 7.64 (d, 1H), 5.70 (s, 1H), 5.36-5.46 (m, 1H), 4.34 (br s, 2H), 4.09 (s, 3H), 3.70 (t, 2H), 3.34-3.62 (m, 4H), 2.02-2.11 (m, 2H), 1.44 (s, 9H).

f) 1-(6-metoxi-5-trifluoro-metil-piridin-3-il)-7-((S)-pirrolidin-3-iloxi)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina

Una solución del terbutil-éster del ácido (S)-3-[1-(6-metoxi-5-trifluoro-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-carboxílico (88 miligramos, 0.18 milimoles) en dicloro-metano (DCM) (1.3 mililitros) se trató con ácido trifluoro-acético (TFA) (0.14 mililitros, 1.77 milimoles), y la mezcla de reacción se agitó a temperatura ambiente durante 17 horas, entonces se apagó con una solución acuosa saturada de Na_2CO_3 y se extrajo con dicloro-metano (DCM). La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró bajo presión reducida, para proporcionar el compuesto del título (66 miligramos, 94 por ciento de rendimiento).

UPLC Rt_{M1} =0.72 minutos; ESIMS: 397 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.28 (d, 1H), 7.79 (d, 1H), 7.65 (s, 1H), 5.68 (s, 1H), 5.31-5.39 (m, 1H), 4.31-4.37 (m, 2H), 4.08 (s, 3H), 3.67-3.72 (m, 2H), 3.01-3.18 (m, 3H), 2.85-2.97 (m, 1H), 2.01-2.13 (m, 1H), 1.82-1.95 (m, 1H).

g) Imidazo-[2,1-b]-tiazol-6-il-{(S)-3-[1-(6-metoxi-5-trifluoro-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona

Una solución del ácido imidazo-[2,1-b]-tiazol-6-carboxílico, y bromhidrato (1:1) (CAS registro 725234-39-9) (25 miligramos, 0.10 milimoles) en dimetil-formamida (DMF) (0.45 mililitros) se trató con HBTU (41 miligramos, 0.11 milimoles), y di-isopropil-etil-amina

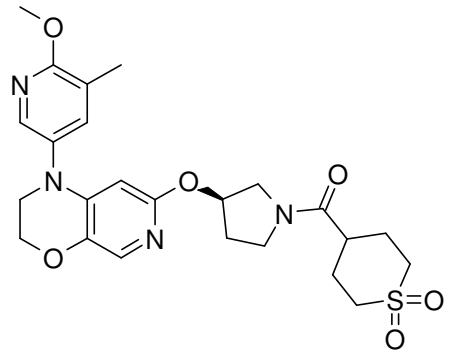
(DIPEA) (0.04 mililitros, 0.21 milimoles). La solución color naranja resultante se agitó a temperatura ambiente durante 5 minutos, y entonces se agregó una solución de 1-(6-metoxi-5-trifluoro-metil-piridin-3-il)-7-((S)-pirrolidin-3-iloxi)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazina (32 miligramos, 0.08 milimoles) en dimetil-formamida (DMF) (0.45 mililitros). La mezcla de reacción se agitó a temperatura ambiente durante 17 horas, entonces se concentró bajo presión reducida, y el residuo se absorbió con EtOAc, y se lavó con salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la HPLC de preparación en fase inversa (RP) (Sunfire Prep C18, 30 x 100 milímetros, 5 micras; solvente A: H_2O + ácido trifluoro-acético (TFA) al 0.1 por ciento por volumen; solvente B: CH_3CN + ácido trifluoro-acético (TFA) al 0.1 por ciento por volumen, gradiente del 15 al 45 por ciento de B en 16 minutos).Después de la filtración sobre un cartucho SPE Agilent PL-HCO_3 MP, se obtuvo el compuesto del título como un sólido (23 miligramos, 52 por ciento de rendimiento).

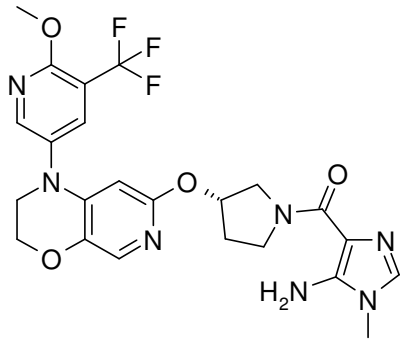
UPLC Rt_{M1} =1.00 minutos; ESIMS: 547 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.49 (dd, 1H), 8.16-8.20 (m, 2H), 7.92 (dd, 1H), 7.57 (d, 1H), 7.37 (dd, 1H), 5.63 (d, 1H), 5.33-5.45 (m, 1H), 4.25-4.31 (m, 2H), 3.52-4.14 (m, 9H), 1.88-2.12 (m, 2H).

Ejemplos G2 a G3: Los compuestos enlistados en la Tabla 7 se prepararon mediante un procedimiento análogo a aquél empleado en el Ejemplo G1.

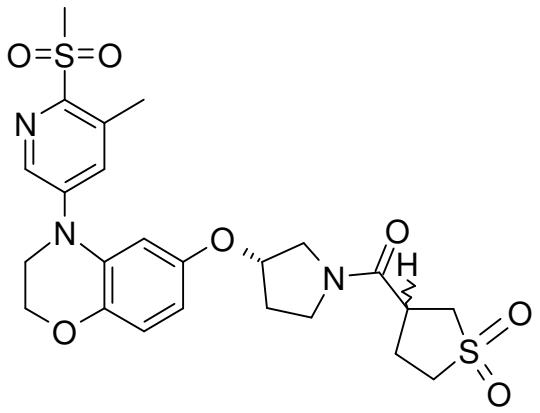
Tabla 7

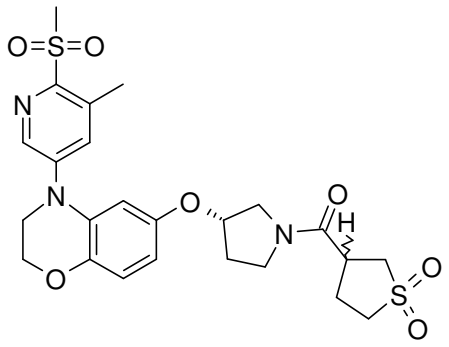
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
G2	 (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(R)-3-[1-(6-metoxi-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA2 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 943995-72-0 / 132945-75-6 / IA9 / 64096-87-3	0.80 (M1)	503

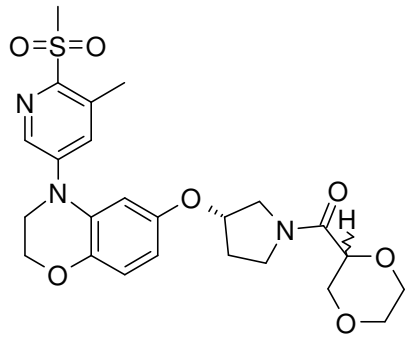
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
G3	 (5-amino-1-metil-1H-imidazol-4-il)-{(S)-3-[1-(6-metoxi-5-trifluoro-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona Condición aminación Buchwald: CA2 Condición de enlace de amida: CB1 Condición de introducción de cadena lateral: CC1 Precursores utilizados: CAS 943995-72-0 / 127423-61-4 / IA21) / IB3) / Producto obtenido después de la reacción de disociación de Boc utilizando ácido trifluoro-acético (TFA) en CH_2Cl_2 hecha de una forma convencional	0.86 (M1M1)	520

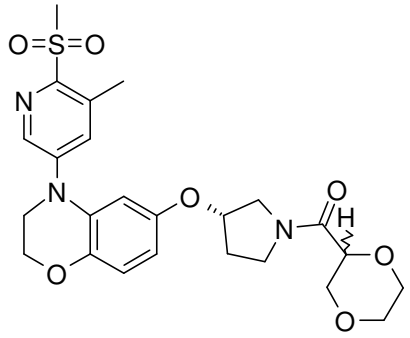
Ejemplos H1 a H16: Los compuestos enlistados en la Tabla 8 se prepararon mediante la separación cromatográfica de los diaestereómeros.

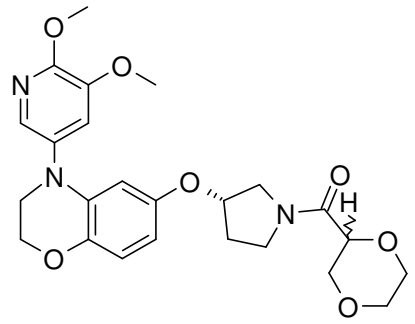
Tabla 8

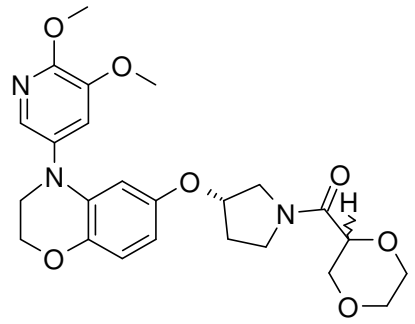
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H1	 (1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-{(S)-3-[1-(6-metan-sulfonil-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2	0.87 (M2)	531

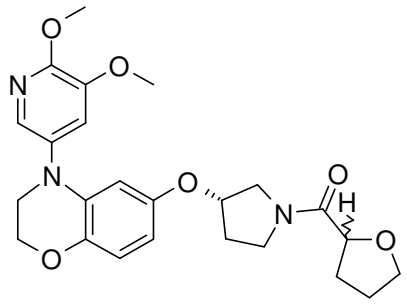
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	Precursores utilizados: IA1,CAS 127423-61-4 / 64096-87-3 Método de separación quiral: CD5		
H2	 (1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-{(S)-3-[1-(6-metan-sulfonil-5-metil-piridin-3-il)-2,3-dihidro-1H-pirido-[3,4-b][1,4]-oxazin-7-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA1,CAS	0.87 (M2)	536

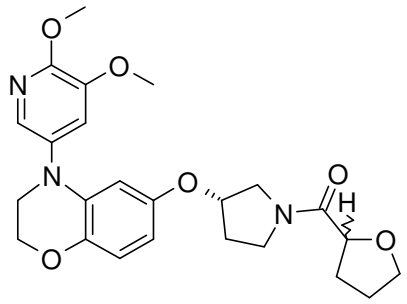
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; (M+1)+]
	127423-61-4 / 64096-87-3 Método de separación quiral: CD5		
H3	 [1,4]-dioxan-2-il-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA1,CAS 127423-61-4 / 89364-41-0 Método de separación quiral: CD6	0.88 (M2)	504

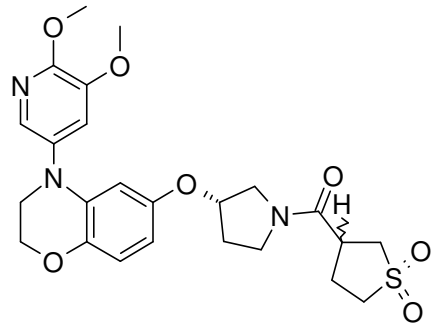
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H4	 [1,4]-dioxan-2-il-{(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA1),CAS 127423-61-4 / 89364-41-0 Método de separación quiral: CD6	0.88 (M2)	504

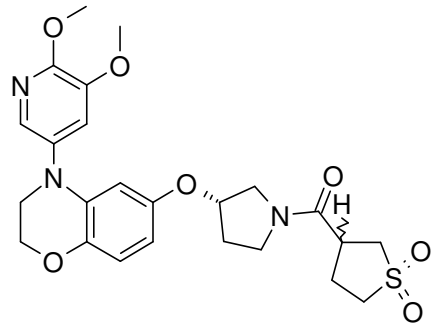
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H5	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-[1,4]-dioxan-2-il-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA31, CAS 52605-98-8, 127423-61-4/ 89364-41-0 Método de separación quiral: CD1	0.91 (M2)	472

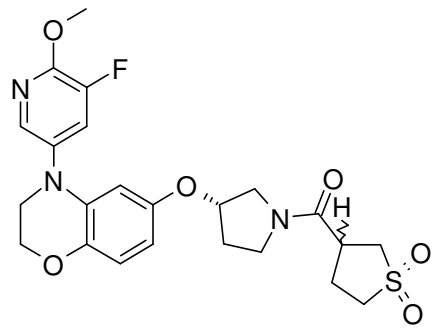
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H6	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-[1,4]-dioxan-2-il-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA31,CAS 52605-98-8, 127423-61-4/ 89364-41-0 Método de separación quiral: CD1	0.91 (M2)	472

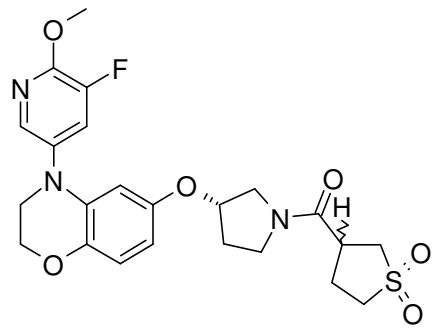
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H7	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidrofuran-2-il)-metanona Condición de aminación de Buchwald: CA9 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA29, CAS 52605-98-8, 127423-61-4 / 1264293-76-6 Método de separación quiral: CD1	0.91 (M2)	472

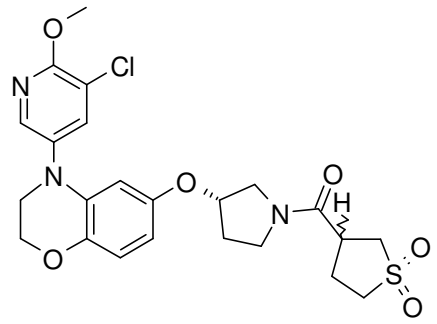
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H8	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidrofuran-2-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA29, CAS 52605-98-8, 127423-61-4 / 1264293-76-6 Método de separación quiral: CD1	0.91 (M2)	472

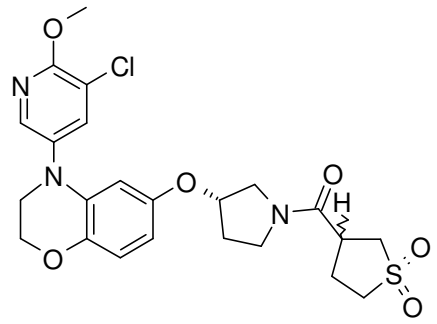
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H9	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA29, CAS 52605-98-8, 127423-61-4/ 64096-87-3 Método de separación quiral: CD1	0.91 (M2)	504

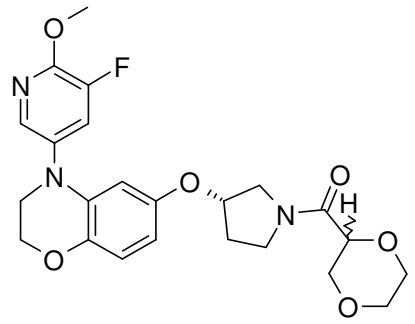
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H10	 {(S)-3-[4-(5,6-dimetoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB4 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA29, CAS 52605-98-8, 127423-61-4/ 64096-87-3 Método de separación quiral: CD1	0.91 (M2)	504

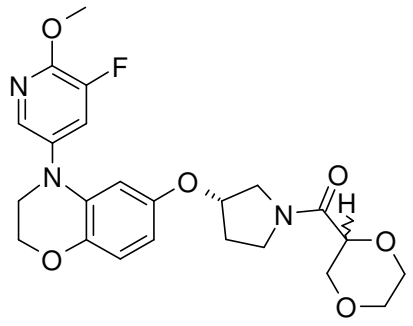
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H11	 (1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA10,CAS 124432-70-8, 127423-61-4 / 64096-87-3 Método de separación quiral: CD1	3.26 (M2)	492

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H12	 (1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA10,CAS 124432-70-8, 127423-61-4 / 64096-87-3 Método de separación quiral: CD1	3.25 (M2)	492

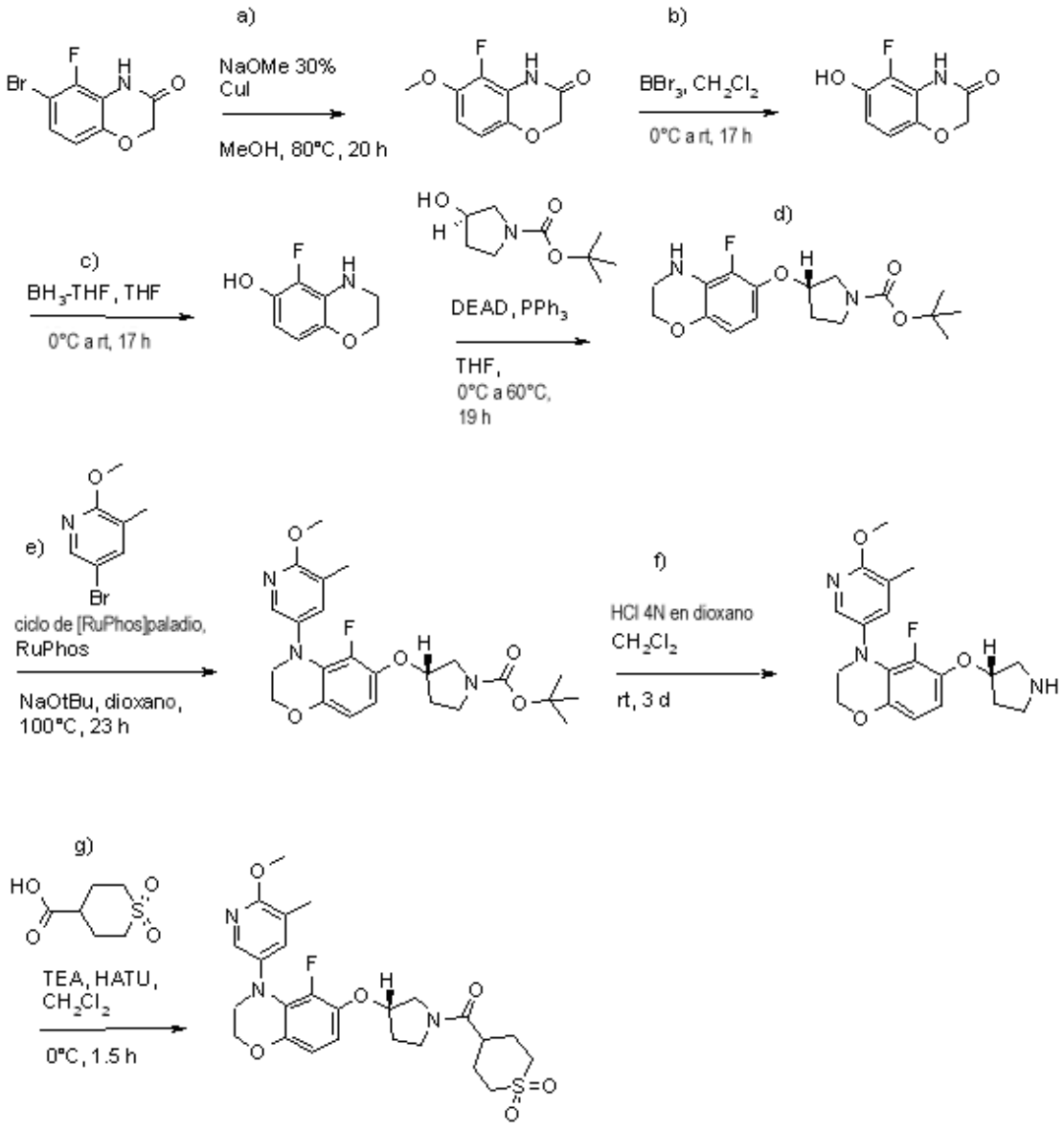
Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H13	 {(S)-3-[4-(5-cloro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA11,CAS 848366-28-9, 127423-61-4 / 64096-87-3 Método de separación quiral: CD2	3.52 (M2)	508

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H14	 {(S)-3-[4-(5-cloro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-tetrahidro-1lambda*6*-tiofen-3-il)-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA11,CAS 848366-28-9, 127423-61-4 / 64096-87-3 Método de separación quiral: CD2	3.52 (M2)	508

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H15	 [1,4]-dioxan-2-il-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA10,CAS 124432-70-8, 127423-61-4 / 89364-41-0 Método de separación quiral: CD1	3.28 (M2)	460

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
H16	 [1,4]-dioxan-2-il-{(S)-3-[4-(5-fluoro-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB5 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IA10,CAS 124432-70-8, 127423-61-4 / 89364-41-0 Método de separación quiral: CD1	3.32 (M2)	460

Ejemplo I1: **(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[5-fluoro-4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona**



a) 5-fluoro-6-metoxi-4H-benzo-[1,4]-oxazin-3-ona

Una solución de la 6-bromo-5-fluoro-4H-benzo-[1,4]-oxazin-3-

ona (CAS registro 1029421-36-0) (5.0 gramos, 20 milimoles) en metanol (10 mililitros) se trató con una solución de metóxido de sodio (al 30 por ciento en MeOH, 11.3 mililitros, 61 milimoles), y CuI (0.4 gramos, 2 milimoles). Después de agitar durante 20 horas a 80°C, la reacción se apagó con una solución acuosa saturada de $NaHCO_3$, y se extrajo con EtOAc. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró bajo presión reducida, para obtener un sólido amarillo pálido. (2.2 gramos, 92 por ciento de rendimiento).

UPLC Rt_{M1} =0.64 minutos.

^1H RMN (400 MHz, DMSO-d_6): δ 6.74 (m, 2H), 4.53 (s, 2H), 3.79 (s, 3H).

b) 5-fluoro-6-hidroxi-4H-benzo-[1,4]-oxazin-3-ona

Una solución de la 5-fluoro-6-metoxi-4H-benzo-[1,4]-oxazin-3-ona (2.0 gramos, 10 milimoles) en dicloro-metano (DCM) (50 mililitros) se trató a 0°C con tribromuro de boro (9.6 mililitros, 101 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 17 horas, entonces se enfrió a 0°C, y se apagó con metanol. La mezcla se concentró bajo presión reducida, y el residuo se absorbió con EtOAc, y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se lavó con una solución acuosa de $Na_2S_2O_4$ al 10 por ciento, se secó sobre Na_2SO_4, se filtró, y se concentró bajo presión reducida. Se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (hexano / EtOAc, de 100:0 a 60:40), como un sólido color café (780 miligramos, 42 por ciento de rendimiento).

UPLC Rt_{M1} =0.49 minutos; ESIMS: 228 [$(M+HCOO)^-$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 11.00 (s, 1H), 6.65 (d, 1H), 6.45 (t, 1H), 4.50 (s, 2H).

c) 5-fluoro-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol

Una solución de la 5-fluoro-6-hidroxi-4H-benzo-[1,4]-oxazin-3-ona (780 miligramos, 4.2 milimoles) en tetrahidrofurano (THF) (10 mililitros) se trató con BH_3*THF (1M en tetrahidrofurano (THF), 12.8 mililitros, 12.8 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 17 horas, entonces se enfrió a 0°C, y se apagó con metanol (30 mililitros). La mezcla de reacción se concentró bajo presión reducida, para obtener un aceite color café (720 miligramos, rendimiento cuantitativo).

UPLC Rt_{M1} =0.54 minutos; ESIMS: 170 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 6.45 (d, 1H), 6.00 (t, 1H), 4.09 (m, 2H), 3.45 (m, 2H).

d) Terbutil-éster del ácido (S)-3-(5-fluoro-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi)-pirrolidin-1-carboxílico

Una solución de trifenil-fosfina (1.5 gramos, 5.7 milimoles) en tetrahidrofurano (THF) (20 mililitros) se trató a 0°C con azodicarboxilato de dietilo (0.900 mililitros, 5.69). La solución color naranja se agitó durante 10 minutos a temperatura ambiente, y entonces se agregaron 5-fluoro-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol (740 miligramos, 4.37 milimoles), y (R)-3-hidroxi-pirrolidin-1-carboxilato de terbutilo (1,065 miligramos, 5.69 milimoles). La mezcla de reacción se agitó durante 19 horas a 60°C, y entonces se

concentró bajo presión reducida. Se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (Hexano / EtOAc, de 100:0 a 70:30), como un aceite incoloro (1.1 gramos, 74 por ciento de rendimiento).

UPLC Rt_{M1} =1.07 minutos; ESIMS: 339 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 6.45 (d, 1H), 6.00 (t, 1H), 5.42 (br.s, 1H), 4.25-4.41 (m, 1H), 4.19 (t, 2H), 3.38-3.66 (m, 6H), 2.00-2.18 (m, 2H), 1.46 (d, 9H).

e) Terbutil-éster del ácido (S)-3-[5-fluoro-4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carboxílico

Una mezcla del terbutil-éster del ácido (S)-3-(5-fluoro-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi)-pirrolidin-1-carboxílico (100 miligramos, 0.296 milimoles), 5-bromo-2-metoxi-3-metil-piridina (CAS registro 760207-87-2, 179 miligramos, 0.887 milimoles), RuPhos (6.90 miligramos, 0.015 milimoles), NaOtBu (85 miligramos, 0.887 milimoles), y (2-diciclohexil-fosfino-2'6'-di-isopropil-11'-bifenil)-(2-(2-amino-etil)-fenil)-paladio(II) (12.07 miligramos, 0.015 milimoles) en dioxano (2 mililitros) se desgasificó con argón, entonces se selló, y la mezcla de reacción se agitó a 100°C durante 23 horas. Después de enfriarse a temperatura ambiente, la mezcla de reacción se filtró a través de Hyflo, se enjuagó con EtOAc, y los filtrados se lavaron con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea

sobre gel de sílice (Hexano / EtOAc, de 100:0 a 70:30), como un aceite amarillo(123 miligramos, rendimiento del 63 por ciento).

UPLC Rt_{M1} =1.29 minutos; ESIMS: 460 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.75 (d, 1H),7.45 (d, 1H), 6.55 (t, 1H), 6.35 (d, 1H), 4.75 (m, 1H), 4.15 (t, 2H), 3.84 (s, 3H), 3.60 (t, 2H), 3.38-3.66 (m, 4H), 2.12 (s, 3H), 2.00-2.18 (m, 2H), 1.46 (d, 9H).

f) 5-fluoro-4-(6-metoxi-5-metil-piridin-3-il)-6-((S)-pirrolidin-3-iloxi)-3,4-dihidro-2H-benzo-[1,4]-oxazina

Una solución del terbutil-éster del ácido (S)-3-[5-fluoro-4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carboxílico (123 miligramos, 0.185 milimoles) en dicloro-metano (DCM) (2 mililitros) se trató con HCl 4N/dioxano (0.046 mililitros, 0.185 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 3 días, y entonces se concentró bajo presión reducida, para obtener un aceite negro (100 miligramos, 79 por ciento de rendimiento).

UPLC Rt_{M1} =0.73 minutos; ESIMS: 360 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.75 (d, 1H),7.45 (d, 1H), 6.80 (m, 1H), 6.75 (m, 1H), 5.20 (m, 1H), 4.15 (t, 2H), 3.84 (s, 3H), 3.60 (t, 2H), 3.38-3.66 (m, 4H), 2.12 (s, 3H), 2.00-2.18 (m, 2H).

g) (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[5-fluoro-4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona

Una solución del ácido 1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-carboxílico (CAS registro 64096-87-3) (33.9 miligramos,

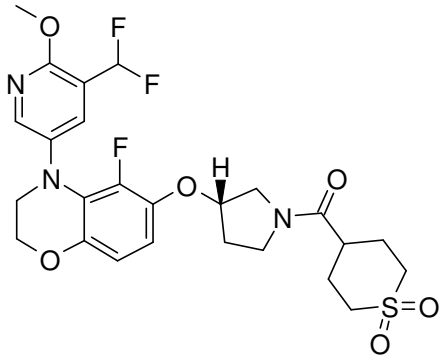
0.15 milimoles) en dicloro-metano (DCM) (2 mililitros) se trató a temperatura ambiente con Et_3N (0.061 mililitros, 0.440 milimoles), y HATU (55.7 miligramos, 0.147 milimoles). La solución color naranja resultante se agitó a temperatura ambiente durante 20 minutos, y entonces se agregó una solución de 5-fluoro-4-(6-metoxi-5-metil-piridin-3-il)-6-((S)-pirrolidin-3-iloxi)-3,4-dihidro-2H-benzo-[1,4]-oxazina (100 miligramos, 0.147 milimoles) en dicloro-metano (DCM) (2 mililitros). La mezcla de reacción se agitó a temperatura ambiente durante 1.5 horas, entonces se diluyó con EtOAc, y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la RP-HPLC de preparación (columna SunFire C18 OBD 5 micras, 30 x 100 milímetros, gradiente del 25 por ciento al 45 por ciento de acetonitrilo (ACN) en 16 minutos). Las fracciones se liofilizaron y se filtraron sobre un cartucho SPE PL-HCO_3 MP para dar un sólido color café (54 miligramos, 71 por ciento de rendimiento).

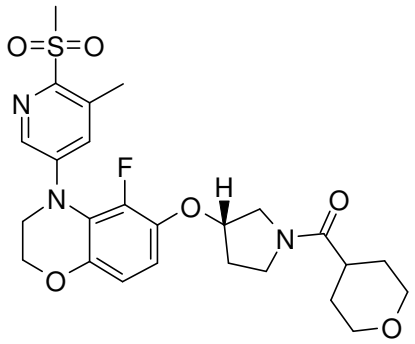
UPLC Rt_{M1} =0.94 minutos; ESIMS: 520 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.75 (d, 1H),7.45 (d, 1H), 6.55 (t, 1H), 6.35 (d, 1H), 4.75 (m, 1H), 4.15 (t, 2H), 3.84 (s, 3H), 3.59-3.79 (m, 3H), 3.41-3.56 (m, 2H), 3.21-3.39 (m, 1H), 2.98-3.21 (m, 4H), 2.67-2.83 (m, 1H), 1.84-2.20 (m, 9H).

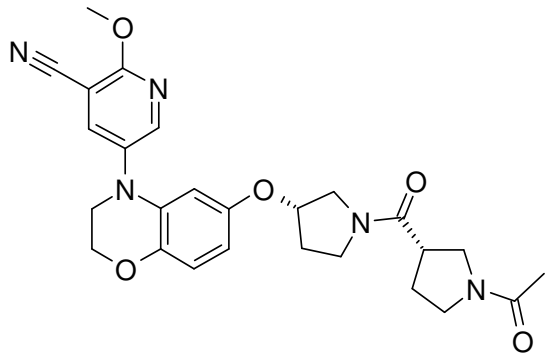
Ejemplos I2 a I3: Los compuestos enlistados en la Tabla 9 se prepararon mediante un procedimiento análogo a aquél empleado en el Ejemplo I1.

Tabla 9

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
I2	 {(S)-3-[4-(5-difluoro-metil-6-metoxi-piridin-3-il)-5-fluoro-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-metanona Condición de aminación de Buchwald: CA11 Condición de enlace de amida: CB3 Condición de introducción de cadena lateral: CC4 Precursores utilizados: IA6,CAS 1254123-51-7 / 127423-61-4, / 64096-87-3	0.97 (M2)	556

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
I3	 {(S)-3-[5-fluoro-4-(6-metan-sulfonil-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona Condición de aminación de Buchwald: CA11 Condición de enlace de amida: CB3 Condición de introducción de cadena lateral: Precursores utilizados: IA1,CAS 127423-61-4 / cloruro de acilo 40191-32-0	0.85 (M2)	520

Ejemplo J: 5-{6-[(S)-1-((S)-1-acetil-pirrolidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo

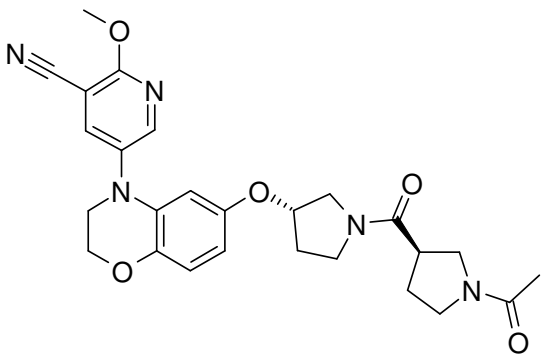


Una solución del 2-metoxi-5-{6-[(S)-1-((S)-pirrolidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo (Ejemplo D39; 23 miligramos, 0.051 milimoles) en dicloro-metano (DCM) (1 mililitro) se trató con Et_3N (0.014 mililitros, 10.4 miligramos, 0.102 milimoles). La solución se agitó a temperatura ambiente durante 10 minutos, y entonces se agregó cloruro de acetilo (0.0044 mililitros, 4.87 miligramos, 0.061 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 1.5 horas. Se agregaron otros 2 equivalentes de Et_3N (0.014 mililitros, 10.4 miligramos, 0.102 milimoles). y 1 equivalente de cloruro de acetilo ((0.0037 mililitros, 4.06 miligramos, 0.051 milimoles), se continuó la agitación a temperatura ambiente durante 1.5 horas. La mezcla de reacción se diluyó con dicloro-metano (DCM) y una solución acuosa saturada de $NaHCO_3$, entonces se pasó a través de

un separador de fases, la capa acuosa se extrajo dos veces con dicloro-metano (DCM), las capas orgánicas combinadas se concentraron, para dar el compuesto del título como un aceite amarillo, el cual se purificó mediante RP-HPLC de preparación (columna SunFire C18, del 10 al 85 por ciento de acetonitrilo (ACN) en 20 minutos). Las fracciones se extrajeron con dicloro-metano (DCM)/$NaHCO_3$, se secaron sobre $MgSO_4$, se concentraron, y se liofilizaron, para dar el compuesto del título como una espuma amarilla (14 miligramos, 53 por ciento de rendimiento).

HPLC Rt_{M10}=2.55 minutos; ESIMS: 492 [$(M+H)^+$].

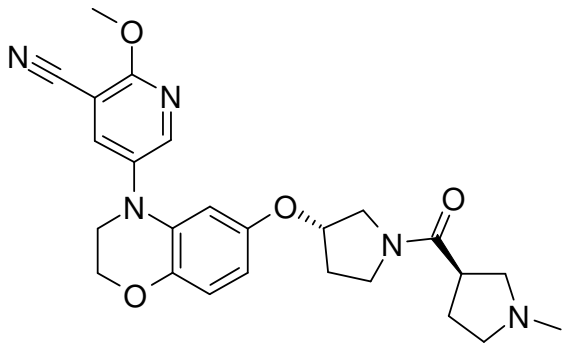
Ejemplo K: 5-{6-[(S)-1-((R)-1-acetil-pirrolidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-nicotinonitrilo



Este Ejemplo se preparó en analogía al Ejemplo **J,** empezando a partir del 2-metoxi-5-{6-[(S)-1-((R)-pirrolidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo (Ejemplo D40).

HPLC Rt_{M10}=2.55 minutos; ESIMS: 492 [$(M+H)^+$].

Ejemplo L: 2-metoxi-5-{6-[(S)-1-((R)-1-metil-pirrolidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo

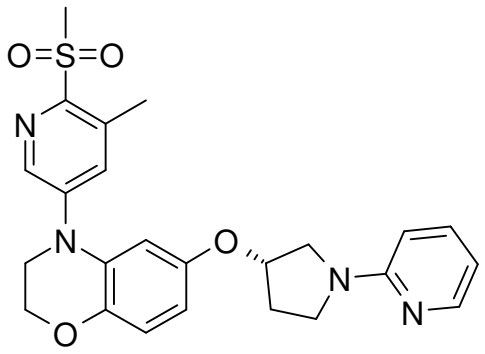


Una solución del 2-metoxi-5-{6-[(S)-1-((R)-pirrolidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo (Ejemplo D40, 26 miligramos, 0.058 milimoles) en metanol (1 mililitro) se trató con una solución acuosa de formaldehído al 37 por ciento (0.043 mililitros, 46.9 miligramos, 0.578 milimoles), y ácido acético (0.004 mililitros, 4.17 miligramos, 0.0069 milimoles). La solución se agitó bajo argón a temperatura ambiente durante 45 minutos, y entonces se agregó $NaBH_3CN$ (5.65 miligramos de un sólido al 90 por ciento, 0.081 milimoles). La mezcla resultante se agitó a temperatura ambiente durante 45 minutos, se diluyó con dicloro-metano (DCM) y una solución acuosa saturada de $NaHCO_3$. La capa acuosa se re-extrajo dos veces con dicloro-metano (DCM), las capas orgánicas combinadas se secaron sobre $MgSO_4$, y

se concentraron, para dar el compuesto del título crudo que se purificó mediante RP-HPLC de preparación (columna SunFire C18, gradiente del 5 al 75 por ciento de acetonitrilo (ACN) en 20 minutos). Las fracciones se extrajeron con dicloro-metano (DCM)/una solución acuosa saturada de $NaHCO_3$, se secaron sobre $MgSO_4$, se concentraron, y se liofilizaron, para dar el compuesto del título como una espuma amarilla (20 miligramos, 72 por ciento de rendimiento).

HPLC Rt_{M11}=2.24 minutos; ESIMS: 464 [$(M+H)^+$].

Ejemplo M: 4-(6-metan-sulfonil-5-metil-piridin-3-il)-6-((S)-1-piridin-2-il-pirrolidin-3-iloxi)-3,4-dihidro-2H-benzo-[1,4]-oxazina



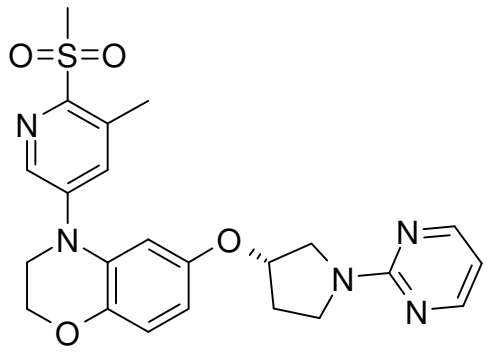
Una solución de la 4-(6-metan-sulfonil-5-metil-piridin-3-il)-6-((S)-1-piridin-2-il-pirrolidin-3-iloxi)-3,4-dihidro-2H-benzo-[1,4]-oxazina (preparada como se describe en el Ejemplo B1; 60 miligramos, 0.154 milimoles), 2-cloro-piridina (CAS 109-09-1, 0.017 mililitros, 21.0 miligramos, 0.185 milimoles), Xphos (8.81 miligramos, 0.018 milimoles), y Cs_2CO_3 (125 miligramos, 0.385 milimoles) en dioxano (1 mililitro), se desgasificó con argón, y entonces se agregó $Pd_2(dba)_3$ (7.05 miligramos, 0.0077 milimoles). La mezcla de reacción se calentó a 80°C durante 6 horas, se agregó XPhos (8.81

miligramos, 0.018 milimoles), la mezcla nuevamente se desgasificó con argón, y se agregó $Pd_2(dba)_3$ (7.05 miligramos, 0.0077 milimoles). Se continuó la agitación durante la noche a 80°C. La mezcla se filtró a través de Celite, y se concentró, para dar el compuesto del título que se purificó mediante NP-HPLC (columna Grace Grom Saphir 65 Si, gradiente de heptano:EtOAc:MeOH, de 68:30:2 a 0:65:35 en 12 minutos), rendimiento de 32 miligramos (45 por ciento).

HPLC Rt_{M1} =0.72 minutos; ESIMS: 467 [$(M+H)^+$]

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.32 (d, 1H), 8.14-8.12 (m, 1H), 7.49-7.39 (m, 2H), 6.86 (d, 1H), 6.61 (d, 1H), 6.57-6.46 (m, 2H), 6.37 (d, 1H), 4.92-4.85 (m, 1H), 4.26-4.24 (m, 2H), 3.76-3.74 (m, 2H), 3.71 (d, 2H), 3.63-3.55 (m, 2H), 3.32 (s, 3H), 2.67 (s, 3H), 2.35-2.27 (m, 1H), 2.26-2.15 (m, 1H).

Ejemplo N: 4-(6-metan-sulfonil-5-metil-piridin-3-il)-6-((S)-1-pirimidin-2-il-pirrolidin-3-iloxi)-3,4-dihidro-2H-benzo-[1,4]-oxazina



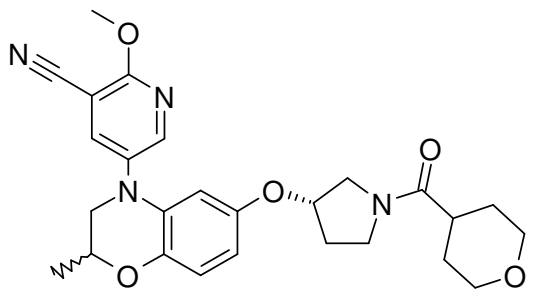
Una solución de la 4-(6-metan-sulfonil-5-metil-piridin-3-il)-6-

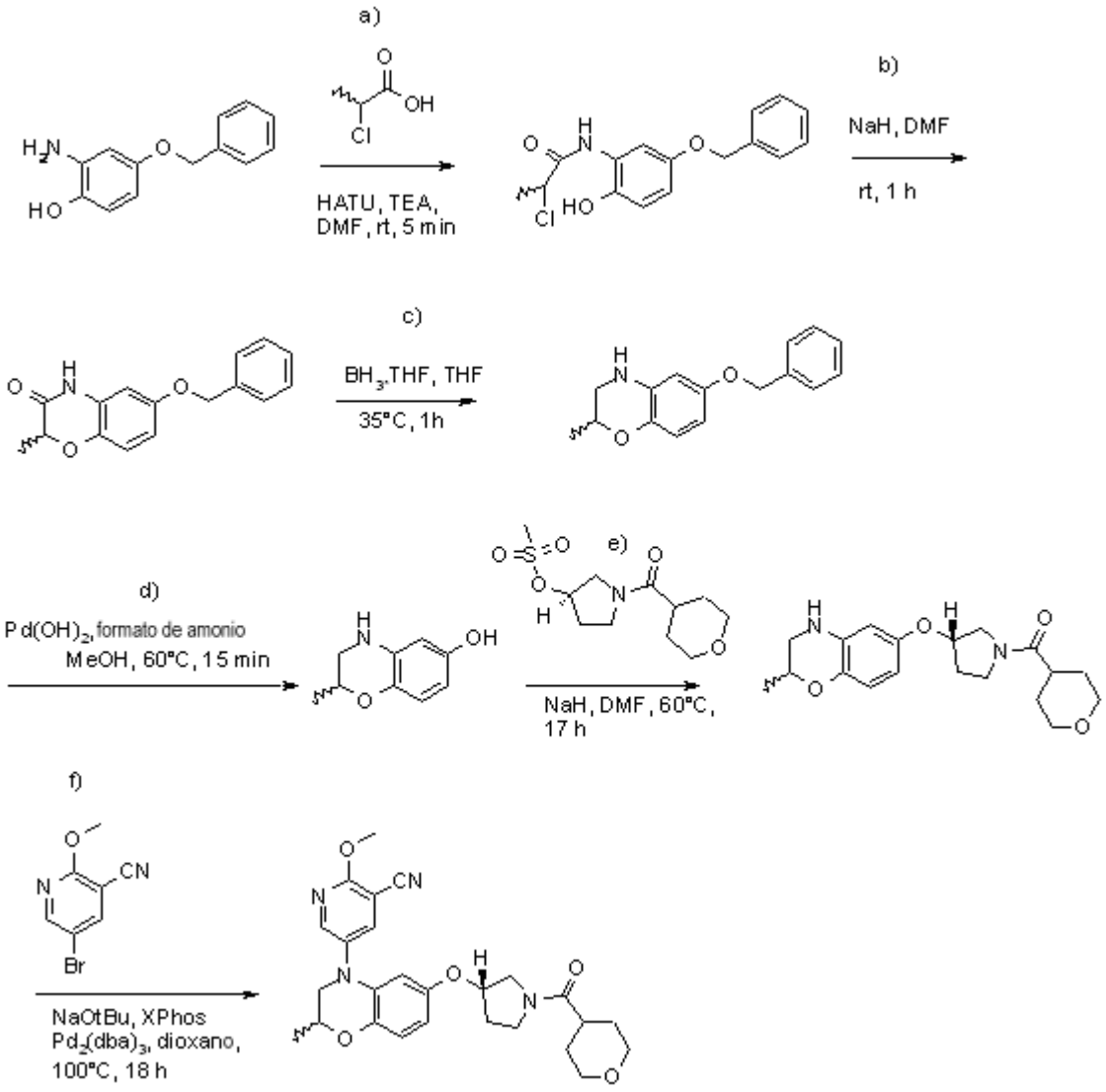
((S)-1-piridin-2-il-pirrolidin-3-iloxi)-3,4-dihidro-2H-benzo-[1,4]-oxazina (preparada como se describe en el Ejemplo B1; 60 miligramos, 0.154 milimoles), 2-cloro-pirimidina (CAS 1722-12-9, 24.7 miligramos, 0.216 milimoles), y di-isopropil-etil-amina (DIPEA) (0.054 mililitros, 39.8 miligramos, 0.308 milimoles) en acetonitrilo (ACN) (1 mililitro), se calentó a 140°C durante 30 minutos en un reactor de microondas. El producto se extrajo con una solución acuosa saturada de $NaHCO_3$ y EtOAc, se filtró, y se concentró, para proporcionar el compuesto del título que se purificó mediante NP-HPLC de preparación (columna Grace Grom Saphir 65 Si, gradiente de heptano:EtOAc:MeOH, de 68:30:2 a 0:65:35 en 12 minutos), rendimiento de 45 miligramos (63 por ciento).

HPLC Rt_{M1}=0.97 minutos; ESIMS: 468 [$(M+H)^+$]

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.37-8.26 (m, 3H), 7.44 (d, 1H), 6.87 (d, 1H), 6.62 (d, 1H), 6.56-6.46 (m, 2H), 4.92-4.84 (m, 1H), 4.27-4.25 (m, 2H), 3.90-3.63 (m, 6H), 3.33 (s, 3H), 2.69 (s, 3H), 2.37-2.13 (m, 2H).

Ejemplo O1: 2-metoxi-5-{2-metil-6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo





a) N-(5-benciloxi-2-hidroxi-fenil)-2-cloro-propionamida

Una solución de ácido 2-cloro-propiónico (CAS registro 598-78-7) (0.914 mililitros, 7.53 milimoles) en dimetil-formamida (DMF) (20 mililitros) se trató con Et_3N (1.259 mililitros, 9.03 milimoles), y HATU (3.05 gramos, 8.03 milimoles). La solución resultante se agitó a temperatura ambiente durante 30 minutos, entonces se agregó el 2-amino-4-benciloxi-fenol (CAS registro 102580-07-4) (1.08 gramos, 5.02 milimoles). La mezcla de reacción se agitó a temperatura

ambiente durante 5 minutos, se diluyó con EtOAc y se concentró. Se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 50:50), como un sólido color naranja (617 miligramos, 40 por ciento de rendimiento).

UPLC Rt_{M14} =1.32 minutos; ESIMS: 306 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 9.50 (d, 1H), 7.70 (br,s 1H), 7.45 (m, 5H), 6.80 (d, 1H), 6.65 (dd, 1H), 5.00 (s, 2H), 2.65 (s, 3H).

b) 6-benciloxi-2-metil-4H-benzo-[1,4]-oxazin-3-ona

Una solución seca de la N-(5-benciloxi-2-hidroxi-fenil)-2-cloro-propionamida (617 miligramos, 2.0 milimoles) en dimetil-formamida (DMF) (15 mililitros) se trató a 0ºC con hidruro de sodio al 95 por ciento (58.1 miligramos, 2.4 milimoles). Después de agitar a temperatura ambiente durante 1 hora, la mezcla de reacción se diluyó con dicloro-metano (DCM), y se lavó con agua. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 80:20), como un sólido blanco (146 miligramos, 27 por ciento de rendimiento).

UPLC Rt_{M14} =1.30 minutos; ESIMS: 270 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 10.80 (s, 1H), 7.45 (m, 5H), 6.85 (d, 1H), 6.65 (m, 2H), 5.00 (s, 2H), 4.55 (q, 1H), 1.45 (d, 3H).

c) 6-benciloxi-2-metil-3,4-dihidro-2H-benzo-[1,4]-oxazina

Una solución de la 6-benciloxi-2-metil-4H-benzo-[1,4]-oxazin-3-

ona (146 miligramos, 0.54 milimoles) en tetrahidrofurano (THF) (4 mililitros) se trató a 0°C con BH_3*THF (1M en tetrahidrofurano (THF), 0.813 mililitros, 0.813 milimoles). Después de agitar a 35°C durante 1 hora, la mezcla de reacción se enfrió a 0°C, se apagó con agua (0.5 mililitros), y una solución acuosa de NaOH 4N (0.5 mililitros), y entonces se diluyó con EtOAc. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título como un sólido blanco (125 miligramos, 90 por ciento de rendimiento).

UPLC Rt_{M14} =1.40 minutos; ESIMS: 256 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.45 (m, 5H), 6.50 (d, 1H), 6.20 (d, 1H), 6.10 (dd, 1H), 5.35 (s, 1H), 4.90 (s, 2H), 4.00 (m, 1H), 3.25 (m, 1H), 2.90 (m, 1H), 1.35 (d, 3H).

d) 2-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol

Una solución de la 6-benciloxi-2-metil-3,4-dihidro-2H-benzo-[1,4]-oxazina (124 miligramos, 0.486 milimoles) en metanol (10 mililitros) se trató a temperatura ambiente con formato de amonio (276 miligramos, 4.37 milimoles), y $Pd(OH)_2$ (68.2 miligramos, 0.486 milimoles). La mezcla de reacción se agitó a 60°C durante 15 minutos. Después de enfriarse a temperatura ambiente, la mezcla de reacción se filtró a través de Hyflo, se enjuagó con dicloro-metano (DCM) y metanol, y entonces los filtrados se concentraron. Se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (dicloro-metano (DCM) / MeOH, de 100:0 a 90:10), como un sólido color café. (69.4 miligramos, 87 por

ciento de rendimiento).

UPLC Rt_{M14} =0.56 minutos; ESIMS: 166 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 6.45 (d, 1H), 6.00 (d, 1H), 5.85 (dd, 1H), 5.25 (s, 1H), 4.00 (m, 1H), 3.25 (m, 1H), 2.90 (m, 1H), 1.35 (d, 3H).

e) [(S)-3-(2-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi)-pirrolidin-1-il]-(tetrahidro-piran-4-il)-metanona

Una solución seca del 2-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol (69 miligramos, 0.42 milimoles), y metan-sulfonato de (R)-1-(tetrahidro-2H-piran-4-carbonil)-pirrolidin-3-ilo (intermediario C1, 209 miligramos, 0.75 milimoles) en dimetil-formamida (DMF) (1.4 mililitros) se trató con hidruro de sodio al 60 por ciento en aceite mineral (15.8 miligramos, 0.63 milimoles), y la mezcla de reacción se agitó a 50°C durante 18 horas. La mezcla de reacción se diluyó con EtOAc, y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (dicloro-metano (DCM) / MeOH, de 100:0 a 95:5), como un sólido pegajoso color rojo-naranja (128 miligramos, 88 por ciento de rendimiento).

UPLC Rt_{M14}=1.01 minutos; ESIMS: 347 [$(M+H)^+$]

^{1}H RMN (400 MHz, DMSO-d_6): δ 6.50 (d, 1H), 6.25 (d, 1H), 6.00 (d, 1H), 6.05 (m, 1H), 5.65 (m, 2H), 5.35 (d, 2H), 4.45 (d, 2H), 3.00-4.00 (m, 6H), 2.00-2.40 (m, 4H), 1.5 (m, 4H)

f) 2-metoxi-5-{2-metil-6-[(S)-1-(tetrahidro-piran-4-carbonil)-

pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo

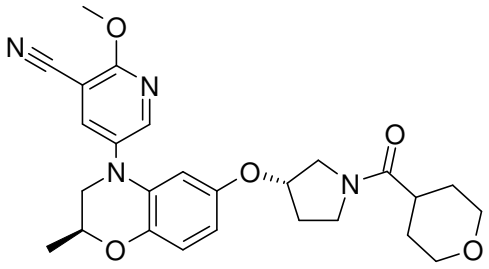
Una mezcla de la (S)-(3-(2-metil-3,4-dihidro-2H-benzo-[b][1,4]-oxazin-6-iloxi)-pirrolidin-1-il)-(tetrahidro-2H-piran-4-il)-metanona (128 miligramos, 0.369 milimoles), 5-bromo-2-metoxi-nicotinonitrilo (CAS registro 941294-54-8, IA12), (94 miligramos, 0.443 milimoles), XPhos (8.81 miligramos, 0.018 milimoles), NaOtBu (53.3 miligramos, 0.554 milimoles), y $Pd_2(dba)_3$ (16.92 miligramos, 0.018 milimoles) en tolueno (2.5 mililitros), se desgasificó con argón. La mezcla de reacción se agitó a 80°C durante 20 minutos. Después de enfriarse a temperatura ambiente, la mezcla de reacción se filtró a través de Hyflo, se enjuagó con EtOAc, y los filtrados se lavaron con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró. Se obtuvo el compuesto del título después de la RP-HPLC de preparación (columna SunFire C18 OBD 5 milímetros, 30 x 100 milímetros, gradiente del 32 por ciento al 67 por ciento de acetonitrilo (ACN) en 15 minutos). Las fracciones se liofilizaron y se filtraron sobre un cartucho SPE PL-HCO_3 MP, para dar un sólido color café (39.1 miligramos, 22 por ciento de rendimiento).

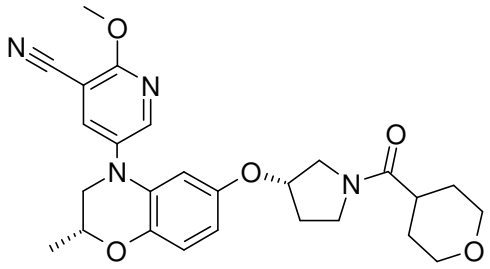
UPLC Rt_{M14} =1.10 minutos; ESIMS: 479 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6, 394 K): δ 8.40-8.30 (m, 1H), 8.10-8.00 (m, 1H), 6.75 (d, 1H), 6.35 (m, 1H), 6.15 (m, 1H), 4.75 (m, 1H), 4.00 (s, 3H), 3.85 (m, 1H), 3.75-3.00 (m, 5H), 2.65 (m, 1H), 2.00 (m, 1H), 1.65 (m, 2H), 1.44 (d, 3H).

Ejemplos O2 a O3: Los compuestos enlistados en la Tabla 10 se prepararon mediante la separación cromatográfica de los diaestereómeros.

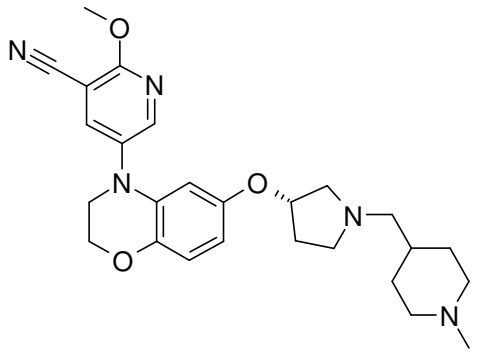
Tabla 10

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
O2	 Pico 1 separación de diaestereómeros 2-metoxi-5-{(S)-2-metil-6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IO, IA12, CAS 104706-47-0/ cloruro de acilo 40191-	19.89 (M15)	

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	32-0 Separación cromatográfica de diaestereómeros: CD11		
O3	 Pico 2 separación de diaestereómeros 2-metoxi-5-{(R)-2-metil-6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo Condición de aminación de Buchwald: CA6 Condición de enlace de amida: CB6 Condición de introducción de cadena lateral: CC2 Precursores utilizados: IO, IA12, CAS 104706-47-0/ cloruro de acilo 40191-	27.33 (M15)	

Ejemplo	Compuesto / Condiciones de reacción	HPLC Rt [min] (método)	MS [m/z; $(M+1)^+$]
	32-0 Separación cromatográfica de diaestereómeros: CD11		

Ejemplo P: 2-metoxi-5-{6-[(S)-1-(1-metil-piperidin-4-il-metil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo



a) (S)-4-((3-(4-(5-ciano-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[b][1,4]-oxazin-6-iloxi)-pirrolidin-1-il)-metil)-piperidin-1-carboxilato de terbutilo

Una solución del 2-metoxi-5-[6-((S)-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-nicotinonitrilo (véase análogo B1, c), 95 miligramos, 0.270 milimoles) en dicloro-etano (4.5 mililitros) se trató con 4-formil-piperidin-1-carboxilato de terbutilo (60 miligramos, 0.281 milimoles). Después de agitar durante 2 días a temperatura

ambiente, la mezcla de reacción se diluyó con dicloro-metano (DCM) y una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 0:100), rendimiento de 66 miligramos (40 por ciento) .

UPLC Rt_{M1} =1.66 minutos; ESIMS: 550 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.35 (d, 1H), 7.75 (d, 1H), 7.35 (s, 1H), 7.85 (d, 1H), 6.35 (dd, 1H), 6.10 (d, 1H), 4.65 (m, 1H), 4.45 (m, 2H), 3.60 (m, 2H), 2.75-2.15 (m, 4H), 1.50 (s, 9H).

b) (S)-2-metoxi-5-(6-(1-(piperidin-4-il-metil)-pirrolidin-3-iloxi)-2H-benzo-[b][1,4]-oxazin-4(3H)-il)-nicotinonitrilo

Una solución del (S)-4-((3-(4-(5-ciano-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[b][1,4]-oxazin-6-iloxi)-pirrolidin-1-il)-metil)-piperidin-1-carboxilato de terbutilo (66 miligramos, 0.120 milimoles) en dicloro-metano (DCM) (2 mililitros) se trató con ácido trifluoro-acético (TFA) (0.093 mililitros, 1.20 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 17 horas, entonces se apagó con una solución acuosa saturada de Na_2CO_3 y se extrajo con dicloro-metano (DCM). La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró bajo presión reducida, para proporcionar el producto del título (36 miligramos, 67 por ciento de rendimiento).

UPLC Rt_{M1} =1.03 minutos; ESIMS: 450 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.35 (d, 1H), 7.80 (d, 1H), 7.25 (s, 1H), 6.80 (d, 1H), 6.25 (m, 1H), 6.15 (d, 1H), 4.65 (m, 1H), 4.45

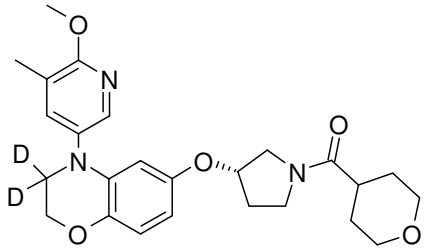
(m, 2H), 3.60 (m, 2H), 2.75-2.15 (m, 4H).

c) (S)-2-metoxi-5-(6-(1-((1-metil-piperidin-4-il)-metil)-pirrolidin-3-iloxi)-2H-benzo-[b][1,4]-oxazin-4(3H)-il)-nicotinonitrilo

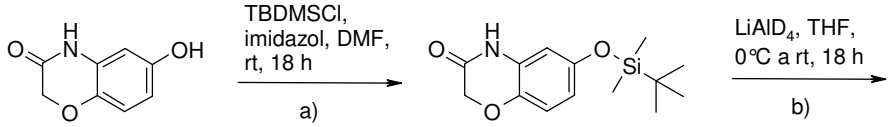
Una solución del (S)-2-metoxi-5-(6-(1-(piperidin-4-il-metil)-pirrolidin-3-iloxi)-2H-benzo-[b][1,4]-oxazin-4(3H)-il)-nicotinonitrilo (36 miligramos, 0.080 milimoles) en dicloro-etano (2 mililitros) se trató con una solución acuosa de formaldehído al 37 por ciento (8.94 microlitros, 0.120 milimoles). La solución se agitó bajo argón a temperatura ambiente durante 15 minutos, y entonces se agregó $NaBH_3CN$ (50.9 miligramos, 0.240 milimoles). La mezcla resultante se agitó a temperatura ambiente durante 30 minutos, se diluyó con dicloro-metano (DCM) y una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4 y se concentró. Se obtuvo el compuesto del título después de la purificación mediante RP-HPLC de preparación (columna SunFire C18, gradiente del 15 al 50 por ciento de acetonitrilo (ACN) en 15 minutos). Las fracciones se extrajeron con dicloro-metano (DCM)/una solución acuosa saturada de $NaHCO_3$, se secaron sobre Na_2SO_4, se concentraron, y se liofilizaron, para dar el compuesto del título (18 miligramos, 48 por ciento de rendimiento).

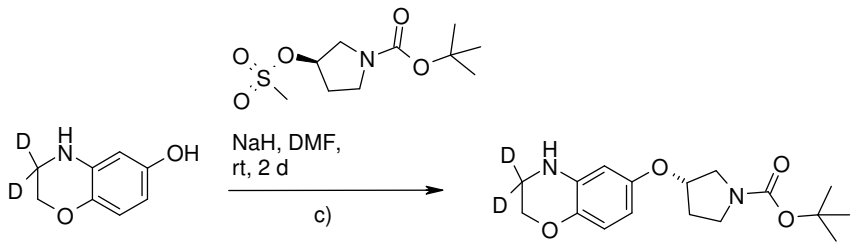
UPLC Rt_{M1} =1.04 minutos; ESIMS: 464 [$(M+H)^+$].

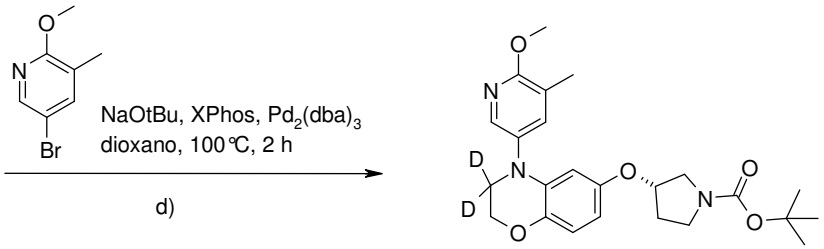
^1H RMN (400 MHz, $CDCl_3$): δ 8.35 (d, 1H), 7.85 (d, 1H), 7.45 (s, 1H), 6.75 (d, 1H), 6.35 (dd, 1H), 6.15 (d, 1H), 4.65 (m, 1H), 4.45 (m, 2H), 3.25 (m, 2H), 2.75-2.15 (m, 4H), 2.65 (s, 3H), 1.95 (m, 2H), 1.65 (m, 2H).

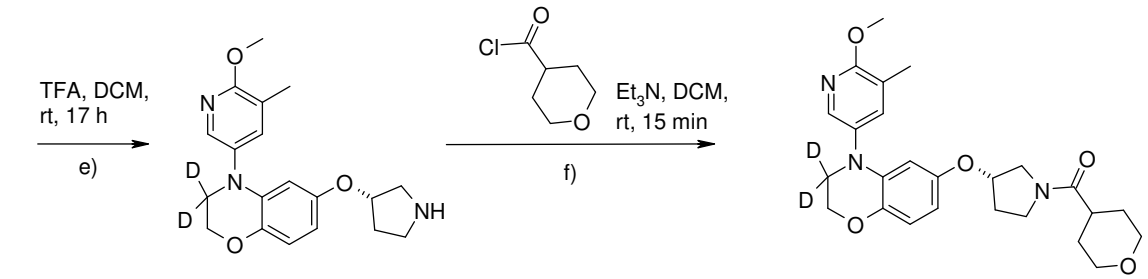


Ejemplo Q: {(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona









a) 6-(terbutil-dimetil-silaniloxi)-4H-benzo-[1,4]-oxazin-3-ona

Una solución de la 6-hidroxi-2H-benzo-[b][1,4]-oxazin-3(4H)-ona (CAS registro 53412-38-7) (1076 miligramos, 6.52 milimoles) en dimetil-formamida (DMF) (8 mililitros) se trató a temperatura ambiente con TBDMSCl (1080 miligramos, 7.17 milimoles) e imidazol (532 miligramos, 7.82 milimoles). Después de agitar durante 18 horas a temperatura ambiente, la mezcla de reacción se diluyó con dicloro-metano (DCM), y se lavó con agua. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 50:50), como un sólido blanco (1.18 gramos, 65 por ciento de rendimiento).

UPLC Rt_{M2} =1.91 minutos; ESIMS: 280 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.85 (br,s 1H), 7.35 (s, 1H), 6.85 (d, 1H), 6.45 (m, 1H), 6.30 (d, 1H), 4.50 (s, 2H), 1.00 (s, 9H), 0.25 (s, 6H).

b) 3,3-dideutero-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol

Una solución de la 6-(terbutil-dimetil-silaniloxi)-4H-benzo-[1,4]-oxazin-3-ona (8.34 gramos, 29.8 milimoles) en tetrahidrofurano (THF) (100 mililitros) se trató a 0°C con deuteriuro de litio y aluminio (2.26 gramos, 59.7 milimoles). Después de agitar durante 18 horas a temperatura ambiente, la mezcla de reacción se agregó a una solución acuosa fría de sal de Rochelle 1 M, y se extrajo con EtOAc. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por

evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 0:100), como un sólido blanco (1.40 gramos, 31 por ciento de rendimiento).

UPLC Rt_{M9} =0.69 minutos; ESIMS: 154 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.50 (s 1H), 6.45 (d, 1H), 6.00 (d, 1H), 5.85 (m, 1H), 5.15 (s, 1H), 4.00 (s, 2H).

c) Terbutil-éster del ácido (S)-3-(3,3-dideutero-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi)-pirrolidin-1-carboxílico

Una solución seca del 3,3-dideutero-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol (1.44 gramos, 9.40 milimoles), y terbutil-éster del ácido (R)-3-metan-sulfoniloxi-pirrolidin-1-carboxílico (CAS registro 127423-61-4) (5.49 gramos, 20.68 milimoles) en dimetil-formamida (DMF) (10 mililitros) se trató con hidruro de sodio al 60 por ciento en aceite mineral (0.752 gramos, 18.80 milimoles), y la mezcla de reacción se agitó a temperatura ambiente durante 2 días. La mezcla de reacción se diluyó con EtOAc, y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 0:100), para proporcionar 4.12 gramos (rendimiento cuantitativo) del compuesto del título.

UPLC Rt_{M1} =1.07 minutos; ESIMS: 323 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 6.65 (m, 1H), 6.15 (m, 2H), 5.35 (m, 1H), 4.85 (m, 2H), 3.50 (m, 4H), 2.15 (m, 2H), 1.50 (s, 9H).

d) Terbutil-éster del ácido (S)-3-[4-(6-metoxi-5-metil-piridin-3-

il)-3,3-dideutero-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carboxílico

Este Ejemplo se preparó en analogía al Ejemplo **G1, e).**

UPLC Rt_{M1} =2.00 minutos; ESIMS: 444 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.95 (br.s, 1H), 7.45 (br.s, 1H), 6.80 (m, 1H), 6.25 (m, 1H), 4.75 (m, 1H), 4.35 (s, 2H), 4.00 (s, 3H), 3.50 (m, 4H), 2.25 (m, 2H), 1.50 (s, 9H).

e) 4-(6-metoxi-5-metil-piridin-3-il)-3,3-dideutero-6-((S)-pirrolidin-3-iloxi)-3,4-dihidro-2H-benzo-[1,4]-oxazina

Este Ejemplo se preparó en analogía al Ejemplo **G1, f).**

UPLC Rt_{M1} =1.26 minutos; ESIMS: 342 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.95 (br.s, 1H), 7.45 (br.s, 1H), 6.80 (m, 1H), 6.25 (m, 1H), 4.75 (m, 1H), 4.35 (s, 2H), 4.00 (s, 3H), 3.15 (m, 2H), 2.75 (m, 2H), 2.25 (m, 2H).

f) {(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona

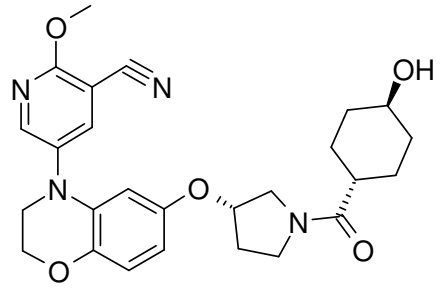
Este Ejemplo se preparó en analogía al Ejemplo **B1, d).**

UPLC Rt_{M1} =1.65 minutos; ESIMS: 456 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$, 298 K): δ 8.45 (m, 1H), 8.29 (s, 1H), 7.21 (t, 1H), 6.20 (t, 1H), 6.10 (s, 1H), 5.00 (d, 1H), 4.37 (t, 2H), 4.00 (m, 3H), 3.39-3.74 (m, 4H), 2.50 (m, 2H), 2.35 (s, 3H), 1.09-2.10 (m, 5H).

Ejemplo R: 5-{6-[(S)-1-(4-hidroxi-ciclohexan-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-2-metoxi-

nicotinonitrilo

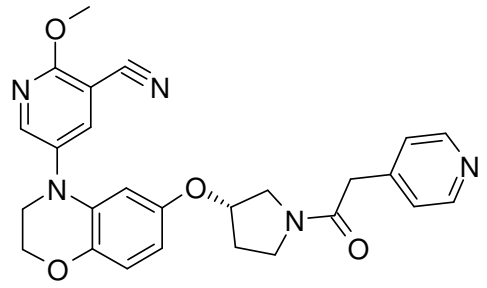


Este Ejemplo se preparó en analogía al Ejemplo **J,** empezando a partir del 2-metoxi-5-{6-[(S)-1-((S)-pirrolidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo.

UPLC Rt_{M14} =0.91 minutos; ESIMS: 478 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d6): δ 8.43 (d, 1H), 8.28 (d, 1H), 6.73 (m, 1H), 6.34 (m, 1H), 6.08 (dd, 1H), 4.76 (d, 1H), 4.51 (m, 1H), 4.22 (s, 2H), 4.00 (s, 3H), 3.20-3.71 (m, 9H), 1.09-2.10 (m, 10H).

Ejemplo S: 2-metoxi-5-{6-[(S)-1-(2-piridin-4-il-acetil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo



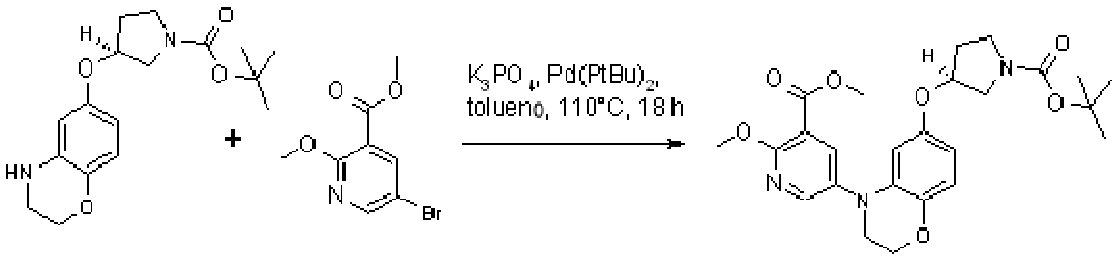
Este Ejemplo se preparó en analogía al Ejemplo **J,** empezando a partir del 2-metoxi-5-{6-[(S)-1-((S)-pirrolidin-3-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo.

UPLC Rt_{M14} =0.82 minutos; ESIMS: 471 [$(M+H)^+$]

^{1}H RMN (400 MHz, DMSO-d6): δ 8.45 (m, 3H), 8.29 (s, 1H), 7.21 (m, 2H), 6.74 (m, 1H), 6.33 (m, 1H), 6.10 (m, 1H), 4.87 (d, 1H), 4.22 (s, 2H), 4.00 (s, 3H), 3.39-3.74 (m, 8H), 1.09-2.10 (m, 2H).

Ejemplo T: {(S)-3-[4-(5-amino-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona

a) metil-éster del ácido 5-[6-((S)-1-terbutoxi-carbonil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-2-metoxi-nicotínico

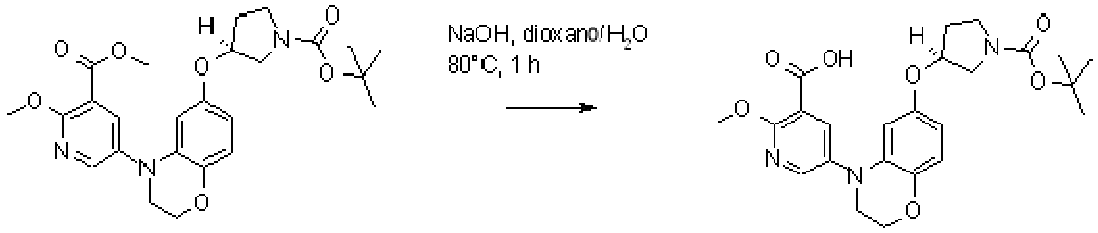


Bajo argón, se agregaron K_3PO_4 (815 miligramos, 2.00 milimoles), y bis-(terbutil-fosfina)-paladio (29.4 miligramos. 0.06 milimoles) a una solución del terbutil-éster del ácido (S)-3-(3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi)-pirrolidin-1-carboxílico (preparado como se describe en el paso a) ejemplo B) (615 miligramos, 1.92 milimoles), y metil-éster del ácido 5-bromo-2-metoxi-nicotínico (IA 22, CAS registro 122433-41-4) (614 miligramos, 1.30 milimoles) en tolueno (6 mililitros). La mezcla de reacción se desgasificó con argón durante 15 minutos, y luego se agitó a 110°C durante 18 horas, se diluyó con EtOAc, y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre $MgSO_4$ y se concentró,

para proporcionar el compuesto del título crudo que se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 90:10 a 0:100), para dar una goma amarilla (474 miligramos, 51 por ciento de rendimiento).

UPLC Rt_{M2} =1.36 minutos; ESIMS: 486 [$(M+H)^+$].

b) Ácido 5-[6-((S)-1-terbutoxi-carbonil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-2-metoxi-nicotínico

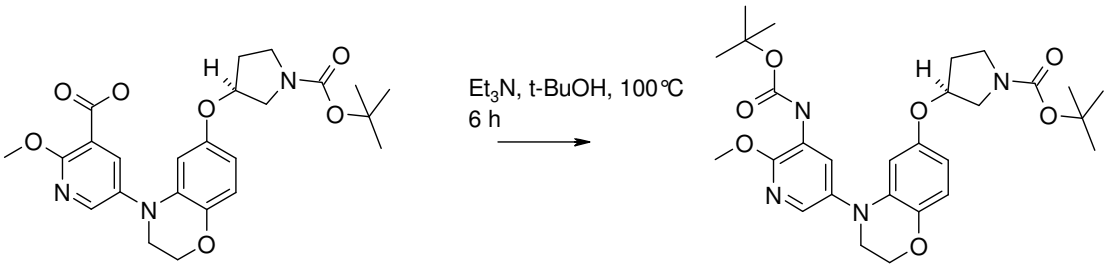


Una solución del metil-éster del ácido 5-[6-((S)-1-terbutoxi-carbonil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-2-metoxi-nicotínico (483 miligramos, 0.99 milimoles) en dioxano (5 mililitros) se trató con una solución de gránulos de hidróxido de sodio (119 miligramos, 2.98 milimoles) en agua (2 mililitros). La solución se agitó a 80°C durante 1 hora. La mezcla de reacción se acidificó hasta un pH de 3 con una solución acuosa de HCl 1N, y se extrajo con EtOAc. Las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron, para proporcionar el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 100:0 a 0:100, entonces EtOAc/MeOH, de 90:10 a 80:20), como un sólido (370 miligramos, 79 por ciento de rendimiento).

UPLC Rt_{M6} =1.79 minutos; ESIMS: 372 [$(M+H-100)^+$]

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.22-8.48 (m, 2H), 6.82 (d, 1H), 6.33 (m,1H), 6.21 (d, 1H), 4.60-4.76 (m, 1H), 4.27-4.41 (m, 2H), 4.15-4.27 (m, 3H), 3.62-3.77 (m, 2H), 3.31-3.58 (m, 5H), 1.85-2.19 (m, 2H), 1.34-1.56 (m, 9H)

c) Terbutil-éster del ácido (S)-3-[4-(5-terbutoxi-carbonil-amino-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carboxílico

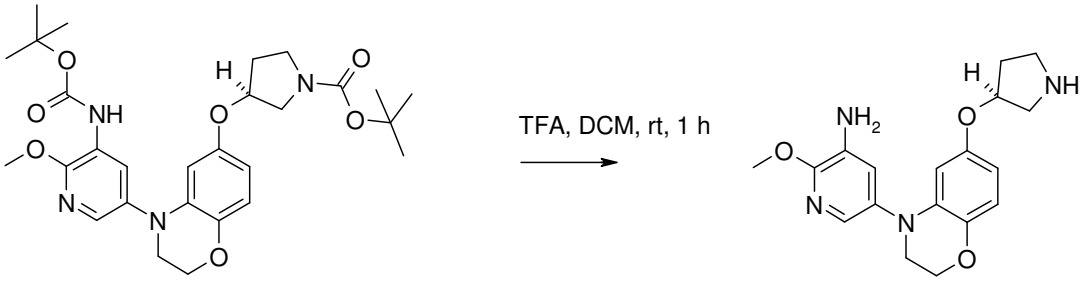


Una solución del ácido 5-[6-((S)-1-terbutoxi-carbonil-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-2-metoxi-nicotínico (370 miligramos, 0.78 milimoles), y Et_3N (0.28 mililitros, 1.96 milimoles) en tBuOH (5 mililitros) se trató con DPPA (CAS registro 26386-88-9) (0.17 mililitros, 0.78 milimoles), y se agitó a 100°C durante 6 horas. Se agregaron dicloro-metano (DCM) y una solución acuosa saturada de $NaHCO_3$, la capa orgánica se separó mediante elución a través de un cartucho de separación de fases, y se concentró, para proporcionar el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 100:0 a 50:50), como un goma color rosado (114 miligramos, 24 por ciento).

UPLC Rt_{M2} =1.36 minutos; ESIMS: 486 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.42 (br s, 1H), 7.75 (d, 1H), 7.02 (s, 1H), 6.78 (d, 1H), 6.15-6.41 (m, 1H), 4.71 (br s, 1H), 4.23-4.39 (m, 2H), 4.09-4.22 (m, 3H), 3.62-3.75 (m, 2H), 3.31-3.58 (m, 4H), 1.86-2.26 (m, 2H), 1.40-1.60 (m, 18H).

d) 2-metoxi-5-[6-((S)-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-piridin-3-il-amina

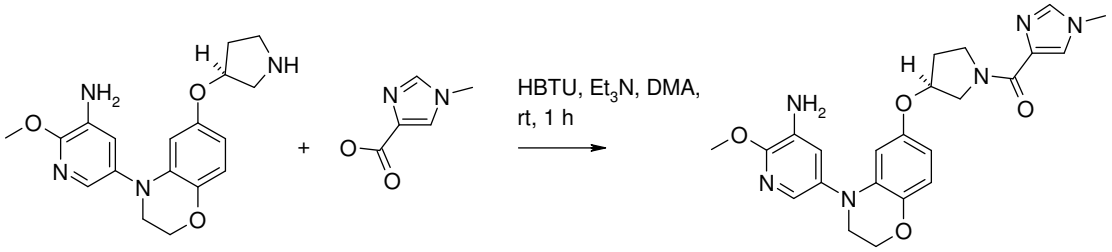


Una solución del terbutil-éster del ácido (S)-3-[4-(5-terbutoxi-carbonil-amino-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carboxílico (130 miligramos, 0.24 mili-moles) en dicloro-metano (DCM) (2 mililitros) se trató con ácido trifluoro-acético (TFA) (CAS registro 76-05-1), y se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró para proporcionar el compuesto del título después de la elución a partir de un cartucho Isolute SCX-2 de 2 gramos (eluyente de MeOH, y luego NH_3/MeOH 2M), como una goma amarilla (88 miligramos, cuantitativo, cruda).

UPLC Rt_{M2} =1.25 minutos; ESIMS: 343 [$(M+H)^+$].

e) {(S)-3-[4-(5-amino-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-

il)-metanona

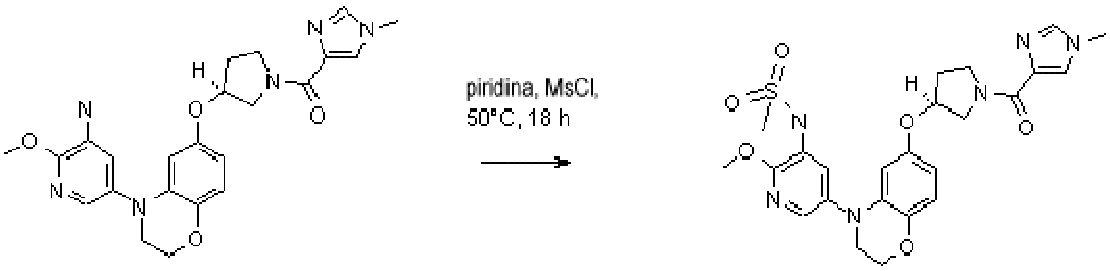


Una solución del ácido 1-metil-1H-imidazol-4-carboxílico (CAS registro 41716-18-1) (36.0 miligramos, 0.26 milimoles), y Et_3N (0.11 mililitros, 0.78 milimoles) en dimetil-formamida (DMF) (1 mililitro) se trató con HBTU (CAS registro 94790-37) (107 miligramos, 0.28 milimoles). Después de agitar a temperatura ambiente durante 20 minutos, la mezcla de reacción se enfrió a 5°C, y se agregó una solución de 2-metoxi-5-[6-((S)-pirrolidin-3-iloxi)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-piridin-3-il-amina (88 miligramos, 0.26 milimoles) en dimetil-formamida (DMF) (3 mililitros). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora, se concentró, y el residuo se absorbió en dicloro-metano (DCM) (10 mililitros), se lavó con una solución acuosa saturada de $NaHCO_3$ (5 mililitros), la capa orgánica se separó mediante elución a través de un cartucho de separación de fases y se concentró. El residuo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 100:0 a 0:100), las fracciones combinadas se concentraron, se disolvieron en $tBuOH/H_2O$ y se liofilizaron, para proporcionar el compuesto del título como un sólido incoloro (21 miligramos, 37 por ciento de rendimiento).

UPLC Rt_{M2} =0.85 minutos; ESIMS: 451 [$(M+H)^+$].

^{1}H RMN (400 MHz, CD_3OD): δ 7.64 (s, 1H), 7.62 (s, 1H), 7.65 m, 1H), 6.93 (m, 1H), 6.70 (m, 1H), 6.20-6.34 (m, 1H), 6.15 (m, 1H), 4.81 (m, 1H), 4.19-4.31 (m, 2H), 3.90-4.05 (m, 4H), 3.55-3.83 (m, 8H), 2.04-2.28 (m, 2H).

Ejemplo U: N-(2-metoxi-5-{6-[(S)-1-(1-metil-1H-imidazol-4-carbonil)-pirrolidin-3-iloxi]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-piridin-3-il)-metan-sulfonamida



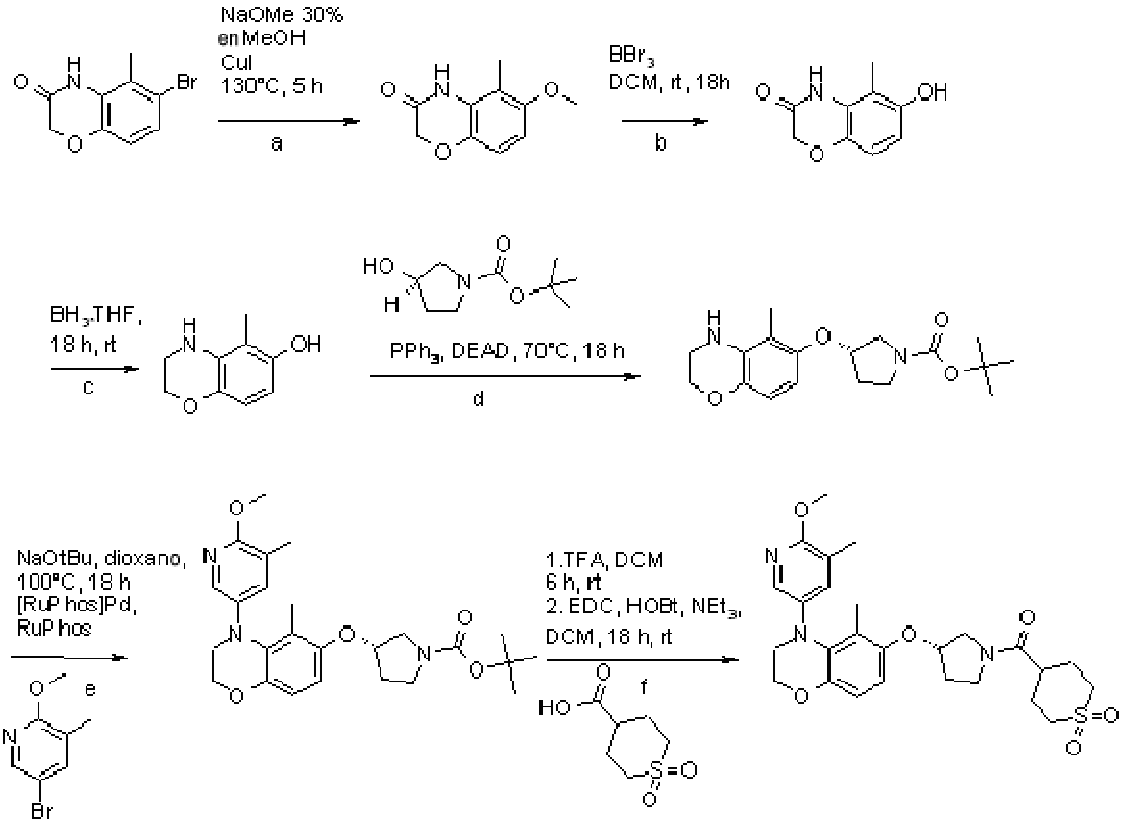
Una solución de la {(S)-3-[4-(5-amino-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxaziniloxi]-pirrolidin-1-il}-(1-metil-1H-imidazol-4-il)-metanona (22.9 miligramos, 0.05 milimoles) en piridina (1 mililitro) se trató con cloruro de metan-sulfonilo (CAS registro 124-63-0) (0.08 mililitros, 0.97 milimoles), y se agitó a 50°C durante 18 horas. La mezcla de reacción se diluyó con dicloro-metano (DCM) y H_2O, la capa orgánica se separó mediante elución a través de un cartucho de separación de fases y se concentró. El residuo se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 100:0 a 0:100, y luego

EtOAc/MeOH, de 90:10 a 80:20), las fracciones combinadas se concentraron, se disolvieron en tBuOH/H_2O y se liofilizaron, para proporcionar el compuesto del título como un sólido incoloro (14 miligramos, 49 por ciento).

UPLC Rt_{M2} =1.39 minutos; ESIMS: 529 [$(M+H)^+$].

^{1}H RMN (400 MHz, CD_3OD): δ 7.87 (d, 1H), 7.41-7.76 (m, 3H), 6.73 (m, 1H), 6.02-6.44 (m, 2H), 4.14-4.39 (m, 2H), 3.87-4.12 (m, 5H), 3.55-3.84 (m, 8H), 2.85-3.08 (m, 3H), 1.75-2.40 (m, 2H).

<u>Ejemplo V:</u> (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona



a) 6-metoxi-5-metil-4H-benzo-[1,4]-oxazin-3-ona

Una solución de la 6-bromo-5-metil-4H-benzo-[1,4]-oxazin-3-ona (CAS registro 1154740-47-2) (1,000 miligramos, 4.13 milimoles), y CuI (79 miligramos, 0.41 milimoles) en NaOMe al 30 por ciento en metanol (8.1 mililitros) se agitó a 130°C durante 5 horas. La mezcla color naranja/café se enfrió a temperatura ambiente, se diluyó con EtOAc, y se lavó con una solución acuosa saturada de $NaHCO_3$. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, y se concentraron, para proporcionar un sólido color naranja. La trituración con ciclohexano proporcionó el compuesto del título como un sólido color rosado (647 miligramos, 70 por ciento de rendimiento).

HPLC Rt_{M1} =0.73 minutos.

^1H RMN (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 6.76 (d, 1H), 6.53 (d, 1H), 4.42 (s, 2H), 3.71 (s, 3H), 2.05 (s, 3H).

b) 6-hidroxi-5-metil-4H-benzo-[1,4]-oxazin-3-ona

Una suspensión de la 6-metoxi-5-metil-4H-benzo-[1,4]-oxazin-3-ona (647 miligramos, 3.35 milimoles) en dicloro-metano (DCM) (30 mililitros) se trató bajo argón a temperatura ambiente con BBr_3 (3.16 mililitros, 33.5 milimoles), y se agitó durante 18 horas a temperatura ambiente. La mezcla de reacción se apagó mediante la adición por goteo de metanol a 0°C hasta la obtención de una solución transparente. Después de la remoción de los solventes, el residuo se vertió sobre hielo / una solución acuosa saturada de $NaHCO_3$, y se

extrajo con EtOAc. La capa orgánica se secó sobre $MgSO_4$ y se concentró, para proporcionar el compuesto del título como un sólido color café (647 miligramos, crudo), el cual se utilizó en el siguiente paso sin mayor purificación.

HPLC Rt_{M1} =0.49 minutos.

^1H RMN (400 MHz, DMSO-d_6): δ 10.11 (s, 1H), 6.43 (d, 1H), 5.98 (d, 1H), 4.57 (s, 2H), 1.89 (s, 3H).

c) 5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol

Una solución de la 6-hidroxi-5-metil-4H-benzo-[1,4]-oxazin-3-ona (647 miligramos, 3.61 milimoles) en tetrahidrofurano (THF) (20 mililitros) se trató bajo argón a 0°C con BH_3*THF (1M en tetrahidrofurano (THF), 10.83 mililitros, 10.83 milimoles), y se agitó durante 18 horas a temperatura ambiente. Se agregó metanol, y la solución se agitó a temperatura ambiente durante 1 hora, y se concentró para proporcionar un residuo, el cual se disolvió en tetrahidrofurano (THF) (20 mililitros), se trató con BH_3*THF (1M en tetrahidrofurano (THF), 10.83 mililitros, 10.83 milimoles), y se agitó a temperatura ambiente durante 18 horas. Se agregó metanol, la solución se agitó a temperatura ambiente durante 4 horas, y se concentró a sequedad, para proporcionar el compuesto del título como un sólido color café (600 miligramos, crudo), el cual se utilizó en el siguiente paso sin mayor purificación.

HPLC Rt_{M1} =0.49 minutos; ESIMS: 166 [$(M+H)^+$].

d) Terbutil-éster del ácido (S)-3-(5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi)-pirrolidin-1-carboxílico

Una solución de trifenil-fosfina (1.33 gramos, 5.09 milimoles) en tetrahidrofurano (THF) (10 mililitros) se trató con azodicarboxilato de dietilo (0.8 mililitros, 5.09 milimoles), seguido por el terbutil-éster del ácido (R)-3-hidroxi-pirrolidin-1-carboxílico (CAS registro 127423-61-4) (1 gramo, 5.45 milimoles), y 5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol (600 miligramos, 3.63 milimoles). La solución color rojo/café resultante se agitó a 70°C durante 18 horas. La mezcla color café se enfrió, se diluyó con EtOAc, y se lavó con una solución acuosa saturada de $NaHCO_3$. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron, y se concentraron, para proporcionar un aceite color café. El producto crudo se purificó tres veces mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 90:10 a 40:60), para proporcionar el compuesto del título como un aceite incoloro (130 miligramos, 11 por ciento de rendimiento)

HPLC Rt_{M1} =1.09 minutos; ESIMS: 335 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 6.44 (d, 1H), 6.22-6.04 (m, 1H), 5.24 (br s, 1H), 4.75 (br s, 1H), 4.07-3.93 (m, 2H), 3.45-3.33 (m, 3H), 3.28 (d, 7H), 2.00 (d, 2H), 1.83 (d, 3H), 1.46-1.32 (m, 9H).

e) Terbutil-éster del ácido (S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carboxílico

Una solución del terbutil-éster del ácido (S)-3-(5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi)-pirrolidin-1-carboxílico (120 miligramos, 0.36 milimoles), 5-bromo-2-metoxi-3-metil-piridina (CAS

registro 760207-87-2) (145 miligramos, 0.72 milimoles), NaOtBu (103 miligramos, 1.08 milimoles), RuPhos (CAS registro 787618-22-8) (8 miligramos, 0.02 milimoles) y un ciclo de [RuPhos]-paladio (CAS registro 787618-22-8) (15 miligramos, 0.02 milimoles) en dioxano (2 mililitros) se agitó a 100°C durante 18 horas. La mezcla color naranja/café se enfrió, se diluyó con EtOAc, y se lavó con agua. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron, y se concentraron, para proporcionar un aceite color café. El producto crudo se purificó tres veces mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 95:05 a 60:40), para proporcionar el compuesto del título como un aceite amarillo (97 miligramos, 60 por ciento de rendimiento).

HPLC Rt_{M1} =1.37 minutos; ESIMS: 456 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.40 (d, 1H), 7.28-7.07 (m, 1H), 6.74 (s, 2H), 4.84 (br s, 1H), 3.96 (br s, 2H), 3.80 (s, 2H), 3.57 (br s, 2H), 3.44-3.19 (m, 10H), 2.08 (s, 3H), 2.05-1.92 (m, 2H), 1.60 (d, 3H), 1.34 (d, 9H).

f) (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona

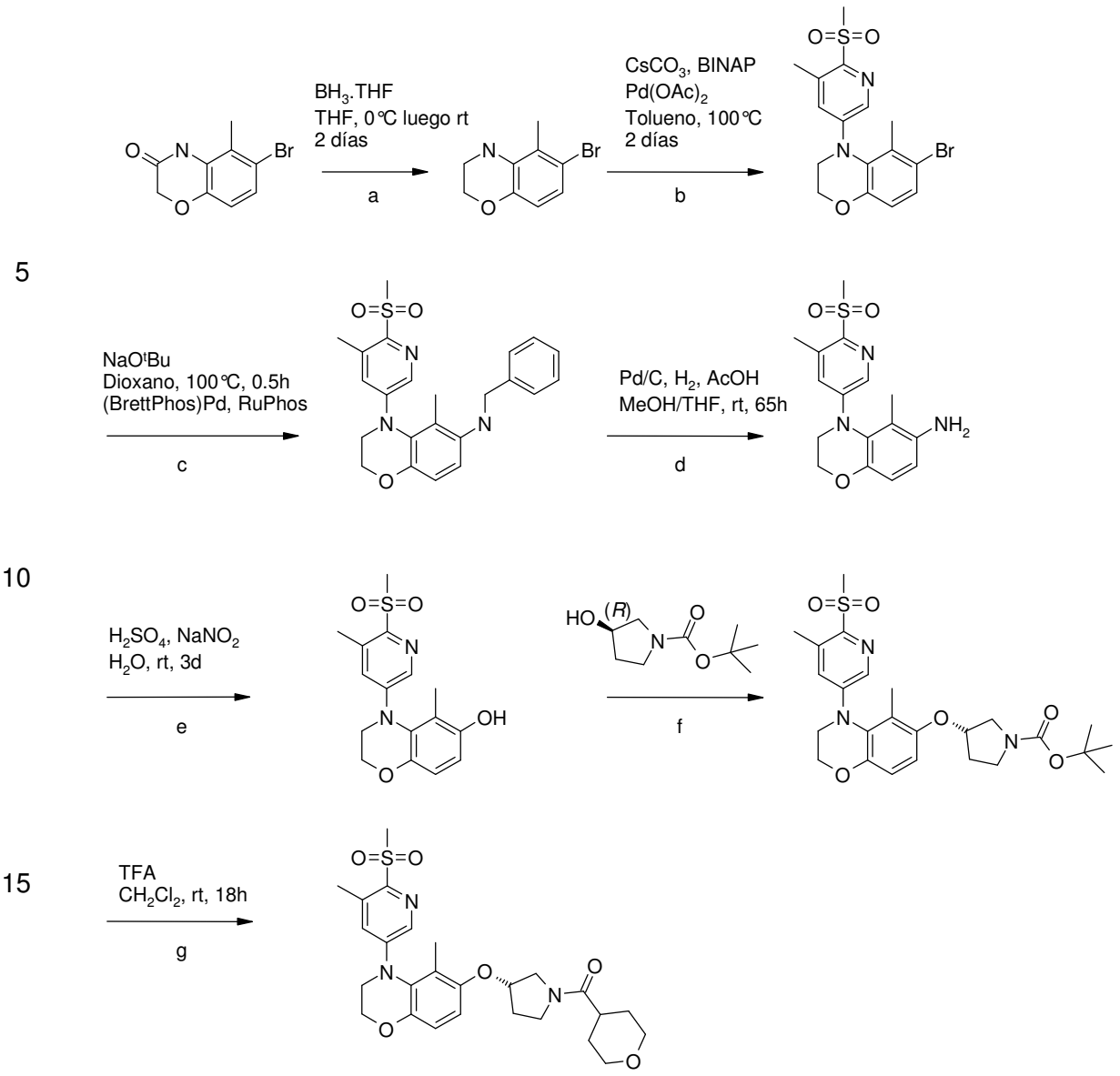
Una solución del terbutil-éster del ácido (S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-carboxílico (97 miligramos, 0.21 milimoles) en dicloro-metano (DCM) (3 mililitros) se trató bajo argón a temperatura ambiente con ácido trifluoro-acético (TFA) (0.16 mililitros, 2.13

milimoles), y se agitó durante 6 horas. La mezcla de reacción se apagó con una solución acuosa saturada de $NaHCO_3$, y la solución orgánica se separó a través de un cartucho de separación de fases, proporcionando una solución amarilla. A la solución amarilla se le agregaron ácido 1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-carboxílico (CAS registro 64096-87-3) (49 miligramos, 0.28 milimoles), Et_3N (0.09 mililitros, 0.64 milimoles), EDC (62 miligramos, 0.32 milimoles), y HOBT (49 miligramos, 0.32 milimoles), y se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se apagó con una solución acuosa saturada de $NaHCO_3$, y la capa orgánica se separó pasándola a través de un cartucho de separación de fases, entonces se concentró y se purificó mediante RP-HPLC de preparación (columna SunFire C18 OBD 5 milímetros, 30 x 100 milímetros, Solvente A: H_2O (ácido trifluoro-acético (TFA) al 0.1 por ciento) Solvente B**:** CH_3CN (ácido trifluoro-acético (TFA) al 0.1 por ciento)), para proporcionar el compuesto del título como un sólido blanco (76 miligramos, 70 por ciento de rendimiento).

HPLC Rt_{M1} =0.98 minutos; ESIMS: 516 [$(M+H)^+$].

^1H RMN (400 MHz, DMSO-d_6, 375K): δ 7.44 (br s, 1H), 7.18 (br s, 1H), 6.75 (s, 2H), 4.88 (br s, 1 H), 4.02 (t, 2H), 3.86 (s, 3H), 3.81-3.33 (m, 6H), 3.24-3.06 (m, 4H), 2.83 (br s, 1H), 1.66 (s, 3H). Rotámeros.

Ejemplo W: {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona



a) 6-bromo-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazina

Una solución de la 6-bromo-5-metil-4H-benzo-[1,4]-oxazin-3-ona (CAS registro 1154740-47-2) (425 miligramos, 1.56 milimoles) en tetrahidrofurano (THF) (9 mililitros) se trató bajo argón a 0°C con BH_3*THF (1M en tetrahidrofurano (THF), 4.7 mililitros, 4.69 milimoles), y se agitó durante 18 horas a temperatura ambiente. Se

agregó BH_3.THF 1M (2 mililitros), y se continuó la agitación durante otras 24 horas. La mezcla de reacción se concentró y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 80:20), para proporcionar el compuesto del título como un sólido color naranja (324 miligramos, 86 por ciento de rendimiento).

HPLC Rt_{M1} =1.04 minutos; ESIMS: 228, 230 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 6.68 (d, 1H), 6.48 (d, 1H), 5.54 (br s, 1H), 4.04 (t, 2H), 3.36-3.26 (m, 2H), 2.11(s, 3H).

b) 6-bromo-4-(6-metan-sulfonil-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazina

Una solución de la 6-bromo-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazina (324 miligramos, 1.42 milimoles), el intermediario IA1 (391 miligramos, 1.56 milimoles), Cs_2CO_3 (1018 miligramos, 3.13 milimoles), BINAP (CAS registro 98327-87-8) (44 miligramos, 0.07 milimoles), y $Pd(OAc)_2$ (CAS registro 3375-31-3) (32 miligramos, 0.14 milimoles) en tolueno (13 mililitros), se agitó a 100°C durante 18 horas. Se volvieron a cargar el catalizador y el ligando, y se continuó la agitación durante otras 24 horas a 100°C, la mezcla de reacción se enfrió a temperatura ambiente, se diluyó con EtOAc, y se lavó con agua. La concentración de la capa orgánica y la purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 97:03 a 40:60) proporcionaron el compuesto del título como un sólido color naranja (345 miligramos, 58 por ciento de rendimiento).

HPLC Rt_{M1} =1.13 minutos; ESIMS: 397,399 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.99 (br. s, 1H), 7.37 (d, 1H), 7.24 (br. s, 1H), 6.83 (d, 1H), 4.13 (t, 2H), 3.97-3.86 (m, 2H), 3.30 (s, 3H), 2.52 (s, 3H), 1.93 (s, 3H).

c) Bencil-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-il]-amina

Una solución de la 6-bromo-4-(6-metan-sulfonil-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazina (324 miligramos, 0.82 milimoles), bencil-amina (350 miligramos, 3.26 milimoles), NaOtBu (157 miligramos, 1.63 milimoles), RuPhos (CAS registro 787618-22-8) (30 miligramos, 0.06 milimoles), y el ciclo de [BrettPhos]-paladio (CAS registro 1148148-01-9) (52 miligramos, 0.06 milimoles) en dioxano (16 mililitros), se agitó a 80°C durante 0.5 horas. La filtración, la concentración del filtrado, y la purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 88:12 a 35:65), proporcionaron el compuesto del título como un aceite amarillo (228 miligramos, 66 por ciento de rendimiento).

HPLC Rt_{M1} =1.13 minutos; ESIMS: 424 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.94 (br s, 1H), 7.40-7.33 (m, 2H), 7.30 (t, 2H), 7.19 (t, 2H), 6.58 (d, 1H), 6.30 (d, 1H), 5.25 (t, 1H), 4.30 (d, 2H), 4.04-3.97 (m, 2H), 3.90 (d, 2H), 3.29 (s, 3H), 2.51 (br s, 3H), 1.76 (s, 3H).

d) 4-(6-metan-sulfonil-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-il-amina

Una solución de la bencil-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-il]-amina (228 miligramos, 0.53 milimoles), ácido acético (0.21 mililitros, 3.70 milimoles), y Pd/C en metanol (MeOH)/tetrahidrofurano (THF) (2.5/2.5 mililitros) se hidrogenó con H_2 a temperatura ambiente durante 65 horas. La filtración y concentración del filtrado proporcionó el compuesto del título como un aceite color verde (200 miligramos, crudo, incluyendo el AcOH restante).

HPLC Rt_{M1} =0.64 minutos; ESIMS: 334 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.96 (br s, 1H), 7.17 (br s, 1H), 6.62-6.54 (d, 1H), 6.54-6.45(d, 1H), 4.48 (br s, 2H), 4.01 (t, 2H), 3.88 (br s, 2H), 3.28 (s, 3H), 1.88 (d, 3H), 1.63 (s, 3H).

e) 4-(6-metan-sulfonil-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol

Una solución de la 4-(6-metan-sulfonil-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-il-amina (200 miligramos, 0.60 milimoles) en agua (3.5 mililitros) y H_2SO_4 (0.32 mililitros) se agregó por goteo a una solución de nitrito de sodio (49.7 miligramos, 0.72 milimoles) en agua (10 mililitros) a 0°C. La mezcla se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se filtró, y el filtrado se apagó con una solución acuosa saturada de $NaHCO_3$ y se extrajo con EtOAc. La capa orgánica se secó sobre $MgSO_4$, se filtró, y se concentró, para proporcionar un aceite color café. La purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (dicloro-metano (DCM) / metanol, de

88:12 a 80:20) proporcionó el compuesto del título como un aceite color café (50 miligramos, 25 por ciento de rendimiento).

HPLC Rt_{M1} =0.78 minutos; ESIMS: 335 [$(M+H)^+$].

f) (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona

Una solución de trifenil-fosfina (55 miligramos, 0.21 milimoles) en tetrahidrofurano (THF) (2.5 mililitros) se trató con azodicarboxilato de dietilo (0.03 mililitros, 0.21 milimoles), seguido por el terbutil-éster del ácido (R)-3-hidroxi-pirrolidin-1-carboxílico (CAS registro 127423-61-4) (33 miligramos, 0.18 milimoles), y 4-(6-metan-sulfonil-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol (50 miligramos, 0.15 milimoles). La solución color rojo/café resultante se agitó a 70°C durante 18 horas. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con EtOAc, y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre $MgSO_4$. Se concentró y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 90:10 a 40:60), para proporcionar el compuesto del título como un sólido color naranja (44 miligramos, 58 por ciento de rendimiento).

HPLC Rt_{M1} =1.16 minutos; ESIMS: 504 [$(M+H)^+$].

g) {(S)-3-[4-(6-metan-sulfonil-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(tetrahidro-piran-4-il)-metanona

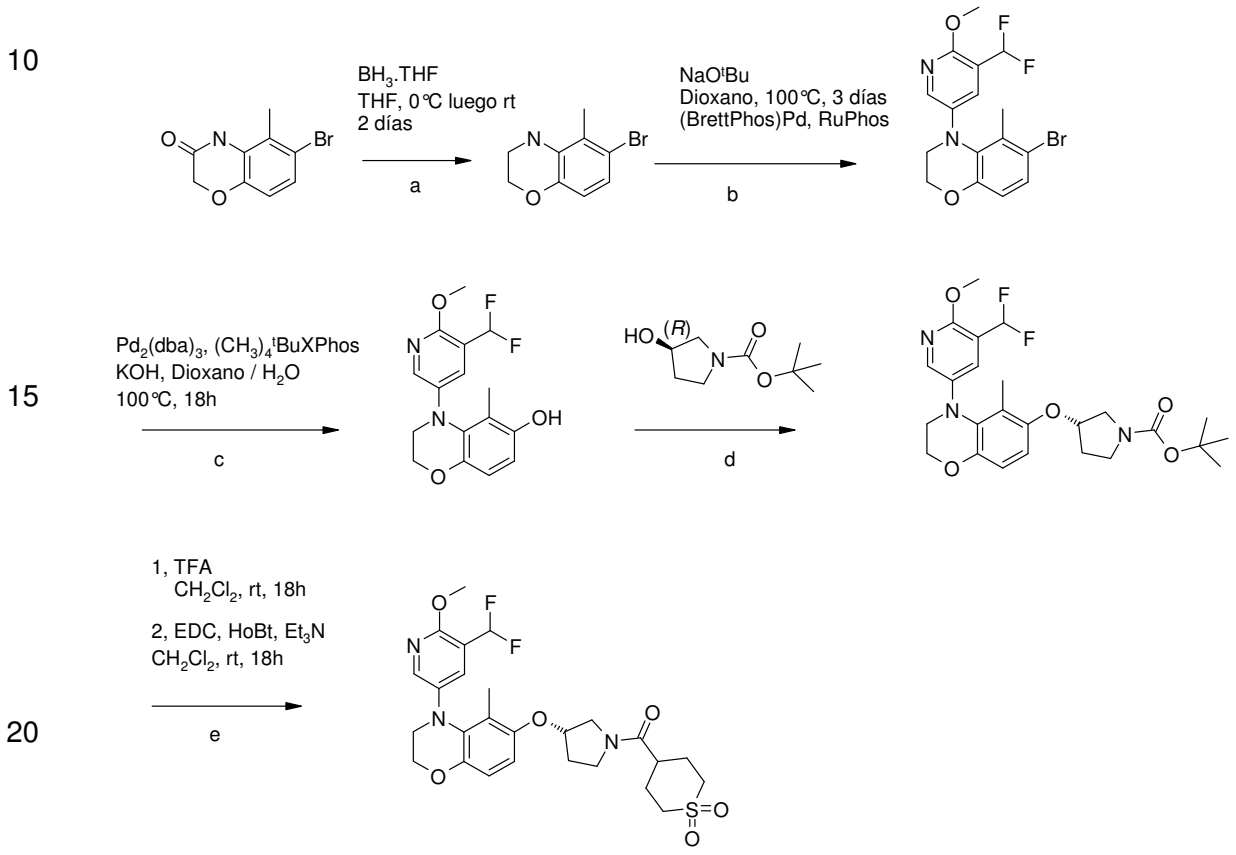
Una solución de la (1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-{(S)-3-[4-(6-metoxi-5-metil-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-metanona (44 miligramos, 0.09 milimoles) en dicloro-metano (DCM) (4 mililitros) se trató bajo argón a temperatura ambiente con ácido trifluoro-acético (TFA) (0.07 mililitros, 0.17 milimoles), y se agitó durante 18 horas. La mezcla de reacción se apagó con una solución acuosa saturada de $NaHCO_3$, y la solución orgánica se separó a través de un cartucho de separación de fases, se concentró, y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (dicloro-metano (DCM) / metanol, de 100:0 a 90:10). El producto obtenido se disolvió en dicloro-metano (DCM) (4 mililitros), y se agregó Et_3N. A la mezcla de reacción se le agregó cloruro de tetrahidro-piran-4-carbonilo (CAS registro 40191-32-0) (15 miligramos, 0.10 milimoles), a 0°C, y la solución color naranja resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se apagó con una solución acuosa saturada de $NaHCO_3$, y la capa orgánica se separó mediante elución a través de un cartucho de separación de fases, se concentró, y se purificó mediante SFC (columna NH_2 (250 x 30 milímetros (longitud x anchura), 60A, 5 micras, Princeton, gradiente de metanol en CO_2 súper-crítico), para proporcionar el compuesto del título como un aceite amarillo (15 miligramos, 32 por ciento de rendimiento).

HPLC Rt_{M1} =0.88 minutos; ESIMS: 516 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6, 375K): δ 7.98 (br s, 1 H), 7.19 (br

s, 1 H), 6.92 - 6.85 (m, 1 H), 6.85 - 6.77 (m, 1 H), 4.95 (br s, 1 H), 4.12 (t, 2 H), 3.92 (t, 2 H), 3.88 (br s, 2 H), 3.61 (br s, 3 H), 3.38 (td, 2 H), 3.27 (s, 3 H), 2.68 (d, 1 H), 2.56 (s, 3 H), 2.17 (br s, 2 H), 1.73 (s, 3 H), 1.58 (br s, 4 H). Rotámeros.

<u>Ejemplo X:</u> {(S)-3-[4-(5-difluoro-metil-6-metoxi-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-metanona



a) 6-bromo-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazina

Una solución de la 6-bromo-5-metil-4H-benzo-[1,4]-oxazin-3-

ona (CAS registro 1154740-47-2) (2.8 gramos, 11.56 milimoles) en tetrahidrofurano (THF) (50 mililitros) se trató bajo argón con BH_3*THF (1M en tetrahidrofurano (THF), 34.7 mililitros, 34.70 milimoles), y se calentó bajo reflujo durante 2 horas. Se agregó metanol, y la solución se agitó a temperatura ambiente durante 1 hora, se concentró, y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 80:20), para proporcionar el compuesto del título como un sólido color naranja (1.8 gramos, 68 por ciento de rendimiento).

HPLC Rt_{M1} =1.04 minutos; ESIMS: 228, 230 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 6.68 (d, 1H), 6.48 (d, 1H), 5.54 (br s, 1H), 4.04 (t, 2H), 3.36-3.26 (m, 2H), 2.11 (s, 3H).

b) 6-bromo-4-(5-difluoro-metil-6-metoxi-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazina

Una solución de la 6-bromo-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazina (500 miligramos, 2.19 milimoles), el intermediario IA6 (574 miligramos, 2.41 milimoles), NaOtBu (421 miligramos, 4.38 milimoles), BrettPhos (CAS registro 1070663-78-3) (59 miligramos, 0.11 milimoles), y un ciclo de [BrettPhos]-paladio (CAS registro 1148148-01-9) (88 miligramos, 0.11 milimoles) en dioxano (11 mililitros), se agitó a 100°C durante 18 horas. Se volvieron a cargar el catalizador y el ligando, y se continuó la agitación a 100°C durante 48 horas. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con EtOAc, y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre $MgSO_4$, y se concentró, para

proporcionar un aceite color café. La purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 80:20) proporcionó el compuesto del título como un aceite color café (150 miligramos, 18 por ciento de rendimiento).

HPLC Rt_{M1} =1.34 minutos; ESIMS: 385, 387 [$(M+H)^+$].

c) 4-(5-difluoro-metil-6-metoxi-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol

Una mezcla de la 6-bromo-4-(5-difluoro-metil-6-metoxi-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazina (150 miligramos, 0.39 milimoles), KOH (65 miligramos, 1.17 milimoles) en agua (0.33 mililitros), tetrametil-terbutil-XPhos (CAS registro 857356-94-6) (18.72 miligramos, 0.04 milimoles), y $Pd_2(dba)_3$ (17.83 miligramos, 0.02 milimoles) en dioxano (2 mililitros), se desgasificó con nitrógeno y se calentó a 100°C durante 18 horas. La filtración, la concentración, y la purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 70:30), proporcionaron el compuesto del título como un aceite color naranja (65 miligramos, 52 por ciento de rendimiento).

HPLC Rt_{M1} =1.01 minutos; ESIMS: 323 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.83 (s, 1H), 7.89 (d, 1H), 7.36 (d, 1H), 7.00 (t, 1H), 6.61 (d, 1H), 6.55 (d, 1H), 3.93 (t, 2H), 3.88 (s, 3H), 3.65 (t, 2H), 1.60 (s, 3H).

d) Terbutil-éster del ácido (S)-3-[4-(5-difluoro-metil-6-metoxi-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-

pirrolidin-1-carboxílico

Una solución de trifenil-fosfina (74 miligramos, 0.28 milimoles) en tetrahidrofurano (THF) (2 mililitros) se trató con azodicarboxilato de dietilo (0.04 mililitros, 0.28 milimoles), seguido por el terbutil-éster del ácido (R)-3-hidroxi-pirrolidin-1-carboxílico (CAS registro 127423-61-4) (45 miligramos, 0.24 milimoles), y 4-(5-difluoro-metil-6-metoxi-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol (65 miligramos, 0.20 milimoles). La solución color rojo/café resultante se agitó a 70°C durante 18 horas, se enfrió a temperatura ambiente, se diluyó con EtOAc, y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre $MgSO_4$, se concentró, y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 70:30), para proporcionar el compuesto del título como un sólido amarillo (51 miligramos, 42 por ciento de rendimiento).

HPLC Rt_{M1} =1.36 minutos; ESIMS: 492 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.92-7.75 (m, 1H), 7.46-7.33 (m, 1H), 7.19-6.84 (t, 1H), 6.77 (s, 2H), 4.86 (br s, 1H), 3.98 (br s, 2H), 3.88 (s, 3H), 3.73-3.55 (m, 2H), 3.46-3.33 (m, 2H), 2.12-1.95 (m, 2H), 1.65-1.55 (m, 3H), 1.34 (br s, 9H). Rotámeros.

e) {(S)-3-[4-(5-difluoro-metil-6-metoxi-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-iloxi]-pirrolidin-1-il}-(1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-il)-metanona

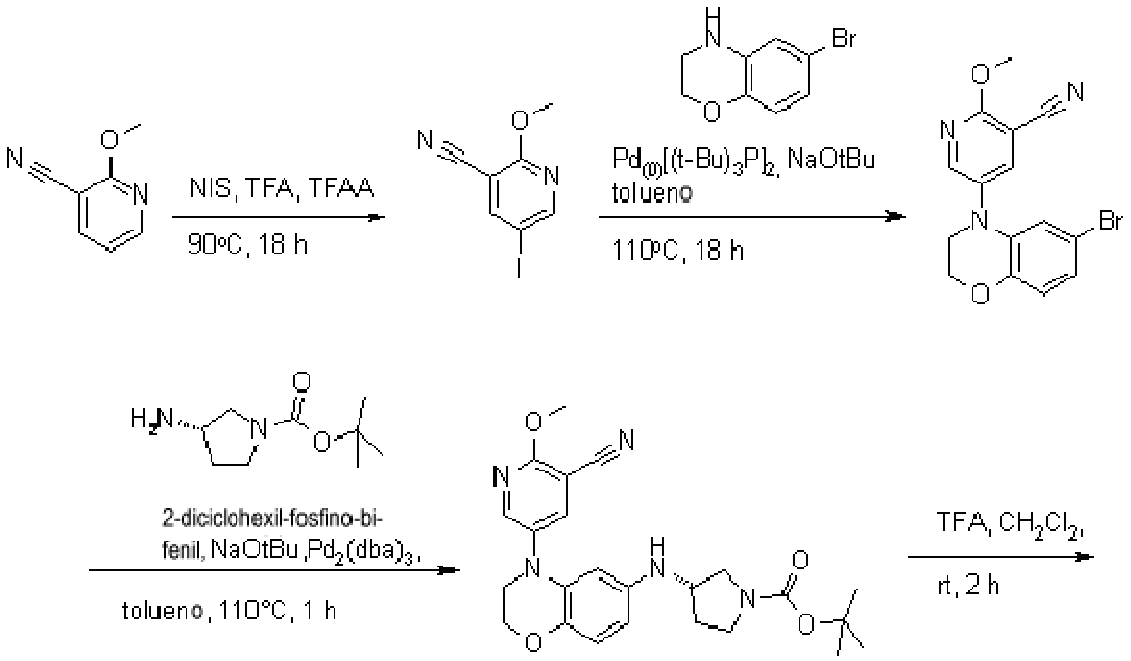
Una solución del terbutil-éster del ácido (S)-3-[4-(5-difluoro-metil-6-metoxi-piridin-3-il)-5-metil-3,4-dihidro-2H-benzo-[1,4]-oxazin-

6-iloxi]-pirrolidin-1-carboxílico (51 miligramos, 0.10 milimoles) en dicloro-metano (DCM) (3 mililitros) se trató bajo argón a temperatura ambiente con ácido trifluoro-acético (TFA) (0.08 mililitros, 1.10 milimoles), y se agitó durante 18 horas. La mezcla de reacción se apagó con una solución acuosa saturada de $NaHCO_3$, y la solución orgánica se separó a través de una separación de fases, proporcionando una solución amarilla. Se agregaron ácido 1,1-dioxo-hexahidro-1lambda*6*-tiopiran-4-carboxílico (CAS registro 64096-87-3) (25 miligramos, 0.14 milimoles), Et_3N (0.05 mililitros, 0.33 milimoles), EDC (31 miligramos, 0.16 milimoles), y HOBT (25 miligramos, 0.16 milimoles), y la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se apagó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se separó mediante elución a través de un cartucho de separación de fases, el producto crudo se purificó sobre SFC (columna Reprosil NH_2 (250 x 30 milímetros (longitud x anchura), 60A, 5 micras, Princeton, gradiente de metanol en CO_2 súper-crítico), para proporcionar el compuesto del título como un aceite amarillo (19 miligramos, 30 por ciento de rendimiento).

HPLC Rt_{M1} =1.00 minutos; ESIMS: 552 [$(M+H)^+$].

^1H RMN (400 MHz, DMSO-d_6, 375K): δ 7.85 (br s, 1 H), 7.43 (br s, 1H), 6.96 (t, 1H), 6.80 (s, 2H), 5.11-4.71 (m, 1H), 4.04 (t, 2 H), 3.94 (s, 3H), 3.70 (d, 2 H), 3.63 (br s, 2 H), 3.52 (br s, 2 H), 3.23-3.04 (m, 4H), 2.92-2.73 (m, 1H), 2.16 (br s, 2 H), 2.06 (br s, 4H), 1.67 (s, 3 H), Rotámeros.

Ejemplo Y: **2-metoxi-5-{6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-il-amino]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo**



a) 5-yodo-2-metoxi-nicotinonitrilo

Una mezcla del 2-metoxi-nicotinonitrilo (CAS registro 7254-34-4) (10 gramos, 74.6 milimoles), y N-yodo-succinimida (CAS registro

516-12-1) (25.2 gramos, 112 milimoles) se trató con ácido trifluoro-acético (TFA) (CAS registro 76-05-1) (68.9 mililitros, 895 milimoles), y anhídrido trifluoro-acético (CAS registro 407-25-0) (31.6 mililitros, 224 milimoles), y la mezcla de reacción se calentó a 90°C durante 18 horas; entonces se enfrió a temperatura ambiente, y se vertió en hielo. La mezcla se basificó lentamente utilizando una solución acuosa de NaOH al 30 por ciento, se diluyó con agua, y se extrajo con EtOAc. La capa orgánica se lavó sucesivamente con una solución acuosa de tiosulfato de sodio al 20 por ciento, y una solución acuosa saturada de $NaHCO_3$, se secó sobre Na_2SO_4, se filtró, y se concentró. Se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 20:80), como un sólido (12.2 gramos, rendimiento del 63 por ciento).

UPLC Rt_{M14} =1.30 minutos; ESIMS: 261 [$(M+H)^+$].

^1H RMN (400 MHz, $CDCl_3$): δ 8.54 (d, 1H), 8.11 (d, 1H), 4.06 (s, 3H).

b) 5-(6-bromo-2,3-dihidro-benzo-[1,4]-oxazin-4-il)-2-metoxi-nicotinonitrilo

Una mezcla de la 6-bromo-3,4-dihidro-2H-benzo-[1,4]-oxazina (CAS registro 105655-01-4) (5.0 gramos, 23.36 milimoles), 5-yodo-2-metoxi-nicotinonitrilo (12.2 gramos, 46.7 milimoles), y NaOtBu (2.69 gramos, 28.0 milimoles) en tolueno (50 mililitros), se desgasificó con argón durante 10 minutos, y entonces se agregó bis-(tri-terbutil-fosfina)-paladio(0) (0.36 gramos, 0.70 milimoles). La mezcla de

reacción se agitó a 110ºC durante 18 horas bajo argón. Después de enfriarse a temperatura ambiente, la mezcla de reacción se filtró a través de Celite, se enjuagó con EtOAc, y los filtrados se lavaron con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 50:50), para proporcionar el compuesto del título (4.2 gramos, 52 por ciento de rendimiento).

UPLC Rt_{M14} =1.55 minutos; ESIMS: 348 [$(M+H)^+$].

^1H RMN (400 MHz, $CDCl_3$): δ 8.31 (d, 1H), 7.80 (d, 1H), 6.89 (dd, 1H), 6.78 (d, 1H), 6.67 (d, 1H), 4.30-4.35 (m, 2H), 4.10 (s, 3H), 3.61-3.66 (m, 2H).

c) Terbutil-éster del ácido (S)-3-[4-(5-ciano-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-il-amino]-pirrolidin-1-carboxílico

Una mezcla del 5-(6-bromo-2,3-dihidro-benzo-[1,4]-oxazin-4-il)-2-metoxi-nicotinonitrilo (300 miligramos, 0.87 milimoles), terbutil-éster del ácido (S)-3-amino-pirrolidin-1-carboxílico (CAS registro 147081-44-5) (0.26 mililitros, 1.47 milimoles), 2-(diciclohexil-fosfino)-bifenilo (CAS registro 247940-06-3) (18.2 miligramos, 0.05 milimoles), y NaOtBu (100 miligramos, 1.04 milimoles) en tolueno (10 mililitros), se desgasificó con argón durante 10 minutos, y entonces se agregó $Pd_2(dba)_3$ (23.8 miligramos, 0.03 milimoles). La mezcla de reacción se agitó a 110ºC durante 1 hora bajo argón. Después de enfriarse a temperatura ambiente, la mezcla de reacción se filtró a

través de Celite, se enjuagó con EtOAc, y los filtrados se concentraron. Se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 70:30) como una espuma amarilla (150 miligramos, 37 por ciento de rendimiento).

UPLC Rt_{M11} = 2.73 minutos; ESIMS: 452 [$(M+H)^+$].

^{1}H RMN (400 MHz, CD_3OD): δ 8.36 (d, 1H), 8.04 (d, 1H), 6.68 (s, 1H), 6.19 (dd, 1H), 6.03 (s, 1H), 4.19-4.24 (m, 2H), 4.06 (s, 3H), 3.81-3.89 (m, 1H), 3.62-3.68 (m, 2H), 3.48-3.56 (m, 1H), 3.35-3.48 (m, 2H), 3.08-3.18 (m, 1H), 2.05-2.18 (m, 1H), 1.75-1.87 (m, 1H), 1.46 (s, 9H).

d) 2-metoxi-5-[6-((S)-pirrolidin-3-il-amino)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-nicotinonitrilo

Una solución del terbutil-éster del ácido (S)-3-[4-(5-ciano-6-metoxi-piridin-3-il)-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-il-amino]-pirrolidin-1-carboxílico (144 miligramos, 0.32 milimoles) en CH_2Cl_2 (4 mililitros) se trató con ácido trifluoro-acético (TFA) (0.49 mililitros, 6.38 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas, se apagó con una solución acuosa saturada de $NaHCO_3$, y se extrajo con dicloro-metano (DCM). La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró bajo presión reducida, para proporcionar el producto del título como una espuma amarilla (120 miligramos, 100 por ciento de rendimiento).

UPLC Rt_{M11} = 2.06 minutos; ESIMS: 352 [$(M+H)^+$].

^{1}H RMN (400 MHz, CD_3OD): δ 8.36 (d, 1H), 8.04 (d, 1H), 6.69

(d, 1H), 6.17 (dd, 1H), 6.00 (d, 1H), 4.19-4.26 (m, 2H), 4.06 (s, 3H), 3.80-3.90 (m, 1H), 3.62-3.69 (m, 2H), 3.10-3.20 (m, 2H), 2.98-3.09 (m, 1H), 2.82-2.90 (m, 1H), 2.06-2.18 (m, 1H), 1.70-1.81 (m, 1H).

e) 2-metoxi-5-{6-[(S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-il-amino]-2,3-dihidro-benzo-[1,4]-oxazin-4-il}-nicotinonitrilo

A 0°C, una solución del 2-metoxi-5-[6-((S)-pirrolidin-3-il-amino)-2,3-dihidro-benzo-[1,4]-oxazin-4-il]-nicotinonitrilo (27 miligramos, 0.08 milimoles) en CH_2Cl_2 (1 mililitro) se trató con Et_3N (0.02 mililitros, 0.12 milimoles), y cloruro de tetrahidro-piran-4-carbonilo (CAS registro 40191-32-0) (11 microlitros, 0.09 milimoles). La mezcla de reacción se agitó a 0°C durante 1 hora, entonces se apagó con una solución acuosa saturada de $NaHCO_3$, y se extrajo con dicloro-metano (DCM). La capa orgánica se secó sobre Na_2SO_4, se filtró, y se concentró, y se obtuvo el compuesto del título después de la RP-HPLC de preparación (columna Sunfire Prep C18 OBD 30 x 100 milímetros, 5 micras; solvente A: H_2O + ácido trifluoro-acético (TFA) al 0.1 por ciento por volumen; solvente B: CH_3CN + ácido trifluoro-acético (TFA) al 0.1 por ciento por volumen, gradiente del 5 al 60 por ciento de B en 20 minutos), y de la filtración sobre un cartucho SPE Agilent PL-HCO_3 MP como un sólido amarillo (9 miligramos, 25 por ciento de rendimiento).

UPLC Rt_{M2} = 1.19 minutos; ESIMS: 464 [$(M+H)^+$].

^{1}H RMN (400 MHz, CD_3OD): δ 8.36 (d, 1H), 8.05 (m, 1H), 6.69 (dd, 1H), 6.15-6.23 (m, 1H), 5.97-6.07 (m, 1H), 4.15-4.29 (m, 2H), 4.06 (s, 3H), 3.82-4.03 (m, 3H), 3.35-3.80 (m, 8H), 2.65-2.84 (m, 1H),

2.03-2.28 (m, 1H), 1.49-2.03 (m, 5H).

Condiciones de acoplamiento

A) Aminaciones o hidroxilaciones de Buchwald

Condición #	Fuente de Pd	Ligando	Base	Solventes usados	Temperatura típica	Tiempo de reacción típico
CA1	$Pd_2(dba)_3$	Rac-BINAP	Cs_2CO_3	tolueno	60-100°C	16 h
CA2	$Pd_2(dba)_3$	XPhos	NaO^tBu	dioxano	100°C	1-18 h
CA3	$Pd_2(dba)_3$	XPhos	Cs_2CO_3	tolueno	100°C	
CA4	$Pd_2(dba)_3$	XPhos	Cs_2CO_3	dioxano	100°C	1-18 h
CA5	$Pd_2(dba)_3$	tetrametil-terbutil-XPhos	KOH	dioxano /H_2O	100°C	18-72 h
CA6	$Pd_2(dba)_3$	XPhos	NaO^tBu	tolueno	80-110°C	20 min-18 h
CA7	$Pd(P(tBu_3)_2$		NaO^tBu	tolueno	140°C (mw)	30 min
CA8	$Pd(P(tBu_3)_2$		NaO^tBu	tolueno	120°C	18 h
CA9	$Pd_2(dba)_3$	XPhos	NaO^tBu	tolueno	125°C (mw)	25 min

Condición #	Fuente de Pd	Ligando	Base	Solventes usados	Temperatura típica	Tiempo de reacción típico
CA10	$Pd(OAc)_2$	Rac-BINAP	Cs_2CO_3	tolueno	60-100°C	21 h
CA11	Pd[Ruphos]	RuPhos	NaO^tBu	dioxano	100°C	18 h
CA12	$Pd(P(tBu_3)_2$		K_3PO_4	tolueno	120°C	18 h
CA13	$Pd_2(dba)_3$	XPhos	K_3PO_4	tolueno	100°C	12 h
CA14	$Pd_2(dba)_3$	XPhos	K_3PO_4	tolueno	110-120°C	12 h
CA15	$Pd(P(tBu_3)_2$		NaO^tBu	THF	110°C	18 h
CA16	$Pd_2(dba)_3$	XPhos	NaO^tBu	THF	110°C	1 h-18 h

B) Condiciones de formación de enlace de amida

Condición#	Reactivos de acoplamiento	Solventes usados	Temperatura típica	Tiempo de reacción típico
CB1	HBTU	DMF o DMA	rt	1 h - 18 h
CB2	HOBT, EDC	DMF	rt	1 h - 18h
CB3	HATU	CH_2Cl_2	0°C a rt	30 min

Condi-ción#	Reactivos de acoplamiento	Solventes usados	Temperatura típica	Tiempo de reacción típico
CB4	HOBT, EDC	CH_2Cl_2	rt	18 h
CB5	COMU, DIPEA	DMF	rt	12 h
CB6	ninguno	CH_2Cl_2	rt	1 h – 18 h
CB7	HBTU	CH_2Cl_2	rt	30 min

C) Condiciones de introducción de cadena lateral

CC1) Utilizando mesilato

A temperatura ambiente, una solución seca del intermediario de piridin-2-ol (1 equivalente), y el intermediario de mesilato (de 1.1 a 2 equivalentes) en dimetil-formamida (DMF) (0.17 M), se trató con NaH en aceite mineral (de 2 a 3 equivalentes), y la mezcla de reacción se agitó a 20-80°C durante 4 a 72 horas.

CC2) Utilizando mesilato

A temperatura ambiente, una solución seca del intermediario de aril-6-ol (1 equivalente), y el intermediario de mesilato (1.1 -2 equivalentes) en dimetil-formamida (DMF) (0.17M), se trató con NaH en aceite mineral (de 2 a 3 equivalentes), y la mezcla de reacción se agitó a 50-80°C durante 4 a 72 horas.

CC3) Utilizando mesilato

A temperatura ambiente, una solución seca del intermediario

de aril-6-ol (1 equivalente), y el intermediario de mesilato (2.5 equivalentes) en dimetil-formamida (DMF) (0.06M), se trató con K_2CO_3 (4 equivalentes), y la mezcla de reacción se agitó de 85°C a 100°C durante 4 a 50 horas.

CC4) Utilizando Mitsunobu

A temperatura ambiente, se agregaron DEAD (1.4 equivalentes), terbutil-éster del ácido (R)-3-hidroxi-pirrolidin-1-carboxílico (1.5 equivalentes), y el intermediario de aril-6-ol (1 equivalente) a una solución de trifenil-fosfina (1.4 equivalentes) en tetrahidrofurano (THF) (0.30M) . La solución color rojo/café se agitó a 70°C durante 18 horas.

D) Condiciones para la cromatografía separación quiral

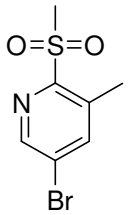
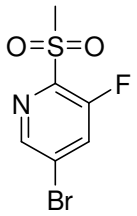
Método#	**Columna**	**Eluyente**	**Detección UV**
CD1	Chiralpak IC 250x30 mm, 5µm	n-Heptano/DMME/IPA/ DEA 20:50:30:0.05	230 nm
CD2	Chiralpak IC 250x30 mm, 5µm	ACN 100%	230 nm
CD3	Chiralcel ODH 250x30 mm, 5µm	EtOH/MeOH 60:40	220 nm

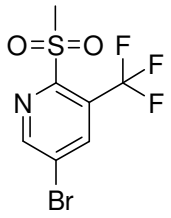
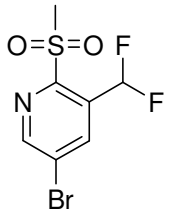
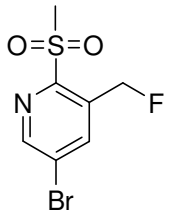
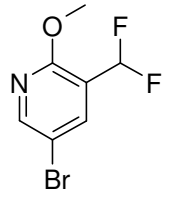
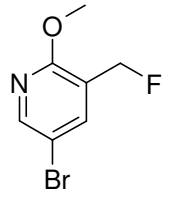
Método#	Columna	Eluyente	Detección UV
CD4	Chiralpak IC 250x30 mm, 5µm	DMME/IPA/MeOH/DEA 70:25:5:0.05,	230 nm
CD5	Chiralpak IC 250x30 mm, 5µm	ACN 100%	220 nm
CD6	Chiralpak IC 250x30 mm, 5µm	MeOH 100%	220 nm
CD7	Chiralpak IC 250X$_4$6 mm, 5µm	n-Heptano/DMME/EtOH/DEA 40:50:10:0.05	240 nm
CD8	Chiralcel OD-H, 4.6 x 250 mm	CO_2/IPA 70:30 (isocrática)	215 nm
CD9	Chiralpak AD-H, 5µm	Heptano/EtOH 60:40	
CD10	Chiralpak IC 250X$_4$6 mm, 5µm	DMME/IPA/MeOH/DEA 70:25:5:0.05,	230 nm

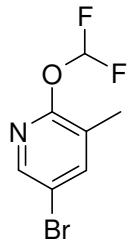
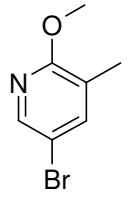
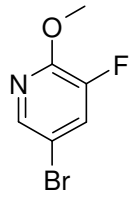
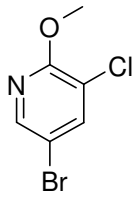
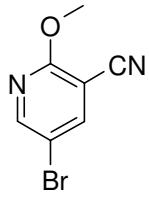
Método#	Columna	Eluyente	Detección UV
CD11	Chiralcel ODH 250x20 mm, 5µm	EtOH/MeOH 60:40	220 nm
CD12	Chiralpak IC 765X$_3$7.5 cm, 20 µm	EtOH/MeOH 50:50	210 nanómetros

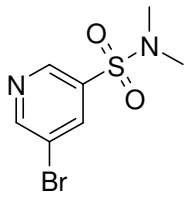
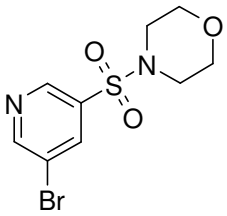
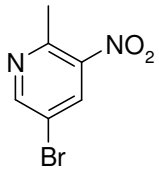
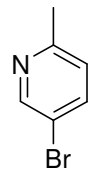
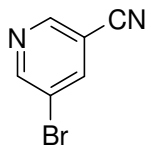
Preparación de Intermediarios

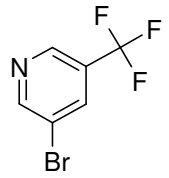
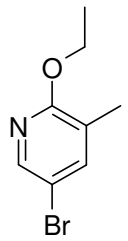
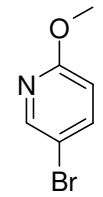
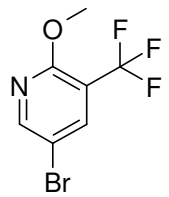
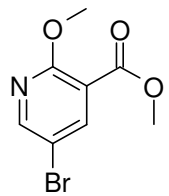
IA) Bromuros aromáticos

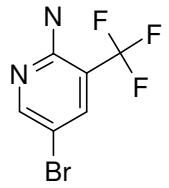
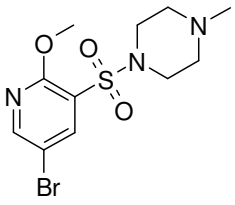
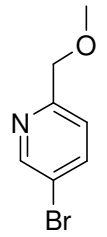
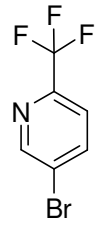
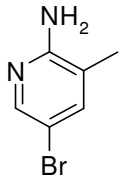
Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA1		5-bromo-2-metan-sulfonil-3-metil-piridina	1 paso de CAS 1289270-74-1
IA2		5-bromo-3-fluoro-2-metan-sulfonil-piridina	1 paso de CAS 1289007-85-7

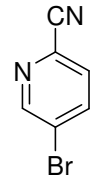
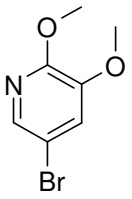
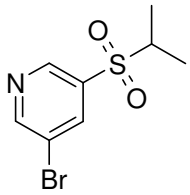
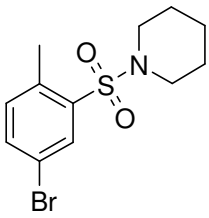
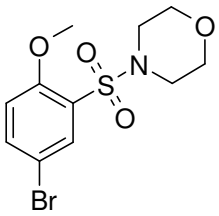
Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA3		5-bromo-2-metan-sulfonil-3-trifluoro-metil-piridina	1 paso de CAS 211122-42-8
IA4		5-bromo-3-difluoro-metil-2-metan-sulfonil-piridina	2 pasos de CAS 852181-11-4
IA5		5-bromo-3-fluoro-metil-2-metan-sulfonil-piridina	2 pasos de CAS 742100-75-0
IA6		5-bromo-3-difluoro-metil-2-metoxi-piridina	CAS 1254123-51-7
IA7		5-bromo-3-fluoro-metil-2-metoxi-piridina	1 paso de CAS 351410-47-4

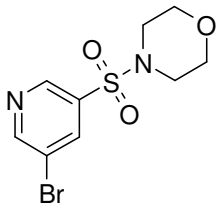
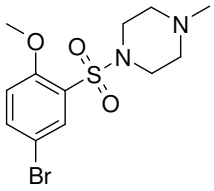
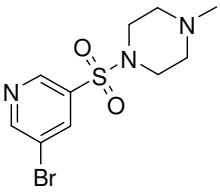
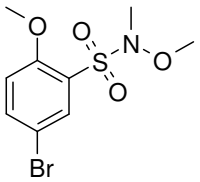
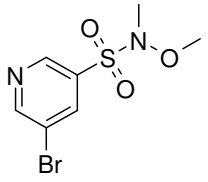
Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA8		5-bromo-2-difluoro-metoxi-3-metil-piridina	CAS 1214337-94-6
IA9		5-bromo-2-metoxi-3-metil-piridina	CAS 760207-87-2
IA10		5-bromo-3-fluoro-2-metoxi-piridina	CAS 124432-70-8
IA11		5-bromo-3-cloro-2-metoxi-piridina	CAS 848366-28-9
IA12		5-bromo-2-metoxi-nicotinonitrilo	CAS 941294-54-8

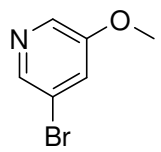
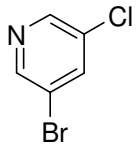
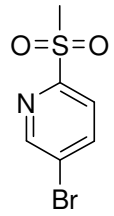
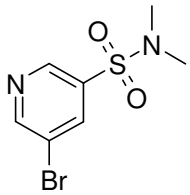
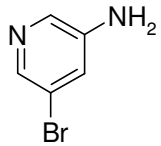
Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA13		dimetil-amida del ácido 5-bromo-piridin-3-sulfónico	CAS 896160-99-9
IA14		4-(5-bromo-piridin-3-sulfonil)-morfolina	CAS 889676-35-1
IA15		5-bromo-2-metil-3-nitro-piridina	CAS 911434-05-4
IA16		5-bromo-2-metil-piridina	CAS 3430-13-5
IA17		5-bromo-nicotinonitrilo	CAS 35590-37-5

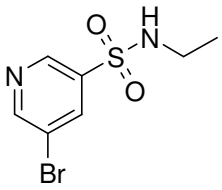
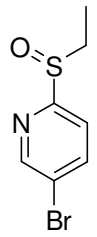
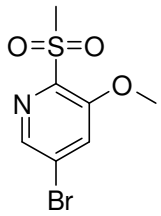
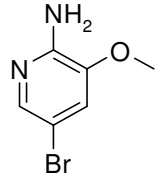
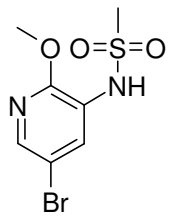
Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA18		5-bromo-trifluoro-metil-piridina	CAS 436799-33-6
IA19		5-bromo-2-etoxi-3-metil-piridina	CAS 610279-03-3
IA20		5-bromo-2-metoxi-piridina	CAS 13472-85-0
IA21		5-bromo-2-metoxi-3-trifluoro-metil-piridina	CAS 1214377-42-0
IA22		metil-éster del ácido 5-bromo-2-metoxi-nicotínico	CAS 122433-41-4

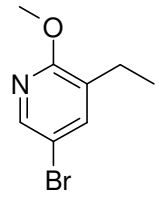
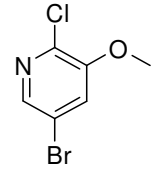
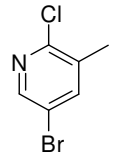
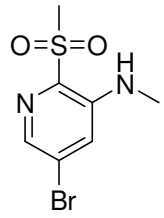
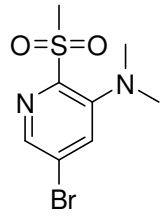
Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA23		2-amino-5-bromo-3-trifluoro-metil-piridina	CAS 79456-34-1
IA24		1-(5-bromo-2-metoxi-piridin-3-sulfonil)-4-metil-piperazina	
IA25		5-bromo-2-metoxi-metil-piridina	CAS 1000787-43-8
IA26		5-bromo-2-trifluoro-metil-piridina	CAS 436799-32-5
IA27		5-bromo-3-metil-piridin-2-il-amina	CAS 3430-21-5

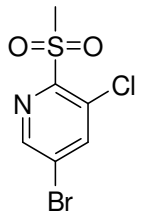
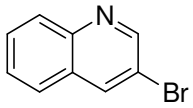
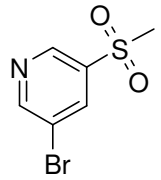
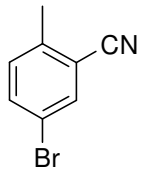
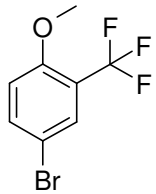
Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA28		5-bromo-piridin-2-carbonitrilo	CAS 97483-77-7
IA29		5-bromo-2,3-dimetoxi-piridina	CAS 52605-98-8
IA30		3-bromo-5-(propan-2-sulfonil)-piridina	
IA31		1-(5-bromo-2-metil-bencen-sulfonil)-piperidina	CAS 364736-61-8
IA32		4-(5-bromo-2-metoxi-bencen-sulfonil)-morfolina	CAS 325809-68-5

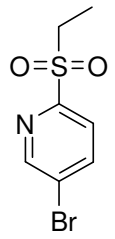
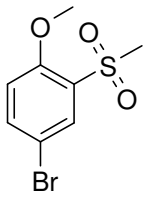
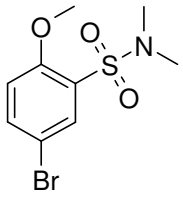
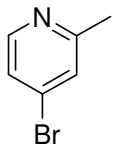
Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA33		4-(5-bromo-piridin-3-sulfonil)-morfolina	CAS 889676-35-1
IA34		1-(5-bromo-2-metoxi-bencen-sulfonil)-4-metil-piperazina	CAS 325809-71-0
IA35		1-(5-bromo-piridin-3-sulfonil)-4-metil-piperazina	CAS 1007212-08-9
IA36		5-bromo-2,N-dimetoxi-N-metil-bencen-sulfonamida	CAS 1247891-51-5
IA37		metoxi-metil-amida del ácido 5-bromo-piridin-	CAS 1248282-54-3

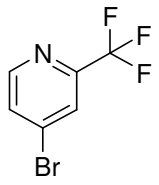
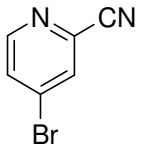
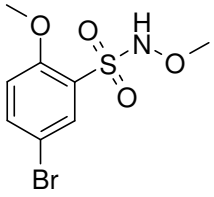
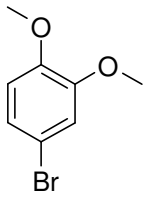
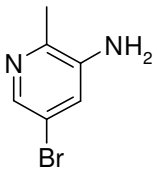
Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
		3-sulfónico	
IA38		3-bromo-5-metoxi-piridina	CAS 50720-12-2
IA39		3-bromo-5-cloro-piridina	CAS 73583-39-8
IA40		5-bromo-2-metan-sulfonil-piridina	CAS 98626-95-0
IA41		dimetil-amida del ácido 5-bromo-piridin-3-sulfónico	CAS 896160-99-9
IA42		5-bromo-piridin-3-il-amina	CAS 13535-01-8

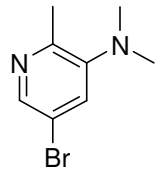
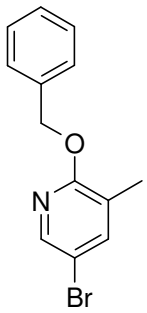
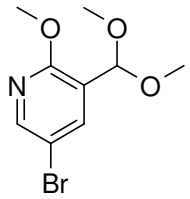
Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA43		etil-amida del ácido 5-bromo-piridin-3-sulfónico	CAS 1065074-78-3
IA44		5-bromo-2-etan-sulfinil-piridina	
IA45		5-bromo-2-metan-sulfonil-3-metoxi-piridina	
IA46		5-bromo-3-metoxi-piridin-2-il-amina	CAS 42409-58-5
IA47		N-(5-bromo-2-metoxi-piridin-3-il)-metan-	CAS 1083327-58-5

Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
		sulfonamida	
IA48		5-bromo-3-etil-2-metoxi-piridina	CAS 1256788-92-7
IA49		5-bromo-2-cloro-3-metoxi-piridina	CAS 286947-03-3
IA50		5-bromo-2-cloro-3-metil-piridina	CAS 29241-60-9
IA51		(5-bromo-2-metan-sulfonil-piridin-3-il)-metil-amina	
IA52		(5-bromo-2-metan-sulfonil-piridin-3-il)-dimetil-amina	

Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA53		5-bromo-3-cloro-2-metan-sulfonil-piridina	1335052-54-4
IA54		3-bromo-quinolina	CAS 5332-24-1
IA55		3-bromo-5-metan-sulfonil-piridina	CAS 445491-71-4
IA56		5-bromo-2-metil-benzonitrilo	CAS 156001-51-3
IA57		4-bromo-1-metoxi-2-trifluoro-metil-benceno	CAS 1514-11-0

Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA58		5-bromo-2-etan-sulfonil-piridina	CAS 223556-06-7
IA59		4-bromo-2-metan-sulfonil-1-metoxi-benceno	CAS 90531-99-0
IA60		5-bromo-2-metoxi-N,N-dimetil-bencen-sulfonamida	CAS 871269-16-8
IA61		4-bromo-2-metil-piridina	CAS 22282-99-1
IA62		4-bromo-2-metoxi-piridina	CAS 100367-39-3

Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA63		4-bromo-2-trifluoro-metil-piridina	CAS 887583-90-6
IA64		4-bromo-piridin-2-carbonitrilo	CAS 62150-45-2
IA65		5-bromo-2,N-dimetoxi-bencen-sulfonamida	
IA66		4-bromo-1,2-dimetoxi-benceno	CAS 2859-78-1
IA67		5-bromo-2-metil-piridin-3-il-amina	CAS 914358-73-9

Intermediario #	IA) Bromuros Aromáticos Estructura	Nombre Autonom	Comentario sobre la síntesis
IA68		(5-bromo-2-metil-piridin-3-il)-dimetil-amina	CAS 1280592-37-1
IA69		2-(benciloxi)-5-bromo-3-metil-piridina	CAS 1289270-73-0
IA70		5-bromo-3-(dimetoxi-metil)-2-metoxi-piridina	CAS 351410-59-8

<u>Intermediario IA1</u>: 5-bromo-2-metan-sulfonil-3-metil-piridina

Una solución de 5-bromo-2-metil-sulfanil-3-metil-piridina (9.04 gramos, 41.4 milimoles) en dicloro-metano (DCM) (83 mililitros) se trató a 0°C con mCPBA (21.46 gramos, 124 milimoles). Después de agitar durante 18 horas a temperatura ambiente, la mezcla de reacción se agregó a una solución acuosa de NaOH 2N, y se extrajo

con dicloro-metano (DCM). La capa orgánica se secó sobre Na_2SO_4, se concentró, y se obtuvo el compuesto del título después de la trituración con ciclohexano, para proporcionar un sólido blanco (9.25 gramos, 89 por ciento de rendimiento).

UPLC Rt_{M1} =0.81 minutos; MS (ESI, m/z): 250.1 [$(M+H^+]$

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.68 (d, 1H), 8.30 (d, 1H), 3.37 (s, 3H), 2.58 (s, 3H).

Intermediario IA2: 5-bromo-3-fluoro2-metan-sulfonil-piridina

Una solución de la 5-bromo-3-fluoro-2-metil-sulfanil-piridina (222 miligramos, 1.0 milimoles) en dicloro-metano (DCM) (5 mililitros) se trató a 0°C con mCPBA (518 miligramos, 3.0 milimoles). Después de agitar durante 1.5 horas a temperatura ambiente, la mezcla de reacción se agregó a una solución acuosa de NaOH 2N, y se extrajo con dicloro-metano (DCM). La capa orgánica se secó sobre Na_2SO_4, se concentró, y se obtuvo el compuesto del título como un sólido blanco (241 miligramos, 95 por ciento de rendimiento), el cual se utilizó sin mayor purificación.

UPLC Rt_{M1} =0.63 minutos;

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.75 (d, 1H), 8.60 (d, 1H), 3.40 (s, 3H).

Intermediario IA3: 5-bromo-2-metan-sulfonil-3-trifluoro-metil-piridina

Una solución de la 5-bromo-2-metil-sulfanil-3-trifluoro-metil-piridina (1.40 gramos, 1.16 milimoles) en dicloro-metano (DCM) (30 mililitros) se trató a 0°C con mCPBA (2.67 gramos, 15.48 milimoles).

Después de agitar durante 18 horas a temperatura ambiente, la mezcla de reacción se agregó a una solución acuosa de NaOH 4N, y se extrajo con dicloro-metano (DCM). La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (hexano / EtOAc, de 100:0 a 70:30), como un sólido blanco (940 miligramos, 60 por ciento de rendimiento).

UPLC Rt_{M1} =0.87 minutos; MS (ESI, m/z): 323.0 [$(M+NH_4)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 9.45 (d, 1H), 8.76 (d, 1H), 3.57 (s, 3H).

Intermediario IA4: 5-bromo-3-difluoro-metil-2-metan-sulfonil-piridina

a) 2,5-dibromo-3-difluoro-metil-piridina

Una solución de trifluoruro de Et_3N (1.80 mililitros, 11.3 milimoles) en dicloro-metano (DCM) (40 mililitros) se trató a 0°C con Xtalfluor-E (2.67 gramos, 15.5 milimoles), y 2,5-dibromo-piridin-3-carbaldehído (1.0 gramo, 3.77 milimoles). Después de agitar durante 19 horas a temperatura ambiente, la mezcla de reacción se diluyó con el terbutil-metil-éter (TBME), y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, y se concentró, para dejar un aceite amarillo (950 miligramos, 88 por ciento de rendimiento), el cual se utilizó sin mayor purificación.

UPLC Rt_{M1} =1.05 minutos;

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.57 (d, 1H), 8.48 (d, 1H), 7.14 (t, 1H), 3.35 (s, 3H).

b) 5-bromo-3-difluoro-metil-2-metan-sulfonil-piridina

Una solución de la 2,5-dibromo-3-difluoro-metil-piridina (1400 miligramos, 1.16 milimoles) en dimetil-formamida (DMF) (10 mililitros) se trató a 0ºC con metan-tiolato de sodio (348 miligramos, 4.97 milimoles). Después de agitar durante 1.5 horas a temperatura ambiente, la reacción se enfrió a 0ºC, y se agregó mCPBA (2857 miligramos, 16.56 milimoles) a la mezcla de reacción. Después de agitar durante 1 hora a temperatura ambiente, la mezcla de reacción se agregó a una solución acuosa de NaOH 4N, y se extrajo con terbutil-metil-éter (TBME). La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (hexano / EtOAc, de 100/0 a 80/20), como un sólido blanco (498 miligramos, 53 por ciento de rendimiento).

UPLC Rt_{M1} =0.86 minutos;

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.67 (d, 1H), 8.45 (d, 1H), 7.37 (t, 1H), 3.37 (s, 3H).

<u>Intermediario IA5</u>: 5-bromo-3-fluoro-metil-2-metan-sulfonil-piridina

a) 5-bromo-2-cloro-3-fluoro-metil-piridina

Una solución de trifluoruro de Et_3N (1.76 mililitros, 10.79 milimoles) en dicloro-metano (DCM) (20 mililitros) se trató a 0ºC con Xtalfluor-E (1.65 gramos, 7.19 milimoles), y (5-bromo-2-cloro-piridin-3-il)-metanol (0.80 gramos, 3.60 milimoles). Después de agitar durante 18 horas a temperatura ambiente, la mezcla de reacción se

diluyó con el terbutil-metil-éter (TBME), y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre Na_2SO_4, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (hexano / EtOAc, de 100/0 a 90/10), como un aceite incoloro (286 miligramos, 35 por ciento de rendimiento).

UPLC Rt_{M1} =0.98 minutos;

^1H RMN (400 MHz, $CDCl_3$): δ 8.53 (d, 1H), 8.45 (d, 1H), 5.52 (d, 1H)

b) 5-bromo-3-fluoro-metil-2-metan-sulfonil-piridina

Una solución de la 2,5-dibromo-3-difluoro-metil-piridina (1.4 gramos, 1.16 milimoles) en dimetil-formamida (DMF) (10 mililitros) se trató a 0°C con metan-tiolato de sodio (348 miligramos, 4.97 milimoles). Después de agitar a temperatura ambiente durante 1.5 horas, la reacción se enfrió a 0°C, y se introdujo mCPBA (2857 miligramos, 16.56 milimoles) a la mezcla de reacción. Después de agitar durante 1 hora a temperatura ambiente, la mezcla de reacción se agregó a una solución acuosa de NaOH 4N, y se extrajo con terbutil-metil-éter (TBME). La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (hexano / EtOAc, de 100/0 a 80/20), como un sólido blanco (498 miligramos, 53 por ciento de rendimiento).

UPLC Rt_{M1} =0.86 minutos;

^1H RMN (400 MHz, $CDCl_3$): δ 8.67 (d, 1H), 8.45 (d, 1H), 7.37 (t,

1H), 3.37 (s, 3H).

Intermediario IA7: 5-bromo-3-fluoro-metil-2-metoxi-piridina

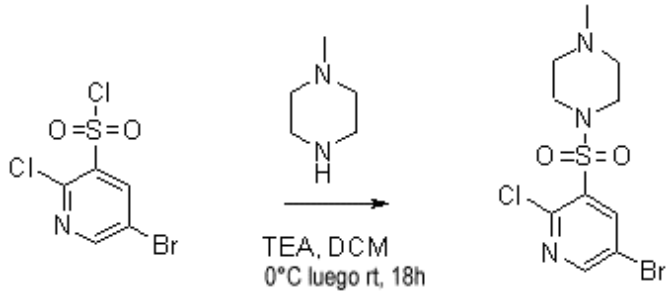
Una solución del (5-bromo-2-metoxi-piridin-3-il)-metanol (343 miligramos, 1.57 milimoles) en dicloro-metano (DCM) (7 mililitros) se trató a 0°C con desoxo-flúor (1.5 mililitros, 3.46 milimoles), y EtOH (27.6 microlitros, 0.47 milimoles). La mezcla de reacción se agitó a temperatura ambiente, se apagó con una solución acuosa saturada de $NaHCO_3$ y se extrajo con dicloro-metano (DCM). La capa orgánica se secó sobre Na_2SO_4, y se concentró para proporcionar el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (hexano/EtOAc, 80:20), como un aceite amarillo (80 miligramos, 23 por ciento de rendimiento).

UPLC Rt_{M1} =1.07 minutos;

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.32 (t, 1H), 8.00 (t, 1H), 5.37 (d, 2H), 3.89 (s, 3H).

Intermediario IA24: 1-(5-bromo-2-metoxi-piridin-3-sulfonil)-4-metil-piperazina

a) (5-bromo-2-metan-sulfonil-piridin-3-il)-metil-amina



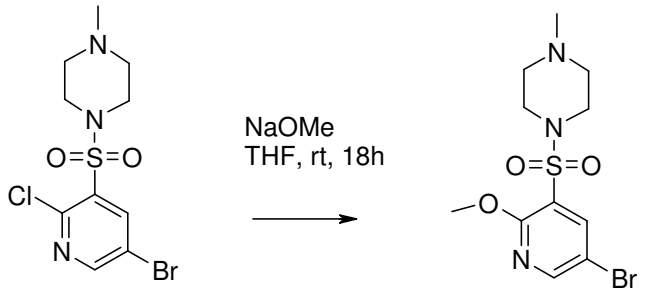
Una solución de cloruro del 5-bromo-2-cloro-piridin-3-sulfonilo (CAS registro 1146290-19-8) (580 miligramos, 1.99 milimoles), y Et_3N

(0.55 mililitros, 3.99 milimoles) en dicloro-metano (DCM) (20 mililitros) a 0°C, se trató con 1-metil-piperazina (0.33 mililitros, 2.99 milimoles); la mezcla resultante se agitó a 0°C durante 20 minutos y a temperatura ambiente durante 18 horas. La mezcla se diluyó con dicloro-metano (DCM) (30 mililitros), y se lavó con una solución acuosa saturada de $NaHCO_3$. La capa orgánica se secó sobre $MgSO_4$, se concentró, y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (dicloro-metano (DCM) / metanol, de 100:0 a 90:10), para proporcionar el compuesto del título como un sólido color naranja (420 miligramos, 59 por ciento de rendimiento).

HPLC Rt_{M2} =1.49 minutos; ESIMS: 356 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.62 (d, 1H), 8.50 (d, 1H), 3.57-3.29 (t, 4H), 2.50 (t, 4H), 2.33(s, 3H).

b) 1-(5-bromo-2-metoxi-piridin-3-sulfonil)-4-metil-piperazina



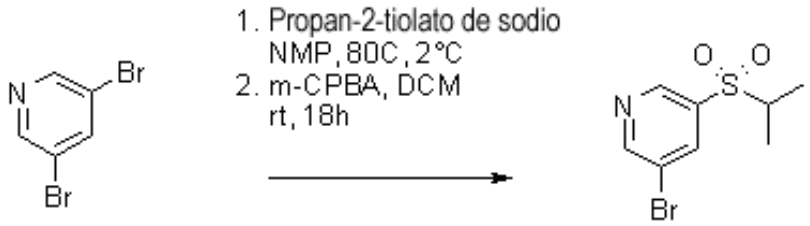
Una solución de la 1-(5-bromo-2-cloro-piridin-3-sulfonil)-4-metil-piperazina (420 miligramos, 1.18 milimoles) en tetrahidrofurano (THF) (10 mililitros) se trató en porciones con metóxido de sodio (192 miligramos, 3.55 milimoles). La mezcla resultante se agitó a temperatura ambiente durante 18 horas. La mezcla se apagó

mediante la adición de agua y se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con una solución acuosa saturada de $NaHCO_3$ y se secaron sobre $MgSO_4$, se concentraron, y se purificaron mediante cromatografía por evaporación instantánea sobre gel de sílice (dicloro-metano (DCM) / metanol, de 100:0 a 90:10), para proporcionar el compuesto del título (358 miligramos, 85 por ciento de rendimiento).

HPLC Rt_{M2} =1.47 minutos; ESIMS: 350, 352 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.36 (d, 1H), 8.28 (d, 1H), 4.05 (s, 3H), 3.35 (br s, 4 H), 2.49 (br s, 4 H), 2.33 (s, 3H).

Intermediario IA30: 3-bromo-5-(propan-2-sulfonil)-piridina



Una solución de la 3,5-dibromo-piridina (CAS registro 625-92-3) (495 miligramos, 2.09 milimoles) en NMP (5 mililitros) se trató con propan-2-tiolato de sodio (CAS registro 20607-43-6) (205 miligramos, 2.09 milimoles); la mezcla resultante se agitó a 80°C durante 2 horas. La mezcla se enfrió y se diluyó con EtOAc, se lavó con agua (2 veces), y entonces con salmuera. La capa orgánica se secó sobre $MgSO_4$ y se concentró. El residuo obtenido se disolvió en dicloro-metano (DCM) (10 mililitros), se trató con mCPBA (1,083 miligramos, 6.27 milimoles), y se agitó a temperatura ambiente durante 18 horas. Se agregó una solución acuosa de sulfito de sodio al 10 por ciento, y

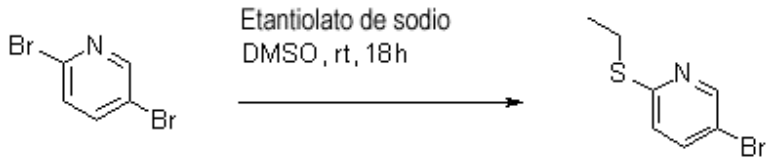
la mezcla se agitó a temperatura ambiente durante 1 hora. Las fases se separaron, y la capa orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$, se concentró, y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 00:100), para proporcionar el compuesto del título (364 miligramos, 59 por ciento de rendimiento).

HPLC Rt_{M2} =0.77 minutos; ESIMS: 264, 266 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.98 (dd, 2H), 8.33 (t, 1H),3.34-3.17 (m, 1H), 1.37 (d, 6H).

<u>Intermediario IA44:</u> 5-bromo-2-etan-sulfinil-piridina

a) 5-bromo-2-etil-sulfanil-piridina

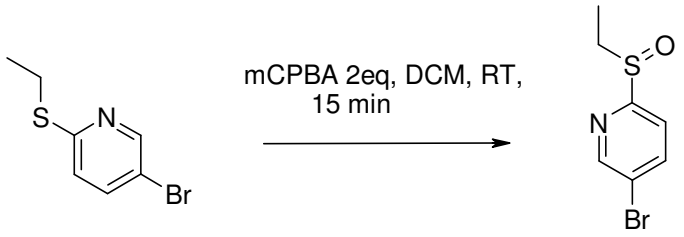


Una mezcla de la 2,5-dibromo-piridina (CAS registro 588729-99-1) (1.15 gramos, 4.85 milimoles), y etantiolato de sodio (CAS registro 811-51-8)-(2.04 gramos, 24.27 milimoles) en sulfóxido de dimetilo (DMSO) (15 mililitros) se agitó a temperatura ambiente durante 18 horas. Se agregó agua, y la mezcla se extrajo con dicloro-metano (DCM). La capa orgánica se secó pasándola a través de un cartucho de separación de fases, se concentró y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 70:30), para proporcionar el compuesto del título como un aceite color naranja (1.09 gramos, 92

por ciento de rendimiento).

HPLC Rt_{M2} =1.25 minutos; ESIMS: 218, 220 [$(M+H)^+$].

b) 5-bromo-2-etan-sulfinil-piridina



Una solución de la 5-bromo-2-etil-sulfanil-piridina (1.09 gramos, 4.49 milimoles) en dicloro-metano (DCM) (15 mililitros) se trató con mCPBA (1.55 gramos, 8.98 milimoles). La solución resultante se agitó a temperatura ambiente durante 15 minutos.

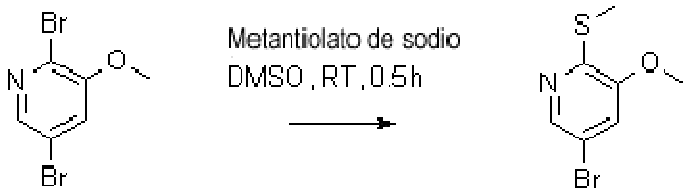
La mezcla se apagó mediante la adición de una solución acuosa de NaOH 2M, y se extrajo con dicloro-metano (DCM). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, y se concentraron. El compuesto se purificó mediante RP-HPLC de preparación (columna SunFire C18 OBD, gradiente del 5 al 60 por ciento de acetonitrilo (ACN) en 15 minutos), para proporcionar el compuesto del título como un aceite incoloro (490 miligramos, 45 por ciento de rendimiento).

HPLC Rt_{M2} =0.65 minutos; ESIMS: 234, 236 [$(M+H)^+$].

^1H RMN (400 MHz, DMSO-d_6): δ 8.85 (d, 1H), 8.37 (dd, 1H), 7.80 (d, 1H), 3.33 (s, 2H), 3.27-3.10 (m, 1H), 2.94-2.72 (m, 1 H), 1.01 (t, 3 H).

<u>Intermediario IA45:</u> 5-bromo-2-metan-sulfonil-3-metoxi-piridina

a)5-bromo-3-metoxi-2-metil-sulfanil-piridina



Una mezcla de la 2,5-dibromo-3-metoxi-piridina (CAS registro 1142191-57-8) (550 miligramos, 2.06 milimoles), y metan-tiolato de sodio (CAS registro 5188-07-8)-(722 miligramos, 10.30 milimoles) en sulfóxido de dimetilo (DMSO) (1.5 mililitros) se agitó a temperatura ambiente durante 0.5 horas. Se agregó agua, y la mezcla se extrajo con dicloro-metano (DCM). La capa orgánica se secó pasándola a través de un cartucho de separación de fases y se concentró, para proporcionar el compuesto del título como un aceite incoloro (1.50 gramos, 93 por ciento de rendimiento, crudo).

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.19 (d, 1H), 7.53 (d, 1H), 3.89 (s, 3H), 3.32 (s, 3H).

b) 5-bromo-2-metan-sulfonil-3-metoxi-piridina



Una solución de la 5-bromo-3-metoxi-2-metil-sulfanil-piridina (1.50 gramos, 2.24 milimoles) en dicloro-metano (DCM) (10 mililitros) se trató con mCPBA (1.55 gramos, 8.97 milimoles). La mezcla resultante se agitó a temperatura ambiente durante 18 horas . La mezcla se apagó mediante la adición de una solución acuosa de

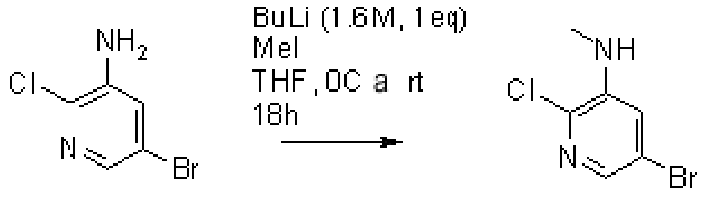
NaOH 2M, y se extrajo con dicloro-metano (DCM). La capa orgánica se secó pasándola a través de un cartucho de separación de fases y se concentró, para proporcionar el compuesto del título (400 miligramos, 33 por ciento de rendimiento como un producto crudo).

HPLC Rt_{M2} =0.75 minutos; ESIMS: 268[$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.41 (d, 1H), 8.17 (s, 1H), 4.01 (s, 3H), 3.30 (s, 3H).

Intermediario IA51: (5-bromo-2-metan-sulfonil-piridin-3-il)-metil-amina

a) (5-bromo-2-cloro-piridin-3-il)-metil-amina



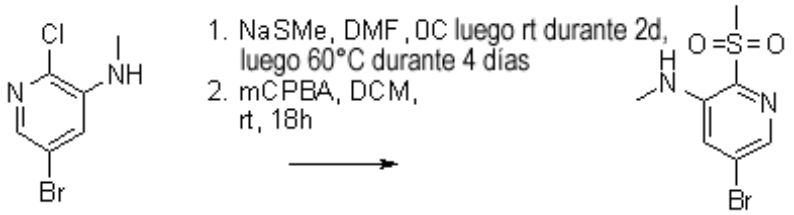
Una solución de la 5-bromo-2-cloro-piridin-3-il-amina (CAS registro 588729-99-1) (565 miligramos, 2.72 milimoles) en tetrahidrofurano (THF) (4 mililitros) a 0°C se trató con BuLi 1.6M en hexano (0.17 mililitros, 0.17 milimoles); la mezcla resultante se agitó a 0°C durante 0.5 horas, y entonces se agregó lentamente yoduro de metilo (0.17 mililitros, 2.72 milimoles). La mezcla de reacción se dejó calentar a temperatura ambiente, y se agitó durante 18 horas. La mezcla color naranja/café se vertió en una solución acuosa saturada de $NaHCO_3$, y se extrajo con EtOAc. La capa orgánica se secó sobre $MgSO_4$, se concentró, y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de

95:5 a 60:40), para proporcionar el compuesto del título como un sólido color naranja (354 miligramos, 59 por ciento de rendimiento).

HPLC Rt_{M1} =0.94 minutos; ESIMS: 221, 223, 225 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.65 (d, 1H), 7.14 (d, 1H), 6.11 (d, 1H), 2.74 (d, 3H).

b) (5-bromo-2-metan-sulfonil-piridin-3-il)-metil-amina



Una solución de la (5-bromo-2-cloro-piridin-3-il)-metil-amina (354 miligramos, 1.60 milimoles) en dimetil-formamida (DMF) (2.6 mililitros) se trató con metan-tiolato de sodio (168 miligramos, 2.40 milimoles) a 0°C. La solución resultante se agitó a temperatura ambiente durante 2 días, y se calentó a 60°C durante 4 días. La mezcla se apagó a 0°C mediante la adición de una solución acuosa de NaOH 2M, y se extrajo con dicloro-metano (DCM). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron, para proporcionar un aceite color naranja, el cual se disolvió en dicloro-metano (DCM) (5 mililitros), y se trató a 0°C con mCPBA (CAS registro 937-14-4) (827 miligramos, 4.79 milimoles), y se agitó durante 18 horas a temperatura ambiente. La mezcla se apagó a 0°C mediante la adición de una solución acuosa de NaOH 2M, y se extrajo con dicloro-metano (DCM). Los materiales orgánicos combinados se secaron sobre $MgSO_4$, se concentraron, y se

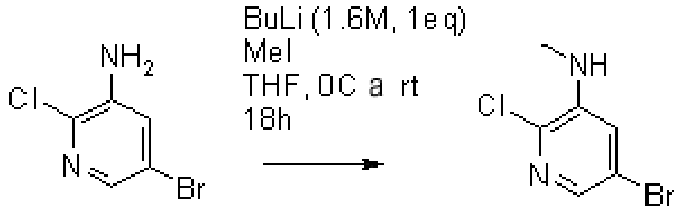
purificaron mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 92:8 a 32:68), para proporcionar el compuesto del título como un sólido color naranja (174 miligramos, 41 por ciento de rendimiento).

HPLC Rt_{M1} =0.78 minutos; ESIMS: 265, 267 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.95 (d, 1H), 7.50 (d, 1H), 6.70-6.59 (m, 1H), 3.26 (s, 3H), 2.82 (d, 3H).

Intermediario IA52: (5-bromo-2-metan-sulfonil-piridin-3-il)-dimetil-amina

a) (5-bromo-2-cloro-piridin-3-il)-metil-amina



Una solución de la 5-bromo-2-cloro-piridin-3-il-amina (CAS registro 588729-99-1) (1 gramo, 4.82 milimoles) en tetrahidrofurano (THF) (7 mililitros) a 0°C se trató con BuLi 1.6M en hexano (6 mililitros, 9.64 milimoles); la mezcla resultante se agitó a 0°C durante 0.5 horas, entonces se agregó lentamente yoduro de metilo (0.60 mililitros, 9.64 milimoles). La mezcla de reacción se dejó calentar a temperatura ambiente, y se agitó durante 18 horas. La mezcla color naranja/café se vertió sobre una solución acuosa saturada de $NaHCO_3$, y se extrajo con EtOAc, la capa orgánica se secó sobre $MgSO_4$, se concentró, y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice

(ciclohexano / EtOAc, de 95:05 a 70:30), para proporcionar el compuesto del título como un sólido color naranja (182 miligramos, 17 por ciento de rendimiento).

HPLC Rt_{M1} =0.94 minutos; ESIMS: 221, 223[$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 7.65 (d, 1H), 7.14 (d, 1H), 6.11 (d, 1H), 2.74 (d, 3H).

b) (5-bromo-2-cloro-piridin-3-il)-dimetil-amina

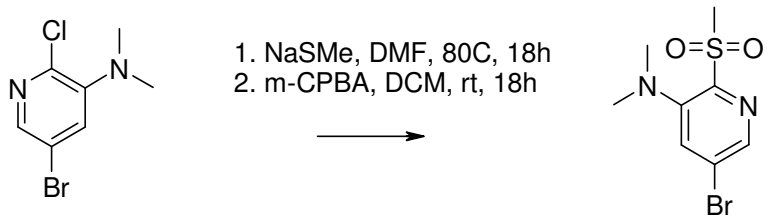


Una solución de la (5-bromo-2-cloro-piridin-3-il)-metil-amina (182 miligramos, 0.82 milimoles) en dimetil-formamida (DMF) (4 mililitros) se trató con NaH (23 miligramos, 0.99 milimoles), a temperatura ambiente, y la mezcla se agitó a temperatura ambiente durante 0.5 horas; se agregó yoduro de metilo (0.06 mililitros, 0.99 milimoles), y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla se diluyó con el terbutil-metil-éter (TBME), y se lavó con a una solución acuosa saturada de $NaHCO_3$, la capa orgánica se secó sobre $MgSO_4$ y se concentró, para proporcionar el compuesto del título como un aceite color naranja (174 miligramos, 90 por ciento de rendimiento). Se utilizó sin mayor purificación.

HPLC Rt_{M1} =1.03 minutos; ESIMS: 235, 237 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.10 (d, 1H), 7.70 (d, 1H), 2.78 (s, 6H).

c) (5-bromo-2-metan-sulfonil-piridin-3-il)-metil-amina



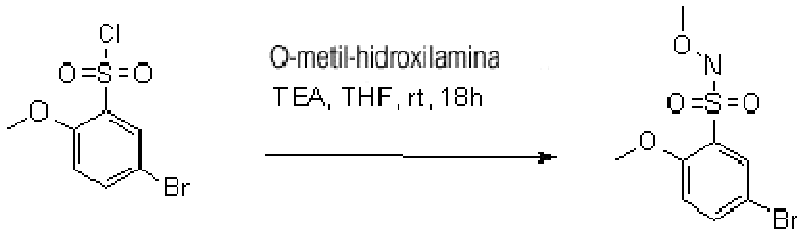
Una solución de la (5-bromo-2-cloro-piridin-3-il)-dimetil-amina (174 miligramos, 0.74 milimoles) en dimetil-formamida (DMF) (5 mililitros) se trató con metan-tiolato de sodio (104 miligramos, 1.48 milimoles), a temperatura ambiente; la solución resultante se agitó a 80°C durante 18 horas. A 0°C, la mezcla se apagó mediante la adición de una solución acuosa de NaOH 2M, y entonces se extrajo con terbutil-metil-éter (TBME). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron, para proporcionar un aceite color naranja, el cual se disolvió en dicloro-metano (DCM) (5 mililitros), se trató a 0°C con mCPBA (CAS registro 937-14-4) (382 miligramos, 2.21 milimoles), y se agitó durante 18 horas a temperatura ambiente. A 0°C, la mezcla se apagó mediante la adición de una solución acuosa de NaOH 2M, y entonces se extrajo con dicloro-metano (DCM). Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se concentraron, y se purificaron mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 88:12 a 00:100), para proporcionar el

compuesto del título como un sólido color naranja (50 miligramos, rendimiento del 24 por ciento).

HPLC Rt_{M1} =0.83 minutos; ESIMS: 279, 281 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 8.25 (d, 1H), 7.90 (d, 1H), 3.29 (s, 3H), 2.91 (s, 6H).

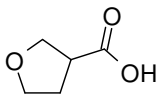
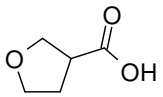
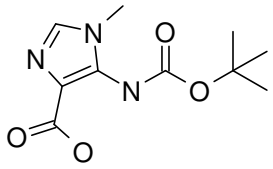
Intermediario IA65: 5-bromo-2,N-dimetoxi-bencen-sulfonamida



Una solución del cloruro de 5-bromo-2-metoxi-bencen-sulfonilo (CAS registro 23095-05-8) (218 miligramos, 0.76 milimoles), y Et_3N (0.55 mililitros, 3.99 milimoles) en dicloro-metano (DCM) (20 mililitros) a 0°C, se agitó durante 15 minutos y se trató con O-metil-hidroxilamina (36 miligramos, 0.76 milimoles); la mezcla resultante se agitó a temperatura ambiente durante 18 horas. La mezcla se dividió entre EtOAc y agua. La capa orgánica se lavó con una solución acuosa saturada de $NaHCO_3$, se secó sobre $MgSO_4$, se concentró, y se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 100:0 a 0:100), para proporcionar el compuesto del título (189 miligramos, 84 por ciento de rendimiento).

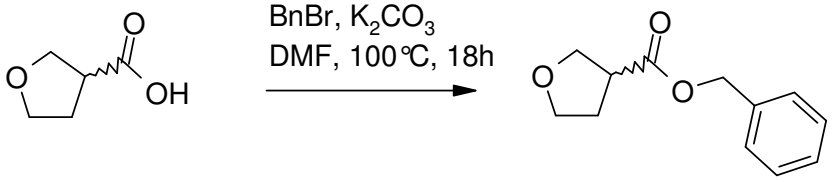
^{1}H RMN (400 MHz, $CDCl_3$): δ 8.10 (d, 1 H), 7.78 (s, 1 H), 7.72 (dd, 1 H), 6.97 (d, 1 H), 4.01 (s, 3 H), 3.81 (s, 3 H).

IB) Ácidos carboxílicos o cloruros de ácidos

Interme-diario #	IB) Ácidos carboxílicos o cloruros de ácidos Estructura	Nombre Autonom
IB1	 Enantiómero 1	Ácido tetrahidrofuran-3-carboxílico (enantiómero puro)
IB2	 Enantiómero 2	Ácido tetrahidrofuran-3-carboxílico (enantiómero puro)
IB3		Ácido 5-terbutoxi-carbonil-amino-1-metil-1H-imidazol-4-carboxílico

<u>Ejemplo IB1/IB2:</u> (S)-ácido tetrahidrofuran-3-carboxílico / (R)-ácido tetrahidrofuran-3-carboxílico

a) Bencil-éster del ácido tetrahidrofuran-3-carboxílico



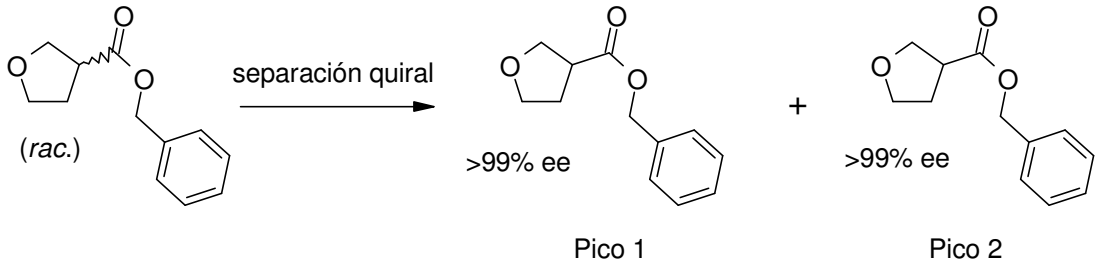
Una solución del ácido tetrahidrofuran-3-carboxílico (CAS registro 89364-31-8) (4.00 gramos, 34.40 milimoles) en dimetil-formamida (DMF) (20 mililitros) se trató con K_2CO_3 (9.52 gramos,

68.9 milimoles), y bromuro de bencilo (CAS registro 100-39-0) (8.18 mililitros, 68.9 milimoles) a 100°C durante 18 horas. La mezcla se enfrió a temperatura ambiente, se diluyó con EtOAc, y se lavó con agua y salmuera. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se concentraron, y se purificaron mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclohexano / EtOAc, de 92:8 a 34:66), para proporcionar el compuesto del título como un aceite incoloro (6.93 gramos, 98 por ciento de rendimiento).

HPLC Rt_{M2} =0.94 minutos; ESIMS: 207 [$(M+H)^+$].

^1H RMN (400 MHz, $CDCl_3$): δ 7.50-7.26 (m, 5H), 5.17 (m, 2H), 4.05-3.75 (m, 4H), 3.29-3.05(m, 1H), 2.36-2.09 (m, 2H).

b) Separación de enantiómeros del bencil-éster del ácido tetrahidrofuran-3-carboxílico



Información del método:

Columna: Chiralpak AD-PREP

Solvente: HEPTANO/ETOH/MEOH, 95/2.5/2.5

Flujo: 1.0 mililitro/minuto

Onda larga: 210 nanómetros

Máquina: Agilent 1200 DAD Magellan

Solución: EtOH

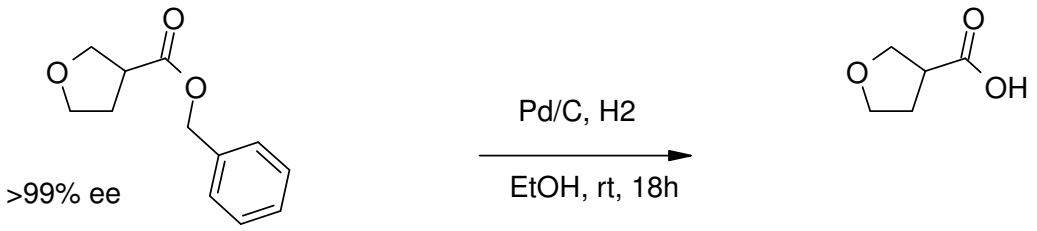
Después de la separación de 6.347 gramos del racémico, se obtuvieron 2 picos: pico 1 en 9.086 minutos (2.43 gramos, exceso enantiomérico (ee) > 99 por ciento), y pico 2 en 10.584 minutos (2.19 gramos, exceso enantiomérico (ee) > 99 por ciento).

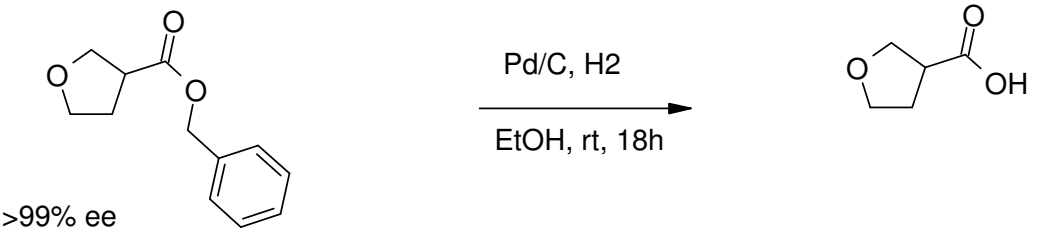
HPLC (pico 1 ó 2) Rt_{M2} = 0.92 minutos; ESIMS: 207 [$(M+H)^+$].

^{1}H RMN (pico 1) (400 MHz, $CDCl_3$): δ 7.48-7.29 (m, 5H), 5.23-5.07 (m, 2H), 4.05-3.77 (m, 4H), 3.23-3.10(m, 1H), 2.35-2.06 (m, 2H).

^{1}H RMN (pico 2) (400 MHz, $CDCl_3$): δ 7.51-7.31 (m, 5H), 5.23-5.09 (m, 2H), 4.07-3.77 (m, 4H), 3.24-3.07 (m, 1H), 2.35-2.06 (m, 2H).

c) (S)-ácido tetrahidrofuran-3-carboxílico / (R)-ácido tetrahidrofuran-3-carboxílico





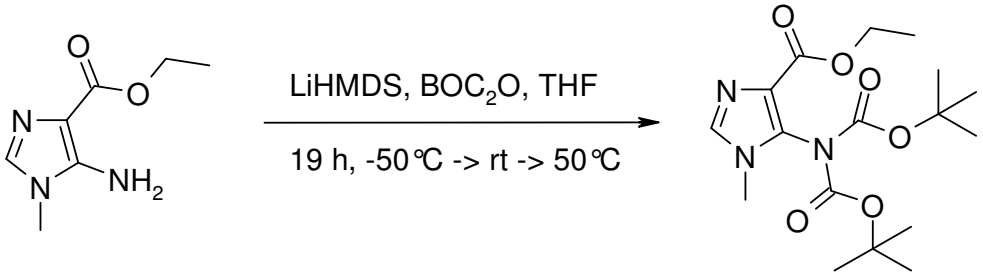
Una solución de un bencil-éster del ácido tetrahidrofuran-3-

carboxílico enantioméricamente puro (pico 1 ó pico 2, 200 miligramos, 0.97 milimoles), Pd/C (103 miligramos, 0.97 milimoles) en EtOH (2 mililitros), se hidrogenó con H_2 a temperatura ambiente durante 18 horas. La filtración de la mezcla de reacción y la concentración del filtrado proporcionaron el compuesto del título como un aceite incoloro (125 miligramos (Pico 1), 111 miligramos (Pico 2), crudo).

^{1}H RMN (ambos enantiómeros) (400 MHz, DMSO-d_6): δ 12.40 (br s, 1H), 3.84-3.59 (m, 4H), 3.00 (m, 1H), 2.08-1.92(m, 1H).

Ejemplo IB3): Ácido 5-terbutoxi-carbonil-amino-1-metil-1H-imidazol-4-carboxílico

a) Etil-éster del ácido 5-di-(terbutoxi-carbonil)-amino-1-metil-1H-imidazol-4-carboxílico



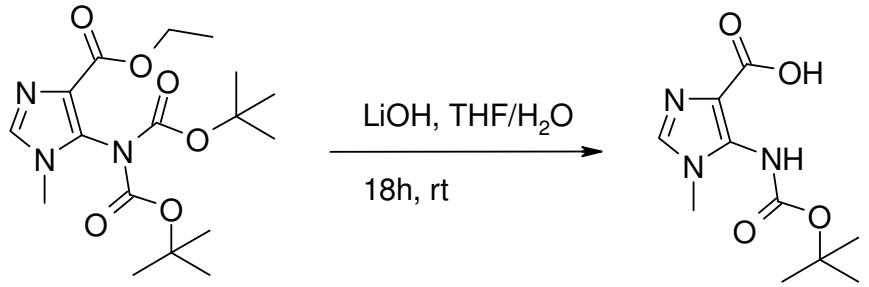
Una solución del etil-éster del ácido 5-amino-1-metil-1H-imidazol-4-carboxílico (CAS registro 54147-04-5) (82 miligramos, 0.49 milimoles) en tetrahidrofurano (THF) (4 mililitros) se trató a -50°C con una solución de LiHMDS 1M en tetrahidrofurano (THF) (0.97 mililitros, 0.97 milimoles), y la mezcla de reacción se agitó a - 50°C durante 10 minutos; entonces se agregó una solución de Boc_2O (237 miligramos, 1.07 milimoles) en tetrahidrofurano (THF)

(1.5 mililitros). La mezcla de reacción se dejó calentar lentamente a temperatura ambiente, entonces hasta 50°C, y se agitó durante 15 horas a 50°C. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con EtOAc, y se apagó con H_2O. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (heptano / EtOAc, de 85:15 a 0:100), como un sólido blanco (140 miligramos, 78 por ciento de rendimiento).

UPLC Rt_{M1} =0.96 minutos; ESIMS: 370 [$(M+H)^+$]

^{1}H RMN (400 MHz, $CDCl_3$, 298 K): δ 4.33 (q, 2H), 3.50 (s, 3H), 1.41 (s, 18H), 1.35 (t, 3H).

b) Ácido 5-terbutoxi-carbonil-amino-1-metil-1H-imidazol-4-carboxílico



Una solución del etil-éster del ácido 5-di-(terbutoxi-carbonil)-amino-1-metil-1H-imidazol-4-carboxílico (167 miligramos, 0.452 milimoles) en tetrahidrofurano (THF) (2.2 mililitros), y H_2O (2.2 mililitros) se trató con LiOH (54.1 miligramos, 2.26 milimoles), y la mezcla de reacción se agitó a temperatura ambiente durante 18 horas, entonces se apagó con una solución acuosa de HCl 1M, para alcanzar un pH

de 2, y se extrajo con EtOAc. La capa orgánica se secó sobre Na_2SO_4, se filtró, se concentró para proporcionar el compuesto del título. (70 miligramos, 65 por ciento de rendimiento).

UPLC Rt_{M1} =0.47 minutos; ESIMS: 242 [$(M+H)^+$]

^1H RMN (400 MHz, DMSO-d_6): δ 12.42 (br.s., 1H), 8.98 (br.s., 1H), 7.82 (s, 1H), 3.45 (s, 3H), 1.41 (s, 9H).

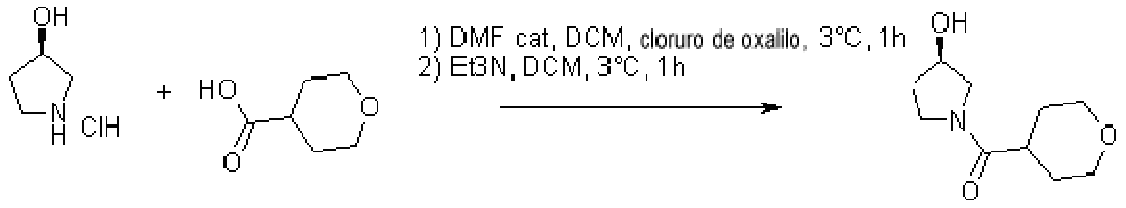
IC) Derivados o análogos de pirrolidinol

Intermediario #	**Nombre Autonom**	**Usado para el Ejemplo #**	**Comentario sobre la síntesis**
IC1	(R)-(tetrahidro-piran-4-carbonil)-pirrolidin-3-il-éster de ácido metan-sulfónico	**C1**	2 pasos de CAS 104706-47-0
IC2	(S)-(tetrahidro-piran-4-carbonil)-pirrolidin-3-il-éster de ácido metan-sulfónico	**C2**	2 pasos de CAS 100243-39-8
IC3	(S)-1-propionil-pirrolidin-3-il-éster de ácido metan-sulfónico	**C3**	2 pasos de CAS 100243-39-8

Intermediario #	Nombre Autonom	Usado para el Ejemplo #	Comentario sobre la síntesis
IC4	(R)-1-propionil-pirrolidin-3-il-éster de ácido metan-sulfónico	**C4**	2 pasos de CAS 2799-21-5

<u>Intermediario IC1</u>: (R)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-il-éster de ácido metan-sulfónico

a) ((R)-3-hidroxi-pirrolidin-1-il)-(tetrahidro-piran-4-il)-metanona



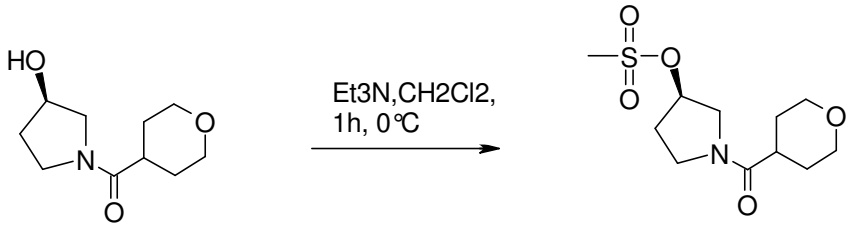
Se agregó cloruro de oxalilo (0.20 mililitros, 3.84 milimoles) a una solución del ácido tetrahidro-piran-4-carboxílico (CAS registro 5337-03-1), y dimetil-formamida (DMF) (0.012 mililitros, 0.15 milimoles). La mezcla de reacción se agitó a 3°C durante 1 hora. La concentración de la mezcla de reacción bajo presión reducida (170 mbar) a 40°C (baño de agua) proporcionó el intermediario de acilo como un aceite incoloro. El Intermediario se disolvió en dicloro-metano (DCM) (2 mililitros), y se agregó a una solución de clorhidrato de (R)-pirrolidin-3-ol (CAS registro 104706-47-0) (190

miligramos, 1.54 milimoles) en dicloro-metano (DCM) (3 mililitros), se enfrió a 3°C, y la suspensión blanca formada se agitó a 3°C durante 1 hora. La mezcla de reacción se concentró; se agregó EtOAc al residuo, el cual se filtró y se lavó con EtOAc. La concentración y la purificación del filtrado mediante cromatografía por evaporación instantánea sobre gel de sílice (DCM /DCM: metanol (9:1), de 100:0 a 60:40 durante 11 minutos) proporcionaron el compuesto del título como un sólido blanco (250 miligramos, 82 por ciento de rendimiento).

ESIMS: 200 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 4.43 - 4.65 (m, 1H), 3.95-4.16 (m, 2H), 3.30-3.82 (m, 6H), 2.45-2.75 (m, 1H), 1.83-2.30 (m, 4H), 1.54-1.78 (m, 3H).

b) (R)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-il-éster de ácido metan-sulfónico



Bajo argón, se agregó cloruro de metan-sulfonilo (CAS registro 124-63-0) (3.52 mililitros, 45.2 milimoles) a una solución de ((R)-3-hidroxi-pirrolidin-1-il)-(tetrahidro-piran-4-il)-metanona (6 gramos, 22.6 milimoles), y Et_3N (6.30 mililitros, 45.2 milimoles) en dicloro-metano (DCM) (100 mililitros) a -10°C. La solución se agitó a 0°C durante 1 hora, se diluyó con H_2O y dicloro-metano (DCM), la capa

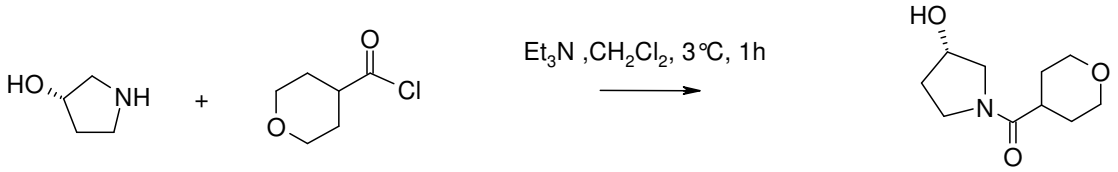
orgánica se lavó dos veces con H_2O y salmuera, y se secó sobre $MgSO_4$. La concentración y trituración del aceite resultante con dietil-éter proporcionó el compuesto del título como un sólido grisáceo (5.3 gramos, 84 por ciento).

ESIMS: 278 [$(M+H)^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 5.22-5.44 (m, 1H), 3.96-4.13 (m, 2H), 3.85-3.96 (m, 1H), 3.56-3.83 (m, 3H), 3.36-3.53 (m, 2H), 3.08 (d, 3H), 2.07-2.75 (m, 3H), 1.93 (m, 2H), 1.51-1.75 (m, 3H).

<u>Intermediario IC2</u>: (S)-(tetrahidro-piran-4-carbonil)-pirrolidin-3-il-éster de ácido metan-sulfónico

a) ((S)-3-hidroxi-pirrolidin-1-il)-(tetrahidro-piran-4-il)-metanona

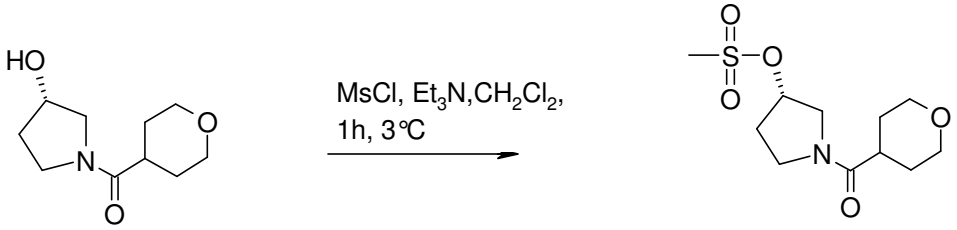


Una solución de cloruro de tetrahidro-piran-4-carbonilo (CAS registro 40191-32-0) (316 miligramos, 2.02 milimoles) en dicloro-metano (DCM) (2 mililitros) se agregó por goteo (0°C <T <10°C) a una solución de (S)-pirrolidin-3-ol (CAS registro 100243-39-8) (250 miligramos, 2.02 milimoles), y Et_3N (0.62 mililitros, 4.45 milimoles) en dicloro-metano (DCM) (5 mililitros). La mezcla de reacción se agitó a 3°C durante 1 hora. Los volátiles se concentraron y se agregó EtOAc al residuo, el sólido restante se filtró y se lavó con EtOAc, y la concentración del filtrado proporcionó el compuesto del título como un sólido blanco (390 miligramos, 97 por ciento de rendimiento).

ESIMS: 200 [(M+H)$^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 4.55 (d, 1H), 3.96-4.11 (m, 2H), 3.36-3.80 (m, 6H), 2.48-2.74 (m, 1H), 1.52-2.20 (m, 7H).

b) (S)-1-(tetrahidro-piran-4-carbonil)-pirrolidin-3-il-éster de ácido metan-sulfónico



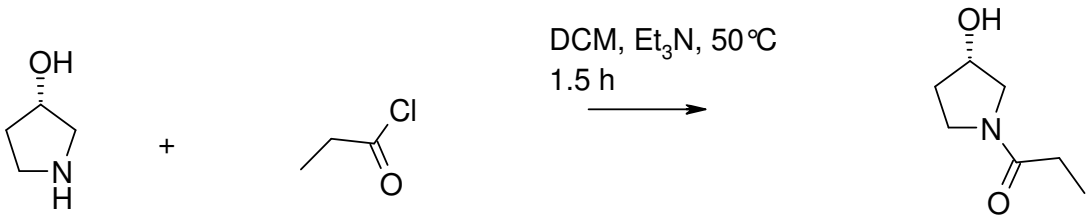
Bajo argón, se agregó cloruro de metan-sulfonilo (CAS registro 124-63-0) (0.23 mililitros, 2.94 milimoles) a una solución de la ((S)-3-hidroxi-pirrolidin-1-il)-(tetrahidro-piran-4-il)-metanona (0.39 gramos, 1.96 milimoles), y Et_3N (0.55 mililitros, 3.91 milimoles) en dicloro-metano (DCM) (10 mililitros) a -10°C. La solución se agitó a 3°C durante 1 hora, se diluyó con H_2O y dicloro-metano (DCM), la capa orgánica se lavó dos veces con H_2O y salmuera, y entonces se secó sobre $MgSO_4$. La concentración y trituración del aceite resultante con dietil-éter proporcionó el compuesto del título como un sólido blanco (0.45 gramos, 83 por ciento de rendimiento).

ESIMS: 278 [(M+H)$^+$].

^{1}H RMN (400 MHz, $CDCl_3$): δ 5.25-5.44 (m, 1H), 3.99-4.16 (m, 2H), 3.85-3.95 (m, 1H), 3.56-3.83 (m, 3H), 3.37-3.54 (m, 2H), 3.08 (d, 3H), 2.09-2.78 (m, 3H), 1.93 (m, 2H), 1.51-1.76 (m, 2H).

<u>Intermediario IC3</u>: (S)-1-propionil-pirrolidin-3-il-éster de ácido metan-sulfónico

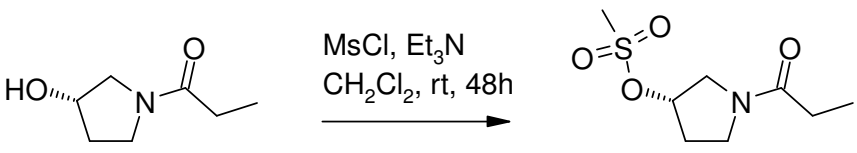
a) 1-((S)-3-hidroxi-pirrolidin-1-il)-propan-1-ona



Se agregó por goteo cloruro de propionilo (CAS registro 79-03-8) (4.78 mililitros, 54.8 milimoles) durante un período de 15 minutos a una solución de (S)-pirrolidin-3-ol (CAS registro 100243-39-8) (4.8 gramos, 55.9 milimoles), y Et_3N (8.74 mililitros, 63.1 milimoles) a 5°C, la solución se dejó calentar a temperatura ambiente, y se agitó durante 1 hora. Se agregaron H_2O (10 mililitros) y una solución acuosa saturada de $NaHCO_3$, (10 mililitros) a la solución, la fase orgánica se lavó con salmuera (10 mililitros) y una solución acuosa de HCl 0.25M (20 mililitros). Las capas acuosas combinadas se concentraron y se extrajeron con EtOAc (100 mililitros, 2 veces), las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron, para proporcionar el compuesto del título como un aceite amarillo pálido (4.80 gramos, 54 por ciento de rendimiento).

^1H RMN (400 MHz, $CDCl_3$): δ 4.54 (d, 1H), 3.31-3.73 (m, 3H), 3.12 (m, 1H), 1.82-2.46 (m, 5H), 1.17 (t, 3H)

b) (S)-1-propionil-pirrolidin-3-il-éster de ácido metan-sulfónico



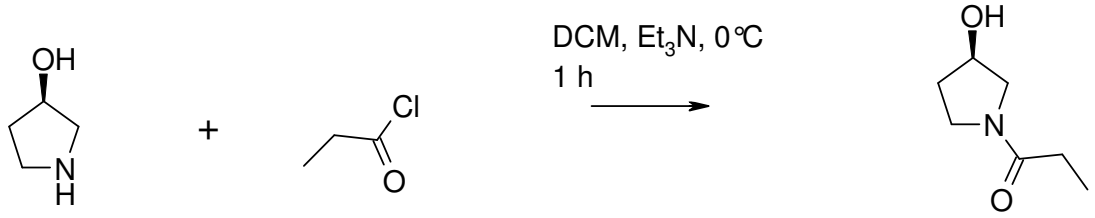
Bajo argón, se agregó cloruro de metan-sulfonilo (CAS registro

124-63-0) (1.36 mililitros, 17.46 milimoles), durante un período de 10 minutos, a una solución de 1-((S)-3-hidroxi-pirrolidin-1-il)-propan-1-ona (2.5 gramos, 17.4 milimoles) y Et_3N (2.43 mililitros, 17.4 milimoles) en dicloro-metano (DCM) (50 mililitros) a 5°C. La solución se dejó calentar a temperatura ambiente, y se agitó durante 18 horas, entonces se agregaron cloruro de metan-sulfonilo (CAS registro 124-63-0) (1.36 mililitros, 17.46 milimoles), y Et_3N (2.43 mililitros, 17.4 milimoles) a la mezcla de reacción, la cual se agitó durante 48 horas a temperatura ambiente. Se agregaron dicloro-metano (DCM) y H_2O a la solución, y la fase orgánica se separó a través de un cartucho de separación de fases, se concentró, y se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (EtOAc / metanol, de 100:0 a 95:5 durante 40 minutos), como un aceite incoloro (2.7 gramos, 66 por ciento de rendimiento).

^1H RMN (400 MHz, $CDCl_3$): δ 5.19-5.42 (m, 1H), 3.48-3.99 (m, 4H), 3.06 (d, 3H). 2.04-2.54 (m, 4H), 1.16 (t, 3H).

<u>Intermediario IC4</u>: (R)-1-propionil-pirrolidin-3-il-éster de ácido metan-sulfónico

a) 1-((R)-3-hidroxi-pirrolidin-1-il)-propan-1-ona



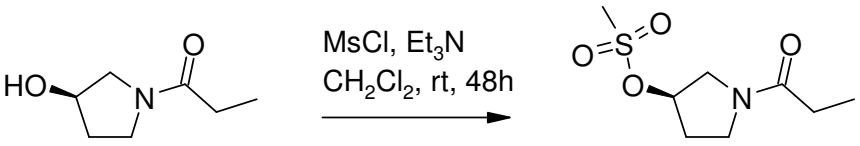
Se agregó cloruro de propionilo (CAS registro 79-03-8) (7.06

mililitros, 81 milimoles) (0°C <T <10°C), durante un período de 15 minutos, a una suspensión de (R)-pirrolidin-3-ol (CAS registro 2799-21-5) (10 gramos, 81 milimoles), y Et_3N (23.6 mililitros, 170 milimoles) en dicloro-metano (DCM) (150 mililitros) que se enfrió previamente a -10°C. La suspensión grisácea se agitó a 0°C durante 2 horas, se agregó metanol (9.82 mililitros, 243 milimoles), y la mezcla se dejó agitándose a temperatura ambiente durante 1 hora. La concentración y dilución del residuo con Et_2O (200 mililitros) proporcionó, después de la filtración y concentración del filtrado, el compuesto del título como un aceite amarillo (11.2 gramos, 95 por ciento).

ESIMS: 144 [$(M+H)^+$].

^{1}H RMN (400 MHz, DMSO-d_6): δ 4.81-5.04 (m, 1H), 4.15-4.38 (m, 1H), 3.35-3.59 (m, 2H), 3.16-3.29 (m, 2H), 2.11-2.33 (m, 2H), 1.65-2.00 (m, 2H), 0.98 (td, 3H).

b) (R)-1-propionil-pirrolidin-3-il-éster de ácido metan-sulfónico

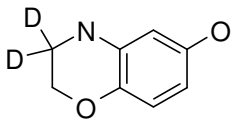


Bajo argón, se agregó por goteo cloruro de metan-sulfonilo (CAS registro 124-63-0) (0.16 mililitros, 2.09 milimoles), durante un período de 5 minutos, a una solución de 1-((R)-3-hidroxi-pirrolidin-1-il)-propan-1-ona (300 miligramos, 2.09 milimoles), y Et_3N (0.29 mililitros, 2.09 milimoles) en dicloro-metano (DCM) (10 mililitros) a

5°C, y la mezcla de reacción se dejó agitándose a temperatura ambiente durante 18 horas. Entonces se agregaron cloruro de metan-sulfonilo (CAS registro 124-63-0) (0.16 mililitros, 2.09 milimoles), y Et_3N (0.29 mililitros, 2.09 milimoles) a la mezcla de reacción, la cual se agitó a temperatura ambiente durante 48 horas. Se agregaron dicloro-metano (DCM) y H_2O a la solución, y la fase orgánica se separó a través de un cartucho de separación de fases y se concentró. Se obtuvo el compuesto del título después de la cromatografía por evaporación instantánea sobre gel de sílice (EtOAc / metanol, de 100:0 a 95:5 durante 25 minutos), como un aceite incoloro (420 miligramos, 86 por ciento).

^{1}H RMN (400 MHz, $CDCl_3$): δ 5.21-5.44 (m, 1H). 3.49-4.03 (m, 4H), 2.98-3.12 (m, 3H), 1.97-2.54 (m, 4H), 1.18 (t, 3H).

ID) Derivados o análogos de DBO

Interme-diario #	**ID) Derivado o análogo de DBO Estructura**	**Nombre Autonom**	**Comentario sobre la síntesis**
ID1		3,3-dideutero-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-ol	2 pasos de CAS 53412-38-7, véase el Ejemplo Q pasos a), b)

Evaluación Biológica

La actividad de un compuesto de acuerdo con la presente invención se puede evaluar mediante los siguientes métodos *in vitro* e *in vivo*.

Ensayos Biológicos

1 Determinación de la inhibición enzimática de las isoformas PI3K alfa y PI3K delta

1.1 Prueba de la actividad de la cinasa de lípido

La eficacia de los compuestos de los Ejemplos 1 a 117 como inhibidores de cinasa PI3 se puede demostrar como sigue:

La reacción de cinasa se lleva a cabo en un volumen final de 50 microlitros por pozo de una placa COSTAR de 96 pozos de media área. Las concentraciones finales de ATP y fosfatidil-inositol en el ensayo son de 5 µM y 6 microgramos/mililitro, respectivamente. La reacción se inicia mediante la adición de cinasa PI3, por ejemplo, la cinasa PI3 δ.

p110δ Los componentes del ensayo se agregan por pozo como sigue:

- 10 microlitros del compuesto de prueba en sulfóxido de dimetilo al 5 por ciento por pozo en las columnas 2-1.
- La actividad total se determina mediante la adición de 10 microlitros de sulfóxido de dimetilo al 5 por ciento por volumen/ volumen en los primeros 4 pozos de la columna 1 y en los últimos 4 pozos de la columna 12.
- El fondo se determina mediante la adición del compuesto

de control 10 µM a los últimos 4 pozos de la columna 1 y a los primeros 4 pozos de la columna 12.

- Se preparan 2 mililitros de 'mezcla de ensayo' por placa:

  1.912 mililitros de regulador de ensayo HEPES,

  8.33 microlitros de un suministro 3 mM de ATP para dar una concentración final de 5 µM por pozo,

  1 microlitro de [^{33}P]ATP en la fecha de actividad, dando 0.05 µCi por pozo,

  30 microlitros de 1 miligramo/mililitro de suministro de PI, dando una concentración final de 6 microgramos/mililitro por pozo,

  5 microlitros de un suministro de $MgCl_2$ 1 M, dando una concentración final de 1 mM por pozo.

- Se agregan 20 microlitros de la mezcla de ensayo por pozo.

- Se preparan 2 mililitros de 'mezcla enzimática' por placa (x^* microlitros de cinasa PI3 p110ß en 2 mililitros de regulador de cinasa). La 'mezcla enzimática' se mantiene sobre hielo durante la adición a las placas de ensayo.

- Se agregan 20 microlitros de 'mezcla enzimática' por pozo para iniciar la reacción.

- La placa se incuba entonces a temperatura ambiente durante 90 minutos.

- La reacción se termina mediante la adición de 50 microlitros de suspensión de perlas WGA-SPA (perlas de Ensayo de

Proximidad de Centelleo recubiertas con aglutinina de germen de trigo) por pozo.

- La placa de ensayo se sella, utilizando un sello de calor TopSeal-S para microplacas de poliestireno (PerkinElmer LAS [Deutschland] GmbH, Rodgau, Alemania), y se incuba a temperatura ambiente durante cuando menos 60 minutos.
- La placa de ensayo entonces se centrifuga a 1,500 revoluciones por minuto durante 2 minutos, utilizando el centrífugo de banco Jouan (Jouan Inc., Nantes, Francia).
- La placa de ensayo se cuenta, utilizando un Packard TopCount, contándose cada pozo durante 20 segundos.

* El volumen de enzima depende de la actividad enzimática del lote en uso.

En un ensayo más preferido, la reacción de cinasa se lleva a cabo en un volumen final de 10 microlitros por pozo de una placa negra de bajo volumen sin enlace CORNING de 384 pozos (Cat. No. #3676). Las concentraciones finales de ATP y fosfatidil-inositol (PI) en el ensayo son de 1 µM y 10 microgramos/mililitro, respectivamente. La reacción se inicia mediante la adición de ATP.

Los componentes del ensayo se agregan por pozo como sigue:

50 nanolitros de los compuestos de prueba en sulfóxido de dimetilo al 90 por ciento por pozo, en las columnas 1-20, 8 concentraciones (1/3 y 1/3.33 paso de dilución en serie) individualmente.

- Control bajo: 50 nanolitros de sulfóxido de dimetilo al 90

por ciento en la mitad de los pozos de las columnas 23-24 (0.45 por ciento final).

- Control alto: 50 nanolitros del compuesto de referencia (por ejemplo, el compuesto del Ejemplo 7 de la Publicación Internacional Número WO 2006/122806) en la otra mitad de las columnas 23-24 (2.5 micras final).
- Estándar: 50 nanolitros del compuesto de referencia como justamente se mencionó, diluido como los compuestos de prueba en las columnas 21-22.
- Se preparan 20 mililitros de 'regulador' por ensayo:
  - 200 microlitros de TRIS•HCl 1M, pH de 7.5 (10 mM final).
  - 60 microlitros de $MgCl_2$ 1M (3 mM final).
  - 500 microlitros de NaCl 2M (50 mM final).
  - 100 microlitros de CHAPS al 10 por ciento (0.05 por ciento final).
  - 200 microlitros de DTT 100mM (1mM final).
  - 18.94 mililitros de agua nanopura.
- Se preparan 10 mililitros de 'PI' por ensayo:
  - 200 microlitros de 1 miligramo/mililitro de L-alfa-fosfatidil-inositol (Hígado Bovino, Avanti Polar Lipids, Cat. No. 840042C MW=909.12) preparado en octil-glucósido al 3 por ciento (10 microgramos/ mililitro final).
  - 9.8 mililitros de 'regulador'.

- Se preparan 10 mililitros ‘ATP’ por ensayo:

  6.7 microlitros de un suministro 3 mM de ATP, dando una concentración final de 1 µM por pozo.

  10 mililitros de ‘regulador’.

- Se preparan 2.5 mililitros de cada construcción de PI3K por ensayo en ‘PI’ con la siguiente concentración final:

  PI3K alfa-EMV B1075 10 nM.

  Beta-EMV BV949 25 nM.

  Delta-EMV BV1060 10 nM.

  Gamma-EMV BV950 150 nM.

- Se agregan 5 microlitros de ‘PI/PI3K’ por pozo.
- Se agregan 5 microlitros de ‘ATP’ por pozo para iniciar la reacción.
- Las placas se incuban entonces a temperatura ambiente durante 60 minutos (alfa, beta, delta) o 120 minutos (gamma).
- La reacción se termina mediante la adición de 10 microlitros de Kinase-Glo (Promega Cat. No. #6714).
- Las placas de ensayo se leen después de 10 minutos en un lector Synergy 2 (BioTek, Vermont, EUA) con un tiempo de integración de 100 milisegundos y la sensibilidad establecida en 191.
- Resultado: El control alto es de alrededor de 60,000 conteos, y el control bajo es de 30,000 ó más bajo.
- Este ensayo de luminiscencia da una proporción Z’ útil de entre 0.4 y 0.7.

El valor Z’ es una medición universal de la seguridad de un

ensayo. Un Z' de entre 0.5 y 1.0 se considera como un ensayo excelente.

Para este ensayo, se preparan las construcciones de PI3K mencionadas como sigue:

1.2 Generación de construcciones genéticas

Se utilizan dos construcciones diferentes, BV 1052 y BV 1075, para generar las proteínas de cinasa PI3 α para el rastreo de los compuestos.

PI3Kα BV-1052 p85(iSH2) - enlazador Gly -p110α(D20aa) - C-term marca His

Se generan los productos de reacción en cadena de la polimerasa (PCR) para el dominio inter-SH2 (iSH2) de la subunidad p85 y para la subunidad p110-α (con una supresión de los primeros 20 aminoácidos), y se fusionan mediante reacción en cadena de la polimerasa (PCR) traslapada.

El producto iSH2 de la reacción en cadena de la polimerasa (PCR) se genera a partir del ADNc de la primera cadena, utilizando inicialmente los cebadores:

gwG130-p01 (5'-CGAGAATATGATAGATTATATGAAGAAT-3') (SEQ ID NO: 1), y gwG130-p02 (5'-TGGTTT-AATGCTGTTCATACG TTTGTCAAT-3') (SEQ ID NO: 2).

Subsiguientemente, en una reacción en cadena de la polimerasa (PCR) secundaria, Gateway (Invitrogen AG, Basilea, Suiza), se agregan los sitios de recombinación AttB1 y las secuencias enlazadoras en los extremos 5' y 3' del fragmento iSH2

de p85, respectivamente, utilizando los cebadores:

gwG130-p03 (5’ - GGGACAAGTTTGTACAAAAAAGCAGGCTAC GAAGGAGATATACATATGCGAGAATATGATAGATTATATGAAGAAT - 3’) (SEQ ID NO: 3) y

gwG152-p04 (5’ - TACCATAATTCCACCACCACCACCGGAAATT CCCCCTGGTTTAATGCTGTTCATACGTTTGTCAAT - 3’) (SEQ ID NO: 4).

El fragmento p110-α también se genera a partir del ADNc de la primera cadena, utilizando inicialmente los cebadores:

gwG152-p01 (5’ - CTAGTGGAATGTTTACTACCAAATGG - 3’) (SEQ ID NO: 5), y

gwG152-p02 (5’ - GTTCAATG-CATGCTGTTTAATTGTGT - 3’) (SEQ ID NO: 6).

En una reacción en cadena de la polimerasa (PCR) subsiguiente, se agregan la secuencia enlazadora y una marca de Histidina en el extremo 5' y en el extremo 3' del fragmento p110-α, respectivamente, utilizando los cebadores:

gw152-p03 (5’ - GGGGGAATTTCCGGTGGTGGTGGTGGAATTA TGGTACTAGTGGAATGTTTACTACCAAATGGA - 3’) (SEQ ID NO: 7), y

gwG152-p06 (5’ - AGCTCCGTGATGGTGATGGTGATGTGCTCC GTTCAATGCATGCTGTTTAATTGTGT - 3’) (SEQ ID NO: 8).

La proteína de fusión p85-iSH2/p110-α se ensambla en una tercera reacción en cadena de la polimerasa (PCR) mediante los enlazadores traslapados en el extremo 3' del fragmento iSH2 y el

extremo 5' del fragmento p110-α, utilizando el cebador gwG130-p03 anteriormente mencionado, y un cebador que contenía una marca de Histidina traslapada y las secuencias de recombinación de AttB2:

(5'-GGGACCACTTTGTACAAGAAAGCTGGGTTTAAGCTCCGTG ATGGTGATGGTGATGTGCTCC-3') (SEQ ID NO: 9).

El producto final se recombina en una reacción OR (Invitrogen) en el vector donador pDONR201 para generar el clon de entrada ORF318. Este clon se verifica mediante secuenciación, y se utiliza en una reacción LR Gateway para transferir el inserto al vector pBlueBac4.5 adaptado con Gateway (Invitrogen) para la generación del vector de expresión de baculovirus LR410.

PI3Kα BV-1075 p85(iSH2) - enlazador 12XGly - p110α(D20aa) - C -term marca His

La construcción para el Baculovirus BV-1075 se genera mediante un ligamiento de tres partes comprendidas de un fragmento p85 y un fragmento p110-α clonado en el vector pBlueBac4.5. El fragmento p85 se deriva a partir del plásmido p1661-2 digerido con Nhe/Spe. El fragmento p110-α derivado a partir de LR410 (véase anteriormente) como un fragmento SpeI/HindIII. El vector de clonación pBlueBac4.5 (Invitrogen) se digiere con Nhe/HindIII. Esto da como resultado la construcción PED 153.8.

El componente (iSH2) de p85 se genera mediante reacción en cadena de la polimerasa (PCR), utilizando el ORF 318 (descrito anteriormente) como una plantilla, y un cebador hacia adelante:

KAC1028 (5' - GCTAGCATGCGAGAATATGATAGATTATATGAA

GAATATACC) (SEQ ID NO: 10),

y dos cebadores en reversa:

KAC1029 (5’ - GCCTCCACCACCTCCGCCTGGTTTAATGCTGT TCATACGTTTGTC) (SEQ ID NO: 11), y

KAC1039 (5’ - TACTAGTCCGCCTCCACCACCTCCGCCTCCAC CACCTCCGCC) (SEQ ID NO: 12).

Los dos cebadores en reversa se traslapan e incorporan el enlazador 12x Gly y la secuencia N-terminal del gen p110α para el sitio SpeI. El enlazador 12x Gly reemplaza al enlazador de la construcción BV1052. El fragmento de la reacción en cadena de la polimerasa (PCR) se clona en pCR2.1 TOPO (Invitrogen). De los clones resultantes, se determina que el p1661-2 es el correcto. Este plásmido se digiere con Nhe y SpeI, y el fragmento resultante se aísla en gel y se purifica para la sub-clonación.

El fragmento de clonación p110-α se genera mediante la digestión enzimática del clon LR410 (véase anteriormente) con Spe I y HindIII. El sitio SpeI está en la región codificante del gen p110α. El fragmento resultante se aísla en gel y se purifica para la sub-clonación.

El vector de clonación, pBlueBac4.5 (Invitrogen), se prepara mediante digestión enzimática con Nhe y HindIII. El vector de corte se purifica con una columna Qiagen (Qiagen N.V, Venlo, Holanda), y entonces se desfosforila con fosfatasa alcalina de intestino de becerro (CIP) (New England BioLabs, Ipswich, MA). Después de completarse la reacción de CIP, nuevamente se purifica en columna

el vector de corte, para generar el vector final. Se lleva a cabo un ligamiento de tres partes, utilizando ligasa Roche Rapid y las especificaciones del vendedor.

PI3Kß BV-949 p85(iSH2) - enlazador Gly - p110ß (longitud completa) - C-term marca His

Se generan los productos de reacción en cadena de la polimerasa (PCR) para el dominio inter-SH2 (iSH2) de la subunidad p85 y para la subunidad p110-ß de longitud completa, y se fusionan mediante reacción en cadena de la polimerasa (PCR) traslapada.

El producto iSH2 de la reacción en cadena de la polimerasa (PCR) se genera a partir del ADNc de la primera cadena inicialmente, utilizando los cebadores:

gwG130-p01 (5'-CGAGAATATGATAGATTATATGAAGAAT-3') (SEQ ID NO: 1), y gwG130-p02 (5'-TGGTTTAATGCTGTTCATACG TTTGTCAAT-3') (SEQ ID NO: 2).

Subsiguientemente, en una reacción en cadena de la polimerasa (PCR) secundaria, se agregan los sitios AttB1 de recombinación Gateway (Invitrogen) y las secuencias enlazadoras en el extremo 5' y en el extremo 3' del fragmento iSH2 de p85, respectivamente, utilizando los cebadores:

gwG130-p03 (5' - GGGACAAGTTTGTACAAAAAAGCAGGCT ACGAAGGAGATATACATATGCGAGAATATGATAGATTATATGAAGAA T - 3') (SEQ ID NO: 3), y

gwG130-p05 (5' - ACTGAAGCATCCTCCTCCTCCTCCTCCT GGTTTAATGCTGTTCATACGTTTGTC - 3') (SEQ ID NO: 13).

El fragmento p110-ß también se genera a partir del ADNc de la primera cadena inicialmente, utilizando los cebadores:

gwG130-p04 (5’ - ATTAAACCAGGAGGAGGAGGAGGAGG ATGCTTCAGTTTCATAATGCC-TCCTGCT - 3’) (SEQ ID NO: 4)

que contiene las secuencias enlazadoras y el extremo 5' de p110-ß, y

gwG130-p06 (5’ - AGCTCCGTGATGGTGATGGTGATGTGC TCCAGATCTGTAGTCTTT-CCGAACTGTGTG - 3’) (SEQ ID NO: 14)

que contiene las secuencias del extremo 3' de p110-ß fusionado con una marca de Histidina.

La proteína de fusión p85-iSH2/p110-ß se ensambla mediante una reacción en cadena de la polimerasa (PCR) traslapada, para la reacción de los enlazadores en el extremo 3' del fragmento iSH2 y en el extremo 5' del fragmento p110-ß, utilizando el cebador gwG130-p03 anteriormente mencionado y un cebador que contiene una marca de Histidina traslapada y la secuencia de recombinación de AttB2:

(5’ - GGGACCACTTTGTACAAGAAAGCTGGGTTTAAGCTCCG TGATGGTGATGGTGATGTGCTCC - 3’) (SEQ ID NO: 15).

Este producto final se recombina en una reacción Gateway (Invitrogen) en el vector donador pDONR201 para generar el clon de entrada ORF253. Este clon se verifica mediante secuenciación, y se utiliza en una reacción LR Gateway para transferir el inserto al vector pBlueBac4.5 adaptado con Gateway (Invitrogen) para la generación del vector de expresión de baculovirus LR280.

PI3Kδ BV-1060 p85(iSH2) - enlazador Gly - p110d (longitud

completa) - C-term marca His

Se generan los productos de la reacción en cadena de la polimerasa (PCR) para el dominio inter-SH2 (iSH2) de la subunidad p85 y para la subunidad p110-d de longitud completa, y se fusionan mediante reacción en cadena de la polimerasa (PCR) traslapada.

El producto iSH2 de la reacción en cadena de la polimerasa (PCR) se genera a partir del ADNc de la primera cadena, utilizando inicialmente los cebadores:

gwG130-p01 (5' - CGAGAATATGATAGATTATATGAAGAAT - 3') (SEQ ID NO: 1), y gwG130-p02 (5' - TGGTTTAATGCTGTTCA-TACGTTTGTCAAT - 3') (SEQ ID NO: 2).

Subsiguientemente, en una reacción en cadena de la polimerasa (PCR) secundaria, se agregan los sitios AttB1 de recombinación Gateway (Invitrogen) y las secuencias enlazadoras en los extremos 5' y 3' del fragmento iSH2 de p85, respectivamente, utilizando los cebadores:

gwG130-p03 (5' - GGGACAAGTTTGTACAAAAAAGCAGGC TACGAAGGAGATATACATATGCGAGAATATGATAGATTATATGAAGA AT - 3') (SEQ ID NO: 3), y

gwG154-p04 (5' - TCCTCCTCCTCCTCCTCCTGGTTTAATG CTGTTCATACGTTTGTC - 3') (SEQ ID NO: 16).

El fragmento p110-α también se genera a partir del ADNc de la primera cadena, utilizando inicialmente los cebadores:

gwG154-p01 (5' - ATGCCCCCTGGGGTGGACTGCCCCAT - 3') (SEQ ID NO: 17), y

gwG154-p02 (5’ - CTACTG-CCTGTTGTCTTTGGACACGT - 3’) (SEQ ID NO: 18).

En una reacción en cadena de la polimerasa (PCR) subsiguiente, se agregan las secuencias enlazadoras y una marca de Histidina en el extremo 5’ y en el extremo 3’ del fragmento p110-d, respectivamente, utilizando los cebadores:

gw154-p03 (5’ - ATTAAACCAGGAGGAGGAGGAGGAGG ACCCCCTGGGGTGGACTGCCCCATGGA - 3’) (SEQ ID NO: 19), y

gwG154-p06 (5’ - AGCTCCGTGATGGTGATGGTGATGTGC TCCCTGCCTGTTGTCTTTGGACACGTTGT - 3’) (SEQ ID NO: 20).

La proteína de fusión p85-iSH2/p110-d se ensambla en una tercera reacción en cadena de la polimerasa (PCR), mediante los enlazadores traslapados en el extremo 3' del fragmento iSH2 y en el extremo 5' del fragmento p110-d, utilizando el cebador gwG130-p03 anteriormente mencionado y un cebador que contenía una marca de Histidina traslapada, y la secuencia de recombinación de AttB2 Gateway (Invitrogen):

(5’ - GGGACCACTTTGTACAAGAAAGCTGGGTTTAAGCTCCGT GATGGTGATGGTGATGTGCTCC - 3’) (SEQ ID NO: 21).

Este producto final se recombina en una reacción Gateway (Invitrogen) en el vector donador pDONR201 para generar el clon de entrada ORF319. Este clon se verifica mediante secuenciación, y se utiliza en una reacción LR Gateway para transferir el inserto al vector pBlueBac4.5 adaptado con Gateway (Invitrogen) para la generación del vector de expresión de baculovirus LR415.

PI3Kγ BV-950 p110g(D144aa)- C-term marca His

Esta construcción se obtiene en Roger Williams Lab, MRC Laboratory of Molecular Biology, Cambridge, Reino Unido (Noviembre, 2003). Descripción de la construcción en: Pacold M. E. y colaboradores (2000) Cell 103, 931-943.

1.3 Expresión y purificación de proteínas

Métodos para generar el baculovirus recombinante y la proteína para las isoformas de PI3K:

Los plásmidos pBlue-Bac4.5 (para las isoformas a, b, y d) o pVL1393 (para g) que contienen los diferentes genes de cinasa PI3, se co-transfectan con el ADN genómico BaculoGold WT (BD Biosciences, Franklin Lakes, NJ, EUA), empleando los métodos recomendados por el vendedor. Subsiguientemente, el baculovirus recombinante obtenido a partir de la transfección se purifica en placa sobre células de insecto Sf9, para proporcionar varios aislados que expresan la proteína recombinante. Los clones positivos se seleccionan mediante Western del anticuerpo anti-HIS o anti-isoforma. Para las isoformas de PI3K alfa y delta, se lleva a cabo una purificación de placa secundaria sobre los primeros suministros del virus clonal de PI3K. La amplificación de todos los aislados de baculovirus se lleva a cabo a una baja multiplicidad de infección (moi) para generar un suministro de alta titulación de pasaje bajo para la producción de la proteína. Los baculovirus se designan como BV1052 (α), y BV1075 (α), BV949 (ß), BV1060 (δ), y BV950 (γ).

La producción de la proteína involucra la infección (pasaje 3 o

más bajo) de las células suspendidas Tn5 (*Trichoplusia ni*) o TiniPro (Expression Systems, LLC, Woodland, CA, EUA) en un medio sin proteínas en una multiplicidad de infección de 2 a 10 durante 39 a 48 horas en matraces Erlenmeyer de vidrio de 2 litros (110 revoluciones por minuto) o bio-reactores de ondas (22 a 25 revoluciones por minuto). Inicialmente, se siembran los bio-reactores con un volumen de procesamiento de 10 litros a una densidad de 3^5 células/mililitro a la mitad de la capacidad (5 litros). El reactor se balancea a 15 revoluciones por minuto en la fase de crecimiento celular durante 72 horas, complementado con oxígeno al 5 por ciento mezclado con aire (0.2 litros por minuto). Inmediatamente antes de la infección, se analizan los cultivos del reactor de ondas para determinar la densidad y la viabilidad, y se diluyen hasta aproximadamente 1.5^6 células/mililitro. Se agregan de 100 a 500 mililitros de virus de alta titulación de pasaje bajo, siguiendo de 2 a 4 horas de cultivo adicional. Se aumenta el oxígeno hasta el 35 por ciento para el período de infección de 39 a 48 horas, y se aumentan las revoluciones por minuto de la plataforma de balanceo a 25. Durante la infección, las células se monitorean mediante el bioproceso del analizador de viabilidad Vicell (Beckman Coulter, Inc, Fullerton, CA, EUA) para determinar la viabilidad, el diámetro, y la densidad. Se toman lecturas en el Nova Bioanalyzer (NOVA Biomedical Corp., Waltham, MA, EUA) de diferentes parámetros y metabolitos (pH, saturación de O_2, glucosa, etc.) cada 12 a 18 horas, hasta la cosecha. Las células del bio-reactor de ondas se recolectan dentro

de 40 horas después de la infección. Las células se recolectan mediante centrifugación (4°C a 1,500 revoluciones por minuto), y subsiguientemente se mantienen sobre hielo durante la agrupación de los gránulos para la lisis y la purificación. Los grupos de gránulos se hacen con pequeñas cantidades de medio de Grace no complementado frío (sin inhibidores de proteasa).

Protocolo de purificación de PI3K alfa para HTS (BV1052)

La PI3K alfa se purifica en tres pasos cromatográficos: cromatografía de afinidad de metal inmovilizado sobre una resina de Ni-Sepharose (GE Healthcare, que pertenece a General Electric Company, Fairfield, CT, EUA), filtración de gel, utilizando una columna Superdex 200 26/60 (GE Healthcare), y finalmente un paso de intercambio de cationes sobre una columna SP-XL (GE Healthcare). Todos los reguladores se enfrían hasta 4°C, y la lisis se lleva a cabo enfriados sobre hielo. El fraccionamiento de la columna se lleva a cabo rápidamente a temperatura ambiente.

Típicamente, las células de insecto congeladas se lisan en un regulador de lisis hipertónico, y se aplican a una columna IMAC preparada. La resina se lava con 3 a 5 volúmenes de columna de regulador de lisis, seguidos por 3 a 5 volúmenes de columna de regulador de lavado que contiene imidazol 45 mM, y entonces se eluye la proteína objetivo con un regulador que contiene imidazol 250 mM. Las fracciones se analizan mediante geles de SDS-PAGE teñidos con Coomassie, y las fracciones que contienen la proteína objetivo se reservan y se aplican a una columna de GFC preparada.

Las fracciones a partir de la columna de GFC se analizan mediante geles de SDS-PAGE teñidos con Coomassie, y se reservan las fracciones que contienen la proteína objetivo. La reserva a partir de la columna de GFC se diluye en un regulador bajo en sal, y se aplica a una columna SP-XL preparada. La columna se lava con regulador bajo en sal hasta que se alcanza una absorbencia de la línea base de A280 estable, y se eluye utilizando un gradiente en 20 volúmenes de columna desde NaCl 0 mM hasta NaCl 500 mM. Nuevamente, las fracciones a partir de la columna SP-XL se analizan mediante geles de SDS-PAGE teñidos con Coomassie, y se reservan las fracciones que contienen la proteína objetivo. La reserva final se dializa en un regulador de almacenamiento que contiene glicerol al 50 por ciento, y se almacena a -20°C. La reserva final se ensaya para determinar la actividad en un ensayo de cinasa de fosfoinositol.

Protocolo de purificación de PI3K beta para HTS (BV949)

La PI3K beta se purifica en dos pasos cromatográficos: cromatografía de afinidad de metal inmovilizado (IMAC) sobre una resina de Ni-Sepharose (GE Healthcare), y filtración de gel (GFC), utilizando una columna Superdex 200 26/60 (GE Healthcare). Todos los reguladores se enfrían hasta 4°C, y la lisis se lleva a cabo enfriados sobre hielo. El fraccionamiento de la columna se lleva a cabo rápidamente a temperatura ambiente.

Típicamente, las células de insecto congeladas se lisan en un regulador de lisis hipertónico, y se aplican a una columna IMAC preparada. La resina se lava con 3 a 5 volúmenes de columna de

regulador de lisis, seguidos por 3 a 5 volúmenes de columna de regulador de lavado que contiene imidazol 45 mM, y entonces se eluye la proteína objetivo con un regulador que contiene imidazol 250 mM. Las fracciones se analizan mediante geles de SDS-PAGE teñidos con Coomassie, y las fracciones que contienen la proteína objetivo se reservan y se aplican a una columna de GFC preparada. Las fracciones a partir de la columna de GFC se analizan mediante geles de SDS-PAGE teñidos con Coomassie, y se reservan las fracciones que contienen la proteína objetivo. La reserva final se dializa en un regulador de almacenamiento que contiene glicerol al 50 por ciento, y se almacena a -20°C. La reserva final se ensaya para determinar la actividad de cinasa de fosfoinositol.

Protocolo de purificación de PI3K gamma para HTS (BV950)

La PI3K gamma se purifica en dos pasos cromatográficos: cromatografía de afinidad de metal inmovilizado (IMAC) sobre una resina de Ni-Sepharose (GE Healthcare), y filtración de gel (GFC), utilizando una columna Superdex 200 26/60 (GE Healthcare). Todos los reguladores se enfrían hasta 4°C, y la lisis se lleva a cabo enfriados sobre hielo. El fraccionamiento de la columna se lleva a cabo rápidamente a temperatura ambiente. Típicamente, las células de insecto congeladas se lisan en un regulador de lisis hipertónico, y se aplican a una columna IMAC preparada. La resina se lava con 3 a 5 volúmenes de columna de regulador de lisis, seguidos por 3 a 5 volúmenes de columna de regulador de lavado que contiene imidazol 45 mM, y entonces se eluye la proteína objetivo con un regulador

que contiene imidazol 250 mM. Las fracciones se analizan mediante geles de SDS-PAGE teñidos con Coomassie, y las fracciones que contienen la proteína objetivo se reservan y se aplican a una columna de GFC preparada. Las fracciones a partir de la columna de GFC se analizan mediante geles de SDS-PAGE teñidos con Coomassie, y se reservan las fracciones que contienen la proteína objetivo. La reserva final se dializa en un regulador de almacenamiento que contiene glicerol al 50 por ciento, y se almacena a -20°C. La reserva final se ensaya para determinar la actividad de cinasa de fosfoinositol.

Protocolo de purificación de PI3K delta para HTS (BV1060)

La PI3K delta se purifica en tres pasos cromatográficos: cromatografía de afinidad de metal inmovilizado sobre una resina de Ni-Sepharose (GE Healthcare), filtración de gel, utilizando una columna Superdex 200 26/60 (GE Healthcare), y finalmente un paso de intercambio de aniones sobre una columna Q-HP (GE Healthcare). Todos los reguladores se enfrían hasta 4°C, y la lisis se lleva a cabo enfriados sobre hielo. El fraccionamiento de la columna se lleva a cabo rápidamente a temperatura ambiente. Típicamente, las células de insecto congeladas se lisan en un regulador de lisis hipertónico, y se aplican a una columna IMAC preparada. La resina se lava con 3 a 5 volúmenes de columna de regulador de lisis, seguidos por 3 a 5 volúmenes de columna de regulador de lavado que contiene imidazol 45 mM, y entonces se eluye la proteína objetivo con un regulador que contiene imidazol 250 mM. Las fracciones se analizan mediante

geles de SDS-PAGE teñidos con Coomassie, y las fracciones que contienen la proteína objetivo se reservan y se aplican a una columna de GFC preparada. Las fracciones a partir de la columna de GFC se analizan mediante geles de SDS-PAGE teñidos con Coomassie, y se reservan las fracciones que contienen la proteína objetivo. La reserva a partir de la columna de GFC se diluye en un regulador bajo en sal, y se aplica a una columna Q-HP preparada. La columna se lava con regulador bajo en sal hasta que se alcanza una absorbencia de la línea base de A280 estable, y se eluye utilizando un gradiente en 20 volúmenes de columna desde NaCl 0 mM hasta NaCl 500 mM. Nuevamente, las fracciones a partir de la columna Q-HP se analizan mediante geles de SDS-PAGE teñidos con Coomassie, y se reservan las fracciones que contienen la proteína objetivo. La reserva final se dializa en un regulador de almacenamiento que contiene glicerol al 50 por ciento, y se almacena a -20°C. La reserva final se ensaya para determinar la actividad de cinasa de fosfoinositol.

La IC_{50} se determina mediante una rutina de ajuste de curva de cuatro parámetros que viene junto con "excel fit". Se emplea una ecuación logística de cuatro parámetros para calcular los valores IC_{50} (IDBS XLfit) del porcentaje de inhibición de cada compuesto en 8 concentraciones (usualmente 10, 3.0, 1.0, 0.3, 0.1, 0.030,0.010 y 0.003 μM). De una manera alternativa, Los valores IC_{50} se calculan utilizando idbsXLfit modelo 204, el cual es un modelo logístico de 4 parámetros.

Todavía de una manera alternativa, para un ensayo de agotamiento de ATP, los compuestos de la fórmula (I) que se van a probar se disuelven en sulfóxido de dimetilo y se distribuyen directamente en una placa blanca de 384 pozos a 0.5 microlitros por pozo. Para iniciar la reacción, se agregan 10 microlitros de cinasa PI3 10 nM y 5 microgramos/mililitro de 1-alfa-fosfatidil-inositol (PI) a cada pozo, seguidos por 10 microlitros de ATP 2 µM. La reacción se lleva a cabo hasta que se agota aproximadamente el 50 por ciento del ATP, y entonces se detiene mediante la adición de 20 microlitros de solución Kinase-Glo (Promega Corp., Madison, WI, EUA). La reacción detenida se incuba durante 5 minutos, y luego se detecta el ATP restante por medio de luminiscencia. Entonces se determinan los valores IC_{50}.

En una modalidad de la presente invención, el inhibidor de PI3K, en donde este inhibidor tiene una acción inhibidora sobre la PI3K isoforma delta, en donde el intervalo de actividad, expresado como IC_{50}, en el ensayo enzimático de PI3K delta, es de entre 1 nM y 500 nM.

En otra modalidad de la presente invención, el inhibidor de PI3K, en donde este inhibidor tiene una acción inhibidora sobre la PI3K isoforma delta, en donde el intervalo de actividad, expresado como IC_{50}, en el ensayo enzimático de PI3K delta, es de entre 1 nM y 100 nM.

En otra modalidad de la presente invención, el inhibidor de PI3K, en donde este inhibidor tiene una acción inhibidora sobre la

PI3K isoforma delta, en donde el intervalo de actividad, expresado como IC_{50}, en el ensayo enzimático de PI3K delta, es de entre 0.5nM y 10 nM.

En una modalidad de la presente invención, el inhibidor de PI3K, en donde este inhibidor tiene una acción inhibidora sobre la PI3K isoforma delta, en donde el intervalo de actividad, expresado como IC_{50}, en el ensayo celular de PI3K delta, es de entre 1 nM y 1000 nM.

En otra modalidad de la presente invención, el inhibidor de PI3K, en donde este inhibidor tiene una acción inhibidora sobre la PI3K isoforma delta, en donde el intervalo de actividad, expresado como IC_{50}, en el ensayo celular de PI3K delta, es de entre 1 nM y 500 nM.

En otra modalidad de la presente invención, el inhibidor de PI3K, en donde este inhibidor tiene una acción inhibidora sobre la PI3K isoforma delta, en donde el inhibidor muestra una selectividad para la PI3K isoforma delta sobre una o más de las otras isoformas, en donde esta selectividad es de cuando menos 10 veces.

En otra modalidad de la presente invención, el inhibidor de PI3K, en donde este inhibidor tiene una acción inhibidora sobre la PI3K isoforma delta, en donde el inhibidor muestra una selectividad para la PI3K isoforma delta sobre una o más de las otras isoformas, en donde esta selectividad es de cuando menos 20 veces.

En otra modalidad de la presente invención, el inhibidor de PI3K, en donde este inhibidor tiene una acción inhibidora sobre la

PI3K isoforma delta, en donde el inhibidor muestra una selectividad para la PI3K isoforma delta sobre los diferentes parálogos PI3K α y ß, en donde esta selectividad es de cuando menos 10 veces.

En otra modalidad de la presente invención, el inhibidor de PI3K, en donde este inhibidor tiene una acción inhibidora sobre la PI3K isoforma delta, en donde el inhibidor muestra una selectividad para la PI3K isoforma delta sobre los diferentes parálogos PI3K α y ß, en donde esta selectividad es de cuando menos 20 veces.

En otra modalidad de la presente invención, el inhibidor de PI3K, en donde este inhibidor tiene una acción inhibidora sobre la PI3K isoforma delta, en donde el intervalo de actividad, expresado como IC_{50}, en el ensayo celular de PI3K delta, es de entre 1 nM y 500 nM, y en donde este inhibidor tiene una acción inhibidora sobre la PI3K isoforma delta, en donde el inhibidor muestra una selectividad para la PI3K isoforma delta sobre los diferentes parálogos PI3K α y ß, en donde esta selectividad es de cuando menos 10 veces.

En otra modalidad de la presente invención, el inhibidor de PI3K, en donde este inhibidor tiene una acción inhibidora sobre la PI3K isoforma delta, en donde el intervalo de actividad, expresado como IC_{50}, en el ensayo celular de PI3K delta, es de entre 1 nM y 500 nM, y en donde este inhibidor tiene una acción inhibidora sobre la PI3K isoforma delta, en donde el inhibidor muestra una selectividad para la PI3K isoforma delta sobre los diferentes parálogos PI3K α y ß, en donde esta selectividad es de cuando

menos 20 veces.

2. Ensayos Celulares

2.1 Fosforilación de Akt 1/2 (S473) mediada por cinasa de fosfoinositida-3 (PI3K) en células de Rata-1

Las células de Rata-1 que sobre-expresan establemente una forma miristoilada de la subunidad catalítica de la cinasa de fosfoinositida-3 (PI3K) alfa, beta o delta humana, se aplicaron en placas de 384 pozos en una densidad de 7,500 (PI3K alfa), 6,200 (PI3K beta), ó 4,000 (PI3K delta) células en 30 microlitros de medio de crecimiento Complete (medio de Eagle modificado por Dulbecco (DMEM alto en glucosa) complementado con suero bovino fetal al 10 por ciento (volumen/volumen), aminoácidos no esenciales MEM al 1 por ciento (volumen/volumen), HEPES 10 mM, L-glutamina 2 mM, 10 microgramos/mililitro de puromicina, y Penicilina/Estreptomicina al 1 por ciento (volumen/volumen)), y se incubaron a 37°C / CO_2 al 5 por ciento / 95 por ciento de humedad, durante 24 horas. Los compuestos se diluyeron en placas con compuesto de 384 pozos, para obtener diluciones en serie de 8 puntos para 40 compuestos de prueba en sulfóxido de dimetilo al 90 por ciento, así como para 4 compuestos de referencia más 16 controles altos y 16 controles bajos (inhibidos). Las placas de pre-dilución se prepararon mediante la dosificación por pipeta de 250 nanolitros de las soluciones de compuestos en placas de polipropileno de 384 pozos, utilizando un dosificador en nanolitros Hummingwell. Los compuestos se diluyeron previamente mediante la adición de 49.75 microlitros de medio de

crecimiento Complete. Se transfirieron 10 microlitros de la solución de compuesto previamente diluida a la placa de células utilizando un portador de pipetas de 384 pozos, lo cual dio como resultado una concentración final en sulfóxido de dimetilo del 0.11 por ciento. Las células se incubaron durante 1 hora a 37°C / CO_2 al 5 por ciento / 95 por ciento de humedad. El sobrenadante se removió, las células se lisaron en 20 microlitros de regulador de lisis para la detección AlfaScreen® *SureFire*®.

Para la detección de p-AKT(Ser473), se utilizó el Kit de Ensayo *SureFire*® p-Akt 1/2 (Ser473) (PerkinElmer, EUA). Se transfirieron 5 microlitros de lisado celular a las placas Proxiplate de 384 pozos de bajo volumen para la detección utilizando un portador de pipetas de 384 pozos. La adición de los reactivos AlfaScreen® *SureFire*® se hizo de acuerdo con el protocolo del fabricante. Primero, se agregaron 5 microlitros de regulador de reacción más la mezcla reguladora de activación que contenía los granos aceptores AlfaScreen®, la placa se selló, y se incubó en un agitador de placas durante 2 horas a temperatura ambiente. Segundo, se agregaron 2 microlitros de regulador de dilución que contenía granos donantes AlfaScreen®, y la placa se incubó en un agitador de placas como anteriormente, durante 2 horas adicionales. La placa se leyó en un lector de placas compatible con AlfaScreen®, los ajustes estándares AlfaScreen®.

2.2 Determinación de la activación de células-B de murino

Se ha reconocido que la PI3Kδ modula la función de las

células-B cuando se estimulan las células a través del receptor de células-B (BCR) (Okkenhaug y colaboradores, Science 297: 1031 (2002)). Para evaluar la propiedad inhibidora de los compuestos sobre la activación de las células-B, se mide la sobre-regulación de los marcadores de activación CD86 y CD69 en las células-B de murino derivadas a partir de anticuerpos de bazo de ratón después de la estimulación con anti-IgM. CD69 es un marcador de activación bien conocido para las células B y T (Sancho y colaboradores, Trends Immunol. 26: 136 (2005). CD86 (también conocido como B7-2) se expresa primordialmente en las células presentadoras de antígeno, incluyendo las células-B. Las células-B en reposo expresan CD86 en bajos niveles, pero lo sobre-regulan en seguida de la estimulación, por ejemplo, del receptor de células-B (BCR) o del receptor de IL-4. El CD86 sobre una célula-B interactúa con el CD28 sobre las células-T. Esta interacción es requerida para una activación óptima de las células-T y para la generación de una respuesta óptima de IgG1 (Carreno y colaboradores, Annu Rev Immunol. 20: 29 (2002)).

Se recolectan los bazos a partir de los ratones Balb/c, se aíslan los esplenocitos, y se lavan dos veces con RPMI conteniendo suero bovino fetal (FBS) al 10 por ciento, HEPES 10 mM, y 100 Unidades/mililitro de penicilina/estreptomicina. El RPMI complementado de esta manera es subsiguientemente referido como el medio. Las células se ajustan a 2.5 X 10^6 células/mililitro en el medio, y se agregan 200 microlitros de la suspensión celular (5 x 10^6

células) a los pozos apropiados de las placas de 96 pozos.

Entonces las células se estimulan mediante la adición de 50 microlitros de mAb anti-IgM en el medio (concentración final: 30 microgramos/mililitro). Después de la incubación durante 24 horas a 37°C, las células se tiñen con los siguientes cócteles de anticuerpos: CD86-FITC anti-ratón, CD69-PerCP-Cy5.5 anti-ratón, CD19-PerCP anti-ratón, para la evaluación de las células-B, y CD3-FITC anti-ratón, CD69-PE anti-ratón, para la evaluación de las células-T (2 microlitros de cada anticuerpo/pozo). Después de una hora a temperatura ambiente (RT) en la oscuridad, las células se transfieren a las placas Deepwell de 96 pozos. Las células se lavan una vez con 1 mililitro de suero regulado con fosfato conteniendo suero bovino fetal (FBS) al 2 por ciento, y después de volver a suspender en 200 microlitros, las muestras se analizan en un citómetro de flujo FACS Calibur. Los linfocitos se pasan a la transferencia de puntos FSC/SSC de acuerdo con el tamaño y la granularidad, y se analizan adicionalmente para la expresión de CD19, CD3, y los marcadores de activación (CD86, CD69). Los datos se calculan a partir de las transferencias de puntos como el porcentaje de las células que se tiñen positivamente para los marcadores de activación dentro de la población de CD19+ o CD3+ utilizando el Software BD CellQest.

Para evaluar la propiedad inhibidora de los compuestos, primero se disuelven los compuestos y se diluyen en sulfóxido de dimetilo, seguido por una dilución a 1:50 en el medio. Los esplenocitos a partir de los ratones Balb/c se aíslan, se vuelven a

suspender, y se transfieren a las placas de 96 pozos, como se describe anteriormente (200 microlitros/pozo). Se agregan los compuestos diluidos o el solvente a las placas (25 microlitros), y se incuban a 37°C durante 1 hora. Entonces los cultivos se estimulan con 25 microlitros de mAb anti-IgM/pozo (concentración final de 30 microgramos/mililitro) durante 24 horas a 37°C, y se tiñen con CD86-FITC anti-ratón y CD19-PerCP anti-ratón (2 microlitros de cada anticuerpo/pozo). La expresión del CD86 en las células-B positivas para CD19 se cuantifica mediante citometría de flujo, como se describe anteriormente.

2.3 Determinación de activación de células-B de rata

Se ha reconocido que PI3Kδ modula la función de las células-B cuando se estimulan las células a través del receptor de células-B (BCR) (Okkenhaug y colaboradores, Science 297: 1031 (2002). Para evaluar la propiedad inhibidora de los compuestos sobre la activación de las células-B, se mide la sobre-regulación de los marcadores de activación CD86 sobre las células-B de rata derivadas a partir de sangre entera después de la estimulación con anti-IgM e IL-4 recombinante. La molécula CD86 (también conocida como B7-2) se expresa primordialmente en las células presentadoras de antígeno, incluyendo las células-B. Las células-B en reposo expresan CD86 en bajos niveles, pero la sobre-regulan en seguida de la estimulación, por ejemplo, del BCR o del receptor de IL-4. La CD86 sobre una célula-B interactúa con CD28 sobre las células-T. Esta interacción se requiere para la activación óptima de las células-

T y para la generación de una respuesta óptima de IgG1 (Carreno y colaboradores, Annu Rev Immunol. 20: 29 (2002)).

Recolección de sangre de rata

Se recolectó sangre entera a partir de la aorta abdominal de ratas Lewis machos adultas (LEW/HanHsd) o utilizando una jeringa de 10 mililitros con aguja hipodérmica previamente recubierta con heparina de sodio. La sangre se transfirió a tubos Falcon de 50 mililitros, y la concentración del anticoagulante se ajustó a 100 Unidades/mililitro.

Estimulación de células-B de rata y tratamiento con un inhibidor específico

Para la evaluación de los efectos *in vitro* de los fármacos inmunosupresores, la sangre heparinizada se diluyó previamente hasta el 50 por ciento con el medio. Como el medio sirvió el DMEM alto en glucosa (Animed cat # 1-26F01-I) complementado con 100 Unidades/mililitro de penicilina, 100 miligramos/mililitro de estreptomicina, L-glutamina 2 mM, 50 miligramos/mililitro de dextrano 40, y suero fetal de becerro al 5 por ciento (FCS, Fetaclone I, Gibco #10270-106). Entonces, 190 microlitros de sangre previamente diluida se salpicaron con 10 microlitros del compuesto de prueba previamente diluido en placas de microtitulación de fondo en U de 96 pozos (Nunc), lo cual dio como resultado una dilución en serie triple con un intervalo de concentración de 20 a 0.0003 µM. Los pozos de control se trataron previamente con sulfóxido de dimetilo (DMSO) para obtener una concentración final de sulfóxido de

dimetilo (DMSO) del 0.5 por ciento. Los cultivos se establecieron por duplicado, se mezclaron bien con agitación sobre un agitador de placas (Heidolph Titramax 101; 30 segundos, velocidad 900), pasándose por pipeta hacia arriba y hacia abajo, y se agitaron sobre el agitador de placas nuevamente. Los cultivos se incubaron a 37°C, con CO_2 al 5 por ciento durante 1 hora. Entonces, se agregaron 20 microlitros de Ab policlonal de IgM de cabra anti-rata (Serotec, cat # 302001), y 10 microlitros de rIL-4 recombinante diluida (Immunotools # 340085) para obtener concentraciones finales de 30 microgramos/mililitro y de 5 nanogramos/mililitro, respectivamente. Las placas se mezclaron con agitación sobre un agitador de placas como anteriormente, y se incubaron durante 24 horas a 37°C, con CO_2 al 5 por ciento.

Determinación de activación de células-B mediante citometría de flujo

Después de la incubación, se agregaron 15 microlitros de una solución de EDTA 25 mM por pozo, y se agitaron durante 15 minutos para desprender las células adherentes. Para el análisis de los marcadores de activación superficiales, las muestras se tiñeron entonces con CD45RA anti-rata marcado con PE-Cy5 (BD cat # 557015) para permitir el paso de las células-B en el análisis FACS. En adición, las muestras se tiñeron con CD86 anti-rata marcado con PE (BD cat # 551396). Todos los procedimientos de teñido se llevaron a cabo a temperatura ambiente durante 30 minutos en la oscuridad. Después de la incubación, las muestras se transfirieron a

las placas de microtitulación de fondo en V de 96 pozos profundos (Corning # 396096) que contenían 2 mililitros/pozo de Solución de Lisis BD (BD # 349202). Después de la lisis de los eritrocitos, las muestras se lavaron con 2 mililitros de CellWASH (BD # 349524). Los datos se adquirieron en un citómetro de flujo LSRII o FACScalibur (BD Biosciences), utilizando el software Cellquest Plus o DIVA (versión 6.1.1), respectivamente. Los linfocitos se pasaron a la transferencia de puntos FSC/SSC de acuerdo con el tamaño y la granularidad, y se analizaron adicionalmente para la expresión de CD45RA y los marcadores de activación. Los datos se calcularon a partir de las transferencias de puntos o los histogramas como el porcentaje de las células positivamente teñidas para los marcadores de activación dentro de la población CD45RA+.

Evaluación Estadística

El porcentaje de inhibición de activación de células-B después de la exposición al fármaco se calculó mediante la siguiente fórmula:

$$\% \text{ Inhibición} = 100 \times \frac{\text{Estimulación sin fármaco - estimulación con fármaco}}{\text{Estimulación sin fármaco - no estimuladas}}$$

Se utilizó el software ORIGIN 7 (OriginLab Corporation, Northampton, MA) para el ajuste de la curva de regresión no lineal. Se obtuvo la concentración del fármaco que daba como resultado una inhibición del 50 por ciento (IC_{50}) mediante el ajuste de la

ecuación de Hill para los datos de inhibición.

2.4 Determinación de IL-6 inducida por TLR9 en esplenocitos de ratón

Preparación de suspensión de células individuales a partir de bazo de ratón

Los bazos se disectaron a partir de ratones C57BL/6 inmediatamente en seguida de la eutanasia. El exceso de grasa se recortó de los bazos antes de triturar el bazo a través de un cernidor de células de 0.4 micras utilizando un émbolo de una jeringa de 5 mililitros. Se preparó una suspensión de células individuales, y el volumen se ajustó a 15 mililitros en un tubo Falcon de 50 mililitros utilizando suero regulado con fosfato (PBS) frío. Las células se centrifugaron a 1500 revoluciones por minuto durante 5 minutos a 4°C antes de remover el sobrenadante y de volver a suspender en 5 mililitros de regulador de lisis de glóbulos rojos sanguíneos por bazo, y de la incubación durante 5 minutos a temperatura ambiente. Se agregó suero regulado con fosfato (PBS) helado (30 mililitros) a las células antes de la centrifugación a 1500 revoluciones por minuto durante 5 minutos a 4°C. El sobrenadante se removió y las células se lavaron dos veces con 40 mililitros del medio de cultivo de esplenocitos de murino (MSCM). El MSCM consistió en RPMI complementado con 100 unidades/mililitro de penicilina y 100 microgramos/mililitro de estreptomicina, aminoácidos no esenciales 1x, piruvato de sodio 1 mM, ß-mercaptoetanol 0.05 mM, y suero bovino fetal (FBS) inactivado por calor al 10 por ciento. Las células

se volvieron a suspender en 10-20 mililitros de MSCM y se contaron utilizando un contador de células Countess. Se obtuvieron aproximadamente 60 x 10^6 esplenocitos a partir de un solo bazo de ratón C57BL/6.

Estimulación de esplenocitos de murino y tratamiento con un inhibidor específico

Los esplenocitos se emplacaron en una densidad final de 2 x 10^5 células/pozo en un volumen de 100 microlitros en placas de fondo plano de 96 pozos, y se incubaron en una incubadora humidificada a 37°C durante 2 a 4 horas. Después, los compuestos que se iban a probar se dosificaron utilizando una máquina automatizada de manejo de líquidos, utilizando placas de suministro de compuestos previamente preparadas. Las placas de suministro consistieron en los compuestos (en un 90 por ciento/10 por ciento de DMSO/ddH_2O) arreglados en 8 a 10 puntos utilizando diluciones dobles o triples. La máquina de manejo de líquidos dosificó 1 microlitro de cada dilución a partir de la placa de fuente de compuesto previamente preparada, hacia el pozo de destino apropiado de la placa de 96 pozos. La concentración de partida final de los compuestos en el cultivo celular fue de 10 µM. La concentración final de sulfóxido de dimetilo (DMSO) en los cultivos celulares fue del 0.5 por ciento. Las células se incubaron con los compuestos durante 1 hora antes de la adición del ligando de TLR. Entonces, se agregó una concentración 10x EC_{80} de CpG1826 en un volumen de 20 microlitros (para un volumen de cultivo final de 200

microlitros), sobre lo cual, los cultivos se incubaron durante la noche en una incubadora humidificada a 37°C.

Determinación de Interleucina-6 mediante ELISA

Después del cultivo durante la noche, las placas se centrifugaron a 2,000 revoluciones por minuto durante 5 minutos a temperatura ambiente. Subsiguientemente, se transfirieron 150 microlitros de cada cultivo a placas de fondo en V de 96 pozos, y se midieron los niveles de IL-6 utilizando un kit de ELISA de emparedado de IL-6 de ratón comercialmente disponible. Dicho de una manera breve, las placas se recubrieron durante la noche con el anticuerpo de captura antes del bloqueo durante 1 hora con suero regulado con fosfato (PBS)/albúmina de suero bovino (BSA) al 0.1 por ciento. Las muestras y los estándares se agregaron en un volumen de 50 microlitros, y la placa se incubó durante 2 horas a temperatura ambiente. Después de la remoción de los estándares/muestras, la placa se lavó utilizando suero regulado con fosfato (PBS)/Tween al 0.05 por ciento antes de la adición de 50 microlitros del anticuerpo de detección biotinilado, sobre lo cual la placa se incubó durante 2 horas a temperatura ambiente con agitación. Las placas se lavaron nuevamente antes de la adición de 50 microlitros de estreptavidina-peroxidasa de radícula roja por pozo durante 20 minutos. En seguida de los lavados adicionales de la placa, se agregaron 50 microlitros de substrato TMB a cada pozo, y las placas se incubaron durante 20 minutos antes de la adición de 25 microlitros/pozo de solución de paro. Se midieron los niveles de IL-6

utilizando un lector de placas SpectraMax 190 (450 nm), y se analizaron utilizando el software SoftMax Pro y GraphPad Prism.

2.5 Determinación de IFNalfa inducido por TLR9 en células humanas mononucleares de sangre periférica (PBMC)

Preparación de células humanas mononucleares de sangre periférica (PBMC) a partir de sangre humana fresca

Se recolectó sangre humana (aproximadamente 75 mililitros) en 10 tubos S-Monovette que contenían Heparina (S-Monovette 7.5 mililitros de NH Heparina, 16 Unidades Internacionales/mililitro de sangre; Starstedt). Los tubos Leucosep^{MR} (30 mililitros, #227290; Greiner Bio-one) se prepararon mediante la adición de 15 mililitros del medio de separación de linfocitos LSM1077^{MR} por tubo (#J15-004; PAA Laboratories), y centrifugación durante 30 segundos a 1,000 g. Se transfirieron unos 25 mililitros de sangre a tubos Leucosep^{MR} en seguida de la dilución con partes iguales de suero regulado con fosfato (PBS) (sin Ca2+/Mg2+; #14190-094). Las muestras se centrifugaron a 800 g durante 20 minutos a 22°C utilizando un centrífugo Eppendorf 5810R sin freno. La capa de células mononucleares de sangre periférica (PBMC) se removió cuidadosamente de la interfase del plasma:medio de separación, y se transfirió a un tubo limpio de 50 mililitros. Las células se lavaron una vez mediante la adición de suero regulado con fosfato (PBS) (hasta 45 mililitros), y se centrifugaron (1,400 revoluciones por minuto, 10 minutos a 22°C) con freno (ajustado a la velocidad 9), utilizando un Eppendorf 5810R. Las células aglomeradas se

volvieron a suspender cuidadosamente en el Medio (RPMI 1640 + GlutaMAX-I, 2-mercaptoetanol 0.05 mM, HEPES 10 mM, y suero fetal de becerro (FCS) al 5 por ciento por volumen/volumen), y las muestras se reservaron. Los componentes del medio de 2-mercaptoetanol (#31350-010; 50 mM), Hepes (#15630-056, 1M), y RPMI 1640 (1x) + GlutaMAX-I (#61870-010) se obtuvieron en Gibco. El suero fetal de becerro (FCS) (#2-01F36-1) se obtuvo en Amimed. Las células mononucleares de sangre periférica (PBMC) se contaron utilizando un contador de células Countess® Automated (la muestra se diluyó previamente a 1:10 en el Medio, antes de la adición de un volumen igual (10 microlitros) de Azul de Tripano). Las células se diluyeron hasta 4 x 10^6 células/mililitro, y se sembraron en placas de 384 pozos (#353962; Becton Dickinson AG), para dar un volumen final de 25 microlitros (es decir, 1 x 10^5 células/pozo).

Estimulación de células mononucleares de sangre periférica (PBMC) y tratamiento con el inhibidor específico

Los compuestos se diluyeron previamente en sulfóxido de dimetilo (DMSO) al 100 por ciento en volumen/volumen (#41640-100 mililitros; Sigma-Aldrich), seguido por la transferencia en el Medio (para alcanzar una concentración final de sulfóxido de dimetilo (DMSO) del 0.25 por ciento). Las células se trataron con la dilución apropiada del compuesto (5 microlitros) o del control de vehículo (5 microlitros), y se incubaron durante 30 minutos a 37°C en una incubadora humidificada en aire con CO_2 al 5 por ciento (volumen/volumen). Las células se estimularon con CpG2216 (0.3 µM; #tlrl-

hodna; Invivogen) o con el control de vehículo (10 microlitros/pozo), y se incubaron durante 20 horas. Las placas se centrifugaron brevemente (200 x g durante 2 minutos a 22°C), y se removieron muestras del sobrenadante (30 microlitros) para la cuantificación de los niveles de IFNα.

Cuantificación de IFNα utilizando la tecnología AlphaLISA

Para la cuantificación de IFNalfa, se utilizó el kit AlphaLISA de interferón humano (#AL264F) de PerkinElmer. Se preparó fresca una mezcla de anticuerpos que contenía gránulos aceptores anti-IFNα (5 microgramos/mililitro final), y anticuerpo biotinilado anti-IFNα (0.5 nM final), y se dosificó (5 microlitros) en placas Optiplates^{MR} de 384 pozos (#6007299; PerkinElmer). Se preparó una dilución de los estándares de IFNα conocidos (IFNα B humano (2b)), y se agregaron junto con los sobrenadantes celulares (5 microlitros) a las placas anteriores. Las placas se centrifugaron brevemente (pulso a 200 g), se cubrieron con película selladora con adhesivo, se pusieron en vórtex, y se incubaron durante 1 hora a temperatura ambiente en la oscuridad. Se prepararon gránulos donadores recubiertos con estreptavidina (20 microgramos/mililitro final), y se agregaron a cada pozo (5 microlitros) en un área luz oscura (mezcla sensible a la luz). Las placas se incubaron durante 30 minutos a temperatura ambiente (Las placas no deben centrifugarse ni cubrirse). Después de la incubación, las placas se leyeron con un lector de múltiples placas EnVision^{MR} equipado con la opción ALPHA utilizando los propios "ajustes estándares AlphaScreen" del instrumento (por ejemplo,

tiempo total de medición: 550 milisegundos, Láser de 680 nanómetros, tiempo de excitación: 180 milisegundos, espejo: D640 as, filtro de emisión: M570w, longitud de onda central de 570 nanómetros, anchura de banda de 100 nanómetros, transmitancia del 75 por ciento). Los datos se recolectaron para el análisis y la cuantificación de los niveles de IFNα.

Evaluación y análisis de datos

Los datos se analizaron utilizando Excel XL Fit 4.0 (Microsoft) con la adición XLfit (IDBS; versión 4.3.2). Se determinaron las concentraciones específicas de IFNα siguiendo la extrapolación a las curvas estándares utilizando el IFNα B humano (2b). Los valores IC_{50} individuales de los compuestos se determinaron mediante regresión no lineal después del ajuste de las curvas a los datos experimentales.

3. Determinación de la producción de anticuerpos en glóbulos rojos sanguíneos de ovejas (SRBC).

En breve, las ratas OFA se inyectaron intravenosamente (i.v.) con eritrocitos de ovejas en el día 0 (d0), y se trataron oralmente en cuatro días consecutivos (d0 a d3) con los compuestos en investigación. Se prepararon suspensiones de células de bazo el día 4 (d4), y los linfocitos se aplicaron a agar blando en la presencia de las células indicadoras (SRBC), y el complemento. La lisis de las células indicadoras debida a la secreción de los anticuerpos específicos de SRBC (predominantemente de la subclase IgM), y a la presencia del complemento, proporcionó las placas. El número de

placas por placa se contó y se expresó como el número de placas por bazo.

Inmunización:

Los grupos de cinco ratas OFA hembras se inmunizaron en el día 0 con 2 x 10^8/mililitro de SRBC (obtenidas en Laboratory Animal Services LAS, Novartis Pharma AG), en un volumen de 0.5 mililitros por rata por inyección intravenosa (i.v.).

Tratamiento con el compuesto:

Los animales se trataron con el compuesto suspendido en CMC al 0.5 por ciento, Tween 80 al 0.5 por ciento, durante 4 días consecutivos (días 0, 1, 2 y 3) empezando en el día de la inmunización. El compuesto se administró oralmente dos veces al día con intervalos de 12 horas entre dosis, en un volumen de aplicación de 5 mililitros/kilogramo de peso corporal.

Preparación de suspensiones de células de bazo:

En el día 4, los animales se sacrificaron con CO_2. Los bazos se removieron, se pesaron, y se depositaron en tubos de plástico que contenían 10 mililitros de solución de sal balanceada de Hank fría (4°C) (HBSS; Gibco, pH de 7.3, conteniendo 1 miligramo de Rojo de Fenol / 100 mililitros) para cada bazo de rata. Los bazos se homogeneizaron con un pistilo de vidrio, se dejaron sobre hielo durante 5 minutos, y se transfirió 1 mililitro del sobrenadante a un nuevo tubo. Las células se lavaron una vez en 4 mililitros de solución de sal balanceada de Hank (HBSS), y entonces los sobrenadantes se desecharon, y los gránulos se volvieron a suspender en 1 mililitro de

solución de sal balanceada de Hank (HBSS). Los números de linfocitos por bazo se determinaron mediante el contador de células automatizado, y las suspensiones de células de bazo se ajustaron a una concentración de células de 30 x 10^6/mililitro.

Ensayo de formación de placas*:*

Se prepararon cajas de Petri de agar blando con agarosa al 0.7 por ciento (SERVA) en solución de sal balanceada de Hank (HBSS).

En adición, se preparó un mililitro de agarosa al 0.7 por ciento en tubos de plástico, y se mantuvo a 48°C en un baño de agua. Se agregaron unos 50 microlitros de una suspensión de células de bazo a 30 x 10^6/mililitro, y 50 microlitros de SRBC a 40 x 10^8/mililitro, se mezclaron rápidamente (Vórtex), y se vertieron sobre los platos de agarosa preparados. Las cajas de Petri se inclinaron ligeramente para lograr una distribución uniforme de la mezcla celular sobre la capa de agarosa. Los platos se dejaron a temperatura ambiente durante 15 minutos, y entonces se incubaron a 37°C durante 60 minutos. Entonces, se agregaron 1.4 mililitros de complemento de cobayo (Harlan; 10 por ciento), y se continuó la incubación durante otros 60 minutos a 37°C. Los anticuerpos específicos de SRBC fueron liberados por las células-B fuera de la placa enlazadas al antígeno (SRBC) en su vecindad. Estos complejos de antígeno-anticuerpo activaron el complemento y condujeron a la lisis de las SRBC, dejando una mancha brillante (placa) dentro de la capa roja de eritrocitos. Las placas se contaron con un microscopio.

Se utilizó la siguiente fórmula para la determinación de la

inhibición de la formación de placa:

% Inhibición = C * 100 / V-100

con: V = número promedio de placas/bazo p0ara el grupo de vehículo; C = número promedio de placas/bazo para el grupo tratado con el compuesto.

Referencias:

N.K. Jerne y A.A. Nordin (1963) Plaque formation in agar by single antibody-producing cells. Science 140: 405.

N.K. Jerne, A.A. Nordin y C. Henry (1963) The agar plaque technique for recognizing antibody-producing cells. En: "Cell Bound Antibodies", B. Amos y H. Koprowski, Editores, Wistar Inst. Press, Filadelfia, páginas 109-125.

Datos Biológicos

Ensayo Enzimático

Ejemplo	PI3K alfa (µM)	PI3K delta (µM)
A1	0.322	0.006
A2	0.047	0.006
A3	0.313	0.003
A4	> 9.1	
A5	4.663	0.037
A6	0.377	0.009

Ejemplo	PI3K alfa (μM)	PI3K delta (μM)
A7	1.915	0.031
A8	5.928	0.04
A9	0.410	0.014
A10	0.220	0.018
A11	2.279	0.069
A12	0.182	0.003
A13	0.292	0.005
A14	> 9.1	5.399
A15	4.892	0.184
A16	> 9.1	0.323
A17	0.104	0.014
A18	0.895	0.011
A19	7.547	0.38
A20	> 9.1	
A21	8.429	
A22	0.757	0.021

Ejemplo	PI3K alfa (µM)	PI3K delta (µM)
A23	1.573	0.17
A24	6.878	0.317
A25	5.755	
A26	0.152	0.022
A27	> 9.1	
A28	0.531	0.016
A29	2.730	0.042
A30	0.260	0.031
A31	6.022	0.088
A32	3.195	0.074
A33	1.702	0.085
A34	0.773	0.009
A35	5.589	1.419
A36	1.269	0.078
A37	0.370	0.078
A38	0.343	0.064

Ejemplo	PI3K alfa (μM)	PI3K delta (μM)
A39	0.071	0.009
A40	5.361	0.462
A41	2.794	0.296
A42	1.141	0.03
A43	4.689	0.054
B1	0.390	0.014
B2	1.641	0.026
B3	> 9.1	
B4	1.234	0.083
B5	0.236	0.025
B6	2.242	0.11
B7	3.544	0.114
B8	0.188	0.025
B9	1.770	0.078
B10	0.870	0.035
B11	0.823	0.014

Ejemplo	PI3K alfa (µM)	PI3K delta (µM)
B12	0.365	0.011
B13	0.862	0.062
B14	0.244	0.006
B15	2.647	0.031
B16	4.117	0.037
B17	2.087	0.023
B18	0.723	0.012
B19	1.158	0.033
B20	0.339	0.047
B21	0.666	0.013
B22	0.589	0.005
B23	1.004	0.028
B24	0.212	0.008
B25	0.665	0.04
B26	0.281	< 0.009
B27	2.507	0.055

Ejemplo	PI3K alfa (μM)	PI3K delta (μM)
B28	0.788	0.012
B29	0.558	0.041
B30	0.216	0.0155
B31	0.977	0.003
B32	0.369	0.036
B33	0.610	< 0.009
B34	0.795	0.046
B35	1.387	0.027
B36	0.801	< 0.003
B37	1.104	0.103
B38	0.166	0.003
B39	0.176	0.011
B40	0.249	0.012
B41	0.421	0.025
B42	0.502	0.033
B43	0.514	0.057

Ejemplo	PI3K alfa (µM)	PI3K delta (µM)
B44	0.071	0.022
B45	0.574	0.0745
B46	2.076	0.2265
B47	0.241	0.0106667
B48	0.109	0.007
B49	0.450	0.007
B50	0.933	0.013
B51	1.026	0.01
B52	0.556	< 0.003
B53	0.343	0.0045
B54	0.756	0.011
B55	3.850	0.065
B56	1.415	0.023
B57	2.270	0.095
B58	0.366	0.004
B59	0.461	0.017

Ejemplo	PI3K alfa (µM)	PI3K delta (µM)
B60	0.463	0.011
B61	0.732	0.037
B62	0.496	0.041
B63	1.518	0.068
B64	0.193	0.032
B65	0.795	0.035
B66	0.446	0.011
B67	0.804	0.025
B68	0.840	0.039
B69	0.189	0.005
B70	0.134	0.003
B71	0.360	0.0055
B72	2.057	0.032
B73	1.771	0.03
B74	0.054	0.009
B75	0.211	0.011

Ejemplo	PI3K alfa (μM)	PI3K delta (μM)
B76	0.399	0.061
B77	0.897	0.032
B78	0.243	0.023
B79	0.661	0.003
B80	0.295	0.004
B81	0.482	0.081
B82	0.353	0.066
B83	0.214	0.029
B84	0.346	0.08
B85		
B86	6.626	0.061
B87	7.092	0.029
B88	0.234	0.008
B89	0.133	0.009
B90	1.456	0.011
B91	0.353	0.012

Ejemplo	PI3K alfa (μM)	PI3K delta (μM)
B92	0.346	0.008
B93	0.525	0.004
B94	0.416	0.005
B95	0.438	0.009
B96	> 9.1	0.118
B97	0.476	0.0215
B98	0.910	0.013
B99	0.302	0.057
B100	0.567	0.014
B101	0.471	0.015
B102	0.209	0.01025
B103	0.241	0.046
B104	1.374	0.162
B105	0.762	0.02
B106	0.247	0.017
B107	0.239	0.004

Ejemplo	PI3K alfa (μM)	PI3K delta (μM)
B108	0.094	< 0.003
B109	0.118	< 0.003
B110	0.148	0.003
B111	0.685	0.06
B112	0.38	0.026
B113	2.73	0.109
B114	1.440	0.071
B115	0.468	0.023
B116	0.304	0.022
B117	1.212	0.008
B118	0.498	0.01
B119	0.124	0.006
B120	0.088	0.006
B121	3.357	0.075
B122	0.425	0.024
C1	0.300	0.0190

Ejemplo	PI3K alfa (µM)	PI3K delta (µM)
C2	1.218	0.243
C3	3.377	1.207
C4	3.001	0.028
C5	5.510	0.095
C6	4.259	0.181
C7	> 9.1	
C8	0.374	0.013
C9	0.185	0.006
C10	0.147	0.015
C11	0.353	0.023
C12	0.303	0.116
C13	0.667	0.077
C14	0.250	0.005
C15	0.383	0.017
C16	0.478	0.015
C17	0.358	0.008

Ejemplo	PI3K alfa (μM)	PI3K delta (μM)
C18	0.425	0.012
C19	0.488	0.021
C20	0.193	0.006
C21	0.698	0.028
C22	0.202	0.02
C23	0.658	0.032
C24	0.560	0.003
C25	0.474	0.0125
C26	6.946	3.219
D1	0.424	0.005
D2	2.743	0.149
D3	4.418	0.219
D4	0.236	
D5	0.802	0.042
D6	0.650	0.009
D7	0.234	

Ejemplo	PI3K alfa (μM)	PI3K delta (μM)
D8	0.463	0.011
D9	0.494	0.015
D10	0.385	0.062
D11	0.442	0.019
D12	0.142	< 0.003
D13	0.5225	0.005
D14	0.415	
D15	0.711	0.058
D16	0.503	0.007
D17	0.705	0.012
D18	0.281	0.019
D19	0.273	0.013
D20	0.206	0.007
D21	0.519	0.041
D22	1.018	0.024
D23	2.534	0.214

Ejemplo	PI3K alfa (μM)	PI3K delta (μM)
D24	> 9.1	7.085
D25	> 9.1	2.693
D26	1.236	0.028
D27	1.574	0.064
D28	0.411	0.005
D29	0.534	0.003
D30	5.150	0.127
D31	0.135	0.009
D32	0.094	0.009
D33	0.117	0.008
D34	0.273	0.009
D35	0.414	< 0.003
D36	0.346	
D37	0.298	0.127
D38	0.516	0.018
D39	0.987	0.036

Ejemplo	PI3K alfa (μM)	PI3K delta (μM)
D40	0.7045	0.025
E1	0.098	0.004
E2		
E3	0.494	< 0.003
E4	0.870	0.010
E5		
E6	0.341	0.009
E7	0.133	0.022
E8		
E9	0.593	0.007
E10	0.229	0.013
E11	0.377	< 0.003
F1	0.109	0.003
F2	0.725	0.005
F3	0.337	0.006
F4	0.577	0.003

Ejemplo	PI3K alfa (µM)	PI3K delta (µM)
F5	0.444	0.025
F6	0.783	0.003
F7	0.071	< 0.003
F8	0.038	0.005
F9	0.028	< 0.003
F10	0.039	< 0.003
F11	0.078	0.076
F12	0.440	< 0.003
F13	0.704	0.024
G1	0.049	0.017
G2	1.195	0.207
G3	0.372	0.056
H1	0.850	0.008
H2	0.913	0.013
H3	0.559	0.008
H4	0.8475	0.011

Ejemplo	PI3K alfa (μM)	PI3K delta (μM)
H5	0.477	0.011
H6	0.846	0.053
H7	0.703	0.005
H8	0.521	0.007
H9	0.616	0.011
H10	0.727	0.018
H11	0.299	0.008
H12	0.530	0.007
H13	0.387	0.009
H14	0.103	0.005
H15	0.724	0.008
H16	0.871	0.016
I1	0.842	0.018
I2	0.308	0.005
I3	0.836	0.006
J	0.998	0.065

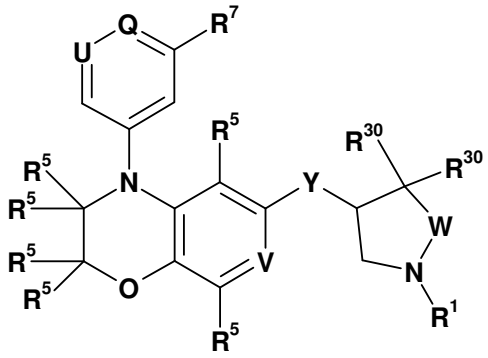
Ejemplo	PI3K alfa (µM)	PI3K delta (µM)
K	0.393	< 0.003
L	0.538	0.013
M	0.304	0.006
N	0.838	0.012
O1	4.574	0.053
O2	5.692	0.049
P	0.954	0.072
Q	1.144	0.014
R	0.602	0.011
S	0.612	0.036
T	1.876	0.076
U	0.192	0.015
V	3.196	0.079
W	2.979	0.056
X	3.575	0.061
Y	1.925	

Ensayos Celulares

Ejemplo	Células PI3Kδ / IC_{50} [µmol l-1]	RWB / IC_{50} CD86 [nmol l-1]
A1	0.043	37
B1	0.154	29
C1	0.081	68
D1	0.147	84
E1	0.007	78
E3	0.018	14
F1	0.011	7
F3	0.050	
F7	0.018	40
Q	0.145	37

REIVINDICACIONES

1. Un compuesto de la fórmula (I):



(I)

o una sal del mismo, en donde:

Y se selecciona a partir de O o NH;

V se selecciona a partir de CR^5 ó N;

W se selecciona a partir de CH_2, u O;

U se selecciona a partir de N o CH;

Q se selecciona a partir de N o CR^6;

en donde U y Q no son ambos N;

R^1 se selecciona a partir de fenilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, 1,2,3-triazinilo, 1,2,4-triazinilo, 1,3,5-triazinilo, o

$-X-R^4$

en donde X se selecciona a partir de C(O), $S(O)_2$ ó CH_2,

y

R^4 se selecciona a partir de alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo

de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, ciano-alquilo de 1 a 8 átomos de carbono, N,N-di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonil-alquilo de 1 a 8 átomos de carbono, fenilo, heterociclilo, heterociclil-oxilo, heterociclil-alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, cicloalquiloxilo de 3 a 12 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono-alquilo de 1 a 8 átomos de carbono, heteroarilo, heteroaril-oxilo, heteroaril-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, o N,N-di-alquilo de 1 a 8 átomos de carbono-amino,

en donde el alquilo de 1 a 8 átomos de carbono en N-alquilo de 1 a 8 átomos de carbono-amino y en N,N-di-alquilo de 1 a 8 átomos de carbono-amino puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono,

en donde el cicloalquilo de 3 a 12 átomos de carbono en cicloalquilo de 3 a 12 átomos de carbono y en cicloalquilo de 3 a 12 átomos de carbono-alquilo de 1 a 8 átomos de carbono puede estar insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono;

en donde el 'heterociclilo' es un sistema de anillo monocíclico de 3 a 7 miembros saturado o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o

S, cada uno de los cuales está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de oxo, halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heterociclilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación,

en donde el 'heteroarilo' es un sistema de anillo monocíclico de 3 a 7 miembros completamente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, o pirazolo-[1,5-a]-pirimidina o imidazo-[2,1-b]-tiazol, cada uno de los cuales está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1

a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heteroarilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación;

R^6 se selecciona a partir de hidrógeno, halógeno, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonilo, alquilo de 1 a 4 átomos de carbono-sulfinilo, alquilo de 1 a 4 átomos de carbono-sulfanilo, halo-alcoxilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono-alquilo de 1 a 4 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino;

R^7 se selecciona a partir de hidrógeno, halógeno, ciano, nitro, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, $N(R^8)_2$-sulfonilo, alquilo de 1 a 4 átomos de carbono-sulfonilo, alquilo de 1 a 4 átomos de carbono-sulfonil-amino, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, o N,N-di-alquilo de 1 a 8 átomos de carbono-amino;

o R^6 y R^7, son juntos CH=CH-CH=CH,

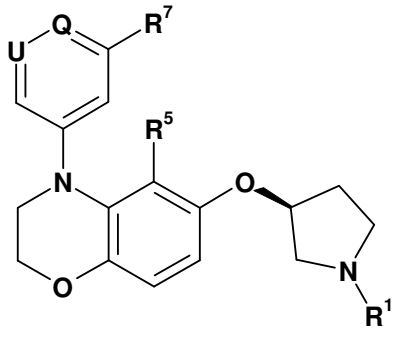
en donde R^8 se selecciona independientemente a

partir de hidrógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, o dos R^8 junto con el nitrógeno con el que están unidos, forman un anillo heterocíclico de 4 a 7 miembros que contiene de 1 a 2 heteroátomos seleccionados a partir de N, O, S, que está insustituido o sustituido por 1 a 3 sustituyentes seleccionados a partir de alquilo de 1 a 4 átomos de carbono;

R^5 se selecciona independientemente a partir de H, D, F o alquilo de 1 a 2 átomos de carbono;

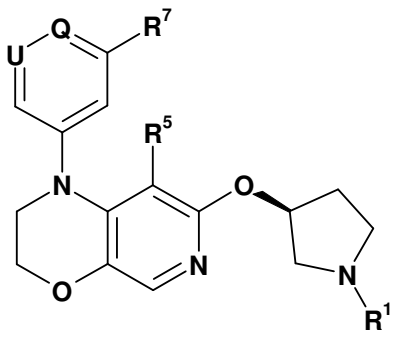
R^{30} se selecciona independientemente a partir de H, D o F.

2. Un compuesto de acuerdo con la reivindicación 1 o una sal del mismo, de la fórmula (Ic'):



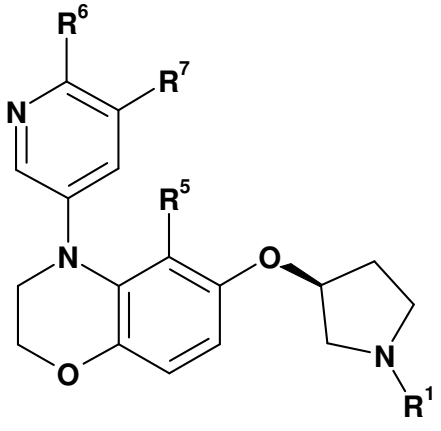
(Ic').

3. Un compuesto de acuerdo con la reivindicación 1 o una sal del mismo, de la fórmula (Id'):



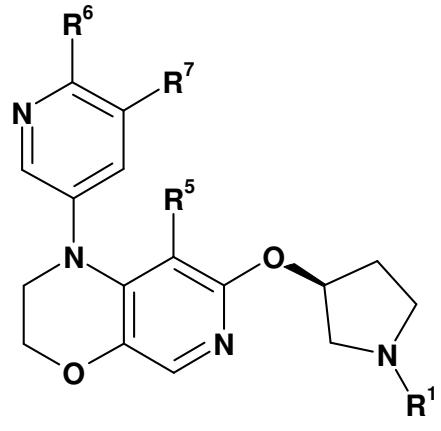
(Id').

4. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 ó 2 o una sal del mismo, de la fórmula (Ie'):



(Ie').

5. Un compuesto de acuerdo con la reivindicación 1 ó 3, o una sal del mismo, de la fórmula (If'):



(If').

6. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, o una sal del mismo, en donde:

R^1 se selecciona a partir de fenilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, 1,2,3-triazinilo, 1,2,4-triazinilo, 1,3,5-triazinilo,

o

-X-R^4, en donde:

R^4 se selecciona a partir de alquilo de 1 a 8 átomos

de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, ciano-alquilo de 1 a 8 átomos de carbono, N,N-di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonil-alquilo de 1 a 8 átomos de carbono, fenilo, heterociclilo, heterociclil-alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heteroarilo, heteroaril-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono en N-alquilo de 1 a 8 átomos de carbono-amino y en N,N-di-alquilo de 1 a 8 átomos de carbono-amino puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono,

en donde el cicloalquilo de 3 a 12 átomos de carbono en cicloalquilo de 3 a 12 átomos de carbono y en cicloalquilo de 3 a 12 átomos de carbono-alquilo de 1 a 8 átomos de carbono puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono;

en donde el 'heterociclilo' es un sistema de anillo monocíclico de 3 a 7 miembros saturado o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, que está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de oxo, halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8

átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heterociclilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación,

en donde el 'heteroarilo' es un sistema de anillo monocíclico de 3 a 7 miembros completamente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, o pirazolo-[1,5-a]-pirimidina o imidazo-[2,1-b]-tiazol, cada uno de los cuales está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heteroarilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los

heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación.

7. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 6 o una sal del mismo, en donde:

R^1 se selecciona a partir de:

-X-R^4, en donde:

R^4 se selecciona a partir de alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, ciano-alquilo de 1 a 8 átomos de carbono, N,N-di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 1 a 8 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonil-alquilo de 1 a 8 átomos de carbono, fenilo, heterociclilo, heterociclil-alquilo de 1 a 8 átomos de carbono, cicloalquilo de 3 a 12 átomos de carbono, heteroarilo, heteroaril-alquilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono, en donde el alquilo de 1 a 8 átomos de carbono en N-alquilo de 1 a 8 átomos de carbono-amino y en N,N-di-alquilo de 1 a 8 átomos de carbono-amino puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono,

en donde el cicloalquilo de 3 a 12 átomos de carbono en cicloalquilo de 3 a 12 átomos de carbono y en cicloalquilo de 3 a 12 átomos de carbono-alquilo de 1 a 8 átomos de carbono puede estar insustituido o sustituido por halógeno, hidroxilo, o alcoxilo de 1 a 4 átomos de carbono;

en donde el ‘heterociclilo’ es un sistema de anillo

monocíclico de 3 a 7 miembros saturado o parcialmente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, que está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de oxo, halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heterociclilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación,

en donde el 'heteroarilo' es un sistema de anillo monocíclico de 3 a 7 miembros completamente insaturado que contiene de 1 a 3 heteroátomos seleccionados a partir de N, O o S, o pirazolo-[1,5-a]-pirimidina o imidazo-[2,1-b]-tiazol, cada uno de los cuales está insustituido o sustituido por 1 a 5 sustituyentes seleccionados a partir de halógeno, alquilo de 1 a 8 átomos de carbono, halo-alquilo de 1 a 8 átomos de carbono, hidroxi-alquilo de 1 a 8 átomos de carbono, hidroxilo, alcoxilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8

átomos de carbono, amino, N-alquilo de 1 a 8 átomos de carbono-amino, N,N-di-alquilo de 1 a 8 átomos de carbono-amino, alquilo de 1 a 8 átomos de carbono-carbonilo, halo-alquilo de 1 a 8 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 8 átomos de carbono-carbonilo o alcoxilo de 1 a 8 átomos de carbono-alquilo de 1 a 8 átomos de carbono-carbonilo; en donde el 'heteroarilo' se puede unir en un heteroátomo o en un átomo de carbono, y en donde los heteroátomos de N y/o S también se pueden oxidar opcionalmente hasta diferentes estados de oxidación;

R^6 se selecciona a partir de halógeno, alcoxilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono-sulfonilo, o halo-alcoxilo de 1 a 4 átomos de carbono

y R^7 se selecciona a partir de hidrógeno, halógeno, ciano, alquilo de 1 a 4 átomos de carbono, halo-alquilo de 1 a 4 átomos de carbono, o alcoxilo de 1 a 4 átomos de carbono.

8. Un compuesto de la reivindicación 1 en una forma cristalina.

9. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, o una sal farmacéuticamente aceptable del mismo, para utilizarse como un medicamento.

10. Una combinación que comprende una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, o una sal farmacéuticamente aceptable del mismo, y uno o más co-agentes terapéuticamente activos.

11. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, o una sal farmacéuticamente aceptable del mismo, para utilizarse en el tratamiento de un trastorno o de una enfermedad seleccionada a partir de artritis reumatoide (RA), pénfigo vulgar (PV), la forma endémica de pénfigo brasileño (Fogo selvagem), púrpura trombocitopénica idiopática (ITP), púrpura trombocitopénica trombótica (TTP), anemia hemolítica autoinmune (AIHA), hemofilia adquirida tipo A (AHA), lupus eritematoso sistémico (SLE), esclerosis múltiple (MS), miastenia grave (MG), síndrome de Sjögren (SS), vasculitidas asociadas con ANCA, crioglobulinemia, urticaria autoinmune crónica (CAU), alergia (dermatitis atópica, dermatitis por contacto, rinitis alérgica), síndrome de Goodpasture, rechazo de trasplante, cánceres de origen hematopoiético, malaria grave y cerebral, tripanosomiasis, Leishmaniasis, toxoplasmosis y neurocisticercosis.

12. Una composición farmacéutica, la cual comprende una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, o una sal farmacéuticamente aceptable del mismo, y uno o más vehículos farmacéuticamente aceptables.

13. Un método para modular la actividad de las enzimas de PI3K, de preferencia de la isoforma PI3Kδ en un sujeto, en donde el método comprende administrar al sujeto, una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, o una sal

farmacéuticamente aceptable del mismo.

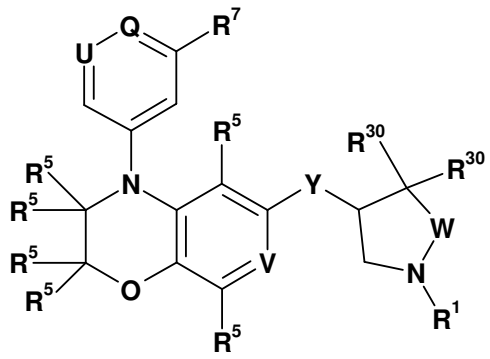
14. Un método para el tratamiento de un trastorno o de una enfermedad seleccionada a partir de artritis reumatoide (RA), pénfigo vulgar (PV), la forma endémica de pénfigo brasileño (Fogo selvagem), púrpura trombocitopénica idiopática (ITP), púrpura trombocitopénica trombótica (TTP), anemia hemolítica autoinmune (AIHA), hemofilia adquirida tipo A (AHA), lupus eritematoso sistémico (SLE), esclerosis múltiple (MS), miastenia grave (MG), síndrome de Sjögren (SS), vasculitidas asociadas con ANCA, crioglobulinemia, urticaria autoinmune crónica (CAU), alergia (dermatitis atópica, dermatitis por contacto, rinitis alérgica), síndrome de Goodpasture, rechazo de trasplante, cánceres de origen hematopoiético, malaria grave y cerebral, tripanosomiasis, Leishmaniasis, toxoplasmosis y neurocisticercosis, el cual comprende administrar a un sujeto, una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, o una sal farmacéuticamente aceptable del mismo.

15. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 8, o de una sal farmacéuticamente aceptable del mismo, en la elaboración de un medicamento para el tratamiento de un trastorno o de una enfermedad seleccionada a partir de artritis reumatoide (RA), pénfigo vulgar (PV), la forma endémica de pénfigo brasileño (Fogo selvagem), púrpura trombocitopénica idiopática (ITP), púrpura trombocitopénica trombótica (TTP), anemia hemolítica autoinmune (AIHA), hemofilia adquirida tipo A (AHA), lupus

eritematoso sistémico (SLE), esclerosis múltiple (MS), miastenia grave (MG), síndrome de Sjögren (SS), vasculitidas asociadas con ANCA, crioglobulinemia, urticaria autoinmune crónica (CAU), alergia (dermatitis atópica, dermatitis por contacto, rinitis alérgica), síndrome de Goodpasture, rechazo de trasplante, cánceres de origen hematopoiético, malaria grave y cerebral, tripanosomiasis, Leishmaniasis, toxoplasmosis y neurocisticercosis.

RESUMEN

La invención se refiere a los compuestos de dihidro-benzo-oxazina y dihidro-pirido-oxazina de la fórmula (I) y/o a las sales farmacéuticamente aceptables y/o solvatos de los mismos:



(I)

en donde Y, V, W, U, Q, R^1, R^5, R^7 y R^{30} son como se definen en la descripción. Estos compuestos son adecuados para el tratamiento de un trastorno o de una enfermedad que sea mediada por la actividad de las enzimas de PI3K.

* * * * *

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

VON SPRECHER, Georg
Novartis Pharma AG
Patent Department
CH-4002 Basel
SUISSE

Date of mailing *(day/month/year)*
23 October 2013 (23.10.2013)

Applicant's or agent's file reference
PAT054932-WO-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/IB2012/057554

International filing date *(day/month/year)*
20 December 2012 (20.12.2012)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
NOVARTIS AG
Lichtstrasse 35
CH-4056 Basel
Switzerland

State of Nationality: CH
State of Residence: CH

Telephone No.
+41 61 324 1111

Facsimile No.
+41 61 322 7532

E-mail address
pip_inbox.phchbs@novartis.com
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
The person identified in Box 2 has been recorded as applicant for all designated States except US.

4. A copy of this notification has been sent to:

☐ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 910 06 10

Authorized officer
Lambert Jean-Francois
e-mail ro.ib@wipo.int
Telephone No. +4122 338 8717

From the INTERNATIONAL BUREAU

PCT

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Facsimile No.

E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

CARAVATTI, Giorgio; CHAMOIN, Sylvie
FURET, Pascal; HÖGENAUER, Klemens; HURTH, Konstanze
KALIS, Christoph; KAMMERTOENS, Karen; LEWIS, Ian
MOEBITZ, Henrik; SMITH, Alexander Baxter; SOLDERMANN, Nicolas
WOLF, Romain; ZECRI, Frédéric

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
The persons identified in Box 2 have been recorded as applicants for US only and inventors for all designated States.

4. A copy of this notification has been sent to:

☐ the receiving Office
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☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

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34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 910 06 10

Authorized officer
Lambert Jean-Francois
e-mail ro.ib@wipo.int
Telephone No. +4122 338 8717

FIG. 1

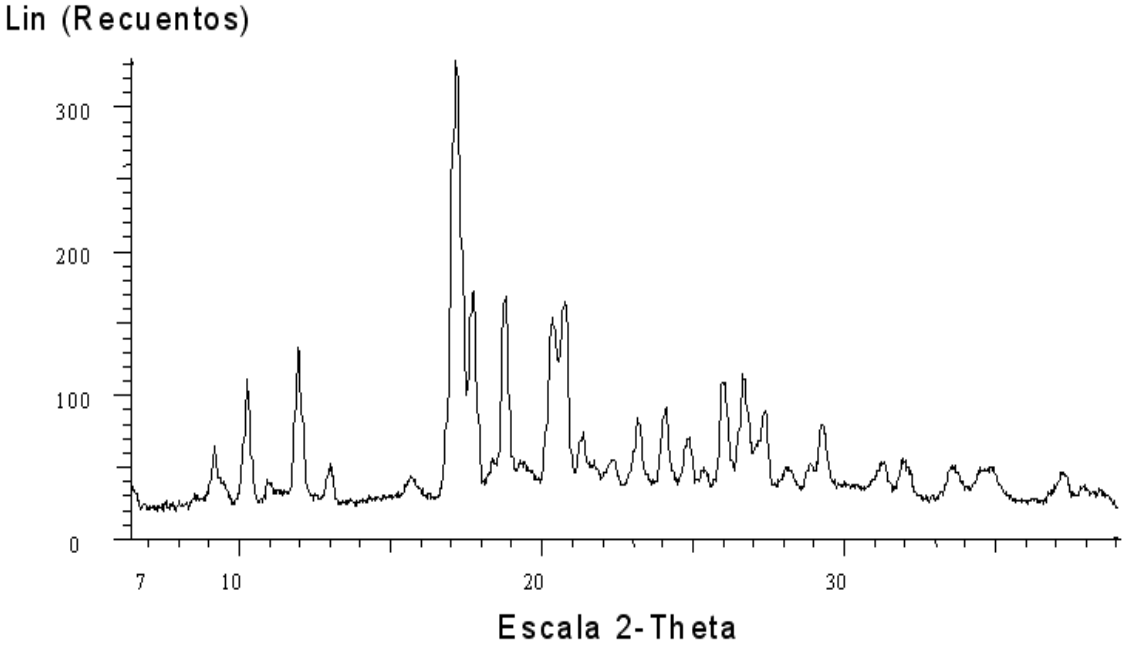
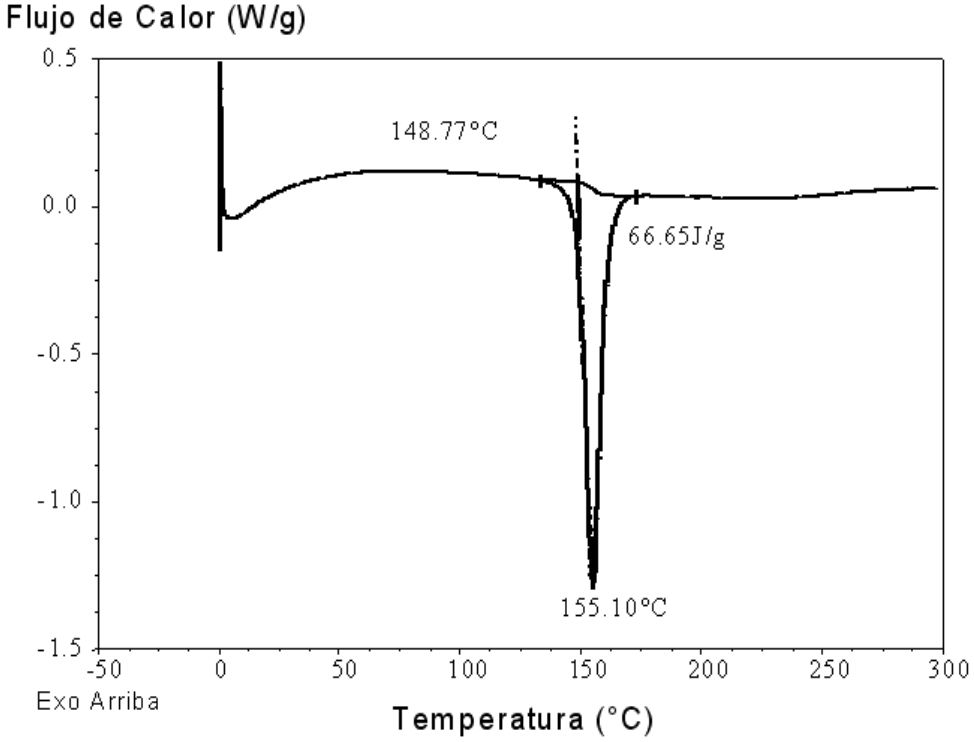

Lin (Recuentos)
300
200
100
0
7
10
20
30
Escala 2-Theta

FIG. 2


Flujo de Calor (W/g)
0.5
0.0
-0.5
-1.0
-1.5
148.77°C
66.65J/g
155.10°C
-50
0
50
100
150
200
250
300
Exo Arriba
Temperatura (°C)

LISTADO DE SECUENCIAS

<110> Novartis AG

<120> Derivados de Dihidro-Benzo-Oxazina y Dihidro-Pirido-Oxazina

<130> PAT054932P1

<160> 21

<170> PatentIn versión 3.3

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 54932-WO-PCT	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/IB2012/057554	International filing date *(day/month/year)* 20/12/2012	(Earliest) Priority Date *(day/month/year)* 22/12/2011
Applicant NOVARTIS AG		

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,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, 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/IB2012/057554

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/IB2012/057554

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 C07D498/04 A61K31/536 A61K31/5365
ADD. A61P19/02 A61P37/08 A61P35/00 A61P33/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/044022 A1 (UCB PHARMA SA [BE]) 17 April 2008 (2008-04-17) claims 1,10 -----	1-15

☐ 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
11 April 2013	18/04/2013

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	Cortés, José

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/057554

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008044022 A1	17-04-2008	EP 2076512 A1	08-07-2009
		US 2010069361 A1	18-03-2010
		WO 2008044022 A1	17-04-2008