SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-065647- -00000-0000
Fecha: 2014-03-27 16:36:34 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 7

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: 3- PIRMIDIN- 4- IL- OXAZOLIDIN- 2- ONAS COMO INHIBIDORES DE LA IDH MUTANTE

SOLICITANTE: NOVARTIS AG.

DIRECCIÓN: Lichtstrasse 35, CH-4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 27 de marzo de 2014

P2014/000049

OLARTEMC
OLARTE MOURE & ASOCIAI

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 14-065647- -00000-0000
Fecha: 2014-03-27 16:36:34 Dep. 2020 DIR.NUEVASCR
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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL

P2014/000049

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
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/IB2012/055133 Fecha Septiembre 26, 2012

Publicación Internacional No. WO 2013/046136 Fecha Abril 04, 2013

(6) Título (54) **3- PIRMIDIN- 4- IL- OXAZOLIDIN- 2- ONAS COMO INHIBIDORES DE LA IDH MUTANTE**

Clasificación Internacional (51) C07D 413/04, C07D 413/14, C07D 417/14, C07 471/04, C07D 487/04, C07D 498/10, C07D 513/04, A61K 31/506, A61P 35/00.

Prioridad
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Septiembre 27, 2011	61/539,553

(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.
X	Poderes, si fuere el caso.
	Documento de cesión del inventor al solicitante o a su causante.
	Declaraciones. 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.
	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. 79.782.747Bta T.P. 74.295

LISTA DE INVENTORES

PCT/IB2012/055133

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Nacionalidad: Estadounidense

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Nacionalidad: China

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0029537

Bogotá D.C., Marzo 17 de 2014 - 13:53:00

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	609953573	14/03/2014	17.818.250.00

*** Conceptos Pagados ***

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

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

Responsable: _____
-******-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-065647- -00000-0000

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Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: 2014 / 03 / 27 (AAAA / MM / DD)	Recorrido:
2020		4

Tipo de Radicación: Entrada: X Salida: ☐ Traslado: ☐ Convenio: ☐

Radicador: | Planilla:

ID	No. Radicación	Consecutivo	Item
1	14-65647	0	7
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***
X	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 7 ARCHIVOS:
7 EN FORMATO PDF, LOS CUALES FUERON PROCESADOS.
EL CD SE ENCUENTRA EN EL FOLIO 6

7
6

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISIÓN A TRÁMITE – NUEVAS CREACIONES

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

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

Completa ☐ Incompleta ☐

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

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

Completa ☒ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

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

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

Completa ☐ Incompleta ☐

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-065647- -00000-0000

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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 **P2014/000049**

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
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

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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/IB2012/055133 Fecha Septiembre 26, 2012

Publicación Internacional No. WO 2013/046136 Fecha Abril 04, 2013

6

Título (54) **3- PIRMIDIN- 4- IL- OXAZOLIDIN- 2- ONAS COMO INHIBIDORES DE LA IDH MUTANTE**

Clasificación Internacional (51) C07D 413/04, C07D 413/14, C07D 417/14, C07 471/04, C07D 487/04, C07D 498/10, C07D 513/04, A61K 31/506, A61P 35/00.

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Septiembre 27, 2011	61/539,553

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.
- [ ] 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.
- [ ] 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

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Cambridge, Massachusetts 02139
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Nacionalidad: Estadounidense

Qian ZHAO
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Emeryville, California
Emeryville CA
Estados Unidos de América
Nacionalidad: China

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
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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

Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

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.

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:

Arthur Canonica

Pascal Traub

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)

M. Staehelin Notar

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

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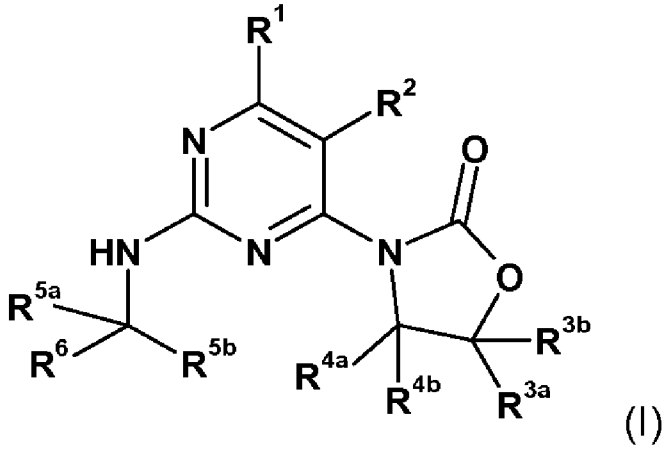
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[Continued on next page]

(54) Title: 3-PYRIMIDIN-4-YL-OXAZOLIDIN-2-ONES AS INHIBITORS OF MUTANT IDH



(I)

(57) Abstract: The invention is directed to a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein R^1-R^6 are defined herein. The invention is also directed to compositions containing a compound of formula (I) and to the use of such compounds in the inhibition of mutant IDH proteins having a neomorphic activity. The invention is further directed to the use of a compound of formual (I) in the treatment of diseases or disorders associated with such mutant IDH proteins including, but not limited to, cell-proliferation disorders, such as cancer.

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3-PYRIMIDIN-4-YL-OXAZOLIDIN-2-ONES AS INHIBITORS OF MUTANT IDH

FIELD OF THE INVENTION

The present invention is directed to novel 3-pyrimidinyl-4-yl-oxazolidin-2-one compounds, compositions containing these compounds, the use of such compounds in the inhibition of mutant IDH proteins having a neomorphic activity and in the treatment of diseases or disorders associated with such mutant IDH proteins including, but not limited to, cell-proliferation disorders, such as cancer.

BACKGROUND OF THE INVENTION

Isocitrate dehydrogenase (IDH) is a key family of enzymes found in cellular metabolism. They are $NADP^+$ / NAD^+ and metal dependent oxidoreductases of the enzyme class EC 1.1.1.42. The wild type proteins catalyze the oxidative decarboxylation of isocitrate to alpha-ketoglutarate generating carbon dioxide and NADPH / NADH in the process. They are also known to convert oxalosuccinate into alpha-ketoglutarate. Mutations in IDH1 (cytosolic) and IDH2 (mitochondrial) have been identified in multiple cancer types including, but not limited to, glioma, glioblastoma multiforme, paraganglioma, supratentorial primordial neuroectodermal tumors, acute myeloid leukemia (AML), prostate cancer, thyroid cancer, colon cancer, chondrosarcoma, cholangiocarcinoma, peripheral T-cell lymphoma, and melanoma. (See L. Deng *et al.*, Trends Mol. Med., 2010, 16, 387; T. Shibata *et al.*, Am. J. Pathol., 2011, 178(3), 1395; Gaal *et al.*, J. Clin. Endocrinol. Metab. 2010; Hayden *et al.*, Cell Cycle, 2009; Balss *et al.*, Acta Neuropathol., 2008). The mutations have been found at or near key residues in the active site: G97D, R100, R132, H133Q, and A134D for IDH1, and R140 and R172 for IDH2. (See L. Deng *et al.*, Nature, 2009, 462, 739; L. Sellner *et al.*, Eur. J. Haematol., 2011, 85, 457).

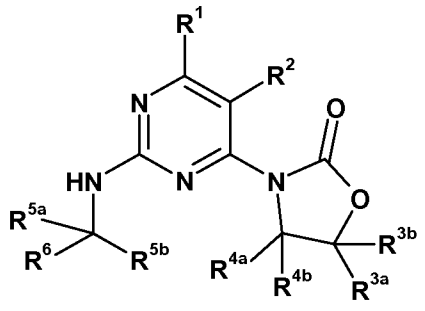
These mutant forms of IDH are shown to have a neomorphic activity (also known as a gain of function activity), reducing alpha-ketoglutarate to 2-hydroxyglutarate (2-HG). (See P.S. Ward *et al.*, Cancer Cell, 2010, 17, 225) In general, production of 2-HG is enantiospecific, resulting in generation of the D-enantiomer (also known as R enantiomer or R-2-HG). Normal cells have low native levels of 2-HG, whereas cells harboring these mutations in IDH1 or IDH2 show significantly elevated levels of 2-HG. High levels of 2-HG have been detected in tumors harboring the mutations. For example, high levels of 2-HG have been detected in the plasma of patients with mutant IDH containing AML. (See S. Gross *et al.*, J. Exp. Med., 2010, 207(2), 339). High levels of 2-HG are highly associated with tumorigenesis.

Mutant IDH2 is also associated with the rare neurometabolic disorder D-2-hydroxyglutaric aciduria type II (D-2-HGA type II). Germline mutations were found at R140 in IDH2 in 15 pateints having D-2-HGA type II. Patients having this disorder also have consistently increased levels of D-2-HG in their urine, plasma and cerebrospinal fluid. (See Kranendijk, M. *et al.*, Science, 2010, 330, 336). Finally, patients with Ollier Disease and Mafucci Syndrome (two rare disorders that predispose to cartilaginous tumors) have been shown to be somatically mosaic for IDH1 and 2 mutations and exhibit high levels of D-2-HG. (See Amary et al., Nature Genetics , 2011 and Pansuriya et al., Nature Genetics, 2011).

Thus, there is a need for small molecule inhibitors of mutant IDH proteins having a neomorphic activity for the treatment of diseases and disorders associated with these proteins.

SUMMARY OF THE INVENTION

In one aspect, this invention provides for a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein R^1-R^6 are defined herein.

In a second aspect, this invention provides for a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

In a third aspect, this invention provides for the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as an inhibitor of a mutant IDH protein having a neomorphic activity such as reducing alpha-ketoglutarate to 2-hydroxyglutarate (2-HG neomorphic activity). Suitably, this invention provides for the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as an inhibitor of mutant IDH1 having a neomorphic activity, such as 2-HG neomorphic activity, and/or mutant IDH2 having a neomorphic activity, such as 2-HG neomorphic activity. This invention further provides for the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as an inhibitor of IDH1 having a mutation at residue 97, 100 or 132, for example G97D, R100Q, R132H, R132C, R132S, R132G, R132L, and R132V;

and/or an inhibitor of IDH2 having a mutation at residue 140 or 172, for example R172K, R172M, R172S, R172G, and R172W.

In a fourth aspect, this invention provides for a method of treating a disease or disorder associated with a mutant IDH protein having a neomorphic activity comprising administration of an effective amount of a compound according to formula (I), or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In one embodiment, the disease or disorder is a cell proliferation disorder, such as cancer. In another embodiment, the cancer is brain cancer, such as glioma, glioblastoma multiforme, paraganglioma, and supratentorial primordial neuroectodermal tumors (pNET); leukemia, such as acute myeloid leukemia (AML), myelodysplastic syndrome, and chronic myelogenous leukemia (CML); skin cancer, including melanoma; prostate cancer; thyroid cancer; colon cancer; lung cancer; sarcoma, including central chondrosarcoma, central and periosteal chondroma; and fibrosarcoma. In another embodiment the disease or disorder is D-2-hydroxyglutaric aciduria.

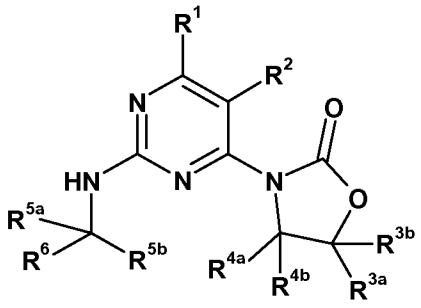
In a fifth aspect the invention provides for a compound of formula (I), or a pharmaceutically acceptable salt thereof, in combination with another therapeutic agent.

These and other aspects of the present invention are described further in the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula (I)

A compound of formula (I)



(I)

wherein:

R^1 and R^2 are each independently hydrogen, deuterium, halo, hydroxyl, NH_2, aryl, heteroaryl, or optionally substituted C_{1-4} alkyl,

wherein said C_{1-4} alkyl is optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, and NH_2;

R^{3a} is hydrogen, deuterium, C_{1-6} alkyl, phenyl, or benzyl and

R^{3b} is hydrogen, deuterium, or C_{1-6} alkyl; or

R^{3a} and R^{3b} are joined together forming an optionally substituted 3-7 membered cycloalkyl ring or an optionally substituted 4-7 membered heterocyclic ring,

wherein said cycloalkyl and heterocyclic rings are each optionally substituted with one or two substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl;

R^{4a} is hydrogen, C_{1-6} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted heteroaryl, or methylene-dibenzene,

wherein said phenyl, benzyl, and heteroaryl rings are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-4} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $-COOR^b$, $-SO_2R^b$, $-NHC(O)R^b$, and $-NR^bR^b$ and

R^{4b} is hydrogen, deuterium, or C_{1-3} alkyl; or

R^{4a} and R^{4b} are joined together forming an optionally substituted 3-7 membered cycloalkyl ring or an optionally substituted 4-7 membered heterocyclic ring,

wherein said cycloalkyl and heterocyclic rings are optionally substituted with one or two substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl,

provided that only one of R^{3a} and R^{3b} and R^{4a} and R^{4b} are joined together forming a ring;

R^{5a} is hydrogen or deuterium;

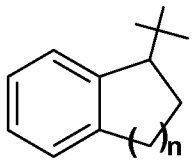
R^{5b} is hydrogen, deuterium, methyl, ethyl, CD_3, CF_3, CH_2F, or CHF_2 and

R^6 is optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted C_{3-10} cycloalkyl,

wherein said C_{1-6} alkyl is optionally substituted with one substituent selected from the group consisting of hydroxyl, C_{1-3} alkoxy and $-OR^a$,

wherein said aryl, heteroaryl, heterocyclic and C_{3-10} cycloalkyl are optionally substituted with one to three substituents each independently selected from the group

consisting of: halo; hydroxyl; cyano; nitro; C_{1-4} alkoxy; C_{1-3} haloalkyl; C_{1-3} haloalkoxy; C_{1-6} alkyl; C_{3-6} cycloalkyl optionally substituted with one to three substituents each independently selected from the group consisting of: hydroxyl, cyano, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} haloalkyl; phenyl optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $-COOR^b$, $-SO_2R^b$, $-NHC(O)R^b$, and $-NR^bR^b$; 5-6 membered heteroaryl optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, C_{1-3} alkyl, C_{1-3} alkoxy; 5-6 membered heterocyclic optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl; $-CH_2R^a$; $-OR^a$; $-C(O)R^a$; $-NR^aR^b$; $-COOR^a$; $-SO_2R^a$; $-SO_2R^b$; $NHC(O)R^a$; $-NHC(O)R^b$; $-C(O)NR^aR^b$; $-C(O)NHR^b$; and $-SO_2NR^bR^b$; or

R^{5b} and R^6 are joined together forming an optionally substituted C_{3-7} cycloalkyl group or an optionally substituted group of formula (a):  (a),

wherein n is 1, 2, or 3 and

said C_{3-7} cycloalkyl and group of formula (a) are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, benzyloxy, $-COOR^b$, $-SO_2R^b$, $-NHC(O)R^b$, and $-NR^bR^b$;

each R^a is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted C_{3-7} cycloalkyl,

wherein said phenyl and heteroaryl are optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, and C_{1-3} alkyl,

wherein said heterocyclic is optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, oxo, C_{1-3}

alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-4} alkyl, C_{3-5} cycloalkyl, $-C(O)R^b$, and $-NR^bR^b$; and

wherein said C_{3-7} cycloalkyl is optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, oxo, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, and C_{1-3} alkyl; and

each R^b is independently hydrogen or C_{1-6} alkyl.

"Alkyl" refers to a monovalent saturated hydrocarbon chain having the specified number of carbon atoms. For example, C_{1-6} alkyl refers to an alkyl group having from 1 to 6 carbon atoms. Alkyl groups may be optionally substituted with one or more substituents as defined in formula (I). Alkyl groups may be straight or branched. Representative branched alkyl groups have one, two, or three branches. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl (n-propyl and isopropyl), butyl (n-butyl, isobutyl, sec-butyl, and t-butyl), pentyl (n-pentyl, isopentyl, and neopentyl), and hexyl.

"Alkoxy" refers to any alkyl moiety attached through an oxygen bridge (i.e. a $-O-C_{1-3}$ alkyl group wherein C_{1-3} alkyl is as defined herein). Examples of such groups include, but are not limited to, methoxy, ethoxy, and propoxy.

"Aryl" refers to a hydrocarbon ring system having an aromatic ring. Aryl groups are monocyclic ring systems or bicyclic ring systems. Monocyclic aryl ring refers to phenyl. Bicyclic aryl rings refer to naphthyl and to rings wherein phenyl is fused to a C_{5-7} cycloalkyl or C_{5-7} cycloalkenyl ring as defined herein. Aryl groups may be optionally substituted with one or more substituents as defined in formula (I).

"Cycloalkyl" refers to a saturated hydrocarbon ring system having the specified number of carbon atoms. Cycloalkyl groups are monocyclic or bicyclic ring systems. For example, C_{5-10} cycloalkyl refers to a cycloalkyl group having from 5 to 10 carbon atoms. Cycloalkyl groups may be optionally substituted with one or more substituents as defined in formula (I). Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and adamantanyl.

"Cycloalkenyl" refers to an unsaturated hydrocarbon ring system having the specified number of carbon atoms and having a carbon-carbon double bond within the ring. For example, C_{5-7} cycloalkenyl refers to a cycloalkenyl group having from 5 to 7 carbon atoms. In certain embodiments, cycloalkenyl groups have one carbon-carbon double bond within the ring. In other embodiments, cycloalkeneyl groups have more

than one carbon-carbon double bond within the ring. Cycloalkenyl rings are not aromatic. Cycloalkenyl groups may be optionally substituted with one or more substituents as defined in formula (I).

"Halo" refers to the halogen radicals fluoro, chloro, bromo, and iodo.

"Haloalkyl" refers to an alkyl group wherein at least one hydrogen atom attached to a carbon atom within the alkyl group is replaced with halo. The number of halo substituents includes, but is not limited to, 1, 2, 3, 4, 5, or 6 substituents. Haloalkyl includes, but is not limited to, monofluoromethyl, difluoroethyl, and trifluoromethyl.

"Haloalkoxy" refers to a haloalkyl moiety attached through an oxygen bridge (i.e. a $-O-C_{1-3}$ haloalkyl group wherein C_{1-3} haloalkyl is as defined herein). An example ofa haloalkoxy group is trifluoromethoxy.

"Heteroaryl" refers to an aromatic ring system containing from 1 to 5 heteroatoms. Heteroaryl groups containing more than one heteroatom may contain different heteroatoms. Heteroaryl groups may be optionally substituted with one or more substituents as defined in formula (I). Heteroaryl groups are monocyclic ring systems or are fused bicyclic ring systems. Monocyclic heteroaryl rings have from 5 to 6 ring atoms. Bicyclic heteroaryl rings have from 8 to 10 member atoms. Bicyclic heteroaryl rings include those ring systems wherein a heteroaryl ring is fused to a phenyl ring. Heteroaryl includes, but is not limited to, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl (including 1,3,4-oxadiazolyl and 1,2,4-oxadiazolyl), thiazolyl, isothiazolyl, thiadiazolyl, furanyl, furanzanyl, thienyl, triazolyl, pyridinyl (including 2-, 3-, and 4-pyridinyl), pyrimidinyl, pyridazinyl, pyrazinyl, trazinyl, tetrazinyl, tetrzolyl, indonyl, isoindolyl, indolizinyl, indazolyl, purinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, benzimidazolyl, benzopyranyl, benzopyranyl, benzoxazolyl, benzoisoxazolyl, benzofuranyl, benzothiazolyl, benzothienyl, naphthyridinyl, 1H-pyrrolo[2,3-b]pyridinyl, tetrazolo[1,5-a]pyridinyl, imidazo[2,1-b][1,3,4]thiadiazolyl and the like.

"Heteroatom" refers to a nitrogen, oxygen, or sulfur atom.

"Heterocyclic" refers to a 3 to 11 membered saturated or unsaturated monocyclic or bicyclic ring containing from 1 to 4 heteroatoms. Heterocyclic ring systems are not aromatic. Heterocyclic groups containing more than one heteroatom may contain different heteroatoms. Heterocyclic includes ring systems wherein a sulfur atom is oxidized to form SO or SO_2. Heterocyclic groups may be optionally substituted with one or more substituents as defined in formula (I). Heterocyclic groups are monocyclic, spiro, or fused or bridged bicyclic ring systems. Monocyclic heterocyclic rings have 3 to 7 ring atoms. Examples of monocyclic heterocyclic groups include oxtanyl, tetrahydrofuranyl, dihydrofuranyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, piperazinyl, piperidinyl, 1,3-

dioxolanyl, imidazolidinyl, imidazolinyl, pyrrolinyl, pyrrolidinyl, tetrahydropyranyl, dihydropyranyl, oxathiolanyl, dithiolanyl, 1,3-dioxanyl, 1,3-dithianyl, oxathianyl, thiomorpholinyl, tetrahydro-thiopyran1,1-dioxide, 1,4-diazepanyl, and the like. Fused heterocyclic ring systems have from 8 to 11 ring atoms and include groups wherein a heterocyclic ring is fused to a phenyl ring, a heteroaryl ring or another heterocyclic ring. Examples of fused heterocyclic rings include 2,3-dihydrobenzo[b][1,4]dioxinyl, octahydro-pyrrolo[1,2-a]pyrazinyl, octahydro-pyrido[1,2-a]pyrazinyl, octahydro-pyrrolo[3,4-c]pyrrolyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazinyl, 5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazinyl and the like. Examples of bridged heterocyclic groups include 3,8-diaza-bicyclo[3.2.1]octanyl, 3,8-diaza-bicyclo[4.2.0]octanyl and the like. Examples of spiro heterocyclic groups include 4,7-diaza-spiro[2.5]octanyl and the like.

"4-7 membered heterocyclic" refers to a heterocyclic group as defined above, having from 4 to 7 ring atoms and containing from 1 to 4 heteroatoms.

"5-6 membered heterocylic" refers to a heterocyclic group as defined above, having 5 or 6 ring atoms and containing from 1 to 4 heteroatoms.

"Optionally substituted" indicates that a group, such as an alkyl, cycloalkyl, heteroaryl, heterocyclic, phenyl, and benzyl may be unsubstitued or the group may be substituted with one or more substituents as defined in formula (I).

"Oxo" refers to a C=O group.

"Pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use. Salts and solvates (e.g. hydrates and hydrates of salts) of compounds of the invention which are suitable for use in medicine are those where in the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of the invention and their pharmaceutically acceptable salts and solvates.

"Substituted" in reference to a group such as alkyl, phenyl, benzyl, heteroaryl, and heterocyclic, indicates that one or more hydrogen atoms attached to an atom within the group is replaced with a substituent selected from the group of defined substituents. It should be understood that the term "substituted" includes the implicit provision that such substitution be in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound (i.e. one that does not spontaneously undergo transformation, for example, by hydrolysis, rearrangement, cyclization, or elimination and that is sufficiently robust to survive isolation from a reaction mixture). When it is stated that a group may contain one or more substituents, one or more (as appropriate) atoms within the group may be substituted. In addition, a

single atom within the group may be substituted with more than one substituent as long as such substitution is accordance with the permitted valence of the atom. Suitable substituents are defined for each substituted or optionally substituted group.

The skilled artisan will appreciate that salts, including pharmaceutically acceptable salts, of the compounds according to formula (I) may be prepared. These salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively.

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).

Solvates, including pharmaceutically acceptable solvates, of the compounds of formula (I) may also be prepared. "Solvate" refers to a complex of variable stoichiometry formed by a solute and solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, MeOH, EtOH, and AcOH. Solvates wherein water is the solvent molecule are typically referred to as hydrates. Hydrates include compositions containing stoichiometric amounts of water, as well as compositions containing variable amounts of water.

The compounds of formula (I), including salts and solvates thereof, may exist in crystalline forms, non-crystalline forms, or mixtures thereof. The compound or salt or solvate thereof may also exhibit polymorphism, i.e. the capacity of occurring in different crystalline forms. These different crystalline forms are typically known as "polymorphs". Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, all of which may be used for identification. One of ordinary skill in the art will appreciate that different polymorphs may be produced, for example, by changing or adjusting the conditions used in crystallizing/recrystallizing a compound of formula (I).

The invention also includes various isomers of the compounds of formula (I). "Isomer" refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. The structural difference may be in constitution (geometric isomers) or in the ability to rotate the plane of polarized light (stereosiomers). With regard to stereoisomers, the compounds of formula (I) may have

one or more asymmetric carbon atom and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof. If the compound contains a double bond, the substituent may be in the 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.

Any asymmetric atom (e.g., carbon or the like) of a compound of formula (I) 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 formula (I) 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.

The invention includes unlabeled forms as well as isotopically labeled forms of compounds of formula (I). 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 reagents in place of the non-labeled reagent previously employed.

Furthermore, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H 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).

Representative Embodiments

Various 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 for further embodiments.

One embodiment of the present invention is a compound according to formula (I) wherein:

each R^1 and R^2 is independently hydrogen, deuterium, halo, hydroxyl, NH_2, aryl, heteroaryl, or optionally substituted C_{1-4} alkyl,

wherein said C_{1-4} alkyl is optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, and NH_2;

R^{3a} is hydrogen, deuterium, C_{1-6} alkyl, phenyl, or benzyl and

R^{3b} is hydrogen, deuterium, or C_{1-6} alkyl; or

R^{3a} and R^{3b} are joined together forming an optionally substituted 3-7 membered cycloalkyl ring or an optionally substituted 4-7 membered heterocyclic ring,

wherein said cycloalkyl and heterocyclic rings are optionally substituted with one or two substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl;

R^{4a} is hydrogen, C_{1-6} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted heteroaryl, or methylene-dibenzene,

wherein said phenyl, benzyl, and heteroaryl rings are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $COOR^b$, SO_2R^b, $NHC(O)R^b$, and NR^bR^b and

R^{4b} is hydrogen, deuterium, or C_{1-3} alkyl; or

R^{4a} and R^{4b} are joined together forming an optionally substituted 3-7 membered cycloalkyl ring or an optionally substituted 4-7 membered heterocyclic ring,

wherein said cycloalkyl and heterocyclic rings are optionally substituted with one or two substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl,

provided that only one of R^{3a} and R^{3b} and R^{4a} and R^{4b} are joined together forming a ring;

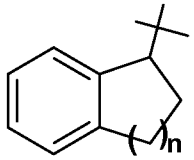
R^{5a} is hydrogen or deuterium;

R^{5b} is hydrogen, deuterium, methyl, ethyl, CD_3, CF_3, CH_2F, or CHF_2 and

R^6 is optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted C_{5-10} cycloalkyl,

wherein said C_{1-6} alkyl is optionally substituted with one substituent selected from the group consisting of hydroxyl, C_{1-3} alkoxy and $-OR^a$;

wherein said aryl, heteroaryl, heterocyclic and C_{5-10} cycloalkyl are optionally substituted with one to three substituents each independently selected from the group consisting of: halo; hydroxyl; cyano; nitro; C_{1-3} alkoxy; C_{1-3} haloalkyl; C_{1-3} haloalkoxy; C_{1-6} alkyl; C_{3-6} cycloalkyl; phenyl optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $COOR^b$, SO_2R^b, $NHC(O)R^b$, and NR^bR^b; 5-6 membered heteroaryl; 5-6 membered heterocyclic optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl; $-CH_2R^a$; $-OR^a$; $-C(O)R^a$; $-NR^aR^b$; $-COOR^a$; $-SO_2R^a$; $NHC(O)R^a$; and $-SO_2NR^bR^b$; or

R^{5b} and R^6 are joined together forming an optionally substituted C_{3-7} cycloalkyl group or an optionally substituted group of formula (a):  (a),

wherein n is 1, 2, or 3 and

said C_{3-7} cycloalkyl and group of formula (a) are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, benzyloxy, $COOR^b$, SO_2R^b, $NHC(O)R^b$, and NR^bR^b;

each R^a is independently optionally substituted phenyl, optionally substituted heteroaryl, or optionally substituted 4-7 membered heterocyclic,

wherein said phenyl and heteroaryl are optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, and C_{1-3} alkyl,

wherein said 4-7 membered heterocyclic is optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, oxo, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, and C_{1-3} alkyl; and

each R^b is independently hydrogen or C_{1-6} alkyl.

In another embodiment of the present invention R^1 is hydrogen, halo, or optionally substituted C_{1-4} alkyl. Suitably R^1 is hydrogen, fluoro, chloro, or methyl. In another embodiment R^1 is hydrogen, fluoro or chloro. Suitably R^1 is hydrogen.

In another embodiment of the present invention R^2 is hydrogen, halo or optionally substituted C_{1-4} alkyl. Suitably R^2 is hydrogen, fluoro, chloro, or methyl. In another embodiment R^2 is hydrogen or fluoro. In another embodiment of the present invention R^2 is hydrogen.

In another embodiment of the present invention R^1 and R^2 are both hydrogen.

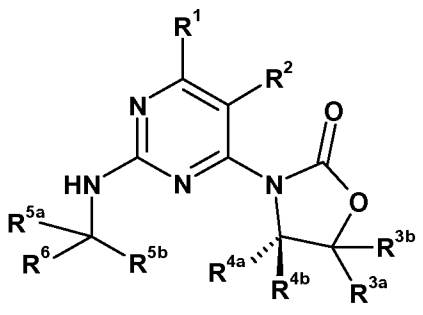
In another embodiment of the present invention R^{3a} is hydrogen, C_{1-6} alkyl, or phenyl. Suitably R^{3a} is hydrogen, methyl, or phenyl. Suitably R^{3a} is hydrogen or methyl. Suitably R^{3a} is hydrogen.

In another embodiment of the present invention R^{3b} is hydrogen or methyl. Suitably R^{3b} is hydrogen.

In another embodiment R^{3a} and R^{3b} are both hydrogen.

In another embodiment of the present invention R^{3a} and R^{3b} are joined together forming oxetanyl or tetrahydro-2H-pyranyl.

Another embodiment of the present invention is a compound according to formula (II).



(II)

In another embodiment of the present invention R^{4a} is hydrogen, C_{1-6} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted heteroaryl, or methylene-dibenzene,

wherein said phenyl, benzyl, and heteroaryl rings are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $-COOR^b$, $-SO_2R^b$,- $NHC(O)R^b$, and- NR^bR^b .

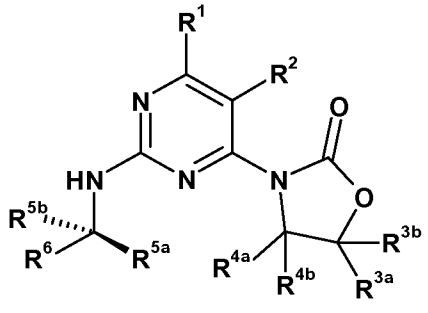
In another embodiment of the present invention R^{4a} is hydrogen, C_{1-4} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted heteroaryl, or methylene-dibenzene. Suitably R^{4a} is hydrogen, C_{1-4} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted pyridinyl, or methylene-dibenzene. More suitably R^{4a} is hydrogen, methyl, isopropyl, isobutyl, t-butyl, phenyl, 4-methoxyphenyl, 4-fluorophenyl, benzyl, or methylene-dibenzene. In another embodiment R^{4a} is hydrogen, methyl, ethyl, isopropyl, phenyl, 4-fluorophenyl, 4-methoxyphenyl, biphenyl, benzyl, or pyridinyl. Suitably R^{4a} is isopropyl.

In another embodiment of the present invention R^{4b} is hydrogen or methyl. Suitably R^{4b} is hydrogen.

In another embodiment R^{4a} is isopropyl and R^{4b} is methyl. In another embodiment R^{4a} is isopropyl and R^{4b} is hydrogen.

In another embodiment of the present invention R^{4a} and R^{4b} are joined together forming cyclopentyl.

Another embodiment of the present invention is a compound according to formula (III).



(III)

In another embodiment of the present invention R^{5a} is hydrogen. In another embodiment R^{5a} is deuterium.

In another embodiment of the present invention R^{5b} is hydrogen, methyl, ethyl, or CF_3. Suitably R^{5b} is methyl.

In another embodiment of the present invention R^6 is isopropyl, optionally substituted aryl, optionally substituted pyrazolyl, optionally substituted pyridinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, or optionally substituted C_{5-10} cycloalkyl. Suitably R^6 is isopropyl, optionally substituted phenyl, optionally substituted naphthyl, pyrazolyl, pyridinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, or C_{5-10} cycloalkyl, wherein said phenyl and naphthyl are each optionally substituted with one to three substituents each independently selected from the group consisting of: fluoro, chloro, bromo, hydroxy, cyano, methoxy, trifluoromethyl, methyl, t-butyl, phenyl, pyrrolyl, piperidinyl, 4-methylpiperazinyl, morpholinyl, phenoxy, and $-SO_2NH_2$.

In another embodiment of the present invention R^6 is optionally substituted heteroaryl, optionally substituted heterocyclic or optionally substituted C_{5-10} cycloalkyl.

In another embodiment of the present invention R^6 is methyl, C_{5-10} cycloalkyl, optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazolyl, optionally substituted pyrazolyl, optionally substituted thiazolyl, optionally substitued 1,3,4-oxadiazolyl, optionally substituted 1,2,4-oxadiazolyl, optionally substitued isoxazolyl, thienyl, oxazolyl, quinolinyl, optionally substituted benzimidazolyl, benzthiazolyl, benzoxazolyl, tetrazolo[1,5-a]pyridinyl, imidazo[2,1-b][1,3,4]thiadiazolyl, optionally substituted piperidinyl, optionally substituted piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, optionally substituted tetrahydro-thiopyran1,1-dioxide, 1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 5,6,7,8-tetrahydro-[1,2,4]trazolo[4,3-a]pyrazinyl, 4,5,6,7-tetrahydro-benzothiazolyl, or indolizinyl, wherein said phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazolyl, pyrazolyl, thiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, isoxazolyl, benzimidazolyl, piperidinyl, piperazinyl, and tetrahydro-thiopyran1,1-dioxide are each optionally substituted with one or two substituents as defined in formula (I). Suitably R^6 is phenyl optionally substituted with one or two substituents. Suitably R^6 is optionally substituted 1,3,4-oxadiazolyl or 1,2,4-optionally substituted oxadiazolyl. Suitably R^6 is pyrimidinyl optionally substituted with one substituent.

In another embodiment R^6 is optionally substituted with one or two substituents each independently selected from the group consisting of: halo; hydroxy; nitro; C_{1-4} alkoxy; C_{1-3} haloalkyl; C_{1-3} haloalkoxy; C_{1-6} alkyl; C_{3-6} cycloalkyl optionally substituted

with one substituent selected from the group consisting of: cyano, C_{1-3} alkyl, and C_{1-3} alkoxy; phenyl optionally substituted with one or two substituents each independently selected from the group consisting of: fluoro, chloro, methyl, cyano, and methoxy; and 5-6 membered heteroaryl (for example, imidazolyl, pyrazolyl, trazolyl, and pyridinyl) optionally substituted with one or two methyl groups.

In another embodiment R^6 is substituted with one $-CH_2R^a$, $-C(O)R^a$, $-NHC(O)R^a$, $-NHC(O)R^b$, $-C(O)NHR^a$, $-C(O)NHR^b$, $-OR^a$, $-NR^aR^b$, $-SO_2NR^bR^b$, $-SO_2R^a$, or $-SO_2R^b$ group. Suitably R^6 is substituted with one $-CH_2R^a$, $-C(O)R^a$, or $-OR^a$ group.

In another embodiment R^6 is phenyl substituted with one fluoro or chloro group and one $-CH_2R^a$, $-C(O)R^a$, or $-C(O)NHR^a$ group wherein the $-CH_2R^a$, $-C(O)R^a$, or $-C(O)NHR^a$ group is in the para position of the phenyl ring. Suitably R^6 is phenyl substituted with one fluoro group and one $-CH_2R^a$, $-C(O)R^a$, or $-C(O)NHR^a$ group wherein the $-CH_2R^a$, $-C(O)R^a$, or $-C(O)NHR^a$ group is in the para position of the phenyl ring. In another embodiment R^6 is phenyl substituted with one $-CH_2R^a$, $-C(O)R^a$, or $-C(O)NHR^a$ group in the para position. In another embodiment R^6 is phenyl substituted by $-CH_2R^a$ in the para position.

In another embodiment R^a is phenyl optionally substituted with one or two substituents each independently selected from the group consisting of fluoro, chloro and bromo.

In another embodiment R^a is an optionally substituted 5-6 membered heteroaryl. Suitably R^a is optionally substituted pyridinyl or optionally substituted pyrimidinyl. Suitably R^a is pyridinyl or pyrimidinyl optionally substituted with one trifluoromethyl.

In another embodiment R^a is C_{5-7} cycloalkyl each of which is optionally substituted with one or two substituents each independently selected from the group consisting of fluoro, hydroxy, methyl, and C_{1-3} haloalkoxy.

In another embodiment R^a is optionally substituted heterocyclic. Suitably R^a is piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, tetrahydro-thiopyran1,1-dioxide, 1,4-diazepanyl, 4,7-diaza-spiro[2.5]octanyl, 3,8-diaza-bicyclo[3.2.1]octanyl, 3,8-diaza-bicyclo[4.2.0]octanyl, octahydro-pyrrolo[1,2-a]pyrazinyl, octahydro-pyrido[1,2-a]pyrazinyl, octahydro-pyrrolo[3,4-c]pyrrolyl, and 5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazinyl each of which is optionally substituted with one to three substituents each independently selected

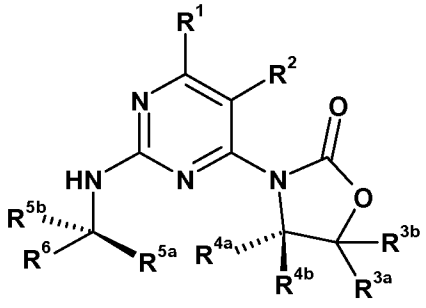
from the group consisting of: hydroxy, fluoro, amino, dimethylamino, C_{1-3} haloalkoxy, C_{1-3} alkyl, and C_{3-5} cycloalkyl. Suitably R^a is piperidinyl, piperazinyl, or morpholinyl each of which is optionally substituted with one to three substituents each independently selected from the group consisting of: hydroxy, fluoro, amino, dimethylamino, C_{1-3} haloalkoxy, C_{1-3} alkyl, and C_{3-5} cycloalkyl.

In another embodiment of the present invention R^{5b} and R^6 are joined together forming an optionally substituted C_{3-7} cycloalkyl group or an optionally substituted group of formula (a).

In another embodiment of the present invention each R^b is independently hydrogen or methyl.

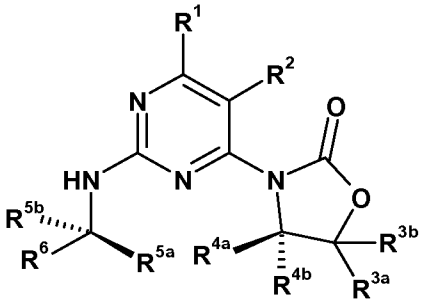
In another embodiment R^1 is hydrogen, R^2 is fluoro and R^{3a}, R^{3b}, R^{4a} and R^{4b} are each hydrogen.

Another embodiment of the present invention is a compound according to formula (IV).



(IV)

Another embodiment of the present invention is a compound according to formula (V):



(V), wherein R^{4a} is phenyl and R^{4b} is hydrogen.

Selected compounds of the present invention include:
(S)-4-isopropy-3-(2-(((S)-1-(4-(2-yl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one;
N-(4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)phenyl)cyclohexanecarboxamide;

(S)-3-(2-(((S)-1-(3-fluoro-4-((4-methylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-isopropyl-3-(2-(((S)-1-(4-((3,3,4-trimethylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one;
2-fluoro-N-(4-hydroxy-4-methylcyclohexyl)-4-((S)-1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)ethyl)benzamide;
(S)-3-(2-((S)-1-(4-((4-amino-4-methylpiperidin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-isopropyl-3-(2-((S)-1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-4-isopropyl-4-methyl-3-(2-((S)-1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-4-isopropyl-3-(2-((S)-1-(6-phenylpyridin-3-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-3-(2-((S)-1-(4-benzoylphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-isopropyl-3-(2-(((S)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl) amino) pyrimidin-4-yl)oxazolidin-2-one;
(4S)-4-isopropyl-3-(2-(1-(5-phenylpyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
3-(5-fluoro-2-((1-(5-(4-fluoro-3-methylphenyl)pyridin-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-4-isopropyl-3-(2-(((S)-1-(1-(3-methoxyphenyl)-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-3-(2-(((S)-1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-isopropyl-3-(2-(((S)-1-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-3-(2-(((S)-1-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(5-(4-fluoro-2-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-Isopropyl-3-{2-[(3-p-tolyl-[1,2,4]oxadiazol-5-ylmethyl)-amino]-pyrimidin-4-yl}-oxazolidin-2-one;

(S)-4-isopropyl-3-(2-((S)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-3-(2-((S)-1-(2-fluoro-4-isopropylphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(4-isobutoxy-3-methylphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(4-isobutoxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(5-fluoro-2-(((S)-1-(4-isobutoxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
2-fluoro-N-(*trans*-4-hydroxycyclohexyl)-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide;
(S)-3-(5-fluoro-2-((S)-1-(3-fluoro-4-(piperidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
N-cyclohexyl-2-fluoro-4-((S)-1-(5-fluoro-4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide;
N-cyclohexyl-2-fluoro-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide; and
(S)-3-(5-fluoro-2-((S)-1-(2-fluoro-4-(trifluoromethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

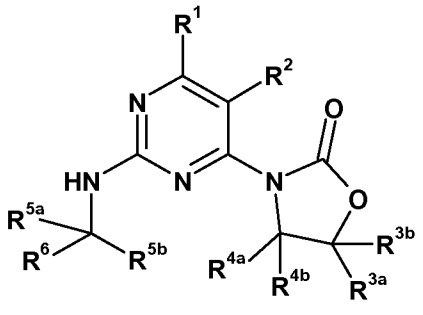
Selected compounds of the present invention include:
(S)-3-(2-(((S)-1-(3-fluoro-4-((3,3,4-trimethylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(4-((4,4-difluoropiperidin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(5-fluoro-2-(1-(4-phenoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-3-(2-((S)-1-(4-(4-fluorophenoxy)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(4-(((2S,6R)-2,6-dimethylmorpholino)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(5-(4-fluoro-3-methylphenyl)pyridin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;

(S)-3-(2-((S)-1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(5-(4-fluorophenoxy)pyrazin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-isopropyl-3-(2-((S)-1-(5-(3-(trifluoromethyl)phenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one; and
(S)-3-(2-((S)-1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

Selected compounds of the present invention include:
(S)-3-(2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)-5-fluoropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one;
(S)-3-(6-chloro-2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-3-(2-((S)-1-(2-fluoro-4-(1-methylcyclopropyl) phenyl) ethylamino) pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(2-fluoro -4-(trifluoromethyl) phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
2-chloro-N-cyclopentyl-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide;
(S)-3-(2-((S)-1-(4-((3,3-difluoropiperidin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(4-(4,7-diazaspiro[2.5]octan-4-ylmethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(4-((4-acetylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(4-isobutoxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(5-fluoro-2-(((S)-1-(4-isobutoxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one; and
2-fluoro-N-(trans-4-hydroxycyclohexyl)-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide.

Enumerated Embodiments

Embodiment 1. A compound of formula (I)



(I)

wherein:

each R^1 and R^2 is independently hydrogen, deuterium, halo, hydroxyl, NH_2, aryl, heteroaryl, or optionally substituted C_{1-4} alkyl,

wherein said C_{1-4} alkyl is optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, and NH_2;

R^{3a} is hydrogen, deuterium, C_{1-6} alkyl, phenyl, or benzyl and

R^{3b} is hydrogen, deuterium, or C_{1-6} alkyl; or

R^{3a} and R^{3b} are joined together forming an optionally substituted 3-7 membered cycloalkyl ring or an optionally substituted 4-7 membered heterocyclic ring,

wherein said cycloalkyl and heterocyclic rings are each optionally substituted with one or two substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl;

R^{4a} is hydrogen, C_{1-6} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted heteroaryl, or methylene-dibenzene,

wherein said phenyl, benzyl, and heteroaryl rings are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $COOR^b$, SO_2R^b, $NHC(O)R^b$, and NR^bR^b and

R^{4b} is hydrogen, deuterium, or C_{1-3} alkyl; or

R^{4a} and R^{4b} are joined together forming an optionally substituted 3-7 membered cycloalkyl ring or an optionally substituted 4-7 membered heterocyclic ring,

wherein said cycloalkyl and heterocyclic rings are optionally substituted with one or two substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl,

provided that only one of R^{3a} and R^{3b} and R^{4a} and R^{4b} are joined together forming a ring;

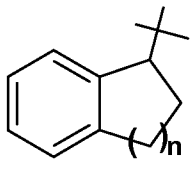
R^{5a} is hydrogen or deuterium;

R^{5b} is hydrogen, deuterium, methyl, ethyl, CD_3, CF_3, CH_2F, or CHF_2 and

R^6 is optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted C_{5-10} cycloalkyl,

wherein said C_{1-6} alkyl is optionally substituted with one substituent selected from the group consisting of hydroxyl, C_{1-3} alkoxy and $-OR^a$;

wherein said aryl, heteroaryl, heterocyclic and C_{5-10} cycloalkyl are optionally substituted with one to three substituents each independently selected from the group consisting of: halo; hydroxyl; cyano; nitro; C_{1-3} alkoxy; C_{1-3} haloalkyl; C_{1-3} haloalkoxy; C_{1-6} alkyl; C_{3-6} cycloalkyl; phenyl optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $COOR^b$, SO_2R^b, $NHC(O)R^b$, and NR^bR^b; 5-6 membered heteroaryl; 5-6 membered heterocyclic optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl; $-CH_2R^a$; $-OR^a$; $-C(O)R^a$; $-NR^aR^b$; $-COOR^a$; $-SO_2R^a$; $NHC(O)R^a$; and $-SO_2NR^bR^b$; or

R^{5b} and R^6 are joined together forming an optionally substituted C_{3-7} cycloalkyl group or an optionally substituted group of formula (a):  (a),

wherein n is 1, 2, or 3 and

said C_{3-7} cycloalkyl and group of formula (a) are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6}

cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, benzyloxy, $COOR^b$, SO_2R^b, $NHC(O)R^b$, and NR^bR^b;

each R^a is independently optionally substituted phenyl, optionally substituted heteroaryl, or optionally substituted 4-7 membered heterocyclic,

wherein said phenyl and heteroaryl are optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, and C_{1-3} alkyl,

wherein said 4-7 membered heterocyclic is optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, oxo, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, and C_{1-3} alkyl; and

each R^b is independently hydrogen or C_{1-6} alkyl; or a pharmaceutically acceptabble salt thereof.

Embodiment 2. The compound according to embodiment 1 wherein R^2 is hydrogen; or a pharmaceutically acceptable salt thereof.

Embodiment 3. The compound according to embodiment 2 wherein R^1 is hydrogen, halo, or optionally substituted C_{1-4} alkyl; or a pharmaceutically acceptable salt thereof.

Embodiment 4. The compound according to embodiment 3 wherein R^1 is hydrogen, fluoro, chloro, or methyl; or a pharmaceutically acceptable salt thereof.

Embodiment 5. The compound according to embodiment 4 wherein R^{3a} is hydrogen, C_{1-6} alkyl, phenyl, or benzyl and R^{3b} is hydrogen or C_{1-6} alkyl; or a pharmaceutically acceptable salt thereof.

Embodiment 6. The compound according to embodiment 5 wherein R^{3b} is hydrogen or methyl; or a pharmaceutically acceptable salt thereof.

Embodiment 7. The compound according to embodiment 6 wherein R^{3a} is hydrogen, methyl, or phenyl; or a pharmaceutically acceptable salt thereof.

Embodiment 8. The compound according to embodiment 7 wherein R^{4a} is hydrogen, C_{1-6} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted heteroaryl, or methylene-dibenzene,

wherein said phenyl, benzyl, and heteroaryl rings are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $COOR^b$, SO_2R^b, $NHC(O)R^b$, and NR^bR^b and

R^{4b} is hydrogen or C_{1-3} alkyl; or a pharmaceutically acceptable salt thereof.

Embodiment 9. The compound according to embodiment 8 wherein R^{4b} is hydrogen or methyl; or a pharmaceutically acceptable salt thereof.

Embodiment 10. The compound according to embodiment 9 wherein R^{4a} is hydrogen, C_{1-4} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted heteroaryl, or methylene-dibenzene; or a pharmaceutically acceptable salt thereof.

Embodiment 11. The compound according to embodiment 10 wherein R^{4a} is hydrogen, methyl, isopropyl, isobutyl, t-butyl, phenyl, 4-methoxyphenyl, 4-fluorophenyl, benzyl, or methylene-dibenzene; or a pharmaceutically acceptable salt thereof.

Embodiment 12. The compound according to embodiment 11 wherein R^{5a} is H; or a pharmaceutically acceptable salt thereof.

Embodiment 13. The compound according to embodiment 12 wherein R^{5b} is hydrogen, methyl, ethyl, or CF_3.

Embodiment 14. The compound according to embodiment 13 wherein R^6 is isopropyl, optionally substituted aryl, optionally substituted pyrazolyl, optionally substituted pyridinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, or optionally substituted C_{5-10} cycloalkyl; or a pharmaceutically acceptable salt thereof.

Embodiment 15. A pharmaceutical composition comprising a compound according to embodiment 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

Embodiment 16. A method for the treatment of a disease or disorder associated with a mutant IDH protein having a neomorphic activity comprising administration of a therapeutically effective amount of a compound according to embodiment 1, or a pharmaceutically acceptable salt thereof, to subject in need of thereof.

Embodiment 17. A method for the treatment of a disease or disorder associated with a mutant IDH protein having a neomorphic activity comprising administration of a therapeutically effective amount of a compound according to embodiment 1, or a pharmaceutically acceptable salt thereof, and another therapeutic agent to subject in need of thereof.

General Synthetic Procedures

The compounds of the present invention may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the Schemes given below.

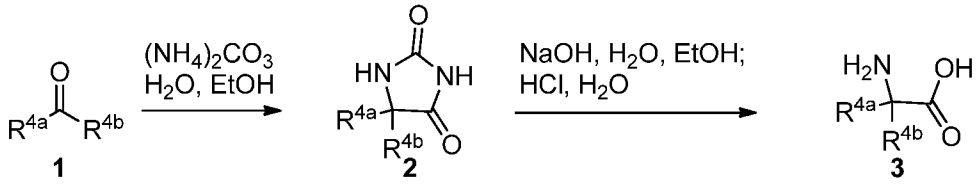
The compounds of formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles or chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of compounds of formula (I).

Those skilled in the art will recognize if a stereocenter exists in the compounds of formula (I). Accordingly, the present invention includes both possible stereoisomers and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for

example, “Stereochemistry of Organic Compounds” by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

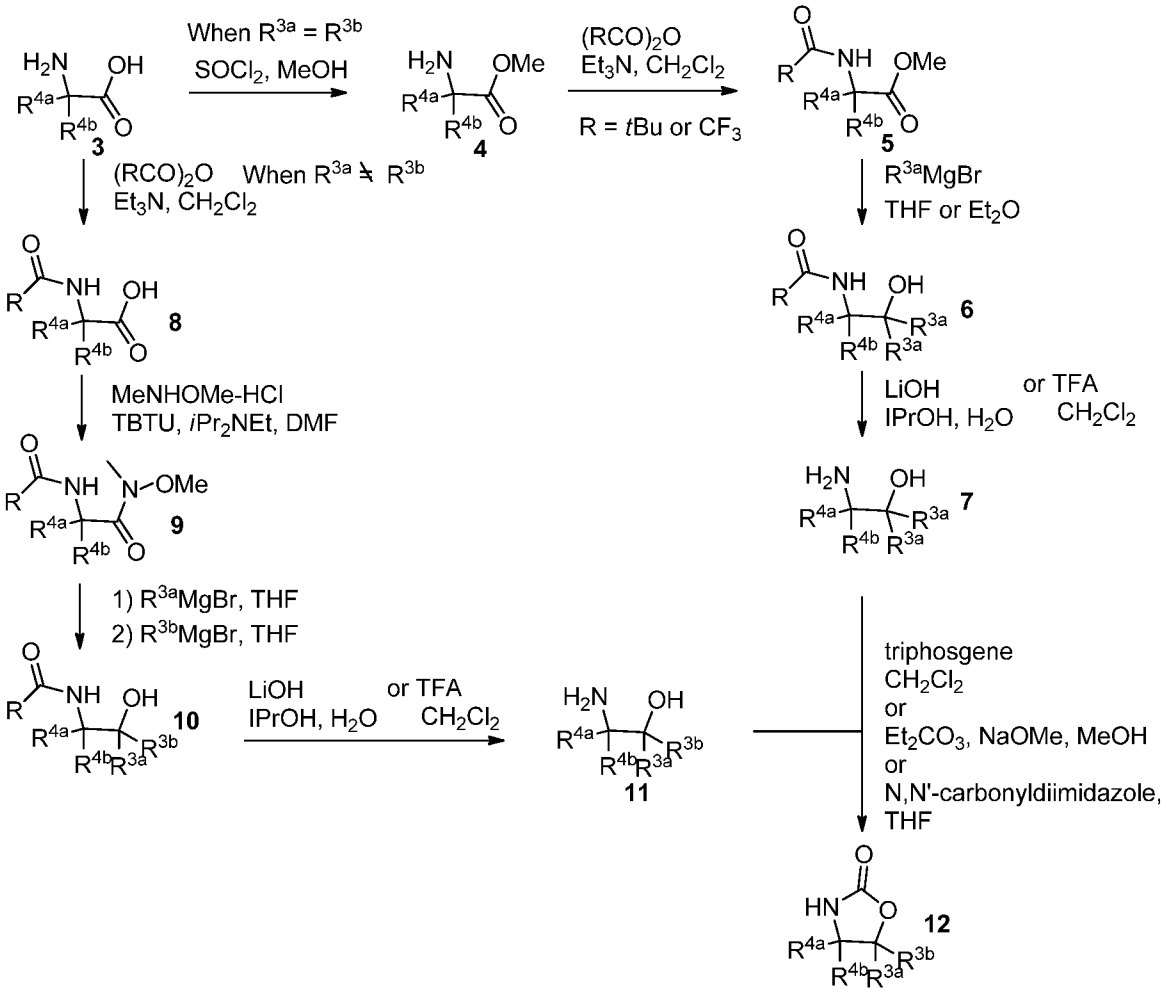
The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, and/or enzymatic processes.

Scheme 1.



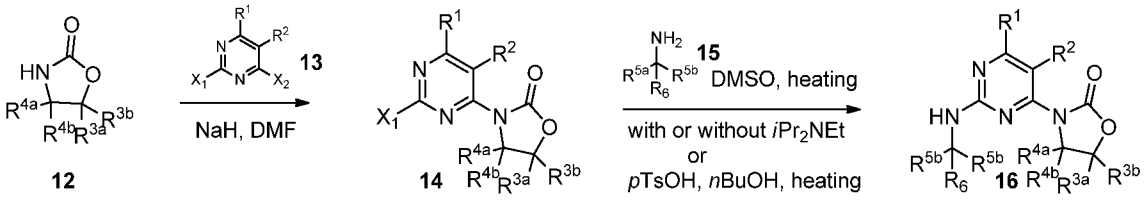
Non-commercial aminoacids can be prepared following the procedures of Scheme 1. Conversion of ketone **1** to the corresponding imidazolidine-2,4-dione **2** followed by hydrolysis provides aminoacid **3**.

Scheme 2.



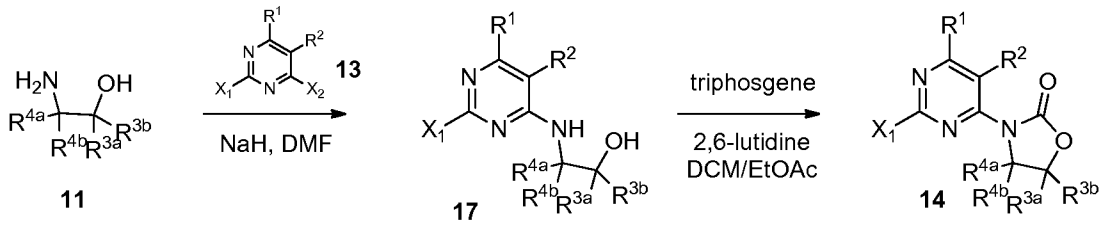
When aminoalcohol, precursor of oxazolidinone, is not commercially available, it can be prepared from aminoacid **3** following the procedures of Scheme 2. When $R^{3a} = R^{3b}$, protected aminoester **5** is treated with an appropriate Grignard reagent to give protected aminoalcohol **6** which goes through basic or acidic deprotection step. When $R^{3a} \neq R^{3b}$, protected aminoacid **8** is converted into Weinreb amide **9** which is treated with different Grignard reagents sequentially to provide protected aminoalcohol **10**. Either basic or acidic deprotection of **10** gives **11**. Insertion of CO unit into **7** or **11** to provide oxazolidinone **12** is accomplished with several reagents, including (but not limited to) triphosgene, Et_2CO_3 or N-N'-darbonyldiimidazole, as shown in Scheme 2.

Scheme 3.



Oxazolidinone **12** is coupled with dihalogen-pyrimidine **13** in the presence of NaH and the resulting **14** is treated with primary amine **15** under several different reaction conditions as shown in Scheme 3 to provide **16**.

Scheme 4.



Alternately intermediate **14** can be prepared by coupling the amino alcohol **11** and dihalogen-pyrimidine **13** in the presence of a base such as diisopropylethyl amine resulting in intermediate **17** which can be treated with triphosgene in the presence of a base such as 2,6-lutidine resulting in intermediate **14**.

Methods of Use

The compounds of the present invention are inhibitors of a mutant IDH protein having a neomorphic activity and are therefore useful in the treatment of diseases or disorders associated with such proteins including, but not limited to, cell proliferation disorders, such as cancer.

Examples of a mutant IDH protein having a neomorphic activity are mutant IDH1 and mutant IDH2. A neomorphic activity associated with mutant IDH1 and mutant IDH2 is the ability to produce 2-hydroxyglutarate (2-HG neomorphic activity), specifically R-2-HG (R-2-HG neomorphic activity). Mutations in IDH1 associated with 2-HG neomorphic activity, specifically R-2-HG neomorphic activity, include mutations at residues 97, 100, and 132, e.g. G97D, R100Q, R132H, R132C, R132S, R132G, R132L, and R132V. Mutations in IDH2 associated with 2-HG neoactivity, specifically R-2-HG neomorphic

activity, include mutations at residues 140 and 172, e.g. R140Q, R140G, R172K, R172M, R172S, R172G, and R172W.

Cell-proliferation disorders associated with a mutant IDH protein having a neomorphic activity include, but are not limited to, cancer. Examples of such cancers include Acute Lymphoblastic Leukemia, Adult; Acute Lymphoblastic Leukemia, Childhood; Acute Myeloid Leukemia, Adult; Adrenocortical Carcinoma; Adrenocortical Carcinoma, Childhood; AIDS-Related Lymphoma; AIDS-Related Malignancies; Anal Cancer; Astrocytoma, Childhood Cerebellar; Astrocytoma, Childhood Cerebral; Bile Duct Cancer, Extrahepatic; Bladder Cancer; Bladder Cancer, Childhood; Bone Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma; Brain Stem Glioma, Childhood; Brain Tumor, Adult; Brain Tumor, Brain Stem Glioma, Childhood; Brain Tumor, Cerebellar Astrocytoma, Childhood; Brain Tumor, Cerebral Astrocytoma/Malignant Glioma, Childhood; Brain Tumor, Ependymoma, Childhood; Brain Tumor, Medulloblastoma, Childhood; Brain Tumor, Supratentorial Primitive Neuroectodermal Tumors, Childhood; Brain Tumor, Visual Pathway and Hypothalamic Glioma, Childhood; Brain Tumor, Childhood (Other); Breast Cancer; Breast Cancer and Pregnancy; Breast Cancer, Childhood; Breast Cancer, Male; Bronchial Adenomas/Carcinoids, Childhood; Carcinoid Tumor, Childhood; Carcinoid Tumor, Gastrointestinal; Carcinoma, Adrenocortical; Carcinoma, Islet Cell; Carcinoma of Unknown Primaiy; Central Nervous System Lymphoma, Primary; Cerebellar Astrocytoma, Childhood; Cerebral Astrocytoma/Malignant Glioma, Childhood; Cervical Cancer; Childhood Cancers; Chronic Lymphocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloproliferative Disorders; Clear Cell Sarcoma of Tendon Sheaths; Colon Cancer; Colorectal Cancer, Childhood; Cutaneous T-Cell Lymphoma; Endometrial Cancer; Ependymoma, Childhood; Epithelial Cancer, Ovarian; Esophageal Cancer; Esophageal Cancer, Childhood; Ewing's Family of Tumors; Extracranial Germ Cell Tumor, Childhood; Extragonadal Germ Cell Tumor; Extrahepatic Bile Duct Cancer; Eye Cancer, Intraocular Melanoma; Eye Cancer, Retinoblastoma; Gallbladder Cancer; Gastric (Stomach) Cancer; Gastric (Stomach) Cancer, Childhood; Gastrointestinal Carcinoid Tumor; Germ Cell Tumor, Extracranial, Childhood; Germ Cell Tumor, Extragonadal; Germ Cell Tumor, Ovarian; Gestational Trophoblastic Tumor; Glioma, Childhood Brain Stem; Glioma, Childhood Visual Pathway and Hypothalamic; Hairy Cell Leukemia; Head and Neck Cancer; Hepatocellular (Liver) Cancer, Adult (Primary); Hepatocellular (Liver) Cancer, Childhood (Primary); Hodgkin's Lymphoma, Adult; Hodgkin's Lymphoma, Childhood; Hodgkin's Lymphoma During Pregnancy; Hypopharyngeal Cancer; Hypothalamic and Visual Pathway Glioma, Childhood; Intraocular Melanoma; Islet Cell Carcinoma (Endocrine Pancreas); Kaposi's Sarcoma; Kidney Cancer; Laryngeal Cancer; Laryngeal

Cancer, Childhood; Leukemia, Acute Lymphoblastic, Adult; Leukemia, Acute Lymphoblastic, Childhood; Leukemia, Acute Myeloid, Adult; Leukemia, Acute Myeloid, Childhood; Leukemia, Chronic Lymphocytic; Leukemia, Chronic Myelogenous; Leukemia, Hairy Cell; Lip and Oral Cavity Cancer; Liver Cancer, Adult (Primary); Liver Cancer, Childhood (Primary); Lung Cancer, Non-Small Cell; Lung Cancer, Small Cell; Lymphoblastic Leukemia, Adult Acute; Lymphoblastic Leukemia, Childhood Acute; Lymphocytic Leukemia, Chronic; Lymphoma, AIDS- Related; Lymphoma, Central Nervous System (Primary); Lymphoma, Cutaneous T-Cell; Lymphoma, Hodgkin's, Adult; Lymphoma, Hodgkin's, Childhood; Lymphoma, Hodgkin's During Pregnancy;Lymphoma, Non-Hodgkin' s, Adult; Lymphoma, Non- Hodgkin's, Childhood; Lymphoma, Non-Hodgkin's During Pregnancy; Lymphoma, Primary Central Nervous System; Macroglobulinemia, Waldenstrom's; Male Breast Cancer; Malignant Mesothelioma, Adult; Malignant Mesothelioma, Childhood; Malignant Thymoma; Medulloblastoma, Childhood; Melanoma; Melanoma, Intraocular; Merkel Cell Carcinoma; Mesothelioma, Malignant; Metastatic Squamous Neck Cancer with Occult Primary; Multiple Endocrine Neoplasia Syndrome, Childhood; Multiple Myeloma/Plasma Cell Neoplasm; Mycosis Fungoides; Myelodysplastic Syndromes; Myelogenous Leukemia, Chronic; Myeloid Leukemia, Childhood Acute; Myeloma, Multiple; Myeloproliferative Disorders, Chronic; Nasal Cavity and Paranasal Sinus Cancer; Nasopharyngeal Cancer; Nasopharyngeal Cancer, Childhood; Neuroblastoma; Non-Hodgkin's Lymphoma, Adult; Non-Hodgkin's Lymphoma, Childhood; Non- Hodgkin's Lymphoma During Pregnancy; Non-Small Cell Lung Cancer; Oral Cancer, Childhood; Oral Cavity and Lip Cancer; Oropharyngeal Cancer; steosarcoma/Malignant Fibrous Histiocytoma of Bone; Ovarian Cancer, Childhood; Ovarian Epithelial Cancer; Ovarian Germ Cell Tumor; Ovarian Low Malignant Potential Tumor; Pancreatic Cancer; Pancreatic Cancer, Childhood; Pancreatic Cancer, Islet Cell; Paranasal Sinus and Nasal Cavity Cancer; Parathyroid Cancer; Penile Cancer; Pheochromocytoma; Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood; Pituitary Tumor; Plasma Cell Neoplasm/Multiple Myeloma; Pleuropulmonary Blastoma; Pregnancy and Breast Cancer; Pregnancy and Hodgkin's Lymphoma; Pregnancy and Non-Hodgkin's Lymphoma; Primary Central Nervous System Lymphoma; Primary Liver Cancer, Adult; Primary Liver Cancer, Childhood; Prostate Cancer; Rectal Cancer; Renal Cell (Kidney) Cancer; Renal Cell Cancer, Childhood; Renal Pelvis and Ureter, Transitional Cell Cancer; Retinoblastoma; Rhabdomyosarcoma, Childhood; Salivary Gland Cancer; Salivary Gland Cancer, Childhood; Sarcoma, Ewing's Family of Tumors; Sarcoma, Kaposi's; Sarcoma (Osteosarcoma)/Malignant Fibrous Histiocytoma of Bone; Sarcoma, Rhabdomyosarcoma, Childhood; Sarcoma, Soft Tissue, Adult; Sarcoma, Soft Tissue, Childhood; Sezary Syndrome; Skin Cancer; Skin Cancer,

Childhood; Skin Cancer (Melanoma); Skin Carcinoma, Merkel Cell; Small Cell Lung Cancer; Small Intestine Cancer; Soft Tissue Sarcoma, Adult; Soft Tissue Sarcoma, Childhood; Squamous Neck Cancer with Occult Primary, Metastatic; Stomach (Gastric) Cancer; Stomach (Gastric) Cancer, Childhood; Supratentorial Primitive Neuroectodermal Tumors, Childhood; T- Cell Lymphoma, Cutaneous; Testicular Cancer; Thymoma, Childhood; Thymoma, Malignant; Thyroid Cancer; Thyroid Cancer, Childhood; Transitional Cell Cancer of the Renal Pelvis and Ureter; Trophoblastic Tumor, Gestational; Unknown Primary Site, Cancer of, Childhood; Unusual Cancers of Childhood; Ureter and Renal Pelvis, Transitional Cell Cancer; Urethral Cancer; Uterine Sarcoma; Vaginal Cancer; Visual Pathway and Hypothalamic Glioma, Childhood; Vulvar Cancer; Waldenstrom's Macro globulinemia; and Wilms' Tumor.

In another embodiment the cancer associated with a mutant IDH protein having a neomorphic acitvity is brain cancer, such as astrocytic tumor (e.g., pilocytic astrocytoma, subependymal giant-cell astrocytoma, diffuse astrocytoma, pleomorphic xanthoastrocytoma, anaplastic astrocytoma, astrocytoma, giant cell glioblastoma, glioblastoma, secondary glioblastoma, primary adult glioblastoma, and primary pediatric glioblastoma); oligodendroglial tumor (e.g., oligodendroglioma, and anaplastic oligodendroglioma); oligoastrocytic tumor (e.g., oligoastrocytoma, and anaplastic oligoastrocytoma); ependymoma (e.g., myxopapillary ependymoma, and anaplastic ependymoma); medulloblastoma; primitive neuroectodermal tumor, schwannoma, meningioma, meatypical meningioma, anaplastic meningioma; and pituitary adenoma. In another embodiment, the brain cancer is glioma, glioblastoma multiforme, paraganglioma, or suprantentorial primordial neuroectodermal tumors (sPNET).

In another embodiment the cancer associated with a mutant IDH protein having a neomorphic acitvity is leukemia, such as acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML), myeloproliferative neoplasm (MPN), MDS.MPN including chronic myelomonocytic leukemia, post MDS AML, post MPN AML, post MDS/MPN AML, del(5q)-associated high risk MDS or AML, blast-phase chronic myelogenous leukemia, angioimmunoblastic lymphoma and acute lymphoblastic leukemia.

In another embodiment the cancer associated with a mutant IDH protein having a neomorphic activity is skin cancer, including melanoma.

In another embodiment the cancer associated with a mutant IDH protein having a neomorphic activity is prostate cancer, thyroid cancer, colon cancer, or lung cancer.

In another embodiment the cancer associated with a mutant IDH protein having a neomorphic activity is sarcoma, including central chondrosarcoma, central and periosteal chondroma, and fibrosarcoma.

In another embodiment the cancer associated with a mutant IDH protein having a neomorphic activity is cholangiocarcinoma.

Another disease or disorder associated with a mutant IDH protein having R-2-HG neomorphic activity is D-2-hydroxyglutaric aciduria.

Another disease or disorder associated with a mutant IDH protein having R-2-HG neomorphic activity is Diller disease and Mafucci syndrome.

As used herein the term “neomorphic activity” refers to a gain of novel activity of a protein that the wild-type protein does not have or does not exhibit to a significant degree. For example, a neomorphic activity associated with a mutant form of IDH1 and IDH2 is the ability to reduce alpha-ketoglutarate to 2-hydroxyglutarate (i.e. 2-HG, specifically R-2-HG). The wild type form of IDH1 and IDH2 does not have the ability to reduce alpha-ketoglutarate to 2-hydroxyglutarate (i.e. 2-HG, specifically R-2-HG) or if it does have this ability, it does not produce significant (i.e. harmful or disease causing) amounts of 2-HG.

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 “therapeutically effective amount” in reference to a compound of the invention means an amount of the compound sufficient to treat the subject’s disease or condition, but low enough to avoid serious sides effects (at a reasonable benefit/risk ratio) within the scope of sound medical judgment. A therapeutically effective amount of a compound will vary with the particular compound chosen (e.g. consider the potency, efficacy, and half-life of the compound); the route of administration chosen; the condition being treated; the severity of the condition being treated; the age, size, weight, and physical condition of the subject being treated; the medical history of the subject being treated; the duration of the treatment; the nature of the concurrent therapy; the desired therapeutic effect; and like factors and can be routinely determined by the skilled artisan.

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.

The compounds of the present invention may be administered by any suitable route including oral and parenteral administration. Parenteral administration is typically by injection or infusion and includes intravenous, intramuscular, and subcontaneous injection or infusion.

The compounds of the invention may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound of the invention depend on the pharmacokinetic properties of that compound, such as absorption, distribution and half life which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound of the invention depend on the disease or condition being treated, the severity of the disease or condition, the age and physical condition of the subject being treated, the medical history of the subject being treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing regimens may require adjustment given an individual subject’s response to the dosing regimen or over time as the individual subject needs change. Typical daily dosages may vary depending upon the particular route of administration chosen. Typical daily dosages for oral administration, to a human weighing approximately 70kg would range from about 5mg to about 500mg of a compound of formula (I).

One embodiment of the present invention provides for a method of treating a disease or disorder associated with a mutant form of IDH having a neomorphic activity comprising administration of a therapeutically effective amount of a compound of formula (I) to a subject in need of treatment thereof. In one embodiment, the disease or disorder associated with a mutant form of IDH having a neomorphic activity is a cell proliferation disorder. In another embodiment, the cell proliferation disorder is cancer. In another embodiment, the cancer is a cancer associated with mutant IDH1 having 2-HG neomorphic activity or mutant IDH2 having 2-HG neomorphic activity. In another embodiment the neomorphic activity is R-2-HG neomorphic activity. In another

embodiment the cancer is associated with mutant IDH1 having 2-HG or R-2-HG neomorphic activity having a mutation at residues 97, 100, or 132, such as G97D, R100Q, R132H, R132C, R132S, R132G, R132L, and R132V. In another embodiment the cancer is associated with mutant IDH2 having 2-HG or R-2-HG neomorphic activity having a mutation at residues 140 or 172, e.g. R140Q, R140G, R172K, R172M, R172S, R172G, and R172W. In another embodiment the cancer is brain cancer, leukemia, skin cancer, prostate cancer, thyroid cancer, colon cancer, lung cancer or sarcoma. In another embodiment the cancer is glioma, glioblastoma multiforme, paraganglioma, suprantentorial primordial neuroectodermal tumors, acute myeloid leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, melanoma, prostate, thyroid, colon, lung, central chondrosarcoma, central and periosteal chondroma tumors, fibrosarcoma, and cholangiocarcinoma.

Another embodiment of the present invention provides for a method of treating a disease or disorder associated with a mutant form of IDH having R-2-HG neomorphic activity comprising administration of a therapeutically effective amount of a compound according to formula (I) to a subject in need thereof wherein the disease or disorder is D-2-hydroxyglutaric aciduria, Ollier Disease, or Mafucci Syndrome.

Another embodiment of the present invention provides for the use of a compound of formula (I) in therapy. In a further embodiment the therapy is a disease or disorder associated with a mutant form of IDH having a neomorphic activity. In another embodiment the therapy is a cell proliferation disorder associated with a mutant form of IDH having a neomorphic activity. In another embodiment the therapy is cancer. In another embodiment the therapy is a cancer associated with a mutant IDH protein having a neomorphic activity, such as mutant IDH1 having 2-HG neomorphic activity or mutant IDH2 having 2-HG neomorphic activity. In another embodiment the neomorphic activity is R-2-HG neomorphic activity. In another embodiment the cancer is associated with mutant IDH1 having 2-HG or R-2-HG neomorphic activity having a mutation at residues 97, 100, or 132, such as G97D, R100Q, R132H, R132C, R132S, R132G, R132L, and R132V. In another embodiment the cancer is associated with mutant IDH2 having 2-HG or R-2-HG neomorphic activity having a mutation at residue at residues R140 or 172, e.g. R140Q, R140G, R172K, R172M, R172S, R172G, and R172W. In another embodiment the cancer is brain cancer, leukemia, skin cancer, prostate cancer, thyroid cancer, colon cancer, lung cancer or sarcoma. In another embodiment the cancer is glioma, glioblastoma multiforme, paraganglioma, suprantentorial primordial neuroectodermal tumors, acute myeloid leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, melanoma, prostate, thyroid, colon, lung, central

chondrosarcoma, central and periosteal chondroma tumors, fibrosarcoma, and cholangiocarcinoma.

Another embodiment of the present invention provides for the use of a compound of formula (I) in therapy wherein the therapy is D-2-hydroxyglutaric aciduria, Ollier Disease, or Mafucci Syndrome.

Another embodiment of the present invention provides for the use of a compound according to formula (I) in the manufacture of a medicament for the treatment of disease or disorder associated with a mutant form of IDH having a neomorphic activity. In one embodiment the disease or disorder associated with a mutant form of IDH having a neomorphic activity is a cell proliferation disorder. In another embodiment, the cell proliferation disorder is cancer. In another embodiment the cancer is a cancer associated with a mutant IDH protein having a neomorphic activity, such as mutant IDH1 having 2-HG neomorphic activity or mutant IDH2 having 2-HG neomorphic activity. In another embodiment the neomorphic activity is R-2-HG neomorphic activity. In another embodiment the cancer is associated with mutant IDH1 having 2-HG or R-2-HG neomorphic activity having a mutation at residues 97, 100, or 132, such as G97D, R100Q, R132H, R132C, R132S, R132G, R132L, and R132V. In another embodiment the cancer is associated with mutant IDH2 having 2-HG or R-2-HG neomorphic activity having a mutation at residue at residues 140 or 172, e.g. R140Q, R140G, R172K, R172M, R172S, R172G, and R172W. In another embodiment the cancer is brain cancer, leukemia, skin cancer, prostate cancer, thyroid cancer, colon cancer, lung cancer or sarcoma. In another embodiment the cancer is glioma, glioblastoma multiforme, paraganglioma, suprantentorial primordial neuroectodermal tumors, acute myeloid leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, melanoma, prostate, thyroid, colon, lung, central chondrosarcoma, central and periosteal chondroma tumors, fibrosarcoma, and cholangiocarcinoma.

Another embodiment of the present invention provides for the use of a compound according to formula (I) in the manufacture of a medicament for the treatment of disease or disorder associated with a mutant form of IDH having R-2-HG neomorphic activity wherein the disease or disorder is D-2-hydroxyglutaric aciduria, Ollier Disease, or Mafucci Syndrome.

Compositions

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier or excipient.

The pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein a therapeutically effective amount of a compound of the invention can be extracted and then given to a subject, such as with powders or syrups. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form wherein each physically discrete unit contains a therapeutically effective amount of a compound of the invention. When prepared in unit dosage form, the pharmaceutical compositions of the invention typically contain from about 5mg to 500mg of a compound of formula (I).

As used herein the term "pharmaceutically acceptable carrier or excipient" means a pharmaceutically acceptable material, composition or vehicle that, for example, are involved in giving form or consistency to the pharmaceutical composition. Each excipient must be compatible with the other ingredients of the pharmaceutical composition when commingled such that interactions which would substantially reduce the efficacy of the compound of the invention when administered to a subject and interactions which would result in pharmaceutical compositions that are not pharmaceutically acceptable are avoided. In addition, each excipient must, of course, be of sufficiently high purity to render it pharmaceutically acceptable.

The compound of the invention and the pharmaceutically acceptable carrier or excipient(s) will typically be formulated into a dosage form adapted for administration to the subject by the desired route of administration. For example, dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, troches, powders, syrups, elixirs, suspensions, solutions, emulsions, sachets, and cachets; and (2) parenteral administration such as sterile solutions, suspensions, and powders for reconstitution. Suitable pharmaceutically acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the carrying or transporting of the compound or compounds of the invention, once administered to the subject, from one organ or portion of the body to another organ or another portion of the body. Certain pharmaceutically acceptable excipients may be chosen for their ability to enhance patient compliance.

Suitable pharmaceutically acceptable excipients include the following types of excipients: diluents, lubricants, binders, disintegrants, fillers, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers,

sweeteners, flavoring agents, flavor masking agents, coloring agents, anti-caking agents, hemectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents.

Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically acceptable carriers and excipients in appropriate amounts for the use in the invention. In addition, there are a number of resources available to the skilled artisan, which describe pharmaceutically acceptable carriers and excipients and may be useful in selecting suitable pharmaceutically acceptable carriers and excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

In one aspect, the invention is directed to a solid oral dosage form such as a tablet or capsule comprising a therapeutically effective amount of a compound of the invention and a diluent or filler. Suitable diluents and fillers include lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives, (e.g. microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. The oral solid dosage form may further comprise a binder. Suitable binders include starch (e.g. corn starch, potato starch, and pre-gelatinized starch) gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (e.g. microcrystalline cellulose). The oral solid dosage form may further comprise a disintegrant. Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid, and sodium carboxymethyl cellulose. The oral solid dosage form may further comprise a lubricant. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate, and talc.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The composition can also be prepared to prolong or sustain the release as, for example, by coating or embedding particulate material in polymers, wax, or the like.

The compounds of the invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyrancopolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the invention may be coupled to a

class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanacrylates and cross-linked or amphipathic block copolymers of hydrogels.

In another aspect, the invention is directed to a liquid oral dosage form. Oral liquids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of a compound of the invention. Syrups can be prepared by dissolving the compound of the invention in a suitably flavored aqueous solution; while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound of the invention in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additives such as peppermint oil or other natural sweeteners or saccharin or other artificial sweeteners and the like can also be added.

In another aspect, the invention is directed to parenteral administration. Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Combinations

The compound of the present invention may be administered either simultaneously with, or before or after, one or more other therapeutic agent(s). 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 agent(s).

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 disorder associated with a mutant form of IDH. 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 excipient, 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 agent 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 disorder associated with a mutant form of IDH, 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 disorder associated with a mutant form of IDH, 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 disorder associated with a mutant form of IDH, 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 disorder associated with a mutant form of IDH, 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 disorder associated with a mutant form of IDH, 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 disorder associated with a mutant form of IDH, 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 disorder associated with a mutant form of IDH, 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 disorder associated with a mutant form of IDH, wherein the patient has previously (*e.g.* within 24 hours) been treated with a compound of formula (I).

In one embodiment, the other therapeutic agent is selected from: vascular endothelial growth factor (VEGF) receptor inhibitors, topoisomerase II inhibitors, smoothen inhibitors, alkylating agents, anti-tumor antibiotics, anti-metabolites, retinoids, and other cytotoxic agents.

Examples of vascular endothelial growth factor (VEGF) receptor inhibitors include, but are not limited to, bevacizumab (sold under the trademark Avastin® by Genentech/Roche), axitinib, (*N*-methyl-2-[[3-[(*E*)-2-pyridin-2-ylethenyl]-1*H*-indazol-6-yl]sulfanyl]benzamide, also known as AG013736, and described in PCT Publication No. WO 01/002369), Brivanib Alaninate ((*S*)-((*R*)-1-(4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate, also known as BMS-582664), motesanib (N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide, and described in PCT Publication No. WO 02/066470), pasireotide (also known as SOM230, and described in PCT Publication No. WO 02/010192), and sorafenib (sold under the tradename Nexavar®).

Examples of topoisomerase II inhibitors, include but are not limited to, etoposide (also known as VP-16 and Etoposide phosphate, sold under the tradenames Toposar®, VePesid® and Etopophos®), and teniposide (also known as VM-26, sold under the tradename Vumon®).

Examples of alkylating agents, include but are not limited to, temozolomide (sold under the tradenames Temodar® and Temodal® by Schering-Plough/Merck), dactinomycin (also known as actinomycin-D and sold under the tradename Cosmegen®), melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, sold under the tradename Alkeran®), altretamine (also known as hexamethylmelamine (HMM), sold under the tradename Hexalen®), carmustine (sold under the tradename BiCNU®), bendamustine (sold under the tradename Treanda®),

busulfan (sold under the tradenames Busulfex® and Myleran®), carboplatin (sold under the tradename Paraplatin®), lomustine (also known as CCNU, sold under the tradename CeeNU®), cisplatin (also known as CDDP, sold under the tradenames Platinol® and Platinol®-AQ), chlorambucil (sold under the tradename Leukeran®), cyclophosphamide (sold under the tradenames Cytoxan® and Neosar®), dacarbazine (also known as DTIC, DIC and imidazole carboxamide, sold under the tradename DTIC-Dome®), altretamine (also known as hexamethylmelamine (HMM) sold under the tradename Hexalen®), ifosfamide (sold under the tradename Ifex®), procarbazine (sold under the tradename Matulane®), mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, sold under the tradename Mustargen®), streptozocin (sold under the tradename Zanosar®), thiotepa (also known as thiophosphoamide, TESPA and TSPA, and sold under the tradename Thioplex®.

Examples of anti-tumor antibiotics include, but are not limited to, doxorubicin (sold under the tradenames Adriamycin® and Rubex®), bleomycin (sold under the tradename lenoxane®), daunorubicin (also known as dauorubicin hydrochloride, daunomycin, and rubidomycin hydrochloride, sold under the tradename Cerubidine®), daunorubicin liposomal (daunorubicin citrate liposome, sold under the tradename DaunoXome®), mitoxantrone (also known as DHAD, sold under the tradename Novantrone®), epirubicin (sold under the tradename Ellence™), idarubicin (sold under the tradenames Idamycin®, Idamycin PFS®), and mitomycin C (sold under the tradename Mutamycin®).

Examples of anti-metabolites include, but are not limited to, claribine (2-chlorodeoxyadenosine, sold under the tradename leustatin®), 5-fluorouracil (sold under the tradename Adrucil®), 6-thioguanine (sold under the tradename Purinethol®), pemetrexed (sold under the tradename Alimta®), cytarabine (also known as arabinosylcytosine (Ara-C), sold under the tradename Cytosar-U®), cytarabine liposomal (also known as Liposomal Ara-C, sold under the tradename DepoCyt™), decitabine (sold under the tradename Dacogen®), hydroxyurea (sold under the tradenames Hydrea®, Droxia™ and Mylocel™), fludarabine (sold under the tradename Fludara®), floxuridine (sold under the tradename FUDR®), cladribine (also known as 2-chlorodeoxyadenosine (2-CdA) sold under the tradename Leustatin™), methotrexate (also known as amethopterin, methotrexate sodim (MTX), sold under the tradenames Rheumatrex® and Trexall™), and pentostatin (sold under the tradename Nipent®).

Examples of retinoids include, but are not limited to, alitretinoin (sold under the tradename Panretin®), tretinoin (all-*trans* retinoic acid, also known as ATRA, sold under the tradename Vesanoid®), Isotretinoin (13-*cis*-retinoic acid, sold under the tradenames Accutane®, Amnesteem®, Claravis®, Clarus®, Decutan®, Isotane®, Izotech®,

Oratane®, Isotret®, and Sotret®), and bexarotene (sold under the tradename Targretin®).

Examples of other cytotoxic agents include, but are not limited to, arsenic trioxide (sold under the tradename Trisenox®), asparaginase (also known as L-asparaginase, and Erwinia L-asparaginase, sold under the tradenames Elspar® and Kidrolase®).

Intermediates and Examples

The following examples are intended to be illustrative only and not limiting in any way. Unless otherwise noted, the following Intermediates and Examples were purified vial silica gel column chromatograph using RediSep® Rf columns from Teledyne Isco, Inc. Abbreviations used are those conventional in the art or the following:

ACN acetonitrial
BSA bovine serum albumin
C Celsius
CDI 1,1'-carbonyldiimidazole
d doublet
dd doublet of doublets
DAST diethylaminosulfur trifluoride
DEAD diethyl azodicarboxylate
DIPEA NN-diisopropylethylamine
DMF N,N-dimethylformamide
DMSO dimethylsulfoxide
DTT dithiothreitol
EtOAc ethyl acetate
EtOH ethanol
g gram
h hour(s)HATU 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HEPES 4-(2-hydroxyethyl)-1-piperazineethylanesulfonic acid
HPLC high pressure liquid chromatography
Hunig's Base NN-diisopropylethylamine
kg kilogram
L liter
LC liquid chromatographyLCMS liquid chromatography and mass spectrometry
MeOH methanol
MS mass spectrometry
m multiplet

min minutes
mL milliliter(s)
µM micromolar
m/z mass to charge ratio
nm nanometer
nM nanomolar
N normal
NADPH nicotinamide adenine dinucleotide phosphate
NMP N-methylpyrrolidone
NMR nuclear magnetic resonance
$PdCl_2(dppf).CH_2Cl_2$ 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex
pTsOH p-toluenesulfonic acid
rac racemic
Rt retention time
s singlet
sat. saturated
t triplet
TBTU O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TCEP tris(2-carboxyethyl)phosphine
TEA triethylamine
TFA trifluoroacetic acid
THF tetrahydrofuran
TLC thin layer chromatography
TMS-CN trimethylsilyl cyanide

Instrumentation

LCMS:

LCMS data (also reported herein as simply MS) were recorded using a Waters System (Acuity UPLC and a Micromass ZQ mass spectrometer; Column: Acuity HSS C18 1.8-micron, 2.1 x 50 mm; gradient: 5-95 % acetonitrile in water with 0.05 % TFA over a 1.8 min period; flow rate 1.2 mL/min; molecular weight range 200-1500; cone Voltage 20 V; column temperature 50 °C). All masses reported are those of the protonated parent ions unless recorded otherwise.

High Resolution Mass Spectrometry (HRMS):

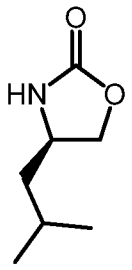
HRMS Method A: ESI-MS data were recorded using a Synapt G2 HDMS (TOF mass spectrometer, Waters) with electrospray ionization source. The resolution of the MS system was approximately 15000. Leucine Enkephalin was used as lock mass (internal standards) infused from lockspary probe. The compound was infused into the mass spectrometer by UPLC (Acquity, Waters) from sample probe. The separation was performed on Acquity UPLC BEH C18 1x50 mm column at 0.2 mL/min flow rate with the gradient from 5% to 95% in 3 min. Solvent A was Water with 0.1% Formic Acid and solvent B was Acetonitrile with 0.1% Formic Acid. The mass accuracy of the system has been found to be <5 ppm with lock mass.

HRMS Method B: LC-MS/ESI-MS data were recorded on an Acquity G2 Xevo QTof - Rs(FWHM) > 20000 Accuracy < 5 ppm. The separation was performed on Acquity CSH 1.7µm 2.1x50mm - 50°C column Eluent A: Water + 3.75 mM ammonium acetate. Eluent B: Acetonitrile. Gradient: from 2 to 98% B in 4.4 min - flow 1.0 mL/min.

HRMS methods A and B are referred to throughout as HRMS(A) or HRMS(B), respectively.

Intermediates

Intermediate A: (*R*)-4-isobutyloxazolidin-2-one

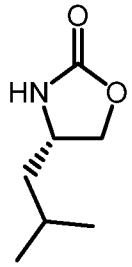
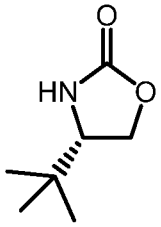
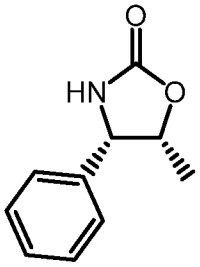
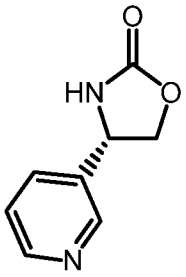
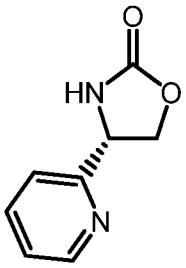
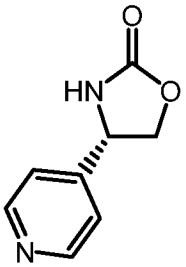
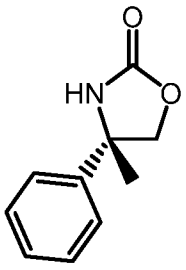
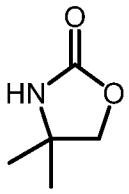
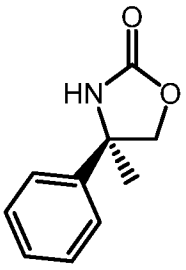


To a cooled (4 °C) solution of (*R*)-2-amino-4-methylpentan-1-ol (2.98 g, 25.4 mmol) and triethylamine (7.6 mL, 54 mmol, 2.1 equiv) in CH_2Cl_2 (80 mL) was added dropwise a solution of triphosgene (2.52g, 8.49 mmol, 0.334 equiv) in 10 ml of CH_2Cl_2 over 30 min. The reaction mixture was stirred at 4 °C for 15 min, warmed up to room temperature and stirred for an additional 1 h. The mixture was treated with saturated NH_4Cl (25 mL), followed by CH_2Cl_2 (50 mL) and the resulting mixture was stirred for 20 min. The layers were separated and the organic layer was washed with water. The combined aqueous layers were extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried

over Na_2SO_4, filtered and concentrated to give (*R*)-4-isobutyloxazolidin-2-one (3.22 g) in 88% yield. The crude product was used for the next reaction without purification. ^{1}H NMR (400 MHz, CD_3OD) δ 4.53 – 4.47 (m, 1 H), 4.00 – 3.92 (m, 2 H), 1.67 (ddq, J = 13, 8.0, 6.5 Hz, 1 H), 1.56 – 1.48 (m, 1 H), 1.40 – 1.32 (m, 1 H), 0.95 (d, J = 6.1 Hz, 3 H), 0.93 (d, J = 6.1 Hz, 3 H).

The Intermediates in Table 1 were prepared by a method similar to the one described for the preparation of Intermediate A.

Table 1.

Intermediate B	Intermediate C	Intermediate D
		
Intermediate E	Intermediate F	Intermediate G
		
Intermediate H	Intermediate I	Intermediate J
		
Intermediate K	Intermediate L	

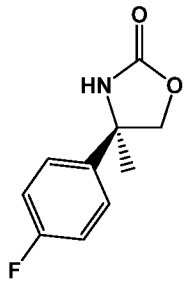
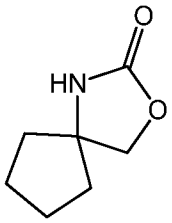
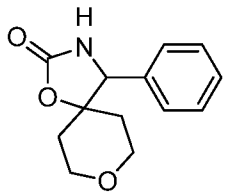
		

Table 2. Chemical name, NMR chemical shifts and LCMS signal for each intermediate listed in Table 1.

Intermediate: Name	^{1}H NMR **(400 MHz)** δ **ppm**	**LCMS**
B: (*S*)-4-isobutyloxazolidin-2-one	($CDCl_3$) 6.59 (br s, 1 H), 4.53 – 4.48 (m, 1 H), 4.01 – 3.92 (m, 2 H), 1.71 – 1.54 (m, 2 H), 1.42 – 1.35 (m, 1 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H).	no UV signal
C: (*S*)-4-tert-butyloxazolidin-2-one	(CD_3OD) 4.37 (t, J = 9.1 Hz, 1 H), 4.23 (dd, J = 9.1, 5.6 Hz, 1 H), 3.61 (dd, J = 9.1, 5.6 Hz, 1 H), 0.90 (s, 9 H)	no UV signal
D: (4S,5R)-5-methyl-4-phenyloxazolidin-2-one	(CD_3OD) δ 7.42 – 7.32 (m, 3 H), 7.27 – 7.24 (m, 2 H), 5.05 (dq, J = 8.0, 6.4 Hz, 1 H), 4.98 (d, J = 8.0 Hz, 1 H), 0.89 (d, J = 6.5 Hz, 3 H)	no UV signal
E: (*S*)-4-(pyridin-3-yl)oxazolidin-2-one		MS *m/z* 165.1 $(M + H)^+$
F: (*S*)-4-(pyridin-2-yl)oxazolidin-2-one	($CDCl_3$) 8.62 (dt, J = 5.4, 1.1 Hz, 1 H), 7.80 (td, J = 7.8, 1.5 Hz, 1 H), 7.45 (d, J = 7.5 Hz, 1 H), 7.33 – 7.28 (m, 1 H), 6.40 (br s, 1 H), 5.12 (dd, J = 8.8, 5.8 Hz, 1 H), 4.86 (t, J = 9.0 Hz, 1 H), 4.43 (dd, J = 8.5, 5.5 Hz, 1 H)	HRMS(B) *m/z* 165.0663 $(M + H)^+$
G: (S)-4-(pyridin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.67 – 8.66 (m, 2 H), 7.36 – 7.34 (m, 2 H), 6.50 (br s, 1 H), 5.04 – 5.00 (m, 1 H), 4.80 (t, J = 8.8 Hz, 1 H), 4.16 (dd, J = 8.5, 6.5 Hz, 1 H)	HRMS(B) *m/z* 165.0664 $(M + H)^+$
H: (*S*)-4-methyl-4-phenyloxazolidin-2-one	($CDCl_3$) 7.45 – 7.33 (m, 5 H), 6.10 (br s, 1 H), 4.39 (q, J = 8.4 Hz, 2 H), 1.79 (s, 3 H)	HRMS(B) *m/z* 178.0871 $(M + H)^+$
I: 4,4-dimethyloxazolidin-2-one	($CDCl_3$) 4.96 (br s, 1 H), 4.12 (s, 2 H), 1.40 (s, 6 H)	no UV signal
J: (*S*)-4-methyl-4-phenyloxazolidin-2-one	($CDCl_3$) 7.33 – 7.19 (m, 5 H), 6.86 (br s, 1 H), 4.32 – 4.27 (m, 2 H), 1.67 (s, 3 H)	MS *m/z* 177.9 $(M + H)^+$
K: (R)-4-(4-fluorophenyl)-4-methyloxazolidin-2-one	($CDCl_3$) δ 7.41 – 7.36 (m, 2 H), 7.14 – 7.08 (m, 2 H), 6.06 (br s, 1 H), 4.39 (d, J = 8.3 Hz, 1 H), 4.33 (d, J = 8.3 Hz, 1 H), 1.78 (s, 3 H)	MS m/z 195.9 (M + H)+

L: 3-oxa-1-azaspiro[4.4]nonan-2-one	($CDCl_3$) δ 5.62 (br s, 1 H), 4.25 (s, 2 H), 1.90 – 1.65 (m, 8 H)	no UV signal

Intermediate M: 4-phenyl-1,8-dioxa-3-azaspiro[4.5]decan-2-one



Step 1: Preparation of 4-(amino(phenyl)methyl)tetrahydro-2H-pyran-4-ol

To dihydro-2H-pyran-4(3H)-one (1001 mg, 10 mmol) and triethylamine (0.279 mL, 2.00 mmol) was slowly added TMS-CN (1190 mg, 12.00 mmol) [Caution: exothermic reaction]. After stirring for 1hour, the mixture was concentrated under reduced pressure. The residue, dissolved in diethyl ether (10 mL), was added dropwise to phenylmagnesium bromide (3M solution in diethyl ether, 4.33 mL, 13.00 mmol). Additional ~5 mL of diethyl ether was added and the suspension was stirred for ~4 hour. To the reaction mixture was added very slowly MeOH (3.0 mL), followed by the careful and slow additions of $NaBH_4$ (454 mg, 12.00 mmol) and MeOH (12 mL) in portions (gas development observed). The reaction mixture was stirred overnight and water (~6 mL) was added carefully, followed by 10% aqueous HCl solution (~20 mL). The mixture was vigrously stirred for 4 hour and diethyl ether was added. The separated organic layer was extracted with 10% aqueous HCl solution (1x ~20 mL). The combined aqueous layers were washed with diethylether (2x). The acidic layers were made basic by the addition of 6N aqueous NaOH solution. The milky white mixture was extracted with DCM (1x), ethyl acetate/THF (1:1; 1x) and ethyl acetate (2x). The organic layers (DCM and ethyl acetate solutions independently) were washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, filtered off and concentrated under reduced pressure providing crude 4-(amino(phenyl)methyl)tetrahydro-2H-pyran-4-ol, which was directly used in the next reaction without further purification.

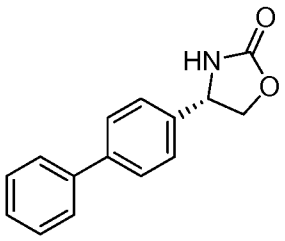
Yellowish liquid. Yield: 451 mg. LCMS *m/z* 208.2 $(M + H)^+$, Rt 0.29 min.

Step 2: Preparation of 4-phenyl-1,8-dioxa-3-azaspiro[4.5]decan-2-one

To a mixture of CDI (388 mg, 2.394 mmol) in THF (1.5 mL) was added slowly a solution of 4-(amino(phenyl)methyl)tetrahydro-2H-pyran-4-ol (451 mg, 2.176 mmol) in THF (3 mL). The mixture was stirred under argon for ~5 hours. The mixture was diluted with saturated aqueous $NaHCO_3$ solution and DCM. The separated aqueous layer was extracted with DCM (2x) and the combined organic layers were washed with 0.5N

aqueous HCl solution and brine, dried over sodium sulfate, filtered off and concentrated under reduced pressure. The residue was purified by column chromatography [SiO_2, 12 g, 0 - 100% heptane/ethyl acetate] providing 4-phenyl-1,8-dioxa-3-azaspiro[4.5]decan-2-one as a white solid. Yield: 330 mg. LCMS *m/z* 234.1 $(M + H)^+$; Rt 0.52 min.

Intermediate N: (S)-4-(biphenyl-4-yl)oxazolidin-2-one



Step 1: Preparation of vinylbiphenyl

To a suspension of methyltriphenylphosphonium bromide (5.10 g, 14.27 mmol) in THF (26 mL) was slowly added potassium tert-butoxide (1M solution in THF, 14.27 mL) over ~20 min at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 10 min. The mixture was cooled to 0°C and a solution of 4-biphenylcarbaldehyde (2.0 g, 10.98 mmol) in THF (9 mL) was added over 20 min. The reaction mixture was allowed to warm up to room temperature and stirred for ~19 hour. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved/suspended in DCM and filtered through a silica pad and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography [SiO_2, 80 g, EtOAc/heptane] to provide vinylbiphenyl (1.845 g) as a white solid. LCMS Rt 0.79 min.

Step 2: Preparation of (S)-tert-butyl 1-(biphenyl-4-yl)-2-hydroxyethylcarbamate

To a solution of tert-butyl carbamate (2.82 g, 24.08 mmol) in 1-propanol (30 mL) was added aqueous NaOH solution (0.38M, 61.5 mL, 23.36 mmol). The mixture was stirred for 5 min and 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (2.351 g, 11.93 mmol) was added. The mixture was stirred stirred for 10 min and $(DHQ)_2PHAL$ (0.303 g, 0.388 mmol), dissolved in 1-propanol (30 mL), was added followed by a solution of vinylbiphenyl (1.4 g, 7.77 mmol) in 1-propanol (60 mL). A suspension of potassium osmate dihydrate (0.114 g, 0.311 mmol) in aqueous NaOH solution, (0.38M, 0.613 mL, 0.233 mmol) was added and the mixture was stirred for ~ 16 hours. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (2x 400 mL), dried over sodium sulfate, filtered off and concentrated under reduced pressure. The residue was purified by column

chromatography [SiO_2, 80 g, EtOAc/heptane] to provide (S)-tert-butyl 1-(biphenyl-4-yl)-2-hydroxyethylcarbamate (609 mg). LCMS *m/z* 258.2 $(M + H; \text{loss of } t\text{-Bu})^+$, Rt 0.97 min. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.62 - 7.56 (m, 4 H), 7.45 - 7.37 (m, 4 H), 7.34 - 7.2(m, 1 H), 4.69 (t, *J* = 5.8 Hz, 1 H), 3.76 - 3.63 (m, 2H), 1.44 (br. s., 9 H)

Step 3: Preparation of (S)-2-amino-2-(biphenyl-4-yl)ethanol

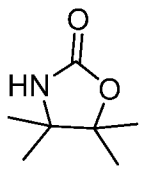
To a solution of (S)-tert-butyl 1-(biphenyl-4-yl)-2-hydroxyethylcarbamate (608 mg, 1.940 mmol) in MeOH (3 mL) was added HCl (4M in dioxane, 8 mL) at room temperature. The mixture was stirred for 1 hour and concentrated under reduced pressure. The residue was dissolved in DCM (10 mL)/water (1.0 mL) and stirred with $NaHCO_3$ for 1 hour. The mixture was filtered off and rinsed with DCM. The filtrate was dried over sodium sulfate, filtered off and concentrated under reduced pressure providing (S)-2-amino-2-(biphenyl-4-yl)ethanol (171 mg) as a white solid. LCMS *m/z* 214.2 $(M + H)^+$, Rt 0.58 min.

Step 4: Preparation of (S)-4-(biphenyl-4-yl)oxazolidin-2-one

To a solution of (S)-2-amino-2-(biphenyl-4-yl)ethanol (171 mg, 0.802 mmol) in THF (12 mL) under argon atmosphere was added CDI (132 mg, 0.814 mmol). The solution was stirred at room temperature for 2 hours. The mixture was diluted with saturated aqueous $NaHCO_3$ solution (40 mL) and extracted with EtOAc (2x 30 mL). The combined organic layers were washed with 0.5M aqueous HCl solution (30 mL), brine (40 mL), dried over sodium sulfate, filtered off and concentrated under reduced pressure. The residue was dissolved in DCM and concentrated under rduced pressure to provide crude (S)-4-(biphenyl-4-yl)oxazolidin-2-one (156 mg) as a beige solid, which was used without further purification. LCMS *m/z* 240.1 $(M + H)^+$, Rt 0.80 min.

^1H NMR (400 MHz, CD_3OD) δ ppm 4.19 (dd, *J*=8.61, 6.50 Hz, 1 H) 4.80 (t, *J*=8.73 Hz, 1 H) 5.05 (dd, *J*=8.78, 6.48 Hz, 1 H) 7.31 - 7.38 (m, 1 H) 7.39 - 7.54 (m, 4 H) 7.55 - 7.71 (m, 4 H).

Intermediate P: 4,4,5,5-tetramethyloxazolidin-2-one



Step 1: Preparation of Methyl 2-(tert-butoxycarbonylamino)-2-methylpropanoate

To a solution of 2-(tert-butoxycarbonylamino)-2-methylpropanoic acid (10.03 g, 49.4 mmol) in MeOH/DCM (60mL/140mL) at room temperature was added drop wise (trimethylsilyl)diazomethane (37.0 mL, 74.0 mmol). The reaction mixture was stirred for 30 minutes. Acetic acid was added drop wise to quench (trimethylsilyl)diazomethane. The reaction mixture was concentrated under reduced pressure to afford the desired product as a white solid (10.56 g). LCMS *m/z* 240.2 $(M + Na)^+$, Rt 0.71 min.

Step 2: Preparation of tert-butyl 3-hydroxy-2,3-dimethylbutan-2-ylcarbamate

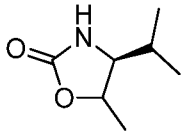
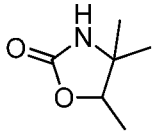
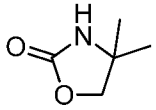
To a solution of methyl 2-(tert-butoxycarbonylamino)-2-methylpropanoate (10.56 g, 48.6 mmol) in THF (300mL) at 0 °C was added drop wise methylmagnesium bromide (64.8 mL, 194 mmol). Cold bath was removed after 1 hour. The reaction was stirred at 20 °C for 4 hours. The reaction was cooled back 0 °C and quenched with saturated NH_4Cl solution (10mL). The reaction mixture was then allowed to warm to room temperature, and diluted with EtOAc (100mL) and water (50mL). The phases were separated and the aqueous layer was extracted with EtOAc (2x100mL). The combined organics were then dried (Na_2SO_4) and concentrated. The residue was purified via silica gel flash chromatography (0-20% EtOAc-Hexanes) to afford the desired product as a white solid (9.02 g). LCMS *m/z* 240.1 $(M + Na)^+$, Rt 0.78 min.

Step 3: Preparation of 4,4,5,5-tetramethyloxazolidin-2-one

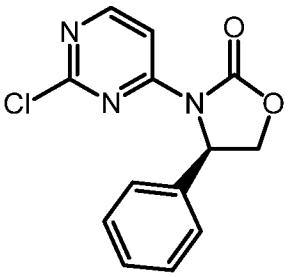
To tert-butyl 3-hydroxy-2,3-dimethylbutan-2-ylcarbamate (10.02 g, 46.1 mmol) in THF (300 ml) was added portion wise potassium 2-methylpropan-2-olate (7.24 g, 64.6 mmol). The reaction was stirred for five hours and quenched with HCl (1M, 66mL) to pH=2. The reaction mixture was then concentrated under vacuum to about one third of the volume, and diluted with water (50mL). The aqueous layer was then extracted with DCM (3x100mL). The combined organic was washed with brine (50mL), dried (Na_2SO_4) and concentrated to give crude product as a light tan oil (6.25 g). LCMS *m/z* 144.1 $(M + H)^+$, Rt 0.42 min.

The Intermediates in Table 2b were prepared by a method similar to the one described for the preparation of Intermediate P.

Table 2b.

Intermediate: Name	Structure	LCMS
Q: (4S)-4-isopropyl-5-methyloxazolidin-2-one		MS *m/z* (M + H)$^+$ 144.4, Rt 0.47 min
R: 4,4,5-trimethyloxazolidin-2-one		MS *m/z* (M + H)$^+$ 130.4, Rt 0.36 min
S: 4,4-dimethyloxazolidin-2-one		MS m/z (M + H)+ 116.0, Rt 0.28 min

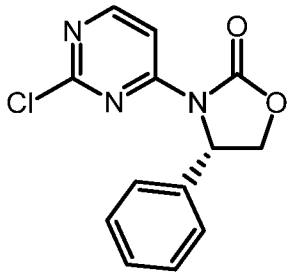
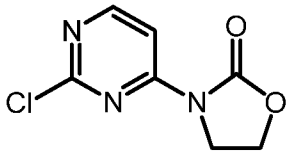
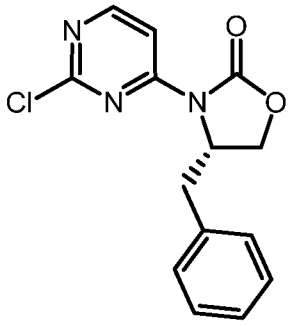
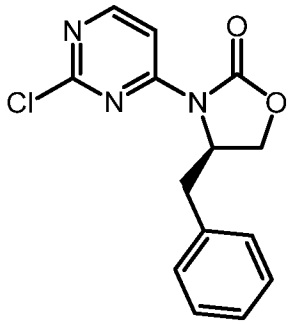
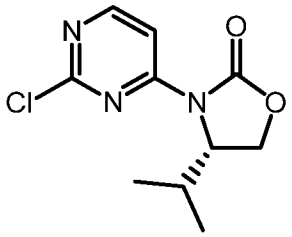
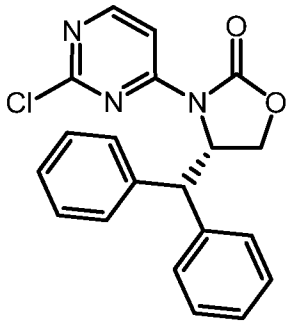
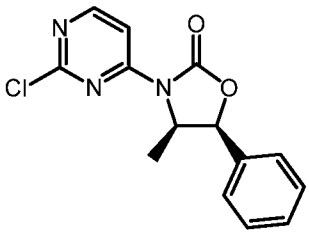
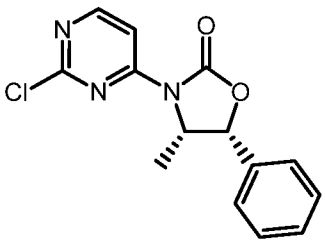
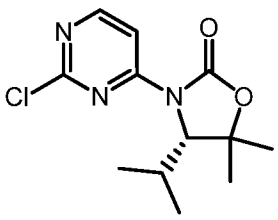
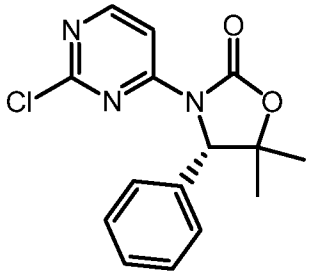
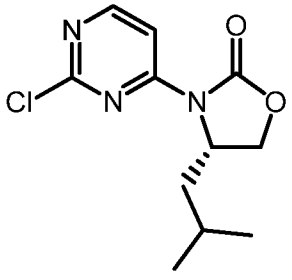
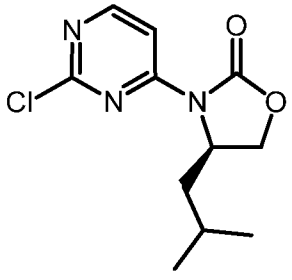
Intermediate 1: (*R*)-3-(2-chloropyrimidin-4-yl)-4-phenyloxazolidin-2-one

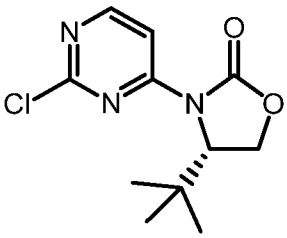
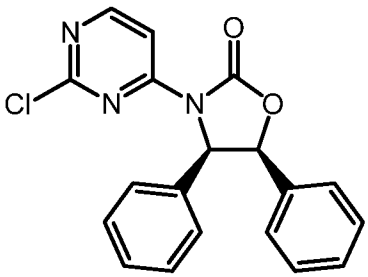
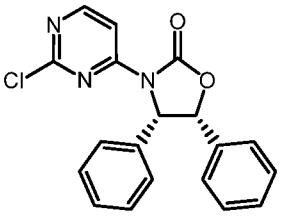
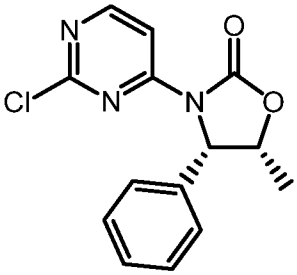
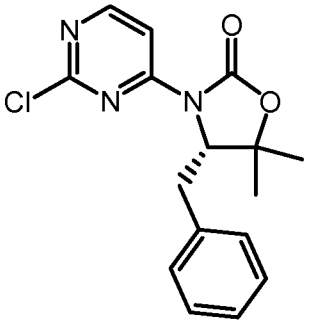
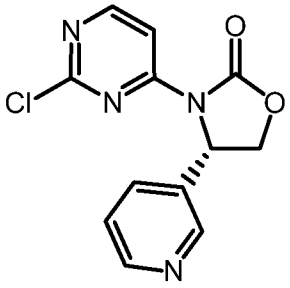
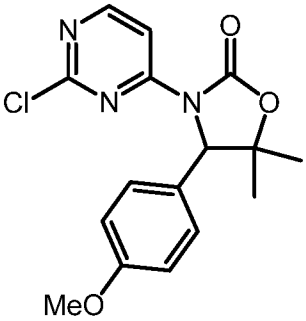
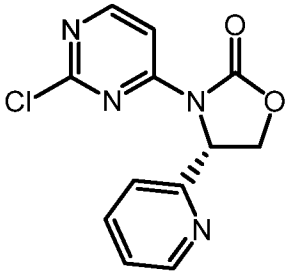
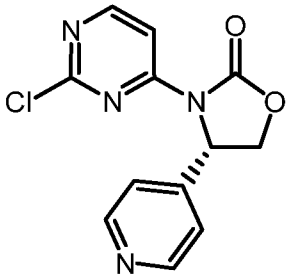
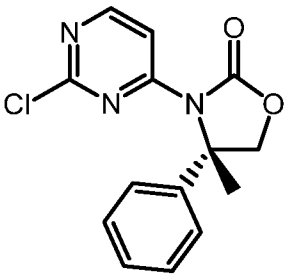
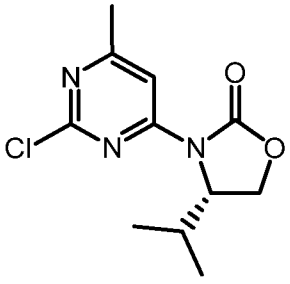
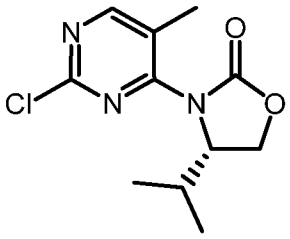


A solution of (*R*)-4-phenyloxazolidin-2-one (2.9484 g, 18.07 mmol) and 2,4-dichloropyrimidine (3.1872 g, 21.39 mmol, 1.184 equiv) in DMF (30 mL) was treated with NaH (95 %, 0.4773 g, 18.89 mmol, 1.046 equiv), then the resulting mixture (yellow to red cloudy) was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc (200 mL), washed with sat. NH_4Cl (75 mL) and 4% aqueous NaCl (2 x 100 mL), dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 0 to 40%) provided (*R*)-3-(2-chloropyrimidin-4-yl)-4-phenyloxazolidin-2-one (2.7020 g, white sticky solid) in 46.9% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (d, J = 5.6 Hz, 1 H), 8.18 (d, J = 6.1 Hz, 1 H), 7.38 – 7.30 (m, 5 H), 5.81 (dd, J = 8.6, 3.5 Hz, 1 H), 4.88 (t, J = 8.6 Hz, 1 H), 4.37 (dd, J = 8.6, 3.5 Hz, 1 H) ; MS *m/z* 276.4 (M + H)$^+$.

The Intermediates in Table 3 were prepared by a method similar to the one described for the preparation of Intermediate 1.

Table 3.

Intermediate 2	Intermediate 3	Intermediate 4
		
Intermediate 5	Intermediate 6	Intermediate 7
		
Intermediate 8	Intermediate 9	Intermediate 10
		
Intermediate 11	Intermediate 12	Intermediate 13
		
Intermediate 14	Intermediate 15	Intermediate 16

		
Intermediate 17	Intermediate 18	Intermediate 19
		
Intermediate 20	Intermediate 21	Intermediate 22
		
Intermediate 23	Intermediate 24	Intermediate 25
		
Intermediate 26	Intermediate 27	Intermediate 28

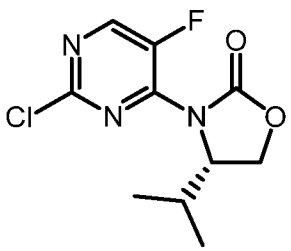
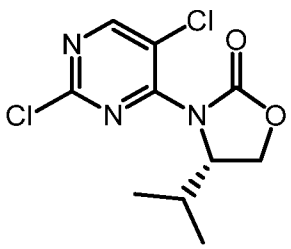
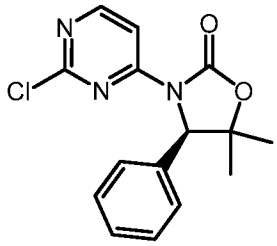
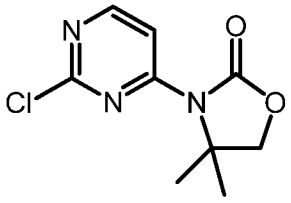
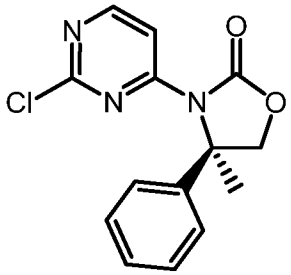
		
Intermediate 29	Intermediate 30	
		

Table 4. Chemical name, NMR chemical shifts and LCMS signal for each intermediate listed in Table 3.

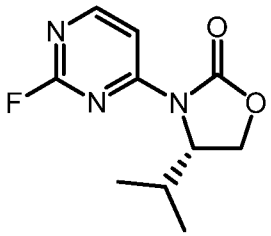
Intermediate: Name	**^{1}H NMR (400 MHz) δ ppm**	**LCMS**
2: (*S*)-3-(2-chloropyrimidin-4-yl)-4-phenyloxazolidin-2-one	($CDCl_3$) 8.47 (d, J = 6.1 Hz, 1 H), 8.18 (d, J = 5.7 Hz, 1 H), 7.39 – 7.29 (m, 5 H), 5.81 (dd, J = 8.6, 3.5 Hz, 1 H), 4.88 (t, J = 8.8 Hz, 1 H), 4.37 (dd, J = 8.8, 3.8 Hz, 1 H)	MS *m/z* 276.5 $(M + H)^+$
3: 3-(2-chloropyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 8.48 (d, J = 6.1 Hz, 1 H), 8.16 (d, J = 6.1 Hz, 1 H), 4.54 (t, J = 7.8 Hz, 2 H), 4.22 (t, J = 8.1 Hz, 2 H)	MS *m/z* 200.4 $(M + H)^+$
4: (*S*)-4-benzyl-3-(2-chloropyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 8.52 (d, J = 6.1 Hz, 1 H), 8.15 (d, J = 6.1 Hz, 1 H), 7.32 – 7.22 (m, 5 H), 5.07 – 5.02 (m, 1 H), 4.46 – 4.37 (m, 2 H), 3.30 – 3.27 (m, 1 H), 3.06 (dd, J = 13, 8.1 Hz, 1 H)	MS *m/z* 290.3 $(M + H)^+$
5: (*R*)-4-benzyl-3-(2-chloropyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 8.51 (d, J = 5.6 Hz, 1 H), 8.13 (d, J = 5.6 Hz, 1 H), 7.31 – 7.21 (m, 5 H), 5.06 – 4.98 (m, 1 H), 4.45 – 4.34 (m, 2 H), 3.30 – 3.25 (m, 1 H), 3.04 (dd, J = 14, 8.1 Hz, 1 H)	MS *m/z* 290.3 $(M + H)^+$
6: (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 8.50 (d, J = 5.9 Hz, 1 H), 8.17 (d, J = 5.8 Hz, 1 H), 4.83 – 4.76 (m, 1 H), 4.48 – 4.43 (m, 2 H), 2.56 (dtd, J = 14, 7.0, 3.8 Hz, 1 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.87 (d, J = 7.1 Hz, 3 H)	MS *m/z* 242.6 $(M + H)^+$
7: (*S*)-4-benzhydryl-3-(2-chloropyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 8.41 (d, J = 5.8 Hz, 1 H), 8.01 (d, J = 5.8 Hz, 1 H), 7.35 – 7.26 (m, 3 H), 7.24 – 7.12 (m, 7 H), 5.86 – 5.70 (m, 1 H), 4.74 (d, J = 7.1 Hz, 1 H),	MS *m/z* 366.1 $(M + H)^+$

	4.64 (t, J = 8.5 Hz, 1 H), 4.45 (dd, J = 9.1, 2.0 Hz, 1 H)	
8: (*4R,5S*)-3-(2-chloropyrimidin-4-yl)-4-methyl-5-phenyloxazolidin-2-one	(CD_3OD) 8.52 (d, J = 6.1 Hz, 1 H), 8.20 (d, J = 6.1 Hz, 1 H), 7.48 – 7.38 (m, 5 H), 5.92 (d, J = 7.6 Hz, 1 H), 5.15 (quin, J = 6.8 Hz, 1 H), 0.98 (d, J =6.6 Hz, 3 H)	MS *m/z* 290.3 $(M + H)^+$
9: (*4S,5R*)-3-(2-chloropyrimidin-4-yl)-4-methyl-5-phenyloxazolidin-2-one	(CD_3OD) 8.52 (d, J = 6.1 Hz, 1 H), 8.20 (d, J = 6.1 Hz, 1 H), 7.48 – 7.38 (m, 5 H), 5.92 (d, J = 7.6 Hz, 1 H), 5.15 (quin, J = 6.7 Hz, 1 H), 0.98 (d, J =6.6 Hz, 3 H)	MS *m/z* 290.3 $(M + H)^+$
10: (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyl-5,5-dimethyloxazolidin-2-one	(CD_3OD) 8.48 (d, J = 5.8 Hz, 1 H), 8.20 (d, J = 5.8 Hz, 1 H), 4.63 (d, J = 3.1 Hz, 1 H), 2.29 (dtd, J = 14, 7.0, 3.1, 1 H), 1.60 (s, 3 H), 1.47 (s, 3 H), 1.05 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H)	MS *m/z* 270.1 $(M + H)^+$
11: (*S*)-3-(2-chloropyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one	(CD_3OD) 8.48 (d, J = 5.8 Hz, 1 H), 8.25 (d, J = 5.8 Hz, 1 H), 7.39 – 7.30 (m, 3 H), 7.22 (br s, 2 H), 1.67 (s, 3 H), 1.04 (s, 3 H)	MS *m/z* 304.3 $(M + H)^+$
12: (*S*)-3-(2-chloropyrimidin-4-yl)-4-isobutyloxazolidin-2-one	(CD_3OD) 8.49 (d, J = 5.9 Hz, 1 H), 8.13 (d, J = 5.9 Hz, 1 H),4.83 (ddt, J = 10, 7.6, 2.9 Hz, 1 H), 4.58 – 4.54 (m, 1 H), 4.31 (dd, J = 8.8, 2.8 Hz, 1 H), 1.87 – 1.81 (m, 1 H), 1.75 – 1.65 (m, 1 H), 1.62 – 1.55 (m, 1 H), 1.05 (d, J = 6.5 Hz, 3 H), 0.99 (d, J = 6.5 Hz, 3 H)	MS *m/z* 256.3 $(M + H)^+$
13: (*R*)-3-(2-chloropyrimidin-4-yl)-4-isobutyloxazolidin-2-one	(CD_3OD) 8.48 (d, J = 5.8 Hz, 1 H), 8.12 (d, J = 6.0 Hz, 1 H),4.87 – 4.79 (m, 1 H), 4.57 (t, J = 8.6 Hz, 1 H), 4.31 (dd, J = 8.6, 2.5 Hz, 1 H), 1.87 – 1.81 (m, 1 H), 1.75 – 1.65 (m, 1 H), 1.62 – 1.56 (m, 1 H), 1.05 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 3 H)	MS *m/z* 256.3 $(M + H)^+$
14: (*S*)-4-tert-butyl-3-(2-chloropyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 8.50 (d, J = 5.9 Hz, 1 H), 8.12 (d, J = 5.9 Hz, 1 H), 4.94 (dd, J = 7.6, 1.5 Hz, 1 H), 4.54 (dd, J = 9.1, 1.5 Hz, 1 H), 4.46 – 4.42 (m, 1 H), 0.95 (s, 9 H)	MS *m/z* 256.4 $(M + H)^+$
15: (*4R,5S*)-3-(2-chloropyrimidin-4-yl)-4,5-diphenyloxazolidin-2-one	(CD_3OD) 8.52 (d, J = 5.9 Hz, 1 H), 8.33 (d, J = 5.9 Hz, 1 H), 7.14 – 7.05 (m, 8 H), 6.93 – 6.91 (m, 2 H), 6.18 – 6.11 (m, 2 H)	MS *m/z* 352.4 $(M + H)^+$
16: (*4S,5R*)-3-(2-chloropyrimidin-4-yl)-4,5-diphenyloxazolidin-2-one	(CD_3OD) 8.52 (d, J = 5.9 Hz, 1 H), 8.33 (d, J = 5.9 Hz, 1 H), 7.14 – 7.05 (m, 8 H), 6.93 – 6.91 (m, 2 H), 6.18 – 6.11 (m, 2 H)	MS *m/z* 352.3 $(M + H)^+$
17: (*4S,5R*)-3-(2-chloropyrimidin-4-yl)-5-methyl-4-phenyloxazolidin-2-one	(CD_3OD) 8.47 (d, J = 5.9 Hz, 1 H), 8.25 (d, J = 5.9 Hz, 1 H), 7.40 – 7.31 (m, 3 H), 7.21 (d, J = 7.0 Hz, 2 H), 5.80 (d, J = 7.5 Hz, 1 H), 5.18 – 5.12 (m, 1 H), 1.02 (d, J = 6.5 Hz, 3 H);	MS *m/z* 290.4 $(M + H)^+$
18: (*S*)-4-benzyl-3-(2-	($CDCl_3$) 8.45 (d, J = 5.8 Hz, 1 H), 8.16	MS *m/z*

chloropyrimidin-4-yl)-5,5-dimethyloxazolidin-2-one	(d, J = 5.8 Hz, 1 H), 7.37 – 7.28 (m, 4 H), 7.25 – 7.21 (m, 1 H), 4.87 (dd, J = 9.0, 4.5 Hz, 1 H), 3.24 (dd, J = 15, 4.5 Hz, 1 H), 2.97 (dd, J = 14, 9.0 Hz, 1 H), 1.51 (s, 3 H), 1.45 (s, 3 H)	318.1 (M + H)$^+$
19: (*S*)-3-(2-chloropyrimidin-4-yl)-4-(pyridin-3-yl)oxazolidin-2-one	($CDCl_3$) 8.76 – 8.75 (m, 1 H), 8.62 (d, J = 3.5 Hz, 1 H), 8.47 (d, J = 5.8 Hz, 1 H), 8.16 (d, J = 5.8 Hz, 1 H), 7.74 (dt, J = 8.0, 2.0 Hz, 1 H), 7.35 (dd, J = 7.8, 4.8 Hz, 1 H), 5.83 (dd, J = 8.8, 3.8 Hz, 1 H), 4.90 (t, J = 9.0 Hz, 1 H), 4.50 (dd, J = 9.0, 3.5 Hz, 1 H)	MS *m/z* 277.4 (M + H)$^+$
20: 3-(2-chloropyrimidin-4-yl)-4-(4-methoxyphenyl)-5,5-dimethyloxazolidin-2-one	($CDCl_3$) 8.44 (d, J = 5.8 Hz, 1 H), 8.25 (d, J = 5.8 Hz, 1 H), 7.13 (br d, J = 7.0 Hz, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 5.39 (s, 1 H), 3.82 (s, 3 H), 1.67 (s, 3 H), 1.11 (s, 3 H)	HRMS(B) *m/z* 334.0954 (M + H)$^+$
21: (*S*)-3-(2-chloropyrimidin-4-yl)-4-(pyridin-2-yl)oxazolidin-2-one	($CDCl_3$) 8.62 – 8.60 (m, 1 H), 8.45 (d, J = 5.8 Hz, 1 H), 8.22 (d, J = 5.8 Hz, 1 H), 7.73 (td, J = 7.7, 1.8 Hz, 1 H), 7.43 (d, J = 7.5 Hz, 1 H), 7.29 – 7.26 (m, 1 H), 5.85 (dd, J = 8.5, 3.5 Hz, 1 H), 4.82 (t, J = 8.8 Hz, 1 H), 4.64 (dd, J = 8.8, 3.8 Hz, 1 H)	MS *m/z* 277.0 (M + H)$^+$
22: (*S*)-3-(2-chloropyrimidin-4-yl)-4-(pyridin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.72 – 8.70 (m, 1 H), 8.52 (d, J = 5.8 Hz, 1 H), 8.20 (d, J = 5.8 Hz, 1 H), 7.43 – 7.42 (m, 1 H), 5.81 (dd, J = 8.8, 3.8 Hz, 1 H), 4.91 (t, J = 9.0 Hz, 1 H), 4.44 (dd, J = 9.3, 3.8 Hz, 1 H)	MS *m/z* 276.9 (M + H)$^+$
23: (*S*)-3-(2-chloropyrimidin-4-yl)-4-methyl-4-phenyloxazolidin-2-one	($CDCl_3$) 8.44 (d, J = 5.8 Hz, 1 H), 8.13 (d, J = 5.8 Hz, 1 H), 7.41 – 7.28 (m, 5 H), 4.46 (d, J = 8.5 Hz, 1 H), 4.38 (d, J = 8.5 Hz, 1 H), 2.23 (s, 3 H)	MS *m/z* 289.9 (M + H)$^+$
24: (*S*)-3-(2-chloro-6-methylpyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) 8.06 (s, 1 H), 4.83 – 4.77 (m, 1 H), 4.44 – 4.34 (m, 2 H), 2.65 – 2.55 (m, 1 H), 2.53 (s, 3 H), 1.00 (d, J = 8 Hz, 3 H), 0.88 (d, J = 8 Hz, 3 H)	MS *m/z* 255.8 (M + H)$^+$
25: (*S*)-3-(2-chloro-5-methylpyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) 8.50 (s, 1 H), 5.01 – 4.96 (m, 1 H), 4.53 (t, J = 9.0 Hz, 1 H), 4.28 (t, J = 8.8 Hz, 1 H), 2.35 (s, 3 H), 2.16 (td, J = 7.0 Hz, J = 4.5 Hz, 1 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H)	MS *m/z* 255.9 (M + H)$^+$
26: (*S*)-3-(2-chloro-5-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO-d_6) 8.95 (d, J = 3.0 Hz, 1 H), 4.79 – 4.73 (m, 1 H), 4.58 (t, J = 9.0 Hz, 1 H), 4.41 (dd, J = 8.5 Hz, J = 6.5 Hz, 1 H), 2.24 – 2.16 (m, 1 H), 0.86 (d, J = 7.0 Hz, 3 H), 0.78 (d, J = 6.5 Hz, 3 H)	MS *m/z* 259.9 (M + H)$^+$
27: (*S*)-3-(2,5-dichloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO-d_6) 9.01 (s, 1 H), 4.81 (ddd, J = 9.1 Hz, J = 7.8 Hz, J = 4.3 Hz, 1 H), 4.59 (t, J = 8.8 Hz, 1 H), 4.38 – 4.33 (m, 1H), 2.06 (td, J = 7.0 Hz, J = 4.3 Hz, 1 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.78 (d, J = 6.8 Hz, 3 H)	MS *m/z* 274.2 (M - H)$^-$
28: (*R*)-3-(2-chloropyrimidin-4-	($CDCl_3$) 8.20 (d, J = 5.8 Hz, 1 H), 8.01	MS *m/z*

yl)-5,5-dimethyl-4-phenyloxazolidin-2-one	(d, J = 5.8 Hz, 1 H), 7.16 – 7.07 (m, 3 H), 6.98 – 6.96 (m, 2 H), 5.19 (s, 1 H), 1.46 (s, 3 H), 0.87 (s, 3 H)	303.9 (M + H)$^+$
29: 3-(2-chloropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	($CDCl_3$) 8.47 (d, J = 5. 8 Hz, 1 H), 8.06 (d, J = 5.8 Hz, 1 H), 4.17 (s, 2 H), 1.77 (s, 6 H)	MS *m/z* 228.3 (M + H)$^+$
30: (*R*)-3-(2-chloropyrimidin-4-yl)-4-methyl-4-phenyloxazolidin-2-one	($CDCl_3$) 8.43 (d, J = 5.8 Hz, 1 H), 8.13 (d, J = 5.8 Hz, 1 H), 7.40 – 7.36 (m, 4 H), 7.35 – 7.28 (m, 1 H), 4.45 (d, J = 8.6 Hz, 1 H), 4.38 (d, J = 8.6 Hz, 1 H), 2.22 (s, 3 H)	MS *m/z* 289.9 (M + H)$^+$

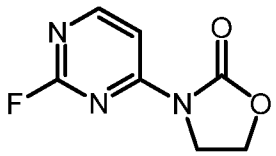
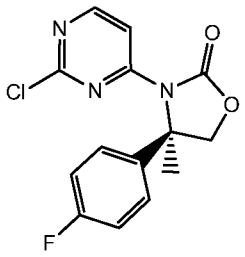
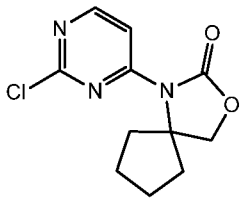
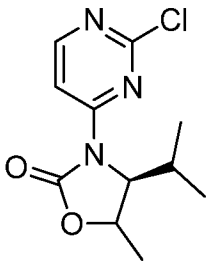
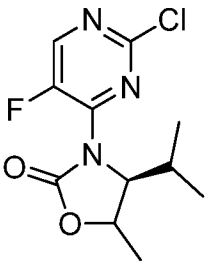
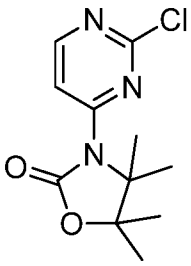
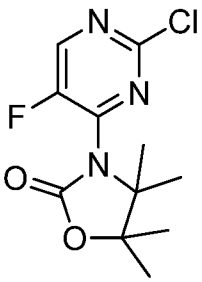
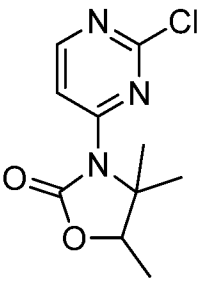
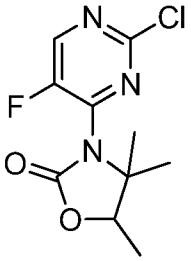
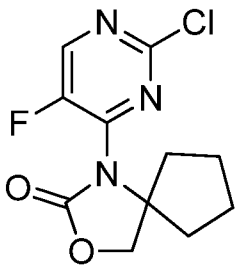
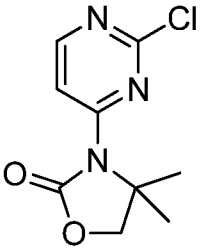
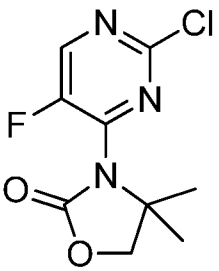
Intermediate 31: (S)-3-(2-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one



A solution of 2,4-difluoropyrimidine (3.5 mL, 41 mmol) and (S)-4-isopropyloxazolidin-2-one (5.3 g 41 mmol) in 30 mL DMF was cooled to 0 °C under N_2 atmosphere. NaH (2.1 g of 60% suspension, 53 mmol) was slowly added. Bubbling exotherm observed. Internal temp was kept below 5 °C. After 5 minutes, cold bath was removed. Reaction mixture (a sandy suspension) was allowed to warm to room temp and stir 18 h. The reaction mixture was diluted with water (100 mL) and extracted with (3 x 75 mL) EtOAc. Organic layer was washed with 50 mL each water, and brine. Dried over Na_2SO_4, and concentrated on silica gel in vacuo. Column chromatography (EtOAc/heptane 10 to 100% gradient) gave 3.1 g (S)-3-(2-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (IV) as a crystalline white solid (33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, J = 5.8, 2.2 Hz, 1H), 8.19 (dd, J = 5.8, 3.8 Hz, 1H), 4.79 (dt, J = 8.1, 3.5 Hz, 1H), 4.48 – 4.34 (m, 2H), 2.64 (heptd, J = 7.0, 3.6 Hz, 1H), 1.01 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H). MS m/z 471.8 and 471.8 (M + H)+.

The Intermediates in Table 4b were prepared by a method similar to the one described for the preparation of Intermediate 1 and 31.

Table 4b.

Intermediate 32	Intermediate 33	Intermediate 34
		
Intermediate 35	Intermediate 36	Intermediate 37
		
Intermediate 38	Intermediate 39	Intermediate 40
		
Intermediate 41	Intermediate 42	Intermediate 43
		
Intermediate 44		

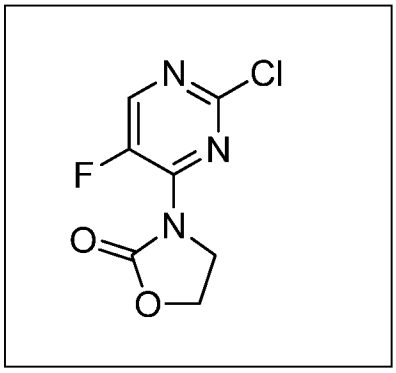
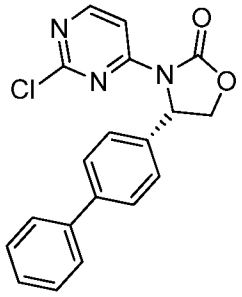


Table 4c. Chemical name, NMR chemical shifts and LCMS signal for each intermediate listed in Table 4b.

Intermediate: Name	**^{1}H NMR (400 MHz) δ ppm**	**LCMS**
32: 3-(2-fluoropyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.51 (dd, J = 5.8, 2.0 Hz, 1 H), 8.17 (dd, J = 5.8, 2.0 Hz, 1 H), 4.61 - 4.57 (m, 2 H), 4.31 - 4.27 (m, 2 H)	MS *m/z* 184.0 (M + H)
33: (R)-3-(2-chloropyrimidin-4-yl)-4-(4-fluorophenyl)-4-methyloxazolidin-2-one	($CDCl_3$) 8.45 (d, J = 5.8 Hz, 1 H), 8.12 (d, J = 5.8 Hz, 1 H), 7.40 – 7.35 (m, 2 H), 7.10 – 7.04 (m, 2 H), 4.40 – 4.37 (m, 2 H), 2.22 (s, 3 H)	MS m/z 308.0 (M + H)+
34: 1-(2-chloropyrimidin-4-yl)-3-oxa-1-azaspiro[4.4]nonan-2-one	($CDCl_3$) 8.48 (d, J = 5.8 Hz, 1 H), 8.12 (d, J = 5.8 Hz, 1 H), 4.22 (s, 2 H), 2.66 – 2.59 (m, 2 H), 2.22 – 2.14 (m, 2 H), 1.75 – 1.62 (m, 4 H)	MS m/z 254.1 (M + H)+
35: (4S)-3-(2-chloropyrimidin-4-yl)-4-isopropyl-5-methyloxazolidin-2-one		MS m/z (M + H)+ 256.2, Rt 0.87 min
36: (4S)-3-(2-chloro-5-fluoropyrimidin-4-yl)-4-isopropyl-5-methyloxazolidin-2-one		MS m/z (M + H)+ 274.1, Rt 0.82 min
37: 3-(2-chloropyrimidin-4-yl)-4,4,5,5-tetramethyloxazolidin-2-one		MS m/z (M + H)+ 256.1, Rt 0.85 min
38: 3-(2-chloro-5-fluoropyrimidin-4-yl)-4,4,5,5-tetramethyloxazolidin-2-one		MS m/z (M + H)+ 274.1, Rt 0.83 min
39: 3-(2-chloropyrimidin-4-yl)-4,4,5-trimethyloxazolidin-2-one		MS m/z (M + H)+ 242.1, Rt 0.81 min
40: 3-(2-chloro-5-fluoropyrimidin-4-yl)-4,4,5-trimethyloxazolidin-2-one		MS m/z (M + H)+ 260.1, Rt 0.77 min
41: 1-(2-chloro-5-fluoropyrimidin-4-yl)-3-oxa-1-azaspiro[4.4]nonan-2-one	($CDCl_3$) 8.47 (d, J = 2 Hz, 1 H), 4.28 (s, 2 H), 2.54 – 2.44 (m, 2 H), 2.11 – 1.99 (m, 2 H), 1.90 – 1.82 (m, 2 H), 1.72 – 1.61 (m, 42 H)	MS m/z (M + H)+ 272.4
42: 3-(2-chloropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one		MS m/z (M + H)+ 228.0, Rt 0.73 min

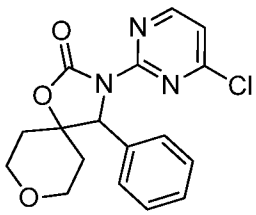
43: 3-(2-chloro-5-fluoropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one		MS m/z (M + H)+ 246.0, Rt 0.70 min
44: 3-(2-chloro-5-fluoropyrimidin-4-yl)oxazolidin-2-one		MS m/z (M + H)+ 218.0, Rt 0.47 min

Intermediate 46: (S)-4-(biphenyl-4-yl)-3-(2-chloropyrimidin-4-yl)oxazolidin-2-one



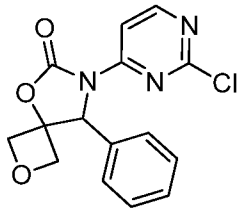
To a solution of 2,4-dichloropyrimidine (46.5 mg, 0.312 mmol) and (S)-4-(biphenyl-4-yl)oxazolidin-2-one (74.7 mg, 0.312 mmol) in DMF (700 µL) was added NaH (60%wt., 10.49 mg, 0.437 mmol) in two portions within ~5 min [Caution: exotherm; gas development] at room temperature (water bath). The reaction mixture was stirred for 1.5 hour. The mixture was diluted with EtOAc (25 mL), stirred for 5 min and then diluted slowly with diluted brine (10 mL; 1:1 brine/water). The mixture was poured into diluted brine (40 mL) and EtOAc (25 mL). The separated organic phase was washed with diluted brine (3x 40 ml), dried over Na_2SO_4, filtered off and concentrated under reduced pressure. The residue was purified by column chromatography [SiO_2, 40 g, EtOAc/heptane] to provide (S)-4-(biphenyl-4-yl)-3-(2-chloropyrimidin-4-yl)oxazolidin-2-one (49.5 mg). LCMS *m/z* 352.2 $(M + H)^+$, Rt 1.06 min.

Intermediate 47 : 3-(2-chloropyrimidin-4-yl)-4-phenyl-1,8-dioxa-3-azaspiro[4.5]decan-2-one



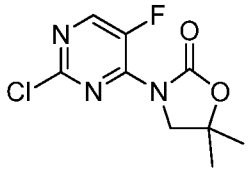
To a mixture of 4-phenyl-1,8-dioxa-3-azaspiro[4.5]decan-2-one (300 mg, 1.286 mmol) and 2,4-dichloropyrimidine (192 mg, 1.286 mmol) in DMF (7 mL) under argon was added NaH (60%wt., 67.9 mg, 2.83 mmol) in two portions. The mixture was stirred for ~1 hour. The reaction mixture was carefully poured into ice-colled 0.25N aqueous HCl solution. DCM and aqueous $NaHCO_3$ solution were added. The separated aqueous layer was extracted with DCM (3x) and ethyl acetate (1x). The organic layers (DCM and ethyl acetate containing layers independently) were washed with brine, dried over Na_2SO_4 and filtered off. The organic layers were combined and concentrated under reduced pressure providing crude 3-(2-chloropyrimidin-4-yl)-4-phenyl-1,8-dioxa-3-azaspiro[4.5]decan-2-one (330 mg) as a yellowish liquid, which was directly used in the next reaction without further purification. LCMS *m/z* 346.1 $(M + H)^+$, Rt 0.83 min.

Intermediate 48 : 7-(2-chloropyrimidin-4-yl)-8-phenyl-2,5-dioxa-7-azaspiro[3.4]octan-6-one



Prepared using similar methods as described above for 3-(2-chloropyrimidin-4-yl)-4-phenyl-1,8-dioxa-3-azaspiro[4.5]decan-2-one, but starting with oxetan-3-one.
LCMS *m/z* 318.1 $(M + H)^+$, Rt 0.78 min.

Intermediate 50: 3-(2-chloro-5-fluoropyrimidin-4-yl)-5,5-dimethyloxazolidin-2-one



Step 1
A solution of 2,4-dichloro-5-fluoropyrimidine (2 g, 11.98 mmol) in acetonitrile (10 mL) was cooled to -40 °C, avoiding freezing. To this solution was added diisopropylamine (3.82 mL, 21.88 mmol) followed by 1-amino-2-methylpropan-2-ol (1.5 g, 16.83 mmol). The reaction mixture was removed from the cooling bath, warmed to room temperature and allowed to stir overnight (~18 hours). Solvents were removed in vacuo and the residue was taken up in a minimum of dichloromethane (~1.5-2 mL) and diluted with heptane

until slightly cloudy.This mixture was loaded onto a 40 gram BioRad silica gel cartridge. Purification by flash chromatorgraphy (Analogix System, 20 min gradient, 0-25% methanol/dichloromethane, 40 mL/min.) provided 1-(2-chloro-5-fluoropyrimidin-4-ylamino)-2-methylpropan-2-ol as a white solid. LCMS *m/z* 220.1, 221.8 $(M + H)^+$, Rt 0.49 min.

Step 2

To a suspension of 1-(2-chloro-5-fluoropyrimidin-4-ylamino)-2-methylpropan-2-ol (400 mg, 1.82) in DCM/ethylacetate (5 mL) was added 2,6-lutidine (1 mL, 8.59 mmol). The reaction was cooled to -78°C and triphosgene (292 mg, 0.983 mmol) was added in a single portion. The reaction was removed from the cooling bath and allowed to warm to room temperature. The reaction had a pinkish coloration at this time. LCMS indicated consumption of starting material and conversion the intermediate acyl chloroformate adduct of 1-(2-chloro-5-fluoropyrimidin-4-ylamino)-2-methylpropan-2-ol. The reaction was sealed and stirred overnight. The reaction was stirred at room temperature overnight to provide only partial closure of the intermediate acyl formate to the cyclic carbamate. The reaction (sealed) was then heated at 60°C for ~4 hours until intermediate acyl chloroformate was consumed. Reaction was cooled to room temperature, diluted with DCM (~50 mL) and washed with water (1x50 mL) and sat. $NaHCO_3$ (1x50 mL). Aqueous layers were back extracted with DCM (~50 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated in vacuo. The solid was dissolved in DCM (~15 mL) and celite (~4 gram) was added. The mixture was concentrated and dried in vacuo to provide a solid pre-load for subsequent purification. Purification by flash chromatography(Analogix System, 80 gram silica gel column, 25 min. gradient, 0-25% methanol/dichloromethane, 40 mL/min) provided 3-(2-chloro-5-fluoropyrimidin-4-yl)-5,5-dimethyloxazolidin-2-one as a white solid. ^1H NMR (400 MHz, METHANOL-*d*4) δ ppm 1.58 (s, 8 H) 4.02 (s, 2 H) 8.59 (d, *J*=3.13 Hz, 1 H): LCMS *m/z* $(M + H)^+$ 246.1, 247.8.0, Rt 0.61 min

The Intermediates in Table 4d were prepared by methods similar to the one described for the preparation of Intermediate 50.

Table 4d.

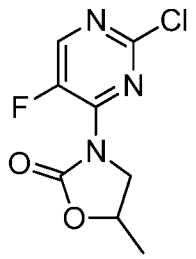
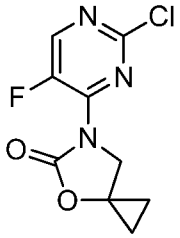
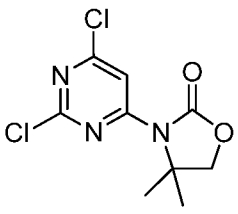
Intermediate 51	Intermediate 52
	

Table 4e. Chemical name, NMR chemical shifts and LCMS signal for each intermediate listed in Table 4d.

Intermediate: Name	^{1}H NMR (400 MHz, METHANOL-d4) δ ppm	LCMS
51: 3-(2-chloro-5-fluoropyrimidin-4-yl)-5-methyloxazolidin-2-one	1.52 (d, *J*=6.26 Hz, 3 H) 3.89 (dd, *J*=9.78, 7.43 Hz, 1 H) 4.26 (dd, *J*=9.78, 7.43 Hz, 1 H) 4.90 - 4.98 (m, 1 H) 8.58 (d, *J*=2.74 Hz, 1 H)	MS *m/z* (M + H)$^+$ 232.0, 233.9, Rt 0.52 min
52: 6-(2-chloro-5-fluoropyrimidin-4-yl)-4-oxa-6-azaspiro[2.4]heptan-5-one	0.90 - 1.08 (m, 2 H) 1.18 - 1.37 (m, 2 H) 4.31 (s, 2 H) 8.61 (d, *J*=3.13 Hz, 1 H)	MS *m/z* (M + H)$^+$ 244.0, 245.8, Rt 0.61 min

Intermediate 53: 3-(2,6-dichloropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one



A solution of 4,4-dimethyloxazolidin-2-one (0.103 g, 0.895 mmol) and 2,4,6-trichloropyrimidine (0.181 g, 0.984 mmol, 1.10 equiv) in DMF (3 mL) was treated with NaH (60 %, 0.0429 g, 1.07 mmol, 1.2 equiv), then the resulting mixture (yellow) was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc (20 mL), washed with saturated aqueous NaCl (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 0 to 40%) provided3-(2,6-dichloropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one (0.146 g, white solid) in 62.3% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s,1 H), 4.16 (s, 2 H), 1.74 (s, 9H); LCMS *m/z* 261.9 (M + H)$^+$, Rt 0.91 min.

The Intermediates in Table 4f were prepared by a method similar to the one described for the preparation of Intermediate 53.

Table 4f.

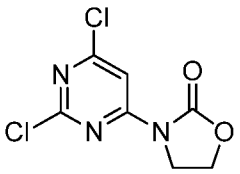
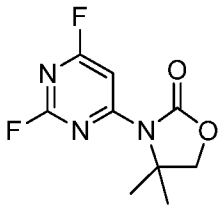
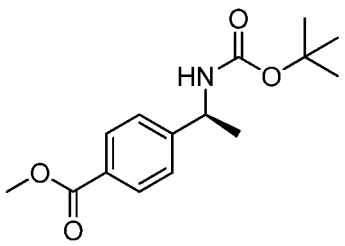
Intermediate 54	Intermediate 55
	

Table 4g. Chemical name, NMR chemical shifts and LCMS signal for each intermediate listed in Table 4f.

Intermediate: Name	**^{1}H NMR (400 MHz) δ ppm**	**LCMS**
54: 3-(2,6-dichloropyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.20 (s, 1 H), 4.59 (t, J = 8.0 Hz, 2 H), 4.29 (t J = 8.0 Hz, 2 H)	MS *m/z* 234.0 (M + H)$^+$, Rt 0.67 min
55: 3-(2,6-difluoropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	($CDCl_3$) 7.68 (d, J = 2.0 Hz, 1 H), 4.16 (s, 2 H), 1.74 (s, 6 H)	MS *m/z* 230.1 (M + H)$^+$, Rt 0.79 min

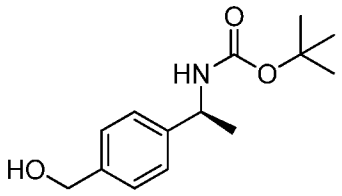
Intermediate 56 : (S)-methyl 4-(1-(tert-butoxycarbonylamino)ethyl)benzoate



To a solution of (S)-methyl 4-(1-aminoethyl)benzoate (4.9 g, 22.7 mmol) in DCM (114 mL) was added di-tert-butyl dicarbonate (5.95 g, 27.3 mmol) and triethylamine (6.97 mL, 50 mmol). The solution was stirred for 16 h at room temperature then washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/heptane 0 to 80%) provided (S)-methyl 4-(1-(tert-butoxycarbonylamino)ethyl)benzoate as a white solid (6.35 g, 100% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.96 (m, 2H), 7.40 – 7.33 (m, 2H), 4.83 (s, 1H), 3.91 (s, 3H), 1.43 – 1.23 (m, 12H); MS m/z 224.0 (M - 56 + H).

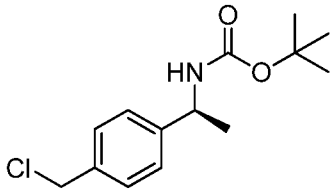
Intermediate 57 : (S)-tert-butyl 1-(4-(hydroxymethyl)phenyl)ethylcarbamate



To a cooled (0 °C) solution of (S)-methyl 4-(1-(tert-butoxycarbonylamino)ethyl)benzoate (6.35 g, 22.7 mmol) in THF (114 mL) was added a solution of LAH in THF (2.0 M, 13.64 mL, 27.3 mmol) and the resulting mixture was stirred at room temperature for 40 min. The reaction mixture was quenched by addition of a 1N NaOH solution until gas evolution ceased. The reaction mixture was filtered, washed with EtOAc. After separation, the aqueous phase was washed with EtOAc (2 x 150 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/heptane 0 to 100%) provided (S)-tert-butyl 1-(4-(hydroxymethyl)phenyl)ethylcarbamate as a white solid (5.01 g, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 4H), 4.80 – 4.71 (m, 1H), 4.67 (s,2H), 2.04 (bs, 1H), 1.47 – 1.37 (m, 12H); MS m/z 196.0 (M - 56 + H).

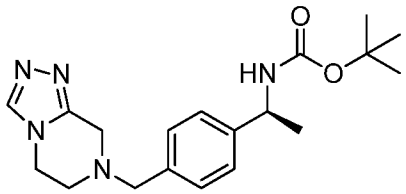
Intermediate 58: (S)-tert-butyl 1-(4-(chloromethyl)phenyl)ethylcarbamate



To a solution of (S)-tert-butyl 1-(4-(hydroxymethyl)phenyl)ethylcarbamate (503 mg, 2 mmol) in DCM (10 mL) was added methanesulfonyl chloride (275 mg, 2.4 mmol) and triethylamine (0.56 mL, 4 mmol). The solution was stirred for 16 h at room temperature then washed with water and brine. After separation, the organic phase was dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/heptane 0 to 80%) provided (S)-tert-butyl 1-(4-(chloromethyl)phenyl)ethylcarbamate as a white solid (254 g, 47.1% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 4H), 4.79 (s, 1H), 4.58 (s, 2H), 1.50 – 1.30 (br m, 12H); MS m/z 214.0 (M - 56 + H).

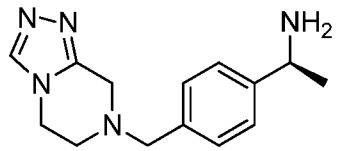
Intermediate 59: (S)-tert-butyl 1-(4-((5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)phenyl)ethylcarbamate



A solution of (S)-tert-butyl 1-(4-(chloromethyl)phenyl)ethylcarbamate (127 mg, 0.47 mmol), 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (91 mg, 0.56 mmol) and DIPEA (183 mg, 1.41 mmol) in DMSO (2.3 mL) was heated at 80 °C for 16 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with water (20 mL). After separation, the aqueous phase was washed with EtOAc (2 x 15 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. The crude product was used to next step without further purification.

MS m/z 358.3 (M + H)

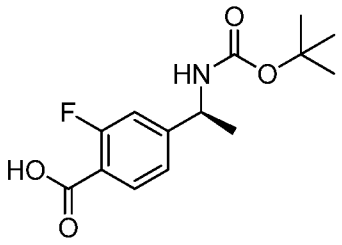
Intermediate 60: (S)-1-(4-((5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)phenyl)ethanamine



To a solution of (S)-tert-butyl 1-(4-((5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)phenyl)ethylcarbamate (168 mg, 0.47 mmol) in DCM (2 mL) was added TFA (2 mL, 26 mmol) slowly at -78 °C. The reaction was stirred at room temperature for 1 h then concentrated and diluted with DCM (10 mL). The solution was stirred with 3 eq. of MP-carbonate resin (3.28 mmol/g, Biotage) for 1 hour at room temperature. The resin was removed by filtration and washed (2 x 5 mL) with DCM. The filtrate was concentrated and the crude residue was used to next step without further purification.

MS m/z 258.2 (M + H).

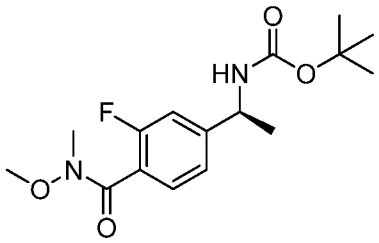
Intermediate 61: (S)-4-(1-(tert-butoxycarbonylamino)ethyl)-2-fluorobenzoic acid



To a solution of (S)-4-(1-aminoethyl)-2-fluorobenzoic acid (5 g, 22.76 mmol) in water (66 mL) and THF (66 mL) was added di-tert-butyl dicarbonate (6.95 g, 31.9 mmol) and sodium carbonate (5.74 g, 68.3 mmol). The solution was stirred for 16 h at room temperature then THF was removed under reduced pressure. The aqueous solution was acidified with 1N HCl to pH 3-4 and extracted with EtOAc (3 x 60 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated to give a white solid (1.94 g, 30.1% yield). The crude product was used to next step without further purification.

^{1}H NMR (400 MHz, MeOD) δ 7.89 (t, J = 7.8 Hz, 1H), 7.20 (dd, J = 8.2, 1.7 Hz, 1H), 7.13 (dd, J = 12.0, 1.6 Hz, 1H), 4.70 (d, J = 7.1 Hz, 1H), 1.47 – 1.35 (m, 12H); MS m/z 282.0 (M - H).

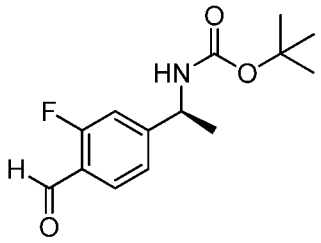
Intermediate 62: (S)-tert-butyl 1-(3-fluoro-4-(methoxy(methyl)carbamoyl)phenyl) ethylcarbamate



A solution of (S)-4-(1-(tert-butoxycarbonylamino)ethyl)-2-fluorobenzoic acid (1.416 g, 5mmol), N,O-dimethylhydroxylamine hydrochloride (732 mg, 7.5 mmol), HATU (2.85 g, 7.5 mmol) and DIPEA (3.49 mL, 20 mmol) in DMF (25 mL) was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc and washed with water. After separation, the aqueous phase was washed with EtOAc (2 x 75 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/heptane 12 to 100%) provided (S)-tert-butyl 1-(3-fluoro-4-(methoxy(methyl)carbamoyl)phenyl)ethylcarbamate as a white solid (1.5 g, 92 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, J = 7.4 Hz, 1H), 7.13 (dd, J = 7.8, 1.6 Hz, 1H), 7.04 (dd, J = 10.7, 1.6 Hz, 1H), 4.80 (br s, 1H), 3.56 (s, 3H), 3.34 (s, 3H), 1.50 – 1.29 (m, 12H); MS m/z 327.1 (M + H).

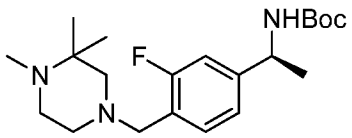
Intermediate 63 : (S)-tert-butyl 1-(3-fluoro-4-formylphenyl)ethylcarbamate



Procedure 1: To a cooled (0 °C) solution of (S)-tert-butyl 1-(3-fluoro-4-(methoxy(methyl)carbamoyl)phenyl)ethylcarbamate (1.175 g, 3.6 mmol) in THF (36 mL) was added a solution of LAH in THF (1.0 M, 18 mL, 18 mmol) and the resulting mixture was stirred at 0 °C for 20 min. The reaction mixture was quenched by addition of a saturated Na_2SO_4 solution until gas evolution ceased. The reaction mixture was extracted with EtOAc (2 x 100 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/heptane 12 to 100%) provided (S)-tert-butyl 1-(3-fluoro-4-formylphenyl)ethylcarbamate as a white solid (760 mg, 79% yield).

Procedure 2: A solution of (S)-tert-butyl 1-(4-bromo-3-fluorophenyl)ethylcarbamate (318 mg, 1 mmol) in dry THF (5 mL) was cooled to -78 °C. BuLi (2.5 M, 840 µL, 2.1 mmol) was added dropwise and the resulting solution was stirred at -78 °C for 1 h. Then DMF (232 µL, 3.00 mmol) was added in one portion. The reaction was stirred for another 30 min at -78 °C then quenched with sat. NH4Cl solution. The reaction was stirred at room temperature for another 30 min then diluted with EtOAc, washed with water and brine. The separated organic was dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/heptane 0 to 80%) provided (S)-tert-butyl 1-(3-fluoro-4-formylphenyl)ethylcarbamate as a white solid (70 mg, 26.2% yield).
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.87 – 7.80 (m, 1H), 7.20 (dd, J = 8.2, 1.3 Hz, 1H), 7.11 (dd, J = 11.5, 1.4 Hz, 1H), 4.80 (br s, 1H), 1.45 (br s, 12H); MS m/z 212.1 (M - 56 + H).

Intermediate 64: (S)-tert-butyl 1-(3-fluoro-4-((3,3,4-trimethylpiperazin-1-yl)methyl)phenyl)ethylcarbamate

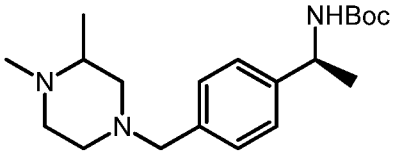


(General procedure A for reductive amination)

A solution of (S)-tert-butyl 1-(3-fluoro-4-formylphenyl)ethylcarbamate (267 mg, 1 mmol) and 1,2,2-trimethylpiperazine dihydrochloride (402 mg, 2 mmol) in THF (5 mL) was stirred at room temperature for 1 h and treated with sodium triacetoxyborohydride (848 mg, 4 mmol). The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (15 mL) and extracted with EtOAc (3 x 25 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (MeOH/CH_2Cl_2 0 to 10%) provided (S)-tert-butyl 1-(3-fluoro-4-((3,3,4-trimethylpiperazin-1-yl)methyl)phenyl)ethylcarbamate as a white solid (186 mg, 49% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J = 7.7 Hz, 1H), 7.03 (dd, J = 7.9, 1.9 Hz, 1H), 6.95 (dd, J = 11.1, 1.8 Hz, 1H), 4.77 (s, 1H), 3.49 (s, 2H), 2.56 (br s, 4H), 2.24 (br s, 5H), 1.42 (br s, 12H), 1.04 (s, 6H); MS m/z 380.4 (M + H).

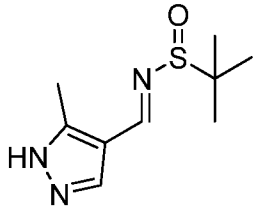
Intermediate 65: tert-butyl (1S)-1-(4-((3,4-dimethylpiperazin-1-yl)methyl)phenyl)ethylcarbamate



A solution of (S)-tert-butyl 1-(4-formylphenyl)ethylcarbamate (84.1 mg, 0.337 mmol) [obtained from (S)-1-(4-bromophenyl)ethanamine following the procedure of Hashihayata, Takashi PCT Int. Appl., 2008081910, 10 Jul 2008] and 1,2-dimethylpiperazine (86.3 mg, 0.756 mmol, 2.24 equiv) in THF (1.5 mL) was stirred at room temperature for 65 min and treated with sodium triacetoxyborohydride (277.2 mg, 1.308 mmol, 3.88 equiv). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (15 mL) and extracted with EtOAc (5 x 15 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (MeOH/CH_2Cl_2 0 to 20%) provided tert-butyl (1S)-1-(4-((3,4-dimethylpiperazin-1-yl)methyl)phenyl)ethyl carbamate (90.7 mg) in 34.5% yield.

^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (s, 4 H), 4.68 (br s, 1 H), 3.54 - 3.47 (m, 2 H), 3.37 (s, 1 H), 2.84 - 2.74 (m, 3 H), 2.38 (td, J = 12, 2.5 Hz, 1 H), 2.31 (s, 3 H), 2.28 - 2.22 (m, 2 H), 1.94 - 1.89 (m, 1 H), 1.40 (br s, 9 H), 1.38 (d, J = 6.9 Hz, 3 H), 1.06 (d, J = 6.3 Hz, 3 H); MS m/z 348.2 (M + H)

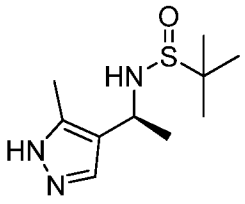
Intermediate 66: (R,E)-2-methyl-N-((3-methyl-1H-pyrazol-4-yl)methylene)propane-2-sulfinamide



3-methyl-1H-pyrazole-4-carbaldehyde (2.03g, 18.44mmol) was dissolved in THF (30ml) and (R)-2-methylpropane-2-sulfinamide (2.35, 19.39mmol) was added followed by Ti(OEt)4 (8.41mmol, 36.90mmol). The resulting reaction mixture was stirred at 80°C for 18h. LCMS shows mostly product. The reaction mixture was diluted with EtOAc (300 mL), washed with 4% aqueous NaCl (2 x 150, 2X50 mL). The combined aq. layers were back extracted with EtOAc (100ml). The combined organic layers were washed with brine (100ml), dried over Na_2SO_4, filtered and concentrated. Purified by column chromatography (REDI 80g, EtOAc/heptane 20-100% over 33 min 100% for 7min.) to give title compound (2.25g, 10.55mmol).

^{1}H NMR (400 MHz, MeOD) δ 8.55 (s, 1H), 2.53 (s, 3H), 1.25 (s, 9H). MS 214.2 m/z (M+H)

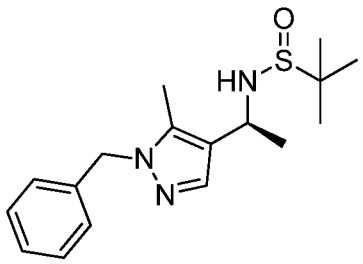
Intermediate 67: (R)-2-methyl-N-((S)-1-(3-methyl-1H-pyrazol-4-yl)ethyl)propane-2-sulfinamide



(R,E)-2-methyl-N-((3-methyl-1H-pyrazol-4-yl)methylene)propane-2-sulfinamide (2.25g, 10.55mmol) was dissolved in THF and cooled to 0C. Methylmagnesium bromide (3M, 12.5ml, 37.5mmol) was added dropwise and the resulting solution was stirred for 1h. Ice

bath was removed and the reaction was stirred for another 15h. Another 2.5eq. of methylmagnesium bromide MeMgBr was added (at 0°C
). Not a lot of change by LCMS.
The reaction mixture was quenched with sat NH4Cl and the aq. layer was washed with THF (2X). Combined organic layers washed with brine, dried over Na_2SO_4, filtered and concentrated to give title compound (1.79g, 7.80mmol)
^{1}H NMR (400 MHz, MeOD) δ 7.48 (s, 1H), 4.49 (qd, J = 6.7, 4.7 Hz, 1H), 2.26 (s, 3H), 1.57 (dd, J = 6.5, 1.3 Hz, 3H), 1.23 (s, 9H). MS 230.2 m/z (M+H)

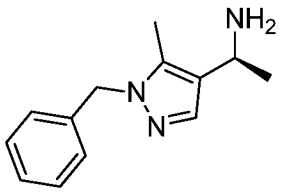
Intermediate 68: (R)-N-((S)-1-(1-benzyl-3-methyl-1H-pyrazol-4-yl)ethyl)-2-methylpropane-2-sulfinamide



(R)-2-methyl-N-((S)-1-(3-methyl-1H-pyrazol-4-yl)ethyl)propane-2-sulfinamide (290mg, 1.26mmol) was dissolved in DMF (5ml) and added dropwise to a solution of Cs2CO3 (458mg, 1.41mmol) in DMF (4ml). The resulting reaction mixture was stirred at room temperature for 15min. benzylbromide (216mg, 1.26mmol) was added and the reaction was stirred at room temperature for 2h. LCMS shows mostly product with some starting pyrazole. Added another 0.1ml of BnBr and 135mg of Cs_2CO_3. Stirred another 24H at 50ºC.The reaction mixture was diluted with EtOAc (300 mL), washed with 4% aqueous NaCl (2 x 150, 2X50 mL). The combined aq. layers were back extracted with EtOAc (100ml). The combined organic layers were washed with brine (100ml), dried over Na_2SO_4, filtered and concentrated. Silica gel chromatography, EtOAc/heptane 20-80% to give title compound (mix of regioisomers, 150mg, 0.470mmol).
^{1}H NMR (400 MHz, MeOD) δ 7.54 (s, 0.6H), 7.46 (s, 0.4H), 7.36 – 6.99 (m, 5H), 5.31 (s, 0.8H), 5.21 (s, 1.2H), 4.44 (t, J = 6.9 Hz, 1H), 2.21 (2s, 3H), 1.54 (2dt, 3H), 1.17 (s, 9H). MS 320.2 m/z (M+H)

Intermediate 69:

(S)-1-(1-benzyl-3-methyl-1H-pyrazol-4-yl)ethanamine hydrochloride



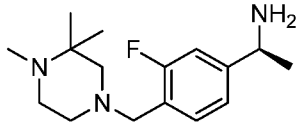
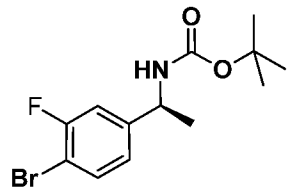
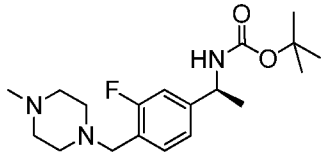
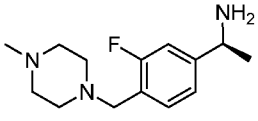
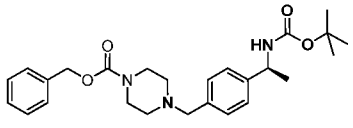
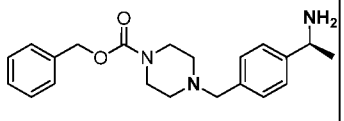
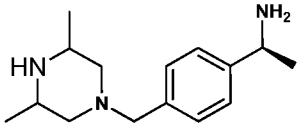
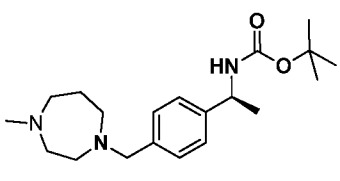
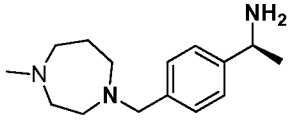
(R)-N-((S)-1-(1-benzyl-3-methyl-1H-pyrazol-4-yl)ethyl)-2-methylpropane-2-sulfinamide was dissolved in dioxane (5ml) and 4N HCl in dioxane (1.2ml, 10eq.) was added. Stirred 1H at room termperature. The solvents were removed and co-vapped twice with CH_2Cl_2. Some t-butyl observed by NMR. Resubmitted to reaction conditions and work-up to give title compound.

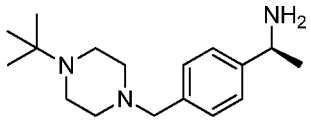
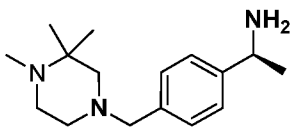
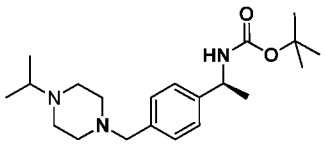
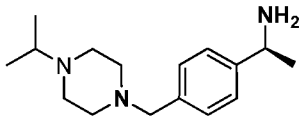
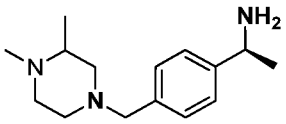
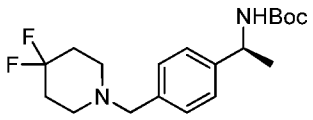
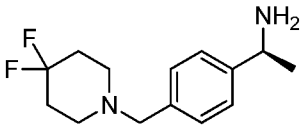
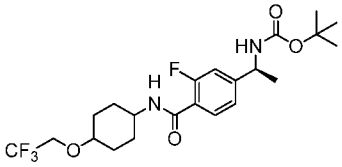
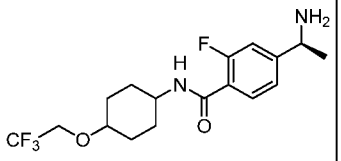
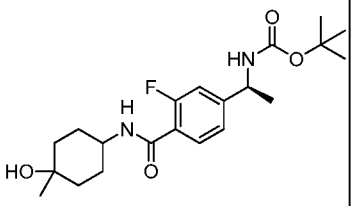
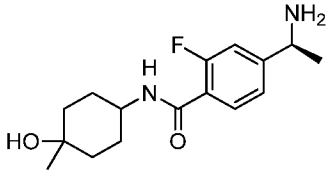
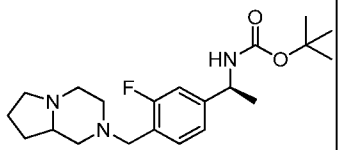
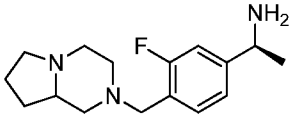
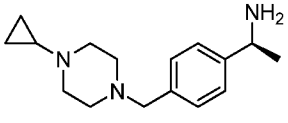
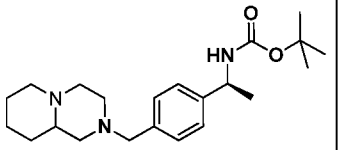
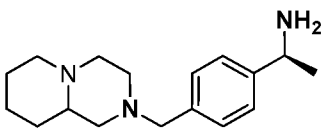
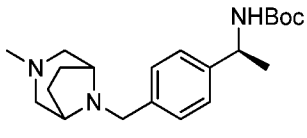
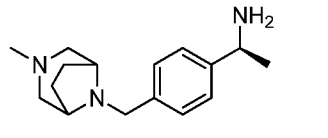
^{1}H NMR mixture of regioisomers (400 MHz, MeOD) δ 8.00 (s, 0.7H), 7.80 (s, 0.3H), 7.52 – 6.96 (m, 5H), 5.40 (s, 0.6H), 5.36 (s, 1.4H), 4.47 (q, J = 6.9 Hz, 1H), 2.34 (s, 2.1H), 2.32 (s, 0.9H), 1.62 (2d, J = 6.9 Hz, 3H).

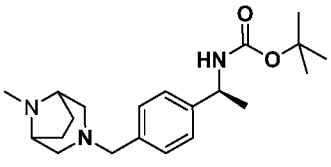
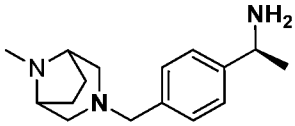
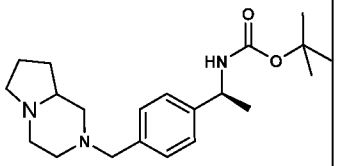
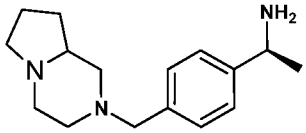
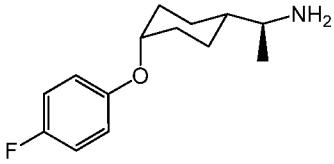
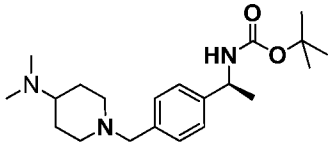
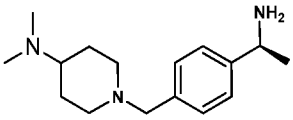
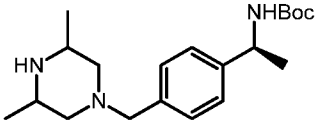
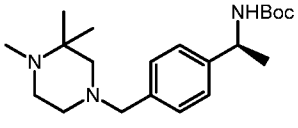
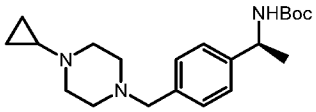
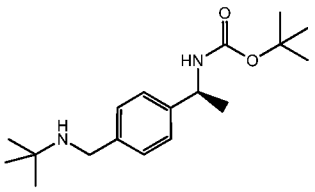
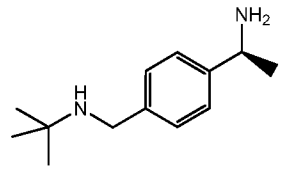
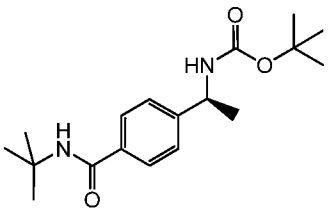
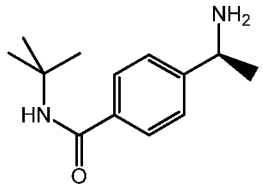
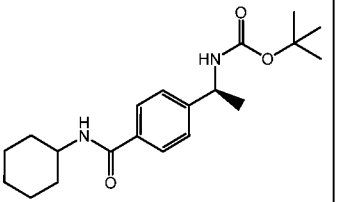
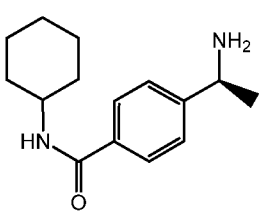
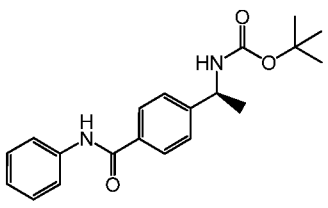
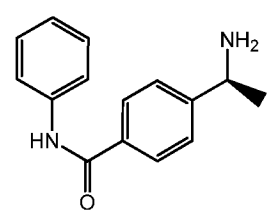
MS 216.3 m/z (M+H)

The Intermediates in Table 4h were prepared by methods substantially similar to those described for the preparation of Intermediates 56 through 69.

Table 4h.

Intermediate 70	Intermediate 71	Intermediate 72
		
Intermediate 73	Intermediate 74	Intermediate 75
		
Intermediate 76	Intermediate 77	Intermediate 78
		

Intermediate 79	Intermediate 80	Intermediate 81
		
Intermediate 82	Intermediate 83	Intermediate 84
		
Intermediate 85	Intermediate 86	Intermediate 87
		
Intermediate 88	Intermediate 89	Intermediate 90
		
Intermediate 91	Intermediate 92	Intermediate 93
		
Intermediate 94	Intermediate 95	Intermediate 96
		
Intermediate 97	Intermediate 98	Intermediate 99

		
Intermediate 100	Intermediate 101	Intermediate 102
		
Intermediate 103	Intermediate 104	Intermediate 105
		
Intermediate 106	Intermediate 107	Intermediate 108
		
Intermediate 109	Intermediate 110	Intermediate 111
		
Intermediate 112	Intermediate 113	Intermediate 114
		
Intermediate 115	Intermediate 116	Intermediate 117

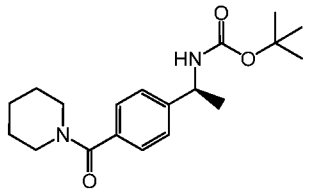
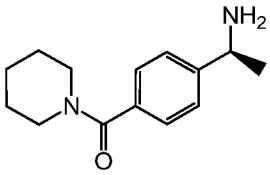
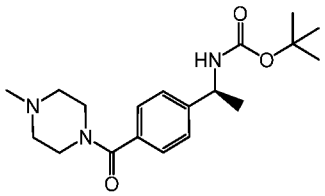
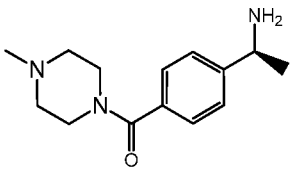
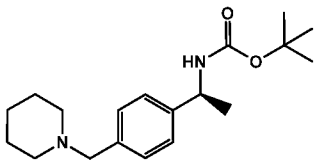
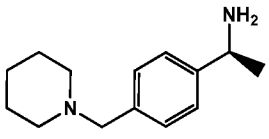
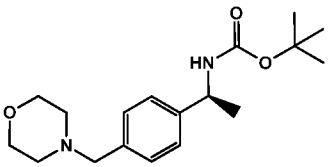
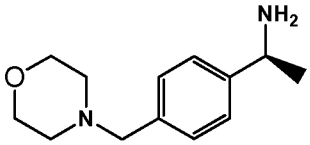
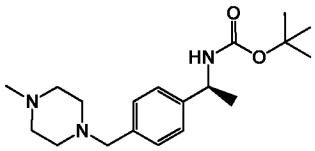
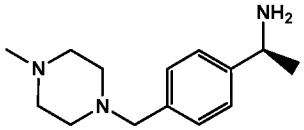
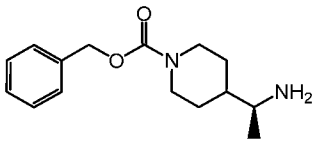
		
Intermediate 118	Intermediate 119	Intermediate 120
		
Intermediate 121	Intermediate 122	Intermediate 123
		
Intermediate 124	Intermediate 125	
		

Table 4i. Chemical name, NMR chemical shifts and LCMS signal for each intermediate listed in Table 4h.

Intermediate: Name	^{1}H NMR **(400 MHz) δ ppm**	**LCMS**
70: (S)-1-(3-fluoro-4-((3,3,4-trimethylpiperazin-1-yl)methyl)phenyl)ethanamine		MS m/z 280.2 (M + H).
71: (S)-tert-butyl 1-(4-bromo-3-fluorophenyl)ethylcarbamate	($CDCl_3$) 7.51 – 7.45 (m, 1H), 7.07 (dd, J = 9.8, 2.0 Hz, 1H), 6.98 (dd, J = 8.4, 2.1 Hz, 1H), 4.67 (br s, 1H),, 1.41(br s, 12H)	MS m/z 317.9 (M + H).
72: (S)-tert-butyl 1-(3-fluoro-4-((4-methylpiperazin-1-yl)methyl)phenyl)ethylcarbamate	($CDCl_3$) 7.28 (t, J = 7.7 Hz, 1H), 7.01 (dd, J = 7.7, 1.8 Hz, 1H), 6.94 (dd, J = 10.8, 1.9 Hz, 1H), 4.86 (br s, 1H), 4.74 (br s, 1H), 3.54 (s, 2H), 2.67 – 2.29 (m, 8H), 2.25 (s, 3H), 1.51 – 1.26 (m, 12H)	MS m/z 353.2 (M + H)
73: (S)-1-(3-fluoro-4-((4-		MS m/z

methylpiperazin-1-yl)methyl)phenyl)ethanamine		252.1 (M + H)
74: (S)-benzyl 4-(4-(1-(tert-butoxycarbonylamino) ethyl)benzyl)piperazine-1-carboxylate	($CDCl_3$) 7.43 – 7.19 (m, 9H), 5.12 (s, 2H), 4.78 (br s, 2H), 3.95 – 3.20 (m, 6H), 2.43 (br s, 4H), 1.43 (br s, 12H)	MS m/z 454.3 (M + H)
75: (S)-benzyl 4-(4-(1-aminoethyl)benzyl)piperazine-1-carboxylate		MS m/z 354.3 (M + H)
76: (1S)-1-(4-((3,5-dimethylpiperazin-1-yl)methyl)phenyl)ethanamine		MS m/z 248.2 (M + H)
77: (S)-tert-butyl 1-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)ethylcarbamate	($CDCl_3$) 7.31 – 7.20 (m, 4H), 4.78 (s, 1H), 3.61 (s, 2H), 2.81-2.69 (m, 8H), 2.44 (s, 3H), 1.94 – 1.85 (m, 2H), 1.43 (br s, 12H)	MS m/z 349.4 (M + H)
78: (S)-1-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)ethanamine		MS m/z 248.1 (M + H)
79: (S)-1-(4-((4-tert-butylpiperazin-1-yl)methyl)phenyl)ethanamine		MS m/z 276.2 (M + H)
80: (S)-1-(4-((3,3,4-trimethylpiperazin-1-yl)methyl)phenyl)ethanamine		MS m/z 262.2 (M + H)
81: (S)-tert-butyl 1-(4-((4-isopropylpiperazin-1-yl)methyl)phenyl)ethylcarbamate	($CDCl_3$) 7.28-7.22 (m, 4H), 4.78 (s, 1H), 3.49 (s, 2H), 2.88 – 2.22 (m, 9H), 1.42 (br s, 12H), 1.05 (d, J = 6.5 Hz, 6H)	MS m/z 363.4 (M + H)
82: (S)-1-(4-((4-isopropylpiperazin-1-yl)methyl)phenyl)ethanamine		MS m/z 262.2 (M + H)
83: (1S)-1-(4-((3,4-dimethylpiperazin-1-yl)methyl)phenyl)ethanamine		MS m/z 248.2 (M + H)
84: (S)-tert-butyl 1-(4-((4,4-difluoropiperidin-1-yl)methyl)phenyl)ethylcarbamate		MS m/z 356.2 (M + H)
85: (S)-1-(4-((4,4-difluoropiperidin-1-yl)methyl)phenyl)ethanamine		MS m/z 255.2 (M + H)
86: (S)-tert-butyl 1-(3-fluoro-4-(4-(2,2,2-trifluoroethoxy) cyclohexylcarbamoyl) phenyl)ethylcarbamate	($CDCl_3$) 8.01 (t, J = 8.1 Hz, 1H), 7.16 (d, J = 7.9, 1H), 7.04 (d, J = 13.2, 1H), 6.67 -6.63(m, 1H), 4.96 (br s, 1H), 4.76 (br s, 1H), 4.06 (br s, 1H), 3.85-3.77 (m, 2H), 3.64 (br s, 1H), 1.92 – 1.74 (m, 4H), 1.73 – 1.59 (m, 4H), 1.40 (br s, 12H)	MS m/z 463.3 (M + H)
87: (S)-4-(1-aminoethyl)-2-fluoro-N-(4-(2,2,2-trifluoroethoxy)cyclohexyl)benzamide		MS m/z 363.2 (M + H)
88: (S)-tert-butyl 1-(3-fluoro-4-(4-hydroxy-4-methylcyclohexylcarbamoyl) phenyl)ethylcarbamate	($CDCl_3$) 8.04 (t, J = 8.1 Hz, 1H), 7.19 (d, J = 8.3, 1H), 7.05 (dd, J = 13.2, 1.7 Hz, 1H), 6.65 (br dd, J = 12.1, 6.6 Hz, 2H), 4.84 (br s, 1H), 4.77 (br s, 1H), 4.17 – 4.06 (m, 1H), 2.09 – 2.00 (m,	MS m/z 395.1 (M + H)

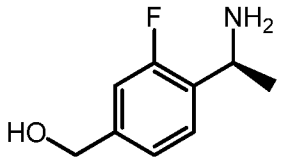
	2H), 1.61-1.59 (m, 4H), 1.55-1.47 (m, 2H), 1.42 (br s, 12H), 1.30 (s, 3H)	
89: (S)-4-(1-aminoethyl)-2-fluoro-N-(4-hydroxy-4-methylcyclohexyl)benzamide		MS m/z 295.2 (M + H)
90: tert-butyl (1S)-1-(3-fluoro-4-((hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)phenyl)ethylcarbamate		MS m/z 376.1 (M - H)
91: (1S)-1-(3-fluoro-4-((hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)phenyl)ethanamine		MS m/z 278.1 (M + H)
92: (S)-1-(4-((4-cyclopropylpiperazin-1-yl)methyl)phenyl)ethanamine		MS m/z 260.2 (M + H)
93: tert-butyl (1S)-1-(4-((dihydro-1H-pyrido[1,2-a]pyrazin-2(6H,7H,8H,9H,9aH)-yl)methyl)phenyl)ethylcarbamate	($CDCl_3$) 7.30 – 7.20 (m, 4H), 4.78 (s, 2H), 3.46 (s, 2H), 2.89 – 2.61 (m, 4H), 2.39 – 2.21 (m, 2H), 2.10 – 1.93 (m, 2H), 1.86 (t, J = 10.7 Hz, 1H), 1.79 – 1.68 (m, 1H), 1.62 (br s, 2H), 1.43 (br s, 13H), 1.32-1.19 (m, 2H)	MS m/z 372.4 (M - H)
94: (1S)-1-(4-((dihydro-1H-pyrido[1,2-a]pyrazin-2(6H,7H,8H,9H,9aH)-yl)methyl)phenyl)ethanamine		MS m/z 274.2 (M + H)
95: tert-butyl (1S)-1-(4-((3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)methyl)phenyl)ethylcarbamate		MS m/z 361.3 (M + H)
96: (1S)-1-(4-((3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)methyl)phenyl)ethanamine		MS m/z 260.2 (M + H)
97: tert-butyl (1S)-1-(4-((8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)methyl)phenyl)ethylcarbamate	($CDCl_3$) 7.28 – 7.19 (m, 4H), 4.77 (br s, 2H), 3.44 (s,2H), 3.03 (br s, 2H), 2.55 (dd, J = 10.8, 2.9 Hz, 2H), 2.29 (d, J = 10.3 Hz, 2H), 2.25 (s, 3H), 1.93 – 1.78 (m, 4H), 1.64 (br s, 1H), 1.43 (br s, 12H)	MS m/z 360.6 (M + H)
98: (1S)-1-(4-((8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)methyl)phenyl)ethanamine		MS m/z 260.2 (M + H).
99: tert-butyl (1S)-1-(4-((hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)phenyl)ethylcarbamate	($CDCl_3$) 7.30 – 7.21 (m, 4H), 4.78 (br s, 1H), 3.61 – 3.44 (m, 2H), 3.05 (td, J = 8.6, 1.9 Hz, 1H), 3.00 – 2.93 (m, 2H), 2.86 – 2.76 (m, 1H), 2.33 – 2.19 (m, 2H), 2.17 – 2.00 (m, 2H), 1.87 – 1.65 (m, 4H), 1.43 (br s, 12H)	MS m/z 361.3 (M + H)
100: (1S)-1-(4-((hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)phenyl)ethanamine		MS m/z 260.2 (M + H)
101: (S)-1-[4-(4-Fluoro-phenoxy)-cyclohexyl]-ethylamine		LC-MS m/z 237.4 (M +

		H)+; RT.: 1.08 min.
102: (S)-tert-butyl 1-(4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)ethylcarbamate	($CDCl_3$) 7.28 – 7.20 (m, 4H), 4.79 (br s, 2H), 3.46 (s, 2H), 2.91 (br d, J = 12.1 Hz, 2H), 2.26 (s, 6H), 2.17–2.09 (m, 1H), 1.94 (td, J = 11.8, 2.4 Hz, 2H), 1.85 (br s, 1H), 1.81 – 1.71 (m, 2H), 1.53 (td, J = 12.1, 3.7 Hz, 2H), 1.44–1.42 (m, 12H)	MS m/z 361.8 (M + H)
103: (S)-1-(4-(1-aminoethyl)benzyl)-N,N-dimethylpiperidin-4-amine		MS m/z 262.1 (M + H)
104: tert-butyl (1S)-1-(4-((3,5-dimethylpiperazin-1-yl)methyl)phenyl)ethylcarbamate	(CD_3OD) 7.29 (s, 4 H), 4.68 (br s, 1 H), 3.52 (s, 2 H), 2.96 - 2.88 (m, 2 H), 2.82 - 2.79 (m, 2 H), 1.69 (t, J = 11 Hz, 2 H), 1.44 (br s, 9 H), 1.40 (d, J = 7.1 Hz, 3 H), 1.06 (d, J = 6.5 Hz, 6 H);	MS *m/z* 348.3 (M + H)
105: (S)-tert-butyl 1-(4-((3,3,4-trimethylpiperazin-1-yl)methyl)phenyl)ethylcarbamate	(CD_3OD) δ 7.35 - 7.25 (m, 4 H), 4.67 (br s, 1 H), 4.59 (s, 1 H), 3.45 (s, 2 H), 3.31 (s, 1 H), 2.62 (br s, 2 H), 2.51 (br s, 1 H), 2.24 (s, 3 H), 2.18 (br s, 1 H), 1.43 (br s, 9 H), 1.40 (d, J = 7.1 Hz, 3 H), 1.07 (s, 6 H);	MS *m/z* 362.3 (M + H)
106: ((S)-tert-butyl 1-(4-((4-cyclopropylpiperazin-1-yl)methyl)phenyl)ethylcarbamate	($CDCl_3$) δ 7.21 - 7.16 (m, 4 H), 5.23 (s, 1 H), 4.72 (br s, 1 H), 3.42 (s, 2 H), 2.58 (br s, 4 H), 2.38 (br s, 4 H), 1.57 - 1.51 (m, 1 H), 1.41 - 1.30 (br m, 12 H), 0.39 - 0.33 (m, 4 H);	MS *m/z* 359.8 (M + H)
107: (S)-tert-butyl 1-(4-((tert-butylamino)methyl)phenyl) ethylcarbamate	($CDCl_3$) 7.32 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 4.77 (s, 1H), 3.72 (s, 1H), 1.43 (d, J = 5.4 Hz, 6H), 1.18 (s, 4H)	MS m/z 308.2 (M + H)+
108: (S)-N-(4-(1-aminoethyl)benzyl)-2-methylpropan-2-amine		MS m/z 207.2 (M + H) +
109: (S)-tert-butyl 1-(4-(tert-butylcarbamoyl)phenyl)ethyl carbamate	($CDCl_3$) 7.71 – 7.62 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 5.90 (s, 1H), 4.80 (br s, 2H), 1.46-1.41 (m, 21H)	MS m/z 321.2 (M + H)+
110: (S)-4-(1-aminoethyl)-N-tert-butylbenzamide hydrochloride		MS m/z 221.3 (M + H) +
111: (S)-tert-butyl 1-(4-(cyclohexylcarbamoyl)phenyl)ethyl carbamate	($CDCl_3$) 7.71 (dd, J = 8.3, 1.8 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 5.91 (d, J = 8.3 Hz, 1H), 4.94 – 4.59 (m, 2H), 3.97 (ddt, J = 10.8, 6.5, 2.9 Hz, 1H), 2.02 (dt, J = 12.6, 3.7 Hz, 2H), 1.75 (dp, J = 11.8, 3.9 Hz, 2H), 1.66 – 1.56 (m, 3H), 1.49 – 1.30 (m, 12H), 1.23 (m, 3H)	MS m/z 347.2 (M + H)+
112: (S)-4-(1-aminoethyl)-N-		MS m/z 247.3

cyclohexylbenzamide hydrochloride		(M + H) +
113: (S)-tert-butyl 1-(4-(phenylcarbamoyl)phenyl)ethyl carbamate	($CDCl_3$) 7.90 – 7.83 (m, 2H), 7.81 – 7.62 (m, 3H), 7.49 – 7.36 (m, 4H), 7.18 (td, J = 7.4, 1.2 Hz, 1H), 4.87 (br s, 2H), 1.58 (s, 3H), 1.46 (m, 9H)	MS m/z 340.6 (M + H) +
114: (S)-4-(1-aminoethyl)-N-phenylbenzamide hydrochloride		MS m/z 241.2 (M + H) +
115: (S)-tert-butyl 1-(4-(piperidine-1-carbonyl)phenyl)ethylcarbamate	($CDCl_3$) 7.33 (q, J = 8.3 Hz, 4H), 4.80 (br s, 2H), 3.70 (br s, 2H), 3.47 – 3.22 (m, 2H), 1.70-1.63 (m, 4H), 1.53 – 1.26 (m, 14H)	MS m/z 333.2 (M + H) +
116: (S)-(4-(1-aminoethyl)phenyl) (piperidin-1-yl)methanone hydrochloride		MS m/z 233.2 (M + H) +
117: (S)-tert-butyl 1-(4-(4-methylpiperazine-1-carbonyl)phenyl)ethylcarbamate	($CDCl_3$) 7.35 (q, J = 8.2 Hz, 4H), 4.81 (br s, 1H), 3.79 (brs, 2H), 3.45 (br s, 2H), 2.50 - 2.32 (m, 7H), 1.61 (s, 1H), 1.51 – 1.29 (m, 12H)	MS m/z 348.2 (M + H) +
118: (S)-(4-(1-aminoethyl)phenyl)(4-methylpiperazin-1-yl)methanone hydrochloride		MS m/z 248.2 (M + H) +
119: (S)-tert-butyl 1-(4-(piperidin-1-ylmethyl)phenyl)ethylcarbamate	($CDCl_3$) 7.27 (q, J = 7.9 Hz, 4H), 4.80 (br s, 2H), 3.49 (s, 2H), 2.60 – 2.28 (m, 4H), 1.60 (p, J = 5.5 Hz, 4H), 1.52 – 1.31 (m, 15H)	MS m/z 319.0 (M + H) +
120: (S)-1-(4-(piperidin-1-ylmethyl)phenyl)ethanamine		MS m/z 219.1 (M + H) +
121: (S)-tert-butyl 1-(4-(morpholinomethyl)phenyl)ethyl carbamate	($CDCl_3$) 7.48 – 7.10 (m, 4H), 4.82 (d, J = 25.7 Hz, 2H), 3.80 – 3.62 (m, 3H), 3.48 (s, 2H), 2.61 – 2.24 (m, 3H), 1.44 (m, 13H)	MS m/z 321.2 (M + H) +
122: (S)-1-(4-(morpholinomethyl) phenyl)ethanamine		MS m/z 220.9 M + H) +
123: (S)-tert-butyl 1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)ethylcarbamate	($CDCl_3$) 7.39 – 7.15 (m, 7H), 4.79 (br s, 2H), 3.51 (s, 2H), 2.41 (m, 9H), 1.46 (m, 11H)	MS m/z 321.2 (M + H) +
124: (S)-1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)ethanamine		MS m/z 234.2 (M + H) +
125: 4-((S)-1-Amino-ethyl)-piperidine-1-carboxylic acid benzyl ester		LC-MS (M+H) = 263.1 RT.: 0.91 min.

5

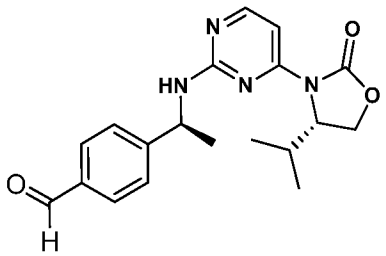
Intermediate 126: (S)-(4-(1-aminoethyl)-3-fluorophenyl)methanol



To a cooled (0 °C) suspension of (S)-methyl 4-(1-aminoethyl)-3-fluorobenzoate hydrochloride (0.109 g, 0.468 mmol) in THF (15 mL) was added a solution of LAH in THF (2.0 M, 1.05 mL, 2.10 mmol, 4.49 equiv) and the resulting mixture was stirred at 0 °C for 2 h 20 min and at room temperature for 2 1/2 h. The reaction mixture was quenched by addition of a mixture of Na_2SO_4 decahydrate and Celite (1:1 by weight) until gas evolution ceased. The reaction mixture was filtered, washed with EtOAc. The filtrate was concentrated and used for the next reaction without purification.

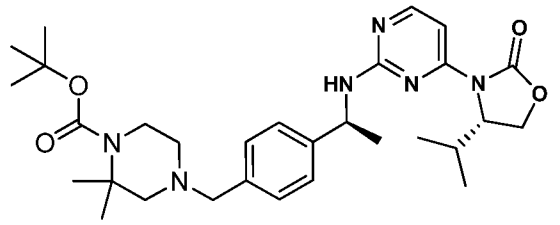
^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (t, J = 7.7 Hz, 1 H), 7.15 (d, J = 8.1 Hz, 1 H), 7.08 (d, J = 12 Hz, 1 H), 4.60 (s, 2 H), 4.32 (q, J = 6.6 Hz, 1 H), 1.42 - 1.40 (m, 3 H).

Intermediate 127: 4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzaldehyde



A solution of (S)-3-(2-((S)-1-(4-(hydroxymethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (285 mg, 0.8 mmol) and manganese dioxide (2.78 g, 32 mmol, 40 equiv) in DCM (16 mL) was stirred at room temperature for 30 min. The solution was filtered through a pad of celite and washed with DCM. The filtrated was concentrated and used to next step without further purification.

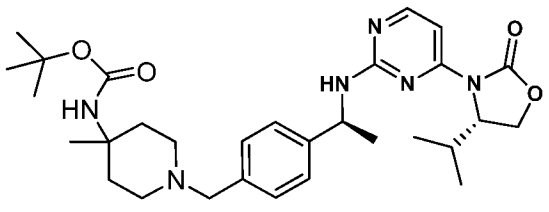
Intermediate 128: tert-butyl 4-(4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzyl)-2,2-dimethylpiperazine-1-carboxylate



A solution of 4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzaldehyde (71 mg, 0.2 mmol) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (47.1 mg, 0.22 mmol) in MeOH (4 mL) was added acetic acid (14.4 mg, 0.24 mmol) and 5-Ethyl-2-methylpyridine borane complex (27 mg, 0.2 mmol, sigma aldrich). The solution was stirred at 50 °C for 4 h then 5 drops of water was added. The solution was stirred at room temperature for another 2 h then diluted with EtOAc (10 mL) and washed with water (10 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 10 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. The crude material was purified through Silica gel column chromatography (MeOH/EtOAc 0 to 10%) to give tert-butyl 4-(4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzyl)-2,2-dimethylpiperazine-1-carboxylate as a white solid (80 mg, 72.4% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.44 (d, J = 5.7 Hz, 1H), 7.24-7.29 (m, 4H), 5.46 (br s, 1H), 5.03 (br s, 1H), 4.59-4.63 (m, 1H), 4.29 (t, J = 8.7 Hz, 1H), 4.22 (dd, J = 9.1, 3.1 Hz, 1H), 3.44 (br s, 4H), 2.40 (s, 2H), 2.16 (s, 2H), 1.54 (d, J = 6.9 Hz, 3H), 1.45 (s, 9H), 1.36 (s, 6H), 0.80 – 0.57 (m, 6H); MS m/z 252.1 (M + H).

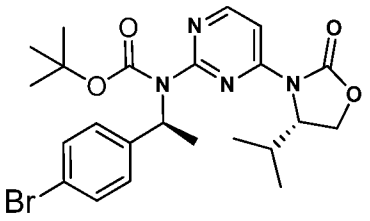
Intermediate 129: tert-butyl 1-(4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzyl)-4-methylpiperidin-4-ylcarbamate



Prepared by a method similar to that described for the preparation of Intermediate 128.

^{1}H NMR (400 MHz, $CDCl_3$) 8.17 (d, J = 5.7 Hz, 1H), 7.43 (d, J = 5.7 Hz, 1H), 7.26 (br s, 4H), 5.40 (br s, 1H), 5.02 (br s, 1H), 4.60 (dt, J = 8.2, 3.1 Hz, 1H), 4.34 – 4.19 (m, 3H), 3.47 (br s, 2H), 2.54 (br s, 2H), 2.26 (br s, 2H), 1.95 (br s, 3H), 1.60 (br s, 2H), 1.53 (d, J = 6.9 Hz, 3H), 1.43 (s, 9H), 1.33 (s, 3H), 0.69 (br s, 3H), 0.63 (br s, 3H). MS m/z 553.6 (M + H).

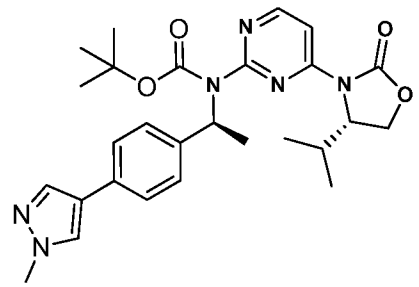
Intermediate 130: tert-butyl (S)-1-(4-bromophenyl)ethyl(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)carbamate



To a solution of (S)-3-(2-((S)-1-(4-bromophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (1.62 g, 4 mmol) in THF (20 mL) was added di-tert-butyl dicarbonate (1.31 g, 6 mmol), DMAP (49 mg, 0.4 mmol) and DIPEA (1.40 mL, 8 mmol). The solution was stirred at 50 °C for 7 days then concentrated under reduced pressure. The residue was diluted with EtOAc (40 mL) and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/heptane 0 to 80%) provided tert-butyl (S)-1-(4-bromophenyl)ethyl(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)carbamate as a white solid (1.03 g, 50.9% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 5.8 Hz, 1H), 7.99 (d, J = 5.8 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.33 – 7.28 (m, 2H), 5.63 (q, J = 7.2 Hz, 1H), 4.63 (dt, J = 8.0, 3.3 Hz, 1H), 4.39 – 4.26 (m, 2H), 2.47-2.39 (m, 1H), 1.66 (d, J = 7.1 Hz, 3H), 1.30 (s, 9H), 0.84 (d, J = 7.0, 3H),0.83 (d, J = 7.0, 3H); MS m/z 507.0 (M + H).

Intermediate 131: tert-butyl 4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl((S)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamate

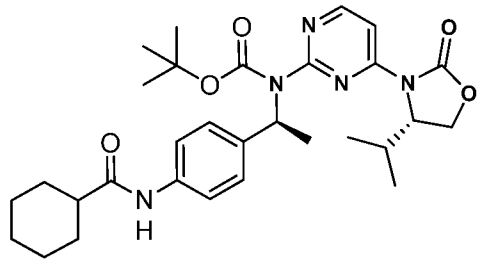


In a 5 mL microwave vial a solution of tert-butyl (S)-1-(4-bromophenyl)ethyl(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)carbamate (101 mg, 0.2 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (50 mg, 0.24 mmol), Sodium bicarbonate (0.2 mL, 0.4 mmol, 2 M aqueous solution) in Dioxane (2 mL) was bubbled

N2 for 3 min then $Cl_2Pd(dppf)CH_2Cl_2$ (16 mg, 0.02 mmol) was added. The capped tube was heated to 100°C for 16 h. After cooling the reaction mixture was diluted with EtOAc (10 mL) and washed with water (10 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 10 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. The crude material was purified through silica gel column chromatography (EtOAc in Heptane 12 to 100%) to give a white solid (50 mg, 49.3% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 5.7 Hz, 1H), 7.97 (d, J = 5.8 Hz, 1H), 7.74 (s, 1H), 7.59 (s, 1H), 7.39 (s, 4H), 5.71 (q, J = 7.0 Hz, 1H), 4.65 (dt, J = 8.1, 3.2 Hz, 1H), 4.36 – 4.24 (m, 2H), 3.94 (s, 3H), 2.50-2.42 (m, 1H), 1.71 (d, J = 7.0 Hz, 3H), 1.29 (s, 9H), 0.82 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H); MS m/z 507.1 (M + H).

Intermediate 132: tert-butyl (S)-1-(4-(cyclohexanecarboxamido)phenyl)ethyl(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)carbamate

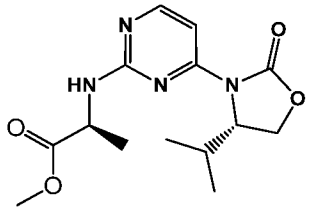


In a 5 ml microwave reaction vial was added tert-butyl (S)-1-(4-bromophenyl)ethyl(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)carbamate (101 mg, 0.2 mmol), cyclohexanecarboxamide (30 mg, 0.24 mol), cesium carbonate (91 mg, 0.28 mmol), XANTPHOS (7 mg, 0.012 mmol, strem chemicals), and $Pd_2(dba)_3$ (4 mg, 0.02 mmol). The vial was sealed, evacuated and purged with dry nitrogen three times before adding dioxane (1.6 mL). The reaction mixture was heated to 100°C for 16 hours in an oil bath. After cooling the reaction was diluted with EtOAc (10 mL) and washed with water (10 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 10 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. The crude material was purified through silica gel column chromatography (EtOAc in Heptane 12 to 100%) to give a white solid (65 mg, 58.9% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 5.8 Hz, 1H), 7.95 (d, J = 5.8 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.38 – 7.32 (m, 2H), 7.13 (br s, 1H), 5.66 (q, J = 7.1 Hz, 1H), 4.64 (dt, J = 8.2, 3.2 Hz, 1H), 4.38 – 4.26 (m, 2H), 2.51 – 2.43 (m, 1H), 2.20 (tt, J = 11.8, 3.5 Hz, 1H), 1.95 (d, J = 13.2, 2H), 1.87 – 1.81 (m, 2H), 1.71– 1.68 (m, 4H), 1.60 – 1.47 (m, 2H),

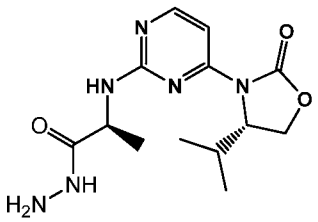
1.33-1.25(m, 12H), 0.85 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H); MS m/z 552.1 (M + H).

Intermediate 133: (S)-methyl 2-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)propanoate



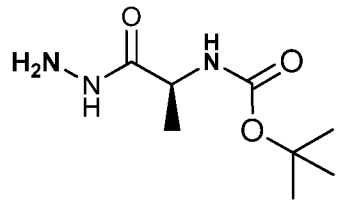
To a solution of (S)-methyl 2-aminopropanoate (270 mg, 2.0 mmol, 1.2 equv.in 10 ml of DMSO) and (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (430 mg, 1.8 mmol, 1.0 equv.) was added DIPEA (805 mg, 6.23 mmol, 3.5 equiv), and the reaction mixture was heated at 110 °C for 120 min. The reaction mixture was poured into water (40ml) and extracted with EtOAc (2x30 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (ethyl acetate in heptane 10 to 80%) to provide (S)-methyl 2-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)propanoate (260 mg, white solid) in 47.4% yield. LCMS *m/z* 309.1 $(M + H)^+$ RT=1.53 min.

Intermediate 134: (S)-2-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)propanehydrazide



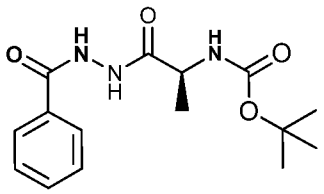
To a solution of (S)-methyl 2-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)propanoate (120 mg, 0.39 mmol in 5 ml of MeOH) was added 99% hydrazine hydrate, the reaction solution was stirred at room temperature overnight (24 hours), the solvent was removed to yield the desired product (99 mg) in 78% yield, and was used for next step without purification. LCMS *m/z* 309.1 $(M + H)^+$ RT=1.25 min.

Intermediate 135: (S)-tert-butyl (1-hydrazinyl-1-oxopropan-2-yl)carbamate



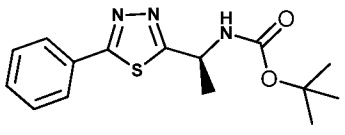
A solution of hydrazine (234 mg, 7.31 mmol, 1.5 equv. in 8 ml of THF) was added to (S)-methyl 2-(tert-butoxycarbonylamino)propanoate (1000 mg, 4.88 mmol, 1.0 equv.), it was stirred in a sealed tube and refluxed (72°C) overnight (18 hours), the solvent was removed to yield the desired product (880 mg, white solid) in 84% yield.

Intermediate 136: (S)-tert-butyl (1-(2-benzoylhydrazinyl)-1-oxopropan-2-yl)carbamate



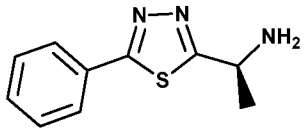
To a solution of (S)-tert-butyl (1-hydrazinyl-1-oxopropan-2-yl)carbamate (293 mg, 1.44 mmol, 1.0 equv. in 3 ml of DCM) was added benzoyl fluoride (179 mg, 1.44 mmol in 2 ml of DCM), the reaction solution was stirred at room temperature for 50 min., the solvent was removed to yield the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.78 (m, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 5.32 (b, 1H), 4.45 (b, 1H), 1.46 (s, 9H).

Intermediate 137: (S)-tert-butyl (1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl)carbamate



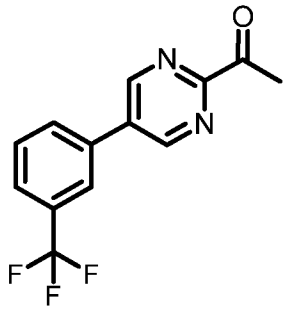
To a solution of (S)-tert-butyl (1-(2-benzoylhydrazinyl)-1-oxopropan-2-yl)carbamate (155 mg, 0.5 mmol, 1.0 equv. in 5 ml of THF) was added Lawesson's reagent (36.4 mg, 0.5 mmol, 1.0 equv.) the reaction mixture was stirred at reflux for 3 hours, the reaction mixture was filtered and the solvent was removed to yield the crude product. Silica gel column chromatography (ethyl acetate in heptane 10 to 50%) to provide (S)-tert-butyl (1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl)carbamate (114.6 mg, white solid) in 70.7% yield. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.94 – 7.72 (m, 2H), 7.52 – 7.26 (m, 3H), 5.59 (b, 1H), 5.11 (b, 1H), 1.57 (d, *J* = 7.0 Hz, 3H), 1.34 (s, 9H).

Intermediate 138: (S)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethanamine



To a solution of (S)-tert-butyl (1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl)carbamate (110 mg, 0.4 mmol, in 5 ml of DCM) was added 1 ml of TFA, the reaction mixture was stirred at room temperature for 3 hours, the solvent was removed to yield the desired product (52 mg) in 66.8% yield. LCMS *m/z* 206.0 $(M + H)^+$ RT=0.97min.

Intermediate 139: 1-(5-(3-(trifluoromethyl)phenyl)pyrimidin-2-yl)ethanone

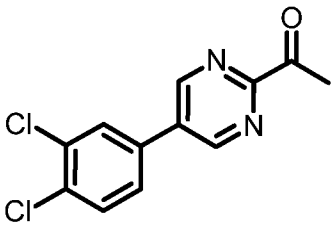


A cloudy solution of 1-(5-bromopyrimidin-2-yl)ethanone (300 mg, 1.49 mmol), 3-(trifluoromethyl)phenylboronic acid (567 mg, 2.98 mmol), K_3PO_4 (950 mg, 4.48 mmol), DavePhos ligand [2-dicyclohexylphosphino-2′-(N,N-dimethylamino)biphenyl] (59 mg, 0.15 mmol), and $Pd(OAc)_2$ (17 mg, 0.075 mmol) in 6 mL toluene was heated at 100°C for 1 h. The mixture was cooled to room temperature, and filtered through Celite. Filter cake was rinsed with 30 mL EtOAc. The filtrate was poured into 20 mL water. Layers were separated, and the aqueous was further extracted with EtOAc (20 mL). Combined organics were washed with water (20mL) and brine (20mL), dried over Na_2SO_4, filtered and concentrated directly onto silica gel. Column chromatography (10 - 100% EtOAc/heptane) gave 0.26 g 1-(5-(3-(trifluoromethyl)phenyl)pyrimidin-2-yl)ethanone (V) as tan solid. MS m/z 267.1 (M + H)+. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 2H), 7.93 – 7.69 (m, 4H), 2.87 (s, 3H).

The Following intermediates were prepared using a method similar to that described for the preparation of **Intermediate 139**. Using Anal. RP-HPLC Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50°C. Eluents =A: Water (5 mM

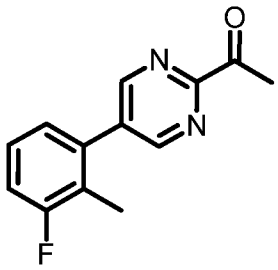
Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.)

Intermediate 140: 1-(5-(3,4-dichlorophenyl)pyrimidin-2-yl)ethanone.



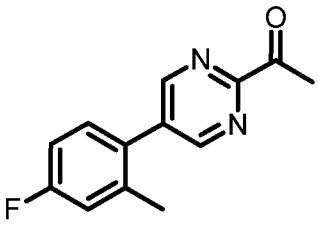
Anal. RP-HPLC tR = 1.17 min. MS m/z 266.9 (M + H)+.

Intermediate 141: 1-(5-(3-fluoro-2-methylphenyl)pyrimidin-2-yl)ethanone.



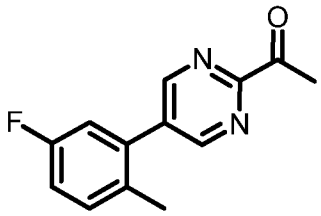
Anal. RP-HPLC tR = 1.07 min. MS m/z 231.1 (M + H)+.

Intermediate 142: 1-(5-(4-fluoro-2-methylphenyl)pyrimidin-2-yl)ethanone.



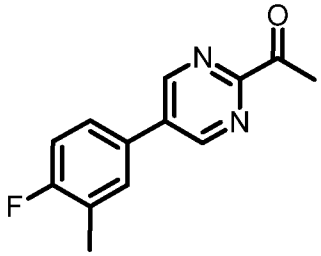
Anal. RP-HPLC tR = 1.18 min.MS m/z 231.1 (M + H)+.

Intermediate 143: 1-(5-(5-fluoro-2-methylphenyl)pyrimidin-2-yl)ethanone



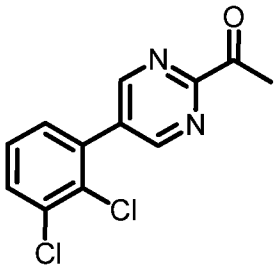
Anal. RP-HPLC tR = 1.16 min. MS m/z 231.2 (M + H)+.

Intermediate 144: 1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethanone



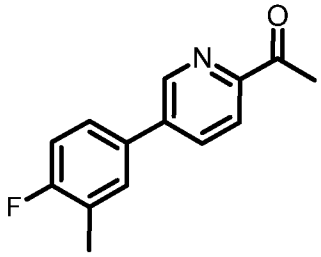
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 2H), 7.52 – 7.41 (m, 2H), 7.24 – 7.16 (m, 1H), 2.85 (s, 3H), 2.41 (d, J = 2.0 Hz, 3H). Anal. RP-HPLC tR = 1.20 min.MS m/z 231.0 (M + H)+.

Intermediate 145: 1-(5-(2,3-dichlorophenyl)pyrimidin-2-yl)ethanone



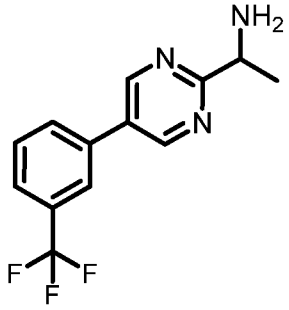
Anal. RP-HPLC tR = 1.15 min. MS m/z 267.9 (M + H)+.

Intermediate 146: 1-(5-(4-fluoro-3-methylphenyl)pyridin-2-yl)ethanone.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, J = 2.3, 0.8 Hz, 1H), 8.13 (dd, J = 8.1, 0.8 Hz, 1H), 7.98 (dd, J = 8.1, 2.3 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.21 – 7.12 (m, 1H), 2.78 (s, 3H), 2.42 – 2.36 (m, 3H). Anal. RP-HPLC tR = 1.40 min. MS m/z 230.8 (M + H)+.

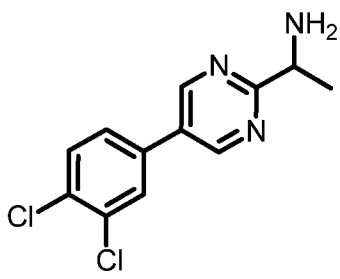
Intermediate 147: 1-(5-(3-(trifluoromethyl)phenyl)pyrimidin-2-yl)ethanamine



1-(5-(3-(Trifluoromethyl)phenyl)pyrimidin-2-yl)ethanone (260 mg, 0.977 mmol), NH4OAc (1.13 g, 14.6 mmol), and NaBH3CN (245 mg, 3.91 mmol) were taken up in 8 mL 200 proof EtOH, and heated at 120ºC for 5 minutes in a microwave apparatus. The mixture was concentrated to remove the EtOH. Crude was taken up in 30 ml water + 25 mL EtOAc. 6N NaOH was added until aqueous pH was ~10. Separated layers, and extracted aqueous with EtOAc (25 ml). The combined organic layer was washed with 25 mL brine and dried with Na_2SO_4. Filtered and concentrated with reduced pressure to give 262 mg crude yellow oil, which was carried forward without further purification. Anal. RP-HPLC tR = 0.90 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 268.1 (M + H)+.

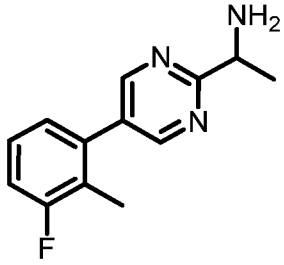
The Following intermediates were prepared using a method similar to that described for the preparation of **Intermediate 147**.

Intermediate 148: 1-(5-(3,4-dichlorophenyl)pyrimidin-2-yl)ethanamine.



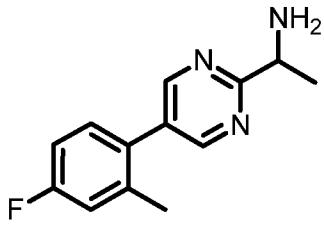
Anal. RP-HPLC tR = 1.09 min (Gradient: 2 to 98% B in 1.7 min - flow 1 mL/min. Eluent A: Water + 3.75 mM NH4Ac + 2% ACN. Column: Acquity CSH 1.7µm 2.1x50mm - 50°C.) MS m/z 268.4 (M + H)+.

Intermediate 149: 1-(5-(3-fluoro-2-methylphenyl)pyrimidin-2-yl)ethanamine.



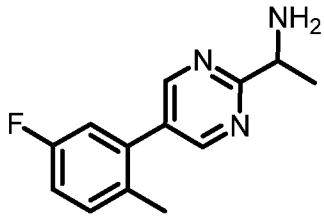
Anal. RP-HPLC tR = 0.99 min. (Gradient: 2 to 98% B in 1.7 min - flow 1 mL/min. Eluent A: Water + 3.75 mM NH4Ac + 2% ACN. Column: Acquity CSH 1.7µm 2.1x50mm - 50°C.) MS m/z 232.4 (M + H)+.

Intermediate 150: 1-(5-(4-fluoro-2-methylphenyl)pyrimidin-2-yl)ethanamine.



Anal. RP-HPLC tR = 0.87 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 231.0 (M)-.

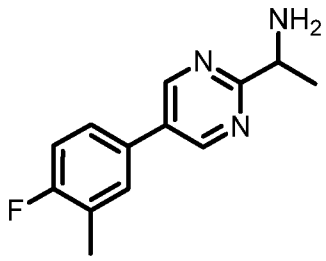
Intermediate 151: 1-(5-(5-fluoro-2-methylphenyl)pyrimidin-2-yl)ethanamine



Anal. RP-HPLC tR = 0.79 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN);

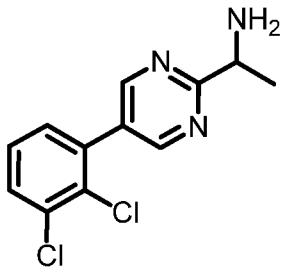
B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 232.0 (M + H)+.

Intermediate 152: 1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethanamine



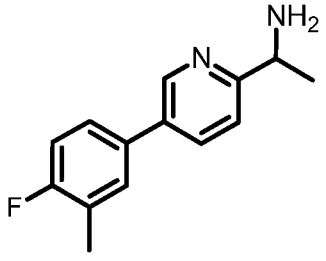
Anal. RP-HPLC tR = 0.81 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 231.9 (M + H)+.

Intermediate 153: 1-(5-(2,3-dichlorophenyl)pyrimidin-2-yl)ethanamine



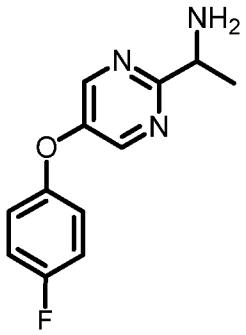
Anal. RP-HPLC tR = 1.01 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 269.0 (M + H)+.

Intermediate 154: 1-(5-(4-fluoro-3-methylphenyl)pyridin-2-yl)ethanamine



Anal. RP-HPLC tR = 0.92 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 230.9 (M + H)+.

Intermediate 155: 1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethanamine

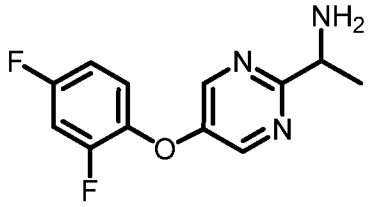


Step 1: A solution of 1-(5-fluoropyrimidin-2-yl)ethanone (700 mg, 5.0 mmol) and 4-fluorophenol (616 mg, 5.50 mmol) in 6 mL DMF was treated with potassium carbonate (829 mg 6.0 mmol) and heated to 50ºC for 3.5 h. The reaction mixture was poured into 20 mL water, and extracted with EtOAc (2 x 20 mL). Organics were washed with 20 mL each water, brine, and dried over Na_2SO_4. Mixture was filtered and concentrated on silica gel. Column chromatography (10 - 100% EtOAc/hept) gave 295 mg (25%) 1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethanone as a white solid used directly in the following step. MS m/z 233.2 (M + H)+. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 2H), 7.23 – 7.07 (m, 4H), 2.78 (s, 3H).

Step 2: 1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethanone (290 mg, 1.25 mmol), NH4OAc (1.9 g, 24.6 mmol), and $NaBH_3CN$ (314 mg, 5.00 mmol) were taken up in 20 mL 200 proof EtOH, and heated at 130 C for 3 minutes in a microwave apparatus. The mixture was concentrated to remove the EtOH. Crude was taken up in 30 ml water + 25 mL EtOAc. 6N NaOH was added until aqueous pH was ~10. Separated layers, and extracted aqueous with EtOAc (25 ml). The combined organic layer was washed with 25 mL brine and dried with Na_2SO_4. Filtered and concentrated with reduced pressure to give 275 mg crude tan oil, which was carried forward without further purification. Major product Anal. RP-HPLC tR = 1.26 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 234.1 (M + H)+.

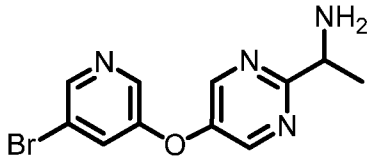
The Following intermediates were prepared using methods similar to those described for the preparation of **Intermediate 155**.

Intermediate 156: 1-(5-(2,4-difluorophenoxy)pyrimidin-2-yl)ethanamine



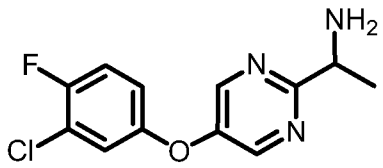
Anal. RP-HPLC tR = 0.81 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 252.1 (M + H)+.

Intermediate 157: 1-(5-(5-bromopyridin-3-yloxy)pyrimidin-2-yl)ethanamine



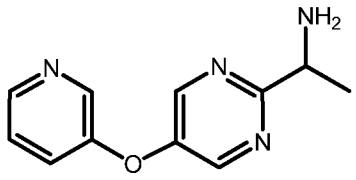
Anal. RP-HPLC tR = 1.29 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 297.3 (M + H)+.

Intermediate 158: 1-(5-(3-chloro-4-fluorophenoxy)pyrimidin-2-yl)ethanamine



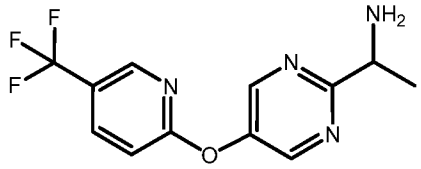
Anal. RP-HPLC tR = 1.40 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 268.0 (M + H)+.

Intermediate 159: 1-(5-(pyridin-3-yloxy)pyrimidin-2-yl)ethanamine



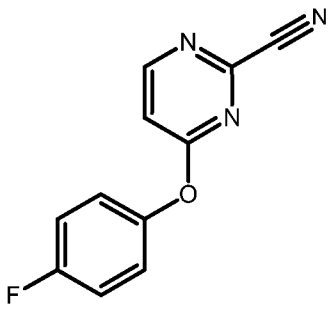
Anal. RP-HPLC tR = 1.21 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 218.4 (M + H)+.

Intermediate 160: 1-(5-(5-(trifluoromethyl)pyridin-2-yloxy)pyrimidin-2-yl)ethanamine



Anal. RP-HPLC tR = 1.16 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 285.4 (M + H)+.

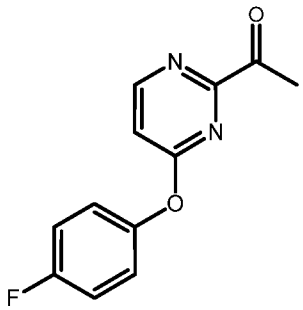
Intermediate 161: 4-(4-fluorophenoxy)pyrimidine-2-carbonitrile



A solution of 4-chloropyrimidine-2-carbonitrile (0.63 g, 4.51 mmol) and 4-fluorophenol (0.51 g, 4.51 mmol) in 5 mL DMF was cooled to 0ºC under N2 atmosphere. NaH (0.217 g of 60% suspension, 5.42 mmol) was slowly added. Bubbling exotherm observed. Internal temp was kept below 5ºC. After 15 minutes, cold bath was removed. The reaction mixture was allowed to warm to room temp and stir 1 h. The reaction mixture was diluted with water (40 mL) and extracted with (3 x 25 mL) EtOAc. The organic layer

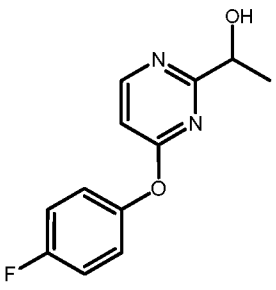
was washed with 40 mL each water, and brine. Dried over Na_2SO_4, and concentrated on silica gel in vacuo. Column chromatography (EtOAc/heptane 10 to 100% gradient) gave 0.72 g (74%) of (4-fluorophenoxy)pyrimidine-2-carbonitrile as a crystalline white solid. Anal. RP-HPLC tR = 1.38 min, Gradient: 2 to 98% B in 1.7 min - flow 1 mL/min. Eluent A: Water + 3.75 mM NH4Ac + 2% ACN. Column: Acquity CSH 1.7µm 2.1x50mm - 50°C. MS m/z 216.1 (M + H)+.

Intermediate 162: 1-(4-(4-fluorophenoxy)pyrimidin-2-yl)ethanone



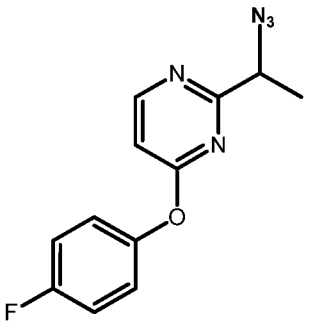
4-(4-fluorophenoxy)pyrimidine-2-carbonitrile (450 mg, 2.09 mmol) was suspended in 12 mL anhydrous ether under N2 atmosphere. Vessel was cooled to 0° C. MeMgBr (3.1 mL of 1.0 M solution in butyl ether, 3.10 mmol) was added over 5 min. The yellow-green suspension was stirred 30 minutes, then quenched with 50 mL sat'd NH4Cl solution. Adjusted pH to ~6 with conc. HCl. The mixture was extracted with (2 x 40 mL) EtOAc. Washed organics with 30 mL brine, and dried over Na_2SO_4. Filtered and concentrated on silica gel. Column chromatography (10 - 100% EtOAc in hept) gave 157 mg (32%) 1-(4-(4-fluorophenoxy)pyrimidin-2-yl)ethanone as a yellow oil. Anal. RP-HPLC tR = 1.44 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50°C. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 233.2 (M + H)+.

Intermediate 163: 1-(4-(4-fluorophenoxy)pyrimidin-2-yl)ethanol



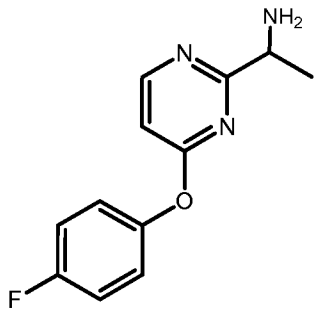
1-(4-(4-fluorophenoxy)pyrimidin-2-yl)ethanone (0.150 g 0.646 mmol) was taken up in 2.5 mL 4:1 MeOH:DCM, and cooled to 0ºC. $NaBH_4$ (49 mg 1.30 mmol) was added. Fizzing was observed. After 10 min, cold bath was removed, and the reaction was stirred 1 h. Solvent was removed in vacuo. White residue was taken up in 10 mL water, and extracted with (2 x 10 mL) EtOAc. Washed organics with 10 mL brine. Dried over Na_2SO_4. Filtered and concentrated to give 143 mg (95%) 1-(4-(4-fluorophenoxy)pyrimidin-2-yl)ethanol as a colorless oil. Anal. RP-HPLC tR = 1.38 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 235.1 (M + H)+.

Intermediate 164: 2-(1-azidoethyl)-4-(4-fluorophenoxy)pyrimidine



Under N_2 atmosphere, 1-(4-(4-fluorophenoxy)pyrimidin-2-yl)ethanol (140 mg, 0.598 mmol) was dissolved in 3 mL anhydrous DCM. Triethylamine (0.175 mL, 1.26 mmol) was added, and the mixture was cooled to 0° C. MsCl (0.070 mL, 0.897 mmol) was added, and the mixture was stirred 15 minutes. Maintaining 0°C, DCM solvent was removed under N_2 stream. Residue was taken up in 2 mL dry DMF. NaN_3 (78 mg, 1.19 mmol) added, and the reaction was stirred at rt for 24 h. Mixture was poured into 20 mL water, and extracted with 20 mL EtOAc. Organic layer was washed with 20 mL brine and dried over Na_2SO_4. Filtered and concentrated to give 120 mg (77%) 2-(1-azidoethyl)-4-(4-fluorophenoxy)pyrimidine as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 5.7 Hz, 1H), 7.16 – 6.90 (m, 4H), 6.70 (d, J = 5.7 Hz, 1H), 4.34 (q, J = 6.9 Hz, 1H), 1.55 – 1.46 (m, 3H).

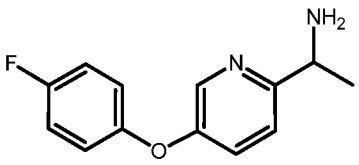
Intermediate 165: 1-(4-(4-fluorophenoxy)pyrimidin-2-yl)ethanamine



2-(1-azidoethyl)-4-(4-fluorophenoxy)pyrimidine (120 mg, 0.463 mmol) was dissolved in 2 mL neat EtOH. 24.6 mg (0.023 mmol) of 10% Palladium on carbon catalyst was added. With vigorous stirring, the reaction vial was evacuated and purged 3 times with H_2. The reaction vessel was fitted with an H_2 balloon and stirred for 2 h. The mixture was filtered through Celite and concentrated in vacuo to give 75 mg (69%) 1-(4-(4-fluorophenoxy)pyrimidin-2-yl)ethanamine as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 5.7 Hz, 1H), 7.13 – 6.92 (m, 4H), 6.59 (d, J = 5.7 Hz, 1H), 4.00 (q, J = 6.8 Hz, 1H), 1.34 – 1.30 (m, 3H). Anal. RP-HPLC tR = 1.18 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 234.2 (M + H)+.

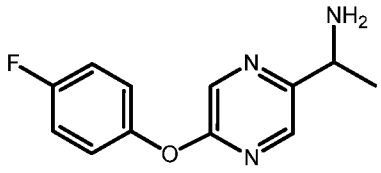
The Following intermediates were prepared using methods similar to those described for the preparation of **Intermediates 161 to 165**.

Intermediate 166: 1-(5-(4-fluorophenoxy)pyridin-2-yl)ethanamine



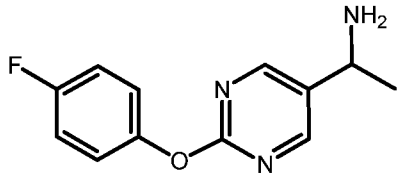
Anal. RP-HPLC tR = 0.91 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 233.1 (M + H)+.

Intermediate 167: 1-(5-(4-fluorophenoxy)pyrazin-2-yl)ethanamine



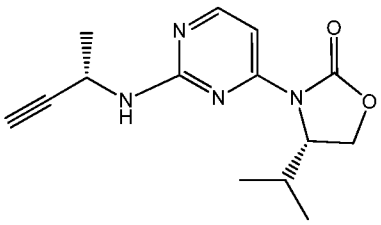
Anal. RP-HPLC tR = 1.39 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 217.1 (Major fragment + H)+.

Intermediate 168: 1-(2-(4-fluorophenoxy)pyrimidin-5-yl)ethanamine



Anal. RP-HPLC tR = 1.20 min. (Column = Inertsil C8 Column, 3.0 µm, 3.0 x 30 mm. Column Temperature =50ºC. Eluents =A: Water (5 mM Ammonium formate, 2% ACN); B: ACN. Flow Rate =2 mL/min. Gradient =0 min 5% B; 5% to 95% B in 1.70 min; 0.3 min 95% B; 2.1 min 1%B.) MS m/z 233.9 (M + H)+.

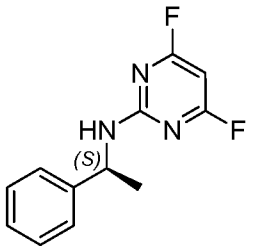
Intermediate 169: (S)-4-Isopropyl-3-[2-((S)-1-methyl-prop-2-ynylamino)-pyrimidin-4-yl]-oxazolidin-2-one



To a solution of compound (S)-3-(2-Chloro-pyrimidin-4-yl)-4-isopropyl-oxazolidin-2-one (1.03 g , 4.3 mmol) in DMSO (12 mL) was added methyl-prop-2-ynylamine HCl salt (450 mg, 4.3 mmol) and diisopropylethylamine (2.2 mL, 12.6 mmol). The reaction was heated to 110C for 18 hours. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude material was purified on silica gel column chromatography (EtOAc/Heptane 0 to 75%) provided (S)-4-Isopropyl-3-[2-((S)-1-methyl-prop-2-ynylamino)-pyrimidin-4-yl]-oxazolidin-2-one (360 mg) in 31% yield.

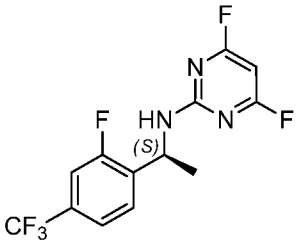
LC-MS m/z : 275.1 (M - Boc)+; RT.: 1.33 min.

Intermediate 170: (S)-4,6-difluoro-N-(1-phenylethyl)pyrimidin-2-amine



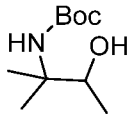
A solution of 2,4,6-trifluoropyrimidine (128.4 mg, 0.96 mmol) and isopropylethylamine (0.50 mL, 2.9 mmol, 3 equiv) in dioxane (5 mL) was cooled to 0 °C with an ice bath. After 30 min, the ice bath was removed, and the reaction was allowed to warm to room temperature. After stirriing overnight, the reaction was concentrated to a light brown oil and purified by silica gel column chromatography (EtOAc/Heptane 0 to 100%) to provide (S)-4,6-difluoro-N-(1-phenylethyl)pyrimidin-2-amine (151.2 mg, white solid) in 45% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 - 7.40 (m, 2H), 7.29 - 7.34 (m, 2H), 7.20 - 7.26 (m, 1H), 5.84 (s, 1H), 5.08 (q, *J* = 6.91 Hz, 1H), 1.52 (d, *J* = 7.04 Hz, 3H); LCMS *m/z* 236.1 $(M + H)^+$, R_t 0.95 min.

Intermediate 171: (S)-4,6-difluoro-N-(1-(2-fluoro-4-(trifluoromethyl)phenyl)ethyl) pyrimidin-2-amine



Intermediate 171 was prepared by a method similar to the one described for the preparation of Intermediate 170. ^{1}H NMR (400 MHz, CD_3OD) 7.58 (t, J = 7.63 Hz, 1H), 7.34 - 7.48 (m, 2H), 5.84 (br. s., 1H), 5.35 (q, J = 6.91 Hz, 1H), 1.54 (d, J = 7.04 Hz, 3H). MS m/z 321.9 (M + H)+, Rt 1.11 min.

Intermediate 172: tert-butyl 3-hydroxy-2-methylbutan-2-ylcarbamate



Step 1: Preparation of tert-butyl 1-(methoxy(methyl)amino)-2-methyl-1-oxopropan-2-ylcarbamate

2-(tert-butoxycarbonylamino)-2-methylpropanoic acid (6.62 g, 32.6 mmol), O,N-dimethylhydroxylamine hydrochloride (3.50 g, 35.8 mmol), and HATU (14.86 g, 39.1 mmol) were combined in DMF (100 mL). To this solution was added Hunig'sBase (17.07 mL, 98 mmol). The reaction was stirred for overnight (17 hours). The reaction was then concentrated under vacuum and the residue was diluted with EtOAc (300mL) and washed with water (2x80mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified via silica gel flash chromatography (10-50 percent EtOAc-Hexanes) to afford the desired product as a white solid (6.36 g). LCMS *m/z* 247.2 $(M + H)^+$, Rt 0.61 min.

Step 2: Preparation of tert-butyl 2-methyl-3-oxobutan-2-ylcarbamate

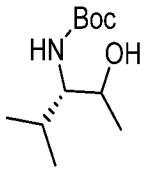
To a solution of tert-butyl 1-(methoxy(methyl)amino)-2-methyl-1-oxopropan-2-ylcarbamate (4.26 g, 17.30 mmol) in THF (100 mL) at -70 °C was added drop wise methyl lithium (32.4 mL, 51.9 mmol). Cold bath was replaced with -40 °C bath and the reaction was stirred for 4 hours. Saturated NH_4Cl solution (10mL) was then added cautiously to quench the reaction. The reaction mixture was then allowed to warm to room temperature, and diluted with EtOAc (100mL) and water (50mL). The phases were separated and the aqueous layer was extracted with EtOAc (2x100mL). The combined organics were then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified via silica gel flash chromatography (10-50% EtOAc-Hexanes) to afford the desired product as a white solid (2.36 g). LCMS *m/z* 224.2 $(M + Na)^+$, Rt 0.7 min.

Step 3: Preparation of tert-butyl 3-hydroxy-2-methylbutan-2-ylcarbamate

To a solution of tert-butyl 2-methyl-3-oxobutan-2-ylcarbamate (2.36g, 11.73 mmol) in MeOH (30mL) at 0 °C was added portion wise $NaBH_4$ (0.887 g, 23.45 mmol). Cold bath was removed and the reaction was stirred for 1 hour. HCl solution (1 M, 0.2mL) was then added cautiously to quench the reaction. The reaction mixture was then concentrated and diluted with EtOAc (50mL) and water (10mL). The phases were separated and the aqueous layer was extracted with EtOAc (2x20mL). The combined organics were then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified via silica gel flash chromatography (10-50% EtOAc-Hexanes) to

afford the desired product as a white solid (2.12 g). LCMS *m/z* 204.1 $(M + H)^+$, Rt 0.69 min.

Intermediate 173: tert-butyl ((3S)-2-hydroxy-4-methylpentan-3-yl)carbamate



Step 1: Preparation of tert-butyl 1-(methoxy(methyl)amino)-2-methyl-1-oxopropan-2-ylcarbamate

To a solution of (S)-2-(tert-butoxycarbonylamino)-3-methylbutanoic acid (5.86 g, 27.0 mmol) in DCM (100mL) at 0 °C was added portion wise di(1H-imidazol-1-yl)methanone (4.81 g, 29.7 mmol). Cold bath was removed and the reaction was stirred at 20 °C for 30 minutes. O,N-dimethylhydroxylamine hydrochloride (3.16 g, 32.4 mmol) was then added and followed by slow addition of triethylamine (3.28 g, 32.4 mmol). The reaction mixture was stirred at 20 °C for overnight (18 hr), and diluted with DCM (200mL) and washed with HCl (1 M, 2x50mL) and saturated $NaHCO_3$ solution (2x50mL), H2O (50mL) and brine (50mL). The organic was then dried (Na_2SO_4) and concentrated under reduced pressure to give crude product (6.61 g). LCMS *m/z* 261.2 $(M + H)^+$, Rt 0.77 min.

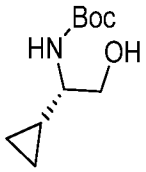
Step 2: Preparation of (S)-tert-butyl 2-methyl-4-oxopentan-3-ylcarbamate

To a solution of (S)-tert-butyl 1-(methoxy(methyl)amino)-3-methyl-1-oxobutan-2-ylcarbamate (4.23 g, 16.25 mmol) in THF (100 mL) at -70 °C was added drop wise methyl lithium (1.071 g, 48.7 mmol). Cold bath was replaced with -40 °C bath (MeCN in dry ice) removed and the reaction was stirred for 4 hours. Saturated NH_4Cl solution (10mL) was then added cautiously to quench the reaction. The reaction mixture was then allowed to warm to room temperature, and diluted with EtOAc (100mL) and water (50mL). The phases were separated and the aqueous layer was extracted with EtOAc (2x100mL). The combined organics were then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified via silica gel flash chromatography (10-50% EtOAc-Hexanes) to afford the desired product as a white solid (3.01 g). LCMS *m/z* 238.2 $(M + Na)^+$, Rt 0.78 min.

Step 3: Preparation of tert-butyl 3-hydroxy-2-methylbutan-2-ylcarbamate

To a solution of (S)-tert-butyl 2-methyl-4-oxopentan-3-ylcarbamate (2.65 g, 12.31 mmol) in MeOH (30mL) at 0 °C was added portion wise $NaBH_4$ (0.931 g, 24.62 mmol). Cold bath was removed and the reaction was stirred for 1 hour. HCl solution (1 M, 0.3 mL) was then added cautiously to quench the reaction. The reaction mixture was then concentrated and diluted with EtOAc (50mL) and water (10mL). The phases were separated and the aqueous layer was extracted with EtOAc (2x20mL). The combined organics were then dried (Na_2SO_4) and concentrated. The residue was purified via silica gel flash chromatography (10-50% EtOAc-Hexanes) to afford the desired product as a white solid (2.05 g). LCMS *m/z* 240.2 $(M + Na)^+$, Rt 0.69 min.

Intermediate 174: (S)-tert-butyl (1-cyclopropyl-2-hydroxyethyl)carbamate



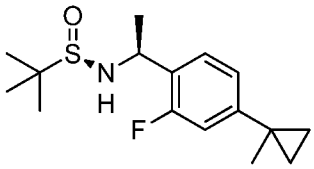
Step 1: Preparation of tert-butyl 1-(methoxy(methyl)amino)-2-methyl-1-oxopropan-2-ylcarbamate

To (S)-2-(tert-butoxycarbonylamino)-2-cyclopropylacetic acid (5.01 g, 23.28 mmol) in MeOH (50mL) was added drop wise trimethylsilyldiazomethane (18.62 ml, 37.2 mmol) until no bubbles. The reaction was stirred for 30 minutes and quenched with drops of HOAc (0.1 mL). The reaction mixture was then concentrated under reduced pressure to give crude product as a light tan oil (5.35 g). LCMS *m/z* 252.1 $(M + Na)^+$, Rt 0.77 min.

Step 2: Preparation of (S)-tert-butyl (1-cyclopropyl-2-hydroxyethyl)carbamate

To a solution of (S)-methyl 2-(tert-butoxycarbonylamino)-2-cyclopropylacetate (5.35 g, 23.33 mmol) in Et_2O (100 ml) was added $LiBH_4$ (0.762 g, 35.0 mmol), followed by drop wise addition of methanol (1.420 ml, 35.0 mmol). The reaction was refluxed at 40 °C for one hour. The reaction mixture was then cooled to 0 °C, and quenched with HCl (1M) until pH=2 for aqueous layer. The phases were separated and the aqueous layer was extracted with DCM (3x100mL). The organic was then dried (Na_2SO_4) and concentrated under reduced pressure to give final crude product (4.16 g). LCMS *m/z* 224.1 $(M + Na)^+$, Rt 0.62 min.

Intermediate 175: (R)-N-((S)-1-(2-fluoro-4-(1-methylcyclopropyl)phenyl)ethyl)-2-methylpropane-2-sulfinamide



Step 1

To an oven dried round bottom flask with stir bar was added 4-bromo-2-fluorobenzaldehyde (5 g, 24.6 mmol), (R)-2-methylpropane-2-sulfinamide (3.28 g, 27.1 mmol) and DCE (49 mL). To this mixture was then added copper (II) sulfate (5.90 g, 36.9 mmol). Reaction mixture was heated in a preheated oil bath to 55 °C for 18 hours. Reaction mixture was filtered through a pad celite, washing the solids with CH_2Cl_2. The filtrate was concentrated to afford a viscous yellow oil of (R,E)-N-(4-bromo-2-fluorobenzylidene)-2-methylpropane-2-sulfinamide (7.73 g, 25.2 mmol, 103 % yield). ^{1}H NMR (400 MHz, $CDCL_3$) δ 1.27 (s, 9 H) 7.31 - 7.42 (m, 2 H) 7.87 (t, *J*=7.87 Hz, 1 H) 8.83 (s, 1 H). LCMS *m/z* 307.9 $(M + H)^+$, Rt 1.01 min.

Step 2

To a solution of (R,E)-N-(4-bromo-2-fluorobenzylidene)-2-methylpropane-2-sulfinamide (7.73 g, 25.2 mmol) in CH_2Cl_2 (252 mL), cooled to 0°C (water/ice bath) under nitrogen, was added 3M methyl magnesium bromide (33.7 mL, 101 mmol) in Et_2O. Reaction mixture allowed to stir for 30 min at 0°C, then gradually allowed to warm to room temperature and stirred for 1 hour at room temperature. Reaction mixture was cooled to 0°C then quenched with the slow addition of a saturated solution of NH_4Cl. Aqueous mixture extracted with EtOAc. Organic phases combined, washed with water, brine, dried (Na_2SO_4), filtered and concentrated onto silica gel. Silica gel column chromatography (EtOAc/Heptane 40 to 100%) provided (R)-N-((S)-1-(4-bromo-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (4.93 g, 15.3 mmol, 60% yield) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCL_3$) δ 1.20 (s, 9 H) 1.56 (d, *J*=6.70 Hz, 3 H) 3.34 (br. s., 1 H) 4.77 - 4.87 (m, 1 H) 7.19 - 7.31 (m, 3 H). LCMS *m/z* 324.0 $(M + H)^+$, Rt 0.90 min.

Step 3

To a microwave vial with stir bar was added (R)-N-((S)-1-(4-bromo-2-fluorophenyl)ethyl)-2-methylpropane-2- (1 g, 3.10 mmol), isopropenyl boronic acid pinacol ester (1.51 ml, 8.07 mmol), DME (8 ml), sodium carbonate (7.76 ml, 15.5 mmol) (2.0 M aq) and $PdCl_2$(dppf). CH_2Cl_2 adduct (0.127 g, 0.155 mmol). Vessel was capped and heated by microwave irradiation for 20 min at 100 °C. Reaction mixture was diluted with a saturated solution of NH_4Cl. The aqueous mixture was extracted with EtOAc. Organic phases combined, washed with water, brine, dried (Na_2SO_4), filtered and concentrated onto silica gel. Silica gel column chromatography (EtOAc/Heptane 50 to 100%) provided (R)-N-((S)-1-(2-fluoro-4-(prop-1-en-2-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (830 mg, 2.93 mmol, 94 % yield) as a pale brown crystalline. ^{1}H NMR (400 MHz, DMSO) δ 1.08 - 1.11 (m, 9 H) 1.47 (d, *J*=6.80 Hz, 3 H) 2.09 (d, *J*=0.54 Hz, 3 H) 4.61 - 4.71 (m, 1 H) 5.14 (t, *J*=1.32 Hz, 1 H) 5.43 (d, *J*=5.58 Hz, 1 H) 5.49 (s, 1 H) 7.24 - 7.30 (m, 1 H) 7.31 - 7.36 (m, 1 H) 7.41 - 7.47 (m, 1 H). LCMS *m/z* 284.0 $(M + H)^+$, Rt 0.93 min.

Step 4

To a round bottom flask containing (R)-N-((S)-1-(2-fluoro-4-(prop-1-en-2-yl)phenyl)ethyl)-2-methylpropane-2- (0.37 g, 1.31 mmol) in DCE (13 mL) at 0 °C was added under argon diethylzinc (1.0M in hexanes) (13.1 mL, 13.1 mmol) followed by the dropwise addition of chloroiodomethane (0.95 mL, 13.1 mmol). Reaction mixture allowed to warm to room temperature and stirred for 1 hour. Reaction mixture was cooled to 0 °C whereupon a second addition of diethylzinc (1.0M in hexanes) (13.1 mL, 13.1 mmol) took place followed by the addition of chloroiodomethane (0.95 mL, 13.1 mmol). Reaction mixture allowed to warm to room temperature and stirred 18 hours under argon. Reaction mixture was cooled to 0 °C in a ice bath and to the cold reaction mixture was slowly added a saturated solution of NH_4Cl. The aqueous mixture was extracted with EtOAc. Organic phases combined, washed with water, brine, dried (Na_2SO_4), filtered and concentrated onto silica gel. Silica gel column chromatography (EtOAc/Heptane 20 to 100%) provided a white crystalline of (R)-N-((S)-1-(2-fluoro-4-(1-methylcyclopropyl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (89 mg, 0.299 mmol, 22.92 % yield). ^{1}H NMR (400 MHz, $CDCL_3$) δ 0.75 - 0.79 (m, 2 H) 0.85 - 0.90 (m, 2 H) 1.20 (s, 9 H) 1.55 (s, 3 H) 1.57 (d, *J*=6.80 Hz, 1 H) 3.34 (d, *J*=5.23 Hz, 1 H) 4.75 - 4.85 (m, 1 H) 6.90 (dd, *J*=12.30, 1.74 Hz, 1 H) 6.97 (dd, *J*=8.05, 1.78 Hz, 1 H) 7.22 (t, *J*=7.97 Hz, 1 H). LCMS *m/z* 298.1 $(M + H)^+$, Rt 1.01 min.

The Intermediates in Table 4k were prepared by a method similar to the one described for the preparation of Intermediate 175.

Table 4k

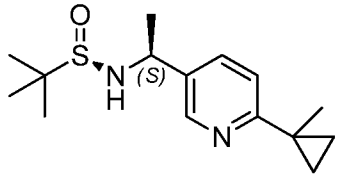
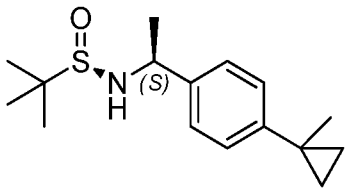
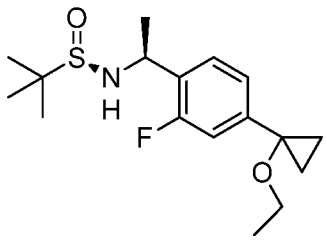
Intermediate 176	Intermediate 177
	

Table 4m. Chemical name, NMR chemical shifts and LCMS signal for each intermediate listed in Table 4k.

Intermediate: Name	^{1}H NMR (400 MHz) δ ppm	LCMS
176: (R)-2-methyl-N-((S)-1-(6-(1-methylcyclopropyl)pyridin-3-yl)ethyl) propane-2-sulfinamide		MS *m/z* 282.1 (M + H)$^+$, Rt 0.48 min.
177: (R)-2-methyl-N-((S)-1-(4-(1-methylcyclopropyl) phenyl)ethyl) propane-2-sulfinamide	($CDCl_3$) 0.71 - 0.76 (m, 2 H) 0.85 - 0.89 (m, 2 H) 1.20 - 1.22 (m, 9 H) 1.41 (s, 3 H) 1.53 (d, *J*=6.65 Hz, 3 H) 3.29 (d, *J*=3.57 Hz, 1 H) 4.50 - 4.57 (m, 1 H) 7.21 (s, 2 H) 7.23 (s, 2 H)	MS *m/z* 280.1 (M + H)$^+$, Rt 0.98 min.

Intermediate 178: (R)-N-((S)-1-(4-(1-ethoxycyclopropyl)-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide



Step 1

To a microwave vial with stir bar was added (R)-N-((S)-1-(4-bromo-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (500 mg, 1.55 mmol) followed by the addition of tributyl(1-ethoxyvinyl)stannane (1.12 g, 3.10 mmol), triethylamine (0.65 ml, 4.65 mmol) and $PdCl_2$(dppf). CH_2Cl_2 adduct (63 mg, 0.078 mmol). To the solids was added toluene (10 ml). Vial capped and heated in a preheated sand bath at 100 °C for 1 hour. Reaction mixture was loaded onto silica gel column. Silica gel column chromatography

(MeOH/ CH_2Cl_2 0 to 10% with 1% NH_4OH buffer) provided (R)-N-((S)-1-(4-(1-ethoxyvinyl)-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (498 mg, 1.59 mmol, 102 % yield) as a brown viscous oil which crystallizes upon standing. ^{1}H NMR (400 MHz, $CDCL_3$) δ 1.20 (s, 9 H) 1.43 (t, *J*=6.97 Hz, 3 H) 1.58 (d, *J*=6.75 Hz, 3 H) 3.35 (d, *J*=4.74 Hz, 1 H) 3.92 (q, *J*=6.96 Hz, 2H) 4.23 (d, *J*=2.79 Hz, 1 H) 4.65 (d, *J*=2.79 Hz, 1 H) 4.79 - 4.89 (m, 1 H) 7.16 - 7.20 (m, 1 H) 7.29 - 7.34 (m, 1 H) 7.39 (dd, *J*=8.07, 1.66 Hz, 1 H).

Step 2

To a round bottom flask containing (R)-N-((S)-1-(4-(1-ethoxyvinyl)-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (0.49 g, 1.56 mmol) and chloroiodomethane (1.14 mL, 15.6 mmol) in toluene (15 mL) at 0 °C under argon was added diethylzinc (1.0M in hexanes) (15.6 mL, 15.6 mmol). Reaction mixture allowed to warm to room temperature and stirred for 1 hour. Reaction mixture was cooled to 0 °C in an ice bath and to the cold reaction mixture was slowly added a saturated solution of NH_4Cl. The aqueous mixture was extracted with EtOAc. Organic phases combined, washed with water, brine, dried (Na_2SO_4), filtered and concentrated onto silica gel. Silica gel column chromatography ($MeOH/CH_2Cl_2$ 0 to 10%) provided (R)-N-((S)-1-(4-(1-ethoxycyclopropyl)-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (145 mg, 0.44 mmol, 28 % yield) as a viscous brown oil. ^{1}H NMR (300 MHz, $CDCL_3$) δ 0.93 - 0.99 (m, 2 H) 1.14 - 1.20 (m, 3 H) 1.21 (s, 9 H) 1.22 - 1.27 (m, 2 H) 1.57 - 1.61 (m, 4 H) 3.35 (d, *J*=4.98 Hz, 1 H) 3.45 (q, *J*=7.07 Hz, 2 H) 4.77 - 4.87 (m, 1 H) 6.98 (dd, *J*=7.58, 1.43 Hz, 3 H) 7.00 - 7.03 (m, 4 H) 7.28 - 7.32 (m, 1 H). LCMS *m/z* 328.1 $(M + H)^+$, Rt 0.95 min.

The Intermediate in Table 4n were prepared by a method similar to the one described for the preparation of Intermediate 178.

Table 4n.

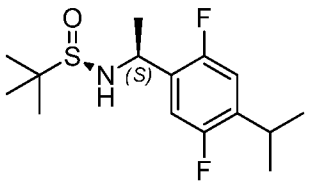
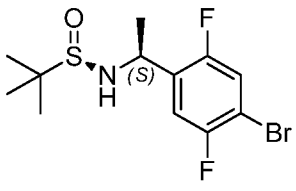
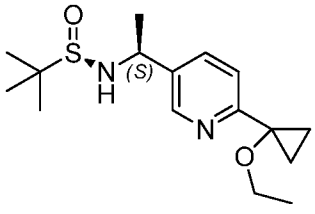
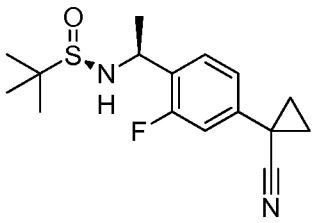
Intermediate 179	Intermediate 180	Intermediate 181
		

Table 4p. Chemical name, NMR chemical shifts and LCMS signal for each intermediate listed in Table 4n.

Intermediate: Name	^{1}H NMR (400 MHz) δ ppm	LCMS
179: (R)-N-((S)-1-(2,5-difluoro-4-isopropylphenyl)ethyl)-2-methylpropane-2-sulfinamid		MS *m/z* 304.2 $(M + H)^+$, Rt 1.04 min.
180: (R)-N-((S)-1-(4-bromo-2,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide		MS *m/z* 340.1, 342.1 $(M + H)^+$, Rt 0.96 min.
181: (R)-N-((S)-1-(6-(1-ethoxycyclopropyl)pyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide		MS *m/z* 311.1 $(M + H)^+$, Rt 0.52 min.

Intermediate 182: (R)-N-((S)-1-(4-(1-cyanocyclopropyl)-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide



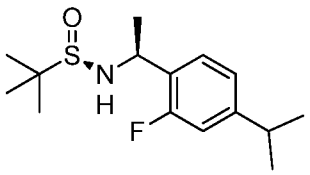
Step 1

To a microwave vial with a stir bar was added (R)-N-((S)-1-(4-bromo-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (300 mg, 0.93 mmol), 4-isoxazoleboronic acid pinacol ester (218 mg, 1.12 mmol), $PdCl_2(dppf).CH_2Cl_2$ adduct (76 mg, 0.09 mmol), potassium fluoride (2.7 mL, 1.0 M in water, 2.79 mmol) and finally DMSO (9 mL). The reaction mixture was degassed with bubbling nitrogen (3 min) and the vial capped and heated in a preheated oil bath at 130 °C for 18 hours. The reaction mixture was diluted with a saturated solution of NH_4Cl and extracted with EtOAc. Organic phases combined, washed with water, brine, dried (Na_2SO_4), filtered and concentrated onto silica gel. Silica gel column chromatography (EtOAc/Heptanes 40 to 100%) provided (R)-N-((S)-1-(4-(cyanomethyl)-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (136 mg, 0.48 mmol, 52 % yield) as a viscous brown oil. ^{1}H NMR (400 MHz, $CDCL_3$) δ 1.19 (s, 9 H) 1.57 (d, *J*=6.80 Hz, 3 H) 3.39 (d, *J*=4.35 Hz, 1 H) 3.74 (s, 2 H) 4.81 - 4.88 (m, 1 H) 7.04 (d, *J*=10.66 Hz, 1 H) 7.11 (d, *J*=7.97 Hz, 1 H) 7.38 (t, *J*=7.73 Hz, 1 H). LCMS *m/z* 283.0 $(M + H)^+$, Rt 0.72 min.

Step 2

To a scintillation vial containing (R)-N-((S)-1-(4-(cyanomethyl)-2-fluorophenyl)ethyl)-2-methylpropane-2- (86 mg, 0.31 mmol) and a stir bar was added toluene (2 mL). To this mixture was then added tetrabutylammonium bromide (19 mg, 0.06 mmol) followed by the addition of NaOH (1.52 ml, 1.0 M (aq), 1.52 mmol) and 1,2-dibromoethane (0.11 ml, 1.22 mmol). Vial capped and reaction mixture was stirred vigorously at room temperature for 18 hours. Whereupon, 1,2-dibromoethane (0.11 ml, 1.22 mmol) and tetrabutylammonium bromide (19 mg, 0.06 mmol) were added and reaction mixture allowed to stir an additional 18 hours. A third addition of 1,2-dibromoethane (0.11 ml, 1.22 mmol) was added and the reaction mixture heated to 50 °C for an additional 18 hours in a preheated aluminum tray. The reaction mixture was quenched with a saturated solution of NH_4Cl and the aqueous mixture extracted with EtOAc. Organics combined and washed twice with water, brine, dried (Na_2SO_4), filtered and concentrated. Crude material was passed through a small plug of silica gel using 10%MeOH:90%DCM to elute product. The solution was concentrated to afford a viscous orange oil of (R)-N-((S)-1-(4-(1-cyanocyclopropyl)-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (23 mg, 0.08 mmol, 24 % yield). ^{1}H NMR (400 MHz, $CDCL_3$) δ 1.20 (s, 9 H) 1.38 - 1.44 (m, 2 H) 1.56 (d, *J*=6.75 Hz, 3 H) 1.73 - 1.79 (m, 2 H) 3.37 (d, *J*=4.45 Hz, 1 H) 4.78 - 4.88 (m, 1 H) 6.94 (dd, *J*=11.35, 1.91 Hz, 1 H) 7.09 (dd, *J*=8.07, 1.91 Hz, 1 H) 7.34 (t, *J*=7.90 Hz, 1 H). LCMS *m/z* 309.2 $(M + H)^+$, Rt 0.83 min.

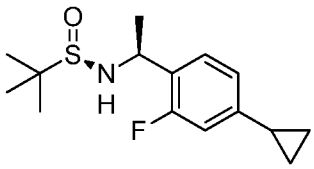
Intermediate 183: (R)-N-((S)-1-(2-fluoro-4-isopropylphenyl)ethyl)-2-methylpropane-2-sulfinamide



To a round bottom flask containing (R)-N-((S)-1-(2-fluoro-4-(prop-1-en-2-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (204 mg, 0.72 mmol) and a stir bar was added MeOH (7.2 mL). To this solution was added palladium on carbon (77 mg, 10%, 0.07 mmol) in MeOH (1 mL). A hydrogen atmosphere was inserted and the resulting reaction mixture stirred at room temperature for 18 hours, at which time more palladium on carbon was added (300 mg) in MeOH (5 mL). A hydrogen atmosphere was inserted again and the reaction mixture allowed to stir an additional 18 hours at room temperature. The reaction mixture was filtered through a syringe filter and concentrated to afford a light brown

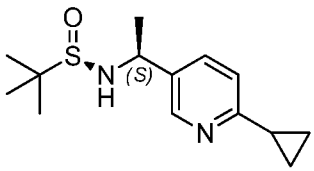
viscous oil of (R)-N-((S)-1-(2-fluoro-4-isopropylphenyl)ethyl)-2-methylpropane-2-sulfinamide (149 mg, 0.52 mmol, 73 % yield) which crystallizes upon standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9 H) 1.24 (d, *J*=5.87 Hz, 6 H) 1.58 (d, *J*=6.70 Hz, 3 H) 2.89 (dt, *J*=13.79, 6.90 Hz, 1 H) 3.35 (d, *J*=5.04 Hz, 1 H) 4.76 - 4.85 (m, 1 H) 6.90 (dd, *J*=12.03, 1.52 Hz, 1 H) 6.98 (dd, *J*=7.90, 1.54 Hz, 1 H) 7.24 (t, *J*=7.97 Hz, 1 H). LCMS *m/z* 286.3 $(M + H)^+$, Rt 1.01 min.

Intermediate 184: (R)-N-((S)-1-(4-cyclopropyl-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide



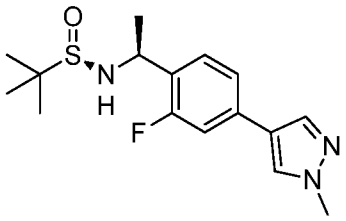
To a microwave vial containing a stir bar was added (R)-N-((S)-1-(4-bromo-2-fluorophenyl) ethyl)-2-methylpropane-2-sulfinamide (100 mg, 0.31 mmol) followed by the addition of potassium cyclopropyltrifluoroborate (459 mg, 3.10 mmol), cesium carbonate (506 mg, 1.55 mmol) and $Pd(OAc)_2$ (7 mg, 0.03 mmol) and di(1-adamantyl)-n-butylphosphine (22 mg, 0.06 mmol), toluene (2.6 mL) and finally water (0.5 mL). The vial capped and heated by microwave irraditation for 20 min at 100 °C, followed by thermal heating at 100°C in a preheated aluminum tray for 18 hours. The reaction mixture was diluted with a saturated solution of NH_4Cl. The aqueous mixture extracted with EtOAc. Organic phases combined, washed with water, brine, dried (Na_2SO_4), filtered and concentrated to afford a yellow crystalline of (R)-N-((S)-1-(4-cyclopropyl-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (116 mg, 0.33 mmol, 106 % yield). LCMS *m/z* 284.0 $(M + H)^+$, Rt 0.90 min.

Intermediate 185: (R)-N-((S)-1-(6-cyclopropylpyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide



(R)-N-((S)-1-(6-cyclopropylpyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide is prepared with a method similar to that used to access Intermediate 184. MS m/z 267.1 (M + H)+, Rt 0.44 min.

Intermediate 186: (R)-N-((S)-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide



To a two microwave vials with stir bars were added (R)-N-((S)-1-(4-bromo-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (1.5 g, 4.65 mmol), 1-methyl-4-1H-pyrazoleboronic acid pinacol ester (2.91 g, 13.9 mmol), DME (20 mL), sodium carbonate (11.6 mL, 23.3 mmol, 2.0 M aq) and $PdCl_2(dppf).CH_2Cl_2$ adduct (190 mg, 0.23 mmol) divided between the two vials. The vials were capped and heated by microwave irradiation for 20 min at 100 °C respectively. The reaction mixtures combined, diluted with a saturated solution of NH_4Cl and EtOAc. The phases were partitioned and the aqueous phase extracted with EtOAc. Organic phases combined, washed with water, brine, dried (Na_2SO_4), filtered and concentrated onto silica gel. Silica gel column chromatography (EtOAc/Heptane 40 to 100%) provided a orange crystalline of (R)-N-((S)-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (1.07 g, 3.31 mmol, 71 % yield. ^{1}H NMR (400 MHz, $CDCL_3$) δ ppm 1.21 (s, 9 H) 1.60 (d, *J*=6.80 Hz, 3 H) 3.36 (d, *J*=4.25 Hz, 1 H) 3.96 (s, 3 H) 4.79 - 4.91 (m, 1 H) 7.13 (dd, *J*=11.69, 1.61 Hz, 1 H) 7.23 (dd, *J*=8.00, 1.64 Hz, 1 H) 7.30 - 7.37 (m, 1 H) 7.60 (s, 1 H) 7.74 (s, 1 H). LCMS *m/z* 324.0 $(M + H)^+$, Rt 0.74 min.

The Intermediates in Table 4q were prepared by a method similar to the one described for the preparation of Intermediate 186.

Table 4q.

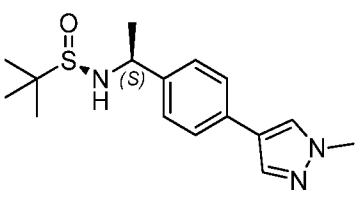
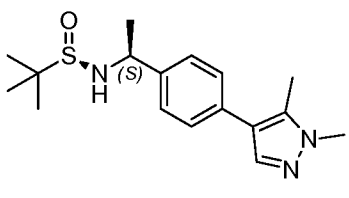
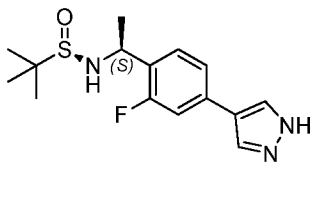
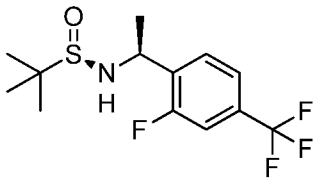
Intermediate 187	Intermediate 188	Intermediate 189
		

Table 4r. Chemical name, NMR chemical shifts and LCMS signal for each intermediate listed in Table 4q.

Intermediate: Name	^{1}H NMR (400 MHz) δ ppm	LCMS
187: (R)-2-methyl-N-((S)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)propane-2-sulfinamide		MS *m/z* 306.0 (M + H)$^+$, Rt 0.71 min.
188: (R)-N-((S)-1-(4-(1,5-dimethyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide		MS *m/z* 320.0 (M + H)$^+$, Rt 0.72 min.
189: (R)-N-((S)-1-(2-fluoro-4-(1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide	(DMSO) 1.10 (s, 9 H) 1.47 (d, *J*=6.75 Hz, 3 H) 4.60 - 4.70 (m, 1 H) 5.41 (d, *J*=5.48 Hz, 1 H) 7.38 - 7.44 (m, 3 H) 7.96 (br. s., 1 H) 8.23 (br. s., 1 H) 12.97 (br. s., 1 H)	MS *m/z* 310.0 (M + H)$^+$, Rt 0.67 min.

Intermediate 190: (R)-N-((S)-1-(2-fluoro-4-(trifluoromethyl)phenyl)ethyl)-2-methylpropane-2-sulfinamide



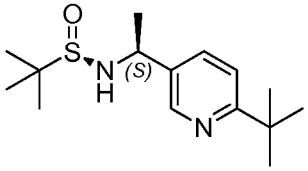
Step 1

To a oven dried round bottom flask with stir bar was added 2-fluoro-4-(trifluoromethyl) benzaldehyde (5 g, 26.0 mmol), (R)-2-methylpropane-2-sulfinamide (3.47 g, 28.6 mmol) and DCE (52 mL). To this mixture was then added copper (II) sulfate (6.23 g, 39.0 mmol). The reaction mixture was heated in a preheated oil bath at 55 °C for 18 hours. The reaction mixture was filtered through a pad celite, washing the solids with DCE. The filtrate was concentrated to afford a viscous green oil of (R,E)-N-(2-fluoro-4-(trifluoromethyl)benzylidene)-2-methyl propane-2-sulfinamide (7.3 g, 24.7 mmol, 95 % yield). Material was taken onto next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.29 (s, 9 H) 7.44 (d, *J*=10.08 Hz, 1 H) 7.51 (d, *J*=8.27 Hz, 1 H) 8.13 (t, *J*=7.46 Hz, 1 H) 8.92 (s, 1 H). LCMS *m/z* 296.0 (M + H)$^+$, Rt 1.02 min.

Step 2

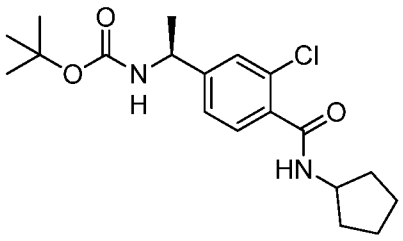
To a solution of (R,E)-N-(2-fluoro-4-(trifluoromethyl)benzylidene)-2-methylpropane-2-sulfinamide (7.3 g, 24.7 mmol) in CH_2Cl_2 (247 mL) cooled to 0°C (water/ice bath) under nitrogen, was added 3M methyl magnesium bromide (33 mL, 99 mmol) in Et_2O. Reaction mixture allowed to stir for 30 min at 0°C, then gradually allowed to warm to room temperature and stirred for 1 hour at room temperature. Reaction mixture was cooled to 0°C then quenched with the slow addition of a saturated solution of NH_4Cl. Aqueous mixture extracted with EtOAc. Organic phases combined, washed with water, brine, dried (Na_2SO_4), filtered and concentrated onto silica gel. Silica gel column chromatography (EtOAc/Heptane 40 to 100%) provided (R)-N-((S)-1-(2-fluoro-4-(trifluoromethyl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (4.68 g, 15.0 mmol, 61% yield) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCL_3$) δ 1.22 (s, 9 H) 1.60 (d, *J*=6.80 Hz, 3 H) 3.38 (d, *J*=4.01 Hz, 1 H) 4.87 - 4.97 (m, 1 H) 7.33 (d, *J*=10.32 Hz, 1 H) 7.39 - 7.45 (m, 1 H) 7.49 - 7.55 (m, 1 H). LCMS *m/z* 312.0 $(M + H)^+$, Rt 0.92 min.

Intermediate 191: (R)-N-((S)-1-(6-tert-butylpyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide



(R)-N-((S)-1-(6-tert-butylpyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide is prepared with methods similar to those used to prepare Intermediate 190. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9 H) 1.37 (s, 9 H) 1.57 (d, *J*=6.75 Hz, 3 H) 3.31 (d, *J*=3.37 Hz, 1 H) 4.56 - 4.65 (m, 1 H) 7.32 (d, *J*=8.22 Hz, 1 H) 7.57 (dd, *J*=8.24, 2.23 Hz, 1 H) 8.54 (d, *J*=2.05 Hz, 1 H). MS m/z 283.1 (M + H)+, Rt 0.51 min.

Intermediate 192: (S)-tert-butyl 1-(3-chloro-4-(cyclopentylcarbamoyl)phenyl)ethyl carbamate



Step 1

To a round bottom flask with stir bar was added 4-((S)-1aminoethyl-2-chlorobenzoic acid HCl salt (1.05 g, 4.45 mmol) followed by the addition of THF (40 mL). To this solution was added DIEA (1.86 ml, 10.7 mmol). The reaction mixture becomes cloudy white followed by the addition of di-tert-butyl dicarbonate (1.07 g, 4.89 mmol). Resulting reaction mixture allowed to stir for 18 hours at room temperature. At which time the reaction mixture was then heated to 60 °C for 2 hours in a oil bath. Di-tert-butyl dicarbonate (1.07 g, 4.89 mmol) and NMP (20 ml) were then added and the resulting reaction mixture allowed to stir for 2 hours at 60 °C. Volatiles were removed. The resulting oil was diluted with a saturated solution of NH_4Cl and the aqueous mixture extracted with EtOAc. The organic phases combined, washed twice with water, brine, dried (Na_2SO_4), filtered and concentrated to a viscous yellow oil of (S)-4-(1-(tert-butoxycarbonylamino)ethyl)-2-chlorobenzoic acid (2.32 g, 6.19 mmol, 139 % yield) which contains some excess di-tert-butyl dicarbonate and NMP. LCMS *m/z* 284.9 $(M + H)^+$(carboxylic acid fragment + CH_3CN adduct), Rt 0.75 min.

Step 2

To a round bottom flask with stir bar was added (S)-4-(1-(tert-butoxycarbonylamino)ethyl)-2-chlorobenzoic acid (450 mg, 1.20 mmol), cyclopentylamine (355 µL, 3.60 mmol), EDC HCl (460 mg, 2.40 mmol), 1-hydroxy-7-aza-benzotriazole (229 mg, 1.68 mmol) and DMF (6 mL). To this mixture was then added DIEA (629 µL, 3.60 mmol). Reaction mixture was allowed to stir at room temperature for 18 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic phases were combined, washed with twice with water, brine, dried (Na_2SO_4), filtered and concentrated to a brown crystalline of (S)-tert-butyl 1-(3-chloro-4-(cyclopentylcarbamoyl) phenyl)ethylcarbamate (476 mg, 1.17 mmol, 97 % yield). LCMS *m/z* 367.0 $(M + H)^+$, Rt 0.90 min.

The Intermediates in Table 4s were prepared by a method similar to the one described for the preparation of Intermediate 192.

Table 4s.

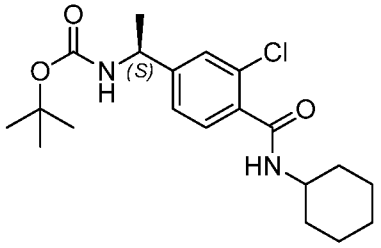
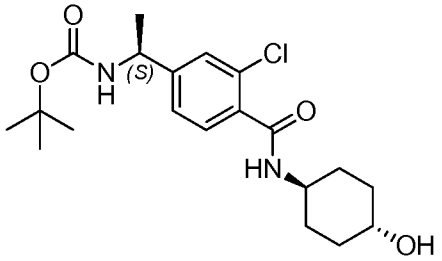
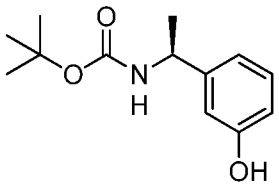
Intermediate 193	Intermediate 194
	

Table 4t. Chemical name and LCMS signal for each intermediate listed in Table 4s.

Intermediate: Name	LCMS
193: (S)-tert-butyl 1-(3-chloro-4-(cyclohexyl carbamoyl) phenyl) ethylcarbamate	MS *m/z* 381.1 (M + H)$^+$, Rt 0.96 min.
194: tert-butyl (S)-1-(3-chloro-4-((1r,4S)-4-hydroxycyclohexyl carbamoyl)phenyl)ethylcarbamate	MS *m/z* 391.1 (M + H)$^+$, Rt 0.71 min.

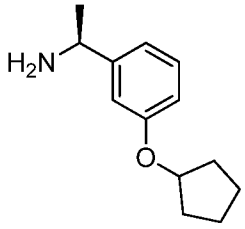
Intermediate 195: (S)-tert-butyl 1-(3-hydroxyphenyl)ethylcarbamate



A slurry of (S)-3-(1-aminoethyl)phenol (1.188 g, 6.84 mmol) and Boc_2O (1.747 mL, 7.53 mmol) in DCM (17.10 mL) was stirred at room temperature under N_2 while slowly adding DIEA (1.434 mL, 8.21 mmol). The initially insoluble starting materials slowly dissolve. The solution was stirred at room temperature for 16 hours and then concentrated. The oily residue was re-dissolved in EtOAc and washed with Na_2CO_3 saturated, followed by brine. The original aqueous layer was re-extracted with EtOAc, which was then washed with brine and combined with the previous EtOAc batch. The combined organics were dried over Na_2SO_4, filtered and concentrated to 2.4g crude clear yellowish oil which was purified by silica gel column chromatography (EtOAc/Heptane 0 to 30%), yielding (S)-tert-butyl 1-(3-hydroxyphenyl)ethylcarbamate as a clear colourless oil, which solidifies upon sitting (1.79 g, 7.55 mmol, 110 % yield). ^1H NMR (400 MHz, $CDCL_3$) δ 1.44 (br. s.,

12 H) 4.08 - 4.18 (m, 1 H) 4.76 (br. s., 1 H) 6.72 (dd, *J*=7.46, 1.83 Hz, 1 H) 6.78 (br. s., 1 H) 6.88 (br. s., 1 H) 7.16 - 7.24 (m, 1 H). LCMS *m/z* 223.0/182.0 (the parent not observed, just the Boc fragments) $(M + H)^+$, Rt 0.71 min.

Intermediate 196: (S)-1-(3-(cyclopentyloxy)phenyl)ethanamine hydrochloride



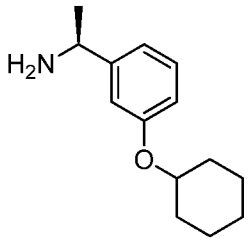
Step 1: Mitsunobu A

To a solution of (S)-tert-butyl 1-(3-hydroxyphenyl)ethylcarbamate (107.5 mg, 0.453 mmol), PPh_3 (238 mg, 0.906 mmol) and cyclopentanol (0.164 ml, 1.812 mmol) in THF (2 ml) at room temperature was added DEAD (0.143 ml, 0.906 mmol) dropwise under N_2. The resulting yellow solution was stirred for 4 hours and then concentrated. The viscous yellow oil was re-dissolved in DMSO and purified by reverse phase HPLC. The combined product fractions were desalted by addition of equal amount of EtOAc and about 250mg Na_2CO_3 in a separatory funnel. The phases were separated and the organic washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield (S)-tert-butyl 1-(3-(cyclopentyloxy)phenyl)ethylcarbamate (75.1 mg, 0.246 mmol, 54.3 % yield) as a white solid film. LCMS *m/z* 291.1/250.0 (the parent not observed, just the Boc fragments) $(M + H)^+$, Rt 1.07 min.

Step 2

(S)-tert-butyl 1-(3-(cyclopentyloxy)phenyl)ethylcarbamate (75.1 mg, 0.246 mmol) was dissolved in 4M HCl in dioxane (1 ml, 4.00 mmol) and the resulting mixture was allowed to sit for 1hour, then concentrated to yield (S)-1-(3-(cyclopentyloxy)phenyl)ethanamine as an HCl salt (yield assumed quantitative). LCMS *m/z* 206.1 $(M + H)^+$, Rt 0.61 min.

Intermediate 197: (S)-1-(3-(cyclohexyloxy)phenyl)ethanamine hydrochloride



Step 1: Mitsunobu B

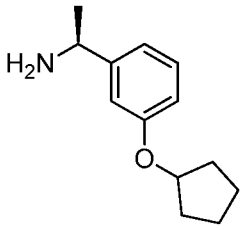
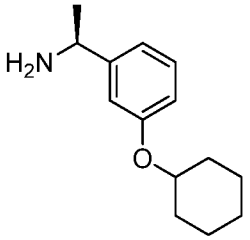
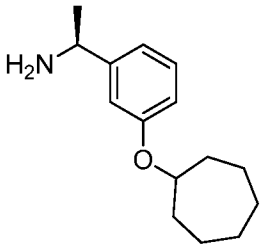
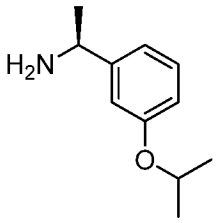
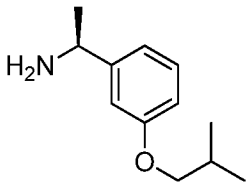
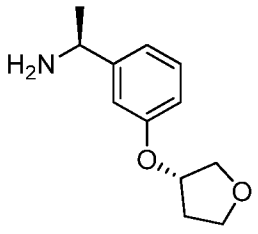
To a solution of (S)-tert-butyl 1-(3-hydroxyphenyl)ethylcarbamate (100 mg, 0.421 mmol), cyclohexanol (0.180 ml, 1.686 mmol) and PPh_3 (221 mg, 0.843 mmol) in THF (2 ml), was added DEAD (0.133 ml, 0.843 mmol) dropwise, under N_2, at room temperature. The resulting yellow solution was stirred for 3 hours, at which point another batch of cyclohexanol (0.180 ml, 1.686 mmol), PPh_3 (221 mg, 0.843 mmol), and 10min later DEAD (0.133 ml, 0.843 mmol), was added at room temperature. The reaction mixture was stirred for 16 hours and then concentrated. The crude clear oil was re-dissolved in DMSO and purified by reverse phase HPLC. The combined product fractions were desalted by addition of equal amount of EtOAc and about 250mg Na_2CO_3 in a separatory funnel. The phases were separated and the organic washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield (S)-tert-butyl 1-(3-(cyclohexyloxy)phenyl)ethylcarbamate (74.1 mg, 0.232 mmol, 55.0 % yield) as a clear colourless film. LCMS *m/z* 305.0/264.0 (the parent not observed, just the Boc fragments) $(M + H)^+$, Rt 1.12 min.

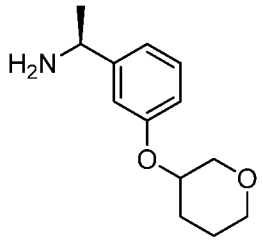
Step 2

(S)-tert-butyl 1-(3-(cyclohexyloxy)phenyl)ethylcarbamate (74.1 mg, 0.232 mmol) was dissolved in 4M HCl in dioxane (1 ml, 4.00 mmol) and the resulting mixture was allowed to sit for 1 hour, then concentrated to yield (S)-1-(3-(cyclohexyloxy)phenyl)ethanamine as an HCl salt (yield assumed quantitative). LCMS *m/z* 220.1 $(M + H)^+$, Rt 0.66 min.

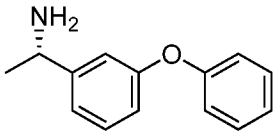
The Intermediates in Table 4v were prepared using either the method described for the preparation of Intermediate 196 or Intermediate 197.

Table 4v.

Intermediate: Name	Structure	LCMS
198: (S)-1-(3-(cyclopentyloxy)phenyl)ethanamine		MS m/z 206.1 (M + H)$^+$, Rt 0.61 min.
199: (S)-1-(3-(cyclohexyloxy)phenyl)ethanamine		MS m/z 220.1 (M + H)$^+$, Rt 0.66 min.
200: (S)-1-(3-(cycloheptyloxy)phenyl)ethanamine		MS m/z 234.1 (M + H)$^+$, Rt 0.73 min.
201: (S)-1-(3-isopropoxyphenyl)ethanamine		MS m/z 180.1 (M + H)$^+$, Rt 0.50 min.
202: (S)-1-(3-isobutoxyphenyl)ethanamine		MS m/z 194.1 (M + H)$^+$, Rt 0.61 min.
203: (S)-1-(3-((S)-tetrahydrofuran-3-yloxy)phenyl)ethanamine		MS m/z 208.1 (M + H)$^+$, Rt 0.41 min.

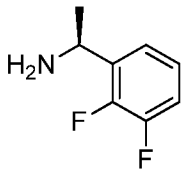
204: (1S)-1-(3-(tetrahydro-2H-pyran-3-yloxy)phenyl)ethanamine		MS m/z 222.1 (M + H)$^+$, Rt 0.46 min.

Intermediate 205: (S)-1-(3-phenoxyphenyl)ethanamine



Into a 20ml microwave vial was weighted 1-(pyridin-2-yl)propan-2-one ligand (90 mg, 0.665 mmol), phenol (407 mg, 4.32 mmol), CuBr (47.7 mg, 0.332 mmol) and Cs_2CO_3 (2166 mg, 6.65 mmol). To the mixture was added DMSO (5 ml) and (S)-1-(3-bromophenyl)ethanamine (0.5 ml, 3.32 mmol). The tube was flushed with N_2, capped, and the black mixture heated in the oil bath at 90°C for 18 hours. The heterogenous mixture was diluted with EtOAc and filtered through a glass-fritted funnel, eluting with EtOAc and another 5mls of DMSO. The volatiles were then removed *in vacuo* and the crude brown liquid was filtered through 1μm PTFE filter and purified by reverse phase HPLC. The combined product fractions were desalted by addition of equal amount of EtOAc and about 250mg Na_2CO_3 in a separatory funnel. The phases were separated and the organic washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield (S)-1-(3-phenoxyphenyl)ethanamine (361.5 mg, 1.678 mmol, 50.5 % yield) as an amber oil. LCMS *m/z* 214.1 (M + H)$^+$, Rt 0.61 min.

Intermediate 206: (S)-1-(2,3-difluorophenyl)ethanamine



Step 1

To a oven dried round bottom flask with stir bar was added 2,3-difluorobenzaldehyde (0.5 g, 3.52 mmol), (R)-2-methylpropane-2-sulfinamide (0.469 g, 3.87 mmol) and DCE

(7.04 mL). To this mixture was then added Copper (II) Sulfate (0.842 g, 5.28 mmol). Reaction mixture heated in a preheated oil bath to 55 °C for 24 hours. The reaction mixture was filtered through a celite pad washing solids with DCE. Combined filtrate was concentrated to afford a viscous yellow oil of (R,E)-N-(2,3-difluorobenzylidene)-2-methylpropane-2-sulfinamide (0.8007 g, 3.26 mmol, 93 % yield). LCMS *m/z* 246.1 (M + H)+, Rt 0.91 min.

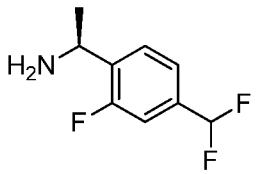
Step 2

To a solution of (R,E)-N-(2,3-difluorobenzylidene)-2-methylpropane-2-sulfinamide (0.800 g, 3.26 mmol) in DCM (32.6 mL), cooled to 0°C (water/icebath) under N2, was added 3M MeMgBr (4.35 mL, 13.05 mmol) in diethyl ether. Reaction mixture allowed to stir for 30 min at 0 °C. Then gradually allowed to warm to room temperature and stirred for 30min at room temperature. Reaction mixture was cooled to 0 °C then quenched with the slow addition of a saturated solution of NH4Cl and diluted with EtOAc. Phases partitioned aqueous phase extracted with EtOAc and the organic layers combined washed with water, brine, dried with MgSO4, filtered and concentrated to afford (R)-N-((S)-1-(2,3-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (0.7868 g, 3.01 mmol, 92 % yield) as yellow solid. LCMS *m/z* 262.0 (M + H)+, Rt 0.70 min.

Step 3

To a round bottom flask containing (R)-N-((S)-1-(2,3-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (786.8 mg, 3.01 mmol) was added Dioxane (10.000 mL). To this solution was added HCl in dioxane 4.0M (1.505 mL, 6.02 mmol) and the solution was allowed to stir 15 min at room temperature. The reaction mixture was concentrated, dissolved in Et2O 10 ml, and concentrated again. Et2O was again added and resulting mixture sonnicated and a solid material was filtered and dried to afford (S)-1-(2,3-difluorophenyl)ethanamine (0.4213 g, 2.176 mmol, 72.3 % yield) as a white crystalline HCl salt. ^{1}H NMR (400 MHz, D2O) d ppm 1.55 (d, J=6.99 Hz, 3 H) 4.71 (q, J=6.96 Hz, 1 H) 7.10 - 7.26 (m, 3 H); LCMS *m/z* 158.0 (M + H)+, Rt 0.37 min.

Intermediate 207: (S)-1-(4-(difluoromethyl)-2-fluorophenyl)ethanamine



Step 1: Preparation of 1-bromo-4-(difluoromethyl)-2-fluorobenzene

A mixture of 4-bromo-3-fluorobenzaldehyde (2.03 g, 10 mmol) and (diethylamino)sulfur trifluoride (DAST; 1.32 mL, 10 mmol) is heated carefully until exothermic reaction occurs, then heated at 60 °C for 15 min, and allowed to cool to room temperature. The mixture was diluted with DCM (20 mL) and poured into ice/water (30 mL). The mixture was neutralized with $NaHCO_3$ to ~pH 8. The separated aqueous layer was extracted with DCM (20 mL). The combined organic layers were dried over Na_2SO_4, filtered off, and concentrated under reduced pressure. The residue was purified by column chromatography [SiO_2, 40 g, heptane/ethyl acetate], providing 1-bromo-4-(difluoromethyl)-2-fluorobenzene (0.845 g) as a clear colorless oil.

Step 2: Preparation of 4-(difluoromethyl)-2-fluorobenzaldehyde

To a solution of 1-bromo-4-(difluoromethyl)-2-fluorobenzene (311 mg, 1.382 mmol) in THF (2.99 mL) was added butyllithium (1.6M solution in hexanes; 0.881 mL, 1.410 mmol) over ~5 min at -78 °C. The reaction mixture was stirred for 30 min at -78 °C then DMF (0.161 mL, 2.073 mmol) was added dropwise over ~1 min. Stirring was continued for 20 min. The reaction mixture was quenched with aqueous 1M HCl solution/MeOH (2:1, 3 mL) and allowed to warm to room temperature. The mixture was diluted with 5 mL of water. The separated aqueous layer was with ether (5 mL). The combined organic layers were washed with 1M aqueous NaOH solution (10 mL) and saturated brine (10 mL), dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Repeated reaction with 420 mg of 1-bromo-4-(difluoromethyl)-2-fluorobenzene and combined crude materials for purification. The crude material was purified by column chromatography [SiO_2, 24 g, heptane/ethyl acetate], providing 4-(difluoromethyl)-2-fluorobenzaldehyde (162.8 mg) as a yellow oil.

Step 3: Preparation of (R,E)-N-(4-(difluoromethyl)-2-fluorobenzylidene)-2-methylpropane-2-sulfinamide

To a mixture of 4-(difluoromethyl)-2-fluorobenzaldehyde (162 mg, 0.930 mmol) and (R)-2-methylpropane-2-sulfinamide (124 mg, 1.023 mmol) in DCE (3 mL) was added copper sulfate (223 mg, 1.396 mmol). Reaction mixture was heated in a preheated oil bath to 55 °C for 38 hours. The mixture was allowed to cool to room temperature, filtered through a pad of celites and washed with DCE. Combined filtrates were concentrated under reduced pressure to afford (R,E)-N-(4-(difluoromethyl)-2-fluorobenzylidene)-2-methylpropane-2-sulfinamide (266 mg) as a yellow oil, which was used without further purification. LCMS *m/z* 278.1 $(M + H)^+$, Rt 0.98 min.

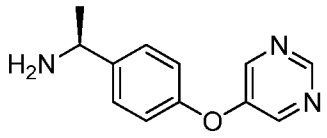
Step 4: Preparation of (R)-N-((S)-1-(4-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide

To a solution of (R,E)-N-(4-(difluoromethyl)-2-fluorobenzylidene)-2-methylpropane-2-sulfinamide (266 mg, 0.959 mmol) in DCM (9.6 mL) was added methylmagnesium bromide (3M in diethylether; 1.20 mL) at 0 °C. The reaction mixture was allowed to stir for 30 min at 0 °C, gradually allowed to warm to room temperature and stirred for 1 hour at room temperature. The mixture was cooled to 0 °C, and carefully quenched with saturated aqueous NH_4Cl solution (3 mL). The separated aqueous phase was extracted with DCM. The combined organic layers were washed with brine, dried over sodium sulfate, filtered off and concentrated under reduced pressure. The crude material was purified by column chromatography [SiO_2, 40 g, heptane/ethyl acetate], providing (R)-N-((S)-1-(4-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (160.5 mg) as a white solid. LCMS *m/z* 294.5 $(M + H)^+$, Rt 0.85 min.

Step 5: Preparation of (S)-1-(4-(difluoromethyl)-2-fluorophenyl)ethanamine

To (R)-N-((S)-1-(4-(difluoromethyl)-2-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (160 mg, 0.545 mmol) was added 4M HCl in dioxane (409 µL) to give a yellow solution. The resulting mixture was stirred at room temperature for ~1hour. To the mixture was added slowly diethylether (~20 mL). The solids were filtered off, suspended in diethylether, filtered off and rinsed with diethylether, dried under reduced pressure providing (S)-1-(4-(difluoromethyl)-2-fluorophenyl)ethanamine (103 mg) as an off-white solid, which was used without further purification. LCMS *m/z* 190.1 $(M + H)^+$, Rt 0.42 min.

Intermediate 208: (S)-1-(4-(pyrimidin-5-yloxy)phenyl)ethanamine



Step 1: Preparation of 4-(pyrimidin-5-yloxy)benzaldehyde

To a solution of pyrimidin-5-ol (500 mg, 5.20 mmol) in DMF (5.20 mL) under argon was added 4-fluorobenzaldehyde (0.558 mL, 5.20 mmol), sodium methanesulfinate (133 mg, 1.30 mmol), and potassium carbonate (1.079 g, 7.81 mmol). The reaction mixture was heated at 120 °C for 3 hour. The mixture was allowed to cool to room temperature and was diluted with water (25 mL). The mixture was extracted with EtOAc (2x 25 mL). The combined organic layers were washed with brine (2x 50 mL), dried over sodium sulfate, filtered off and concentrated under reduced pressure. The residue was purified by

column chromatography [SiO_2, 24 g, heptane/ethyl acetate], providing 4-(pyrimidin-5-yloxy)benzaldehyde (666 mg) as a yellow solid. LCMS *m/z* 201.0 $(M + H)^+$, Rt 0.52 min.

Step 2: Preparation of (R,E)-2-methyl-N-(4-(pyrimidin-5-yloxy)benzylidene)propane-2-sulfinamide

A mixture of 4-(pyrimidin-5-yloxy)benzaldehyde (666 mg, 3.33 mmol), (R)-(+)-tert-butanesulfinamide (450 mg, 3.71 mmol) and copper sulfate (796 mg, 4.99 mmol) in anhydrous in dichloroethane (7.648 mL) and under argon was heated at 55 °C for ~21 hours. The reaction mixture was allowed to cool to room temperature. The slurry was filtered through a celite pad, eluted with DCM (5x 10 mL). The combined filtrates were concentrated under reduced pressure and the resulting yellowish oil was purified by column chromatography [SiO_2, 24 g, heptane/ethyl acetate] providing (R,E)-2-methyl-N-(4-(pyrimidin-5-yloxy)benzylidene)propane-2-sulfinamide (836 mg) as a pale viscous oil. LCMS *m/z* 304.0 $(M + H)^+$, Rt 0.79 min.

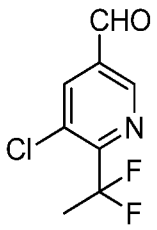
Step 3: Preparation of 2-methyl-N-((S)-1-(4-(pyrimidin-5-yloxy)phenyl)ethyl)propane-2-sulfinamide

A solution of (R,E)-2-methyl-N-(4-(pyrimidin-5-yloxy)benzylidene)propane-2-sulfinamide (830 mg, 2.74 mmol) in DCM (6.72 mL) was cooled to -40 °C. To the solution was added methylmagnesium bromide (3M in diethylether; 1.81 mL) dropwise over 10 min. Additional DCM (5 mL) were added to retain stirring. The yellow suspension was stirred at -40 °C for ~30 min while warming to -20 °C. The mixture was cooled to -40 °C and additional methylmagnesium bromide (3M in diethylether; 1.8 mL) was added. The suspension was stirred for ~3 hour while slowly warming to -20 °C. The mixture was cooled to ~-40 °C, and additional methylmagnesium bromide (3M in diethylether; 0.4mL) was added. The suspension was stirred for 30 min and allowed to warm to -10 °C. The mixture was quenched slowly over 10 min with saturated aqueous NH_4Cl solution (10 mL). The mixture was diluted with saturated aqueous NH_4Cl solution (30 mL) and water (15 mL). The separated aqueous phase was extract with DCM (2x 75 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered off and concentrated under reduced pressure. The residue was purified by column chouromatography [SiO_2, 40 g, heptane/ethyl acetate followed by 5% MeOH in EtOAc] providing 2-methyl-N-((S)-1-(4-(pyrimidin-5-yloxy)phenyl)ethyl)propane-2-sulfinamide (55 mg; purity ~87%) as an off-white solid. LCMS *m/z* 320.0 $(M + H)^+$, Rt 0.69 min.

Step 4: Preparation of (S)-1-(4-(pyrimidin-5-yloxy)phenyl)ethanamine

To 2-methyl-N-((S)-1-(4-(pyrimidin-5-yloxy)phenyl)ethyl)propane-2-sulfinamide (55 mg, 0.172 mmol) was added 4M HCl in dioxane (800 µL, 3.20 mmol) to give a white suspension. This resulting mixture was stirred at room temperature for ~35 min and concentrated under reduced pressure to provide crude (S)-1-(4-(pyrimidin-5-yloxy)phenyl)ethanamine (44 mg) as its HCl salt, which was used without further purification. LCMS *m/z* 217.1 $(M + H)^+$, Rt 0.37 min.

Intermediate 209: 5-chloro-6-(1,1-difluoroethyl)nicotinaldehyde



Step 1: Preparation of ethyl 5,6-dichloronicotinate

To a solution of 5,6-dichloronicotinic acid (20.01 g, 104 mmol) in EtOH (500 mL) at 20 °C was added chlorotrimethylsilane (132 mL, 1042 mmol). The reaction was stirred for 72 hours. The reaction mixture was then concentrated and diluted with EtOAc (500mL), and washed with saturated $NaHCO_3$ (2x100mL) and brine (100mL). The organic was then dried (Na_2SO_4) and concentrated under reduced pressure to give final crude product (21.25 g). LCMS *m/z* 220.1 $(M + H)^+$, Rt 0.94 min.

Step 2: Preparation of ethyl 6-acetyl-5-chloronicotinate

To a suspension of ethyl 5,6-dichloronicotinate (5.26 g, 23.90 mmol) and tetraethylammonium-chloride (11.88 g, 71.7 mmol) in MeCN (50 mL) was added tributyl(1-ethoxyvinyl)stannane (9.50 g, 26.3 mmol) and $PdCl_2(PPh_3)_2$ (0.671 g, 0.956 mmol). The reaction was sealed, heated at 80 °C for 5 hours. A dark color clear solution resulted. The reaction mixture was then cooled to 20 °C, concentrated and diluted with EtOAc (200mL), and washed with water (50mL) and brine (50mL). The organic was then dried (Na_2SO_4) and concentrated to give crude ethyl 5-chloro-6-(1-ethoxyvinyl)nicotinate. The residue was then dissolved in THF (100mL) and HCl (20mL, 3M in H_2O) was added. The reaction mixture was stirred at 20 °C for 5 hours, and saturated $NaHCO_3$ solution was added until pH=8. The mixture was then diluted with EtOAc (200mL) and water (50mL). The phases were separated and the aqueous layer was extracted with EtOAc (2x50mL). The combined organics was washed with brine

(20mL), dried (Na_2SO_4) and concentrated to afford the desired product (3.56 g). LCMS *m/z* 228.5 $(M + H)^+$, Rt 0.83 min.

Step 3: Preparation of ethyl 5-chloro-6-(1,1-difluoroethyl)nicotinate

To a solution of ethyl 6-acetyl-5-chloronicotinate (3.01 g, 13.22 mmol) in CHCl3 (7 mL) was added DAST (5.20 mL, 39.7 mmol) and ethanol (0.061 g, 1.32 mmol). The reaction was sealed, heated at 60 °C for 24 hours. A dark color clear solution resulted. The reaction mixture was then cooled to 20 °C, and added cautiously with cold concentrated $NaHCO_3$ aqueous solution (50mL). The aqueous layer was extracted with DCM (2x100mL). The combined organic was then dried (Na_2SO_4) and concentrated. The residue was purified via silica gel flash chromatography (0-20percent EtOAc-Hexanes) to afford the desired product as yellow oil (2.88 g). LCMS *m/z* 250.1 $(M + H)^+$, Rt 0.99 min.

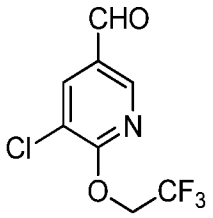
Step 4: Preparation of (5-chloro-6-(1,1-difluoroethyl)pyridin-3-yl)methanol

To a solution of ethyl 5-chloro-6-(1,1-difluoroethyl)nicotinate (2.68 g, 10.74 mmol) in Et_2O (40mL) was added $LiBH_4$ (0.351 g, 16.10 mmol), followed by dropwise addition of methanol (0.653 mL, 16.10 mmol). The reaction was refluxed at 40 °C for one hour. The reaction mixture was then cooled to 0 °C, and quenched with HCl (1M) until pH=2 for aqueous layer. The phases were separated and the aqueous layer was extracted with DCM (3x50mL). The organic was then dried (Na_2SO_4) and concentrated under reduced pressure to give final crude product (2.12 g). LCMS *m/z* 208.0 $(M + H)^+$, Rt 0.63 min.

Step 5: Preparation of 5-chloro-6-(1,1-difluoroethyl)nicotinaldehyde

To a solution of (5-chloro-6-(1,1-difluoroethyl)pyridin-3-yl)methanol (2.12 g, 10.21 mmol) in DCM (100 ml) was added PCC (3.30 g, 15.32 mmol). The reaction was stirred at 20 °C for 3 hours. A dark color suspension resulted. LCMS showed clean conversion to the product. The reaction mixture was then filtered through a pad of celite, and washed with DCM (200mL). The filtrate was then concentrated to give crude product (1.78 g). LCMS *m/z* 224.0 $(M + H2O + H)^+$, Rt 0.72 min.

Intermediate 210: 5-chloro-6-(2,2,2-trifluoroethoxy)nicotinaldehyde



Step 1: Preparation of ethyl 5-chloro-6-(2,2,2-trifluoroethoxy)nicotinate

To a solution of ethyl 5,6-dichloronicotinate (6.28 g, 28.5 mmol) and 2,2,2-trifluoroethanol (2.71 ml, 37.1 mmol) in THF (90 ml) at -73oC was added NaHMDS (37.1 ml, 37.1 mmol). The reaction was stirred at -73 °C for 30 minutes, then at 0 °C for 5 hours. The reaction was quenched with 30 mL saturated NH_4Cl solution. The reaction mixture was then poured into 50 mL brine and phases were separated. The aqueous layer was extracted with DCM (2x100mL). The combined organics were dried (Na_2SO_4) and concentrated. Silica gel chromatography with 100% heptane to 30% EtOAc in heptane provided final product (7.51 g). LCMS *m/z* 284.1 $(M + H)^+$, Rt 1.07 min.

Step 2: Preparation of (5-chloro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanol

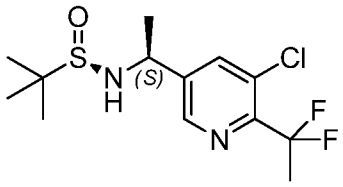
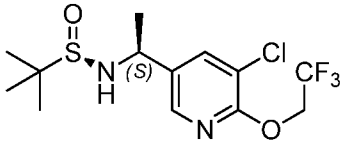
To a solution of ethyl 5-chloro-6-(2,2,2-trifluoroethoxy)nicotinate (7.51 g, 26.5 mmol) in Et2O (200mL) was added $LiBH_4$ (0.865 g, 39.7 mmol), followed by drop wise addition of methanol (1.611 ml, 39.7 mmol). The reaction was refluxed at 40 °C for one hour. The reaction mixture was then cooled to 0 °C, and quenched with HCl (1M) until pH=2 for aqueous layer. The phases were separated and the aqueous layer was extracted with DCM (3x200mL). The organic was then dried (Na_2SO_4) and concentrated under reduced pressure to give final crude product (6.31 g). LCMS *m/z* 242.1 $(M + H)^+$, Rt 0.77 min.

Step 3: Preparation of 5-chloro-6-(2,2,2-trifluoroethoxy)nicotinaldehyde

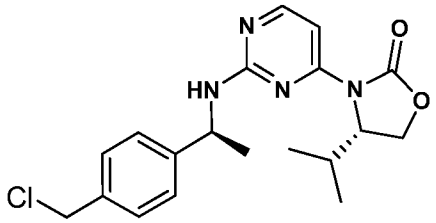
To a solution of (5-chloro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)methanol (4.00 g, 16.56 mmol) in EtOAc (15 mL) was added manganese(IV) oxide (16.93 g, 166 mmol). The reaction was heated with microwave at 120 °C for 30 minutes. The mixture was then filtered through a pad of celite, and rinsed with EtOAc. The filtrated was concentrated to give crude product (3.38 g).

The intermediates in Table 4w were prepared with procedures similar to those used to prepare Intermediate 210 and 192.

Table 4w.

Intermediate: Name	Structure	LCMS
211: (R)-N-((S)-1-(5-chloro-6-(1,1-difluoroethyl)pyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide		MS *m/z* 325.2 $(M + H)^+$, Rt 0.85 min.
212: (R)-N-((S)-1-(5-chloro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide		MS *m/z* 359.1 $(M + H)^+$, Rt 0.95 min.

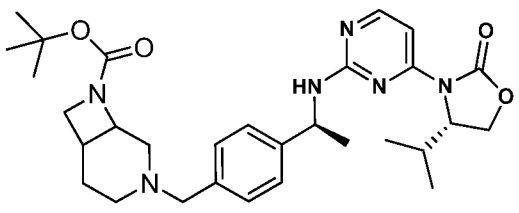
Intermediate 213 : (S)-3-(2-((S)-1-(4-(chloromethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one



To a solution of (S)-3-(2-((S)-1-(4-(hydroxymethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (71 mg, 0.2 mmol) in DCM (2 mL) was added methanesulfonyl chloride (27 mg, 0.24 mmol) and DIPEA (0.070 mL, 0.4 mmol). The solution was stirred for 16 h at room temperature then washed with water and brine. After separation, the organic phase was dried over Na_2SO_4, filtered and concentrated. The crude product was used to next step without further purification.

MS m/z 373.4 (M - H).

Intermediate 214: tert-butyl 3-(4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate

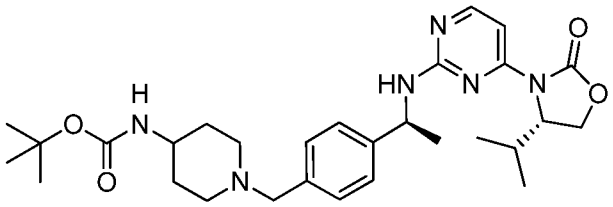


Title compound was prepared as a white solid (64 mg, 58.1% yield), with procedures similar to those used to prepare Intermediate 128, but utilizing 4-((S)-1-(4-((S)-4-

isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzaldehyde and tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate.

^{1}H NMR (400 MHz, CDCl3) δ 8.17 (dd, J = 5.9, 0.9 Hz, 1H), 7.42 (d, J = 5.7 Hz, 1H), 7.28 - 7.23 (m, 4H), 5.39 (br s, 1H), 5.02 (br s, 1H), 4.62-4.59 (m, 1H), 4.28 (t, J = 8.7 Hz, 1H), 4.21 (dd, J = 9.0, 3.2 Hz, 2H), 3.89 (td, J = 7.7, 1.9 Hz, 1H), 3.54 - 3.50 (m, 2H), 3.03 (d, J = 12.2 Hz, 1H), 2.65 - 2.60 (m, 1H), 2.54 – 2.40 (m, 2H), 2.10 (br s, 1H), 1.99 - 1.88 (m, 1H), 1.79 - 1.72 (m, 1H), 1.65 (br s, 1H), 1.52 (dd, J = 6.8, 1.9 Hz, 3H), 1.38 (t, J = 7.7 Hz, 9H), 0.71 (br s, 3H), 0.66 (br s, 3H). MS m/z 569.1 (M + H).

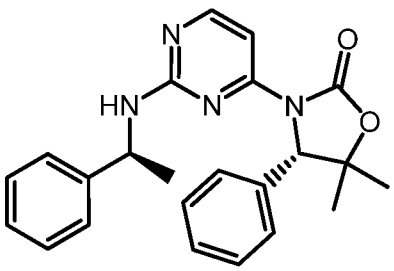
Intermediate 215: tert-butyl 1-(4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzyl)piperidin-4-ylcarbamate



Title compound was prepared as a white solid (32 mg, 59% yield), with procedures similar to those used to prepare Intermediate 128, but utilizing 4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzaldehyde and tert-butyl piperidin-4-ylcarbamate. MS m/z 539.4 (M + H).

Examples

Example 1: (*S*)-5,5-dimethyl-4-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one

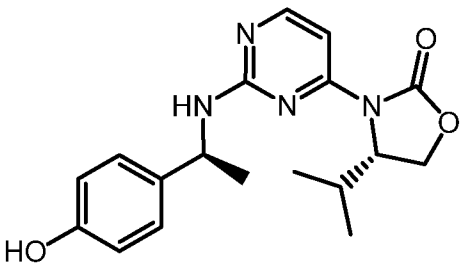


A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one (33.9 mg, 0.112 mmol) and (*S*)-(-)-1-phenylethanamine (0.15 mL, 1.2 mmol, 10 equiv) in DMSO (1 mL) was heated at 110 °C for 140 min. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was

extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 50%) provided (*S*)-5,5-dimethyl-4-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl) oxazolidin-2-one (37.0 mg, white solid) in 85% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, J = 5.8 Hz, 1 H), 7.43 (d, J = 5.8 Hz, 1 H), 7.31 – 7.24 (m, 3 H), 7.19 – 7.11 (m, 5 H), 7.01 (br s 2 H), 5.48 (s, 1 H), 4.86 – 4.80 (m, 1 H), 1.65 (s, 3 H), 1.43 (d, J = 7.0 Hz, 3 H), 0.98 (s, 3 H); HRMS(B) *m/z* 389.1987 $(M + H)^+$.

Alternative Procedure

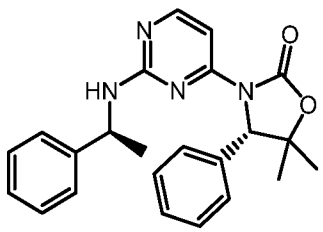
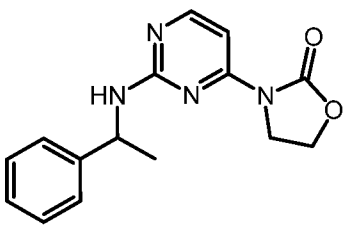
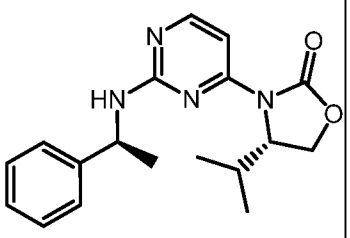
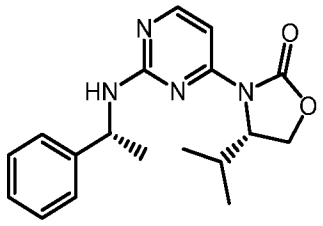
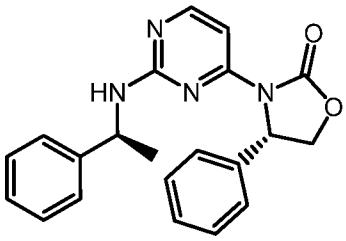
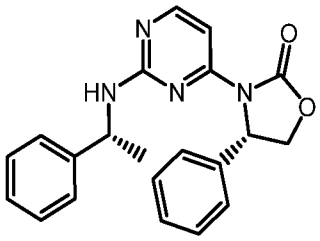
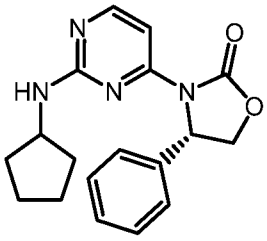
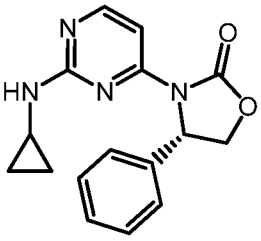
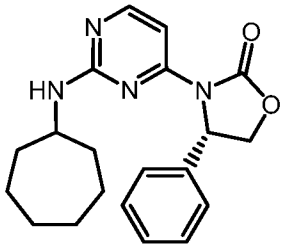
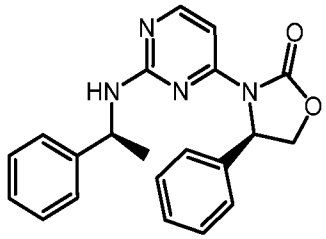
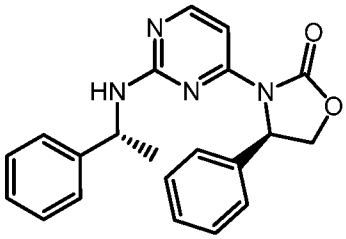
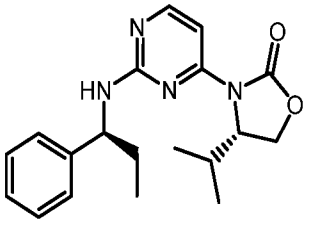
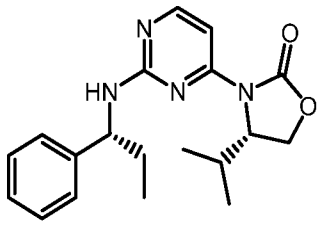
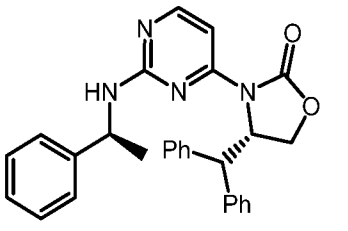
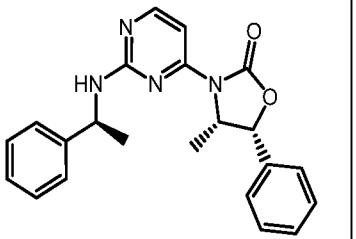
Example 113: (*S*)-3-(2-((*S*)-1-(4-hydroxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one

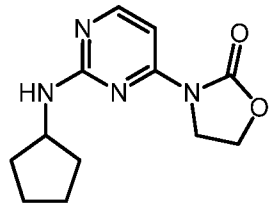
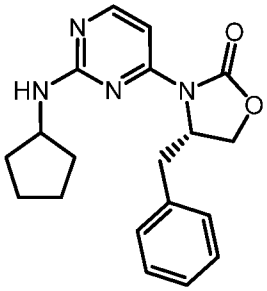
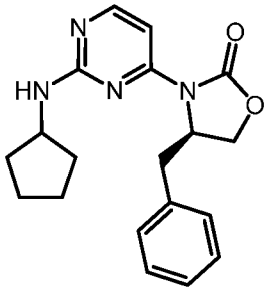
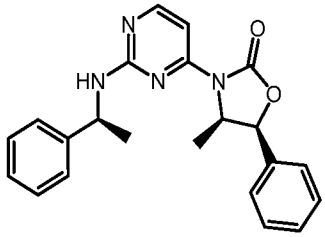
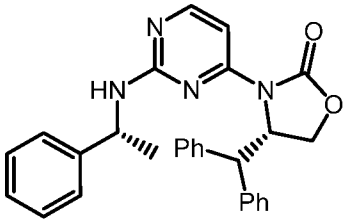
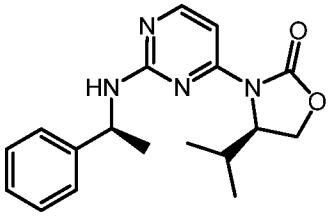
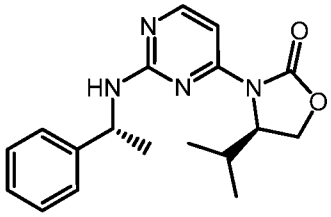
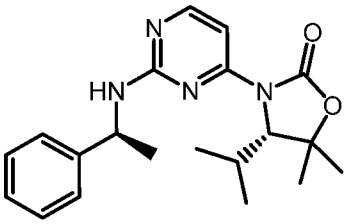
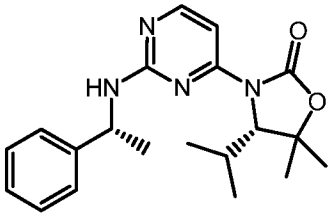
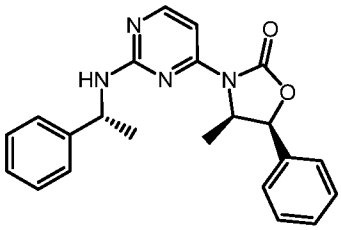
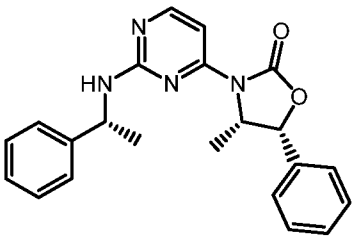
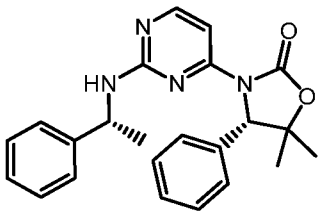
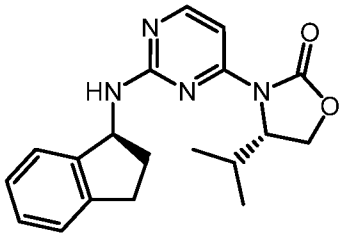
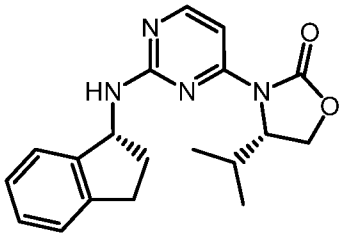
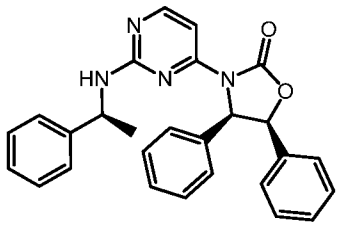


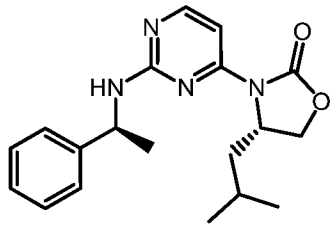
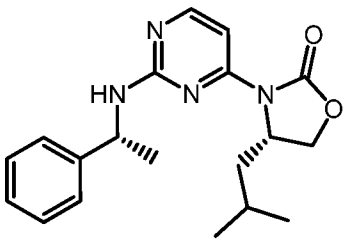
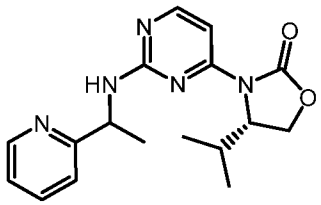
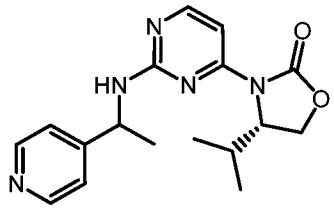
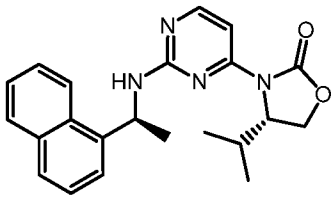
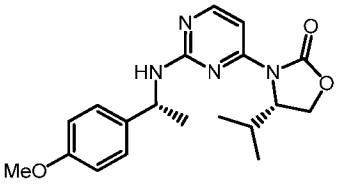
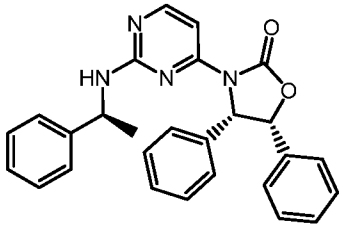
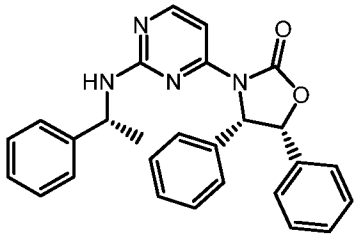
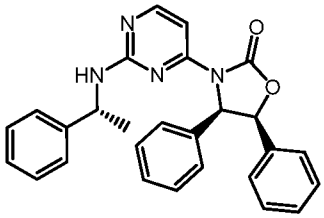
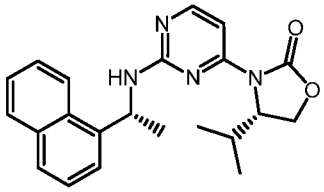
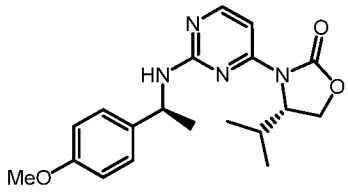
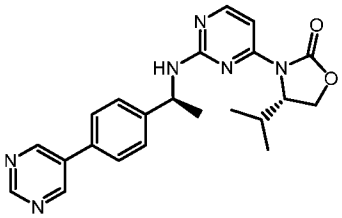
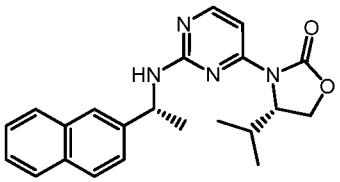
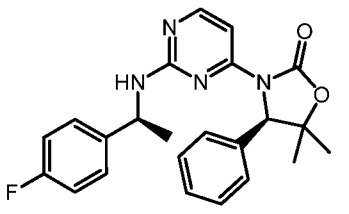
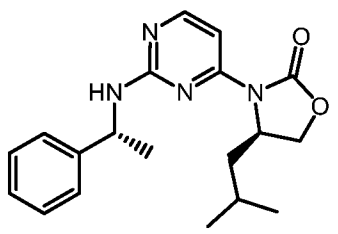
A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (42 mg, 0.17 mmol), (*S*)-4-(1-aminoethyl)phenol hydrochloride (107 mg, 0.616 mmol, 3.5 equiv) and *i*Pr_2Net (0.121 mL, 0.695 mmol, 4.0 equiv) in DMSO (1 mL) was heated at 110 °C for 3 h and at 130 °C for additional 2 h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 80%) provided (*S*)-3-(2-((*S*)-1-(4-hydroxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (3 mg) in 5 % yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, J = 5.8 Hz, 1 H), 7.33 (d, J = 5.8 Hz, 1 H), 7.12 (d, J 8.1 Hz, 2 H), 6.72 – 6.68 (m, 2 H), 4.95 (q, J = 6.9 Hz, 1 H), 4.69 – 4.65 (m, 1 H), 4.35 – 4.28 (m, 2 H), 1.47 (d, J = 7.1 Hz, 3 H), 0.75 (br s, 3 H), 0.62 (br s, 3 H); HRMS(B) *m/z* 343.1776 $(M + H)^+$.

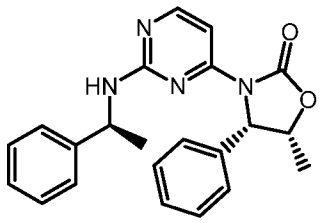
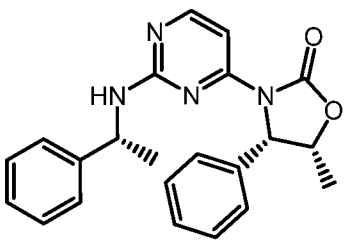
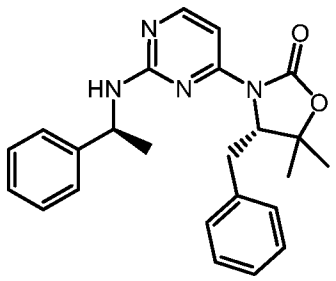
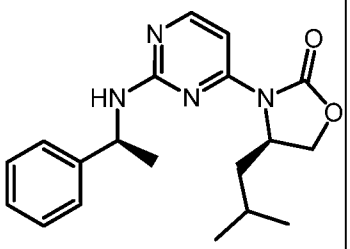
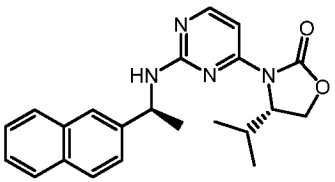
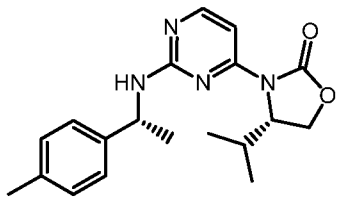
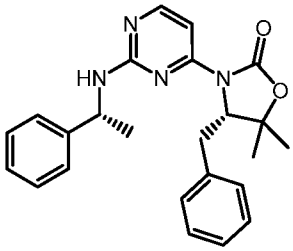
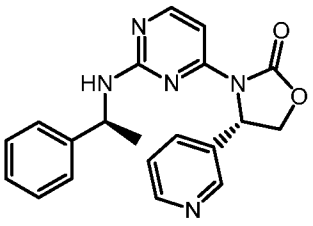
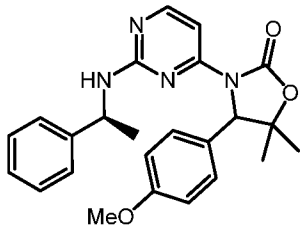
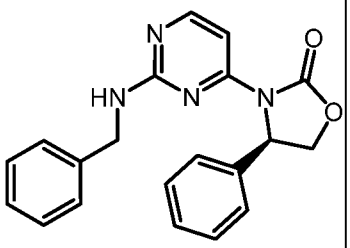
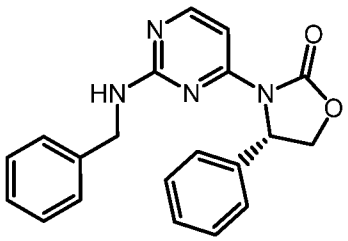
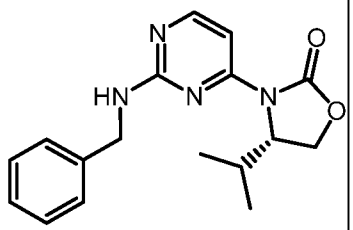
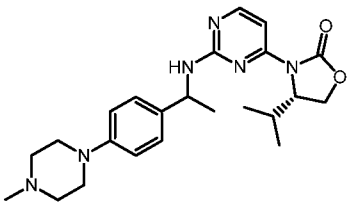
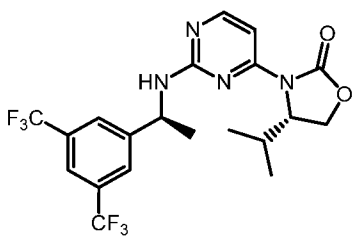
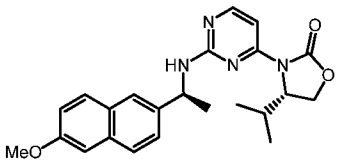
The compounds in Table 5 were prepared using methods similar to those described for the preparation of Examples 1 and 113.

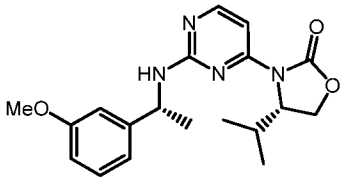
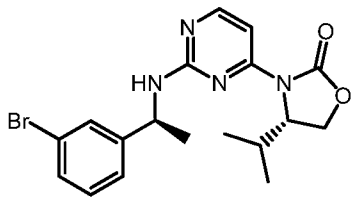
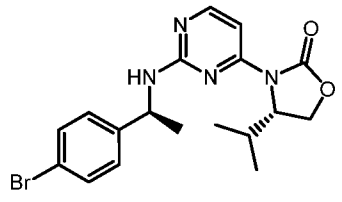
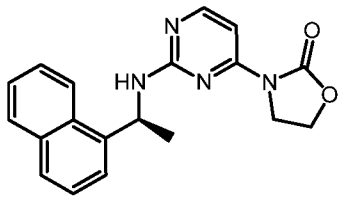
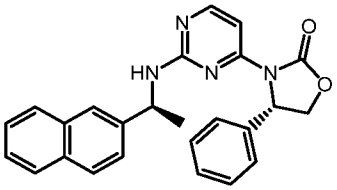
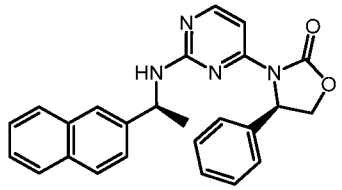
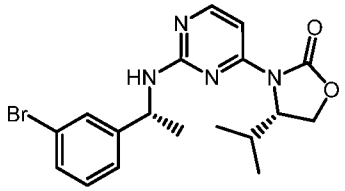
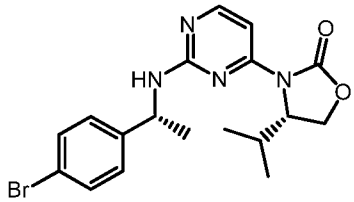
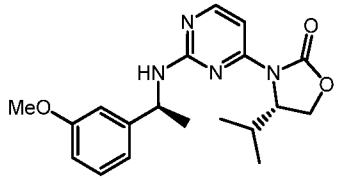
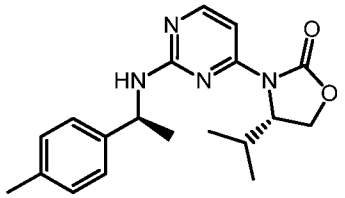
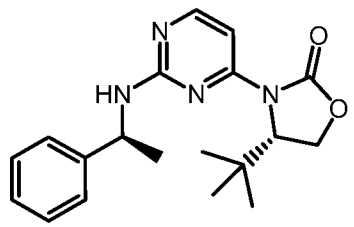
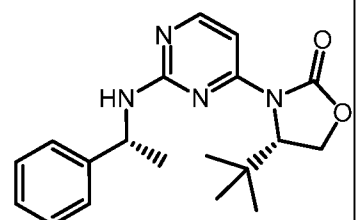
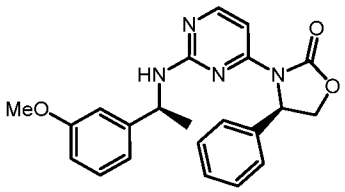
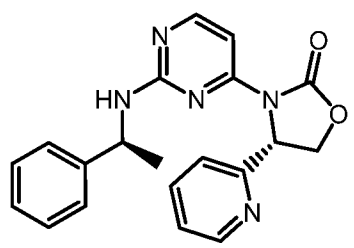
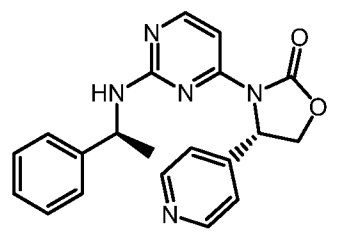
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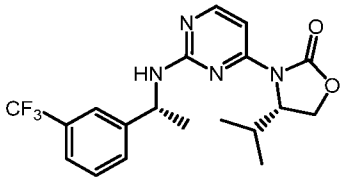
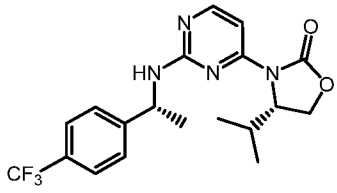
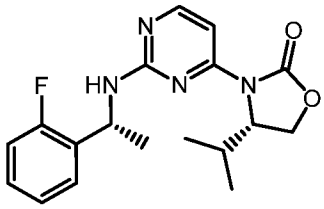
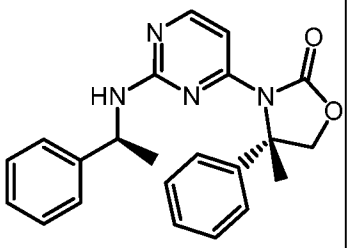
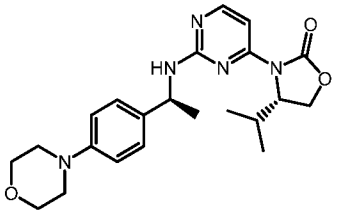
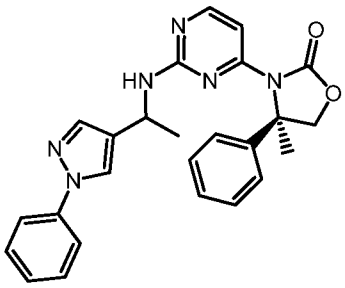
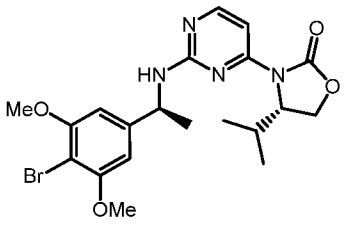
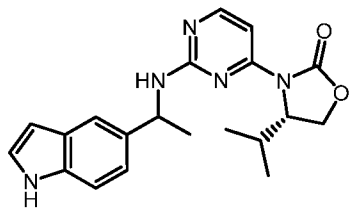
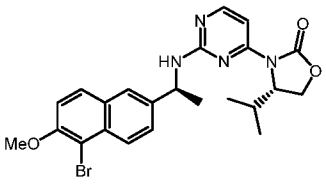
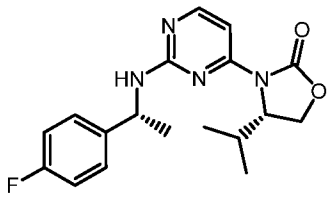
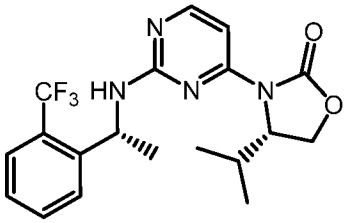
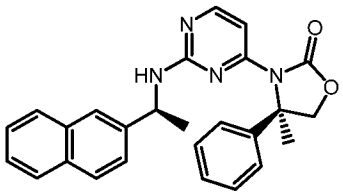
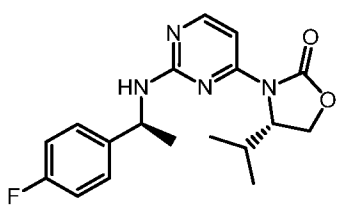
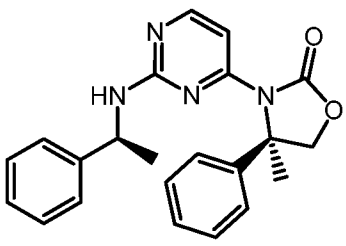
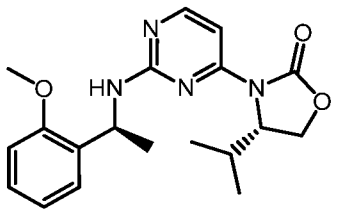
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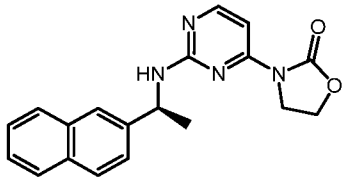
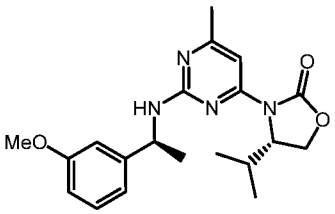
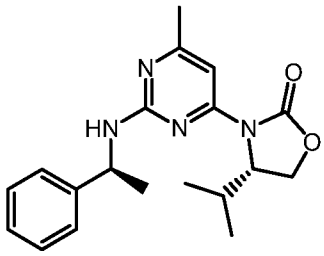
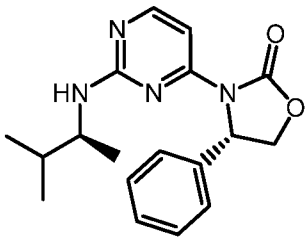
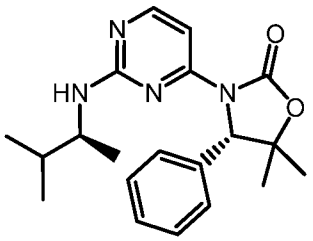
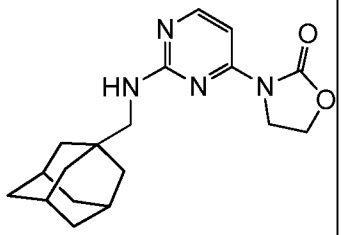
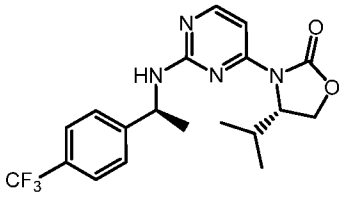
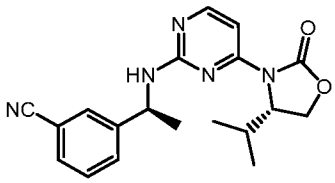
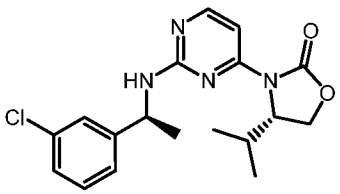
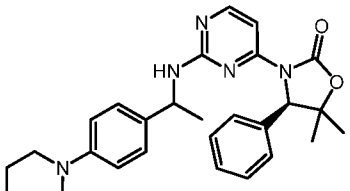
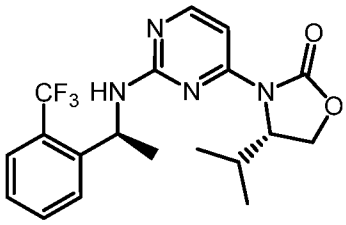
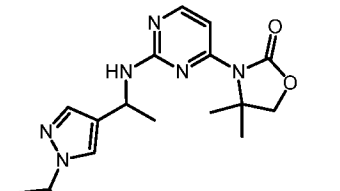
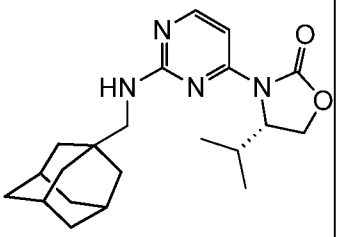
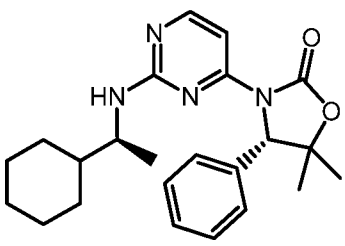
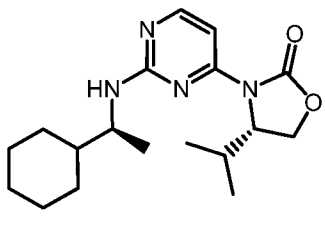
		
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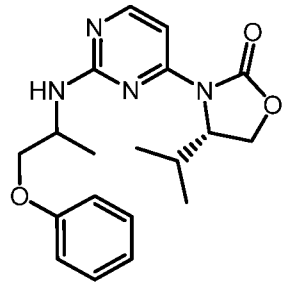
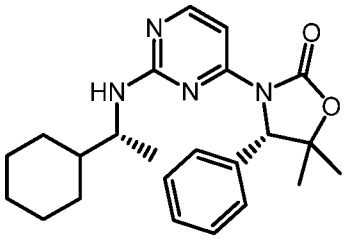
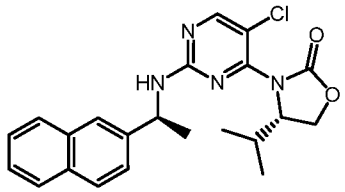
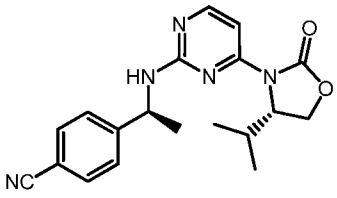
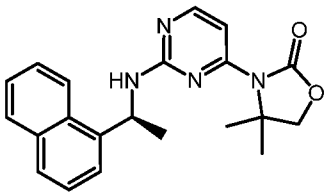
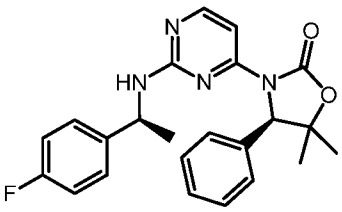
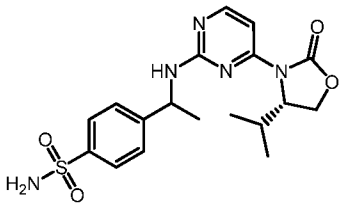
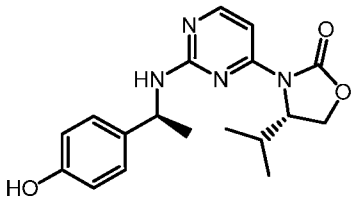
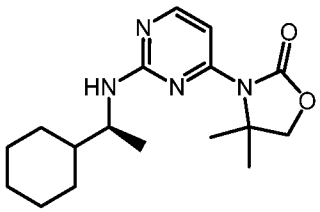
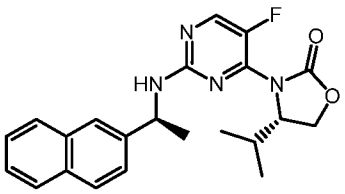
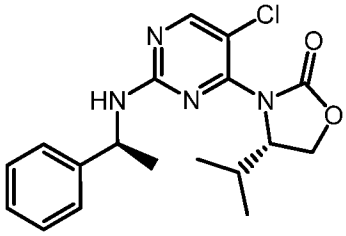
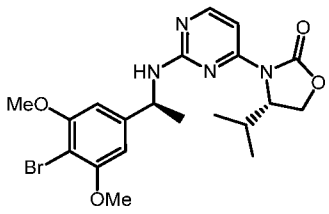
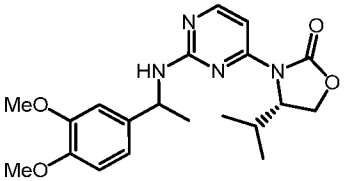
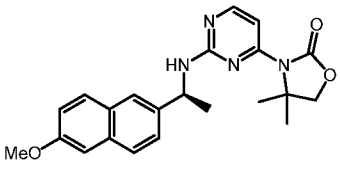
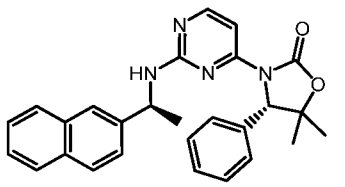
		
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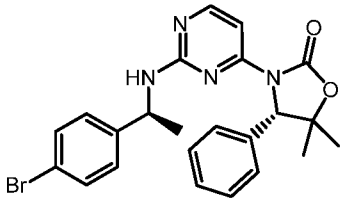
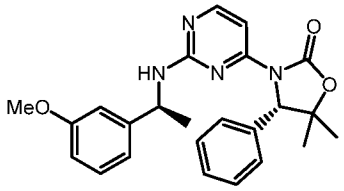
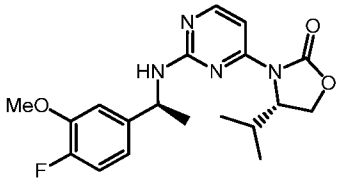
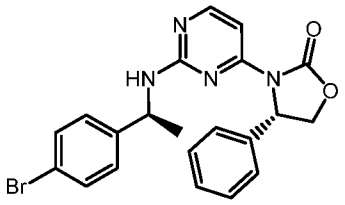
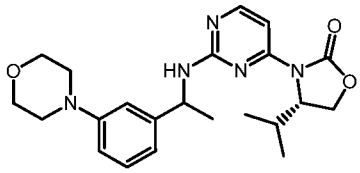
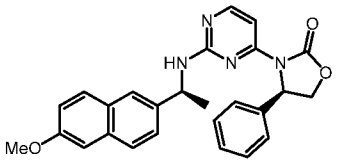
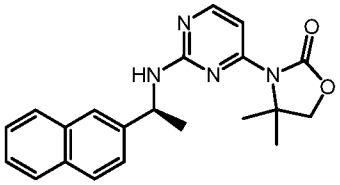
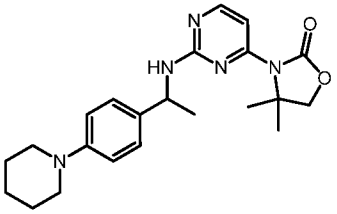
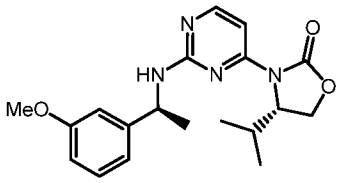
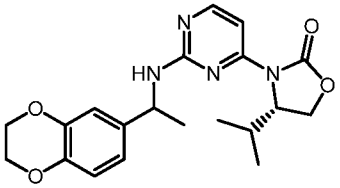
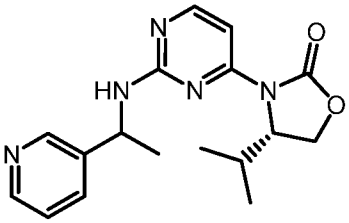
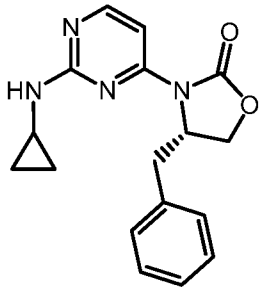
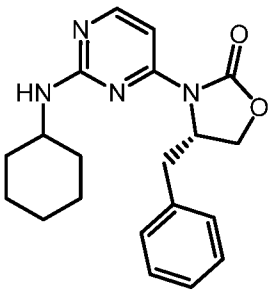
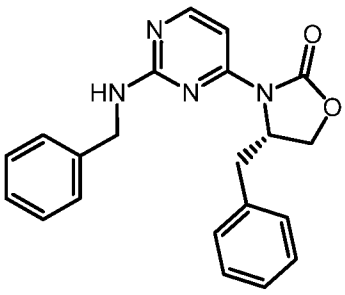
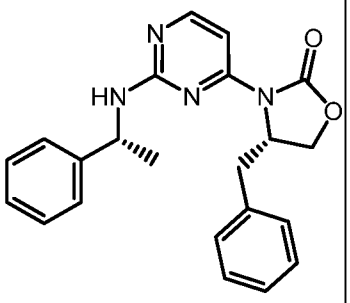
		
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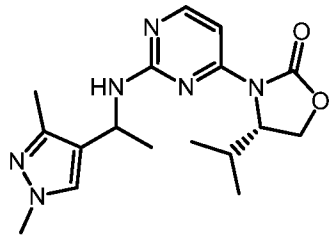
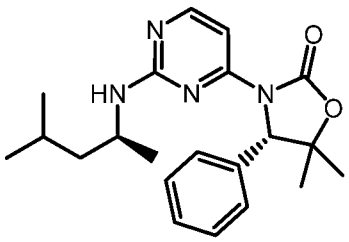
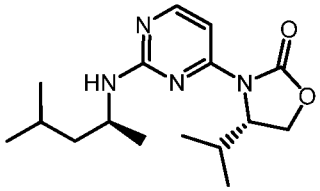
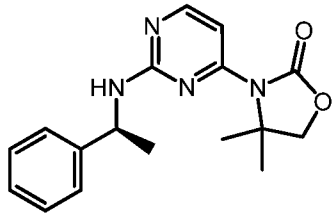
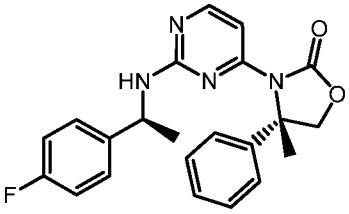
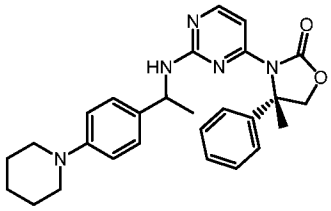
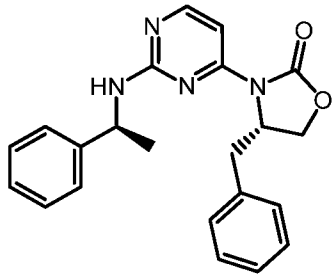
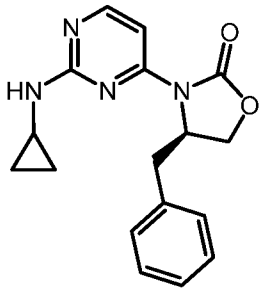
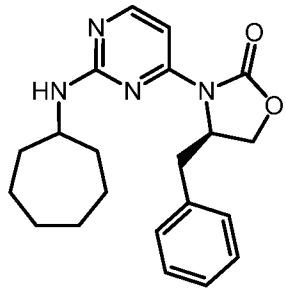
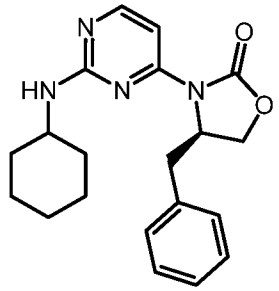
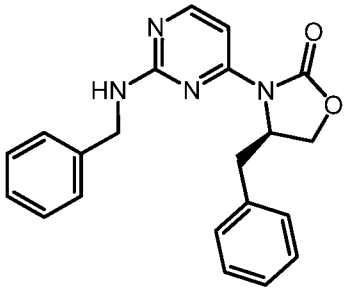
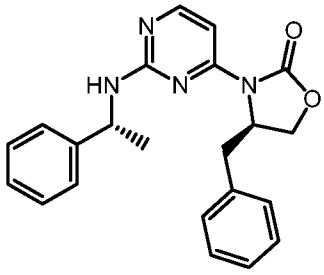
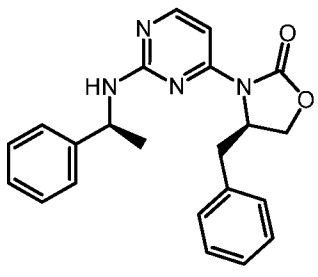
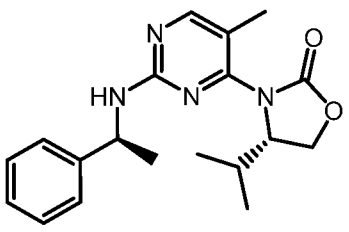
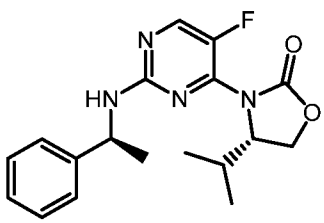
		
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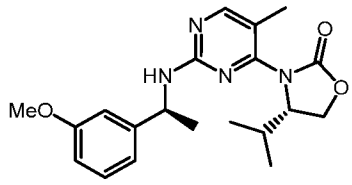
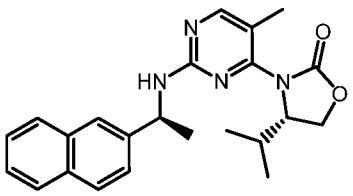
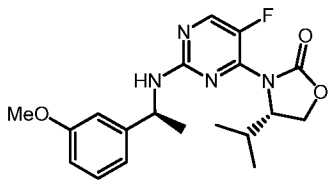
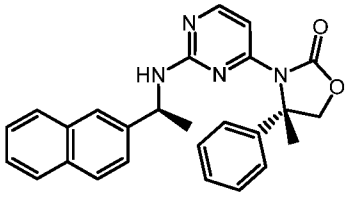
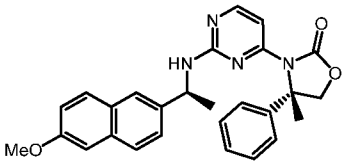
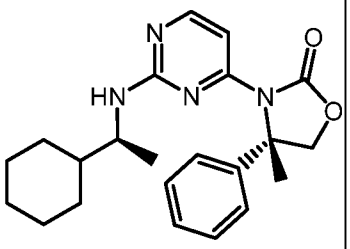
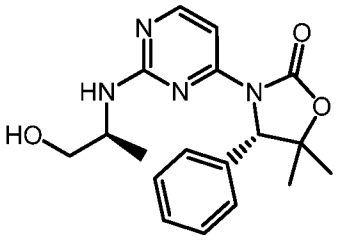
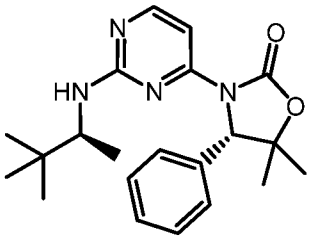
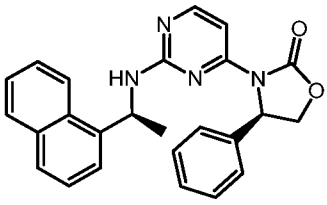
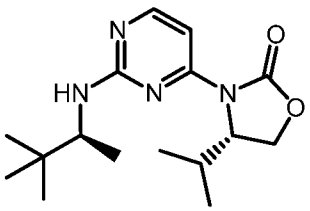
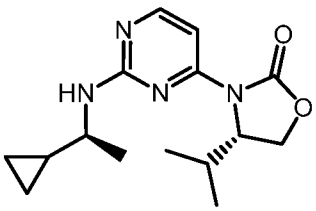
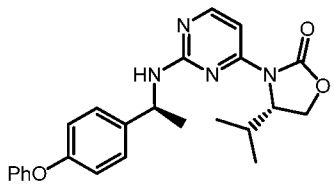
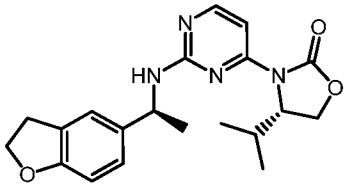
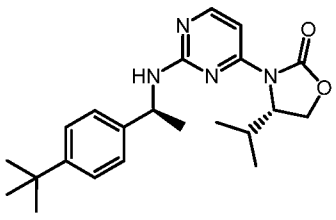
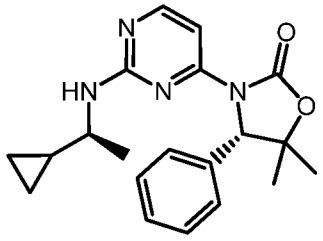
		
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91	92	93

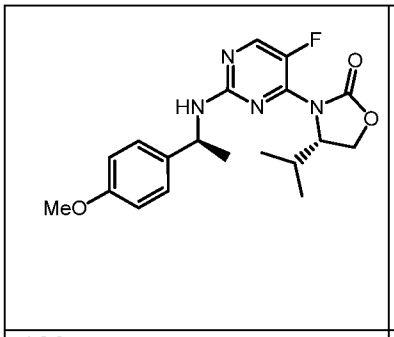
		
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106	107	108

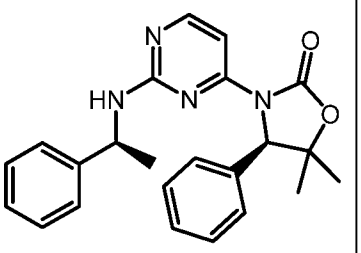
		
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121	122	123

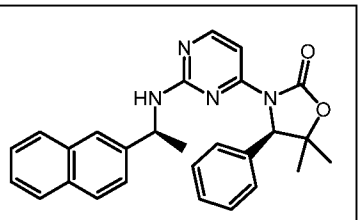
		
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133	134	135
		
136	137	138

		
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169

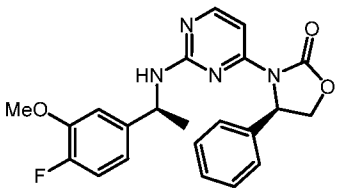


Table 6. Chemical name, NMR chemical shifts and LCMS signal for each compound listed in Table 5.

Example: Name	^{1}H NMR **(400 MHz,** CD_3OD**) δ ppm (other solvents described)**	**LCMS**
1: (*S*)-5,5-dimethyl-4-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.06 (d, J = 5.8 Hz, 1 H), 7.43 (d, J = 5.8 Hz, 1 H), 7.31 – 7.24 (m, 3 H), 7.19 – 7.11 (m, 5 H), 7.01 (br s 2 H), 5.48 (s, 1 H), 4.86 – 4.80 (m, 1 H), 1.65 (s, 3 H), 1.43 (d, J = 7.0 Hz, 3 H), 0.98 (s, 3 H)	HRMS(B) *m/z* 389.1987 $(M + H)^+$
2: 3-(2-(1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.06 (d, J = 6.1 Hz, 1 H), 7.37 – 7.26 (m, 5 H), 7.22 – 7.15 (m, 1 H), 5.04 (q, J = 6.9 Hz, 1 H), 4.43 (sxt, J = 8.2 Hz, 2 H), 4.17 (td, J = 9.8, 7.1 Hz, 1 H), 3.92 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 284.1275 M^+
3: (*S*)-4-isopropyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, J = 5.6 Hz, 1 H), 7.34 – 7.26 (m, 5 H), 7.22 – 7.13 (m, 1 H), 5.04 (q, J = 7.1 Hz, 1 H), 4.64 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.85 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.70 (br s, 3 H), 0.57 (br s, 3 H)	HRMS(B) *m/z* 326.1745 M^+
4: (*S*)-4-isopropyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.10 (d, J = 5.8 Hz, 1 H), 7.35 – 7.27 (m, 5 H), 7.23 – 7.15 (m, 1 H), 4.96 (q, J = 6.9 Hz, 1 H), 4.44 (br s, 1 H), 4.34 – 4.23 (m, 2 H), 2.72 – 2.58 (m, 1 H), 1.51 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 326.1746 M^+
5: (*S*)-4-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.07 (d, J = 5.6 Hz, 1 H), 7.38 (d, J = 5.6 Hz, 1 H), 7.28 – 7.05 (m, 10 H), 5.84 (dd, J = 8.6, 3.5 Hz, 2 H), 4.88 (q, J = 6.8 Hz, 1 H), 4.83 – 4.79 (m, 1 H), 4.24 (dd, J = 8.6, 3.5 Hz, 1 H), 1.44 (d, J = 6.8 Hz, 3 H)	HRMS(B) *m/z* 361.1666 $(M + H)^+$
6: (*S*)-4-phenyl-3-(2-((*R*)-1-	8.08 (d, J = 5.8 Hz, 1 H), 7.43 – 7.18 (m, 11 H), 5.55 (br s, 1H), 4.74 (t, J = 8.6 Hz, 1	HRMS(B) *m/z*

phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	H), 4.63 (br s, 1 H), 4.18 (dd, J = 8.3, 3.8 Hz, 1 H), 1.19 (d, J = 6.7 Hz, 3 H)	360.1591 M^+
7: (*S*)-3-(2-(cyclopentylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.06 (d, J = 6.1 Hz, 1 H), 7.39 – 7.28 (m, 6 H), 5.80 (dd, J = 8.8, 3.8 Hz, 1 H), 4.83 – 4.80 (m, 1 H), 4.20 (dd, J = 8.6, 4.0 Hz, 1 H), 3.79 (br m, 1 H), 1.90 – 1.99 (m, 1 H), 1.72 – 1.53 (m, 4 H), 1.49 – 1.35 (m, 3 H)	HRMS(B) *m/z* 325.1671 $(M + H)^+$
8: (*S*)-3-(2-(cyclopropylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.10 (d, J = 5.6 Hz, 1 H), 7.44 (d, J = 5.6 Hz, 1 H), 7.36 – 7.26 (m, 5 H), 5.86 (dd, J = 8.6, 3.5 Hz, 1 H), 4.83 – 4.80 (m, 1 H), 4.26 (dd, J = 8.6, 3.5 Hz, 1 H), 2.40 (br s, 1 H), 0.64 – 0.71 (m, 1 H), 0.54 (br s, 1 H), 0.44 – 0.37 (m, 1 H), 0.25 (br s, 1 H)	HRMS(B) *m/z* 297.1356 $(M + H)^+$
9: (*S*)-3-(2-(cycloheptylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.06 (d, J = 6.1 Hz, 1 H), 7.38 – 7.27 (m, 6 H), 5.82 (dd, J = 8.6, 3.5 Hz, 1 H), 4.83 – 4.80 (m, 1 H), 4.21 (dd, J = 8.6, 3.5 Hz, 1 H), 3.57 (br s, 1 H), 1.90 (br s, 1 H), 1.69 – 1.42 (m, 8 H), 1.32 – 1.18 (m, 3 H)	HRMS(B) *m/z* 353.1961 $(M + H)^+$
10: (*R*)-4-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.08 (d, J = 5.8 Hz, 1 H), 7.43 – 7.18 (m, 11 H), 5.54 (br s, 1 H), 4.74 (t, J = 8.6 Hz, 1 H), 4.62 (br s, 1 H), 4.18 (dd, J = 8.8, 3.8 Hz, 1 H), 1.19 (d, J = 6.6 Hz, 3 H)	HRMS(B) *m/z* 361.1712 $(M + H)^+$
11: (*R*)-4-phenyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.07 (d, J = 5.8 Hz, 1 H), 7.38 (d, J = 5.8 Hz, 1 H), 7.28 – 7.05 (m, 10 H), 5.84 (dd, J = 8.3, 3.3 Hz, 1 H), 4.88 (q, J = 6.9 Hz, 1 H), 4.82 – 4.78 (m, 1 H), 4.24 (dd, J = 8.6, 3.5 Hz, 1 H), 1.44 (d, J = 6.9 Hz, 3 H)	HRMS(B) *m/z* 361.1661 $(M + H)^+$
12: (*S*)-4-isopropyl-3-(2-((*S*)-1-phenylpropylamino)pyrimidin-4-yl)oxazolidin-2-one	8.11 (d, J = 5.6 Hz, 1 H), 7.33 – 7.26 (m, 5 H), 7.22 – 7.15 (m, 1 H), 4.83 – 4.79 (m, 1 H), 4.68 (br s, 1 H), 4.36 – 4.28 (m, 2 H), 1.84 (quin, J = 7.3 Hz, 2 H), 0.99 (t, J = 7.3 Hz, 3 H), 0.76 (br s, 3 H), 0.59 (br s, 3 H)	HRMS(B) *m/z* 341.1974 $(M + H)^+$
13: (*S*)-4-isopropyl-3-(2-((*R*)-1-phenylpropylamino)pyrimidin-4-yl)oxazolidin-2-one	8.09 (d, J = 5.8 Hz, 1 H), 7.34 – 7.27 (m, 5 H), 7.24 – 7.16 (m, 1 H), 4.74 (t, J = 6.8 Hz, 1 H), 4.52 (br s, 1 H), 4.36 – 4.26 (m, 2 H), 2.66 (td, J = 6.9, 3.8 Hz, 1 H), 1.95 – 1.75 (m, 2 H), 1.02 (d, J = 7.1 Hz, 3 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.86 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 341.1976 $(M + H)^+$
14: provided (*S*)-4-benzhydryl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.09 (d, J = 5.8 Hz, 1 H), 7.32 – 7.23 (m, 3 H), 7.20 – 7.16 (br m, 6 H), 7.00 (br s, 5 H), 6.72 (br s, 2 H), 5.76 – 5.68 (m, 1 H), 5.04 (q, J = 7.1 Hz, 1 H), 4.59 (t, J = 8.8 Hz, 1 H), 4.50 (br s, 1H), 4.47 (dd, J = 9.1, 2.5 1H), 1.44 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 451.2126 $(M + H)^+$
15: (*4S,5R*)-4-methyl-5-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1 H), 7.45 – 7.30 (m, 8 H), 7.20 (t, J = 7.6 Hz, 2 H), 7.10 – 7.07 (m, 1 H), 5.80 (d, J = 7.1 Hz, 1 H), 5.10 – 4.92 (m, 2 H), 1.49 (d, J = 7.0 Hz, 3 H), 0.37 (br s, 3 H)	HRMS(B) *m/z* 375.1823 $(M + H)^+$
16: 3-(2-(cyclopentylamino)pyrimidin-4-yl)oxazolidin-2-one	8.07 (d, J = 5.7 Hz, 1 H), 7.32 (d, J = 5.8 Hz, 1 H),4.48 (t, J = 8.1 Hz, 2 H), 4.22 – 4.16 (m, 3 H), 2.02 (dq, J = 12, 6.1 Hz, 2 H), 1.70 – 1.80 (m, 2 H), 1.67 – 1.47 (m, 4 H)	HRMS(B) *m/z* 248.1275 M^+

17: (*S*)-4-benzyl-3-(2-(cyclopentylamino)pyrimidin-4-yl)oxazolidin-2-one	8.13 (d, J = 5.8 Hz, 1 H), 7.35 – 7.21 (m, 6 H), 5.14 – 5.04 (m, 1 H), 4.36 (t, J = 8.4 Hz, 1 H), 4.33 – 4.24 (m, 2 H), 3.37 – 3.33 (m, 1 H), 3.06 (dd, J = 13, 8.3 Hz, 1 H), 2.11 – 1.98 (m, 2 H), 1.86 – 1.71 (m, 2 H), 1.70 – 1.53 (m, 4 H)	HRMS(B) *m/z* 338.1749 M^+
18: (*R*)-4-benzyl-3-(2-(cyclopentylamino)pyrimidin-4-yl)oxazolidin-2-one	8.13 (d, J = 5.6 Hz, 1 H), 7.35 – 7.21 (m, 6 H), 5.14 – 5.05 (m, 1 H), 4.36 (t, J = 8.5 Hz, 1 H), 4.32 – 4.26 (m, 2 H), 3.37 – 3.33 (m, 1 H), 3.06 (dd, J = 13, 8.3 Hz, 1 H), 2.13 – 1.99 (m, 2 H), 1.85 – 1.71 (m, 2 H), 1.70 – 1.51 (m, 4 H)	HRMS(B) *m/z* 338.1748 M^+
19: (*4R,5S*)-4-methyl-5-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.11 (d, J = 5.8 Hz, 1 H), 7.48 – 7.28 (m, 10 H), 7.24 – 7.21 (m, 1 H), 5.70 (d, J = 6.8 Hz, 1 H), 4.96 – 4.90 (m, 1 H), 4.65 (br s, 1 H)1.49 (d, J = 7.1 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H)	HRMS(B) *m/z* 375.1824 $(M + H)^+$
20: (*S*)-4-benzhydryl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.13 (d, J = 5.8 Hz, 1 H), 7.47 – 7.40 (m, 2 H), 7.35 – 7.22 (m, 5 H), 7.19 – 7.10 (m, 5 H), 7.01 – 6.99 (m, 2 H), 6.89 (br s, 2 H), 5.26 (br s, 1 H), 5.09 (br s, 1 H), 4.76 (br s, 1 H), 4.54 – 4.44 (m, 2 H), 1.37 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 451.2134 $(M + H)^+$
21: (*R*)-4-isopropyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.10 (d, J = 5.8 Hz, 1 H), 7.35 – 7.27 (m, 5 H), 7.20 – 7.17 (m, 1 H), 4.96 (q, J = 6.7 Hz, 1 H), 4.44 (br s, 1 H), 4.32 (dd, J = 9.1, 2.5 Hz, 1 H), 4.25 (t, J = 8.6 Hz, 1 H), 2.65 (dtd, J = 14, 7.0, 3.5 Hz, 1 H), 1.51 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 327.1824 $(M + H)^+$
22: (*R*)-4-isopropyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1 H), 7.37 – 7.25 (m, 5 H), 7.19 – 7.16 (m, 1H), 5.04 (q, J = 6.9 Hz, 1 H), 4.64 (br s, 1 H), 4.35 – 4.26 (m, 2 H), 1.88 (br s, 1 H), 1.50 (d, J = 6.6 Hz, 3 H), 0.70 (br s, 3 H), 0.57 (br s, 3 H)	HRMS(B) *m/z* 327.1821 $(M + H)^+$
23: (*S*)-4-isopropyl-5,5-dimethyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.13 (d, J = 5.8 Hz, 1 H), 7.35 – 7.26 (m, 5 H), 7.19 – 7.16 (m, 1H), 5.08 – 5.03 (m, 1 H), 4.45 (br s, 1 H), 1.99 (br s, 1 H), 1.52 (s, 3 H), 1.50 (d, J = 7.1 Hz, 3 H), 1.41 (s, 3 H), 0.73 (br s, 3 H), 0.58 (br s, 3 H)	HRMS(B) *m/z* 355.2132 $(M + H)^+$
24: (*S*)-4-isopropyl-5,5-dimethyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.10 (d, J = 5.8 Hz, 1 H), 7.34 – 7.25 (m, 5 H), 7.18 – 7.15 (m, 1 H), 4.93 (br s, 1 H), 4.32 (br s, 1 H), 2.25 (td, J = 6.8, 3.5 Hz, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 1.49 (s, 3 H), 1.09 (br s, 3 H), 1.03 (d, J = 7.1 Hz, 3 H), 0.95 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 355.2128 $(M + H)^+$
25: (*4R,5S*)-4-methyl-5-phenyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1 H), 7.45 – 7.30 (m, 8 H), 7.20 (t, J = 7.3 Hz, 2 H), 7.10 – 7.06 (m, 1 H), 5.80 (d, J = 7.0 Hz, 1 H), 5.01 – 4.94 (m, 2 H), 1.49 (d, J 7.0 Hz, 3 H), 0.30 (br s, 3 H)	HRMS(B) *m/z* 375.1823 $(M + H)^+$
26: (*4S,5R*)-4-methyl-5-phenyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.10 (d, J = 5.8 Hz, 1 H), 7.48 – 7.28 (m, 10 H), 7.24 – 7.20 (m, 1 H), 5.69 (br s, 1 H), 5.01 – 4.93 (m, 1 H), 4.59 (br s, 1 H)1.49 (d, J = 7.1 Hz, 3 H), 0.96 (d, J = 6.5	HRMS(B) *m/z* 375.1819 $(M + H)^+$

	Hz, 3 H)	
27: (*S*)-5,5-dimethyl-4-phenyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	δ 8.08 (d, J = 5.9 Hz, 1 H), 7.44 – 7.39 (m, 3 H), 7.36 – 7.29 (m, 5 H), 7.22 – 7.17 (m, 3 H), 5.16 (br s, 1 H), 4.55 (br s, 1 H), 1.49 (s, 3 H), 1.18 (d, J = 6.8 Hz, 3 H), 0.96 (s, 3 H)	HRMS(B) *m/z* 389.1974 $(M + H)^+$
28: (*S*)-3-(2-((*S*)-2,3-dihydro-1H-inden-1-ylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.16 (d, J = 5.8 Hz, 1 H), 7.41 (d, J = 5.9 Hz, 1 H), 7.25 – 7.13 (m, 4 H), 5.48 (t, J = 7.8 Hz, 1 H), 4.79 – 4.68 (m, 1 H), 4.36 (d, J = 6.1 Hz, 2 H), 3.01 (ddd, J = 16, 8.6, 3.0 Hz, 1 H), 2.94 – 2.81 (m, 1 H), 2.66 – 2.54 (m, 2 H), 2.01 – 1.92 (m, 1 H), 0.86 (d, J = 6.9 Hz, 3 H), 0.85 (d, J = 6.9 Hz, 3 H)	HRMS(B) *m/z* 339.1825 $(M + H)^+$
29: (*S*)-3-(2-((*R*)-2,3-dihydro-1H-inden-1-ylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.15 (d, J = 5.8 Hz, 1 H), 7.41 (d, J = 5.8 Hz, 1 H), 7.29 – 7.15 (m, 4 H), 5.48 (t, J = 7.6 Hz, 1 H), 4.83 – 4.79 (m, 1 H), 4.41 – 4.36 (m, 2 H), 3.03 (ddd, J = 16, 8.8, 3.3 Hz, 1 H), 2.86 (dt, J = 16, 8.0 Hz, 1 H), 2.64 – 2.50 (m, 2 H), 2.00 – 1.91 (m, 1 H), 0.93 (d, J = 7.1 Hz, 3 H), 0.87 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 339.1830 $(M + H)^+$
30: (*4R,5S*)-4,5-diphenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1 H), 7.48 (d, J = 5.8 Hz, 1 H), 7.33 – 7.20 (m, 5 H), 7.13 – 7.08 (m, 6 H), 7.03 – 7.00 (m, 2 H), 6.88 – 6.86 (m, 2 H), 5.99 (d, J = 8.0 Hz, 1 H), 5.76 (br s, 1 H), 4.53 (br s, 1 H), 1.11 (br s, 3 H)	HRMS(B) *m/z* 437.1982 $(M + H)^+$
31: (*S*)-4-isobutyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.11 (d, J = 5.8 Hz, 1 H), 7.36 – 7.28 (m, 5 H), 7.21 – 7.18 (m, 1 H), 5.18 (q, J = 6.9 Hz, 1 H), 4.83 – 4.79 (m, 1 H), 4.46 (t, J = 8.5 Hz, 1 H), 4.23 (dd, J = 9.0, 3.0 Hz, 1 H), 1.57 (br s, 2 H), 1.53 (d, J = 7.0 Hz, 3 H), 1.33 (br s, 1 H), 0.82 (br s, 3 H), 0.73 (br s, 3 H)	HRMS(B) *m/z* 341.1974 $(M + H)^+$
32: (*S*)-4-isobutyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.09 (d, J = 5.8 Hz, 1 H), 7.36 – 7.27 (m, 5 H), 7.21 – 7.18 (m, 1 H), 5.16 (q, J = 7.0 Hz, 1 H), 4.69 (br s, 1 H), 4.42 (t, J = 8.3 Hz, 1 H), 4.24 (dd, J = 8.8, 2.8 Hz, 1 H), 1.92 – 1.86 (m, 1 H), 1.80 – 1.70 (m, 1 H), 1.58 (ddd, J = 13, 10, 4.8 Hz, 1 H), 1.52 (d, J = 7.0 Hz, 3 H), 1.07 (d, J = 6.5 Hz, 3 H), 0.98 (d, J = 6.5 Hz, 3 H)	HRMS(B) *m/z* 341.1972 $(M + H)^+$
33: (4*S*)-4-isopropyl-3-(2-(1-(pyridin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.49 – 8.48 (m, 1 H), 8.13 (dd, J = 10, 5.8 Hz, 1 H), 7.75 (td, J = 7.7, 1.8 Hz, 1 H), 7.43 – 7.36 (m, 2 H), 7.29 – 7.23 (m, 1 H), 5.08 – 4.99 (m, 1 H), 4.60 (br s, 0.5 H), 4.34 – 4.22 (m, 2.5 H), 2.63 – 2.56 (m, 0.5 H), 1.55 (d, J = 7.0 Hz, 1.5 H), 1.54 (d, J = 7.0 Hz, 1.5 H), 1.53 (br s, 0.5 H), 0.97 (d, J = 7.1 Hz, 1.5 H), 0.83 (d, J = 7.1 Hz, 1.5 H), 0.65 (br s, 1.5 H), 0.55 (br s, 1.5 H)	HRMS(B) *m/z* 328.1762 $(M + H)^+$
34: (4*S*)-4-isopropyl-3-(2-(1-(pyridin-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.45 – 8.43 (m, 2 H), 8.14 (dd, J = 12, 5.6 Hz, 1 H), 7.43 – 7.37 (m, 2 H), 5.05 (q, J = 7.1 Hz, 0.5 H), 4.99 – 4.95 (br m, 0.5 H), 4.59 (br s, 0.5 H), 4.33 – 4.26 (m, 2.5 H), 2.64 – 2.59 (m, 0.5 H), 1.53 (d, J = 7.1 Hz,	HRMS(B) *m/z* 328.1772 $(M + H)^+$

	3.5 H), 0.97 (d, J = 7.1 Hz, 1.5 H), 0.84 (d, J = 7.1 Hz, 1.5 H), 0.62 (br s, 1.5 H), 0.57 (br s, 1.5 H)	
35: (*S*)-4-isopropyl-3-(2-((*S*)-1-(naphthalen-1-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.19 – 8.16 (m, 2 H), 7.88 (d, J = 8.1 Hz, 1 H), 7.72 (d, J = 8.1 Hz, 1 H), 7.56 – 7.45 (m, 3 H), 7.40 – 7.32 (m, 2 H), 5.80 (q, J = 6.6 Hz, 1 H), 4.32 (br s, 1 H), 4.17 – 4.13 (m, 1 H), 4.05 (br s, 1 H), 1.64 (d, J = 7.1 Hz, 3 H), 1.15 (br s, 1 H), 0.23 (br s, 3 H), -0.31 (br s, 3 H)	HRMS(B) *m/z* 377.1969 $(M + H)^+$
36: (*S*)-4-isopropyl-3-(2-((*R*)-1-(4-methoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.09 (d, J = 5.6 Hz, 1 H), 7.33 (d, J = 6.1 Hz, 1 H), 7.28 – 7.24 (m, 2 H), 6.87 – 6.83 (m, 2 H), 4.93 (q, J = 6.9 Hz, 1 H), 4.52 (br s, 1 H), 4.35 – 4.26 (m, 2 H), 3.75 (s, 3 H), 2.65 (ddt, J = 10, 6.9, 3.5, 1 H), 1.48 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.83 (d, J = 6.8 Hz, 3 H)	HRMS(B) *m/z* 357.1928 $(M + H)^+$
37: (*4S,5R*)-4,5-diphenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.10 (d, J = 5.8 Hz, 1 H), 7.50 (d, J = 5.8 Hz, 1 H), 7.12 – 7.09 (m, 6 H), 7.06 – 7.03 (m, 2 H), 7.01 – 6.97 (m, 5 H), 6.83 – 6.81 (m, 2 H), 6.10 (s, 2 H), 4.86 – 4.81 (br m, 1 H), 1.42 (d, J = 6.5 Hz, 3 H)	HRMS(B) *m/z* 437.1984 $(M + H)^+$
38: (*4S,5R*)-4,5-diphenyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.11 – 8.09 (m, 1 H), 7.47 (d, J = 5.8 Hz, 1 H), 7.32 – 7.20 (m, 5 H), 7.12 – 7.07 (m, 6 H), 7.02 – 6.99 (m, 2 H), 6.86 (d, J = 6.5 Hz, 2 H), 5.98 – 5.93 (br m, 1 H), 5.75 (br s, 1 H), 4.53 (br s, 1 H), 1.11 (br s, 3 H)	HRMS(B) *m/z* 437.1970 $(M + H)^+$
39: (*4R,5S*)-4,5-diphenyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.09 (d, J = 5.9 Hz, 1 H), 7.50 (d, J = 5.8 Hz, 1 H), 7.11 – 7.09 (m, 6 H), 7.05 – 7.03 (m, 2 H), 7.00 – 6.95 (m, 5 H), 6.82 – 6.80 (m, 2 H), 6.09 (s, 2 H), 4.87 – 4.81 (br m, 1 H), 1.41 (d, J = 7.0 Hz, 3 H)	HRMS(B) *m/z* 437.1975 $(M + H)^+$
40: (*S*)-4-isopropyl-3-(2-((*R*)-1-(naphthalen-1-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.16 (d, J = 8.4 Hz, 1 H), 8.12 (d, J = 5.8 Hz, 1 H), 7.73 (d, J = 8.2 Hz, 1 H), 7.56 – 7.45 (m, 3 H), 7.42 – 7.38 (m, 1 H), 7.33 (d, J = 5.8 Hz, 1 H), 5.81 (q, J = 6.6 Hz, 1 H), 4.15 (br s, 1 H), 4.03 (br s, 1 H), 2.56 (td, J = 7.1, 3.5 Hz, 1 H), 1.65 (d, J = 7.1 Hz, 3 H), 0.78 (d, J = 6.6 Hz, 3 H), 0.74 (br s, 3 H)	HRMS(B) *m/z* 377.1981 $(M + H)^+$
41: (*S*)-4-isopropyl-3-(2-((*S*)-1-(4-methoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.11 (d, J = 5.8 Hz, 1 H), 7.33 (d, J = 5.9 Hz, 1 H), 7.22 (d, J = 8.6 Hz, 2 H), 6.85 – 6.82 (m, 2 H), 4.98 (q, J = 6.9 Hz, 1 H), 4.67 – 4.63 (m, 1 H), 4.34 – 4.27 (m, 2 H), 3.75 (s, 3 H), 1.94 (br s, 1 H), 1.48 (d, J = 7.1 Hz, 3 H), 0.73 (br s, 3 H), 0.61 (br s, 3 H)	HRMS(B) *m/z* 357.1922 $(M + H)^+$
42: (*S*)-4-isopropyl-3-(2-((*S*)-1-(4-(pyrimidin-5-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	9.11 (s, 1 H), 9.03 (s, 2 H), 8.14 (d, J = 5.8 Hz, 1 H), 7.69 – 7.66 (m, 2 H), 7.52 (d, J = 8.1 Hz, 2 H), 7.35 (d, J = 5.8 Hz, 1 H), 5.11 (q, J = 6.9 Hz, 1 H), 4.65 (br s, 1 H), 4.35 – 4.26 (m, 2 H), 1.80 (br s, 1 H), 1.55 (d, J = 7.1 Hz, 3 H), 0.66 (br s, 3 H), 0.55 (br s, 3 H)	HRMS(B) *m/z* 405.2035 $(M + H)^+$
43: (*S*)-4-isopropyl-3-(2-	8.10 (d, J = 5.9 Hz, 1 H), 7.80 – 7.75 (m, 4	HRMS(B)

((*R*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	H), 7.51 – 7.48 (m, 1 H), 7.43 – 7.36 (m, 2 H), 7.32 (d, J = 5.8 Hz, 1 H), 5.15 – 5.07 (m, 1 H), 4.36 (br s, 1 H), 4.24 (dd, J = 9.1, 2.5 Hz, 1 H), 4.14 – 4.06 (br m, 1 H), 2.67 (dtd, J = 14, 6.9, 3.5 Hz, 1 H), 1.60 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.83 (d, J = 7.1 Hz, 3 H)	*m/z* 377.1984 $(M + H)^+$
44: (*R*)-3-(2-((*S*)-1-(4-fluorophenyl)ethylamino)pyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one	8.09 – 8.07 (m, 1 H), 7.41 – 7.18 (m, 8 H), 7.12 – 7.07 (m, 2 H), 5.21 (s, 1 H), 4.99 – 4.93 (m, 1 H), 1.50 (s, 3 H), 1.24 (d, J = 7.1 Hz, 3 H), 0.98 (s, 3 H)	HRMS(B) *m/z* 407.188 $(M + H)^+$
45: (*R*)-4-isobutyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.10 (d, J = 5.8 Hz, 1 H), 7.36 – 7.27 (m, 5 H), 7.22 – 7.17 (m, 1 H), 5.18 (q, J = 6.9 Hz, 1 H), 4.82 – 4.78 (m, 1 H), 4.46 (t, J = 8.6 Hz, 1 H), 4.22 (dd, J = 8.6, 3.0 Hz, 1 H), 1.62 – 1.54 (m, 2 H), 1.53 (d, J = 7.0 Hz, 3 H), 1.36 – 1.30 (m, 1 H), 0.82 (br s, 3 H), 0.73 (br s, 3 H)	HRMS(B) *m/z* 341.1967 $(M + H)^+$
46: (*4S,5R*)-5-methyl-4-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.05 (d, J = 5.8 Hz, 1 H), 7.42 (d, J = 5.8 Hz, 1 H), 7.31 – 7.26 (m, 3 H), 7.19 – 7.11 (m, 5 H), 7.02 (br s, 2 H), 5.80 (d, J = 7.5 Hz, 1 H), 5.11 – 5.04 (m, 1 H), 4.85 (q, J = 6.7 Hz, 1 H), 1.44 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H)	HRMS(B) *m/z* 375.1828 $(M + H)^+$
47: (*4S,5R*)-5-methyl-4-phenyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.06 (d, J = 5.8 Hz, 1 H), 7.43 – 7.40 (m, 3 H), 7.37 – 7.30 (m, 5 H), 7.23 – 7.17 (m, 3 H), 5.51 (br d, J = 7.1 Hz, 1 H), 4.99 (quin, J = 6.8 Hz, 1 H), 4.63 (br s, 1 H), 1.16 (br d, J = 6.3 Hz, 3 H), 0.95 (d, J = 6.5 Hz, 3 H)	HRMS(B) *m/z* 375.1819 $(M + H)^+$
48: (*S*)-4-benzyl-5,5-dimethyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.18 (d, J = 5.7 Hz, 1 H), 7.43 (d, J = 5.7 Hz, 1 H), 7.31 – 7.17 (m, 10 H), 5.34 (br s, 1 H), 5.14 (quin, J = 7.0 Hz, 1 H), 4.85 (dd, J = 10, 3.5 Hz, 1 H), 3.22 (br d, J = 14 Hz, 1 H), 2.72 (br s, 1 H), 1.57 (d, J = 6.5 Hz, 3 H), 1.42 (s, 3 H), 1.33 (s, 3 H)	HRMS(B) *m/z* 403.2133 $(M + H)^+$
49: (*R*)-4-isobutyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.09 (d, J = 6.1 Hz, 1 H), 7.36 – 7.27 (m, 5 H), 7.21 – 7.17 (m, 1 H), 5.16 (q, J = 7.1 Hz, 1 H), 4.69 (t, J = 8.6 Hz, 1 H), 4.41 (t, J = 8.3 Hz, 1 H), 4.23 (dd, J = 8.6, 3.0 Hz, 1 H), 1.92 – 1.86 (m, 1 H), 1.79 – 1.69 (m, 1 H), 1.57 (ddd, J = 13, 10, 4.8 Hz, 1 H), 1.52 (d, J = 7.1 Hz, 3 H), 1.07 (d, J = 6.6 Hz, 3 H), 0.98 (d, J = 6.6 Hz, 3 H)	HRMS(B) *m/z* 341.1973 $(M + H)^+$
50: (*S*)-4-isopropyl-3-(2-((*S*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.15 (d, J = 5.7 Hz, 1 H), 7.81 – 7.73 (m, 4 H), 7.49 – 7.38 (m, 3 H), 7.33 (d, J = 5.8 Hz, 1 H), 5.18 (q, J = 7.1 Hz, 1 H), 4.57 (br s, 1 H), 4.30 – 4.25 (m, 1 H), 4.20 (br s, 1 H), 1.60 (d, J = 7.1 Hz, 3 H), 1.59 (br s, 1 H), 0.34 (br s, 6 H)	HRMS(B) *m/z* 377.1979 $(M + H)^+$
51: (*S*)-4-isopropyl-3-(2-((*R*)-1-p-tolylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.08 (d, J = 5.6 Hz, 1 H), 7.32 (d, J = 5.6 Hz, 1 H), 7.22 (d, J = 8.1 Hz, 2 H), 7.10 (d, J = 8.1 Hz, 2 H), 4.95 – 4.90 (m, 1 H), 4.48 (br s, 1 H), 4.32 (dd, J 9.1, 3.0 Hz, 1 H),	HRMS(B) *m/z* 341.1972 $(M + H)^+$

	4.25 (t, J = 8.8 Hz, 1 H), 2.65 (dtd, J = 14, 7.1, 3.5 Hz, 1 H), 2.28 (s, 3 H), 1.48 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.84 (d, J = 7.1 Hz, 3 H)	
52: (*S*)-4-benzyl-5,5-dimethyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.17 (d, J = 5.7 Hz, 1 H), 7.44 (d, J = 5.7 Hz, 1 H), 7.38 – 7.21 (m, 10 H), 5.32 (br s, 1 H), 5.02 (br s, 1 H), 4.69 – 4.68 (br m, 1 H), 3.34 (dd, J = 15, 4.0 Hz, 1 H), 2.93 (dd, J = 15, 9.5 Hz, 1 H), 1.51 (d, J = 6.9 Hz, 3 H), 1.35 (s, 3 H), 1.29 (s, 3 H)	HRMS(B) *m/z* 403.2133 $(M + H)^+$
53: (*S*)-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)-4-(pyridin-3-yl)oxazolidin-2-one	($CDCl_3$) 8.56 – 8.53 (br m, 2 H), 8.18 (d, J = 5.7 Hz, 1 H), 7.48 (d, J = 5.7 Hz, 1 H), 7.45 – 7.34 (m, 1 H), 7.30 – 7.16 (m, 6 H), 5.77 (dd, J = 8.8, 3.8 Hz, 1 H), 5.26 (br s, 1 H), 4.83 (br s, 1 H), 4.81 (t, J = 8.8 Hz, 1 H), 4.31 (dd, J = 8.8, 3.8 Hz, 1 H), 1.51 (d, J = 6.8 Hz, 3 H)	HRMS(B) *m/z* 362.1620 $(M + H)^+$
54: 4-(4-methoxyphenyl)-5,5-dimethyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.06 (d, J = 5.7 Hz, 1 H), 7.55 – 7.52 (m, 1 H), 7.37 – 7.20 (m, 4 H), 7.13 – 6.99 (m, 3 H), 6.91 (d, J = 8.0 Hz, 1 H), 6.78 (d, J = 8.0 Hz, 1 H), 5.87 (br s, 0.5 H), 5.67 (br s, 0.5 H), 5.01 (br s, 0.5 H), 4.82 (br s, 0.5 H), 4.64 (br s, 0.5 H), 3.83 (s, 1.5 H), 3.78 (s, 1.5 H), 3.36 (br s, 0.5 H), 1.66 (s, 1.5 H), 1.51 (d, J = 6.9 Hz, 1.5 H), 1.49 (s, 1.5 H), 1.29 – 1.27 (m, 1.5 H), 1.04 (s, 1.5 H), 1.00 (s, 1. 5 H)	HRMS(B) *m/z* 419.2093 $(M + H)^+$
55: (*R*)-3-(2-(benzylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.08 (d, J = 5.8 Hz, 1 H), 7.41 (d, J = 5.8 Hz, 1 H), 7.30 – 7.17 (m, 8 H), 7.09 (br d, J = 7.1 Hz, 2 H), 5.69 (br dd, J =8.1, 3.0 Hz, 1 H), 4.76 (t, J = 8.8 Hz, 1 H), 4.28 (dd, J = 44, 15 Hz, 2 H), 4.19 (dd, J = 8.8, 3.8 Hz, 1 H)	HRMS(B) *m/z* 347.1512 $(M + H)^+$
56: (*S*)-3-(2-(benzylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.10 (d, J = 5.7 Hz, 1 H), 7.42 (d, J = 5.9 Hz, 1 H), 7.31 – 7.16 (m, 8 H), 7.09 (br d, J = 7.1 Hz, 2 H), 5.71 (br m, 1 H), 4.78 (t, J = 8.8 Hz, 1 H), 4.28 (dd, J = 45, 15 Hz, 2 H), 4.21 (dd, J = 8.6, 3.5 Hz, 1 H)	HRMS(B) *m/z* 347.1499 $(M + H)^+$
57: (*S*)-3-(2-(benzylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.13 (d, J = 5.8 Hz, 1 H), 7.37 (d, J = 5.8 Hz, 1 H), 7.28 (d, J = 4.6 Hz, 4 H), 7.20 (dq, J = 8.5, 4.2 Hz, 1 H), 4.64 (br s, 1 H), 4.56 (dd, J = 51, 16 Hz, 2 H), 4.35 – 4.29 (m, 2 H), 2.31 (br s, 1 H), 0.77 (br s, 3 H), 0.72 (br d, J = 6.6 Hz, 3 H)	HRMS(B) *m/z* 312.1584 M^+
58: (4*S*)-4-isopropyl-3-(2-(1-(4-(4-methylpiperazin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.23 (d, J = 5.8 Hz, 1 H), 7.40 (d, J = 5.8 Hz, 1 H), 7.28 – 7.24 (m, 2 H), 7.01 – 6.98 (m, 2 H), 4.85 – 4.82 (m, 1 H), 4.44 – 4.39 (m, 2 H), 4.03 – 3.98 (m, 1 H), 3.93 – 3.90 (m, 4 H), 3.30 (s, 3 H), 3.21 – 3.18 (m, 4 H), 2.60 (dtt, J = 10, 6.9, 3.5 Hz, 1 H), 1.37 (d, J = 7.1 Hz, 3 H), 1.00 (d, J = 7.1 Hz, 3 H), 0.87 (d, J = 6.9 Hz, 3 H)	HRMS(B) *m/z* 425.2651 $(M + H)^+$
59: (*S*)-3-(2-((*S*)-1-(3,5-bis(trifluoromethyl)phenyl)ethylamino)pyrimidin-4-yl)-	8.17 (br d, J = 5.0 Hz, 1 H), 7.93 (s, 2 H), 7.82 (s, 1 H), 7.40 (d, J = 5.9 Hz, 1 H), 5.21 (q, J = 7.1 Hz, 1 H), 4.59 (br s, 1 H),	HRMS(B) *m/z* 463.1564

4-isopropyloxazolidin-2-one	4.33 – 4.25 (m, 2 H), 1.69 (br s, 1 H), 1.57 (d, J = 7.1 Hz, 3 H), 0.57 (br s, 6 H)	$(M + H)^+$
60: (*S*)-4-isopropyl-3-(2-((*S*)-1-(6-methoxynaphthalen-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.14 (d, J = 5.8 Hz, 1 H), 7.71 (d, J = 8.6 Hz, 1 H), 7.67 – 7.64 (m, 2 H), 7.42 (dd, J = 8.3, 1.8 Hz, 1 H), 7.33 (d, J = 5.8 Hz, 1 H), 7.19 (d, J = 2.5 Hz, 1 H), 7.08 (dd, J = 9.1, 2.5 Hz, 1 H), 5.15 (q, J = 7.1 Hz, 1 H), 4.59 (br s, 1 H), 4.29 (t, J = 8.8 Hz, 1 H), 4.24 – 4.19 (br m, 1 H), 3.88 (s, 3 H), 1.74 (br s, 1 H), 1.58 (d, J = 7.1 Hz, 3 H), 0.39 (br s, 6 H)	HRMS(B) *m/z* 407.2084 $(M + H)^+$
61: (*S*)-4-isopropyl-3-(2-((*R*)-1-(3-methoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.09 (d, J = 5.8 Hz, 1 H), 7.33 (d, J = 5.9 Hz, 1 H), 7.20 (t, J = 7.8 Hz, 1 H), 6.92 – 6.90 (m, 2 H), 6.75 (ddd, J = 8.1, 2.5, 1.0 Hz, 1 H), 4.94 – 4.89 (m, 1 H), 4.46 (br s, 1 H), 4.34 – 4.23 (m, 2 H), 3.75 (s, 3 H), 2.65 (dtd, J = 14, 6.9, 3.5 Hz, 1 H), 1.49 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 6.9 Hz, 3 H)	HRMS(B) *m/z* 357.1927 $(M + H)^+$
62: (*S*)-3-(2-((*S*)-1-(3-bromophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.14 (d, J 5.8 Hz, 1 H), 7.48 (s, 1 H), 7.37 – 7.28 (m, 3 H), 7.20 (t, J = 7.1 Hz, 1 H), 5.01 (q, J = 7.1 Hz, 1 H), 4.62 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.83 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.71 (br s, 3 H), 0.59 (br s, 3 H)	HRMS(B) *m/z* 405.0937 $(M + H)^+$
63: (*S*)-3-(2-((*S*)-1-(4-bromophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.13 (d, J 5.8 Hz, 1 H), 7.44 – 7.41 (m, 2 H), 7.35 (d, J = 5.8 Hz, 1 H), 7.26 – 7.22 (m, 2 H), 4.98 (q, J = 7.1 Hz, 1 H), 4.60 (br s, 1 H), 4.33 – 4.26 (m, 2 H), 1.73 (br s, 1 H), 1.49 (d, J = 7.1 Hz, 3 H), 0.68 (br s, 3 H), 0.58 (br s, 3 H)	HRMS(B) *m/z* 405.0912 $(M + H)^+$
64: (*S*)-3-(2-(1-(naphthalen-1-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.23 (d, J = 8.1 Hz, 1 H), 8.07 (d, J = 5.8 Hz, 1 H), 7.88 – 7.86 (m, 1 H), 7.73 (d, J = 8.1 Hz, 1 H), 7.58 (d, J = 7.1 Hz, 1 H), 7.54 – 7.45 (m, 2 H), 7.42 – 7.39 (m, 1 H), 7.29 (d, J = 5.8 Hz, 1 H), 5.90 (q, J = 6.7 Hz, 1 H), 4.32 (br s, 1 H), 4.22 (br s, 1 H), 3.98 (br s, 1 H), 3.37 (br s, 1 H), 1.65 (d, J = 6.9 Hz, 3 H)	HRMS(B) *m/z* 335.1500 $(M + H)^+$
65: (*S*)-3-(2-((*S*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.11 (d, J = 5.8 Hz, 1 H), 7.80 – 7.77 (m, 1 H), 7.73 – 7.68 (m, 2 H), 7.56 (s, 1 H), 7.45 – 7.40 (m, 2 H), 7.37 (d, J = 5.8 Hz, 1 H), 7.23 (dd, J = 8.6, 1.5 Hz, 1 H), 7.08 – 7.00 (m, 5 H), 5.80 (dd, J = 8.8, 3.8 Hz, 1 H), 5.07 (q, J = 6.9 Hz, 1 H), 4.79 (t, J = 8.7 Hz, 1 H), 4.20 (dd, J = 8.6, 3.5 Hz, 1 H), 1.55 (d, J = 6.9 Hz, 3 H)	HRMS(B) *m/z* 411.1820 $(M + H)^+$
66: (*R*)-3-(2-((*S*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.10 (d, J = 5.8 Hz, 1 H), 7.82 – 7.78 (m, 3 H), 7.69 (s, 1 H), 7.47 – 7.40 (m, 5 H), 7.38 – 7.29 (m, 4 H), 5.53 (dd, J = 8.8, 3.8 Hz, 1 H), 4.82 (q, J = 6.9 Hz, 1 H), 4.68 (t, J = 8.6 Hz, 1 H), 4.15 (dd, J = 8.6, 4.0 Hz, 1 H), 1.31 (d, J = 6.9 Hz, 3 H)	HRMS(B) *m/z* 411.1821 $(M + H)^+$
67: (*S*)-3-(2-((*R*)-1-(3-bromophenyl)ethylamino)	8.10 (d, J 5.8 Hz, 1 H), 7.53 – 7.50 (m, 1 H), 7.36 – 7.31 (m, 3 H), 7.21 (t, J = 7.8	HRMS(B)

pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Hz, 1 H), 4.94 – 4.86 (m, 1 H), 4.42 (br s, 1 H), 4.33 (dd, J = 9.1, 2.5, 1 H), 4.26 (t, J = 8.8 Hz, 1 H), 2.65 (dtd, J = 14, 7.0, 3.8 Hz, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 1.00 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 3 H)	*m/z* 405.0930 $(M + H)^+$
68: (*S*)-3-(2-((*R*)-1-(4-bromophenyl)ethylamino) pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.10 (d, J 5.8 Hz, 1 H), 7.45 – 7.42 (m, 2 H), 7.35 (d, J = 5.9 Hz, 1 H), 7.29 – 7.25 (m, 2 H), 4.95 – 4.90 (m, 1 H), 4.44 (br s, 1 H), 4.34 – 4.25 (m, 2 H), 2.63 (dtd, J = 14, 6.9, 3.5 Hz, 1 H), 1.49 (d, J = 7.1 Hz, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.84 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 405.0934 $(M + H)^+$
69: (*S*)-4-isopropyl-3-(2-((*S*)-1-(3-methoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1 H), 7.34 (d, J = 6.0 Hz, 1 H), 7.20 – 7.16 (m, 1 H), 6.89 – 6.87 (m, 2 H), 6.75 – 6.73 (m, 1 H), 4.99 (q, J = 6.7 Hz, 1 H), 4.63 (br s, 1 H), 4.34 – 4.25 (m, 2 H), 3.74 (s, 3 H), 1.84 (br s, 1 H), 1.49 (d, J = 7.1 Hz, 3 H), 0.68 (br s, 3 H), 0.57 (br s, 3 H)	HRMS(B) *m/z* 357.1918 $(M + H)^+$
70: (*S*)-4-isopropyl-3-(2-((*S*)-1-p-tolylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.11 (d, J = 5.8 Hz, 1 H), 7.33 (d, J = 5.9 Hz, 1 H), 7.18 (d, J = 8.1 Hz, 2 H), 7.08 (d, J = 8.1 Hz, 2 H), 4.99 (q, J = 7.1 Hz, 1 H), 4.63 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 2.28 (s, 3 H), 1.86 (br s, 1 H), 1.48 (d, J = 7.1 Hz, 3 H), 0.69 (br s, 3 H), 0.58 (br s, 3 H)	HRMS(B) *m/z* 341.1977 $(M + H)^+$
71: (*S*)-4-tert-butyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.14 (d, J = 5.7 Hz, 1 H), 7.37 – 7.34 (m, 2 H), 7.30 – 7.26 (m, 2 H), 7.19 – 7.15 (m, 2 H), 5.00 (q, J = 6.9 Hz, 1 H), 4.76 (br s, 1 H), 4.41 – 4.33 (m, 2 H), 1.48 (d, J = 7.1 Hz. 3 H), 0.55 (br s, 9 H)	HRMS(B) *m/z* 341.1979 $(M + H)^+$
72: (*S*)-4-tert-butyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.09 (d, J = 5.7 Hz, 1 H), 7.35 – 7.32 (m, 2 H), 7.29 – 7.24 (m, 3 H), 7.19 – 7.15 (m, 1 H), 5.01 – 4.96 (m, 1 H), 4.68 (br s, 1 H), 4.39 (d, H = 9.2 Hz, 1 H), 4.15 (br s, 1 H), 1.50 (d, J = 7.0 Hz. 3 H), 0.94 (s, 9 H)	HRMS(B) *m/z* 341.1974 $(M + H)^+$
73: (*R*)-3-(2-((*S*)-1-(3-methoxyphenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.09 (d, J = 5.8 Hz, 1 H), 7.42 – 7.37 (m, 3 H), 7.34 – 7.28 (m, 3 H), 7.21 (t, J = 7.8 Hz, 1 H), 6.86 – 6.83 (m, 2 H), 6.78 – 6.76 (m, 1 H), 5.58 (dd, J = 8.6, 4.0 Hz, 1 H), 4.74 (t, J = 8.7 Hz, 1 H), 4.66 – 4.61 (m, 1 H), 4.18 (dd, J = 8.6, 4.0 Hz, 1 H), 3.77 (s, 3 H), 1.20 (d, J = 6.9 Hz, 3 H)	HRMS(B) *m/z* 391.1768 $(M + H)^+$
74: (*S*)-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)-4-(pyridin-2-yl)oxazolidin-2-one	8.55 (d, J = 4.5 Hz, 1 H), 8.10 (d, J = 6.0 Hz, 1 H), 7.64 (d, J = 6.0 Hz, 1 H), 7.43 (br s, 1 H), 7.26 – 7.15 (m, 4 H), 7.06 (br s, 2 H), 6.92 (br s, 1 H), 5.84 (dd, J = 8.7, 3.2 Hz, 1 H), 4.94 (br s, 1 H), 4.88 – 4.78 (m, 2 H), 4.48 (dd, J = 8.7, 3.2 Hz, 1 H), 1.51 (d, J = 6.9 Hz, 3 H)	HRMS(B) *m/z* 362.1624 $(M + H)^+$
75: (*S*)-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)-4-(pyridin-4-yl)oxazolidin-2-one	8.43 (br s, 2 H), 8.16 (br d, J = 5.0 Hz, 1 H), 7.65 (br s, 1 H), 7.36 – 7.09 (br m, 6 H), 6.90 (br s, 1 H), 5.88 (br s, 1 H), 4.83 (t, J = 8.8 Hz, 1 H), 4.78 (br s, 1 H), 4.23 (br s, 1 H), 1.34 (d, J = 7.0 Hz, 3 H)	HRMS(B) *m/z* 362.1623 $(M + H)^+$
76: (*S*)-4-isopropyl-3-(2-	8.11 (d, J = 5.8 Hz, 1 H), 7.66 (s, 1 H),	HRMS(B)

((*R*)-1-(3-(trifluoromethyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	7.64 – 7.61 (m, 1 H), 7.53 – 7.49 (m, 2 H), 7.36 (d, J = 5.9 Hz, 1 H), 5.05 – 4.99 (m, 1 H), 4.42 (br s, 1 H), 4.33 (dd, J = 9.1, 3.0 Hz, 1 H), 4.24 (t, J = 8.6 Hz, 1 H), 2.68 – 2.60 (m, 1 H), 1.54 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.0 Hz, 3 H)	*m/z* 395.1686 $(M + H)^+$
77: (*S*)-4-isopropyl-3-(2-((*R*)-1-(4-(trifluoromethyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.11 (d, J = 5.8 Hz, 1 H), 7.60 (d, J = 8.3 Hz, 2 H), 7.54 (d, J = 8.3 Hz, 2 H), 7.36 (d, J = 5.8 Hz, 1 H), 5.07 – 5.00 (m, 1 H), 4.39 (br s, 1 H), 4.33 – 4.30 (m, 1 H), 4.27 – 4.23 (m, 1 H), 2.63 (dtd, J = 14, 7.1, 3.5 Hz, 1 H), 1.54 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.84 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 395.1698 $(M + H)^+$
78: (*S*)-3-(2-((*R*)-1-(2-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.10 (d, J = 5.8 Hz, 1 H), 7.40 – 7.34 (m, 2 H), 7.24 – 7.18 (m, 1 H), 7.10 – 7.02 (m, 2 H), 5.28 (q, J = 7.1 Hz, 1 H), 4.42 (br s, 1 H), 4.32 (dd, J = 9.1, 2.5 Hz, 1 H), 4.24 (t, J = 8.8 Hz, 1 H), 2.64 (dtd, J = 14, 7.0, 3.8 Hz, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.84 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 345.1727 $(M + H)^+$
79: (*S*)-4-methyl-4-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.15 (d, J = 5.8 Hz, 1 H), 7.44 – 7.38 (m, 3 H), 7.36 – 7.21 (m, 6 H), 7.15 – 7.13 (m, 2 H), 5.40 (br s, 1 H), 4.22 – 4.17 (m, 2 H), 4.15 (br s, 1 H), 1.63 (br s, 3 H), 1.15 (d, J 6.6 Hz, 3 H)	HRMS(B) *m/z* 375.1809 $(M + H)^+$
80: (*S*)-4-isopropyl-3-(2-((*S*)-1-(4-morpholinophenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.11 (d, J = 5.8 Hz, 1 H), 7.33 (d, J = 5.8 Hz, 1 H), 7.22 – 7.19 (m, 2 H), 6.92 – 6.89 (m, 2 H), 5.00 – 4.95 (m, 1 H), 4.66 (br s, 1 H), 4.58 (br s, 1 H), 4.35 – 4.27 (m, 2 H), 3.82 – 3.80 (m, 4 H), 3.09 – 3.07 (m, 4 H), 1.48 (d, J = 7.1 Hz, 3 H), 0.73 (br s, 3 H), 0.60 (br s, 3 H)	HRMS(B) *m/z* 412.2359 $(M + H)^+$
81: (4*R*)-4-methyl-4-phenyl-3-(2-((1-(1-phenyl-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one		HRMS(B) *m/z* 441.2049 $(M + H)^+$
82: (*S*)-3-(2-((*S*)-1-(4-bromo-3,5-dimethoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.16 (d, J = 5.8 Hz, 1 H), 7.36 (d, J = 5.8 Hz, 1 H), 6.64 (s, 2 H), 5.00 – 4.95 (m, 1 H), 4.58 (br s, 1 H), 4.33 – 4.23 (m, 2 H), 3.79 (s, 6 H), 1.54 (d, J = 7.0 Hz, 3 H), 0.55 (br s, 6 H)	HRMS(B) *m/z* 465.1134 $(M + H)^+$
83: (4*S*)-3-(2-(1-(1*H*-indol-5-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.11 (d, J = 5.8 Hz, 0.5 H), 8.09 (d, J = 5.8 Hz, 0.5 H), 7.52 (s, 0.5 H), 7.46 (s, 0.5 H), 7.32 – 7.29 (m, 2 H), 7.19 – 7.18 (m, 1 H), 7.10 (ddd, J = 14, 8.6, 1.5 Hz, 1 H), 6.36 (dt, J = 4.0, 3.0 Hz, 1 H), 5.11 (q, J = 6.9 Hz, 0.5 H), 5.05 (q, J = 6.8 Hz, 0.5 H), 4.64 (br s, 0.5 H), 4.50 (br s, 0.5 H), 4.33 – 4.19 (m, 2 H), 2.74 – 2.64 (m, 0.5 H), 1.86 (br s, 0.5 H), 1.55 (d, J = 7.1 Hz, 3 H), 1.02 (d, J = 7.1 Hz, 1.5 H), 0.86 (d, J = 7.1 Hz, 1.5 H), 0.57 (br s, 1.5 H), 0.46 (br s, 1.5 H)	HRMS(B) *m/z* 366.1928 $(M + H)^+$
84: (*S*)-3-(2-((*S*)-1-(5-	δ 8.16 – 8.12 (m, 2 H), 7.80 (d, J = 9.1 Hz,	HRMS(B)

bromo-6-methoxynaphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	1 H), 7.72 (s, 1 H), 7.56 (dd, J = 8.8, 1.8 Hz, 1 H), 7.37 (d, J = 9.1 Hz, 1 H), 7.32 (d, J = 5.7 Hz, 1 H), 5.18 (q, J = 6.7 Hz, 1 H), 4.60 – 4.54 (m, 1 H), 4.28 (t, J = 8.8 Hz, 1 H), 4.19 (dd, J = 9.1, 3.0 Hz, 1 H), 3.99 (s, 3 H), 1.72 (br s, 1 H), 1.61 (d, J = 7.1 Hz, 3 H), 0.39 (br d, J = 6.6 Hz, 3 H), 0.43 (br d, J = 6.1 Hz, 3 H)	*m/z* 485.1184 $(M + H)^+$
85: (*S*)-3-(2-((*R*)-1-(4-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.09 (d, J = 5.9 Hz, 1 H), 7.38 – 7.33 (m, 3 H), 7.04 – 6.98 (m, 2 H), 4.96 (q, J = 6.7 Hz, 1 H), 4.48 (br s, 1 H), 4.35 – 4.25 (m, 2 H), 2.64 (dtd, J = 14, 7.1, 3.5 Hz, 1 H), 1.50 (d, J = 6.6 Hz, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.0 Hz, 3 H)	HRMS(B) *m/z* 345.1725 $(M + H)^+$
86: (S)-4-isopropyl-3-(2-((R)-1-(2-(trifluoromethyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1 H), 7.77 (d, J = 8.1 Hz, 1 H), 7.66 (d, J = 8.1 Hz, 1 H), 7.60 (t, J = 7.6 Hz, 1 H), 7.42 – 7.36 (m, 2 H), 5.58 (q, J = 6.7 Hz, 1 H), 4.70 (dt, J = 7.8, 3.7 Hz, 1 H), 4.38 – 4.31 (m, 2 H), 2.58 (dtd, J = 14, 7.0, 3.8 Hz, 1 H), 1.50 (d, J = 6.9 Hz, 3 H), 0.98 (d, J = 7.0 Hz, 3 H), 0.85 (d, J = 6.9 Hz, 3 H)	HRMS(B) *m/z* 395.1706 $(M + H)^+$
87: (*R*)-4-methyl-3-(2-((*S*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one		HRMS(B) *m/z* 425.1967 $(M + H)^+$
88: (*S*)-3-(2-((*S*)-1-(4-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1 H), 7.35 – 7.31 (m, 3 H), 7.03 – 6.97 (m, 2 H), 5.03 (q, J = 7.1 Hz, 1 H), 4.66 – 4.63 (br m, 1 H), 4.35 – 4.27 (m, 2 H), 1.85 (br s, 1 H), 1.49 (d, J = 7.0 Hz, 3 H), 0.71 (br s, 3 H), 0.60 (br s, 3 H)	HRMS(B) *m/z* 345.1724 $(M + H)^+$
89: (*R*)-4-methyl-4-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.12 (d, J = 5.8 Hz, 1 H), 7.43 (d, J = 5.8 Hz, 1 H) 7.32 – 7.20 (m, 8 H), 6.99 (br s, 2 H), 5.20 (br s, 1 H), 4.33 (br s, 1 H), 4.32 – 4. 27 (m, 2 H), 2.20 (s, 3 H), 1.41 (d, J = 6.8 Hz, 3 H)	HRMS(B) *m/z* 375.1822 $(M + H)^+$
90: (*S*)-4-isopropyl-3-(2-((*S*)-1-(2-methoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.11 (d, J = 5.8 Hz, 1 H), 7.33 (d, J = 5.8 Hz, 3 H), 7.20 – 7.16 (m, 2 H), 6.95 (d, J = 8.1 Hz, 1 H), 6.86 – 6.82 (m, 1 H), 5.28 (q, J = 7.1 Hz, 1 H), 4.63 (br s, 1 H), 4.35 – 4.26 (m, 2 H), 3.87 (s, 3 H), 1.86 (br s, 1 H), 1.46 (d, J = 6.9 Hz, 3 H), 0.69 (br s, 3 H), 0.56 (br s, 3 H)	HRMS(B) *m/z* 357.1924 $(M + H)^+$
91: (*S*)-3-(2-(1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.08 (d, J = 5.8 Hz, 1 H), 7.82 – 7.78 (m, 4 H), 7.52 (dd, J = 8.6, 1.5 Hz, 1 H), 7.45 – 7.38 (m, 2 H), 7.29 (d, J = 5.8 Hz, 1 H), 5.23 (q, J = 6.9 Hz, 1 H), 4.46 – 4.33 (m, 2 H), 4.21 – 4.15 (m, 1 H), 3.93 – 3.86 (m, 1 H), 1.61 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 335.1509 $(M + H)^+$
92: (*S*)-4-isopropyl-3-(2-((*S*)-1-(3-methoxyphenyl)ethylamin	($CDCl_3$) 15.12 (br s, 1 H), 9.23 (br s, 1 H), 7.67 – 7.56 (m, 1 H), 7.24 (dd, J = 8, 8 Hz, 1 H), 6.92 – 6.72 (m, 3 H), 5.04 – 4.86 (m,	HRMS(B) *m/z* 371.2082

o)-6-methylpyrimidin-4-yl)oxazolidin-2-one hydrochloride	1 H), 4.72 – 4.51 (m, 1 H), 4.42 – 4.25 (m, 2 H), 3.81 (s, 3 H), 2.56 (s, 3 H), 1.90 – 1.76 (m, 1 H), 1.64 (br s, 3 H), 0.73 (d, J = 8 Hz, 3 H), 0.64 (d, J = 8 Hz, 3 H)	$(M + H)^+$
93: (*S*)-4-isopropyl-3-(6-methyl-2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 7.57 – 7.19 (m, 6 H), 5.05 – 4.86 (m, 1 H), 4.63 – 4.09 (m, 3 H), 2.561 / 2.49 (2 x s, 3 H), 1.91 – 1.70 (m, 1 H), 1.62 / 1.54 (2 x d, 3 H), 0.75 – 0.45 (m, 6 H)	HRMS(B) *m/z* 341.1982 $(M + H)^+$
94: (*S*)-3-(2-(((*S*)-3-methylbutan-2-yl)amino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	(DMSO-d_6) 8.11 (d, *J* = 5.5 Hz, 1 H), 7.39 – 7.32 (m, 2 H), 7.31 – 7.19 (m, 4 H), 6.95 – 6.82 (m, 1 H), 5.83 – 5.73 (m, 1 H), 4.82 (t, *J* = 8.5 Hz, 1 H), 4.15 (br s., 1 H), 1.37 – 1.21 (m, 1 H), 0.97 (d, *J* = 7.0 Hz, 3 H), 0.58 (br s., 3 H), 0.47 (br s., 3 H)	HRMS(B) *m/z* 327.1822 $(M + H)^+$
95: (*S*)-5,5-dimethyl-3-(2-(((*S*)-3-methylbutan-2-yl)amino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	(DMSO-d_6) 8.10 (d, *J* = 5.5 Hz, 1 H), 7.39 – 7.32 (m, 2 H), 7.31 – 7.23 (m, 2 H), 7.18 (br. s, 1 H), 6.93 – 6.79 (m, 1 H), 5.43 (s, 1 H), 1.62 (s, 3 H), 1.30 – 1.14 (m, 1 H), 0.96 (d, *J* = 6.5 Hz, 3 H), 0.90 (s, 3 H), 0.54 (d, *J* = 5.0 Hz, 3 H), 0.43 (d, *J* = 5.0 Hz, 3 H)	HRMS(B) *m/z* 355.2123 $(M + H)^+$
96: 3-(2-(((3r,5r,7r)-adamantan-1-ylmethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	(DMSO-d_6) 8.11 (br s, 1 H), 7.15 (br s, 1 H), 4.52 – 4.36 (m, 2 H), 4.09 (br s, 2 H), 3.03 (br s, 2 H), 1.92 (br s, 3 H), 1.74 – 1.31 (m, 12 H)	HRMS(B) *m/z* 329.1971 $(M + H)^+$
97: (*S*)-4-isopropyl-3-(2-((*S*)-1-(4-(trifluoromethyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.14 (d, J = 5.8 Hz, 1 H), 7.59 (d, J = 8.1 Hz, 2 H), 7.51 (d, J = 8.1 Hz, 2 H), 7.36 (d, J = 5.8 Hz, 1 H), 5.08 (q, J = 6.9 Hz, 1 H), 4.59 (br s, 1 H), 4.33 – 4.25 (m, 2 H), 1.57 (br s, 1 H), 1.54 (d, J = 7.1 Hz, 3 H), 0.60 (br s, 3 H), 0.53 (br s, 3 H)	HRMS(B) *m/z* 395.1686 $(M + H)^+$
98: 3-((*S*)-1-(4-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzonitrile	8.14 (d, J = 5.8 Hz, 1 H), 7.69 – 7.65 (m, 2 H), 7.58 – 7.56 (m, 1 H), 7.48 (t, J = 7.7 Hz, 1 H), 7.37 (d, J = 5.8 Hz, 1 H), 5.09 (q, J = 7.1 Hz, 1 H), 4.64 (br s, 1 H), 4.35 – 4.27 (m, 2 H), 1.74 (br s, 1 H), 1.52 (d, J = 7.1 Hz, 3 H), 0.71 (br s, 3 H), 0.60 (br s, 3 H)	HRMS(B) *m/z* 352.1764 $(M + H)^+$
99: (*S*)-3-(2-((*S*)-1-(3-chlorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.14 (d, J = 5.8 Hz, 1 H), 7.36 (d, J = 5.8 Hz, 1 H), 7.32 (br s, 1 H), 7.29 – 7.23 (m, 2 H), 7.20 – 7.17 (m, 1 H), 5.02 (q, J = 6.9 Hz, 1 H), 4,63 (br s, 1 H), 4.34 – 4.27 (m, 2 H), 1.82 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.70 (br s, 3 H), 0.59 (br s, 3 H)	HRMS(B) *m/z* 361.1424 $(M + H)^+$
100: (4*R*)-5,5-dimethyl-4-phenyl-3-(2-(1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.07 (d, J = 5.8 Hz, 0.5 H), 8.06 (d, J = 5.8 Hz, 0.5 H), 7.41 – 7.37 (m, 2 H), 7.34 – 7.26 (m, 2 H), 7.19 – 7.14 (m, 3 H), 6.95 – 6.89 (m, 2 H), 6.81 – 6.78 (m, 1 H), 5.46 (s, 0.5 H), 5.25 (s, 0.5 H), 4.73 – 4.68 (m, 0.5 H), 4.60 – 4.55 (m, 0.5 H), 3.12 – 3.07 (m, 4 H), 1.73 – 1.68 (m, 4 H), 1.65 (s, 1.5 H), 1.61 – 1.57 (m, 2 H), 1.54 (s, 1.5 H), 1.41 (d, J = 6.9 Hz, 1.5 H), 1.14 (d, J = 6.9 Hz, 1.5 H), 0.99 (d, J = 4.7 Hz, 3 H)	HRMS(B) *m/z* 472.2715 $(M + H)^+$
101: (*S*)-4-isopropyl-3-(2-((*S*)-1-(2-	8.15 (d, J = 5.8 Hz, 1 H), 7.74 (d, J = 8.1 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 1 H), 7.58 (t,	HRMS(B) *m/z*

(trifluoromethyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	J = 7.6 Hz, 1 H), 7.42 – 7.35 (m, 2 H), 5.35 (q, J = 6.6 Hz, 1 H), 4.65 (dt, J = 8.0, 3.8 Hz, 1 H), 4.35 – 4.26 (m, 2 H), 1.76 (br s, 1 H), 1.52 (d, J = 6.6 Hz, 3 H), 0.64 (br d, J = 5.5 Hz, 3 H), 0.58 (br d, J = 6.3 Hz, 3 H)	395.1682 $(M + H)^+$
102: 4,4-dimethyl-3-(2-(1-(1-phenyl-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.22 (d, J = 5.8 Hz, 1 H), 7.87 (s, 1 H), 7.69 – 7.65 (m, 3 H), 7.48 – 7.43 (m, 2 H), 7.35 – 7.28 (m, 2 H), 5.34 (br s, 1 H), 5.24 – 5.17 (m, 1 H), 4.09 – 4.05 (m, 2 H), 1.74 (s, 3 H), 1.64 (d, J = 7.1 Hz, 3 H), 1.58 (s, 3 H)	HRMS(B) *m/z* 379.1890 $(M + H)^+$
103: (*S*)-3-(2-(((3*S*,5*S*,7*S*)-adamantan-1-ylmethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO-d_6) 8.13 (d, *J* = 5.5 Hz, 1 H), 7.20 (br s., 1 H), 7.17 (d, *J* = 5.5 Hz, 1 H), 4.69 – 4.63 (m, 1 H), 4.44 – 4.33 (m, 2 H), 3.11 – 2.85 (m, 2 H), 2.54 (br s, 1 H), 1.92 (br s., 3 H), 1.70 – 1.53 (m, 6 H), 1.47 (br s., 6 H), 0.93 (d, *J* = 7.0 Hz, 3 H), 0.78 (d, *J* = 6.5 Hz, 3 H);	HRMS(B) *m/z* 371.2448 $(M + H)^+$
104: (*S*)-3-(2-(((*S*)-1-cyclohexylethyl)amino)pyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one	(DMSO-d_6) 8.09 (d, *J* = 5.5 Hz, 1 H), 7.40 – 7.32 (m, 2 H), 7.32 – 7.23 (m, 3 H), 6.83 (d, *J* = 9.0 Hz, 1 H), 5.42 (s, 1 H), 3.36 (br s, 1 H), 1.72 – 1.23 (m, 9 H), 1.02 – 0.82 (m, 10 H), 0.62 (s, 1 H), 0.20 – 0.04 (m, 1 H)	HRMS(B) *m/z* 395.2446 $(M + H)^+$
105: (*S*)-3-(2-(((*S*)-1-cyclohexylethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO-d_6) 8.13 (d, *J* = 5.8 Hz, 1 H), 7.19 – 7.09 (m, 2 H), 4.68 (br s, 1 H), 4.41 – 4.33 (m, 2 H), 3.77 (br s, 1 H), 2.47 (br s, 1 H), 1.76 – 1.58 (m, 5 H), 1.43 – 1.35 (m, 1 H), 1.15 – 1.04 (m, 6 H), 0.97 – 0.88 (m, 5 H), 0.77 (d, *J* = 6.8 Hz, 3 H);	HRMS(B) *m/z* 333.2288 $(M + H)^+$
106: (4*S*)-4-isopropyl-3-(2-((1-phenoxypropan-2-yl)amino)pyrimidin-4-yl)oxazolidin-2-one	(DMSO-d_6) 8.19 (d, *J* = 5.6 Hz, 1 H), 7.30 – 7.24 (m, 3 H), 7.18 (br s, 1 H), 6.96 – 6.85 (m, 3 H), 4.70 – 4.52 (m, 1 H), 4.39 – 4.19 (m, 3 H), 4.12 – 4.00 (m, 1 H), 3.92 – 3.78 (m, 1 H), 2.46 (br s, 1 H), 1.29 – 1.21 (m, 3 H), 0.93 – 0.58 (m, 6 H)	HRMS(B) *m/z* 357.1921 $(M + H)^+$
107: (S)-3-(2-(((R)-1-cyclohexylethyl)amino)pyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one	(DMSO-d_6) 8.09 (d, *J* = 5.6 Hz, 1 H), 7.38 – 7.12 (m, 6 H), 6.71 (br s, 1 H), 5.36 (s, 1 H), 1.77 – 1.56 (m, 9 H), 1.31 – 1.05 (m, 4 H), 0.92 (s, 6 H), 0.48 (br s., 2 H)	HRMS(B) *m/z* 395.2440 $(M + H)^+$
108: (*S*)-3-(5-chloro-2-((*S*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) 8.29 (s, 1 H), 7.84 – 7.74 (m, 4 H), 7.49 – 7.43 (m, 3 H), 5.76 (br s, 1 H), 5.17 – 5.10 (m, 1 H), 4.39 – 4.30 (m, 1 H), 4.31 (t, J = 8.1 Hz, 1 H), 4.09 – 4.05 (m, 1 H), 1.66 (d, J = 7.0 Hz, 3 H), 1.40 – 1.30 (m, 1 H), 0.52 (d, J = 6.1 Hz, 3 H), 0.27 (br s, 3 H)	HRMS(B) *m/z* 411.1588 $(M + H)^+$
109: 4-((*S*)-1-(4-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzonitrile	8.14 (d, J = 5.8 Hz, 1 H), 7.68 – 7.66 (m, 2 H), 7.52 (d, J = 8.1 Hz, 3 H), 7.36 (d, J = 5.9 Hz, 1 H), 5.08 (q, J = 7.1 Hz, 1 H), 4.61 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.60 (br s, 1 H), 1.52 (d, J = 7.1 Hz, 3 H), 0.65 (br s, 3 H), 0.58 (br s, 3 H)	HRMS(B) *m/z* 352.1775 $(M + H)^+$
110: (*S*)-4,4-dimethyl-3-(2-(1-(naphthalen-1-	($CDCl_3$) 8.10 (d, J = 5.8 Hz, 1 H), 8.01 (d, J = 8.6 Hz, 1 H), 7.81 – 7.78 (m, 1 H), 7.66	HRMS(B) *m/z*

yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	(d, J = 8.1 Hz, 1 H), 7.52 (d, J = 6.6 Hz, 1 H), 7.48 – 7.39 (m, 2 H), 7.36 – 7.32 (m, 1 H), 7.19 – 7.18 (m, 1 H), 5.66 (br s, 2 H), 3.78 – 3.69 (m, 2 H), 1.65 (s, 3 H), 1.64 (s, 3 H), 1.35 (br s, 3 H)	363.1822 $(M + H)^+$
111: (*R*)-3-(2-((*S*)-1-(4-fluorophenyl)ethylamino)pyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one	8.09 (d, J = 5.7 Hz, 1 H), 7.41 – 7.07 (m, 10 H), 5.21 (s, 3 H), 4.96 (q, J = 7.1 Hz, 1 H), 1.50 (s, 3 H), 1.24 (d, J = 7.1 Hz, 3 H), 0.98 (s, 3 H)	HRMS(B) *m/z* 407.188 $(M + H)^+$
112: 4-(1-(4-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzenesulfonamide	8.13 (d, J = 5.8 Hz, 0.5 H), 8.11 (d, J = 5.8 Hz, 0.5 H), 7.85 – 7.80 (m, 2 H), 7.51 (d, J = 8.6 Hz, 1 H), 7.49 (d, J = 8.6 Hz, 1 H), 7.36 (d, J = 5.7 Hz, 0.5 H), 7.35 (d, J = 5.7 Hz, 0.5 H), 5.09 (q, J = 6.9 Hz, 0.5 H), 5.03 – 4.97 (br m, 0.5 H), 4.61 (br s, 0.5 H), 4.33 – 4.24 (m, 2.5 H), 2.66 – 2.58 (m, 0.5 H), 1.62 (br s, 0.5 H), 1.532 (d, J = 7.1 Hz, 1.5 H), 1.527 (d, J = 7.1 Hz, 1.5 H), 0.98 (d, J = 7.0 Hz, 1.5 H), 0.84 (d, J = 7.0 Hz, 1.5 H), 0.67 (br s, 1.5 H), 0.56 (br s, 1.5 H)	HRMS(B) *m/z* 406.1553 $(M + H)^+$
113: (*S*)-3-(2-((*S*)-1-(4-hydroxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.11 (d, J = 5.8 Hz, 1 H), 7.33 (d, J = 5.8 Hz, 1 H), 7.12 (d, J 8.1 Hz, 2 H), 6.72 – 6.68 (m, 2 H), 4.95 (q, J = 6.9 Hz, 1 H), 4.69 – 4.65 (m, 1 H), 4.35 – 4.28 (m, 2 H), 1.47 (d, J = 7.1 Hz, 3 H), 0.75 (br s, 3 H), 0.62 (br s, 3 H)	HRMS(B) *m/z* 343.1776 $(M + H)^+$
114: (*S*)-3-(2-(1-cyclohexylethylamino)pyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	($CDCl_3$) 8.14 (d, J = 5.8 Hz, 1 H), 7.24 (d, J = 5.8 Hz, 1 H), 5.08 (br s, 1 H), 4.10 (s, 2 H), 3.87 (q, J = 7.0 Hz, 1 H), 1.83 – 1.68 (m, 6 H), 1.75 (s, 3 H), 1.74 (s, 3 H), 1.48 (dddd, J = 12, 8.7, 5.7, 2.8 Hz, 1 H), 1.28 – 1.03 (m, 4 H), 1.17 (d, J = 6.8 Hz, 3 H)	HRMS(B) *m/z* 319.2132 $(M + H)^+$
115: (*S*)-3-(5-fluoro-2-((*S*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) 8.15 (d, J = 3.5 Hz, 1 H), 7.83 – 7.72 (m, 4 H), 7.49 – 7.42 (m, 3 H), 5.06 – 5.03 (m, 1 H), 4.35 – 4.28 (m, 2 H), 4.10 – 4.08 (m, 1 H), 1.65 (d, J = 7.0 Hz, 3 H), 1.33 – 1.26 (m, 1 H), 0.38 (br s, 3 H), 0.14 (br s, 3 H)	HRMS(B) *m/z* 395.1884 $(M + H)^+$
116: (*S*)-3-(5-chloro-2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO-d_6) 8.39 – 8.31 (m, 2 H), 7.35 – 7.32 (m, 2 H), 7.28 (t, J = 7.8 Hz, 2 H), 7.17 (t, J = 7.8 Hz, 1 H), 4.89 -4.82 (m, 1 H), 4.49 – 4.45 (m, 2 H), 4.16 (br s, 1 H), 1.42 (d, J = 7.0 Hz, 3 H), 1.24 (br s, 1 H), 0.86 – 0.78 (m, 3 H), 0.48 (br s, 3 H)	HRMS(B) *m/z* 361.1431 $(M + H)^+$
117: (*S*)-3-(2-((*S*)-1-(4-bromo-3,5-dimethoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.16 (d, J = 5.8 Hz, 1 H), 7.36 (d, J = 5.8 Hz, 1 H), 6.64 (s, 2 H), 5.00 – 4.95 (m, 1 H), 4.58 (br s, 1 H), 4.33 – 4.23 (m, 2 H), 3.79 (s, 6 H), 1.54 (d, J = 7.0 Hz, 3 H), 0.55 (br s, 6 H)	HRMS(B) *m/z* 465.1134 $(M + H)^+$
118: (4*S*)-3-(2-(1-(3,4-dimethoxyphenyl)ethylami	8.12 (d, J = 5.8 Hz, 0.5 H), 8.10 (d, J = 5.8 Hz, 0.5 H), 7.35 – 7.32 (m, 1 H), 6.97 –	HRMS(B) *m/z*

no)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	6.85 (m, 3 H), 5.00 – 4.91 (m, 1 H), 4.65 (br s, 0.5 H), 4.55 (br s, 0.5 H), 4.36 – 4.27 (m, 2 H), 3.80 – 3.79 (m, 6 H), 2.69 – 2.61 (m, 0.5 H), 1.87 (br s, 0.5 H), 1.50 (d, J = 7.1 Hz, 3 H), 1.00 (d, J = 7.1 Hz, 1.5 H), 0.86 (d, J = 7.0 Hz, 1.5 H), 0.69 (br s, 1.5 H), 0.60 (br s, 1.5 H)	387.2035 $(M + H)^+$
119: (*S*)-3-(2-(1-(6-methoxynaphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	($CDCl_3$) 8.09 (d, J = 5.8 Hz, 1 H), 7.64 – 7.59 (m, 3 H), 7.36 (dd, J = 8.3, 1.8 Hz, 1 H), 7.20 – 7.18 (m, 1 H), 7.07 – 7.03 (m, 2 H), 5.56 (br s, 1 H), 5.07 – 5.03 (br m, 1 H), 3.91 – 3.82 (m, 5 H), 1.61 (s, 3 H), 1.56 (d, J = 6.8 Hz, 3 H), 0.97 (br s, 3 H)	HRMS(B) *m/z* 393.1925 $(M + H)^+$
120: (*S*)-5,5-dimethyl-3-(2-((*S*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.09 (d, J = 5.8 Hz, 1 H), 7.81 – 7.79 (m, 1 H), 7.74 – 7.68 (m, 2 H), 7.52 (br s, 1 H), 7.46 – 7.41 (m, 3 H), 7.18 (br s, 1 H), 7.02 (br s, 2 H), 6.99 (s, 3 H), 5.43 (s, 1 H), 5.02 (q, 6.6 Hz, 1 H), 1.62 (s, 3 H), 1.53 (d, J = 6.6 Hz, 3 H), 0.93 (s, 3 H)	HRMS(B) *m/z* 439.2131 $(M + H)^+$
121: (*S*)-3-(2-((*S*)-1-(4-bromophenyl)ethylamino)pyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one	8.08 (d, J = 5.8 Hz, 1 H), 7.44 (d, J = 5.8 Hz, 1 H), 7.29 – 7.24 (m, 5 H), 7.06 (br s, 2 H), 6.92 (br s, 2 H), 5.44 (s, 1 H), 4.88 – 4.84 (m, 1 H), 1.63 (s, 3 H), 1.42 (d, J = 7.1 Hz, 3 H), 0.95 (s, 3 H)	HRMS(B) *m/z* 467.1088 $(M + H)^+$
122: (*S*)-3-(2-((*S*)-1-(3-methoxyphenyl)ethylamino)pyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one	8.07 (d, J = 5.8 Hz, 1 H), 7.42 (d, J = 5.8 Hz, 1 H), 7.28 – 7.21 (m, 3 H), 7.11 – 7.08 (m, 3 H), 6.72 (dd, J = 8.3, 1.8 Hz, 1 H), 6.66 (br s, 1 H), 6.62 (br s, 1 H), 5.46 (s, 1 H), 4.80 – 4.74 (m, 1 H), 3.73 (s, 3 H), 1.64 (s, 3 H), 1.42 (d, J = 7.1 Hz, 3 H), 0.98 (s, 3 H)	HRMS(B) *m/z* 419.2067 $(M + H)^+$
123: (*S*)-3-(2-((*S*)-1-(4-fluoro-3-methoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.14 (d, J = 6.6 Hz, 1 H), 7.57 (d, J = 6.6 Hz, 1 H), 7.08 – 6.99 (m, 2 H), 6.88 (ddd, J = 8.5, 4.2, 2.0 Hz, 1 H), 5.07 (q, J = 7.1 Hz, 1 H), 4.68 (dt, J = 7.8, 3.7 Hz, 1 H), 4.40 – 4.32 (m, 2 H), 3.86 (s, 3 H), 1.99 (br s, 1 H), 1.57 (d, J = 7.1 Hz, 3 H), 0.75 (d, J = 7.1 Hz, 3 H), 0.66 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 375.1824 $(M + H)^+$
124: (*S*)-3-(2-((*S*)-1-(4-bromophenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.10 (d, J = 5.8 Hz, 1 H), 7.39 (d, J = 5.8 Hz, 1 H), 7.29 – 7.26 (m, 2 H), 7.25 – 7.21 (m, 3 H), 7.12 (dd, J = 6.3, 2.8 Hz, 2 H), 6.96 (d, J = 8.6 Hz, 2 H), 5.80 (dd, J = 8.6, 3.5 Hz, 1 H), 4.87 (q, J = 7.1 Hz, 1 H), 4.79 (t, J = 8.6 Hz, 1 H), 4.20 (dd, J = 8.6, 3.5 Hz, 1 H), 1.43 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 439.0763 $(M + H)^+$
125: (4*S*)-4-isopropyl-3-(2-((1-(3-morpholinophenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	8.215 (d, J = 6.1 Hz, 0.5 H), 8.212 (d, J = 6.1 Hz, 0.5 H), 7.52 (t, J = 7.1 Hz, 2 H), 7.46 (dd, J = 5.8, 3.8 Hz, 1 H), 7.43 – 7.34 (m, 3 H), 5.86 (qd, J = 8.2, 4.0 Hz, 1 H), 4.83 – 4.75 (m, 1 H), 4.42 – 4.33 (m, 2 H), 2.62 (dtd, J = 14, 7.0, 3.8 Hz, 0.5 H), 2.28 (br s, 0.5 H), 1.02 (d, J = 7.1 Hz, 1.5 H), 0.91 (d, J = 7.1 Hz, 1.5 H), 0.88 (d, J = 7.11 Hz, 1.5 H), 0.73 (d, J = 7.1 Hz, 1.5 H)	HRMS(B) *m/z* 412.2342 $(M + H)^+$
126: (*R*)-3-(2-((*S*)-1-(6-	8.10 (d, J = 5.6 Hz, 1 H), 7.69 (d, J = 9.1	HRMS(B)

methoxynaphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	Hz, 1 H), 7.72 (d, J = 8.6 Hz, 1 H), 7.62 (s, 1 H), 7.44 – 7.29 (m, 7 H), 7.20 (d, J = 2.5 Hz, 1 H), 7.11 (dd, J = 9.1, 2.5 Hz, 1 H), 5.55 (dd, J = 8.8, 3.8 Hz, 1 H), 4.80 (q, J = 7.1 Hz, 1 H), 4.69 (t, J = 8.6 Hz, 1 H), 4.16 (dd, J = 8.6, 4.0 Hz, 1 H), 3.90 (s, 3 H), 1.28 (d, J = 7.1 Hz, 3 H)	*m/z* 441.1929 $(M + H)^+$
127: (*S*)-4,4-dimethyl-3-(2-(1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.20 (d, J = 5.8 Hz, 1 H), 7.84 – 7.79 (m, 4 H), 7.51 – 7.43 (m, 3 H), 7.29 (d, J = 5.8 Hz, 1 H), 5.65 (br s, 1 H), 5.19 – 5.16 (br m, 1 H), 3.98 (d, J = 8.1 Hz, 1 H), 3.91 (d, J = 8.1 Hz, 1 H), 1.70 (s, 3 H), 1.66 (d, J = 6.9 Hz, 3 H), 1.02 (br s, 3 H)	HRMS(B) *m/z* 363.1819 $(M + H)^+$
128: 4,4-dimethyl-3-(2-(1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.17 (d, J = 5.8 Hz, 1 H), 7.26 – 7.22 (m, 3 H), 6.91 (d, J = 8.6 Hz, 2 H), 5.39 (br s, 1 H), 5.01 – 4.94 (m, 1 H), 4.04 – 3.99 (m, 2 H), 3.14 – 3.12 (m, 4 H), 1.75 – 1.69 (m, 8 H), 1.61 – 1.57 (m, 2 H), 1.55 (d, J = 7.1 Hz, 3 H), 1.34 – 1.29 (br m, 2 H)	HRMS(B) *m/z* 396.2396 $(M + H)^+$
129: (*S*)-3-(2-((*S*)-1-(3-methoxyphenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.09 (d, J = 5.8 Hz, 1 H), 7.36 (d, J = 5.8 Hz, 1 H), 7.26 – 7.16 (m, 5 H), 7.11 (t, J = 7.8 Hz, 3 H), 6.74 – 6.66 (m, 3 H), 5.81 (dd, J = 8.6, 3.5 Hz, 1 H), 4.86 – 4.79 (m, 2 H), 4.23 (dd, J = 8.8, 3.8 Hz, 1 H), 3.73 (s, 3 H), 1.44 (d, J 7.1 Hz, 3 H)	HRMS(B) *m/z* 391.1771 $(M + H)^+$
130: (4*S*)-3-(2-(1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.11 (d, J = 5.8 Hz, 0.5 H), 8.09 (d, J = 5.8 Hz, 0.5 H), 7.34 – 7.33 (m, 1 H), 6.81 – 6.71 (m, 3 H), 4.93 – 4.88 (m, 1 H), 4.65 (br s, 0.5 H), 4.52 (br s, 0.5 H), 4.36 – 4.27 (m, 2 H), 4.20 – 4.17 (m, 4 H), 2.66 (dtd, J = 14, 6.9, 3.5 Hz, 0.5 H), 1.99 (br s, 0.5 H), 1.456 (d, J = 7.1 Hz, 1.5 H), 1.454 (d, J = 7.1 Hz, 1.5 H), 1.00 (d, J = 7.1 Hz, 1.5 H), 0.85 (d, J = 7.1 Hz, 1.5 H), 0.75 (br s, 1.5 H), 0.63 (br s, 1.5 H)	HRMS(B) *m/z* 385.1854 $(M + H)^+$
131: (4*S*)-4-isopropyl-3-(2-(1-(pyridin-3-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.545 (d, J = 6.1 Hz, 0.5 H), 8.540 (d, J = 6.1 Hz, 0.5 H), 8.39 (dt, J = 4.9, 1.6 Hz, 1 H), 8.13 (dd, J = 11, 5.7 Hz, 1 H), 7.86 – 7.80 (m, 1 H), 7.40 – 7.36 (m, 2 H), 5.12 (q, J = 7.1 Hz, 0.5 H), 5.02 (m, 0.5 H), 4.65 (br s, 0.5 H), 4.42 (br s, 0.5 H), 4.35 – 4.25 (m, 2 H), 2.67 – 2.62 (m, 0.5 H), 1.76 (br s, 0.5 H), 1.56 (d, J = 7.1 Hz, 1.5 H), 1.55 (d, J = 7.1 Hz, 1.5 H), 0.99 (d, J = 7.1 Hz, 1.5 H), 0.85 (d, J = 7.1 Hz, 1.5 H), 0.70 (br s, 1.5 H), 0.60 (br s, 1.5 H)	HRMS(B) *m/z* 328.1771 $(M + H)^+$
132: (*S*)-4-benzyl-3-(2-(cyclopropylamino)pyrimidin-4-yl)oxazolidin-2-one	8.17 (d, *J* = 5.5 Hz, 1 H), 7.46 (d, *J* = 6.0 Hz, 1 H), 7.32 – 7.18 (m, 4 H), 7.15 (d, *J* = 7.0 Hz, 2 H), 5.04 – 4.91 (m, 1 H) 5.39 (br s, 1 H), 4.25 – 4.11 (m, 2 H), 3.51 (d, *J* = 13.0 Hz, 1 H), 2.80 (dd, *J* = 13.3, 9.79 Hz, 1 H), 2.76 – 2.69 (m, 1 H), 0.84 – 0.71 (m, 2 H), 0.60 – 0.47 (m, 2 H)	HRMS(B) *m/z* 311.1515 $(M + H)^+$
133: (*S*)-4-benzyl-3-(2-(cyclohexylamino)pyrimidi	($CDCl_3$) 8.18 (d, *J* = 5.5 Hz, 1 H), 7.48 (d, *J* = 6.0 Hz, 1 H), 7.42 – 7.31 (m, 3 H), 7.26	HRMS(B)

n-4-yl)oxazolidin-2-one	(d, *J* = 7.0 Hz, 2 H), 5.56 (br s, 1 H), 5.02 (ddd, *J* = 9.9, 3.6, 3.5 Hz, 1 H), 4.33 – 4.22 (m, 2 H), 3.96 – 3.83 (m, 1 H), 3.53 (d, *J* = 12.6 Hz, 1 H), 2.85 (dd, *J* = 13.3, 9.8 Hz, 1 H), 1.89 – 1.75 (m, 2 H), 2.16 – 2.05 (m, 2 H), 1.73 – 1.63 (m, 1 H), 1.52 – 1.26 (m, 7 H)	*m/z* 353.1979 $(M + H)^+$
134: (*S*)-4-benzyl-3-(2-(benzylamino)pyrimidin-4-yl)oxazolidin-2-one	8.17 (d, *J* = 5.8 Hz, 1 H), 7.38 (d, *J* = 5.8 Hz, 1 H), 7.36 – 7.30 (m, 2 H), 7.30 – 7.11 (m, 6 H), 7.02 (br s, 2 H), 4.95 (br s, 1 H), 4.76 – 4.65 (m, 1 H), 4.65 – 4.55 (m, 1 H), 4.30 (t, *J* = 8.4 Hz, 1 H), 4.26 – 4.18 (m, 1 H), 3.05 (br s, 1 H), 2.84 (br s, 1 H)	HRMS(B) *m/z* 361.1669 $(M + H)^+$
135: (*S*)-4-benzyl-3-(2-(((*R*)-1-phenylethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.22 (d, *J* = 5.5 Hz, 1 H), 7.48 (d, *J* = 5.5 Hz, 1 H), 7.42 – 7.29 (m, 8 H), 7.19 (d, *J* = 7.0 Hz, 2 H), 5.62 (br s, 1 H), 5.15 (t, *J* = 6.8 Hz, 1 H), 4.77 (br s, 1 H), 4.25 – 4.16 (m, 2 H), 3.45 (dd, *J* = 13.8, 3.3 Hz, 1 H), 2.94 (dd, *J* = 13.6, 9.0 Hz, 1 H), 1.61 (d, *J* = 7.0 Hz, 3 H)	HRMS(B) *m/z* 375.1817 $(M + H)^+$
136: (4*S*)-3-(2-(1-(1,3-dimethyl-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.14 (d, J = 5.8 Hz, 0.5 H), 8.13 (d, J = 5.8 Hz, 0.5 H), 7.42 (s, 0.5 H), 7.35 (s, 0.5 H), 7.35 (d, J = 5.7 Hz, 0.5 H), 7.34 (d, J = 5.8 Hz, 0.5 H), 5.10 – 5.00 (m, 1 H), 4.75 (dq, J = 7.8, 4.0 Hz, 1 H), 4.41 – 4.32 (m, 2 H), 3.76 (s, 1.5 H), 3.74 (s, 1.5 H), 2.64 – 2.57 (m, 0.5 H), 2.41 – 2.32 (m, 0.5 H), 2.18 (s, 3 H), 1.493 (d, J = 7.1 Hz, 1.5 H), 1.488 (d, J = 7.1 Hz, 1.5 H), 0.97 (d, J = 7.1 Hz, 1.5 H), 0.88 (d, J = 7.1 Hz, 3 H), 0.78 (d, J = 7.1 Hz, 1.5 H)	HRMS(B) *m/z* 345.2038 $(M + H)^+$
137: (*S*)-3-[2-((*S*)-1,3-dimethyl-butylamino)-pyrimidin-4-yl]-5,5-dimethyl-4-phenyl-oxazolidin-2-one	(DMSO-d_6) 8.10 (m, 1 H), 7.34 (m, 2 H), 7.26 (m, 3 H), 7.17 (br s, 1 H), 6.83 (s, 1 H), 5.39 (s, 1 H), 1.61 (s, 3 H), 1.39 (s, 1 H), 1.26 (s, 1 H), 1.02 (m, 4 H), 0.90 (s, 3 H), 0.81 (s, 1 H), 0.71 (s, 3 H), 0.41 (s, 3 H)	HRMS(B) *m/z* 369.2297 $(M + H)^+$
138: (*S*)-3-[2-((*S*)-2-hydroxy-1-methyl-ethylamino)-pyrimidin-4-yl]-5,5-dimethyl-4-phenyl-oxazolidin-2-one	(DMSO-d_6) 8.14 (d, *J* = 5.8 Hz, 1 H), 7.17 (d, *J* = 5.8 Hz, 1 H), 7.03 (br s, 1 H), 4.67 (br s, 1 H), 4.42 – 4.34 (m, 2 H), 3.96 (br s, 1 H), 2.46 (m, 1 H), 1.63 (m, 1 H), 1.47 (m, 1 H), 1.21 (m, 1 H), 1.09 (d, *J* = 6.3 Hz, 3 H), 0.89 (d, *J* = 7.3 Hz, 3 H), 0.87 (d, *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 6.5 Hz, 3 H), 0.77 (d, *J* = 6.8 Hz, 3 H)	HRMS(B) *m/z* 307.2141 $(M + H)^+$
139: (*S*)-4,4-dimethyl-3-(2-(1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.08 (d, J = 5.8 Hz, 1 H), 7.27 – 7.20 (m, 4 H), 7.17 (d, J = 5.6 Hz, 1 H), 7.15 – 7.11 (m, 1 H), 5.42 (br s, 1 H), 4.94 – 4.87 (m, 1 H), 3.92 – 3.86 (m, 2 H), 1.58 (s, 3 H), 1.47 (d, J = 6.9 Hz, 3 H), 1.06 (br s, 3 H)	HRMS(B) *m/z* 313.1668 $(M + H)^+$
140: (*S*)-3-(2-((*S*)-1-(4-fluorophenyl)ethylamino)p	($CDCl_3$) 8.17 (d, J = 5.8 Hz, 1 H), 7.45 – 7.31 (m, 4 H), 7.28 – 7.24 (m, 2 H), 7.09 –	HRMS(B) *m/z*

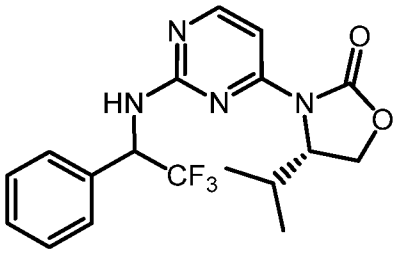
yrimidin-4-yl)-4-methyl-4-phenyloxazolidin-2-one	7.06 (m, 2 H), 7.01 – 6.95 (m, 2 H), 5.21 (br s, 1 H), 4.20 (s, 2 H), 4.13 (br s, 1 H), 1.65 (br s, 3 H), 1.13 (d, J = 6.8 Hz, 3 H)	393.1729 $(M + H)^+$
141: (4*S*)-4-methyl-4-phenyl-3-(2-(1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.14 (d, J = 5.8 Hz, 0.35 H), 8.12 (d, J = 5.8 Hz, 0.65 H), 7.42 – 7.27 (m, 6 H), 7.04 (d, J = 8.6 Hz, 0.65 H), 6.91 – 6.82 (m, 3.35 H), 5.16 (br s, 0.35 H), 5.02 (br s, 0.65 H), 4.30 (s, 1.3 H), 4.22 (s, 0.7 H), 4.19 (br s, 1 H), 3.16 – 3.13 (m, 4 H), 2.20 (s, 1.95 H), 1.79 – 1.70 (br m, 5.05 H), 1.62 – 1.56 (m, 2 H), 1.37 (d, J = 6.8 Hz, 1.95 H), 1.06 (d, J = 6.3 Hz, 1.05 H)	HRMS(B) *m/z* 458.2551 $(M + H)^+$
142: (*S*)-4-benzyl-3-(2-(((*S*)-1-phenylethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	8.15 (d, *J* = 5.77 Hz, 1 H), 7.40 – 7.30 (m, 3 H), 7.25 – 7.13 (m, 5 H), 7.07 (t, *J* = 7.0 Hz, 1 H), 6.91 (br s, 2 H), 5.13 (q, *J* = 7.0 Hz, 1 H), 5.01 (t, *J* = 7.4 Hz, 1 H), 4.34 (t, *J* = 8.5 Hz, 1 H), 4.20 (dd, *J* = 8.9, 2.4 Hz, 1 H), 2.64 (br s, 1 H), 2.47 (br s, 1 H), 1.54 (d, *J* = 7.3 Hz, 3 H)	HRMS(B) *m/z* 375.1817 $(M + H)^+$
143: (*R*)-4-benzyl-3-(2-(cyclopropylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.19 (d, *J* = 5.0 Hz, 1 H), 7.62 (d, *J* = 6.0 Hz, 1 H), 7.41 – 7.29 (m, 4 H), 7.26 – 7.19 (m, 2 H), 6.42 (br s, 1 H), 5.07 (t, *J* = 8.3 Hz, 1 H), 4.30 – 4.24 (m, 2 H), 3.60 (d, *J* = 12.6 Hz, 1 H), 2.97 – 2.79 (m, 2 H), 0.95 – 0.81 (m, 2 H), 0.75 – 0.62 (m, 2 H)	HRMS(B) *m/z* 311.1516 $(M + H)^+$
144: (*R*)-4-benzyl-3-(2-(cycloheptylamino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, *J* = 6.0 Hz, 1 H), 7.36 – 7.28 (m, 3 H), 7.28 – 7.19 (m, 3 H), 5.15 – 5.05 (m, 1 H), 4.37 (t, *J* = 8.5 Hz, 1 H), 4.30 – 4.24 (m, 1 H), 4.04 (br s., 1 H), 3.09 (dd, *J* = 13.6, 8.0 Hz, 1 H), 2.11 – 1.94 (m, 2 H), 1.78 – 1.48 (m, 11 H)	HRMS(B) *m/z* 367.2134 $(M + H)^+$
145: (*R*)-4-benzyl-3-(2-(cyclohexylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.18 (d, *J* = 5.0 Hz, 1 H), 7.48 (d, *J* = 6.0 Hz, 1 H), 7.42 – 7.29 (m, 3 H), 7.26 (d, *J* = 7.0 Hz, 2 H), 5.55 (br s, 1 H), 5.10 – 4.94 (m, 1 H), 4.33 – 4.22 (m, 2 H), 3.96 – 3.82 (m, 1 H), 3.53 (d, *J* = 12.1 Hz, 1 H), 2.85 (dd, *J* = 13.3, 9.8 Hz, 1 H), 2.22 – 2.01 (m, 2 H), 1.81 (td, *J* = 13.6, 4.0 Hz, 2 H), 1.68 (dd, *J* = 9.0, 3.5 Hz, 1 H), 1.51 – 1.22 (m, 6 H)	HRMS(B) *m/z* 353.1981 $(M + H)^+$
146: (*R*)-4-benzyl-3-(2-(benzylamino)pyrimidin-4-yl)oxazolidin-2-one	8.17 (d, *J* = 5.8 Hz, 1 H), 7.38 (d, *J* = 6.0 Hz, 1 H), 7.35 – 7.30 (m, 2 H), 7.29 – 7.18 (m, 5 H), 7.15 (t, *J* = 7.3 Hz, 1 H), 7.02 (br s, 2 H), 4.95 (br s, 1 H), 4.75 – 4.65 (m, 1 H), 4.65 – 4.56 (m, 1 H), 4.30 (t, *J* = 8.5 Hz, 1 H), 4.27 – 4.20 (m, 1 H), 3.05 (br s, 1 H), 2.82 (br s, 1 H)	HRMS(B) *m/z* 361.1659 $(M + H)^+$
147: (*R*)-4-benzyl-3-(2-(((*R*)-1-phenylethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.21 (d, *J* = 5.5 Hz, 1 H), 7.50 (d, *J* = 6.0 Hz, 1 H), 7.43 – 7.29 (m, 5 H), 7.28 – 7.12 (m, 4 H), 7.00 (br s., 2 H), 5.97 (br s, 1 H), 5.17 (t, *J* = 6.8 Hz, 1 H), 5.03 – 4.89 (m, 1 H), 4.28 (t, *J* = 8.5 Hz, 1 H), 4.19 (dd, *J* = 9.0, 3.0 Hz, 1 H), 2.97 (br s, 1 H), 2.53 (br s, 1 H), 1.63 (d, *J* = 7.0 Hz, 3 H)	HRMS(B) *m/z* 375.1822 $(M + H)^+$
148: (*R*)-4-benzyl-3-(2-	($CDCl_3$) 8.21 (d, *J* = 6.0 Hz, 1 H), 7.49 (d, *J*	HRMS(B)

(((*S*)-1-phenylethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	= 5.5 Hz, 1 H), 7.44 – 7.29 (m, 8 H), 7.19 (d, *J* = 6.5 Hz, 2 H), 5.69 (br s, 1 H),, 5.15 (t, *J* = 7.0 Hz, 1 H), 4.76 (br s, 1 H), 4.24 – 4.16 (m, 2 H), 3.45 (dd, *J* = 13.8, 3.3 Hz, 1 H), 2.94 (dd, *J* = 13.6, 9.5 Hz, 1 H), 1.61 (d, *J* = 7.0 Hz, 3 H)	*m/z* 375.1816 $(M + H)^+$
149: (*S*)-4-isopropyl-3-(5-methyl-2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.13 (s, 1 H), 7.35 – 7.28 (m, 4 H), 7.24 – 7.20 (m, 1 H), 5.73 (br s, 1 H), 5.00 – 4.92 (m, 1 H), 4.59 – 4.51 (m, 1 H), 4.38 (t, J = 8.8 Hz, 1 H), 4.12 (t, J = 8.8 Hz, 1 H), 2.14 (s, 3 H), 1.55 (d, J = 6.5 Hz, 3 H), 1.44 (br s, 1 H), 0.59 (d, J = 6.5 Hz, 3 H), 0.53 (d, J = 5.0 Hz, 3 H)	HRMS(B) *m/z* 341.1974 $(M + H)^+$
150: (*S*)-3-(5-fluoro-2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) 8.18 (d, J = 3.0 Hz, 1 H), 7.32 – 7.28 (m, 4 H), 7.25 – 7.20 (m, 1 H), 5.64 (br s, 1 H), 4.92 – 4.87 (m, 1 H), 4.47 – 4.40 (m, 1 H), 4.39 (t, J = 8.5 Hz, 1 H), 4.17 (t, J = 8.6 Hz, 1 H), 1.86 (br s, 1 H), 1.54 (d, J = 7.0 Hz, 3 H), 0.68 – 0.56 (m, 6 H)	HRMS(B) *m/z* 345.1724 $(M + H)^+$
151: (*S*)-4-isopropyl-3-(2-((*S*)-1-(3-methoxyphenyl)ethylamino)-5-methylpyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.11 (s, 1 H), 7.24 – 7.20 (m, 1 H), 6.94 – 6.89 (m, 2H), 6.76 (dd, J = 7.6 Hz, J = 2.5 Hz, 1 H), 5.99 (br s, 1 H), 4.97 (quin, J = 6.8 Hz, 1 H), 4.58 (td, J = 8.8 Hz, J = 5.1 Hz, 1 H), 4.39 (t, J = 8.8 Hz, 1 H), 4.13 (t, J = 8.6 Hz, 1 H), 3.80 (s, 3 H), 2.16 (s, 3 H), 1.62 – 1.56 (m, 1 H), 1.57 (d, J = 6.5 Hz, 3 H), 0.64 (d, J = 7.1 Hz, 3 H), 0.59 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 371.2083 $(M + H)^+$
152: (*S*)-4-isopropyl-3-(5-methyl-2-((*S*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.13 (s, 1 H), 7.81 – 7.74 (m, 4 H), 7.48 – 7.40 (m, 3 H), 5.87 (br s, 1 H), 5.17 – 5.10 (m, 1 H), 4.42 (td, J = 8.7 Hz, J = 4.8 Hz, 1 H), 4.29 (t, J = 8.8 Hz, 1 H), 4.02 (t, J = 8.6 Hz, 1 H), 2.13 (s, 3 H), 1.64 (d, J = 7.0 Hz, 3 H), 1.35 – 1.28 (m, 1 H), 0.42 (d, J = 7.1 Hz, 3 H), 0.17 (d, J = 7.0 Hz, 3 H)	HRMS(B) *m/z* 391.2135 $(M + H)^+$
153: (*S*)-3-(5-fluoro-2-((*S*)-1-(3-methoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) 8.16 (d, J = 2.5 Hz, 1 H), 7.23 (t, J = 7.8 Hz, 1 H), 6.91 – 6.83 (m, 2 H), 6.78 – 6.74 (m, 1 H), 6.05 (br s, 1 H), 4.86 (br s, 1 H), 4.49 – 4.38 (m, 2 H), 4.19 (t, J = 7.8 Hz, 1 H), 3.79 (s, 3 H), 1.54 (d, J = 8.0 Hz, 3 H), 1.32 – 1.25 (m, 1 H), 0.66 – 0.58 (m, 6 H)	HR-MS *m/z* (M + H)$^+$
154: (*S*)-4-methyl-3-(2-((*S*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	($CDCl_3$) 8.17 (d, J = 5.8 Hz, 1 H), 7.84 – 7.78 (m, 3 H), 7.55 (s, 1 H), 7.51 – 7.43 (m, 5 H), 7.39 – 7.36 (m, 1 H), 7.29 – 7.25 (m, 3 H), 5.54 (br s, 1 H), 4.31 (br s, 1 H), 4.19 – 4.12 (m, 2 H), 1.84 (br s, 3 H), 1.24 (d, J = 6.8 Hz, 3 H)	HRMS(B) *m/z* 425.1972 $(M + H)^+$
155: (*S*)-3-(2-((*S*)-1-(6-methoxynaphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4-methyl-4-phenyloxazolidin-2-one	($CDCl_3$) 8.18 (d, J = 5.8 Hz, 1 H), 7.69 (t, J = 7.8 Hz, 2 H), 7.47 – 7.41 (m, 4 H), 7.38 – 7.34 (m, 1 H), 7.28 – 7.23 (m, 3 H), 7.17 – 7.13 (m, 2 H), 5.31 (br s, 1 H), 4.31 (br s, 1 H), 4.19 – 4.13 (m, 2 H), 3.94 (s, 3 H), 1.56	HRMS(B) *m/z* 455.2081

	(br s, 3 H), 1.20 (d, J = 6.6 Hz, 3 H)	$(M + H)^+$
156: (*S*)-3-(2-((*S*)-1-cyclohexylethylamino)pyrimidin-4-yl)-4-methyl-4-phenyloxazolidin-2-one	($CDCl_3$) 8.11 (d, J = 5.8 Hz, 1 H), 7.38 – 7.32 (m, 5 H), 7.29 – 7.25 (m, 1 H), 4.81 (br s, 1 H), 4.31 – 4.26 (m, 2 H), 3.16 (br s, 1 H), 2.17 (s, 3 H), 1.77 – 1.57 (m, 6 H), 1.28 – 1.09 (m, 4 H), 0.99 – 0.85 (m, 2 H), 0.55 (br s, 2 H)	HRMS(B) *m/z* 381.2280 $(M + H)^+$
157: (*S*)-3-[2-((*S*)-2-hydroxy-1-methyl-ethylamino)-pyrimidin-4-yl]-5,5-dimethyl-4-phenyl-oxazolidin-2-one	(DMSO-d_6) 8.13 (m, 1 H), 7.36 (m, 2 H), 7.29 (m, 3 H), 7.19 (br s, 1 H), 6.65 (s, 1 H), 5.44 (s, 1 H), 4.30 (br s, 1 H), 2.95 (br s, 1 H), 2.77 (br s, 3 H), 1.61 (s, 3 H), 1.25 (s, 1 H), 1.04 (m, 3 H), 0.92 (s, 3 H)	HRMS(B) *m/z* 343.1778 $(M + H)^+$
158: (*S*)-5,5-dimethyl-4-phenyl-3-[2-((*S*)-1,2,2-trimethyl-propylamino)-pyrimidin-4-yl]-oxazolidin-2-one	(DMSO-d_6) 8.10 (d, *J* = 5.5 Hz, 1 H), 7.37 – 7.33 (m, 2 H), 7.29 – 7.25 (m, 3 H), 7.20 (br s, 1 H), 6.75 (d, *J* = 10 Hz, 1 H), 5.42 (s, 1 H), 3.47 (m, 1 H), 1.62 (s, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.88 (s, 3 H), 0.46 (s, 9 H)	HRMS(B) *m/z* 369.2277 $(M + H)^+$
159: (*R*)-3-(2-((*S*)-1-(naphthalen-1-yl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.11 (d, J = 6.1 Hz, 1 H), 8.04 (d, J = 8.6 Hz, 1 H), 7.89 (d, J = 8.1 Hz, 1 H), 7.74 (d, J = 8.1 Hz, 1 H), 7.60 – 7.56 (m, 1 H), 7.53 – 7.49 (m, 1 H), 7.46 – 7.44 (m, 1 H), 7.42 – 7.31 (m, 5 H), 7.21 – 7.18 (m, 2 H), 5.52 (q, J = 6.9 Hz, 1 H), 5.44 (dd, J = 8.8, 3.8 Hz, 1 H), 4.63 (t, J = 8.7 Hz, 1 H), 4.10 (dd, J = 8.6, 4.0 Hz, 1 H), 1.33 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 411.1823 $(M + H)^+$
160: (*S*)-4-isopropyl-3-[2-((*S*)-1,2,2-trimethyl-propylamino)-pyrimidin-4-yl]-oxazolidin-2-one	(DMSO-d_6) 8.14 (d, *J* = 5.5 Hz, 1 H), 7.16 (d, *J* = 5.5 Hz, 1 H), 7.00 (br. s, 1 H), 4.73 – 4.66 (m, 1 H), 4.41 – 4.34 (m, 2 H), 3.92 (br s, 1 H), 2.46 (br s, 1 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 0.91 (d, *J* = 7.3 Hz, 3 H), 0.87 (s, 9 H), 0.77 (d, *J* = 6.8 Hz, 3 H)	HRMS(B) *m/z* 307.2130 $(M + H)^+$
161: (*S*)-3-[2-((*S*)-1-cyclopropyl-ethylamino)-pyrimidin-4-yl]-4-isopropyl-oxazolidin-2-one	(DMSO-d_6) 8.13 (d, *J* = 5.5 Hz, 1 H), 7.17 (d, *J* = 5.5 Hz, 1 H), 7.09 (br s, 1 H), 4.67 – 4.63 (m, 1 H), 4.37 (m, 2 H), 3.52 – 3.43 (m, 1 H), 2.46 (br s, 1 H), 1.19 (d, *J* = 6.8 Hz, 3 H), 1.01 – 0.93 (m, 1 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 0.77 (d, *J* = 6.8 Hz, 3 H), 0.41 (m, 1 H), 0.33 (m, 1 H), 0.22 (br s, 1 H), 0.10 (br s, 1 H)	HRMS(B) *m/z* 291.1812 $(M + H)^+$
162: (*S*)-4-isopropyl-3-(2-((*S*)-1-(4-phenoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.13 (d, J = 5.8 Hz, 1 H), 7.34 – 7.28 (m, 5 H), 7.09 – 7.05 (m, 1 H), 6.96 – 6.90 (m, 4 H), 5.06 (q, J = 7.1 Hz, 1 H), 4.71 – 4.67 (m, 1 H), 4.37 – 4.28 (m, 2 H), 2.08 (br s, 1 H), 1.52 (d, J = 7.1 Hz, 3 H), 0.76 (d, J = 7.1 Hz, 3 H), 0.67 (d, J = 7.1 Hz, 3 H)	HRMS(B) *m/z* 419.2081 $(M + H)^+$
163: (*S*)-3-(2-((*S*)-1-(2,3-dihydrobenzofuran-5-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.12 (d, J = 5.6 Hz, 1 H), 7.32 (d, J = 5.6 Hz, 1 H), 7.17 (s, 1 H), 7.04 – 7.02 (m, 1 H), 6.63 (d, J = 8.1 Hz, 1 H), 4.98 (q, J = 7.1 Hz, 1 H), 4.69 – 4.65 (m, 1 H), 4.51 – 4.47 (m, 2 H), 4.36 – 4.27 (m, 2 H), 3.16 – 3.12 (m, 2 H), 2.09 (br s, 1 H), 1.48 (d, J = 7.0 Hz, 3 H), 0.75 (d, J = 7.0 Hz, 3 H), 0.65	HRMS(B) *m/z* 369.1915 $(M + H)^+$

	(d, J = 7.1 Hz, 3 H)	
164: (*S*)-3-(2-((*S*)-1-(4-tert-butylphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1 H), 7.34 – 7.31 (m, 3 H), 7.24 – 7.21 (m, 2 H), 5.02 (q, J = 7.1 Hz, 1 H), 4.66 – 4.63 (m, 1 H), 4.35 – 4.25 (m, 2 H), 1.95 (br s, 1 H), 1.50 (d, J = 7.0 Hz, 3 H), 1.29 (s, 9 H), 0.69 (d, J = 7.0 Hz, 3 H), 0.58 (d, J = 6.9 Hz, 3 H)	HRMS(B) *m/z* 383.2449 $(M + H)^+$
165: (*S*)-3-[2-((*S*)-1-cyclopropyl-ethylamino)-pyrimidin-4-yl]-5,5-dimethyl-4-phenyl-oxazolidin-2-one	(DMSO-d_6) 8.10 (d, *J* = 5.5 Hz, 1 H), 7.37 – 7.33 (m, 2 H), 7.30 – 7.24 (m, 3 H), 7.15 (br s, 1 H), 7.00 (br s, 1 H), 5.37 (s, 1 H), 2.82 (br s, 1 H), 1.61 (s, 3 H), 1.07 (d, *J* = 6.5 Hz, 3 H), 0.89 (s, 3 H), 0.65 (br s, 1 H), 0.17 (br s, 1 H), 0.00 (br s, 1 H), -0.23 (br s, 1 H), -0.65 (br s, 1 H)	HRMS(B) *m/z* 353.1974 $(M + H)^+$
166: (*S*)-3-(5-fluoro-2-((*S*)-1-(4-methoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO-d_6) 8.36 (br s, 1 H), 7.95 (br s, 1 H), 7.24 (d, J = 8.5 Hz, 2 H), 6.82 (d, J = 9.0 Hz, 2 H), 6.05 (br s, 1 H), 4.77 (br s, 1 H), 4.54 – 4.45 (m, 2 H), 4.24 (br s, 1 H), 3.70 (s, 3 H), 1.38 (d, J = 7.0 Hz, 3 H), 1.26 – 1.22 (m, 1 H), 0.66 – 0.47 (m, 6 H)	HRMS(B) *m/z* 375.1815 $(M + H)^+$
167: (*R*)-5,5-dimethyl-4-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.08 (d, J = 5.8 Hz, 1 H), 7.42 – 7.38 (m, 3 H), 7.35 – 7.27 (m, 5 H), 7.22 – 7.17 (m, 3 H), 5.18 (s, 1 H), 4.62 – 4.57 (m,1 H), 1.51 (s, 3 H), 1.19 (d, J = 7.0 Hz, 3 H), 0.98 (s, 3 H)	HRMS(B) *m/z* 389.1975 $(M + H)^+$
168: (*R*)-5,5-dimethyl-3-(2-((*S*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.10 (d, J = 5.8 Hz, 1 H), 7.82 (d, J = 8.1 Hz, 3 H), 7.73 (s, 1 H), 7.48 – 7.33 (m, 7 H), 7.19 (d, J = 7.1 Hz, 2 H), 5.07 (s, 1 H), 4.74 (q, J = 6.6 Hz, 1 H), 1.32 (d, J = 6.9 Hz, 3 H), 1.29 (s, 3 H), 0.92 (s, 3 H)	HRMS(B) *m/z* 439.2132 $(M + H)^+$
169: (*R*)-3-(2-((*S*)-1-(4-fluoro-3-methoxyphenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	δ 8.10 (d, J = 5.8 Hz, 1 H), 7.41 – 7.28 (m, 6 H), 7.02 – 6.97 (m, 2 H), 6.82 (ddd, J = 8.2, 4.4, 2.0 Hz, 1 H), 5.61 (dd, J = 8.6, 4.0 Hz, 1 H), 4.77 (t, J = 8.6 Hz, 1 H), 4.65 (q, J = 7.1 Hz, 1 H), 4.19 (dd, J = 9.1, 4.0 Hz, 1 H), 3.83 (s, 3 H), 1.20 (d, J = 7.9 Hz, 3 H)	HRMS(B) *m/z* 409.1677 $(M + H)^+$

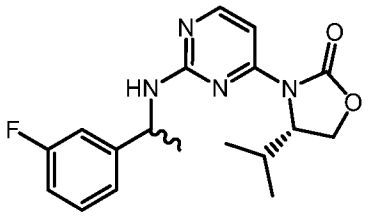
Example 170: (4*S*)-4-isopropyl-3-(2-(2,2,2-trifluoro-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one



A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (163 mg, 0.674 mmol), 2,2,2-trifluoro-1-phenylethanamine (624 mg, 3.56 mmol, 5.3 equiv) and *p*-

toluenesulfonic acid monohydrate (321 mg, 1.69 mmol, 2.5 equiv) in n-BuOH (3 mL) was heated at 110 °C for 2 h and treated with additional *p*-toluenesulfonic acid monohydrate (321 mg, 1.69 mmol, 2.5 equiv), then heated at 110 °C for 1 ½ h. After cooling, the solid reaction mixture was treated with MeCN, sonicated and filtered. The filtrated was concentrated and purified by silica gel column chromatography (EtOAc/Heptane 0 to 30%) to give (4*S*)-4-isopropyl-3-(2-(2,2,2-trifluoro-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one (65 mg) in 25% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 8.215 (d, J = 6.1 Hz, 0.5 H), 8.212 (d, J = 6.1 Hz, 0.5 H), 7.52 (t, J = 7.1 Hz, 2 H), 7.46 (dd, J = 5.8, 3.8 Hz, 1 H), 7.43 – 7.34 (m, 3 H), 5.86 (qd, J = 8.2, 4.0 Hz, 1 H), 4.83 – 4.75 (m, 1 H), 4.42 – 4.33 (m, 2 H), 2.62 (dtd, J = 14, 7.0, 3.8 Hz, 0.5 H), 2.28 (br s, 0.5 H), 1.02 (d, J = 7.1 Hz, 1.5 H), 0.91 (d, J = 7.1 Hz, 1.5 H), 0.88 (d, J = 7.11 Hz, 1.5 H), 0.73 (d, J = 7.1 Hz, 1.5 H); HRMS(B) *m/z* 381.1545 $(M + H)^+$.

Examples 171 and 172



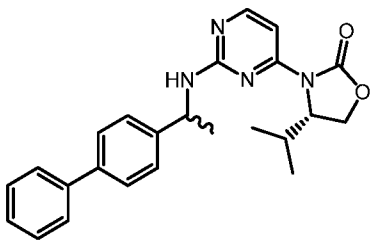
A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (106 mg, 0.439 mmol) and 1-(3-fluorophenyl)ethanamine (196 mg, 1.41 mmol, 3.21 equiv) in DMSO (1 mL) was heated at 110 °C for 1 ½ h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 50%) provided (*S*)-3-(2-((*R*)-1-(3-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (*S*)-3-(2-((*S*)-1-(3-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

Example 171 first eluted product (28 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, J = 5.8 Hz, 1 H), 7.36 – 7.27 (m, 2 H), 7.16 (d, J = 7.6 Hz, 1 H), 7.07 (dt, J = 10, 2.0 Hz, 1 H), 6.92 – 6.88 (m, 1 H), 4.98 – 4.93 (m, 1 H), 4.42 (br s, 1 H), 4.32 (dd, J = 9.1, 2.8 Hz, 1 H), 4.26 (t, J = 8.7 Hz, 1 H), 2.64 (dtd, J = 14, 7.1, 3.5 Hz, 1 H), 1.50 (d, J = 7.0 Hz, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.0 Hz, 3 H); HRMS(B) *m/z* 345.1729 $(M + H)^+$.

Example 172 second eluted product (22 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (d, J = 5.7 Hz, 1 H), 7.36 (d, J = 5.8 Hz, 1 H), 7.29 (td, J = 8.1, 6.1 Hz, 1 H), 7.13 (d, J = 7.6 Hz,

1 H), 7.06 – 7.04 (m, 1 H), 6.94 – 6.87 (m, 1 H), 5.03 (q, J = 7.1 Hz, 1 H), 4.64 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.79 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.70 (br s, 3 H), 0.58 (br s, 3 H); HRMS(B) *m/z* 345.1727 $(M + H)^+$.

Examples 173 and 174

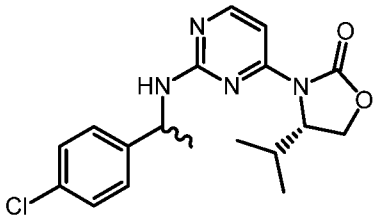


A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (90 mg, 0.37 mmol), *i*Pr_2NEt (0.455 mL, 2.61 mmol, 7.0 equiv) and 1-(biphenyl-4-yl)ethanamine hydrochloride (87 mg, 0.37 mmol) in DMSO (1 mL) was heated at 110 °C for 2 h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 50%) provided (*S*)-3-(2-((*R*)-1-(biphenyl-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (*S*)-3-(2-((*S*)-1-(biphenyl-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

Example 173 first eluted product (17 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, J = 5.8 Hz, 1 H), 7.59 – 7.54 (m, 4 H), 7.43 – 7.28 (m, 6 H), 5.01 (q, J = 6.8 Hz, 1 H), 4.49 (br s, 1 H), 4.32 (dd, J = 9.1, 3.0 Hz, 1 H), 4.26 (t, J = 8.6 Hz, 1 H), 2.67 (dtd, J = 14, 7.0, 3.5 Hz, 1 H), 1.55 (d, J = 7.1 Hz, 3 H), 1.01 (d, J = 7.1 Hz, 3 H), 0.86 (d, J = 7.0 Hz, 3 H); HRMS(B) *m/z* 403.2141 $(M + H)^+$.

Example 174 second eluted product (21 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 5.8 Hz, 1 H), 7.58 – 7.52 (m, 4 H), 7.42 – 7.28 (m, 6 H), 5.06 (q, J = 7.1 Hz, 1 H), 4.63 (br s, 1 H), 4.34 – 4.25 (m, 2 H), 1.79 (br s, 1 H), 1.55 (d, J = 7.1 Hz, 3 H), 0.65 (br s, 3 H), 0.53 (br s, 3 H); HRMS(B) *m/z* 403.2139 $(M + H)^+$.

Examples 175 and 176

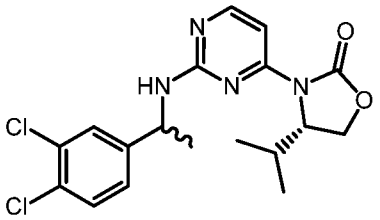


A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (96 mg, 0.40 mmol) and 1-(4-chlorophenyl)ethanamine (204 mg, 1.31 mmol, 3.3 equiv) in DMSO (1 mL) was heated at 110 °C for 3 h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 50%) provided (*S*)-3-(2-((*R*)-1-(4-chlorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (*S*)-3-(2-((*S*)-1-(4-chlorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

Example 175 first eluted product (32 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 5.8 Hz, 1 H), 7.36 – 7.28 (m, 5 H), 4.95 (q, J = 6.7 Hz, 1 H), 4.45 (br s, 1 H), 4.35 – 4.26 (m, 2 H), 2.64 (dtt, J = 11, 7.0, 3.4 Hz, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 361.1430 $(M + H)^+$.

Example 176 second eluted product (40 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (d, J = 5.7 Hz, 1 H), 7.36 – 7.26 (m, 5 H), 5.00 (q, J = 7.1 Hz, 1 H), 4,62 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.77 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.68 (br s, 3 H), 0.59 (br s, 3 H); HRMS(B) *m/z* 361.1431 $(M + H)^+$.

Examples 177 and 178



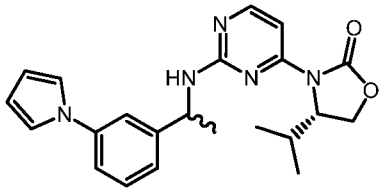
A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (93 mg, 0.38 mmol) and 1-(3,4-dichlorophenyl)ethanamine (73.1 mg, 0.385 mmol, 1.0 equiv) in DMSO (1 mL) was heated at 110 °C for 1 ½ h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted

with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 50%) provided (*S*)-3-(2-((*R*)-1-(3,4-dichlorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (*S*)-3-(2-((*S*)-1-(3,4-dichlorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

Example 177 first eluted product (21 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 5.8 Hz, 1 H), 7.50 (d, J = 2.0 Hz, 1 H), 7.44 (d, J = 8.2 Hz, 1 H), 7.37 (d, J = 5.8 Hz, 1 H), 7.28 (dd, J = 8.6, 2.0 Hz, 1 H), 4.94 – 4.88 (m, 1 H), 4.43 (br s, 1 H), 4.35 – 4.26 (m, 2 H), 2.68 – 2.60 (m, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 395.1035 $(M + H)^+$.

Example 178 second eluted product (28 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, J = 5.8 Hz, 1 H), 7.47 – 7.42 (m, 2 H), 7.37 (d, J = 5.8 Hz, 1 H), 7.25 (dd, J = 8.1, 2.0 Hz, 1 H), 5.01 – 4.96 (m, 1 H), 4.61 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.72 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.67 (br s, 3 H), 0.60 (br s, 3 H); HRMS(B) *m/z* 395.1044 $(M + H)^+$.

Examples 179 and 180



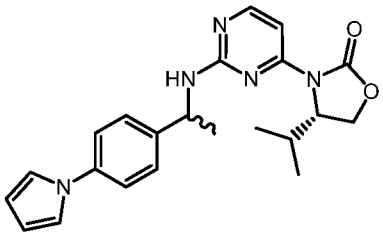
A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (86 mg, 0.36 mmol) and 1-(3-(1*H*-pyrrol-1-yl)phenyl)ethanamine (100 mg, 0.537 mmol, 1.5 equiv) in DMSO (1 mL) was heated at 110 °C for 1 ½ h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 50%) provided (*S*)-3-(2-((*R*)-1-(3-(1H-pyrrol-1-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (*S*)-3-(2-((*S*)-1-(3-(1H-pyrrol-1-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

Example 179 first eluted product (14 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8. 11 (d, J = 5.8 Hz, 1 H), 7.45 (t, J = 1.8 Hz, 1 H), 7.39 – 7.29 (m, 3 H), 7.23 (d, J = 7.6 Hz, 1 H), 7.13 (t, J = 2.0 Hz, 2 H), 6.25 (t, J = 2.1 Hz, 2 H), 5.03 – 4.97 (m, 1 H), 4.46 (br s, 1 H), 4.31 –

4.20 (m, 2 H), 2.64 (dtd, J = 14, 7.0, 3.8 Hz, 1 H), 1.56 (d, J = 7.1 Hz, 3 H), 0.95 (d, J = 7.1 Hz, 3 H), 0.84 (d, J = 7.0 Hz, 3 H); HRMS(B) *m/z* 392.2092 $(M + H)^+$.

Example 180 second eluted product (10 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 5.7 Hz, 1 H), 7.42 (br s, 1 H), 7.38 – 7.28 (m, 3 H), 7.20 (d, J = 7.6 Hz, 1 H), 7.12 (t, J = 2.3 Hz, 2 H), 6.25 (t, J = 2.0 Hz, 2 H), 5.09 (q, J = 6.9 Hz, 1 H), 4.64 (br s, 1 H), 4.32 – 4.23 (m, 2 H), 1.84 (br s, 1 H), 1.55 (d, J = 7.1 Hz, 3 H), 0.54 (br s, 6 H); HRMS(B) *m/z* 392.2090 $(M + H)^+$.

Examples 181 and 182

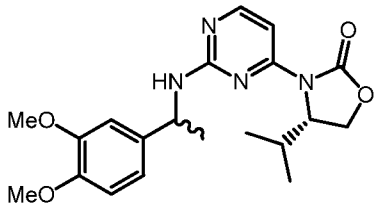


A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (44 mg, 0.18 mmol) and 1-(4-(1*H*-pyrrol-1-yl)phenyl)ethanamine (33.9 mg, 0.182 mmol, 1 equiv) in DMSO (1 mL) was heated at 110 °C for 2 h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 50%) provided (*S*)-3-(2-((*R*)-1-(4-(1H-pyrrol-1-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (*S*)-3-(2-((*S*)-1-(4-(1H-pyrrol-1-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

Example 181 first eluted product (18 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, J = 5.8 Hz, 1 H), 7.44 – 7.39 (m, 4 H), 7.35 (d, J = 5.9 Hz, 1 H), 7.13 (t, J = 2.2 Hz, 2 H), 6.24 (t, J = 2.0 Hz, 2 H), 5.02 – 4.96 (m, 1 H), 4.49 (br s, 1 H), 4.34 – 4.25 (m, 2 H), 2.66 (dtd, J = 14, 7.0, 3.3 Hz, 1 H), 1.53 (d, J = 7.1 Hz, 3 H), 1.00 (d, J = 7.1 Hz, 3 H), 0.86 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 392.2089 $(M + H)^+$.

Example 182 second eluted product (9 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 5.8 Hz, 1 H), 7.39 (s, 4 H), 7.35 (d, J = 5.9 Hz, 1 H), 7.12 (t, J = 2.2 Hz, 2 H), 6.25 (t, J = 2.0 Hz, 2 H), 5.05 (q, J = 7.1 Hz, 1 H), 4.64 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.87 (br s, 1 H), 1.53 (d, J = 7.1 Hz, 3 H), 0.68 (br s, 3 H), 0.57 (br s, 3 H); HRMS(B) *m/z* 392.2082 $(M + H)^+$.

Examples 183 and 184

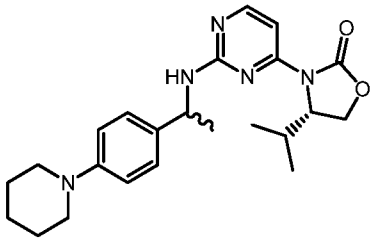


A mixture of (4*S*)-3-(2-((1-(3,4-dimethoxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (example 118) was resolved on a column (AS-H 4.6 x 100 mm) using 30% *i*PrOH in CO_2 to give (*S*)-3-(2-((*R*)-1-(3,4-dimethoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (*S*)-3-(2-((*S*)-1-(3,4-dimethoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

Example 183 first eluted product (13 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, J = 5.8 Hz, 1 H), 7.33 (d, J = 5.8 Hz, 1 H), 6.97 (br d, J = 1.5 Hz, 1 H), 6.92 – 6.88 (m, 2 H), 4.96 (q, J = 6.7 Hz, 1 H), 4.61 – 4.55 (m, 1 H), 4.35 – 4.28 (m, 2 H), 3.803 (s, 3 H), 3.800 (s, 3 H), 2.63 (dtd, J = 14, 7.0, 3.5 Hz, 1 H), 1.51 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.86 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 387.2031 $(M + H)^+$.

Example 184 second eluted product (10 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (d, J = 5.8 Hz, 1 H), 7.32 (d, J = 5.7 Hz, 1 H), 6.94 (br d, J = 1.1 Hz, 1 H), 6.89 – 6.84 (m, 2 H), 4.99 (q, J = 7.1 Hz, 1 H), 4.67 – 4.63 (m, 1 H), 4.36 – 4.26 (m, 2 H), 3.79 (s, 6 H), 2.01 (br s, 1 H), 1.51(d, J = 7.1 Hz, 3 H), 0.71 (d, J = 7.1 Hz, 3 H), 0.63 (d, J = 7.0 Hz, 3 H); HRMS(B) *m/z* 387.2029 $(M + H)^+$.

Examples 185 and 186

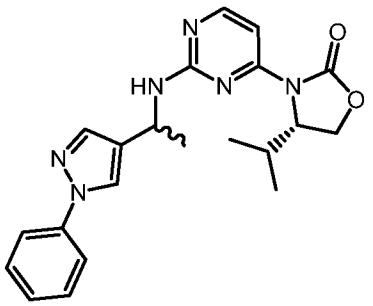


A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (93 mg, 0.38 mmol) and 1-(4-(piperidin-1-yl)phenyl)ethanamine (410 mg, 2.01 mmol, 5.2 equiv) in DMSO (1 mL) was heated at 110 °C for 2 h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 100%)

provided (4*S*)-4-isopropyl-3-(2-((1-(4-(piperidin-1-yl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one (57 mg) in 36% yield. A mixture of (4*S*)-4-isopropyl-3-(2-(1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one was resolved on a column (AD-H 4.6 x 100 mm) using 5 to 55% MeOH with 0.2% Et_2NH in CO_2 to give (*S*)-4-isopropyl-3-(2-((*R*)-1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one and (*S*)-4-isopropyl-3-(2-((*S*)-1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one.

Example 185 first eluted product (16 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 5.8 Hz, 1 H), 7.31 (d, J = 5.8 Hz, 1 H), 7.24 – 7.20 (m, 2 H), 6.94 – 6.91 (m, 2 H), 4.93 (q, J = 7.1 Hz, 1 H), 4.58 – 4.54 (m, 1 H), 4.34 – 4.27 (m, 2 H), 3.11 – 3.08 (m, 4 H), 2.63 (dtd, J = 14, 7.1, 3.5 Hz, 1 H), 1.73 – 1.67 (m, 4 H), 1.60 – 1.54 (m, 2 H), 1.49 (d, J = 7.1 Hz, 3 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.86 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 410.2555 $(M + H)^+$.
Example 186 second eluted product (16 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, J = 5.8 Hz, 1 H), 7.31 (d, J = 5.8 Hz, 1 H), 7.20 – 7.16 (m, 2 H), 6.93 – 6.89 (m, 2 H), 4.98 (q, J = 6.9 Hz, 1 H), 4.69 – 4.65 (m, 1 H), 4.36 – 4.26 (m, 2 H), 3.10 – 3.07 (m, 4 H), 2.07 (br s, 1 H), 1.73 – 1.67 (m, J = 4 H), 1.60 – 1.54 (m, 2 H), 1.48 (d, J = 7.1 Hz, 3 H), 0.75 (d, J = 7.0 Hz, 3 H), 0.63 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 410.2556 $(M + H)^+$.

Examples 187 and 188

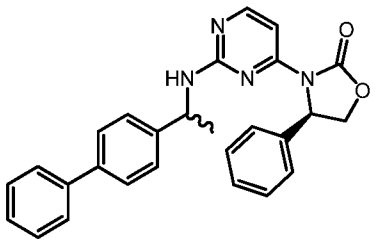


A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (96 mg, 0.40 mmol) and 1-(1-phenyl-1*H*-pyrazol-4-yl)ethanamine (387 mg, 2.97 mmol, 5.2 equiv) in DMSO (1.5 mL) was heated at 110 °C for 1 ½ h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 20 to 80%) provided (*S*)-4-isopropyl-3-(2-((*R*)-1-(1-phenyl-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one and (*S*)-4-isopropyl-3-(2-((*S*)-1-(1-phenyl-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one.

Example 187 first eluted product (13 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, J = 5.8 Hz, 1 H), 8.10 (s, 1 H), 7.70 – 7.66 (m, 3 H), 7.48 – 7.43 (m, 2 H), 7.37 (d, J = 5.7 Hz, 1 H), 7.32 – 7.28 (m, 1 H), 5.20 (q, J = 6.6 Hz, 1 H), 4.75 (dt, J = 7.7, 4.0 Hz, 1 H), 4.40 – 4.33 (m, 2 H), 2.61 (dtt, J = 11, 7.0, 3.6 Hz, 1 H), 1.60 (d, J = 6.9 Hz, 3 H), 0.96 (d, J = 7.1 Hz, 3 H), 0.87 (d, J = 6.9 Hz, 3 H); HRMS(B) *m/z* 393.2029 $(M + H)^+$.

Example 188 second eluted product (11 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, J = 5.8 Hz, 1 H), 8.03 (s, 1 H), 7.68 – 7.62 (m, 3 H), 7.48 – 7.43 (m, 2 H), 7.37 (d, J = 5.8 Hz, 1 H), 7.32 – 7.27 (m, 1 H), 5.19 (q, J = 7.1 Hz, 1 H), 4.74 (dt, J = 8.5, 3.6 Hz, 1 H), 4.38 – 4.29 (m, 2 H), 2.37 – 2.33 (m, 1 H), 1.60 (d, J = 7.1 Hz, 3 H), 0.79 (d, J = 7.1 Hz, 3 H), 0.73 (s, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 393.2039 $(M + H)^+$.

Examples 189 and 190



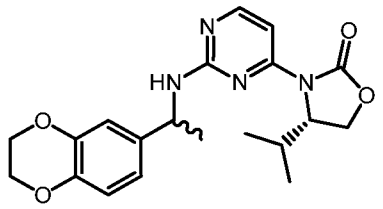
A solution of (*R*)-3-(2-chloropyrimidin-4-yl)-4-phenyloxazolidin-2-one (97 mg, 0.35 mmol), 1-(biphenyl-4-yl)ethanamine hydrochloride (304 mg, 1.30 mmol, 3.7 equiv) and *i*Pr_2NEt (0.307 mL, 1.76 mmol, 5.0 equiv) in DMSO (1 mL) was heated at 110 °C for 1 ½ h and at 130 °C for 20 h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 50%) provided (*R*)-3-(2-((*R*)-1-(biphenyl-4-yl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one and (*R*)-3-(2-((*S*)-1-(biphenyl-4-yl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one.

Example 189 first eluted product (12 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 5.8 Hz, 1 H), 7.58 – 7.55 (m, 2 H), 7.44 – 7.37 (m, 6 H), 7.33 – 7.28 (m, 1 H), 7.24 – 7.14 (m, 6 H), 5.84 (dd, J = 8.6, 3.5 Hz, 1 H), 4.94 (q, J = 6.7 Hz, 1 H), 4.81 (t, J = 8.6 Hz, 1 H), 4.22 (dd, J = 8.8, 3.8 Hz, 1 H), 1.49 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 437.1981 $(M + H)^+$.

Example 190 second eluted product (11 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 5.8 Hz, 1 H), 7.60 – 7.54 (m, 4 H), 7.44 – 7.28 (m, 11 H), 5.60 (dd, J = 8.6, 4.0 Hz, 1 H),

4.77 – 4.69 (m, 2 H), 4.19 (dd, J = 8.6, 4.0 Hz, 1 H), 1.25 (d, J = 7.0 Hz, 3 H); HRMS(B) *m/z* 437.1971 $(M + H)^+$.

Examples 191 and 192

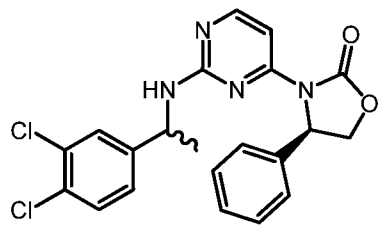


(4*S*)-3-(2-(1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (example 130, 52 mg) was resolved on a column (IA 4.6 x 100 mm) using 40% *i*PrOH in CO_2 to give (*S*)-3-(2-((*R*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (*S*)-3-(2-((*S*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

Example 191 first eluted product (7 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 5.6 Hz, 1 H), 7.33 – 7.31 (m, 1 H), 6.82 – 6.74 (m, 3 H), 4.88 (q, J = 7.1 Hz, 1 H), 4.58 – 4.53 (m, 1 H), 4.34 – 4.28 (m, 2 H), 4.21 – 4.18 (m, 4 H), 2.63 (td, J = 7.1, 3.5 Hz, 1 H), 1.47 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.86 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 385.1875 $(M + H)^+$.

Example 192 second eluted product (19 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 5.8 Hz, 1 H), 7.33 – 7.31 (m, 1 H), 6.78 – 6.72 (m, 3 H), 4.93 (q, J = 6.7 Hz, 1 H), 4.68 – 4.64 (m, 1 H), 4.36 – 4.27 (m, 2 H), 2.08 (br s, 1 H), 1.47 (d, J = 7.1 Hz, 3 H), 0.76 (d, J = 7.1 Hz, 3 H), 0.65 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 385.1873 $(M + H)^+$.

Examples 193 and 194



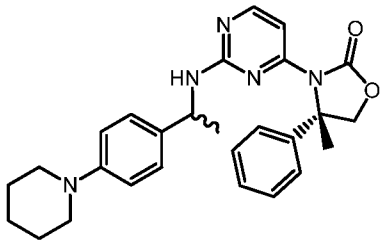
A solution of (*R*)-3-(2-chloropyrimidin-4-yl)-4-phenyloxazolidin-2-one (83 mg, 0.30 mmol) and 1-(3,4-dichlorophenyl)ethanamine (260 mg, 1.37 mmol, 4.5 equiv) in DMSO (1.5 mL) was heated at 110 °C for 1 ½ h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and

concentrated. Silica gel column chromatography (EtOAc/Heptane 0 to 40%) provided (*R*)-3-(2-((*R*)-1-(3,4-dichlorophenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one and (*R*)-3-(2-((*S*)-1-(3,4-dichlorophenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one.

Example 193 first eluted product (13 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (d, J = 5.6 Hz, 1 H), 7.44 – 7.38 (m, 5 H), 7.35 – 7.31 (m, 1 H), 7.27 – 7.25 (m, 2 H), 7.18 (dd, J = 8.3, 2.3 Hz, 1 H), 5.53 (dd, J = 8.8, 3.8 Hz, 1 H), 4.76 (t, J = 8.8 Hz, 1 H), 4.59 – 4.53 (m, 1 H), 4.18 (dd, J = 8.8, 4.3 Hz, 1 H), 1.22 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 429.0899 (M + H)$^+$.

Example 194 second eluted product (26 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (d, J = 5.6 Hz, 1 H), 7.41 (d, J = 6.1 Hz, 1 H), 7.25 – 7.18 (m, 5 H), 7.09 – 7.06 (m, 2 H), 6.95 – 6.93 (m, 1 H), 5.78 (dd, J = 8.6, 3.5 Hz, 1 H), 4.89 (q, J = 6.7 Hz, 1 H), 4.79 (t, J = 8.6 Hz, 1 H), 4.18 (dd, J = 8.8, 3.8 Hz, 1 H), 1.42 (d. J = 7.1 Hz, 3 H); HRMS(B) *m/z* 429.0887 (M + H)$^+$.

Examples 195 and 196

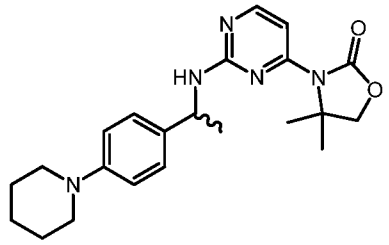


(4*S*)-4-methyl-4-phenyl-3-(2-(1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one (example 141, 51 mg) was resolved on a column (IA 4.6 x 100 mm) using 45% MeOH in CO_2 to give (*S*)-4-methyl-4-phenyl-3-(2-((*S*)-1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one and (*S*)-4-methyl-4-phenyl-3-(2-((*R*)-1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one.

Example 195 first eluted product (21.6 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 5.8 Hz, 1 H), 7.41 (d, J = 5.8 Hz, 1 H), 7.36 – 7.33 (m, 4 H), 7.32 – 7.26 (m, 1 H), 6.88 – 6.82 (br m, 4 H), 5.01 (br s, 1 H), 4.30 (s, 2 H), 3.16 – 3.13 (m, 4 H), 2.20 (s, 3 H), 1.76 – 1.57 (br m, 6 H), 1.37 (d, J = 6.7 Hz, 3 H); HRMS(B) *m/z* 458.2558 (M + H)$^+$.

Example 196 second eluted product (20.6 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 5.8 Hz, 1 H), 7.50 – 7.27 (m, 6 H), 7.05 (d, J = 8.6 Hz, 2 H), 6.96 – 6.92 (br m, 2 H), 5.27 (br s, 1 H), 4.22 (s, 2 H), 3.21 – 3.13 (m, 4 H), 1.78 – 1.76 (br m, 7 H), 1.63 – 1.57 (br m, 2 H), 1.07 (d, J = 6.1 Hz, 3 H); HRMS(B) *m/z* 458.2559 (M + H)$^+$.

Examples 197 and 198

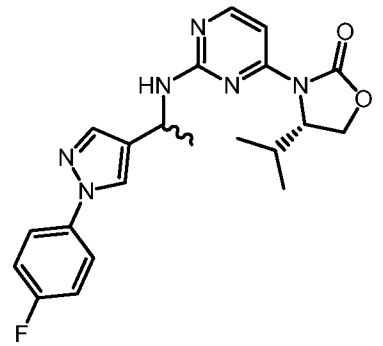


4,4-dimethyl-3-(2-(1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one (example 183, 70 mg) was resolved on a column (IA 4.6 x 100 mm) using 40% MeOH in CO_2 to give (*S*)-4,4-dimethyl-3-(2-(1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one and (*R*)-4,4-dimethyl-3-(2-(1-(4-(piperidin-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one.

Example 197 first eluted product (23.8 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br d, J = 5.8 Hz, 1 H), 7.28 – 7.23 (m, 3 H), 6.93 (br d, J = 7.7 Hz, 2 H), 5.44 (br s, 1 H), 4.97 (br s, 1 H), 4.05 – 3.99 (m, 2 H), 3.15 – 3.12 (m, 4 H), 1.77 – 1.70 (m, 8 H), 1.61 – 1.54 (m, 5 H), 1.32 (br s, 2 H); HRMS(B) *m/z* 396.2413 $(M + H)^+$.

Example 198 second eluted product (22.3 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br d, J = 5.5 Hz, 1 H), 7.28 – 7.23 (m, 3 H), 6.94 (br d, J = 7.5 Hz, 2 H), 5.48 (br s, 1 H), 4.97 (br s, 1 H), 4.05 – 3.99 (m, 2 H), 3.15 – 3.12 (m, 4 H), 1.77 – 1.70 (m, 8 H), 1.61 – 1.54 (m, 5 H), 1.31 (br s, 2 H); HRMS(B) *m/z* 396.2410 $(M + H)^+$.

Examples 199 and 200



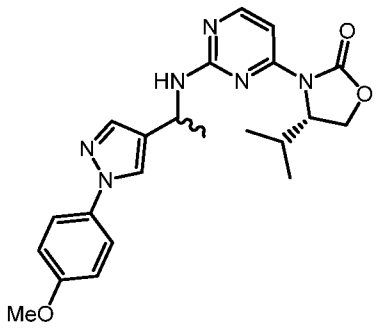
A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (98 mg, 0.41 mmol), 1-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)ethanamine hydrochloride (502 mg, 2.08 mmol, 5.1 equiv) and *i*Pr_2NEt (0.637 mL, 3.65 mmol, 9.0 equiv) in DMSO (1.5 mL) was heated at 110 °C for 16 h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with

EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 20 to 80%) provided (*S*)-3-(2-((*R*)-1-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (*S*)-3-(2-((*S*)-1-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

Example 199 first eluted product (49 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, J = 5.8 Hz, 1 H), 8.06 (s, 1 H), 7.71 – 7.67 (m, 3 H), 7.37 (d, J = 5.9 Hz, 1 H), 7.22 – 7.16 (m, 2 H), 5.20 (q, J = 6.6 Hz, 1 H), 4.74 (dt, J = 7.6, 3.8 Hz, 1 H), 4.40 – 4.34 (m, 2 H), 2.60 (dtd, J = 14, 7.0, 3.5 Hz, 1 H), 1.59
(d, J = 6.9 Hz, 3 H), 0.96 (d, J = 7.1 Hz, 3 H), 0.87 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 411.1943 $(M + H)^+$.

Example 200 second eluted product (27 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, J = 5.8 Hz, 1 H), 8.00 (s, 1 H), 7.69 – 7.66 (m, 2 H), 7.61 (s, 1 H), 7.37 (d, J = 5.9 Hz, 1 H), 7.22 – 7.16 (m, 2 H), 5.19 (q, J = 6.7 Hz, 1 H), 4.73 (dt, J = 8.1, 3.5 Hz, 1 H), 4.39 – 4.30 (m, 2 H), 2.38 – 2.31 (m, 1 H), 1.59 (d, J = 6.8 Hz, 3 H), 0.79 (d, J = 7.1 Hz, 3 H), 0.73 (d, J = 7.0 Hz, 3 H); HRMS(B) *m/z* 411.1937 $(M + H)^+$.

Examples 201 and 202

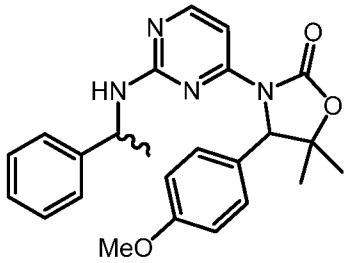


A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (93 mg, 0.38 mmol), 1-(1-(4-methoxyphenyl)-1H-pyrazol-4-yl)ethanamine hydrochloride (514 mg, 2.03 mmol, 5.3 equiv) and *i*Pr_2NEt (0.605 mL, 3.46 mmol, 9.0 equiv) in DMSO (1.5 mL) was heated at 110 °C for 16 h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 70%) provided (*S*)-4-isopropyl-3-(2-((*R*)-1-(1-(4-methoxyphenyl)-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one and (*S*)-4-isopropyl-3-(2-((*S*)-1-(1-(4-methoxyphenyl)-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one.

Example 201 first eluted product (17 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, J = 5.8 Hz, 1 H), 7.98 (s, 1 H), 7.63 (s, 1 H), 7.58 – 7.54 (m, 2 H), 7.37 (d, J = 5.8 Hz, 1 H), 7.03 – 6.99 (m, 2 H), 5.19 (q, J = 7.1 Hz, 1 H), 4.75 (dt, J = 7.7, 4.0 Hz, 1 H), 4.40 – 4.33 (m, 2 H), 3.83 (s, 3 H), 2.61 (dtd, J = 14, 7.1, 3.5 Hz, 1 H), 1.59 (d, J = 7.1 Hz, 3 H), 0.96 (d, J = 7.1 Hz, 3 H), 0.87 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 423.2138 $(M + H)^+$.

Example 202 second eluted product (18 mg) ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, J = 5.8 Hz, 1 H), 7.91 (s, 1 H), 7.58 – 7.53 (m, 3 H), 7.37 (d, J = 5.9 Hz, 1 H), 7.03 – 6.99 (m, 2 H), 5.18 (q, J = 6.7 Hz, 1 H), 4.76 – 4.72 (m, 1 H), 4.39 – 4.30 (m, 2 H), 3.83 (s, 3 H), 2.31 (br s, 1 H), 1.59 (d, J = 7.1 Hz, 3 H), 0.80 (d, J = 7.1 Hz, 3 H), 0.73 (d, J = 7.1 Hz, 3 H); HRMS(B) *m/z* 423.214 $(M + H)^+$.

Examples 203 and 204

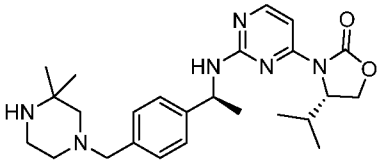


4-(4-methoxyphenyl)-5,5-dimethyl-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one (example 54, 62 mg) was resolved in on a column (AD-H 4.6 x 100 mm) with 30% MeOH modified with 0.2% Et_2NH in CO_2 to give (*S*)-4-(4-methoxyphenyl)-5,5-dimethyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one and (*R*)-4-(4-methoxyphenyl)-5,5-dimethyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one.

Example 203 first eluted product (22 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br d, J = 5.6 Hz, 1 H), 7.53 (d, J = 5.7 Hz, 1 H), 7.37 – 7.24 (m, 5 H), 7.08 – 7.05 (m, 2 H), 6.92 – 6.89 (m, 2 H), 5.47 (br s, 1 H), 5.02 (br s, 1 H), 4.66 (br s, 1 H), 3.83 (s, 3 H), 1.50 (s, 3 H), 1.28 (br d, J = 6.6 Hz, 3 H), 1.01 (s, 3 H); HRMS(B) *m/z* 419.208 $(M + H)^+$.

Example 204 second eluted product (22.2 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (br d, J = 6.1 Hz, 1 H), 7.55 (d, J = 5.8 Hz, 1 H), 7.28 – 7.22 (m, 3 H), 7.08 (br s, 2 H), 7.01 (d, J = 8.6 Hz, 2 H), 6.79 (d, J = 8.6 Hz, 2 H), 5.40 (br s, 1 H), 5.30 (s, 1 H), 4.83 (br s, 1 H), 3.78 (s, 3 H), 1.66 (s, 3 H), 1.51 (d, J = 6.8 Hz, 3 H), 1.04 (s, 2 H); HRMS(B) *m/z* 419.2083 $(M + H)^+$.

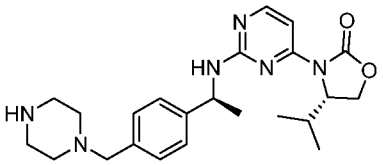
Example 205



To a solution of tert-butyl 4-(4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzyl)-2,2-dimethylpiperazine-1-carboxylate (78 mg, 0.14 mmol) in DCM (1 mL) was added TFA (1 mL, 12 mmol) slowly at -78 °C. The reaction was stirred at room temperature for 1 h then was concentrated and diluted with DCM (10 mL). The solution was stirred with 3 eq. of MP-carbonate resin (3.28 mmol/g, Biotage) for 1 h at room temperature. The resin was removed by filtration and washed (2 x 5 mL) with DCM. The filtrate was concentrated and purified through HPLC to give (S)-3-(2-(((S)-1-(4-((3,3-dimethylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one as a white solid (23 mg, 36% yield).

^{1}H NMR (400 MHz, MeOD) δ 8.07 (d, J = 5.8 Hz, 1H), 7.30 (d, J = 5.8 Hz, 1H), 7.26 – 7.18 (m, 4H), 5.00 (q, J = 6.9 Hz, 1H), 4.62 (br s, 1H), 4.36 – 4.16 (m, 2H), 3.36 (s, 2H), 2.81 (br t, J = 5.1 Hz, 2H), 2.30 (br s, 2H), 2.10 (br s, 2H), 1.82 (br s, 1H), 1.45 (d, J = 7.0 Hz, 3H), 1.08 (s, 6H), 0.67 (br s, 3H), 0.52 (br s, 3H); HRMS(B) m/z 453.2969 (M + H)+.

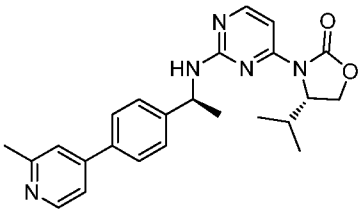
Example 206



A mixture of benzyl 4-(4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzyl)piperazine-1-carboxylate (190 mg, 0.34 mmol) and 10% Pd-C (40 mg, 0.038 mmol) in ethanol (3.4 ml) is stirred under 1 atmosphere pressure of hydrogen for 3 h. The mixture is filtered and concentrated to give (S)-4-isopropyl-3-(2-(((S)-1-(4-(piperazin-1-ylmethyl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one as a white solid (97 mg, 67.2% yield).

^{1}H NMR (400 MHz, MeOD) δ 8.08 (d, J = 5.8 Hz, 1H), 7.30 (d, J = 5.8 Hz, 1H), 7.28 – 7.19 (m, 4H), 5.01 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.37 – 4.14 (m, 2H), 3.44 (s, 2H), 2.78 (t, J = 5.0 Hz, 4H), 2.39 (br s, 4H), 1.89 (br s, 1H), 1.45 (d, J = 7.0 Hz, 3H), 0.68 (br s, 3H), 0.52 (br s, 3H); HRMS(B) m/z 425.2662 (M + H)+.

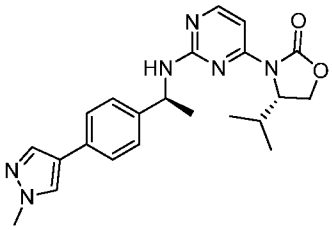
Example 207



In a 5 mL microwave vial a solution of (S)-3-(2-((S)-1-(4-bromophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (86 mg, 0.21 mmol), pyridin-4-ylboronic acid (26 mg, 0.21 mmol), Sodium bicarbonate (0.21 mL, 0.42 mmol, 2 M solution) in Dioxane (1 mL) was bubbled N2 for 3 min then Cl2Pd(dppf).CH_2Cl_2 (17 mg, 0.021 mmol) was added. The capped tube was heated to 100°C for 16 h. After cooling the reaction mixture was diluted with EtOAc (10 mL) and washed with water (10 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 10 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. The crude material was purified through silica gel column chromatography (EtOAc in Heptane 12 to 100%) to yield (S)-4-isopropy-3-(2-(((S)-1-(4-(2-yl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one as a white solid (27 mg, 30.5% yield).

^{1}H NMR (400 MHz, MeOD) δ 8.35 (d, J = 5.4 Hz, 1H), 8.08 (d, J = 5.9 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.49 (br d, J = 1.8 Hz, 1H), 7.43 – 7.39 (m, 3H), 7.30 (d, J = 5.8 Hz, 1H), 5.02 (q, J = 6.8 Hz, 1H), 4.55 (br s, 1H), 4.27 – 4.18 (m, 2H), 2.52 (s, 3H), 1.65 (br s, 1H), 1.49 (d, J = 7.1 Hz, 3H), 0.55 (br s, 3H), 0.43 (br s, 3H); HRMS(B) m/z 418.2227 (M + H)+.

Example 208

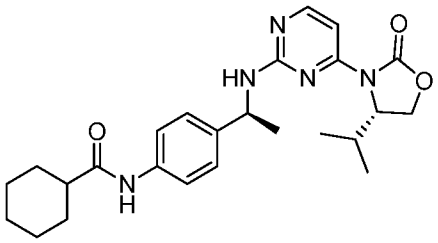


To a solution of tert-butyl 4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl((S)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamate (45 mg, 0.09 mmol) in DCM (1 mL) was added TFA (1 mL, 12 mmol) slowly at -78 °C. The reaction was stirred at room temperature for 1 h then was concentrated and diluted with DCM (10 mL). The solution was washed with saturated $NaHCO_3$ solution and brine. After separation, the aqueous phase was extracted with DCM (3 x 10 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated to give (S)-4-isopropyl-3-(2-(((S)-1-(4-(1-methyl-1H-

pyrazol-4-yl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one as a white solid (35 mg, 97% yield).

^{1}H NMR (400 MHz, MeOD) δ 8.09 (d, J = 5.9 Hz, 1H), 7.86 (s, 1H), 7.72 (d, J = 0.8 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.30 (d, J = 5.8 Hz, 1H), 7.25 (d, J = 7.9 Hz, 2H), 4.97 (q, J = 7.0 Hz, 1H), 4.58 (br s, 1H), 4.30 – 4.21 (m, 2H), 3.86 (s, 3H), 1.66 (br s, 1H), 1.48 (d, J = 7.0 Hz, 3H), 0.60 (br s, 3H), 0.48 (br s, 3H); HRMS(B) m/z 407.2179 (M + H)+.

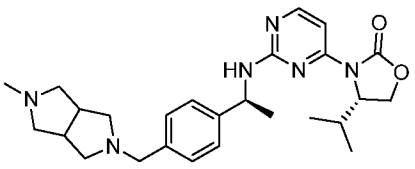
Example 209



Following the above procedure for Example 208, N-(4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)phenyl)cyclohexanecarboxamide was prepared as a white solid (45 mg, 92 % yield) from tert-butyl (S)-1-(4-(cyclohexanecarboxamido)phenyl)ethyl(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)carbamate.

^{1}H NMR (400 MHz, MeOD) δ 8.08 (d, J = 5.9 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.30 (d, J = 5.8 Hz, 1H), 7.23 – 7.16 (m, 2H), 4.95 (q, J = 7.0 Hz, 1H), 4.60 (br s, 1H), 4.32 – 4.19 (m, 2H), 2.30 (tt, J = 11.8, 3.3 Hz, 1H), 1.89 – 1.72 (m, 4H), 1.72 – 1.63 (m, 1H), 1.54 – 1.39 (m, 5H), 1.39 – 1.14 (m, 4H), 0.67 (br s, 3H), 0.54 (br s, 3H); HRMS(B) m/z 452.2636 (M + H)+.

Example 210

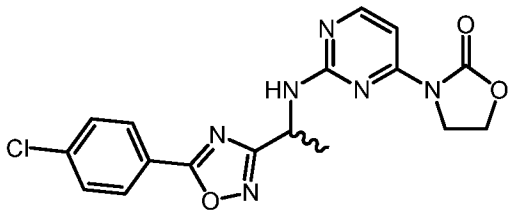


A solution of 4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzaldehyde (35 mg, 0.1 mmol) and 2-methyloctahydropyrrolo[3,4-c]pyrrole (14 mg, 0.11 mmol) in MeOH (2 mL) was added acetic acid (7.2 mg, 0.12 mmol) and 5-Ethyl-2-methylpyridine borane complex (14 mg, 0.1 mmol, sigmaaldrich). The solution was stirred at 50 °C for 4 h then 5 drops of water was added. The solution was stirred at room temperature for another 2 h then diluted with EtOAc (10 mL) and

washed with water (10 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 10 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. The crude material was purified through HPLC to give (4S)-4-isopropyl-3-(2-(((1S)-1-(4-((5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one as a white solid (10 mg, 21.7% yield).

^{1}H NMR (400 MHz, MeOD) δ 8.07 (d, J = 5.8 Hz, 1H), 7.29 (d, J = 5.8 Hz, 1H), 7.25 – 7.20 (m, 4H), 5.00 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.31 – 4.23 (m, 2H), 3.55 – 3.48 (m, 2H), 2.68 (dh, J = 13.6, 4.3, 3.7 Hz, 2H), 2.64 – 2.48 (m, 4H), 2.36 – 2.29 (m, 4H), 2.28 (s, 4H), 1.84 (br s, 1H), 1.45 (d, J = 7.0 Hz, 3H), 0.68 (br s, 3H), 0.52 (br s, 3H); HRMS(B) m/z 465.2975 (M + H)+.

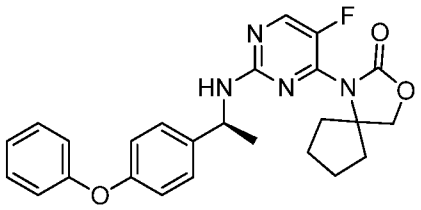
Example 211



A solution of 3-(2-fluoropyrimidin-4-yl)oxazolidin-2-one (89.1 mg, 0.487 mmol), 1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethanamine (115.9 mg, 0.518 mmol, 1.06 equiv), and DIPEA (0.20 mL, 1.1 mmol, 2.4 equiv) in DMSO (1.5 mL) was heated at 110 °C for 100 min. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (MeOH in CH_2Cl_2 0 to 5%) provided 3-(2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one (18.2 mg, white solid) in 10.3% yield.

^{1}H NMR (400 MHz, DMSO-d_6) 8.21 (br s, 1 H), 8.00 – 7.97 (m, 2 H), 7.65 – 7.61 (m, 2 H), 7.30 (br s, 1 H), 5,28 (br s, 1 H), 4.44 – 4.38 (br m, 2 H), 4.14 – 4.08 (m, 1 H), 3.99 (br s, 0.5 H), 3.75 (br s, 0.5 H), 1.64 (d, J = 7.0 Hz, 3 H); HRMS(B) *m/z* 387.0962 $(M + H)^+$

Example 212

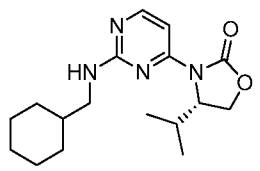
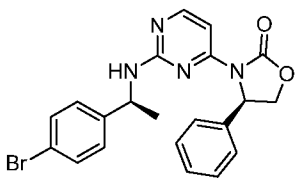
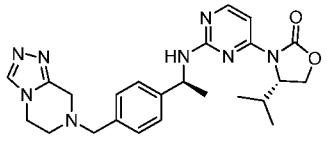


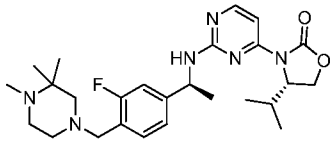
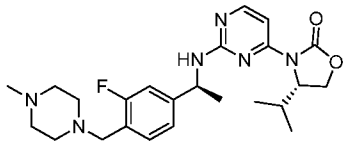
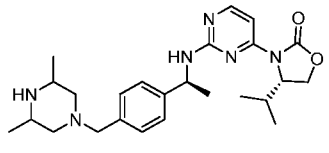
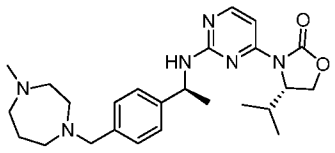
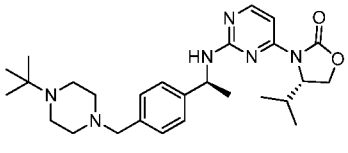
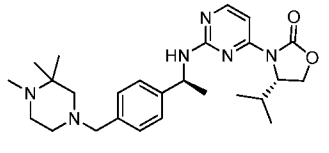
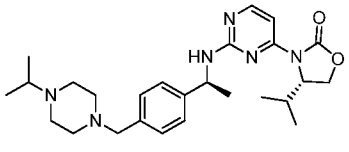
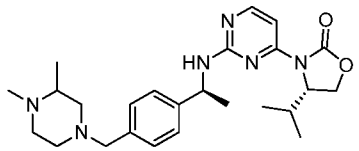
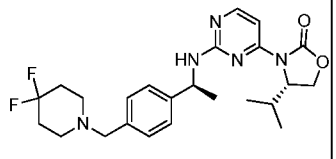
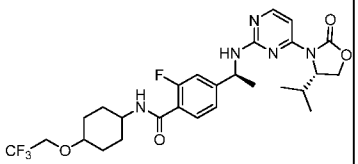
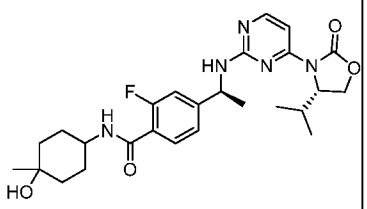
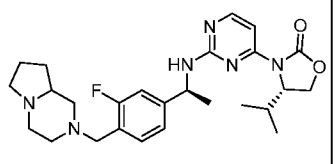
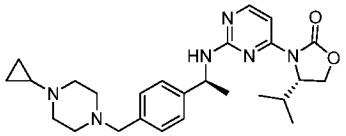
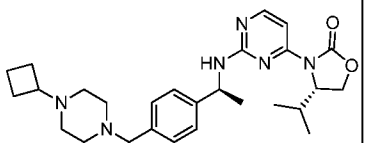
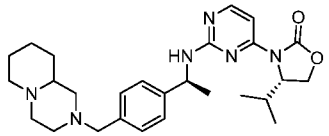
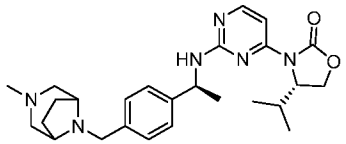
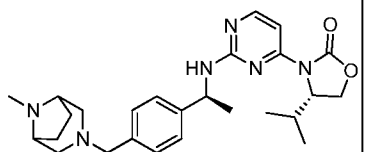
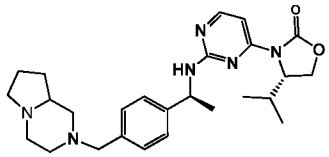
A solution of (S)-1-(4-phenoxyphenyl)ethanamine hydrochloride (281mg, 1.125mmol), 3-(2-chloro-5-fluoropyrimidin-4-yl)oxazolidin-2-one (103mg, 0.379mmol) and DIPEA (0.331ml, 1.896mmol) in DMSO was heated to 110°C for 1h. LCMS showed little product. Heated for an additional 16h. LCMS still showed starting material. Added an additional 5 equivalents of DIPEA and 1 equivalent of KF. Heated to 110°C for 2h. LCMS shows product. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Purified by column chromatography (10% to 50% EtOAc/Heptane) to give (S)-1-(5-fluoro-2-(1-(4-phenoxyphenyl)ethylamino) pyrimidin-4-yl)-3-oxa-1-azaspiro[4.4]nonan-2-one (62mg, 0.138mmol).

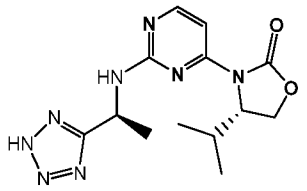
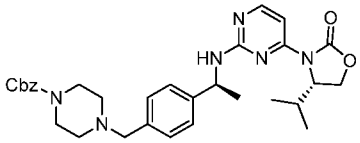
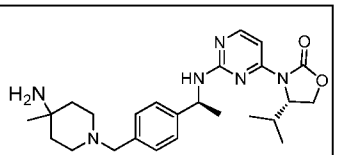
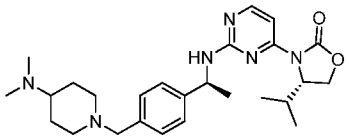
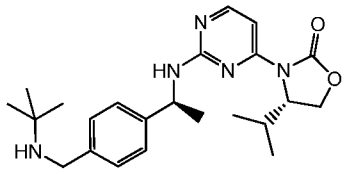
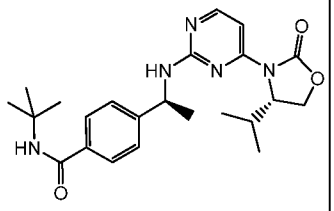
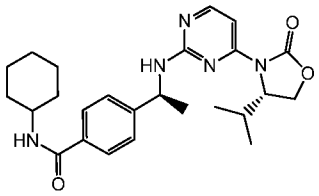
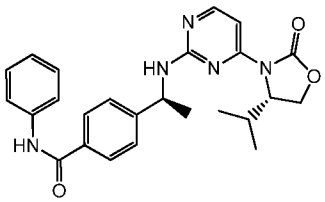
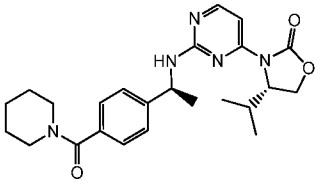
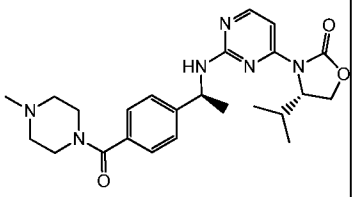
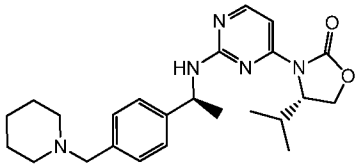
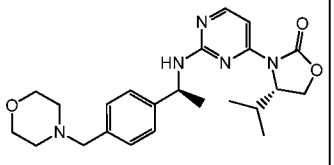
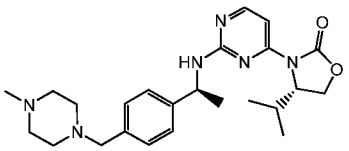
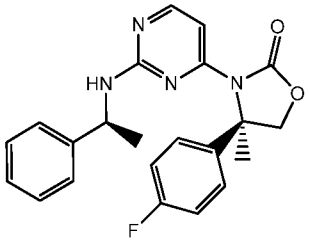
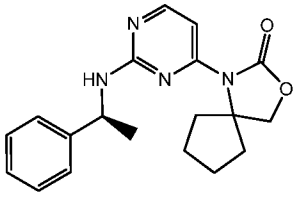
^{1}H NMR (400 MHz, MeOD) δ 8.25 (d, J = 2.8 Hz, 1H), 7.34 (ddd, J = 8.7, 4.9, 2.3 Hz, 4H), 7.16 – 7.04 (m, 1H), 7.02 – 6.90 (m, 4H), 4.96 (q, J = 7.0 Hz, 1H), 4.30 – 4.25 (m, 2H), 2.38 (dt, J = 13.1, 8.4 Hz, 1H), 2.02 (br s, 1H), 1.80 (ddd, J = 12.7, 7.3, 4.2 Hz, 1H), 1.71 – 1.63 (br m, 2H), 1.61 – 1.49 (m, 3H), 1.53 (d, J = 7.0 Hz, 3 H). HRMS(B) (M+H) 449.1984 Calc'd (M+H) 449.1989

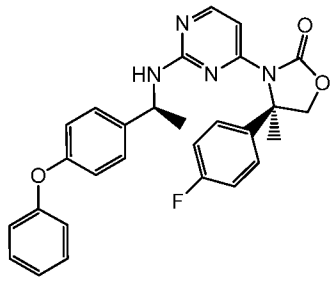
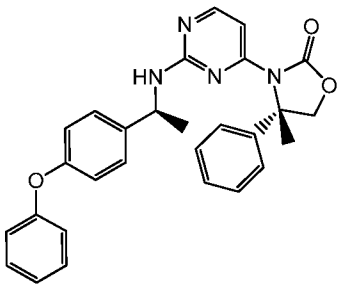
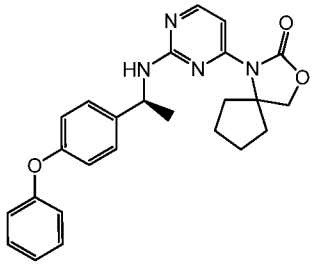
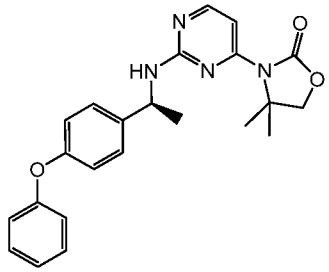
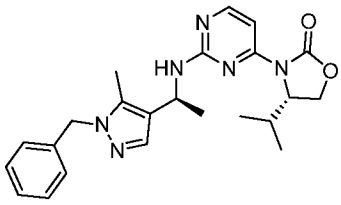
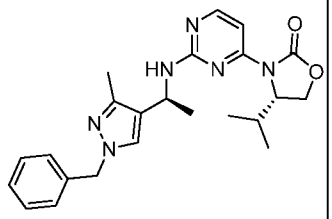
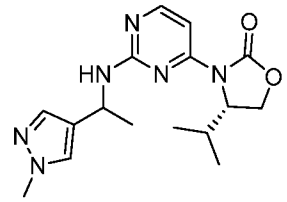
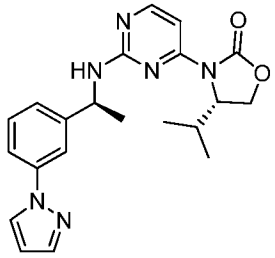
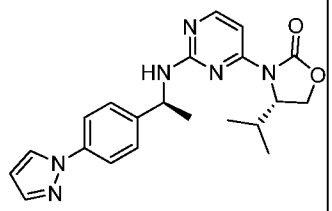
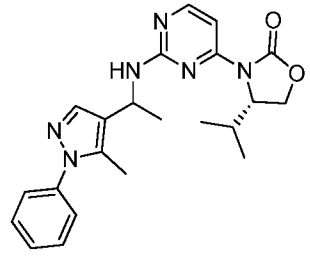
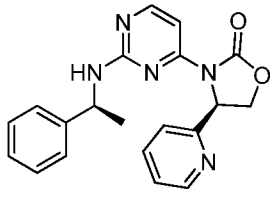
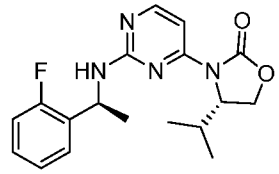
The compounds in Table 7 were prepared using methods substantially similar to those described for the preparation of Examples 1, 113, 211 and 212.

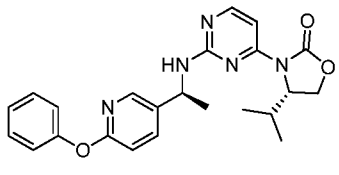
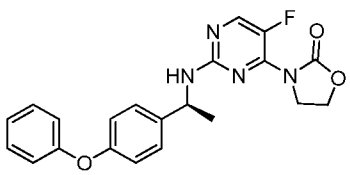
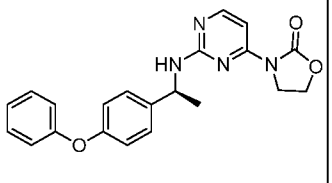
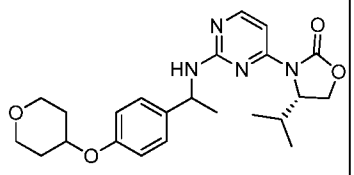
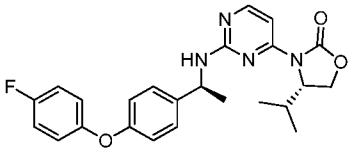
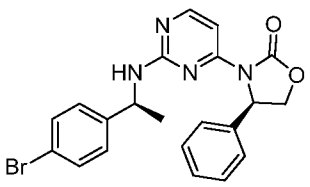
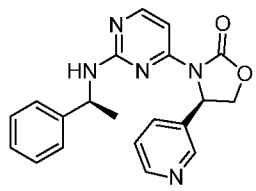
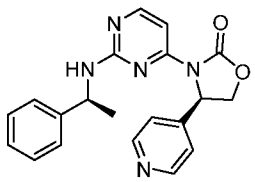
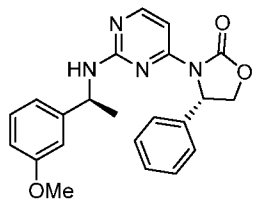
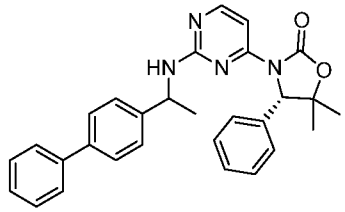
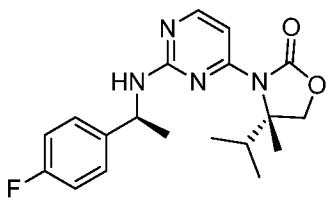
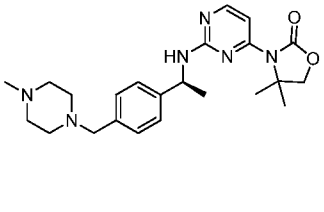
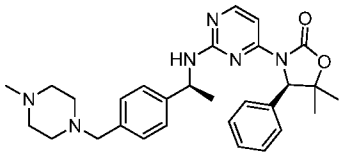
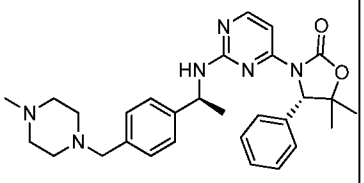
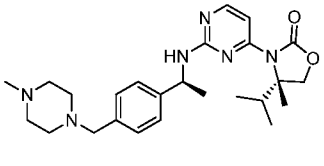
Table 7.

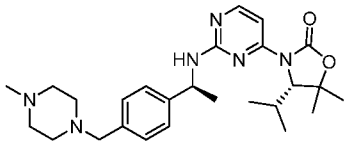
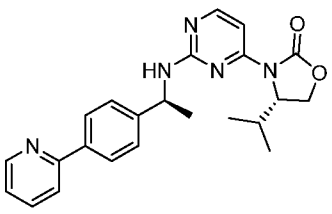
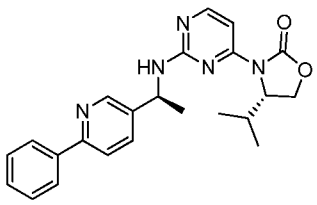
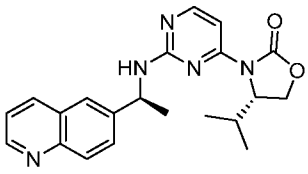
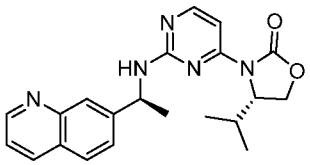
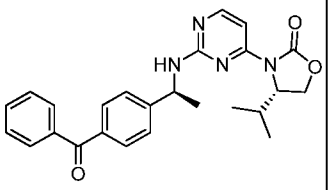
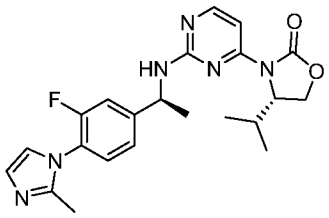
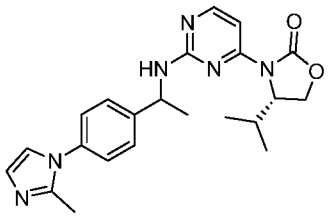
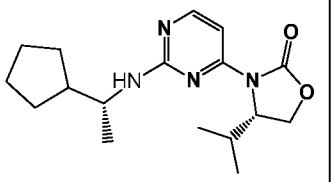
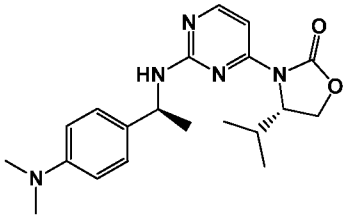
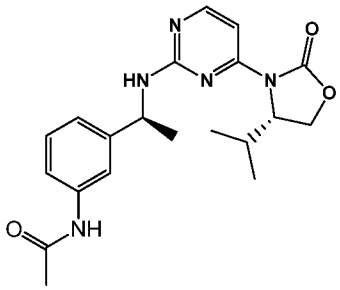
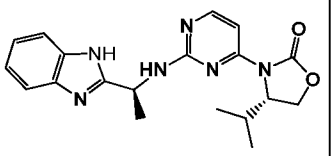
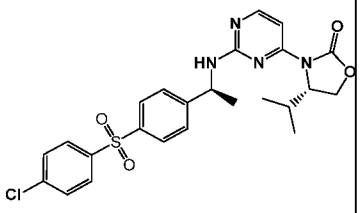
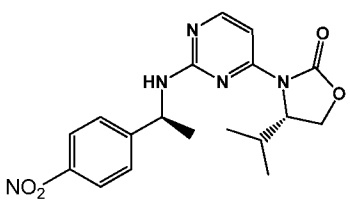
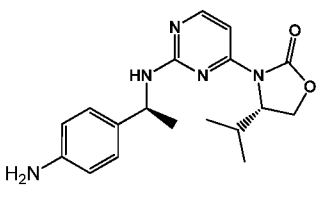
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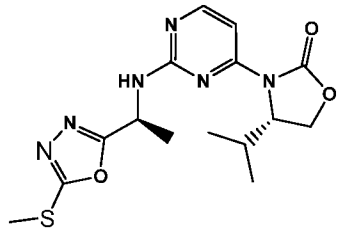
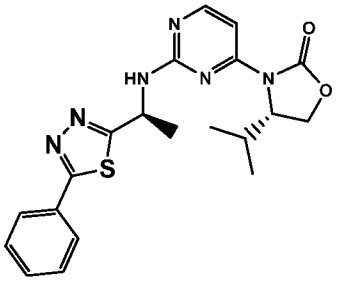
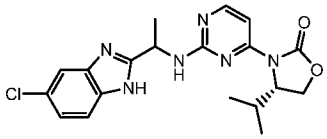
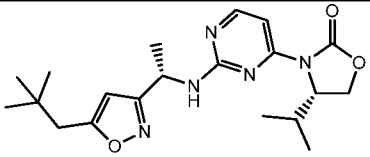
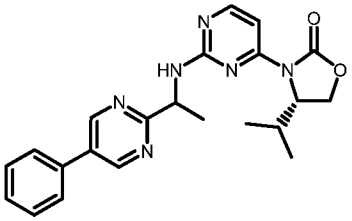
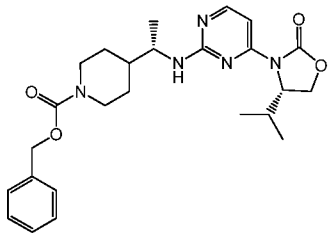
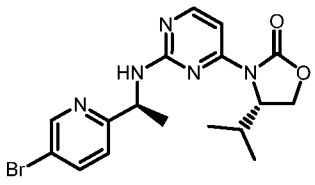
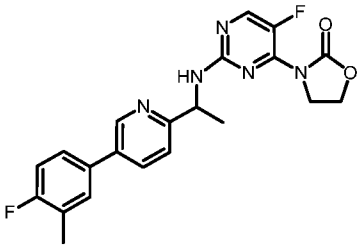
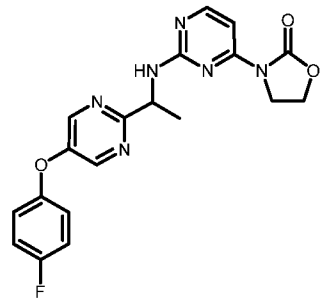
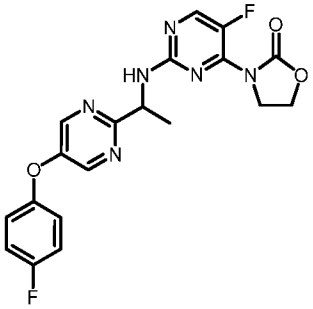
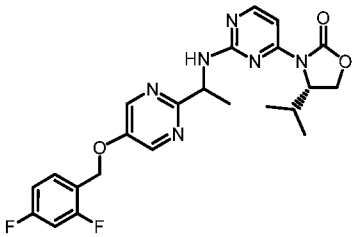
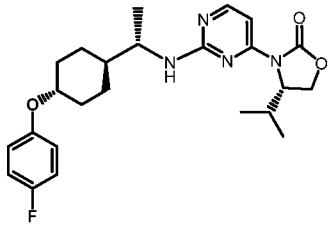
		
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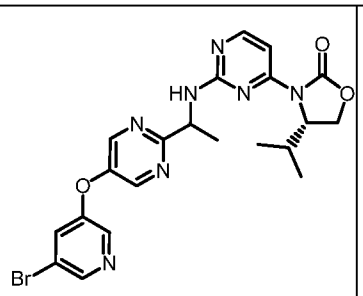
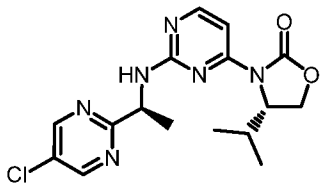
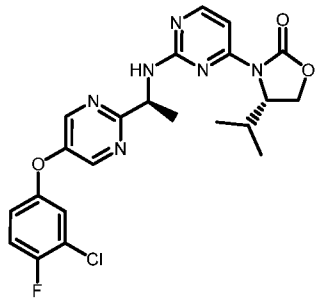
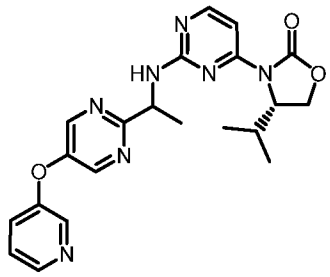
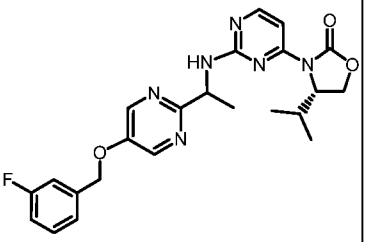
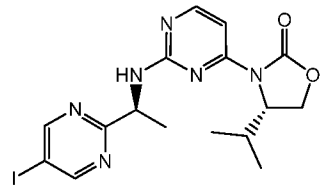
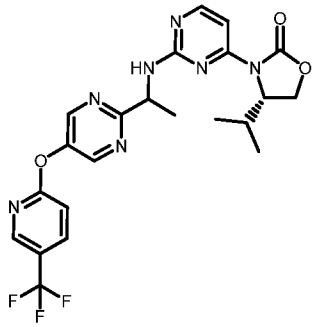
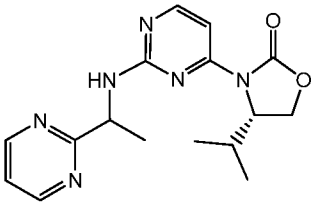
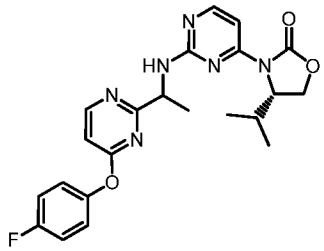
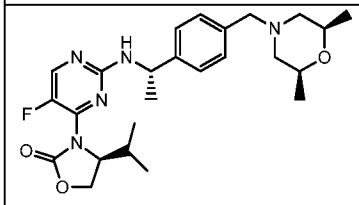
		
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Table 8. Chemical name, NMR chemical shifts and LCMS signal for each compound listed in Table 7.

Example: Name	^{1}H NMR **(400 MHz,** CD_3OD**) δ ppm (other solvents described)**	**LCMS**
213: (S)-3-(2-((cyclohexylmethyl)amino) pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.08 (d, J = 5.8 Hz, 1 H), 7.33 (d, J = 5.8 Hz, 1 H), 4.80 - 4.76 (m, 1 H), 4.42 - 4.37 (m, 2 H), 3.24 (dd, J = 13, 6.3 Hz, 1 H), 3.10 (dt, J = 13, 6.8 Hz, 1 H), 2.68 - 2.60 (m, 1 H), 1.82 - 1.56 (m, 7 H), 1.31 - 1.18 (m, 4 H), 0.98 (d, J = 7.1 Hz, 3 H), 0.87 (d, J = 7.0 Hz, 3 H);	HRMS(B) m/z 319.2132 (M + H)+
214: (R)-3-(2-(((S)-1-(4-bromophenyl)ethyl)amino) pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.46 (d, *J* = 5.8 Hz, 1H), 7.85 – 7.73 (m, 5H), 7.73 – 7.67 (m, 1H), 7.64 (dd, *J* = 7.1, 1.8 Hz, 2H), 7.58 – 7.52 (m, 2H), 5.92 (dd, *J* = 8.6, 4.0 Hz, 1H), 5.13 (t, *J* = 8.7 Hz, 1H), 4.98 (d, *J* = 7.0 Hz, 1H), 4.55 (dd, *J* = 8.7, 4.0 Hz, 1H), 1.58 (d, *J* = 7.0 Hz, 3H);	HRMS(B) *m/z* 439.0762 M^+
215: (S)-3-(2-(((S)-1-(4-((5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.38 (s, 1H), 8.07 (d, J = 5.9 Hz, 1H), 7.30 (d, J = 6.0 Hz, 1H), 7.28 (s, 4H), 5.03 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.31 – 4.23 (m, 2H), 4.08 (t, J = 5.5 Hz, 2H), 3.78 – 3.69 (m, 4H), 2.89 (td, J = 5.4, 2.1 Hz, 2H), 1.80 (br s, 1H), 1.46 (d, J = 7.0 Hz, 3H), 0.68 (br s, 3H), 0.53 (br s, 3H)	HRMS(B) m/z 463.2567 (M + H)+
216: (S)-3-(2-(((S)-1-(3-fluoro-4-((3,3,4-trimethylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.04 (d, J = 5.9 Hz, 1H), 7.36 – 7.15 (m, 2H), 7.02 (dd, J = 7.9, 1.8 Hz, 1H), 6.94 (dd, J = 11.0, 1.8 Hz, 1H), 4.95 (q, J = 7.0 Hz, 1H), 4.58 (br s, 1H), 4.32 – 4.11 (m, 2H), 3.38 (br s, 2H), 2.46 (br t, J = 4.9 Hz, 2H), 2.32 (br s, 2H), 2.14 (br s, 2 H), 2.10 (s, 3H), 1.73 (br s, 1H), 1.40 (d, J = 7.1 Hz, 3H), 0.95 (s, 3H), 0.95 (s, 3H), 0.63 (br s, 3H), 0.49 (br s, 3H)	HRMS(B) m/z 485.3107 (M + H)+
217: (S)-3-(2-(((S)-1-(3-fluoro-4-((4-methylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.09 (d, J = 6.0 Hz, 1H), 7.41 – 7.20 (m, 2H), 7.11 (dd, J = 7.8, 1.7 Hz, 1H), 7.04 (dd, J = 11.0, 1.8 Hz, 1H), 5.01 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.36 – 4.16 (m, 2H), 3.57 (s, 2H), 2.82 (br s, 4H), 2.60 (br s, 4H), 2.51 (s, 3H), 1.83 (br s, 1H), 1.45 (d, J = 7.1 Hz, 3H), 0.69 (s, 3H), 0.54 (s, 3H)	HRMS(B) m/z 457.2699 (M + H)+.
218: (4S)-3-(2-(((1S)-1-(4-((3,5-dimethylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.07 (d, J = 5.8 Hz, 1H), 7.30 (d, J = 5.8 Hz, 1H), 7.28 – 7.19 (m, 4H), 5.01 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.34 – 4.18 (m, 2H), 3.46 – 3.39 (m, 2H), 2.89 – 2.76 (m, 2H), 2.76 – 2.67 (m, 2H), 1.82 (br s, 1H), 1.59 (t, J = 10.9 Hz, 2H), 1.45 (d, J = 7.0 Hz, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.68 (br s, 3H), 0.52 (br s, 3H)	HRMS(B) m/z 453.2971 (M + H)+
219: (S)-4-isopropyl-3-(2-(((S)-1-(4-((4-methyl-1,4-diazepan-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-	8.07 (d, J = 5.8 Hz, 1H), 7.30 (d, J = 5.9 Hz, 1H), 7.28 – 7.24 (m, 4H), 5.02 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.35 – 4.22 (m, 2H), 3.67 – 3.59 (m, 2H), 3.09 – 3.07 (m, 2H), 2.99 (dd, J = 6.2, 3.5 Hz, 2H),	HRMS(B) m/z 453.2968 (M + H)+

yl)oxazolidin-2-one	2.79 – 2.77 (m, 2H), 2.72 (t, J = 6.0 Hz, 2H), 2.63 (s, 3H), 1.93 – 1.87 (m, 3H), 1.80 (br s, 1H), 1.45 (d, J = 7.0 Hz, 3H), 0.69 (br s, 3H), 0.54 (br s, 3H)	
220: (S)-3-(2-(((S)-1-(4-((4-(tert-butyl)piperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.07 (d, J = 5.9 Hz, 1H), 7.30 (d, J = 5.8 Hz, 1H), 7.24 (q, J = 8.2 Hz, 4H), 5.01 (q, J = 6.9 Hz, 1H), 4.63 (br s, 1H), 4.31 – 4.24 (m, 2H), 3.49 – 3.42 (m, 2H), 2.60 (br s, 4H), 2.46 (br s, 4H), 1.76 (br s, 1H), 1.45 (d, J = 7.0 Hz, 3H), 1.03 (s, 9H), 0.69 (s, 3H), 0.53 (s, 3H)	HRMS(B) m/z 481.3283 (M + H)+
221: (S)-4-isopropyl-3-(2-(((S)-1-(4-((3,3,4-trimethylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	8.08 (d, J = 5.8 Hz, 1H), 7.30 (d, J = 5.8 Hz, 1H), 7.26 – 7.18 (m, 4H), 5.01 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.31 – 4.24 (m, 2H), 3.37 (s, 2H), 2.54 (br t, J = 5.0 Hz, 2H), 2.38 (br s, 2H), 2.17 (s, 3H),2.14 (br s, 2H), 1.85 (br s, 1H), 1.45 (d, J = 7.0 Hz, 3H), 1.01 (s, 6H), 0.68 (br s, 3H), 0.53 (br s, 3H)	HRMS(B) m/z 467.3127 (M + H)+
222: (S)-4-isopropyl-3-(2-(((S)-1-(4-((4-isopropylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	8.07 (d, J = 5.8 Hz, 1H), 7.30 (d, J = 5.8 Hz, 1H), 7.24 (q, J = 8.3 Hz, 4H), 5.01 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.31 – 4.24 (m, 2H), 3.46 (s, 2H), 2.63 – 2.44 (m, 9H), 1.84 (br s, 1H), 1.45 (d, J = 7.1 Hz, 3H), 1.02 (d, J = 6.5 Hz, 6H), 0.68 (br s, 3H), 0.53 (br s, 3H)	HRMS(B) m/z 467.3120 (M + H)+
223: (4S)-3-(2-(((1S)-1-(4-((3,4-dimethylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.07 (d, J = 5.9 Hz, 1H), 7.30 (d, J = 5.8 Hz, 1H), 7.23 (q, J = 8.1 Hz, 4H), 5.01 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.35 – 4.20 (m, 2H), 3.51 – 3.35 (m, 2H), 2.82 – 2.61 (m, 3H), 2.36 – 2.24 (m, 1H), 2.23 (s, 3H), 2.20 – 2.08 (m, 2H), 1.89 – 1.80 (m, 2H), 1.45 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 6.3 Hz, 3H), 0.68 (br s, 3H), 0.52 (br s, 3H)	HRMS(B) m/z 453.2960 (M + H)+
224: (S)-3-(2-(((S)-1-(4-((4,4-difluoropiperidin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.08 (d, J = 5.8 Hz, 1H), 7.31 (d, J = 5.8 Hz, 1H), 7.25 (q, J = 8.2 Hz, 4H), 5.02 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.32 – 4.24 (m, 2H), 3.51 (s, 2H), 2.52 (br t, J = 5.8 Hz, 4H), 1.98 – 1.87 (m, 4H), 1.81 (br s, 1H), 1.46 (d, J = 7.0 Hz, 3H), 0.68 (br s, 3H), 0.52 (br s, 3H)	HRMS(B) m/z 460.2514 (M + H)+
225: 2-fluoro-4-((S)-1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)ethyl)-N-(4-(2,2,2-trifluoroethoxy)cyclohexyl)benzamide	8.09 (d, J = 5.7 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 5.8 Hz, 1H), 7.20 (dd, J = 7.9, 1.6 Hz, 1H), 7.13 (dd, J = 12.1, 1.7 Hz, 1H), 5.03 (q, J = 7.0 Hz, 1H), 4.61 (br s, 1H), 4.31 – 4.24 (m, 2H), 3.97 – 3.80 (m, 3H), 3.65 (dt, J = 4.7, 2.3 Hz, 1H), 1.90 (dt, J = 12.5, 4.0 Hz, 2H), 1.72 – 1.58 (m, 6H), 1.47 (d, J = 7.0 Hz, 3H), 0.68 (br s, 3H), 0.56 (br s, 3H)	HRMS(B) m/z 568.2549 (M + H)+
226: 2-fluoro-N-(4-hydroxy-4-methylcyclohexyl)-4-((S)-1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-	8.09 (d, J = 6.0 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 5.8 Hz, 1H), 7.20 (dd, J = 8.0, 1.6 Hz, 1H), 7.13 (dd, J = 12.0, 1.7 Hz, 1H), 5.03 (q, J = 7.0 Hz, 1H), 4.61 (br s, 1H), 4.31 – 4.25 (m, 2H), 3.89 (dt, J = 9.4,	HRMS(B) m/z 500.2589 (M + H)+

yl)pyrimidin-2-yl)amino)ethyl)benzamide	4.7 Hz, 1H), 1.95 – 1.82 (m, 2H), 1.75 – 1.49 (m, 7H), 1.47 (d, J = 7.0 Hz, 3H), 1.21 (s, 3H), 0.68 (br s, 3H), 0.56 (br s, 3H)	
227: (4S)-3-(2-(((1S)-1-(3-fluoro-4-((hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.09 (d, J = 5.8 Hz, 1H), 7.32 (d, J = 5.8 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.10 (dd, J = 7.9, 1.8 Hz, 1H), 7.03 (dd, J = 11.0, 1.8 Hz, 1H), 5.00 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.31 – 4.24 (m, 2H), 3.62 – 3.53 (m, 2H), 2.98 – 2.91 (m, 3H), 2.80 – 2.75 (m, 1H), 2.34 – 2.18 (m, 2H), 2.18 – 2.01 (m, 2H), 1.90 (t, J = 10.4 Hz, 1H), 1.83 – 1.65 (m, 4H), 1.45 (d, J = 7.0 Hz, 3H), 1.36 – 1.27 (m, 1H), 0.68 (br s, 3H), 0.54 (br s, 3H)	HRMS(B) m/z 483.2878 (M + H)+
228: (S)-3-(2-((S)-1-(4-((4-cyclopropylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.07 (d, J = 5.9 Hz, 1H), 7.30 (d, J = 5.8 Hz, 1H), 7.23 (q, J = 8.0 Hz, 4H), 5.01 (q, J = 7.0 Hz, 1H), 4.62 (br s, 1H), 4.35 – 4.19 (m, 2H), 3.45 (s, 2H), 2.62 (br s, 4H), 2.41 (br s, 4H), 1.79 (br s, 1H), 1.65 – 1.56 (m, 1H), 1.45 (d, J = 7.0 Hz, 3H), 0.67 (br s, 3H), 0.52 (br s, 3H), 0.45 – 0.38 (m, 2H), 0.38 – 0.29 (m, 2H)	HRMS(B) m/z 465.2975 (M + H)+
229: (S)-3-(2-((S)-1-(4-((4-cyclobutylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.08 (d, J = 7.2 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.47 – 7.24 (m, 4H), 5.28 – 5.06 (m, 1H), 4.66 (q, J = 4.8, 4.4 Hz, 1H), 4.34 (d, J = 5.7 Hz, 2H), 3.91 (s, 2H), 3.61 (p, J = 8.3 Hz, 1H), 3.20 (br s, 4H), 3.02 (br s, 4H), 2.32 – 2.04 (m, 4H), 1.90 – 1.66 (m, 3H), 1.52 (d, J = 7.0 Hz, 3H), 0.71 (d, J = 7.0 Hz, 3H), 0.54 (d, J = 6.7 Hz, 3H)	HRMS(B) m/z 479.3165 (M + H)+
230: (4S)-3-(2-((1S)-1-(4-((dihydro-1H-pyrido[1,2-a]pyrazin-2(6H,7H,8H,9H,9aH)-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.07 (d, J = 5.8 Hz, 1H), 7.34 – 7.19 (m, 5H), 5.01 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.33 – 4.22 (m, 2H), 3.49 – 3.39 (m, 2H), 2.83 – 2.71 (m, 2H), 2.66 (dq, J = 11.0, 2.2 Hz, 2H), 2.32 – 2.14 (m, 2H), 2.09 – 1.94 (m, 2H), 1.82 (t, J = 10.8 Hz, 1H), 1.70 (dt, J = 12.4, 3.5 Hz, 1H), 1.64 – 1.50 (m, 2H), 1.48 – 1.39 (m, 5H), 1.35 – 1.21 (m, 1H), 1.14 (tdd, J = 13.0, 10.8, 3.6 Hz, 1H), 0.68 (br s, 3H), 0.52 (br s, 3H)	HRMS(B) m/z 479.3131 (M + H)+
231: (4S)-4-isopropyl-3-(2-((1S)-1-(4-((3-methyl-3,8-diazabicyclo[3.2.1]octan-8-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.07 (d, J = 5.9 Hz, 1H), 7.36 – 7.21 (m, 5H), 5.01 (q, J = 7.0 Hz, 1H), 4.62 (br s, 1H), 4.33 – 4.21 (m, 2H), 3.45 (s, 2H), 3.07 (qd, J = 4.6, 4.2, 1.9 Hz, 2H), 2.63 – 2.50 (m, 2H), 2.25 (ddd, J = 10.7, 4.4, 1.8 Hz, 2H), 2.15 (s, 3H), 2.04 – 1.93 (m, 2H), 1.83 – 1.72 (m, 3H), 1.45 (d, J = 7.0 Hz, 3H), 0.67 (br s, 3H), 0.51 (br s, 3H)	HRMS(B) m/z 465.2964 (M + H)+
232: (4S)-4-isopropyl-3-(2-((1S)-1-(4-((8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.17 (d, J = 5.7 Hz, 1H), 7.42 (d, J = 5.7 Hz, 1H), 7.23 (s, 4H), 5.46 (br s, 1H), 5.01 (br s, 1H), 4.60 (dt, J = 6.9, 3.3 Hz, 1H), 4.28 (t, J = 8.7 Hz, 1H), 4.21 (dd, J = 9.1, 3.1 Hz, 1H), 3.42 (d, J = 1.7 Hz, 2H), 3.10 – 2.96 (m, 2H), 2.58 – 2.48 (m, 2H), 2.33 – 2.18 (m, 5H), 2.06 – 1.84 (m, 3H),	HRMS(B) m/z 465.2963 (M + H)+

	1.81 (dd, J = 7.8, 4.4 Hz, 2H), 1.52 (d, J = 6.8 Hz, 3H), 0.71 (br s, 3H), 0.64 (br s, 3H)	
233: (4S)-3-(2-((1S)-1-(4-((hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1H), 7.34 (d, J = 5.8 Hz, 1H), 7.33 – 7.24 (m, 4H), 5.05 (q, J = 7.0 Hz, 1H), 4.67 (br s, 1H), 4.38 – 4.26 (m, 2H), 3.64 – 3.49 (m, 2H), 3.11 – 3.00 (m, 2H), 2.96 (br d, J = 11.0 Hz, 1H), 2.83 (br d, J = 11.2 Hz, 1H), 2.45 – 2.34 (m, 1H), 2.32– 2.25 (m, 3H), 1.94 (t, J = 10.5 Hz, 1H), 1.88 – 1.77 (m, 4H), 1.49 (d, J = 7.0 Hz, 3H), 1.47 – 1.35 (m, 1H), 0.72 br (s, 3H), 0.56 (br s, 3H)	HRMS(B) m/z 465.2972 (M + H)+
234: (S)-3-(2-(((S)-1-(2H-tetrazol-5-yl) ethyl) amino) pyrimidin-4-yl)-4-isopropyloxazolidin-2-one		HRMS(B) m/z 319.1624 (M+H)+, RT=1.33 min.
235: benzyl 4-(4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzyl)piperazine-1-carboxylate	8.07 (d, J = 5.8 Hz, 1H), 7.34 – 7.18 (m, 10H), 5.05 (s, 2H), 5.01 (q, J = 6.9 Hz, 1H), 4.62 (br s, 1H), 4.32 – 4.18 (m, 2H), 3.49 – 3.34 (m, 4H), 3.46 (s, 2H), 2.36 (t, J = 5.1 Hz, 4H), 1.75 (br s, 1H), 1.45 (d, J = 7.0 Hz, 3H), 0.66 (br s, 3H), 0.50 (br s, 3H)	HRMS(B) m/z 559.3026 (M + H)+
236: (S)-3-(2-((S)-1-(4-((4-amino-4-methylpiperidin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.07 (d, J = 5.8 Hz, 1H), 7.30 (d, J = 5.8 Hz, 1H), 7.27 – 7.21 (m, 4H), 5.01 (q, J = 7.0 Hz, 1H), 4.63 (br s, 1H), 4.34 – 4.18 (m, 2H), 3.53 – 3.40 (m, 2H), 2.59 – 2.21 (br m, 4H), 1.78 (br s, 1H), 1.52 (ddt, J = 11.8, 8.7, 5.2 Hz, 4H), 1.45 (d, J = 7.0 Hz, 3H), 1.07 (s, 3H), 0.67 (br s, 3H), 0.51 (br s, 3H)	HRMS(B) m/z 453.2972 (M + H)+
237: (S)-3-(2-((S)-1-(4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) 8.17 (d, J = 5.7 Hz, 1H), 7.42 (d, J = 5.7 Hz, 1H), 7.25 (d, J = 8.2 Hz, 4H), 5.43 (br s, 1H), 5.01 (br s, 1H), 4.60 (dt, J = 8.6, 3.3 Hz, 1H), 4.28 (t, J = 8.7 Hz, 1H), 4.21 (dd, J = 9.1, 3.2 Hz, 1H), 3.44 (s, 2H), 2.89 (dp, J = 11.5, 2.8 Hz, 2H), 2.26 (s, 6H), 2.11 (tt, J = 11.3, 3.6 Hz, 1H), 1.93 (td, J = 11.9, 2.4 Hz, 2H), 1.90 (br s, 1H), 1.75 (dq, J = 12.0, 2.8 Hz, 2H), 1.60 – 1.43 (m, 2H), 1.53 (d, J = 6.8 Hz, 3H), 0.70 (br s, 3H), 0.63 (br s, 3H)	HRMS(B) m/z 467.3121 (M + H)+
238: (S)-3-(2-((S)-1-(4-((tert-butylamino)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) δ 8.18 (dd, J = 5.8, 1.3 Hz, 1H), 7.44 (dd, J = 5.7, 1.2 Hz, 1H), 7.37 – 7.22 (m, 5H), 5.52 (br s, 1H), 5.15 – 4.95 (m, 1H), 4.70 – 4.55 (m, 1H), 4.30 (td, J = 8.8, 2.1 Hz, 1H), 4.23 (dd, J = 9.1, 3.0 Hz, 1H), 3.71 (d, J = 2.0 Hz, 2H), 2.06 (s, 1H), 1.54 (dd, J = 7.1, 1.9 Hz, 3H), 1.18 (sm, 9H), 0.85 – 0.59 (m, 6H);	HRMS(B) m/z 412.2701 (M + H)+
239: N-tert-butyl-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-	($CDCl_3$) δ 8.16 (dd, J = 5.8, 1.2 Hz, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.43 (dd, J = 5.8, 0.9 Hz, 1H), 7.35 (d, J = 7.9 Hz, 2H), 5.88 (s, 1H), 5.57 (br s, 1H), 5.04 (br s, 1H),	HRMS(B) m/z 426.2488 (M + H)+

ylamino)ethyl)benzamide	4.55 (br s, 1H), 4.26 (t, J = 8.7 Hz, 1H), 4.19 (dd, J = 9.2, 3.2 Hz, 1H), 1.53 (d, J = 6.9 Hz, 3H), 1.45 (s, 9H), 0.64 (m, 6H)	
240: N-cyclohexyl-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide	($CDCl_3$) δ 8.17 (d, J = 5.7 Hz, 1H), 7.69 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 5.8 Hz, 1H), 7.36 (d, J = 7.9 Hz, 2H), 5.91 (d, J = 8.3 Hz, 1H), 5.51 (br s, 1H), 5.04 (br s, 1H), 4.53 (br s, 1H), 4.26 (t, J = 8.7 Hz, 1H), 4.19 (dd, J = 9.1, 3.2 Hz, 1H), 4.04 – 3.89 (m, 1H), 2.07 – 1.95 (m, 2H), 1.74 (dp, J = 11.5, 3.8 Hz, 2H), 1.64 (tt, J = 7.4, 3.7 Hz, 2H), 1.54 (d, J = 6.9 Hz, 3H), 1.42 (qt, J = 12.4, 3.5 Hz, 2H), 1.30 – 1.17 (m, 3H), 0.64 (br s, 6H)	HRMS(B) m/z 452.2640 (M + H)+
241: 4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)-N-phenylbenzamide	($CDCl_3$) δ 8.19 (d, J = 5.8 Hz, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.77 (s, 1H), 7.68 – 7.59 (m, 2H), 7.48 – 7.41 (m, 3H), 7.37 (dd, J = 8.5, 7.3 Hz, 2H), 7.22 – 7.11 (m, 1H), 5.48 (br s, 1H), 5.08 (br s, 1H), 4.56 (br s, 1H), 4.27 (t, J = 8.7 Hz, 1H), 4.20 (dd, J = 9.2, 3.2 Hz, 1H), 1.57 (t, J = 5.6 Hz, 3H), 0.65 (br s, 6H);	HRMS(B) m/z 446.2170 (M + H)+
242: (S)-4-isopropyl-3-(2-((S)-1-(4-(piperidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) δ 8.18 (d, J = 5.7 Hz, 1H), 7.45 (d, J = 5.7 Hz, 1H), 7.33 (s, 4H), 5.45 (br s, 1H), 5.05 (br s, 1H), 4.59 (dt, J = 7.3, 2.9 Hz, 1H), 4.27 (t, J = 8.7 Hz, 1H), 4.21 (dd, J = 9.1, 3.2 Hz, 1H), 3.51 (d, J = 141.8 Hz, 4H), 1.60 (dd, J = 52.4, 5.9 Hz, 10H), 0.68 (d, J = 25.5 Hz, 6H);	HRMS(B) m/z 438.2492 (M + H)+
243: (S)-4-isopropyl-3-(2-((S)-1-(4-(4-methylpiperazine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) δ 8.18 (d, J = 5.7 Hz, 1H), 7.45 (d, J = 5.7 Hz, 1H), 7.35 (s, 4H), 5.42 (br s, 1H), 5.05 (br s, 1H), 4.58 (br s, 1H), 4.28 (t, J = 8.8 Hz, 1H), 4.21 (dd, J = 9.2, 3.1 Hz, 1H), 3.78 (br s, 2H), 3.44 (br s, 2H), 2.53 – 2.39 (m, 2H), 2.32 (s, 4H), 1.65 (m, 2H), 1.53 (d, J = 6.9 Hz, 3H), 0.82 – 0.50 (m, 6H)	HRMS(B) m/z 453.2611 (M + H)+
244: (S)-4-isopropyl-3-(2-((S)-1-(4-(piperidin-1-ylmethyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) δ 8.16 (d, J = 5.7 Hz, 1H), 7.42 (d, J = 5.7 Hz, 1H), 7.24 (s, 4H), 5.58 (br s, 1H), 5.15 – 4.85 (m, 1H), 4.60 (dt, J = 8.4, 3.4 Hz, 1H), 4.27 (t, J = 8.7 Hz, 1H), 4.20 (dd, J = 9.1, 3.2 Hz, 1H), 3.43 (s, 2H), 2.54 – 2.22 (m, 4H), 1.99 (br s, 1H), 1.61 – 1.48 (m, 7H), 1.42 (q, J = 6.6, 6.0 Hz, 2H), 0.86 – 0.41 (m, 6H);	HRMS(B) m/z 424.2704 (M + H) +
245: (S)-4-isopropyl-3-(2-((S)-1-(4-(morpholinomethyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) δ 8.18 (d, J = 5.7 Hz, 1H), 7.45 (d, J = 5.7 Hz, 1H), 7.28 (s, 4H), 5.56 (br s, 1H), 5.16 – 4.94 (m, 1H), 4.63 (dt, J = 7.6, 3.5 Hz, 1H), 4.30 (t, J = 8.8 Hz, 1H), 4.23 (dd, J = 9.0, 3.1 Hz, 1H), 3.72 (t, J = 4.6 Hz, 4H), 3.49 (s, 2H), 2.45 (t, J = 4.6 Hz, 4H), 2.19 – 1.82 (m, 1H), 1.55 (d, J = 6.9 Hz, 3H), 0.90 – 0.46 (m, 6H);	HRMS(B) m/z 426.2487 (M + H) +
246: (S)-4-isopropyl-3-(2-((S)-1-(4-((4-	($CDCl_3$) δ 8.17 (d, J = 5.8 Hz, 1H), 7.43 (d, J = 5.8 Hz, 1H), 7.27 (d, J = 6.2 Hz, 4H),	HRMS(B) m/z

methylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	5.52 (br s, 1H), 5.03 (br s, 0H), 4.62 (dt, J = 8.5, 3.4 Hz, 1H), 4.29 (t, J = 8.7 Hz, 1H), 4.22 (dd, J = 9.1, 3.2 Hz, 1H), 3.48 (s, 2H), 2.46 (br s, 9H), 2.30 (s, 3H), 1.54 (d, J = 6.9 Hz, 3H), 0.97 – 0.57 (m, 6H);	439.2801 (M + H) +
247: (R)-4-(4-fluorophenyl)-4-methyl-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) δ 8.18 (d, J = 5.8 Hz, 1 H), 7.41 (d, J = 5.8 Hz, 1 H), 7.33 – 7.29 (m, 2 H), 7.25 – 7.20 (m, 3 H), 7.15 – 7.06 (m, 4 H), 5.17 (br s, 1 H), 4.21 (br s, 1 H), 4.20 – 4.15 (m, 2 H), 1.61 (s, 3 H), 1.21 (d, J = 7.1 Hz, 3 H)	HRMS(B) m/z 393.1726 (M + H)+.
248: (S)-1-(2-(1-phenylethylamino)pyrimidin-4-yl)-3-oxa-1-azaspiro[4.4]nonan-2-one	($CDCl_3$) δ 8.19 (d, J = 5.8 Hz, 1 H), 7.37 – 7.33 (m, 4 H), 7.29 – 7.24 (m, 2 H), 5.39 (br s, 1 H), 5.12 – 5.05 (m, 1 H), 4.09 – 4.05 (m, 2 H), 2.83 – 2.75 (m, 1 H), 2.35 (br s, 1 H), 1.95 – 1.86 (m, 1 H), 1.71 (br s, 1 H), 1.67 – 1.61 (m, 2 H), 1.58 (d, J = 7.0 Hz, 3 H), 1.45 (br s, 2 H)	HRMS(B) m/z 339.1805 (M + H)+
249: (R)-4-(4-fluorophenyl)-4-methyl-3-(2-((S)-1-(4-phenoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) δ 8.18 (d, J = 5.8 Hz, 1 H), 7.42 (d, J = 5.8 Hz, 1 H), 7.38 – 7.33 (m, 2 H), 7.26 – 7.22 (m, 2 H), 7.14 – 7.06 (m, 5 H), 7.00 – 6.94 (m, 4 H), 5.21 (br s, 1 H), 4.23 – 4.17 (m, 3 H), 1.71 (br s, 3 H), 1.20 (d, J = 6.8 Hz, 3 H)	HRMS(B) m/z 485.1979 (M + H)+
250: (S)-4-methyl-3-(2-((S)-1-(4-phenoxyphenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	($CDCl_3$) δ 8.17 (dd, J = 5.9, 1.1 Hz, 1H), 7.47 – 7.23 (m, 8H), 7.16 – 7.05 (m, 3H), 7.02 – 6.91 (m, 4H), 5.10 (br s, 1H), 4.22 (s, 2H), 1.73 (s, 3H), 1.67 – 1.53 (m, 1H), 1.14 (d, J = 7.0 Hz, 3H);	HRMS(B) m/z 467.2065 (M + H) +
251: (S)-1-(2-(1-(4-phenoxyphenyl)ethylamino)pyrimidin-4-yl)-3-oxa-1-azaspiro[4.4]nonan-2-one	($CDCl_3$) δ 8.19 (d, J = 5.8 Hz, 1 H), 7.37 – 7.28 (m, 5 H), 7.13 – 7.09 (m, 1 H), 7.01 – 6.96 (m, 4 H), 5.47 (br s, 1 H), 5.12 – 5.05 (m, 1 H), 4.11 – 4.07 (m, 2 H), 2.84 – 2.76 (m, 1 H), 2.42 (br s, 1 H), 1.97 – 1.88 (m, 1 H), 1.77 (br s, 1 H), 1.68 – 1.61 (m, 2 H), 1.58 (d, J = 6.9 Hz, 3 H), 1.54 – 1.46 (m, 2 H)	HRMS(B) m/z 431.2073 (M + H)+
252: (S)-4,4-dimethyl-3-(2-(1-(4-phenoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) δ 8.19 (d, J = 5.8 Hz, 1H), 7.38 – 7.26 (m, 5H), 7.11 (tt, J = 7.4, 1.1 Hz, 1H), 7.01 – 6.94 (m, 4H), 5.37 (br s, 1H), 5.01 (d, J = 9.1 Hz, 1H), 4.09 – 3.93 (m, 2H), 1.71 (s, 3H), 1.57 (d, J = 6.9 Hz, 3H), 1.28 (m, 3H);	MS m/z 405.1 (M + H) +
253: (S)-3-(2-(((S)-1-(1-benzyl-5-methyl-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.49 (d, J = 5.7 Hz, 1H), 7.84 – 7.38 (m, 7H), 5.65 (s, 1.2H), 5.55 (s, 0.8H), 5.43 (dq, J = 8.9, 6.9 Hz, 1H), 5.11 (tt, J = 6.1, 3.6 Hz, 1H), 4.79 – 4.60 (m, 2H), 2.76 (dtt, J = 22.3, 7.2, 3.5 Hz, 1H), 2.56 (2s, 3H), 1.87 (2d, J =6.9 Hz, 3H), 1.22 (2d, J = 7.1 Hz, 3H), 1.13 (dd, J = 6.9 Hz, 3H)	HRMS(B) (M+H) 421.2338
254: (S)-3-(2-(((S)-1-(1-benzyl-3-methyl-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-	8.14 (d, J = 5.8 Hz, 1H), 7.50 (s, 1H), 7.38 (d, J = 5.8 Hz, 1H), 7.36 – 7.25 (m, 3H), 7.24 – 7.17 (m, 2H), 5.21 (s, 2H), 5.06 (q, J = 6.9 Hz, 1H), 4.76 (dt, J = 7.5, 3.9 Hz, 1H), 4.42 – 4.32 (m, 2H), 2.38 (br s, 1H),	HRMS(B) (M+H) 421.2340

2-one	2.22 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H).	
255: (4S)-4-isopropyl-3-(2-(1-(1-methyl-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	^{1}H NMR (400 MHz, MeOD) δ 8.16 (d, J = 5.8 Hz, 0.5H), 8.14 (d, J = 5.8 Hz, 0.5H), 7.54 (s, 0.5H), 7.48 (s, 0.5H), 7.44 (s, 0.5H), 7.40 (d, J = 2.0 Hz, 0.5H), 7.38 (d, J = 2.0 Hz, 0.5H), 7.38 (s, 0.5H), 5.11 (q, J = 6.9 Hz, 1H), 4.75 (dq, J = 9.4, 3.7 Hz, 1H), 4.46 – 4.29 (m, 2H), 3.85 (d, J = 5.5 Hz, 3H), 2.62 (ddq, J = 10.4, 7.0, 3.5 Hz, 0.5H), 2.40 (br s, 0.5H), 1.53 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 7.1 Hz, 1.5H), 0.88 (d, J = 7.1 Hz, 1.5H), 0.86 (d, J = 7.0 Hz, 1.5H), 0.78 (d, J = 7.0 Hz, 1.5H). HRMS(B) (M+H) 421.2340 Calc'd (M+H) 421.2352	HRMS(B) (M+H) 421.2340
256: (S)-3-(2-((S)-1-(3-(1H-pyrazol-1-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.20 (d, J = 2.5 Hz, 1H), 8.16 (d, J = 5.8 Hz, 1H), 7.75 (t, J = 2.0 Hz, 1H), 7.72 (d, J = 1.8 Hz, 1H), 7.58 (ddd, J = 8.0, 2.2, 1.0 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.37 (d, J = 5.8 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 6.56 – 6.49 (m, 1H), 5.13 (q, J = 7.0 Hz, 1H), 4.66 (br s, 1H), 4.39 – 4.19 (m, 2H), 1.82 (br s, 1H), 1.58 (d, J = 7.0 Hz, 3H), 0.56 (br s, 6H).	HRMS(B) (M+H) 393.2036
257: (S)-3-(2-((S)-1-(4-(1H-pyrazol-1-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.18 (d, J = 2.5 Hz, 1H), 8.16 (d, J = 5.8 Hz, 1H), 7.72 (d, J = 1.8 Hz, 1H), 7.69 (d, J = 1.9 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.37 (d, J = 5.8 Hz, 1H), 6.56 – 6.49 (m, 1H), 5.11 (q, J = 7.1 Hz, 1H), 4.68 (s, 1H), 4.40 – 4.24 (m, 2H), 1.86 (s, 1H), 1.57 (d, J = 7.1 Hz, 3H), 0.71 (s, 3H), 0.59 (s, 3H).	HRMS(B) (M+H) 393.2050
258: (4S)-4-isopropyl-3-(2-(1-(5-methyl-1-phenyl-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.17 (dd, J = 5.8, 4.6 Hz, 1H), 7.67 (s, 0.5H), 7.61 (s, 0.5H), 7.55 (dd, J = 8.5, 6.7 Hz, 2H), 7.52 – 7.47 (m, 1H), 7.44 (ddd, J = 8.1, 3.3, 1.4 Hz, 2H), 7.40 (d, J = 5.8 Hz, 1H), 5.17 (dq, J = 10.4, 6.9 Hz, 1H), 4.83 – 4.77 (m, 1H), 4.45 – 4.34 (m, 2H), 2.66 (td, J = 7.0, 3.5 Hz, 0.5H), 2.45 (br s, 0.5H), 2.32 (s, 1.5H), 2.31 (s, 1.5H), 1.59 (dd, J = 6.8, 1.7 Hz, 3H), 1.01 (d, J = 7.0 Hz, 1.5H), 0.94 – 0.85 (m, 3H), 0.81 (d, J = 6.9 Hz, 1.5H).	HRMS(B) (M+H) 407.2202
259: (R)-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)-4-(pyridin-2-yl)oxazolidin-2-one	8.60 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.10 (d, J = 5.7 Hz, 1H), 7.89 (td, J = 7.7, 1.8 Hz, 1H), 7.46 – 7.36 (m, 3H), 7.33 – 7.28 (m, 4H), 7.21 (ddd, J = 8.6, 5.5, 2.2 Hz, 1H), 5.66 (br s, 1H), 4.79 (t, J = 8.9 Hz, 1H), 4.60 (br s, 1H), 4.31 (dd, J = 8.9, 3.8 Hz, 1H), 1.22 (d, J = 6.6 Hz, 3H).	HRMS(B) (M+H) 362.1617
260: (S)-3-(2-((S)-1-(2-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-	8.51 (d, J = 5.7 Hz, 1H), 7.76 – 7.51 (m, 3H), 7.48 – 7.37 (m, 2H), 5.71 (q, J = 7.0 Hz, 1H), 5.06 – 5.02 (m, 1H), 4.75 – 4.61	HRMS(B) (M+H) 393.2026

isopropyloxazolidin-2-one	(m, 2H), 2.30 (br s, 1H), 1.89 (d, J = 7.0, 3H), 1.10 (d, J = 7.1 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H).	
261: (S)-4-isopropyl-3-(2-((S)-1-(6-phenoxypyridin-3-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.25 – 8.05 (m, 2H), 7.83 (dd, J = 8.6, 2.5 Hz, 1H), 7.50 – 7.34 (m, 3H), 7.27 – 7.16 (m, 1H), 7.15 – 7.02 (m, 2H), 6.89 (d, J = 8.5 Hz, 1H), 5.10 (q, J = 7.1 Hz, 1H), 4.75 – 4.61 (m, 1H), 4.41 – 4.29 (m, 2H), 1.94 (br s, 1H), 1.56 (d, J = 7.1 Hz, 3H), 0.78 (br s, 3H), 0.70 (br s, 3H).	HRMS(B) (M+H) 420.2019
262: (S)-3-(5-fluoro-2-(1-(4-phenoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.16 (d, J = 3.5 Hz, 1H), 7.45 – 7.28 (m, 4H), 7.09 (tt, J = 7.3, 1.1 Hz, 1H), 7.02 – 6.89 (m, 4H), 4.99 (q, J = 6.9 Hz, 1H), 4.58 – 4.48 (m, 2H), 4.18 (ddd, J = 9.7, 8.5, 7.2 Hz, 1H), 3.99 (br s, 1H), 1.52 (d, J = 6.9 Hz, 3H).	HRMS(B) (M+H) 395.1507
263: (S)-3-(2-(1-(4-phenoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.09 (d, J = 5.8 Hz, 1H), 7.43 – 7.29 (m, 5H), 7.09 (tt, J = 7.3, 1.1 Hz, 1H), 7.00 – 6.90 (m, 4H), 5.07 (q, J = 7.0 Hz, 1H), 4.53 – 4.41 (m, 2H), 4.21 (ddd, J = 10.5, 9.2, 7.0 Hz, 1H), 4.01 (br s, 1H), 1.53 (d, J = 7.0 Hz, 3H).	HRMS(B) (M+H) 377.1600
264: (4S)-4-isopropyl-3-(2-((1-(4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (dd, J = 8.5, 5.8 Hz, 1H), 7.35 (dd, J = 5.8, 1.0 Hz, 1H), 7.32 – 7.19 (m, 2H), 6.95 – 6.86 (m, 2H), 4.98 (dq, J = 25.6, 7.2 Hz, 1H), 4.68 (br s, 0.5H), 4.59 – 4.48 (m, 1.5H), 4.39 – 4.25 (m, 2H), 4.01 – 3.90 (m, 2H), 3.65 – 3.53 (m, 2H), 2.74 – 2.61 (m, 0.5H), 2.08 – 1.96 (m, 2H), 1.95 (br s, 0.5H), 1.78 – 1.64 (m, 2H), 1.50 (dd, J = 6.9, 1.6 Hz, 3H), 1.01 (d, J = 7.0 Hz, 1.5H), 0.88 (d, J = 6.9 Hz, 1.5H), 0.75 (br s, 1.5H), 0.62 (br s, 1.5H).	
265: (S)-3-(2-((S)-1-(4-(4-fluorophenoxy)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.14 (d, J = 5.8 Hz, 1H), 7.37 (d, J = 5.8 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.12 – 7.05 (m, 2H), 7.01 – 6.94 (m, 2H), 6.94 – 6.89 (m, 2H), 5.06 (q, J = 7.0 Hz, 1H), 4.71 (br s, 1H), 4.41 – 4.29 (m, 2H), 1.99 (br s, 1H), 1.52 (d, J = 7.0 Hz, 3H), 0.77 (br s, 3H), 0.67 (br s, 3H).	HRMS(B) (M+H) 437.1981
266: (R)-3-(2-((S)-1-(4-bromophenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.46 (d, J = 5.8 Hz, 1H), 7.84 – 7.73 (m, 5H), 7.72 – 7.67 (m, 1H), 7.64 (dd, J = 7.1, 1.8 Hz, 2H), 7.59 – 7.53 (m, 2H), 5.92 (dd, J = 8.6, 4.0 Hz, 1H), 5.13 (t, J = 8.7 Hz, 1H), 4.98 (q, J = 8.4, 7.5 Hz, 1H), 4.55 (dd, J = 8.7, 4.0 Hz, 1H), 1.58 (d, J = 7.0 Hz, 3H).	HRMS(B) (M+H) 439.0762
267: (R)-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)-4-(pyridin-3-yl)oxazolidin-2-one	8.60 (d, J = 2.5 Hz, 1H), 8.55 (dd, J = 4.8, 1.5 Hz, 1H), 8.12 (d, J = 5.8 Hz, 1H), 7.81 (dt, J = 7.8, 2.0 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.41 (d, J = 5.8 Hz, 1H), 7.36 – 7.25 (m, 4H), 7.25 – 7.17 (m, 1H), 5.60 (br s, 1H), 4.80 (t, J = 8.9 Hz, 1H), 4.61 (br s, 1H), 4.27 (dd, J = 9.0, 4.1 Hz, 1H), 1.25 (br d, J = 7.5 Hz, 3H).	HRMS(B) (M+H) 362.1615

268: (R)-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)-4-(pyridin-4-yl)oxazolidin-2-one	8.61 – 8.60 (m, 2H), 8.14 (d, J = 5.8 Hz, 1H), 7.43 (d, J = 5.8 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.28 – 7.17 (m, 3H), 5.57 (br s, 1H), 4.80 (t, J = 9.0 Hz, 1H), 4.55 (br s, 1H), 4.22 (dd, J = 9.0, 4.1 Hz, 1H), 1.20 (br s, 3H).	HRMS(B) (M+H) 362.1610
269: (S)-3-(2-((S)-1-(3-methoxyphenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.46 (d, J = 5.7 Hz, 1H), 7.73 (d, J = 5.8 Hz, 1H), 7.64 – 7.52 (m, 5H), 7.48 (t, J = 7.8 Hz, 1H), 7.11 – 7.03 (m, 3H), 6.18 (dd, J = 8.7, 3.7 Hz, 1H), 5.25 – 5.13 (m, 2H), 4.60 (dd, J = 8.7, 3.7 Hz, 1H), 4.10 (s, 3H), 1.81 (d, J = 7.0 Hz, 3H).	HRMS(B) (M+H) 391.1771
270: (4S)-3-(2-(1-(biphenyl-4-yl)ethylamino)pyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one	8.50 – 8.45 (m, 1H), 7.95 (ddt, J = 7.6, 5.3, 2.3 Hz, 3H), 7.83 – 7.64 (m, 8H), 7.63 – 7.54 (m, 2H), 7.49 (dd, J = 4.9, 3.0 Hz, 2H), 5.83 (s, 0.5H), 5.57 (s, 0.5H), 5.29 – 5.24 (m, 0.5H), 5.04 – 4.99 (m, 0.5H), 2.02 (s, 1.5H), 1.85 – 1.84 (m, 3H), 1.62 (d, J = 7.0 Hz, 1.5H), 1.35 (d, J = 3.3 Hz, 3H).	HRMS(B) (M+H) 465.2284
271: (S)-3-(2-((S)-1-(4-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyl-4-methyloxazolidin-2-one	8.15 (d, J = 5.8 Hz, 1H), 7.41 – 7.29 (m, 2H), 7.25 (d, J = 5.8 Hz, 1H), 7.09 – 6.98 (m, 2H), 4.96 (q, J = 7.1 Hz, 1H), 4.29 (d, J = 9.0 Hz, 1H), 3.88 (d, J = 8.9 Hz, 1H), 2.17 (br s, 1H), 1.70 (s, 3H), 1.53 (d, J = 7.0 Hz, 3H), 0.70 (br s, 3H), 0.44 (br s, 3H).	HRMS(B) (M+H) 359.1889
272: (S)-4,4-dimethyl-3-(2-(1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1H), 7.35 – 7.26i (m, 4H), 7.17 (d, J = 5.9 Hz, 1H), 5.02 (q, J = 6.9 Hz, 1H), 4.06 (q, J = 8.4 Hz, 2H), 3.51 (s, 2H), 2.49 (br s, 8H), 2.28 (s, 3H), 1.70 (s, 3H), 1.53 (d, J = 7.0 Hz, 3H), 1.15 (br s, 3H).	HRMS(B) (M+H) 425.2661
273: (R)-5,5-dimethyl-3-(2-((S)-1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.09 (d, J = 5.8 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.36 (tt, J = 7.1, 1.4 Hz, 1H), 7.30 (s, 4H), 7.21 (br s, 2H), 5.22 (br s, 1H), 4.58 (br s, 1H), 3.53 (s, 2H), 2.50 (br s, 8H), 2.28 (s, 3H), 1.52 (s, 3H), 1.19 (d, J = 6.8 Hz, 3H), 0.99 (s, 3H).	HRMS(B) (M+H) 501.2971
274: (S)-5,5-dimethyl-3-(2-((S)-1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	8.08 (d, J = 5.8 Hz, 1H), 7.45 (d, J = 5.8 Hz, 1H), 7.38 – 7.23 (m, 3H), 7.16 (t, J = 7.5 Hz, 4H), 7.00 (br s, 2H), 5.51 (s, 1H), 4.89 – 4.83 (m, 1H), 3.49 (d, J = 2.3 Hz, 2H), 2.50 (br s, 8H), 2.29 (s, 3H), 1.67 (s, 3H), 1.44 (d, J = 6.9 Hz, 3H), 1.00 (s, 3H).	HRMS(B) (M+H) 501.2981
275: (S)-4-isopropyl-4-methyl-3-(2-((S)-1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.14 (d, J = 5.9 Hz, 1H), 7.29 (s, 4H), 7.24 (d, J = 5.9 Hz, 1H), 4.97 (p, J = 7.0 Hz, 1H), 4.60 (br s, 1H), 4.29 (d, J = 8.8 Hz, 1H), 3.88 (d, J = 9.0 Hz, 1H), 3.51 (s, 2H), 2.59 (br s, 8H), 2.28 (s, 3H), 1.71 (s, 3H), 1.52 (d, J = 6.9 Hz, 3H), 0.70 (br s, 3H), 0.39 (br s, 3H).	
276: (S)-4-isopropyl-5,5-dimethyl-3-(2-(((S)-1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)ethyl)ami	8.14 (d, J = 5.8 Hz, 1H), 7.39 – 7.20 (m, 5H), 5.09 (q, J = 7.0 Hz, 1H), 4.49 (br s, 1H), 3.52 (s, 2H), 2.57 (br s, 8H), 2.32 (s, 3H), 2.03 (br s, 1H), 1.54 (s, 3H), 1.51 (d, J	HRMS(B) (M+H) 453.2975

no)pyrimidin-4-yl)oxazolidin-2-one	= 7.0 Hz, 3H), 1.42 (s, 3H), 0.75 (br s, 3H), 0.62 (br s, 3H).	
277: (S)-4-isopropyl-3-(2-((S)-1-(4-(pyridin-2-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.60 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 8.16 (d, J = 5.8 Hz, 1H), 7.94 – 7.86 (m, 3H), 7.84 (dt, J = 7.9, 1.2 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.41 – 7.32 (m, 2H), 5.12 (q, J = 7.0 Hz, 1H), 4.67 (br s, 1H), 4.40 – 4.18 (m, 2H), 1.83 (br s, 1H), 1.58 (d, J = 7.1 Hz, 3H), 0.68 (br s, 3H), 0.56 (br s, 3H).	HRMS(B) (M+H) 404.2089
278: (S)-4-isopropyl-3-(2-((S)-1-(6-phenylpyridin-3-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.60 (d, J = 2.2 Hz, 1H), 8.18 (d, J = 5.8 Hz, 1H), 7.95 – 7.89 (m, 2H), 7.87 (dd, J = 8.2, 2.3 Hz, 1H), 7.81 (dd, J = 8.3, 0.8 Hz, 1H), 7.55 – 7.42 (m, 3H), 7.40 (d, J = 5.8 Hz, 1H), 5.16 (q, J = 7.1 Hz, 1H), 4.66 (br s, 1H), 4.40 – 4.22 (m, 2H), 1.74 (br s, 1H), 1.62 (d, J = 7.0 Hz, 3H), 0.67 (br s, 3H), 0.57 (br s, 3H).	HRMS(B) (M+H) 404.2079
279: (S)-4-isopropyl-3-(2-((S)-1-(quinolin-6-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.81 (dd, J = 4.3, 1.6 Hz, 1H), 8.32 (dt, J = 8.2, 1.1 Hz, 1H), 8.18 (d, J = 5.8 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.89 – 7.76 (m, 2H), 7.53 (dd, J = 8.3, 4.4 Hz, 1H), 7.37 (d, J = 5.8 Hz, 1H), 5.24 (q, J = 7.1 Hz, 1H), 4.59 (br s, 1H), 4.30 (t, J = 8.7 Hz, 1H), 4.22 (br s, 1H), 1.64 (d, J = 7.1 Hz, 3H), 1.49 (br s, 1H), 0.35 (br s, 6H).	HRMS(B) (M+H) 378.1930
280: (S)-4-isopropyl-3-(2-((S)-1-(quinolin-7-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.81 (dd, J = 4.3, 1.7 Hz, 1H), 8.34 (dt, J = 8.4, 1.2 Hz, 1H), 8.13 (d, J = 5.9 Hz, 1H), 8.00 (d, J = 1.6 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.68 (dd, J = 8.6, 1.8 Hz, 1H), 7.50 (dd, J = 8.3, 4.4 Hz, 1H), 7.36 (d, J = 5.8 Hz, 1H), 5.23 – 5.17 (m, 1H), 4.50 (br d, J = 84.2 Hz, 1H), 4.35 – 4.25 (m, 1H), 4.19 (br s, 1H), 2.68 (pd, J = 7.0, 3.5 Hz, 1H), 1.65 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H).	HRMS(B) (M+H) 378.1941
281: (S)-3-(2-((S)-1-(4-benzoylphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.17 (d, J = 5.8 Hz, 1H), 7.81 – 7.71 (m, 4H), 7.69 – 7.61 (m, 1H), 7.59 – 7.49 (m, 4H), 7.39 (d, J = 5.8 Hz, 1H), 5.15 (q, J = 7.1 Hz, 1H), 4.67 (br s, 1H), 4.41 – 4.23 (m, 2H), 1.75 (br s, 1H), 1.58 (d, J = 7.1 Hz, 3H), 0.69 (br s, 3H), 0.61 (br s, 3H).	HRMS(B) (M+H) 431.2072
282 : (S)-3-(2-((S)-1-(3-fluoro-4-(2-methyl-1H-imidazol-1-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.18 (d, J = 7.1 Hz, 1H), 7.75 (d, J = 7.3 Hz, 1H), 7.71 – 7.62 (m, 3H), 7.58 (dd, J = 10.9, 1.9 Hz, 1H), 7.51 (dd, J = 8.2, 1.8 Hz, 1H), 5.33 (br s, 1H), 4.81 – 4.73 (m, 1H), 4.46 – 4.36 (m, 2H), 2.54 (s, 3H), 2.03 (br s, 1H), 1.64 (d, J = 7.0 Hz, 3H), 0.84 (br d, J = 7.2 Hz, 3H), 0.70 (br d, J = 7.2 Hz, 3H).	HRMS(B) (M+H) 425.2093
283: (4S)-4-isopropyl-3-(2-(1-(4-(2-methyl-1H-imidazol-1-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.15 (dd, J = 8.9, 5.8 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.42 – 7.32 (m, 3H), 7.14 (dd, J = 13.3, 1.5 Hz, 1H), 6.96 (dd, J = 3.5, 1.5 Hz, 1H), 5.17 (q, J = 7.1 Hz, 0.5H), 5.07 (d, J = 7.4 Hz, 0.5H), 4.71 (br s, 0.5H), 4.50 (br s, 0.5H), 4.40 – 4.24 (m, 2H), 2.67 (ddq, J = 10.6, 7.0, 3.6 Hz, 0.5H), 2.323 (s, 1.5H),	HRMS(B) (M+) 406.2217

	2.321 (s, 1.5H), 1.95 (br s, 0.5H), 1.58 (dd, J = 7.0, 2.3 Hz, 3H), 1.02 (d, J = 7.0 Hz, 1.5H), 0.88 (d, J = 6.9 Hz, 1.5H), 0.76 (br s, 1.5H), 0.64 (br s, 1.5H).	
284: (S)-3-(2-(((R)-1-cyclopentylethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one		HRMS(B) m/z 319.2133 (M+H)+, RT=2.68 min.
285: (S)-3-(2-(((S)-1-(4-(dimethylamino)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one		HRMS(B) m/z 370.2227 (M+H)+, RT=2.47 min.
286: N-(3-((S)-1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino) Ethylphenyl)acetamide		HRMS(B) m/z 384.2032 (M+H)+, RT=1.97 min
287: (S)-3-(2-(((S)-1-(1H-benzo[d]imidazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one		HRMS(B) m/z 367.1887 (M+H)+ RT=2.39 min.
288: (S)-3-(2-(((S)-1-(4-((4-chlorophenyl)sulfonyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one		HRMS(B) m/z 501.1343, (M+H)+ RT=2.68 min.
289: (S)-4-isopropyl-3-(2-(((S)-1-(4-nitrophenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one		HRMS(B) m/z 372.1672, (M+H)+, RT=2.59 min.
290: (S)-3-(2-(((S)-1-(4-aminophenyl)ethyl)amino) pyrimidin-4-yl)-4-isopropyloxazolidin-2-one		HRMS(B) m/z 342.1931, (M+H)+, RT=2.17 min
291: (S)-4-isopropyl-3-(2-(((S)-1-(5-(methylthio)-1,3,4-oxadiazol-2-yl)ethyl)amino) pyrimidin-4-yl)oxazolidin-2-one		HRMS(B) m/z 365.1367, (M+H)+, RT=1.88 min.
292: (S)-4-isopropyl-3-(2-(((S)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl)	($CDCl_3$) δ 8.15 (d, J = 5.9 Hz, 1H), 7.87 – 7.74 (m, 2H), 7.51 (d, J = 5.9 Hz, 1H), 7.46 – 7.28 (m, 3H), 6.39 (b, 1H), 5.43 (s, 1H),	HRMS(B) m/z 411.1596(

amino) pyrimidin-4-yl)oxazolidin-2-one	4.58 (dt, J = 8.3, 3.3 Hz, 1H), 4.29 – 4.12 (m, 2H), 1.94 – 1.80 (b, 1H), 1.74 (d, J = 7.0 Hz, 3H), 0.69 (d, J = 6.8 Hz, 3H), 0.60 (d, J = 7.2 Hz, 3H)	M +H)+, RT=2.54min.
293: (S)-3-{2-[1-(5-Chloro-1H-benzoimidazol-2-yl)-ethylamino]-pyrimidin-4-yl}-4-isopropyl-oxazolidin-2-one		HRMS(B) m/z 400.1414, RT=2.04 min.
294: (S)-3-(2-{(S)-1-[5-(2,2-Dimethyl-propyl)-isoxazol-3-yl]-ethylamino}-pyrimidin-4-yl)-4-isopropyl-oxazolidin-2-one	($CDCl_3$) δ 8.22 (d, J = 5.7 Hz, 1.0 H), 7.52 (d, J = 5.8 Hz, 0.95 H), 5.92 (s, 0.96 H), 5.50 (d, J = 7.5 Hz, 0.97 H), 5.22 (s, 0.83H), 4.72 (d, J = 8.3 Hz, 1.0 H), 4.42 – 4.20 (m, 2.06 H), 3.51 (s, 0.27 H), 2.61 (s, 2.05 H), 1.62 (d, J = 7.0 Hz, 4.13 H), 0.97 (s, 8.95 H), 0.90 (d, J = 7.0 Hz, 2.56 H), 0.80 (d, J = 7.0 Hz, 2.93 H).	HRMS(B) m/z 387.2271
295: (4S)-4-isopropyl-3-(2-(1-(5-phenylpyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) δ 8.93 (d, J = 5.9 Hz, 4H), 8.26 – 8.17 (m, 2H), 7.64 – 7.44 (m, 12H), 6.41 (br s, 1H), 5.31 (br s, 1H), 4.79 – 4.65 (m, 2H), 4.41 – 4.24 (m, 4H), 2.65 (dddd, J = 27.4, 14.1, 7.1, 3.5 Hz, 1H), 2.20 (br s, 1H), 1.75-1.64 (m, 4H), 1.07 – 0.85 (m, 9H), 0.78 (s, 3H).	HRMS(B) m/z 405.2024 and 405.2025 (M + H)+.
296: 4-{(S)-1-[4-((S)-4-Isopropyl-2-oxo-oxazolidin-3-yl)-pyrimidin-2-ylamino]-ethyl}-piperidine-1-carboxylic acid benzyl ester		HRMS(B) (M+) = 467.2533 RT.: 2.83 min.
297: (S)-3-(2-((S)-1-(5-bromopyridin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.		HRMS(B) m/z 406.0870 (M + H)+. RT.: 2.50 min.
298: 3-(5-fluoro-2-((1-(5-(4-fluoro-3-methylphenyl)pyridin-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one		HRMS(B) m/z 412.1578 (M + H)+. RT.: 2.35 min.
299: 3-(2-(1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one.		HRMS(B) m/z 411.1572 (M + H)+. RT.: 2.25 min.
300: 3-(5-fluoro-2-(1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one.		HRMS(B) m/z 415.1320 (M + H)+. RT.: 2.26 min.
301: (4S)-3-(2-(1-(5-(2,4-	($CDCl_3$) δ 8.45 (d, J = 4.6 Hz, 4H), 8.21 (d,	MS m/z

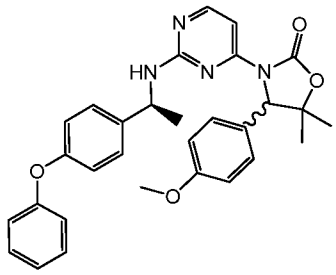
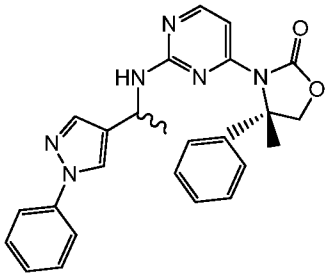
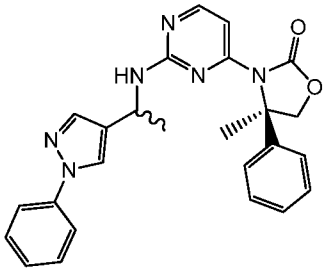
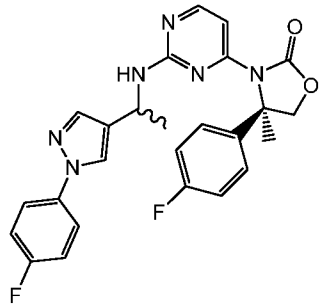
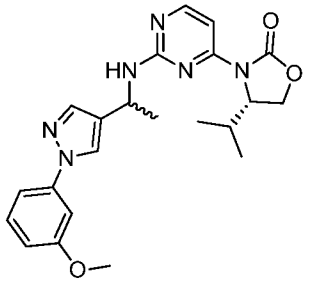
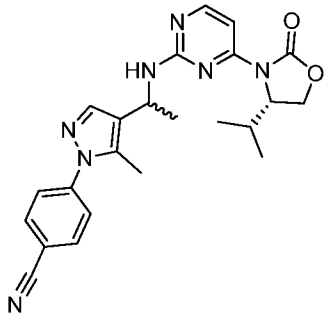
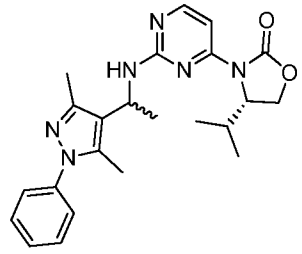
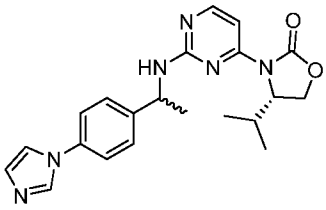
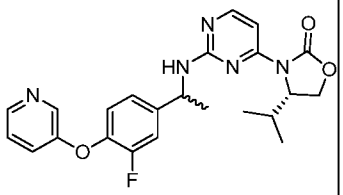
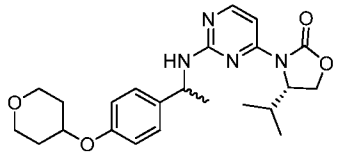
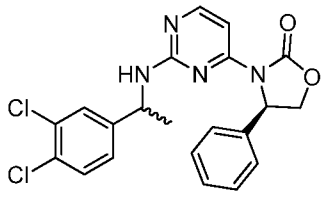
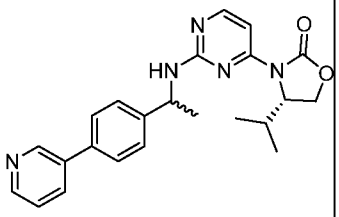
difluorobenzyloxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	J = 5.8 Hz, 2H), 7.53 – 7.41 (m, 4H), 6.93 (ddddd, J = 19.9, 9.8, 8.7, 2.6, 1.2 Hz, 4H), 6.21 (s, 1H), 6.11 (s, 1H), 5.21 (br s, 2H), 5.18 (s, 2H), 5.16 (s, 2H), 4.74 (dt, J = 7.7, 3.3 Hz, 1H), 4.66 (d, J = 7.4 Hz, 1H), 4.38 – 4.24 (m, 4H), 2.65 (ddq, J = 10.5, 7.1, 3.5 Hz, 1H), 2.30 (br s, 1H), 1.65-1.59 (m, 6H), 1.01 (d, J = 7.0 Hz, 3H), 0.89 (dq, J = 7.6, 4.9, 4.4 Hz, 6H), 0.79 (d, J = 6.5 Hz, 3H).	471.8 (M + H)+.
302: (S)-3-(2-{(S)-1-[4-(4-Fluoro-phenoxy)-cyclohexyl]-ethylamino}-pyrimidin-4-yl)-4-isopropyl-oxazolidin-2-one		LC-MS m/z 442.53 (M + H)+; RT.: 1.77 min.
303: (4S)-3-(2-(1-(5-(5-bromopyridin-3-yloxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) δ 8.62 – 8.49 (m, 6H), 8.44 – 8.36 (m, 2H), 8.22 (dd, J = 5.7, 0.6 Hz, 2H), 7.57 – 7.46 (m, 4H), 6.14 (br s, 2H), 5.33 (br s, 2H), 4.76 (dt, J = 8.2, 3.4 Hz, 1H), 4.67 (s, 1H), 4.40 – 4.26 (m, 4H), 2.67 (pd, J = 7.0, 3.4 Hz, 1H), 2.32 (br s, 1H), 1.69 – 1.61 (m, 6H), 1.02 (d, J = 7.0 Hz, 3H), 0.99 – 0.80 (m, 9H).	HRMS(B) m/z 500.1038 and 500.1034 (M + H)+.
304: (S)-3-(2-((S)-1-(5-chloropyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.	($CDCl_3$) δ 8.58 (s, 2H), 8.12 (d, J = 5.8 Hz, 1H), 7.40 (d, J = 5.8 Hz, 1H), 5.97 (br s, 1H), 5.17 (br s, 1H), 4.63 (dt, J = 8.0, 3.2 Hz, 1H), 4.29 – 4.15 (m, 2H), 2.10 (br s, 1H), 1.50 – 1.46 (m, 3H), 0.88 – 0.66 (m, 6H).	LC-MS m/z 363.1 (M + H)+; RT.: 1.39 min.
305: (S)-3-(2-((S)-1-(5-(3-chloro-4-fluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.	($CDCl_3$) δ 8.36 (s, 2H), 8.13 (s, 1H), 7.41 (d, J = 5.4 Hz, 1H), 7.15 – 7.00 (m, 2H), 6.85 (ddd, J = 9.0, 3.7, 3.0 Hz, 1H), 6.08 (s, 1H), 5.21 (br s, 1H), 4.66 (dt, J = 8.3, 3.4 Hz, 1H), 4.30 – 4.16 (m, 2H), 2.25 (br s, 1H), 1.56-1.51 (m, 3H), 0.85-0.78 (m, 3H), 0.77 – 0.70 (m, 3H).	HRMS(B) m/z 473.1484 (M + H)+.
306: (4S)-4-isopropyl-3-(2-(1-(5-(pyridin-3-yloxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one		HRMS(B) m/z 422.1938, RT 1.91min and 422.1944, RT 2.01min (M + H)+.
307: (4S)-3-(2-(1-(5-(3-fluorobenzyloxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) δ 8.43 (d, J = 4.9 Hz, 4H), 8.21 (d, J = 5.7 Hz, 2H), 7.49 – 7.34 (m, 4H), 7.26 – 7.02 (m, 6H), 6.20 (br s, 1H), 6.11 (br s, 1H), 5.22 (br s, 2H), 5.16 (s, 2H), 4.74 (dt, J = 7.7, 3.3 Hz, 1H), 4.66 (br s, 1H), 4.38 – 4.23 (m, 4H), 2.66 (heptd, J = 7.0, 3.5 Hz, 1H), 2.26 (br s, 1H), 1.64-1.58 (m, 6H), 1.00 (d, J = 7.0 Hz, 3H), 0.94 – 0.85 (m,	HRMS(B) m/z 453.2048 and 453.2047 (M + H)+.

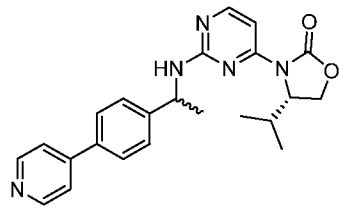
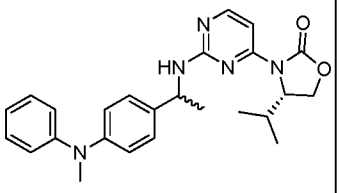
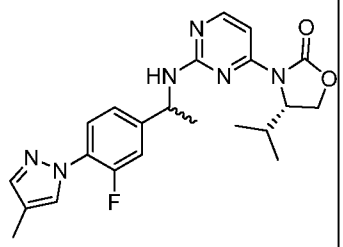
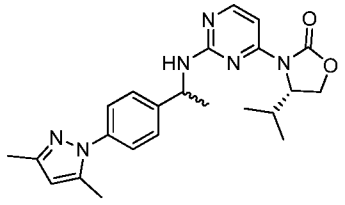
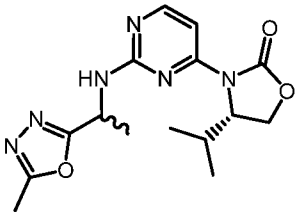
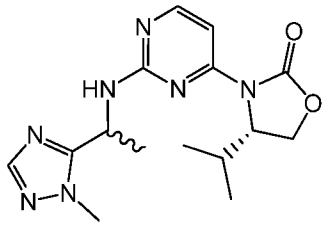
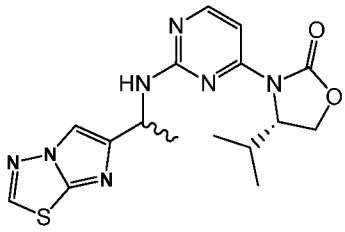
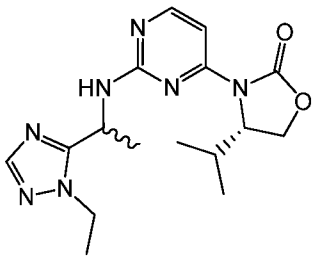
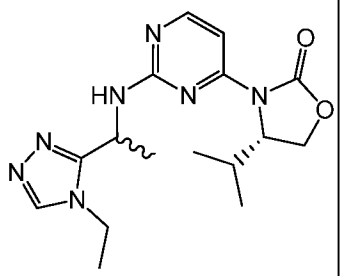
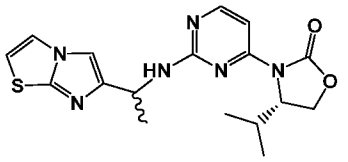
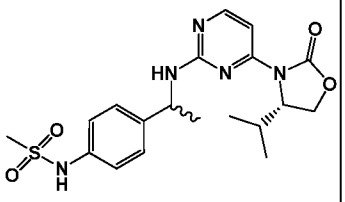
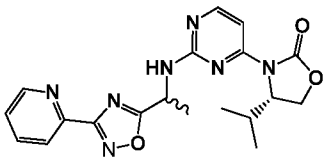
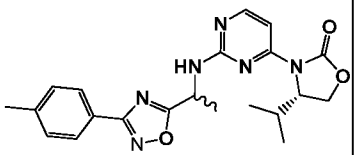
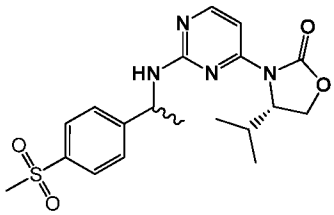
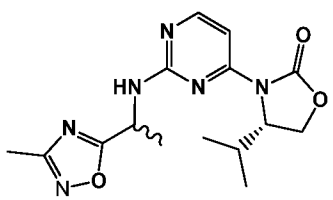
	6H), 0.78 (br s, 3H).	
308: (S)-3-(2-((S)-1-(5-iodopyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.		HRMS(B) m/z 454.0614 (M +). RT 2.35min
309: (4S)-4-isopropyl-3-(2-(1-(5-(5-(trifluoromethyl)pyridin-2-yloxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one		HRMS(B) m/z 490.1800, RT 2.17min and 490.1795, RT 2.23min (M + H)+.
310: (4S)-4-isopropyl-3-(2-(1-(pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one		HRMS(B) m/z 329.1728, RT 1.81min and 329.1726, RT 1.93min (M + H)+.
311: (4S)-3-(2-(1-(4-(4-fluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) δ 8.56 (dd, J = 5.7, 2.3 Hz, 2H), 8.20 (dd, J = 5.7, 4.0 Hz, 2H), 7.46 (dd, J = 5.7, 4.4 Hz, 2H), 7.20 – 7.00 (m, 8H), 6.71 (dd, J = 5.7, 2.0 Hz, 2H), 6.03 (br s, 1H), 5.87 (br s, 1H), 5.11 (br s, 2H), 4.72 – 4.61 (m, 2H), 4.40 – 4.23 (m, 4H), 2.59 (ddp, J = 10.5, 7.1, 3.5 Hz, 1H), 2.21 (br s, 1H), 1.59-1.55 (m, 6H), 1.00 – 0.85 (m, 9H), 0.80 (d, J = 6.3 Hz, 3H).	HRMS(B) m/z 439.1887 and 439.1887 (M + H)+.
312: (S)-3-(2-((S)-1-(4-(((2S,6R)-2,6-dimethylmorpholino)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	^{1}H NMR (400 MHz, CD_3OD) δ ppm 0.63 (br. s., 3 H) 0.79 (br. s., 3 H) 1.20 (dd, J=6.26, 2.74 Hz, 6 H) 1.58 (d, J=7.04 Hz, 3 H) 2.54 - 2.82 (m, 2H) 3.73 - 3.90 (m, 2 H) 4.32 (d, J=3.52 Hz, 2 H) 4.39 (d, J=5.87 Hz, 2 H) 4.68 - 4.78 (m, 1 H) 5.15 - 5.31 (m, 1 H) 7.51 (s, 4 H) 7.62 - 7.76 (m, 1 H) 8.08 - 8.22 (m, 1 H)	LCMS m/z 454.3 (M + H)+, Rt 0.57 min

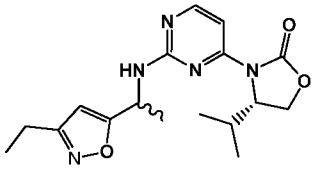
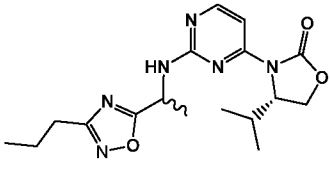
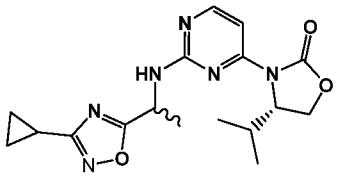
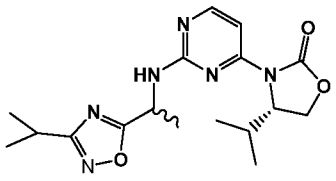
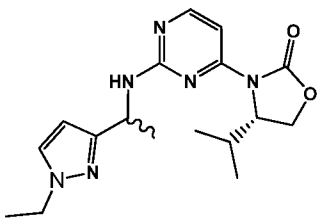
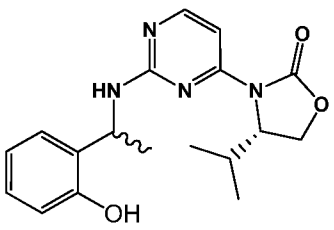
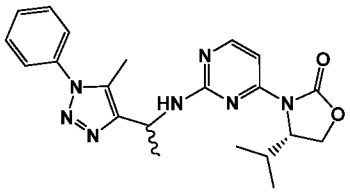
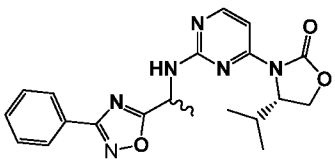
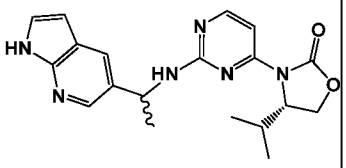
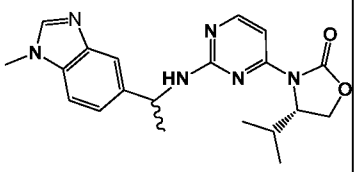
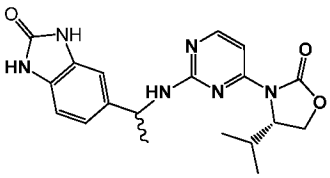
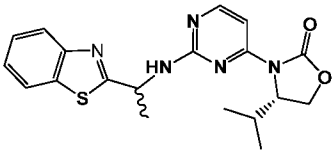
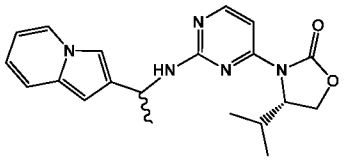
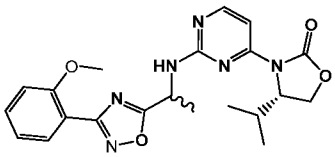
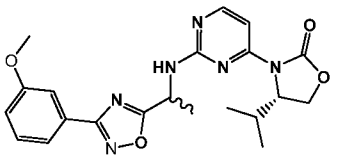
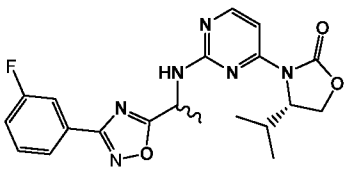
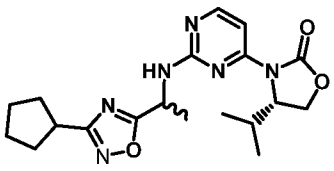
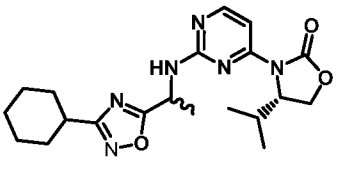
The compounds in Table 9 were prepared using methods substantially similar to those described for the preparation of Examples 1, 113, and 171 through 212, including chiral separation to isolate the two diastereomers.

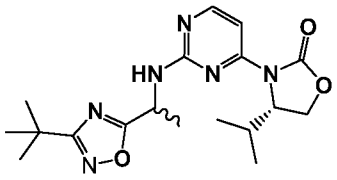
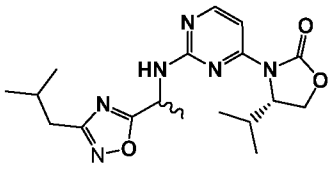
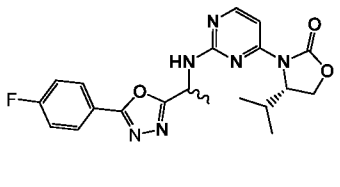
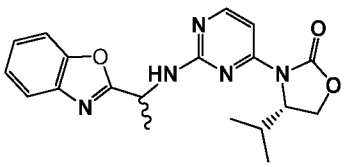
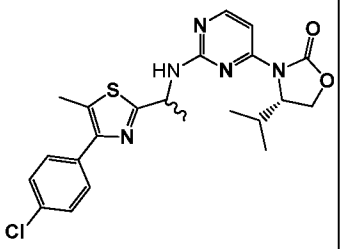
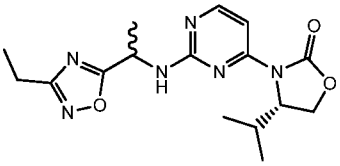
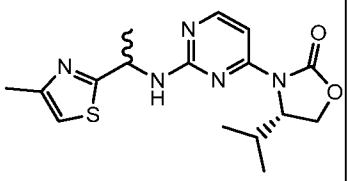
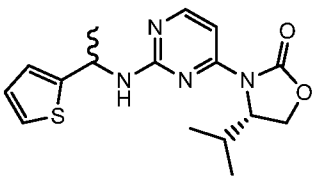
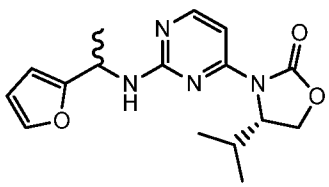
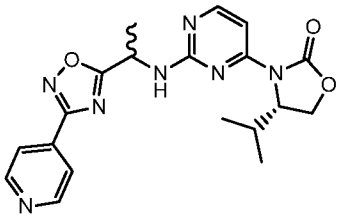
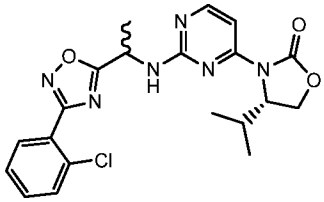
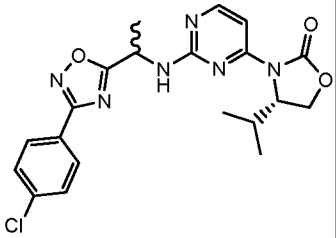
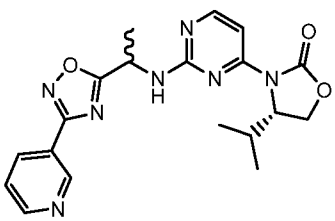
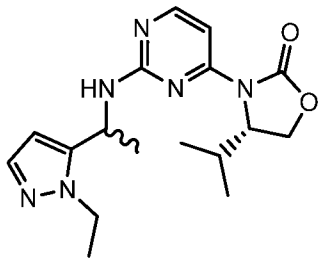
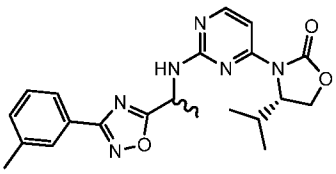
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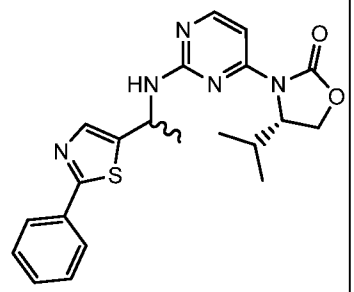
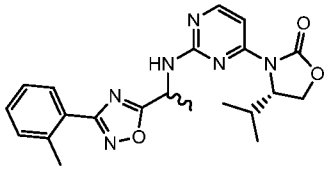
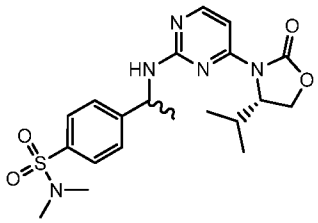
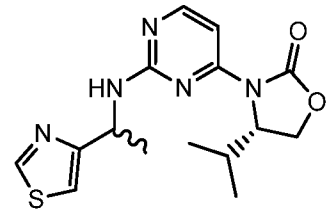
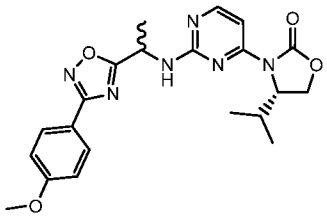
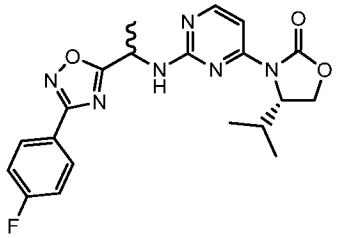
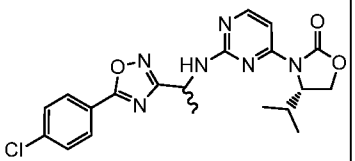
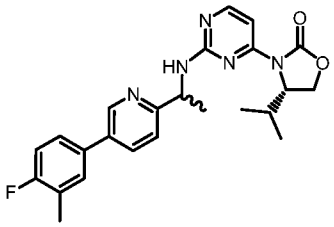
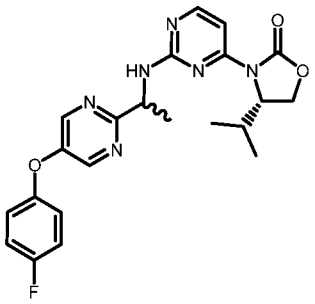
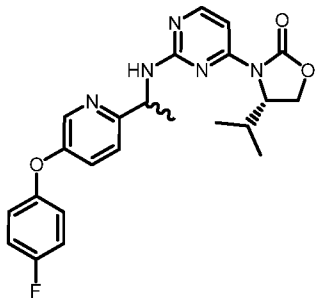
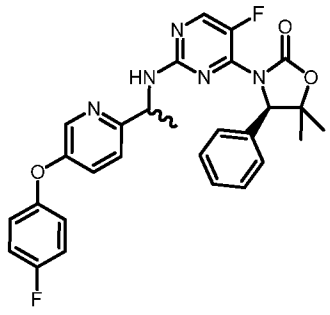
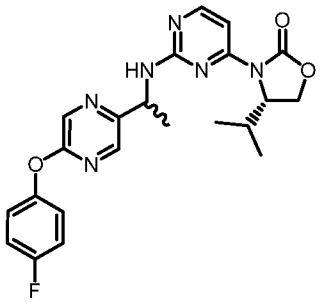
Table 9.

313 & 314	315 & 316	317 & 318
		
319 & 320	321 & 322	323 & 324
		
325 & 326	327 & 328	329 & 330
		
331 & 332	333 & 334	335 & 336
		
337 & 338	339 & 340	341 & 342

		
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427	428 & 429	430
		
431 & 432	433 & 434	435 & 436

		
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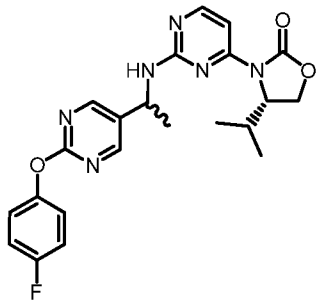
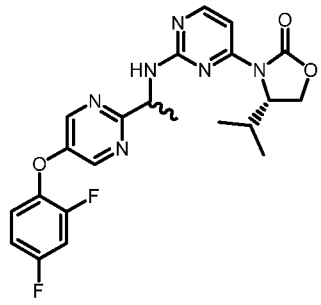
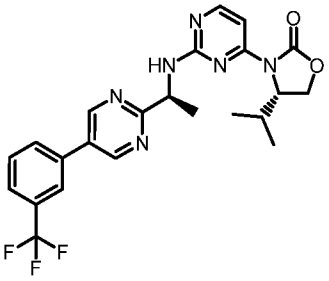
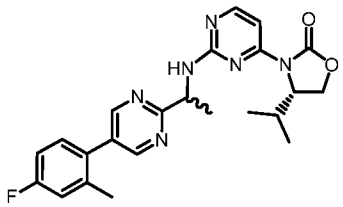
		
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Table 10. Chemical name, NMR chemical shifts, chiral separation conditions and LCMS signal for each compound listed in Table 9.

Example: Name	**Chiral separation conditions, peak identification and analytical data**
331 & 314: 4-(4-methoxyphenyl)-5,5-dimethyl-3-(2-((S)-1-(4-phenoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	The chiral separation was carried out with SFC (IA-H, 5μM, 20 x 50 mm) using 28% MeOH in CO2 to give (R)-4-(4-methoxyphenyl)-5,5-dimethyl-3-(2-(((S)-1-(4-phenoxyphenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-(4-methoxyphenyl)-5,5-dimethyl-3-(2-(((S)-1-(4-phenoxyphenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st Peak 313: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 5.9, 1.6 Hz, 1H), 7.43 (d, J = 5.7 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.20 – 7.14 (m, 2H), 7.06 – 7.00 (m, 1H), 6.98 (d, J = 8.2 Hz, 2H), 6.94 – 6.86 (m, 4H), 6.83 – 6.76 (m, 2H), 5.24 (br s, 1H), 5.01 (s, 1H), 4.57 (br s, 1H), 3.72 (s, 3H), 1.46 (s, 3H), 1.24 – 1.09 (m, 3H), 0.92 (s, 3H); HRMS(B) m/z 511.2326 (M + H) +. 2nd Peak 314 : ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 5.7 Hz, 1H), 7.51 (d, J = 5.7 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.10 (tt, J = 7.3, 1.2 Hz, 1H), 7.06 – 6.90 (m, 6H), 6.89 – 6.82 (m, 2H), 6.82 – 6.75 (m, 2H), 5.29 (s, 1H), 5.09 (br s, 1H), 4.80 (br s, 1H), 3.72 (s, 3H), 1.63 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H), 1.01 (s, 3H); HRMS(B) m/z 511.2323 (M + H) +.

315 & 316: (S)-4-methyl-4-phenyl-3-(2-(1-(1-phenyl-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	The chiral separation was carried out with SFC (IA, 5µm, 20 x 250 mm) using 45% iPrOH with 0.2% Et2NH in CO2 to give (S)-4-methyl-4-phenyl-3-(2-(((R)-1-(1-phenyl-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-methyl-4-phenyl-3-(2-(((S)-1-(1-phenyl-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st Peak 315: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 5.8 Hz, 1 H), 7.63 – 7.60 (m, 2 H), 7.49 – 7.44 (m, 4 H), 7.37 – 7.28 (m, 4 H), 7.26 – 7.22 (m, 2 H), 7.12 – 7.08 (m, 1 H), 4.94 (br s, 1 H), 4.45 (br s, 1 H), 4.31 – 4.27 (m, 2 H), 2.19 (s, 3 H), 1.44 (d, J = 6.8 Hz, 3 H); HRMS(B) m/z 441.2036 (M + H)+. 2nd Peak 316: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 5.8 Hz, 1 H), 7.67 – 7.63 (m, 3 H), 7.53 (s, 1 H), 7.49 – 7.44 (m, 3 H), 7.40 – 7.37 (m, 2 H), 7.33 – 7.30 (m, 4 H), 4.99 (br s, 1 H), 4.38 (br s, 1 H), 4.26 (s, 2 H), 2.00 (s, 3 H), 1.07 (br s, 3 H); HRMS(B) m/z 441.2039 (M + H)+.
317 & 318: (R)-4-methyl-4-phenyl-3-(2-(1-(1-phenyl-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	The chiral separation was carried out with SFC (IA, 5µm, 20 x 250 mm) with 45% iPrOH modified with 0.2% Et2NH in CO2 to give (R)-4-methyl-4-phenyl-3-(2-(((S)-1-(1-phenyl-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-methyl-4-phenyl-3-(2-(((S)-1-(1-phenyl-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st peak 317: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 5.8 Hz, 1 H), 7.68 – 7.63 (m, 3 H), 7.53 (s, 1 H), 7.49 – 7.44 (m, 3 H), 7.41 – 7.37 (m, 2 H), 7.33 – 7.30 (m, 4 H), 4.98 (br s, 1 H), 4.39 (br s, 1 H), 4.26 (s, 2 H), 2.00 (s, 3 H), 1.07 (br s, 3 H); HRMS(B) m/z 441.2037 (M + H)+. 2nd peak 318: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 5.8 Hz, 1 H), 7.63 – 7.60 (m, 2 H), 7.49 – 7.44 (m, 4 H), 7.36 – 7.29 (m, 4 H), 7.26 – 7.22 (m, 2 H), 7.12 – 7.08 (m, 1 H), 5.02 (br s, 1 H), 4.45 (br s, 1 H), 4.31 – 4.26 (m, 2 H), 2.19 (s, 3 H), 1.44 (d, J = 6.8 Hz, 3 H); HRMS(B) m/z 441.2039 (M + H)+.
319 & 320: (R)-4-(4-fluorophenyl)-3-(2-(1-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)-4-methyloxazolidin-2-one	Separation was achieved on a normal phase silica gel column with 10 to 50% ethylacetate / heptane to give (R)-4-(4-fluorophenyl)-3-(2-(((R)-1-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)-4-methyloxazolidin-2-one and (R)-4-(4-fluorophenyl)-3-(2-(((S)-1-(1-(4-fluorophenyl)-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)-4-methyloxazolidin-2-one. 1st peak 319: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 5.8 Hz, 1 H), 7.53 – 7.48 (m, 3 H), 7.44 (s, 1 H), 7.36 (d, J = 5.8 Hz, 1 H), 7.22 – 7.17 (m, 2 H), 7.09 – 7.03 (m, 2 H), 7.01 – 6.95 (m, 2 H), 4.98 (br s, 1 H), 4.33 (br s, 1 H), 4.15 (q, J = 8.6 Hz, 2 H), 1.90 (s, 3 H), 1.04 (br s, 3 H); HRMS(B) m/z 477.1827 (M + H)+. 2nd peak 320: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 5.8 Hz, 1 H), 7.62 – 7.56 (m, 2 H), 7.45 – 7.39 (m, 3 H), 7.31 – 7.26 (m, 2 H), 7.18 – 7.12 (m, 2 H), 6.93 (t, J = 8.6 Hz, 2 H), 5.01 (br s, 1 H), 4.50 (br s, 1 H), 4.30 –

	4.23 (m, 2 H), 2.17 (s, 3 H), 1.45 (d, J = 6.8 Hz, 3 H); HRMS(B) m/z 477.1829 (M + H)+.
321 & 322: (S)-4-isopropyl-3-(2-(1-(1-(3-methoxyphenyl)-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	Separation was achieved on a normal phase silica gel column with 10 to 50% ethylacetate / heptane to give (S)-4-isopropyl-3-(2-(((R)-1-(1-(3-methoxyphenyl)-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(1-(3-methoxyphenyl)-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st peak 321: ^{1}H NMR (400 MHz, MeOD) δ 8.18 (dd, J = 3.3, 2.5 Hz, 2H), 7.70 (s, 1H), 7.42 (d, J = 5.8 Hz, 1H), 7.38 (t, J = 8.1 Hz, 1H), 7.31 (t, J = 2.3 Hz, 1H), 7.27 (ddd, J = 8.0, 2.1, 0.9 Hz, 1H), 6.89 (ddd, J = 8.1, 2.5, 0.9 Hz, 1H), 5.21 (q, J = 6.8 Hz, 1H), 4.81 – 4.73 (m, 1H), 4.44 – 4.34 (m, 2H), 3.87 (s, 3H), 2.64 (pd, J = 7.0, 3.5 Hz, 1H), 1.61 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H).HRMS(B) (M+H) 423.2141 Calc'd (M+H) 423.2145 2nd peak 322: ^{1}H NMR (400 MHz, MeOD) δ 8.18 (d, J = 5.8 Hz, 1H), 8.10 (s, 1H), 7.63 (s, 1H), 7.41 (d, J = 5.8 Hz, 1H), 7.37 (t, J = 8.2 Hz, 1H), 7.28 (t, J = 2.3 Hz, 1H), 7.24 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 6.88 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H), 5.19 (q, J = 6.9 Hz, 1H), 4.74 (dt, J = 7.6, 3.5 Hz, 1H), 4.42 – 4.28 (m, 2H), 3.86 (s, 3H), 2.31 (br s, 1H), 1.61 (d, J = 6.9 Hz, 3H), 0.79 (br s, 3H), 0.75 – 0.64 (br m, 3H). HRMS(B) (M+H) 423.2139 Calc'd (M+H) 423.2145
323 & 324: 4-(4-(1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)-5-methyl-1H-pyrazol-1-yl)benzonitrile	Chiral separation was achieved by SFC. (Column: Chiralpak-ID (Semi-Prep 20mm x 250mm) Isocratic:65%CO2:35%MeOH (5mM NH4OH additive) to give (S)-4-isopropyl-3-(2-(((R)-1-(1-(3-methoxyphenyl)-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(1-(3-methoxyphenyl)-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st peak 323: ^{1}H NMR (400 MHz, MeOD) δ 8.16 (d, J = 5.8 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.75 (s, 1H), 7.73 – 7.67 (m, 2H), 7.40 (d, J = 5.8 Hz, 1H), 5.19 (q, J = 6.9 Hz, 1H), 4.79 (td, J = 5.7, 3.5 Hz, 1H), 4.40 (d, J = 5.7 Hz, 2H), 2.65 (pd, J = 7.0, 3.6 Hz, 1H), 2.41 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H). HRMS(B) (M+H) 432.2138 Calc'd (M+H) 432.2148 2nd peak 324: ^{1}H NMR (400 MHz, MeOD) δ 8.17 (d, J = 5.8 Hz, 1H), 7.97 – 7.84 (m, 2H), 7.77 – 7.63 (m, 3H), 7.40 (d, J = 5.8 Hz, 1H), 5.16 (q, J = 6.8 Hz, 1H), 4.79 (dt, J = 7.5, 3.8 Hz, 1H), 4.43 – 4.33 (m, 2H), 2.41 (s, 4H), 1.59 (d, J = 6.9 Hz, 3H), 0.87 (br d, J = 7.1 Hz, 3H), 0.80 (br d, J = 6.9 Hz, 3H). HRMS(B) (M+H) 432.2137 Calc'd (M+H) 432.2148
325 & 326: (S)-3-(2-(1-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-	Chiral separation was achieved by chiral SFC column chromatography (Column AD-H 5mM 20x250mm column 15% MeOH+DEA) to give (S)-3-(2-(((R)-1-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-

2-one	one and (S)-3-(2-(((S)-1-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one. 1st peak 325: ^{1}H NMR (400 MHz, MeOD) δ 8.16 (d, J = 5.8 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.48 – 7.42 (m, 1H), 7.42 – 7.38 (m, 3H), 5.12 (q, J = 7.0 Hz, 1H), 4.78 (td, J = 5.6, 3.5 Hz, 1H), 4.44 – 4.36 (m, 2H), 2.63 (td, J = 7.0, 3.6 Hz, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 1.59 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H). HRMS(B) (M+H) 421.2348 Calc'd (M+H) 421.2352 2nd peak 326: ^{1}H NMR (400 MHz, MeOD) δ 8.18 (d, J = 5.8 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.48 – 7.41 (m, 1H), 7.40 – 7.35 (m, 3H), 5.07 (q, J = 7.1 Hz, 1H), 4.78 (dt, J = 7.8, 3.8 Hz, 1H), 4.44 – 4.32 (m, 2H), 2.33 (s, 3H), 2.31 (br s, 1H) 2.29 (s, 3H), 1.59 (d, J = 7.1 Hz, 3H), 0.85 (br d, J = 7.0 Hz, 3H), 0.77 (br d, J = 6.9 Hz, 3H). HRMS(B) (M+H) 421.2347 Calc'd (M+H) 421.2352
327 & 328: (S)-3-(2-(1-(4-(1H-imidazol-1-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Separation was achieved by reverse HPLC (10-85% ACN/water 0.1% NH4OH modifier) to give (S)-3-(2-(((R)-1-(4-(1H-imidazol-1-yl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(4-(1H-imidazol-1-yl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one. 1st peak 327: ^{1}H NMR (400 MHz, MeOD) δ 8.25 – 8.00 (m, 2H), 7.53 (d, J = 0.7 Hz, 5H), 7.38 (d, J = 5.9 Hz, 1H), 7.15 (s, 1H), 5.04 (q, J = 7.1 Hz, 1H), 4.50 (br s, 1H), 4.40 – 4.19 (m, 2H), 2.68 (pd, J = 7.0, 3.6 Hz, 1H), 1.57 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 7.0 Hz, 3H). HRMS(B) (M+H) 393.2042 Calc'd (M+H) 393.2039 2nd peak 328: ^{1}H NMR (400 MHz, MeOD) δ 8.16 (d, J = 5.8 Hz, 1H), 8.10 (t, J = 1.2 Hz, 1H), 7.55 (t, J = 1.4 Hz, 1H), 7.52 (s, 4H), 7.38 (d, J = 5.8 Hz, 1H), 7.15 (t, J = 1.2 Hz, 1H), 5.12 (q, J = 7.0 Hz, 1H), 4.67 (br s, 1H), 4.44 – 4.23 (m, 2H), 1.84 (br s, 1H), 1.57 (d, J = 7.0 Hz, 3H), 0.71 (br s, 3H), 0.60 (br s, 3H). HRMS(B) (M+H) 393.2026 Calc'd (M+H) 393.2039
329 & 330: (S)-3-(2-(1-(3-fluoro-4-(pyridin-3-yloxy)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (Column AD-H 5mM 20x250mm column 15% MeOH+DEA) to give (S)-3-(2-(((R)-1-(3-fluoro-4-(pyridin-3-yloxy)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-fluoro-4-(pyridin-3-yloxy)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one. 1st peak 329: ^{1}H NMR (400 MHz, MeOD) δ 8.32 – 8.23 (m, 2H), 8.15 (d, J = 5.8 Hz, 1H), 7.45 – 7.35 (m, 3H), 7.31 (dd, J = 11.8, 2.0 Hz, 1H), 7.26 (dd, J = 8.5, 2.0 Hz, 1H), 7.19 (t, J = 8.2 Hz, 1H), 5.15 – 4.95 (m, 1H), 4.51 (s, 1H), 4.41 – 4.26 (m, 2H), 2.68 (pd, J = 7.1, 3.6 Hz, 1H), 1.56 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H). HRMS(B) (M+H) 438.1935 Calc'd (M+H) 438.1941 2nd peak 330: ^{1}H NMR (400 MHz, MeOD) δ 8.28 (dd, J = 4.7, 1.4 Hz, 1H), 8.26 (d, J = 2.8 Hz, 1H), 8.17 (d, J =

	5.8 Hz, 1H), 7.43 – 7.40 (m, 2H), 7.36 (ddd, J = 8.4, 2.9, 1.5 Hz, 1H), 7.30 (dd, J = 11.8, 2.0 Hz, 1H), 7.25 (dd, J = 8.4, 2.0 Hz, 1H), 7.19 (t, J = 8.2 Hz, 1H), 5.10 (q, J = 7.1 Hz, 1H), 4.72 (br s, 1H), 4.43 – 4.29 (m, 2H), 1.93 (br s, 1H), 1.55 (d, J = 7.0 Hz, 3H), 0.78 (br s, 3H), 0.69 (br s, 3H). HRMS(B) (M+H) 438.1928 Calc'd (M+H) 438.1941
331 & 332: (4S)-4-isopropyl-3-(2-((1-(4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (Column IA-H 5mM 20x250mm column 30% MeOH) to give (S)-4-isopropyl-3-(2-(((R)-1-(4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st peak 331: HRMS(B) (M+) 426.2267, RT = 2.45min 2nd peak 332: HRMS(B) (M+) 426.2267, RT = 2.37min
333 & 334: (R)-3-(2-(1-(3,4-dichlorophenyl)ethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	Separation was achieved on a normal phase silica gel column with 10 to 40% ethylacetate / heptane to give (R)-3-(2-(((S)-1-(3,4-dichlorophenyl)ethyl)amino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one and (R)-3-(2-(((R)-1-(3,4-dichlorophenyl)ethyl)amino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one 1st peak 333: ^{1}H NMR (400 MHz, MeOD) δ 8.49 (d, J = 5.7 Hz, 1H), 7.85 – 7.74 (m, 5H), 7.74 – 7.68 (m, 1H), 7.66 – 7.61 (m, 2H), 7.55 (dd, J = 8.3, 2.1 Hz, 1H), 5.90 (dd, J = 8.9, 4.0 Hz, 1H), 5.14 (t, J = 8.7 Hz, 1H), 4.97 – 4.89 (m, 1H), 4.56 (dd, J = 8.8, 4.1 Hz, 1H), 1.60 (d, J = 7.0 Hz, 3H). HRMS(B) (M+H) 429.0899 Calc'd (M+H) 429.0885 2nd peak 334: ^{1}H NMR (400 MHz, MeOD) δ 8.50 (d, J = 5.7 Hz, 1H), 7.79 (d, J = 5.9 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.57 (dt, J = 4.6, 2.3 Hz, 3H), 7.45 (dd, J = 6.4, 2.9 Hz, 2H), 7.31 (dd, J = 8.3, 2.2 Hz, 1H), 6.16 (dd, J = 8.6, 3.5 Hz, 1H), 5.26 (q, J = 6.9 Hz, 1H), 5.16 (t, J = 8.6 Hz, 1H), 4.97 – 4.88 (m, 1H), 4.56 (dd, J = 8.8, 3.6 Hz, 1H), 1.80 (d, J = 7.0 Hz, 3H). HRMS(B) (M+H) 429.0887 Calc'd (M+H) 429.0885
335 & 336: (S)-4-isopropyl-3-(2-(1-(4-(pyridin-3-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (Column IA-H 5mM 20x250mm column 40% MeOH, 10mM NH4OH) to give (S)-4-isopropyl-3-(2-(((R)-1-(4-(pyridin-3-yl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(4-(pyridin-3-yl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st peak 335: ^{1}H NMR (400 MHz, MeOD) δ 8.81 (br s, 1H), 8.52 (br s, 1H), 8.14 (br s, 1H), 8.10 (dt, J = 8.2, 1.7 Hz, 1H), 7.71 – 7.59 (m, 2H), 7.58 – 7.46 (m, 3H), 7.37 (d, J = 5.8 Hz, 1H), 5.04 (dd, J = 11.2, 5.3 Hz, 1H), 4.50 (br s, 1H), 4.40 – 4.19 (m, 2H), 2.69 (ddd, J = 10.4, 7.0, 3.5 Hz, 1H), 1.58 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H). HRMS(B) (M+H) 404.2085 Calc'd (M+H) 404.2086 2nd peak 336: ^{1}H NMR (400 MHz, MeOD) δ 8.82 (br s,

	1H), 8.55 (br s, 1H), 8.17 (br s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.70 – 7.59 (m, 2H), 7.54 (br s, 1H), 7.51 – 7.45 (m, 2H), 7.38 (d, J = 5.7 Hz, 1H), 5.11 (q, J = 7.0 Hz, 1H), 4.66 (br s, 1H), 4.36 – 4.30 (m, 2H), 1.80 (br s, 1H), 1.58 (d, J = 7.0 Hz, 3H), 0.67 (br s, 3H), 0.56 (br s, 3H). HRMS(B) (M+H) 404.2079 Calc'd (M+H) 404.2086
337 & 338: (S)-4-isopropyl-3-(2-(1-(4-(pyridin-4-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	Separation was achieved on a normal phase silica gel column with 20 to 100% ethylacetate / heptane to give (S)-4-isopropyl-3-(2-(((R)-1-(4-(pyridin-4-yl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(4-(pyridin-4-yl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st peak 337: ^{1}H NMR (400 MHz, MeOD) δ 8.58 (br s, 2H), 8.14 (d, J = 5.9 Hz, 1H), 7.83 – 7.66 (m, 4H), 7.60 – 7.46 (m, 2H), 7.37 (d, J = 5.8 Hz, 1H), 5.15 – 4.96 (m, 1H), 4.48 (br s, 1H), 4.38 – 4.15 (m, 2H), 2.69 (ddp, J = 10.5, 7.0, 3.5 Hz, 1H), 1.58 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H). HRMS(B) (M+H) 404.2068 Calc'd (M+H) 404.2086 2nd peak 338: ^{1}H NMR (400 MHz, MeOD) δ 8.59 (br s, 2H), 8.17 (br s, 1H), 7.80 – 7.68 (m, 4H), 7.56 – 7.44 (m, 2H), 7.38 (d, J = 5.8 Hz, 1H), 5.11 (q, J = 7.0 Hz, 1H), 4.65 (br s, 1H), 4.31 (dt, J = 17.1, 9.0 Hz, 2H), 1.76 (br s, 1H), 1.58 (d, J = 7.1 Hz, 3H), 0.66 (br s, 3H), 0.55 (br s, 3H). HRMS(B) (M+H) 404.1939 Calc'd (M+H) 404.2086
339 & 340: (S)-4-isopropyl-3-(2-(1-(4-(methyl(phenyl)amino)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	Separation was achieved on a normal phase silica gel column with 40 to 100% ethylacetate / heptane to give (S)-4-isopropyl-3-(2-(((R)-1-(4-(methyl(phenyl)amino)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(4-(methyl(phenyl)amino)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st peak 339: ^{1}H NMR (400 MHz, MeOD) δ 8.12 (d, J = 5.8 Hz, 1H), 7.37 (d, J = 5.8 Hz, 1H), 7.31 – 7.18 (m, 4H), 7.03 – 6.94 (m, 4H), 6.91 (tt, J = 7.4, 1.1 Hz, 1H), 4.99 – 4.93 (m, 1H), 4.57 (br s, 1H), 4.42 – 4.27 (m, 2H), 3.28 (s, 3H), 2.68 (ddq, J = 10.5, 6.9, 3.4 Hz, 1H), 1.53 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H). HRMS(B) (M+H) 432.2390 Calc'd (M+H) 432.2400 2nd peak 340: ^{1}H NMR (400 MHz, MeOD) δ 8.15 (d, J = 5.8 Hz, 1H), 7.37 (d, J = 5.8 Hz, 1H), 7.30 – 7.18 (m, 4H), 7.02 – 6.92 (m, 4H), 6.89 (tt, J = 7.3, 1.1 Hz, 1H), 5.04 (q, J = 7.0 Hz, 1H), 4.77 – 4.67 (m, 1H), 4.43 – 4.26 (m, 2H), 3.27 (s, 3H), 2.11 (br s, 1H), 1.52 (d, J = 7.0 Hz, 3H), 0.79 (br s, 3H), 0.68 (br s, 3H). HRMS(B) (M+H) 432.2386 Calc'd (M+H) 432.2400
341 & 342: S)-3-(2-(1-(3-fluoro-4-(4-methyl-1H-pyrazol-1-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column (IC 20x250nm 45% IPA in CO2, 75g/min Flow) to give (S)-3-(2-(((R)-1-(3-fluoro-4-(4-methyl-1H-pyrazol-1-yl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-fluoro-4-(4-methyl-1H-pyrazol-1-yl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-

	isopropyloxazolidin-2-one. 1st peak 341: ^{1}H NMR (400 MHz, MeOD) δ 8.15 (d, J = 5.8 Hz, 1H), 7.81 (dt, J = 2.9, 0.9 Hz, 1H), 7.66 (t, J = 8.3 Hz, 1H), 7.56 (s, 1H), 7.40 (d, J = 5.8 Hz, 1H), 7.36 – 7.25 (m, 2H), 5.01 (d, J = 7.5 Hz, 1H), 4.46 (br s, 1H), 4.38 – 4.25 (m, 2H), 2.68 (pd, J = 7.0, 3.5 Hz, 1H), 2.17 (d, J = 0.6 Hz, 3H), 1.56 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.1 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H). HRMS(B) (M+H) 425.2089 Calc'd (M+H) 425.2101 2nd peak 342: ^{1}H NMR (400 MHz, MeOD) δ 8.17 (d, J = 5.8 Hz, 1H), 7.80 (d, J = 2.6 Hz, 1H), 7.66 (t, J = 8.3 Hz, 1H), 7.56 (s, 1H), 7.40 (d, J = 5.8 Hz, 1H), 7.35 – 7.26 (m, 2H), 5.10 (q, J = 7.0 Hz, 1H), 4.69 (br s, 1H), 4.43 – 4.24 (m, 2H), 2.17 (s, 3H), 1.80 (br s,1H), 1.56 (d, J = 7.1 Hz, 3H), 0.73 (br s, 3H), 0.62 (br s, 3H). HRMS(B) (M+H) 425.2081 Calc'd (M+H) 424.2101
343 & 344: (S)-3-(2-(1-(4-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (Column IA 20x250mm column 25% MeOH, 0.2% DEA) to give (S)-3-(2-(((R)-1-(4-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(4-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one. 1st peak 343: ^{1}H NMR (400 MHz, MeOD) δ 8.14 (d, J = 5.8 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.41 – 7.34 (m, 3H), 6.06 (s, 1H), 5.07 – 5.02 (m, 1H), 4.46 (br s, 1H), 4.39 – 4.22 (m, 2H), 2.79 – 2.60 (m, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 1.58 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H). HRMS(B) (M+H) 421.2332 Calc'd (M+H) 421.2352 2nd peak 344: ^{1}H NMR (400 MHz, MeOD) δ 8.15 (d, J = 5.8 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.41 – 7.33 (m, 3H), 6.06 (s, 1H), 5.17 (q, J = 7.0 Hz, 1H), 4.74 (br s, 1H), 4.45 – 4.19 (m, 2H), 2.26 (s, 3H), 2.25 (s, 3H), 2.07 (br s, 1H), 1.56 (d, J = 7.0 Hz, 3H), 0.80 (br s, 3H), 0.65 (br s, 3H). HRMS(B) (M+H) 421.2335 Calc'd (M+H) 421.2352
345 & 346: (S)-4-isopropyl-3-(2-((1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 99 bar, eluting 10% MeOH/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st peak 345: HRMS(B) m/z 333.1668 (M + H)+. RT=1.96 min. 2nd peak 346: HRMS(B) m/z 333.1668 (M + H)+. RT=1.58 min.
347 & 348: (S)-4-isopropyl-3-(2-((1-(1-methyl-1H-1,2,4-triazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one.	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 99 bar, eluting 10% MeOH/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(1-methyl-1H-1,2,4-triazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(1-methyl-1H-1,2,4-triazol-5-

	yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st peak 347: HRMS(B) m/z 332.1831 (M + H)+. RT=1.68 min. 2nd peak 348: HRMS(B) m/z 332.1833 (M + H)+. RT=1.57 min.
349 & 350: (S)-3-(2-((1-(imidazo[2,1-b][1,3,4]thiadiazol-6-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 99 bar, eluting 10% MeOH/CO2) to give (S)-3-(2-(((R)-1-(imidazo[2,1-b][1,3,4]thiadiazol-6-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(imidazo[2,1-b][1,3,4]thiadiazol-6-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one. 1st peak 349: HRMS(B) m/z 374.1384 (M + H)+. RT=2.01 min. 2nd peak 350: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.12 (d, J = 5.8 Hz, 1H), 7.60 (s, 1H), 7.38 (d, J = 5.8 Hz, 1H), 5.13 (s, 1H), 4.60 (dt, J = 8.3, 3.3 Hz, 1H), 4.33 – 4.07 (m, 2H), 2.25 (b, 1H), 1.57 (d, J = 6.8 Hz, 3H), 0.84 – 0.52 (b, 6H). HRMS(B) m/z 373.1321 (M +), RT=1.88 min.
351 & 352: (S)-3-(2-((1-(1-ethyl-1H-1,2,4-triazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 99 bar, eluting 10% MeOH/CO2) to give (S)-3-(2-(((R)-1-(1-ethyl-1H-1,2,4-triazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(1-ethyl-1H-1,2,4-triazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 351: HRMS(B) m/z 346.1985 (M + H)+. RT=1.89 min. 2nd peak 352: HRMS(B) m/z 346.1983 (M + H)+, RT=1.75 min.
353 & 354: (S)-3-(2-((1-(4-ethyl-4H-1,2,4-triazol-3-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 99 bar, eluting 10% MeOH/CO2) to give (S)-3-(2-(((R)-1-(4-ethyl-4H-1,2,4-triazol-3-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(4-ethyl-4H-1,2,4-triazol-3-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 353: HRMS(B) m/z 346.1984 (M + H)+. RT=1.80 min. 2nd peak 354:HRMS(B) m/z 346.1982 (M + H)+, RT=1.77 min.
355 & 356: (S)-3-(2-((1-(imidazo[2,1-b]thiazol-6-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 75 ml/min, 120 bar, eluting 20-30% MeOH/CO2) to give (S)-3-(2-(((R)-1-(imidazo[2,1-b]thiazol-6-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(imidazo[2,1-b]thiazol-6-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 355: HRMS(B) m/z 373.1436 (M + H)+. RT=1.92 min.

	2nd peak 356: HRMS(B) m/z 373.1439 (M +H)+, RT=1.84 min.
357 & 358: N-(4-(1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)ethyl)phenyl)methanesulfonamide	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 96 bar, eluting 25% MeOH/CO2) to give N-(4-((R)-1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)ethyl)phenyl)methanesulfonamide and N-(4-((S)-1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)ethyl)phenyl)methanesulfonamide 1st peak 357: HRMS(B) m/z 420.1689 (M + H)+. RT=2.08 min. 2nd peak 358: HRMS(B) m/z 420.1687 (M +H)+, RT=1.98 min.
359 & 360: (S)-4-isopropyl-3-(2-((1-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Separation was achieved by silica gel chromatography (10 to 40% EtOAc / heptane) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 359: HRMS(B) m/z 396.1784 (M + H)+. RT=2.26 min. 2nd peak 360: HRMS(B) m/z 396.1784 (M +H)+, RT=2.20 min.
361 & 362: (S)-4-isopropyl-3-(2-((1-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Separation was achieved by silica gel chromatography (10 to 40% EtOAc / heptane) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one. 1st peak 361: HRMS(B) m/z 409.1985 (M + H)+. RT=2.88 min. 2nd peak 362: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 5.8 Hz, 1H), 8.03 (d, J = 5.9 Hz, 2H), 7.59 (d, J = 5.8 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 5.41 (b, 1H), 4.67 (dt, J = 8.2, 3.3 Hz, 1H), 4.36 – 4.18 (m, 2H), 2.42 (s, 3H), 2.29 – 2.13 (m, 1H), 1.78 (d, J = 7.2 Hz, 3H), 0.81 (d, J = 7.1 Hz, 3H), 0.73 (d, J = 7.0 Hz, 3H). HRMS(B) m/z 409.1985 (M +H)+, RT=2.85 min.
363 & 364: (S)-4-isopropyl-3-(2-((1-(4-(methylsulfonyl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 74 ml/min, 100 bar, eluting 25% MeOH/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(4-(methylsulfonyl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(4-(methylsulfonyl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 363: HRMS(B) m/z 405.1594 (M + H)+. RT=2.26 min. 2nd peak 364: HRMS(B) m/z 405.1595 (M +H)+, RT=2.14 min.
365 & 366: (S)-4-isopropyl-3-(2-((1-(3-methyl-1,2,4-oxadiazol-5-	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 100 bar, eluting 20% IPA/CO2) to give (S)-4-

yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	isopropyl-3-(2-(((R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 365: HRMS(B) m/z 333.1679 (M + H)+. RT=2.19 min. 2nd peak 366: HRMS(B) m/z 333.1680 (M +H)+, RT=2.12 min.
367 & 368: (S)-3-(2-((1-(3-ethylisoxazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 79 ml/min, 100 bar, eluting 20% IPA/CO2) to give (S)-3-(2-(((R)-1-(3-ethylisoxazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-ethylisoxazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 367: HRMS(B) m/z 346.1886 (M + H)+. RT=2.51 min. 2nd peak 368: HRMS(B) m/z 346.1882 (M +H)+, RT=2.45 min.
369 & 370: (S)-4-isopropyl-3-(2-((1-(3-propyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 75 ml/min, 100 bar, eluting 20% IPA/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-propyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-propyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 369: HRMS(B) m/z 361.1989 (M + H)+. RT=2.52 min. 2nd peak 370: HRMS(B) m/z 361.1985 (M +H)+, RT=2.49 min.
371 & 372: (S)-3-(2-((1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 100 bar, eluting 15% IPA/CO2) to give (S)-3-(2-(((R)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 371: HRMS(B) m/z 359.1830 (M + H)+. RT=2.42 min. 2nd peak 372: HRMS(B) m/z 359.1833 (M +H)+, RT=2.37 min.
373 & 374: (S)-4-isopropyl-3-(2-((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 100 bar, eluting 20% IPA/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 373: HRMS(B) m/z 361.1990 (M + H)+. RT=2.58 min. 2nd peak 374: HRMS(B) m/z 361.1987 (M +H)+, RT=2.54 min.
375 & 376: (S)-3-(2-((1-(1-ethyl-1H-pyrazol-3-	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 78

yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	ml/min, 100 bar, eluting 20% IPA/CO2) to give (S)-3-(2-(((R)-1-(1-ethyl-1H-pyrazol-3-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(1-ethyl-1H-pyrazol-3-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 375: HRMS(B) m/z 345.2046 (M + H)+. RT=2.31 min. 2nd peak 376: HRMS(B) m/z 345.2050 (M +H)+, RT=2.26 min.
377 & 378: (S)-3-(2-((1-(2-hydroxyphenyl)ethyl) amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral column chromatography (OJ-H , 4.6x250 mm column , 1 ml/min, eluting 25% ethanol /Heptane) to give (S)-3-(2-(((R)-1-(2-hydroxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(2-hydroxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 377: HRMS(B) m/z 343.1767 (M + H)+. RT=2.41 min. 2nd peak 378: HRMS(B) m/z 343.1767 (M +H)+, RT=2.36 min.
379 & 380: (S)-4-isopropyl-3-(2-((1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 874ml/min, 100 bar, eluting 30% IPA/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 379: HRMS(B) m/z 408.2135 (M + H)+. RT=2.37 min. 2nd peak 380: HRMS(B) m/z 408.2140 (M +H)+, RT=2.31 min.
381 & 382: (S)-4-isopropyl-3-(2-((1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 74 ml/min, 100 bar, eluting 20% -35% IPA/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 381: HRMS(B) m/z 395.1792 (M + H)+. RT=2.63 min. 2nd peak 382: HRMS(B) m/z 395.1818(M +H)+, RT=2.58min.
383 & 384: (S)-3-(2-(((R)-1-(1H-pyrrolo[2,3-b]pyridin-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA , 20x250 mm column , 74 ml/min, 99 bar, eluting 45% MeOH w ith 5mM NH4OH /CO2) to give (S)-3-(2-(((R)-1-(1H-pyrrolo[2,3-b]pyridin-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(1H-pyrrolo[2,3-b]pyridin-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 383: HRMS(B) m/z 367.1862 (M + H)+. RT=2.10 min. 2nd peak 384: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 2.2 Hz, 1H), 8.19 (d, J = 5.8 Hz, 1H), 7.94 (d, J = 2.1

	Hz, 1H), 7.47 (d, J = 5.8 Hz, 1H), 7.38 (d, J = 3.5 Hz, 1H), 6.46 (d, J = 3.5 Hz, 1H), 5.30 – 5.08 (m, 1H), 4.73 – 4.51 (m, 1H), 4.28 (t, J = 8.8 Hz, 1H), 4.19 (dd, J = 9.0, 3.1 Hz, 1H), 1.78 (dd, J = 31.8, 17.0 Hz, 1H), 1.66 (d, J = 6.9 Hz, 3H), 0.56 (s, 6H). HRMS(B) m/z 367.1870(M +H)+, RT=2.00min.
385 & 386: (S)-4-isopropyl-3-(2-((1-(1-methyl-1H-benzo[d]imidazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 99 bar, eluting 20% IPA/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(1-methyl-1H-benzo[d]imidazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(1-methyl-1H-benzo[d]imidazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 385: HRMS(B) m/z 381.2026 (M + H)+. RT=2.05 min. 2nd peak 386: HRMS(B) m/z 381.2022(M +H)+, RT=1.96min.
387 & 388: (S)-4-isopropyl-3-(2-((1-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 100 bar, eluting 25% IPA/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 387: HRMS(B) m/z 383.1811 (M + H)+. RT=1.90 min. 2nd peak 388: HRMS(B) m/z 383.1815(M +H)+, RT=1.85min.
389 & 390: (S)-3-(2-((1-(benzo[d]thiazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (ID, 5uM, 20x250 mm column , 74 ml/min, 100 bar, eluting 35%MeOH/CO2) to give (S)-3-(2-(((R)-1-(benzo[d]thiazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(benzo[d]thiazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 389: HRMS(B) m/z 384.1488 (M + H)+. RT=2.44 min. 2nd peak 390: HRMS(B) m/z 384.1473(M +H)+, RT=2.36min.
391 & 392: (S)-3-(2-((1-(indolizin-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (OJ , 5uM, 20x250 mm column , 75 ml/min, 120 bar, eluting 15-55% MeOH/CO2) to give (S)-3-(2-(((R)-1-(indolizin-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(indolizin-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 391: HRMS(B) m/z 366.1926 (M + H)+. RT=2.66 min. 2nd peak 392: HRMS(B) m/z 366.1918(M +H)+, RT=2.63min.
393 & 394: (S)-4-isopropyl-3-(2-((1-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 80 ml/min, 100 bar, eluting 5-55% MeOH/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-(2-methoxyphenyl)-1,2,4-

yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-(2-methoxyphenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 393: HRMS(B) m/z 425.1925 (M + H)+. RT=2.57 min. 2nd peak 394: HRMS(B) m/z 425.1916(M +H)+, RT=2.52min.
395 & 396: (S)-4-isopropyl-3-(2-((1-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA, 5uM, 20x250 mm column , 74 ml/min, 100 bar, eluting m25% MeOH/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 395: HRMS(B) m/z 425.1924 (M + H)+. RT=2.60 min. 2nd peak 396: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dt, J = 7.7, 1.2 Hz, 1H), 7.49 (dt, J = 3.7, 1.8 Hz, 2H), 7.29 (t, J = 8.0 Hz, 2H), 6.96 (ddd, J = 8.3, 2.7, 0.9 Hz, 1H), 5.34 (b, 1H), 4.58 (dt, J = 8.2, 3.3 Hz, 1H), 4.37 – 4.03 (m, 2H), 3.78 (s, 3H), 2.12 (b, 1H), 1.68 (d, J = 7.1 Hz, 3H), 0.73 (d, J = 7.1 Hz, 3H), 0.65 (d, J = 7.0 Hz, 3H). HRMS(B) m/z 425.1924(M +H)+, RT=2.54min.
397 & 398: (S)-3-(2-((1-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H , 5uM, 20x250 mm column , 75 ml/min, 100 bar, eluting 20% MeOH/CO2) to give (S)-3-(2-(((R)-1-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 397: HRMS(B) m/z 413.1729 (M + H)+. RT=2.66 min. 2nd peak 398: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dt, J = 7.8, 1.2 Hz, 1H), 7.77 (ddd, J = 9.4, 2.7, 1.5 Hz, 2H), 7.60 (d, J = 5.3 Hz, 1H), 7.46 (td, J = 8.0, 5.7 Hz, 1H), 7.22 (tdd, J = 8.4, 2.6, 1.0 Hz, 1H), 5.44 (b, 1H), 4.68 (dt, J = 8.3, 3.3 Hz, 1H), 4.44 – 4.11 (m, 2H), 2.18 (d, J = 8.4 Hz, 1H), 1.78 (d, J = 7.1 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H). HRMS(B) m/z 413.1732(M +H)+, RT=2.61min.
399 & 400: (S)-3-(2-((1-(3-cyclopentyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA , 5uM, 20x250 mm column , 74 ml/min,99 bar, eluting 15% MeOH/CO2) to give (S)-3-(2-(((R)-1-(3-cyclopentyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-cyclopentyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 399: HRMS(B) m/z 387.2133 (M + H)+. RT=2.54 min. 2nd peak 400: HRMS(B) m/z 387.2117(M +H)+, RT=2.50min.

401 & 402: (S)-3-(2-((1-(3-cyclohexyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA, 5uM, 20x250 mm column , 74 ml/min, 99 bar, eluting 30% MeOH/CO2) to give (S)-3-(2-(((R)-1-(3-cyclohexyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-cyclohexyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 401: HRMS(B) m/z 401.2277 (M + H)+. RT=2.71 min. 2nd peak 402: HRMS(B) m/z 401.2288(M +H)+, RT=2.68min.
403 & 404: (S)-3-(2-((1-(3-(tert-butyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA, 5uM, 20x250 mm column , 74 ml/min, 100 bar, eluting 15% MeOH/CO2) to give (S)-3-(2-(((R)-1-(3-(tert-butyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-(tert-butyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 403: HRMS(B) m/z 375.2131 (M + H)+. RT=2.47 min. 2nd peak 404: HRMS(B) m/z375.2130 (M +H)+, RT=2.44min.
405 & 406: (S)-3-(2-((1-(3-isobutyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA, 5uM, 20x250 mm column , 74 ml/min, 100 bar, eluting 15% MeOH/CO2) to give (S)-3-(2-(((R)-1-(3-isobutyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-isobutyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 405: HRMS(B) m/z 375.2120 (M + H)+. RT=2.45 min. 2nd peak 406: HRMS(B) m/z 375.2135 (M +H)+, RT=2.44min.
407 & 408: (S)-3-(2-((1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA, 5uM, 20x250 mm column , 74 ml/min, 99 bar, eluting 30% IPA/CO2) to give (S)-3-(2-(((R)-1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 407: HRMS(B) m/z 413.1713 (M + H)+. RT=2.31 min. 2nd peak 408: HRMS(B) m/z 413.1721 (M +H)+, RT=2.25min.
409 & 410: (S)-3-(2-((1-(benzo[d]oxazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA, 5uM, 20x250 mm column , 74 ml/min, 99 bar, eluting 25% MeOH/CO2) to give (S)-3-(2-(((R)-1-(benzo[d]oxazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(benzo[d]oxazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one

	1st peak 409: HRMS(B) m/z 368.1729 (M + H)+. RT=2.66 min. 2nd peak 410: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.61 (m, 1H), 7.54 (s, 1H), 7.51 – 7.42 (m, 2H), 7.40 – 7.21 (m, 2H), 6.40 (b, 1H), 5.39 (s, 1H), 4.64 (dt, J = 8.1, 3.2 Hz, 1H), 4.36 – 4.17 (m, 2H), 2.11 (b, 1H), 1.77 (d, J = 6.9 Hz, 3H), 0.64 (b, 6H). HRMS(B) m/z 368.1727 (M +H)+, RT=2.60min.
411 & 412: (S)-3-(2-((1-(4-(4-chlorophenyl)-5-methylthiazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Separation was achieved by silica gel chromatography (10 to 50% EtOAc / heptane) to give (S)-3-(2-(((R)-1-(4-(4-chlorophenyl)-5-methylthiazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(4-(4-chlorophenyl)-5-methylthiazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 411: HRMS(B) m/z 458.1401 (M + H)+. RT=3.02 min. 2nd peak 412: HRMS(B) m/z 458.1401 (M +H)+, RT=2.92min.
413 & 414: (S)-3-(2-((1-(3-ethyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H column (80 g/min, 80 bar, 20 x 250 mm) eluting 15% MeOH/CO2) to give (S)-3-(2-(((R)-1-(3-ethyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-ethyl-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 413: HRMS(B) m/z 346.1753 RT=2.13 min. 2nd peak 414: HRMS(B) m/z 346.1753 RT=2.05 min.
415 & 416: (S)-4-isopropyl-3-(2-((1-(4-methylthiazol-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H column (75 ml/min, 120 bar, 20 x 250 mm) eluting 10-25% MeOH/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(4-methylthiazol-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(4-methylthiazol-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 415: HRMS(B) m/z 347.1416 RT=2.25 min. 2nd peak 416: HRMS(B) m/z 347.1416 RT=2.17 min.
417 & 418: (S)-4-isopropyl-3-(2-((1-(thiophen-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H column (75 ml/min, 120 bar, 20 x 250 mm) eluting 10-25% MeOH/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(thiophen-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(thiophen-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 417: HRMS(B) m/z 332.1307 RT=2.54 min. 2nd peak 418: HRMS(B) m/z 332.1307 RT=2.53 min.
419 & 420: (S)-3-(2-((1-(furan-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD-H column (75 ml/min, 120 bar, 20 x 250 mm) eluting 10-25% MeOH/CO2) to give (S)-3-(2-(((S)-1-(furan-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((R)-1-(furan-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 419: HRMS(B) m/z 316.1535 RT=2.37 min.

	2nd peak 420: HRMS(B) m/z 316.1535 RT=2.39 min.
421 & 422: (S)-4-isopropyl-3-(2-((1-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA column (75 ml/min, 120 bar, 20 x 250 mm) eluting 15-25% MeOH/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 421: HRMS(B) m/z 395.1706 RT=1.75 min. 2nd peak 422: HRMS(B) m/z 395.1706 RT=2.25 min.
423 & 424: (S)-3-(2-((1-(3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA column (75 ml/min, 120 bar, 20 x 250 mm) eluting 15-25% MeOH/CO2) to give (S)-3-(2-(((R)-1-(3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 423: HRMS(B) m/z 428.1364 RT=3.01 min. 2nd peak 424: HRMS(B) m/z 428.1364 RT=2.79 min.
425 & 426: (S)-3-(2-((1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA column (75 ml/min, 120 bar, 20 x 250 mm) eluting 15-25% MeOH/CO2) to give (S)-3-(2-(((R)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 425: HRMS(B) m/z 428.1364 RT=2.65 min. 2nd peak 426: ^{1}H NMR (400 MHz, MeOD) δ 8.22 (d, J = 5.8 Hz, 1.0H), 8.08 – 7.97 (m, 2.07 H), 7.63 – 7.40 (m, 3.09 H), 5.41 (q, J = 7.2 Hz, 1.04 H), 4.75 – 4.63 (m, 0.97 H), 4.33 (d, J = 6.3 Hz, 2.18 H), 1.76 (d, J = 7.2 Hz, 3.31 H), 1.07 – 0.85 (m, 0.95 H), 0.70 (d, J = 38.0 Hz, 5.81 H). HRMS(B) m/z 428.1364
427: (S)-4-isopropyl-3-(2-((1-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IA column (75 ml/min, 120 bar, 20 x 250 mm) eluting 15-25% MeOH/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-(pyridin-3-yl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 2nd peak 427: HRMS(B) m/z 395.1706 RT=2.24 min.
428 & 429: (S)-3-(2-((1-(1-ethyl-1H-pyrazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD column (75 g/min, 120 bar, 20 x 250 mm) eluting 25% IPA/0.2% DEA/CO2) to give (S)-3-(2-(((R)-1-(1-ethyl-1H-pyrazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(1-ethyl-1H-pyrazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 428: HRMS(B) m/z 345.2005 (M+H) RT=2.28 min. 2nd peak 429: HRMS(B) m/z 345.2044 (M+H) RT=2.21 min.

430: (S)-4-isopropyl-3-(2-(((S)-1-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD column (75 g/min, 120 bar, 20 x 250 mm) eluting 25-35% IPA/0.2% DEA/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 2nd peak 430: HRMS(B) m/z 345.2044 (M+H) RT=2.82 min.
431 & 432: (S)-4-isopropyl-3-(2-((1-(2-phenylthiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD column (75 g/min, 120 bar, 20 x 250 mm) eluting 40% IPA/0.2% DEA/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(2-phenylthiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(2-phenylthiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 431: HRMS(B) m/z 409.1573 RT=2.33 min. 2nd peak 432: ^{1}H NMR (400 MHz, MeOD) δ 8.19 (d, J = 5.8 Hz, 1H), 7.92 – 7.78 (m, 2H), 7.65 (d, J = 1.1 Hz, 1H), 7.53 – 7.27 (m, 4H), 5.43 (q, J = 6.9 Hz, 1H), 4.74 (dt, J = 7.8, 3.7 Hz, 1H), 4.41 – 4.20 (m, 2H), 2.16 (s, 1H), 1.69 (d, J = 7.0 Hz, 3H), 1.15 (d, J = 6.1 Hz, 1H), 0.88 – 0.49 (m, 6H). HRMS(B) m/z 409.1573
433 & 434: (S)-4-isopropyl-3-(2-((1-(3-(o-tolyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AD column (75 g/min, 120 bar, 20 x 250 mm) eluting 25-40% IPA/0.2% DEA/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-(o-tolyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-(o-tolyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 433: HRMS(B) m/z 409.1 (M+H) RT=2.25 min. 2nd peak 434: ^{1}H NMR (400 MHz, MeOD) δ 8.20 (d, J = 5.8 Hz, 1H), 7.90 (dd, J = 7.7, 1.4 Hz, 1H), 7.47 (d, J = 5.8 Hz, 1H), 7.41 – 7.25 (m, 3H), 5.40 (q, J = 7.2 Hz, 1H), 4.69 (s, 1H), 4.44 – 4.22 (m, 2H), 3.34 (s, 2H), 2.54 (s, 3H), 1.75 (d, J = 7.2 Hz, 3H), 1.15 (d, J = 6.1 Hz, 1H), 0.69 (d, J = 35.0 Hz, 6H). HRMS(B) m/z 409.1 (M+H)
435 & 436: 4-(1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)ethyl)-N,N-dimethylbenzenesulfonamide	Chiral separation was achieved by chiral SFC column chromatography (AS-H column (80 g/min, 120 bar, 20 x 250 mm) eluting 15% IPA/0.2% DEA/CO2) to give 4-((R)-1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)ethyl)-N,N-dimethylbenzenesulfonamide and 4-((S)-1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)ethyl)-N,N-dimethylbenzenesulfonamide 1st peak 435: HRMS(B) m/z 433.1784 RT=2.45 min. 2nd peak 436: HRMS(B) m/z 433.1784 RT=2.32 min.
437 & 438: (S)-4-isopropyl-3-(2-((1-(thiazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (IC column (75 g/min, 120 bar, 20 x 250 mm) eluting 25% IPA/0.2% DEA/CO2) to give (S)-4-isopropyl-3-(2-(((S)-1-(thiazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((R)-1-(thiazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one

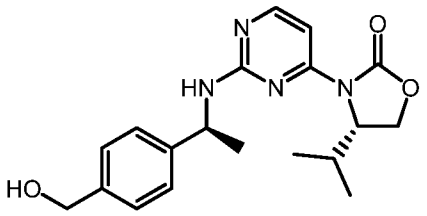
	1st peak 437: HRMS(B) m/z 333.1259 RT=1.88 min. 2nd peak 438: HRMS(B) m/z 333.1259 RT=1.98 min.
439 & 440: (S)-4-isopropyl-3-(2-((1-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AI column (70 g/min, 120 bar, 20 x 250 mm) eluting 20% IPA/0.2% DEA/CO2) to give (S)-4-isopropyl-3-(2-(((R)-1-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-(((S)-1-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one 1st peak 438: HRMS(B) m/z 425.1921 (M+H) RT=2.49 min. 2nd peak 439: HRMS(B) m/z 425.1923 (M+H) RT=2.42 min.
441 & 442: (S)-3-(2-((1-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (AI column (70 g/min, 120 bar, 20 x 250 mm) eluting 25% IPA/0.2% DEA/CO2) to give (S)-3-(2-(((R)-1-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 441: HRMS(B) m/z 413.1719 (M+H) RT=2.58 min. 2nd peak 442: HRMS(B) m/z 413.1719 (M+H) RT=2.52 min.
443: (S)-3-(2-(((S)-1-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (ID-H column (80 g/min, 120 bar, 20 x 250 mm) eluting 30% MeOH/CO2) to give (S)-3-(2-(((R)-1-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-(((S)-1-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 2nd peak 443: ^{1}H NMR (400 MHz, MeOD) δ 8.25 – 8.03 (m, 6H), 7.71 – 7.55 (m, 4H), 7.44 (d, J = 5.7 Hz, 2H), 5.26 (d, J = 5.6 Hz, 2H), 4.71 (d, J = 7.9 Hz, 2H), 4.46 – 4.26 (m, 4H), 3.37 (s, 1H), 2.66 (heptd, J = 7.0, 3.3 Hz, 2H), 1.69 (d, J = 7.1 Hz, 6H), 1.17 (d, J = 6.2 Hz, 1H), 1.04 (d, J = 7.1 Hz, 6H), 0.88 (d, J = 6.9 Hz, 6H). HRMS(B) m/z 428.1364 RT=2.77 min.
444 & 445: (S)-3-(2-(1-(5-(4-fluoro-3-methylphenyl)pyridin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Separation was achieved by silica gel chromatography (10 to 100% EtOAc / heptane) to give (S)-3-(2-((R)-1-(5-(4-fluoro-3-methylphenyl)pyridin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-((S)-1-(5-(4-fluoro-3-methylphenyl)pyridin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 444: HRMS(B) m/z 436.2126 (M + H)+, RT=2.78min 2nd peak 445: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, J = 2.3, 0.9 Hz, 1H), 8.23 (d, J = 5.8 Hz, 1H), 7.78 (dd, J = 8.1, 2.4 Hz, 1H), 7.49 (d, J = 5.7 Hz, 1H), 7.41 – 7.27 (m, 3H), 7.12 (dd, J = 9.4, 8.4 Hz, 1H), 5.95 (d, J = 6.5 Hz, 1H), 5.16 (br s, 1H), 4.66 (br s, 1H), 4.34 – 4.19 (m,

	2H), 2.37 (d, J = 1.9 Hz, 3H), 1.93 (br s, 1H), 1.65 – 1.61 (m, 3H), 0.71 (br s, 6H). HRMS(B) m/z 436.2131 (M + H)+.
446 & 447: (S)-3-(2-(1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Chiral separation was achieved by chiral SFC column chromatography (Column IA 20x250mm column 30% IPA, 70% CO2) to give (S)-3-(2-((S)-1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-((R)-1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 446: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 2H), 8.21 (d, J = 5.8 Hz, 1H), 7.49 (d, J = 5.7 Hz, 1H), 7.18 – 6.99 (m, 4H), 6.18 (br s 1H), 5.28 (br s, 1H), 4.75 (dt, J = 8.2, 3.4 Hz, 1H), 4.39 – 4.25 (m, 2H), 2.34 (br s, 1H), 1.65 – 1.59 (m, 3H), 0.95 – 0.86 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H). HRMS(B) m/z 439.1876 (M + H)+. 2nd peak 447: HRMS(B) m/z 439.1883 (M + H)+, RT = 3.37min
448 & 449: (S)-3-(2-(1-(5-(4-fluorophenoxy)pyridin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	Separation was achieved by silica gel chromatography (20 to 100% EtOAc / heptane) to give (S)-3-(2-((R)-1-(5-(4-fluorophenoxy)pyridin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-((S)-1-(5-(4-fluorophenoxy)pyridin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st peak 448: HRMS(B) m/z 438.1922 (M + H)+. RT = 2.62min 2nd peak 449: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, J = 2.7, 0.8 Hz, 1H), 8.21 (d, J = 5.8 Hz, 1H), 7.49 (d, J = 5.8 Hz, 1H), 7.33 – 7.18 (m, 3H), 7.14 – 6.95 (m, 3H), 5.95 (d, J = 7.1 Hz, 1H), 5.14 (br s, 1H), 4.68 (d, J = 7.8 Hz, 1H), 4.36 – 4.22 (m, 2H), 1.75 (br s, 1H), 1.61 – 1.57 (m, 3H), 0.95 - 0.75 (m, 6H). HRMS(B) m/z 438.1950 (M + H)+.
450 & 451: (R)-3-(5-fluoro-2-(1-(5-(4-fluorophenoxy)pyridin-2-yl)ethylamino)pyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one	Separation was achieved by silica gel chromatography (10 to 100% EtOAc / heptane) to give (R)-3-(5-fluoro-2-((S)-1-(5-(4-fluorophenoxy)pyridin-2-yl)ethylamino)pyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one and (R)-3-(5-fluoro-2-((R)-1-(5-(4-fluorophenoxy)pyridin-2-yl)ethylamino)pyrimidin-4-yl)-5,5-dimethyl-4-phenyloxazolidin-2-one 1st peak 450: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.17 (m, 1H), 8.08 (d, J = 2.8 Hz, 1H), 7.31 – 6.86 (m, 11H), 5.83 (d, J = 7.2 Hz, 1H), 5.28 (s, 1H), 4.69 (br s, 1H), 1.58 (s, 3H), 1.29 – 1.11 (m, 3H), 0.98 (s, 3H). HRMS(B) m/z 518.2005 (M + H)+. 2nd peak 451: HRMS(B) m/z 518.2003 (M + H)+, RT = 3.08min
452 & 453: (S)-3-(2-(1-(5-(4-fluorophenoxy)pyrazin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.	Separation was achieved by silica gel chromatography (25 to 100% EtOAc / heptane) to give (S)-3-(2-((R)-1-(5-(4-fluorophenoxy)pyrazin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-((S)-1-(5-(4-fluorophenoxy)pyrazin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one. 1st peak 452: HRMS(B) m/z 439.1877 (M + H)+, RT =

	2.66min 2nd peak 453: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 1.4 Hz, 1H), 8.20 (d, J = 5.8 Hz, 1H), 8.09 (s, 1H), 7.49 (d, J = 5.8 Hz, 1H), 7.12 (d, J = 6.3 Hz, 4H), 5.71 (s, 1H), 5.20 (br s, 1H), 4.66 (dt, J = 7.7, 2.9 Hz, 1H), 4.36 – 4.22 (m, 2H), 2.10 (br s, 1H), 1.61 (d, J = 6.9 Hz, 3H), 0.94 – 0.78 (m, 6H). HRMS(B) m/z 439.1882 (M + H)+.
454 & 455: (S)-3-(2-(1-(2-(4-fluorophenoxy)pyrimidin-5-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.	Separation was achieved by silica gel chromatography (25 to 100% EtOAc / heptane) to give (S)-3-(2-((R)-1-(2-(4-fluorophenoxy)pyrimidin-5-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-((S)-1-(2-(4-fluorophenoxy)pyrimidin-5-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one. 1st peak 454: HRMS(B) m/z 439.1904 (M + H)+, RT = 3.09 min 2nd peak 455: HRMS(B) m/z 439.1897 (M + H)+ , RT = 3.17 min
456: (S)-3-(2-(1-(5-(2,4-difluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.	Separation was achieved on a normal phase silica gel column with 20 to 100% ethylacetate / heptane to give (S)-3-(2-((R)-1-(5-(2,4-difluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-((S)-1-(5-(2,4-difluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one. 2nd Peak 456: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 2H), 8.09 (d, J = 5.9 Hz, 1H), 7.42 (d, J = 5.9 Hz, 1H), 7.08 (td, J = 8.9, 5.4 Hz, 1H), 6.98 – 6.81 (m, 2H), 5.18 (br s, 1H), 4.64 (dt, J = 7.9, 3.1 Hz, 1H), 4.30 – 4.16 (m, 2H), 2.11 (br s, 1H), 1.53-1.49 (m, 3H), 0.85 – 0.77 (m, 3H), 0.71 (d, J = 6.8 Hz, 3H). HRMS(B) m/z 457.1797 (M + H)+.
457: (S)-4-isopropyl-3-(2-(1-(5-(3-(trifluoromethyl)phenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one.	Separation was achieved on a normal phase silica gel column with 25 to 100% gradient of (25% methanol in ethylacetate) and heptane to give (S)-4-isopropyl-3-(2-((R)-1-(5-(3-(trifluoromethyl)phenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-((S)-1-(5-(3-(trifluoromethyl)phenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one. Peak 2 457: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 2H), 8.14 (d, J = 5.7 Hz, 1H), 7.77 – 7.54 (m, 4H), 7.40 (d, J = 5.7 Hz, 1H), 6.11 (br s, 1H), 5.25 (br s, 1H), 4.67 (dt, J = 7.8, 3.2 Hz, 1H), 4.33 – 4.15 (m, 2H), 2.92 2.15 (br s, 1H), 1.55 (d, J = 8.6 Hz, 3H), 0.85 – 0.76 (m, 3H), 0.70 (br s, 3H). HRMS(B) m/z 473.1897 (M + H)+.
458: (S)-3-(2-((S)-1-(5-(4-fluoro-2-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	The chiral separation was carried out with SFC (IA, 5µm, 20 x 250 mm) using 35% MeOH in CO2 to give (S)-3-(2-((S)-1-(5-(4-fluoro-2-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-((R)-1-(5-(4-fluoro-2-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one 1st Peak 458: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 2H), 8.24 (d, J = 5.8 Hz, 1H), 7.49 (d, J = 5.7 Hz, 1H), 7.17

	(dd, J = 8.4, 5.8 Hz, 1H), 7.10 – 6.98 (m, 2H), 6.28 (br s, 1H), 5.34 (br s, 1H), 4.78 (dt, J = 8.2, 3.3 Hz, 1H), 4.40 – 4.25 (m, 2H), 2.30 (s, 3H), 1.79 (br s, 1H), 1.73 (d, J = 7.1 Hz, 3H), 0.95 – 0.75 (m, 6H). HRMS(B) m/z 437.2086 (M + H)+.

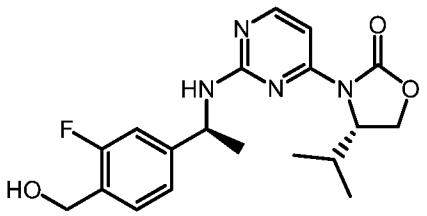
Example 459



A solution of (S)-(4-(1-aminoethyl)phenyl)methanol hydrochloride (4.0301 g, 21.47 mmol, purchased from NetChem), (S)-3-(2-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (5.3648 g, 23.82 mmol, 1.11 equiv) and DIPEA (38.0 mL, 218 mmol, 10.1 equiv) in DMSO (40 mL) was heated at 110 °C for 135 min. The reaction mixture was diluted with EtOAc (200 mL) and washed with water (200 mL). After separation, the aqueous phase was washed with EtOAc (2 x 150 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/heptane 30 to 100%) provided (S)-3-(2-((S)-1-(4-(hydroxymethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (6.42 g) in 84% yield.

^{1}H NMR (400 MHz, CD_3OD) δ 8.13 (d, J = 5.8 Hz, 1 H), 7.36 - 7.28 (m, 5 H), 5.06 (q, J = 7.0 Hz, 1 H), 4.68 (br s, 1 H), 4.58 (s, 2 H), 4.37 - 4.29 (m, 2 H), 1.80 (br s, 1 H), 1.52 (d, J = 7.1 Hz, 3 H), 0.74 (br s, 3 H), 0.61 (br s, 3 H); MS *m/z* 355.1 (M - H)

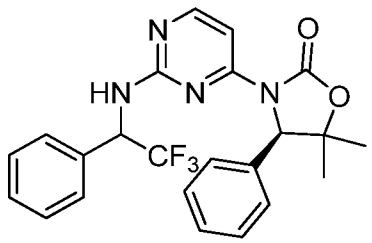
Example 460



S)-3-(2-((S)-1-(3-fluoro-4-(hydroxymethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one was prepared using a method similar to that described for the preparation of Example 459. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 5.9 Hz, 1 H), 7.51 - 7.49 (m, 1 H), 7.37 (t, J = 7.7 Hz, 1 H), 7.11 (d, J = 7.8 Hz, 1 H), 7.01 (d, J = 11, Hz, 1 H), 6.09 (br s, 1 H), 5.00 (br s, 1 H), 4.73 (s, 2 H), 4.61 - 4.55 (m, 1 H), 4.30 (t, J = 8.7

Hz, 1 H), 4.25 - 4.21 (m, 1 H), 3.00 (s, 1 H), 1.89 (br s, 1 H), 1.54 (d, J = 7.1 Hz, 3 H), 0.67 (br s, 6 H); MS *m/z* 375.0 (M + H)

Example 461

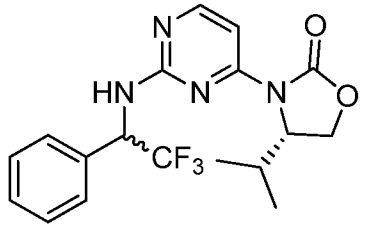


A solution of (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (50mg, 0.165mmol), 2,2,2-trifluoro-1-phenylethanamine (160mg, 0.913mmol) and pTsOH (78mg, 0.412mmol)in 2-BuOH was heated at 110°C for 2.5h. LCMS shows starting material as well as product. Another 78mg of pTsOH was added followed by 98mg of 2,2,2-trifluoro-1-phenylethanamine and heated at 110C for 1.5h. Mostly product some SM.

After cooling down mixture solidified. Added acetonitrial and sonicated. Filtered off solids (pTsOH salt of 2,2,2-trifluoro-1-phenylethanamine). The mother liquor was concentrated and purified by column chromatography (0-40% EtOAc/Hept followed by reverse HPLC (XBridge C18 5uM 10-85% ACN/Water over 12 minutes with 0.01%NH4OH modifier) to give (4R)-5,5-dimethyl-4-phenyl-3-(2-(2,2,2-trifluoro-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one (28mg, 0.063mmol).

^{1}H NMR (400 MHz, MeOD) δ 8.20 (d, J = 5.8 Hz, 1H), 7.58 (dd, J = 11.4, 5.8 Hz, 1H), 7.51 (br d, J = 6.8 Hz, 1H), 7.40 (dtd, J = 15.9, 9.2, 4.5 Hz, 5H), 7.33 – 7.22 (m, 3H), 7.10 (br s, 1H), 5.50 (s, 0.5H), 5.38 (s, 0.5H), 5.29 (br s, 1 H), 1.70 (s, 1.5H), 1.64 (s, 1.5H), 1.04 (s, 1.5H), 1.03 (s, 1.5H). HRMS(B) (M+H) 443.1682 Calc'd (M+H) 443.1695

Example 462 & 463



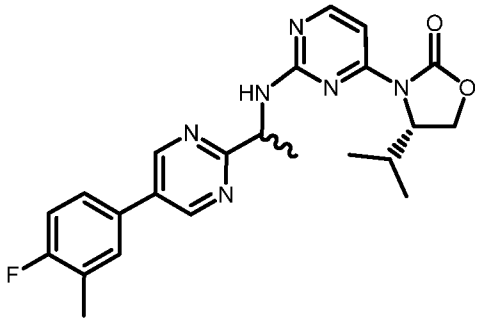
A solution of (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (163 mg, 0.674 mmol), 2,2,2-trifluoro-1-phenylethanamine (624 mg, 3.56 mmol, 5.3 equiv) and p-toluenesulfonic acid monohydrate (321 mg, 1.69 mmol, 2.5 equiv) in n-BuOH (3 mL) was

heated at 110 °C for 2 h and treated with additional p-toluenesulfonic acid monohydrate (321 mg, 1.69 mmol, 2.5 equiv), then heated at 110 °C for 1 ½ h. After cooling, the solid reaction mixture was treated with MeCN, sonicated and filtered. The filtrated was concentrated and purified by silica gel column chromatography (EtOAc/Heptane 0 to 30%) to give (4S)-4-isopropyl-3-(2-(2,2,2-trifluoro-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one (65 mg) in 25% yield. HRMS(B) m/z 381.1545 (M + H)+. Anal. RP-HPLC tR = 4.31//4.46 min (1.0 mL/min flow rate with gradient from 5% to 15% acetonitrile with 0.05% formic acid in 5.00 min and then 15% to 95% acetonitrile with 0.05% formic acid from 5.00 min to 9.50 min, aqueous phase modified with 0.1% formic acid. Silica gel column chromatography separated the two diastereomers (S)-4-isopropyl-3-(2-((R)-2,2,2-trifluoro-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one and (S)-4-isopropyl-3-(2-((S)-2,2,2-trifluoro-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one.

1st Peak : ^{1}H NMR (400 MHz, MeOD) δ 8.23 (d, J = 5.8 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.50 (d, J = 5.8 Hz, 1H), 7.42 (qt, J = 5.0, 2.2 Hz, 3H), 5.93 – 5.86 (m, 1H), 4.80 (dt, J = 7.5, 3.9 Hz, 1H), 4.48 – 4.33 (m, 2H), 2.65 (ddp, J = 10.4, 7.0, 3.4 Hz, 1H), 1.05 (d, J = 7.0 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H).

2nd Peak: ^{1}H NMR (400 MHz, MeOD) δ 8.23 (d, J = 5.8 Hz, 1H), 7.55 (dd, J = 7.3, 2.1 Hz, 2H), 7.49 (d, J = 5.8 Hz, 1H), 7.45 – 7.32 (m, 3H), 5.92 – 5.86 (m, 1H), 4.86 – 4.82 (m, 1H), 4.44 – 4.38 (m, 2H), 2.26 (br s, 1H), 0.94 (d, J = 7.0 Hz, 3H), 0.74 (br s, 3H).

Example 464

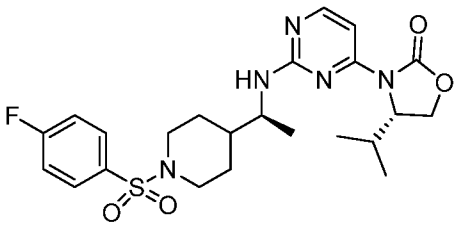


A solution of (*S*)-3-(2-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (1055 mg, 4.68 mmol), 1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethanamine (1300 mg, 5.62 mmol, 1.2 equiv) and diisopropylethylamine (908mg, 7.03mmol, 1.5 equiv) in DMSO (20 mL) was heated at 110 °C for 1 h. The reaction mixture was poured into water (60 mL) and extracted with EtOAc (2x50 mL). Combined organics were washed with water (40mL), brine (40mL), dried over Na_2SO_4, filtered and concentrated directly onto silica gel. Silica gel chromatography provided the mixed distereomers of (S)-3-(2-(1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethylamino) pyrimidin-4-yl)-4-isopropyloxazolidin-2-one

(560mg). Chiral separation was carried out with SFC (ID, 5µm, 20 x 250 mm) using 35% MeOH in CO2 to give (S)-3-(2-((S)-1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (S)-3-(2-((R)-1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

Example 464 first eluted product (302 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 2H), 8.23 (d, J = 5.8 Hz, 1H), 7.49 (d, J = 5.7 Hz, 1H), 7.43 – 7.30 (m, 2H), 7.21 – 7.11 (m, 1H), 6.26 (br s, 1H), 5.31 (br s, 1H), 4.75 (dt, J = 7.9, 3.3 Hz, 1H), 4.39 – 4.24 (m, 2H), 2.38 (s, 3H), 2.09 (br s, 1H), 1.66-1.62 (m, 3H), 0.90 (dd, J = 9.8, 6.0 Hz, 3H), 0.78 (br s, 3H). HRMS(B) m/z 437.2093 (M + H)+.

Example 465



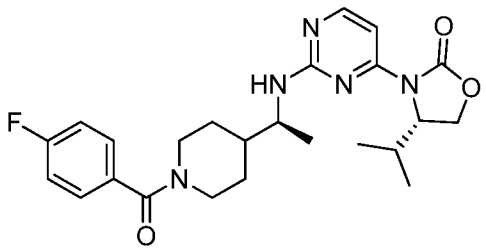
A solution of (S)-4-isopropyl-3-(2-((S)-1-(piperidin-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one (225mg, 0.675mmol), 4-fluorobenzene-1-sulfonyl chloride (146mg, 0.750mmol) and DIPEA (1ml) in CH_2Cl_2 was stirred at room temperature for 2h.

The reaction mixture was diluted with CH_2Cl_2 and washed with water. Aqueous layer was extracted with CH_2Cl_2. Combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to give (S)-3-(2-((S)-1-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (4.5mg, 0.009mmol).

^{1}H NMR (400 MHz, MeOD) δ 8.45 (d, J = 6.0 Hz, 1H), 8.23 – 8.15 (m, 2H), 7.73 – 7.63 (m, 3H), 5.13 (dt, J = 7.4, 3.7 Hz, 1H), 4.78 – 4.69 (m, 2H), 4.26 (p, J = 6.7 Hz, 1H), 4.17 (dddd, J = 11.8, 6.4, 4.7, 2.3 Hz, 2H), 2.89 (ddq, J = 10.7, 7.1, 3.5 Hz, 1H), 2.69 (tdd, J = 11.6, 8.9, 2.6 Hz, 2H), 2.27 – 2.11 (m, 2H), 1.82 (dddt, J = 11.9, 9.0, 5.8, 2.9 Hz, 1H), 1.77 – 1.64 (m, 2H), 1.52 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 7.1 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H). HRMS(B) (M+H) 492.2069 Calc'd (M+H) 492.2081

The following examples were prepared using methods substantially similar to those described for Example 465:

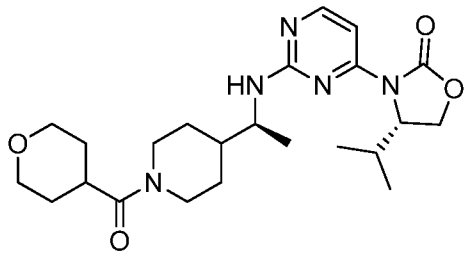
Example 466



Purified by column chromatography (20% to 100% EtOAc/Hept), followed by reverse phase preparative chromatography (C18 column, 10-85% ACN/Water 0.1% NH4OH modifier over 12 min.) to give (S)-3-(2-((S)-1-(1-(4-fluorobenzoyl)piperidin-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (12mg, 0.026mmol).

^{1}H NMR (400 MHz, MeOD) δ 8.12 (d, J = 5.8 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.36 (d, J = 5.8 Hz, 1H), 7.25 – 7.15 (m, 2H), 4.82 (td, J = 5.9, 3.6 Hz, 1H), 4.68 (br s, 1H), 4.41 (d, J = 5.7 Hz, 2H), 3.98 (p, J = 6.7 Hz, 1H), 3.78 (br s, 1H), 3.12 (br s, 1H), 2.82 (br s, 1H), 2.60 (pd, J = 7.1, 6.5, 3.7 Hz, 1H), 1.92 (br s, 1H), 1.80 (dtd, J = 15.3, 9.4, 7.0, 3.6 Hz, 2H), 1.31 (br s, 2H), 1.22 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H). HRMS(B) (M+H) 456.2384 Calc'd (M+H) 456.2411

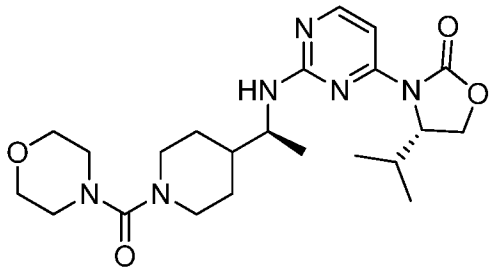
Example 467



Purified by column chromatography (MeOH/CH_2Cl_2 0 to 20%) to give (S)-4-isopropyl-3-(2-((S)-1-(1-(tetrahydro-2H-pyran-4-carbonyl)piperidin-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one (15mg, 0.034mmol).

^{1}H NMR (400 MHz, MeOD) δ 8.12 (d, J = 5.8 Hz, 1H), 7.36 (d, J = 5.8 Hz, 1H), 4.81 (td, J = 5.6, 3.3 Hz, 1H), 4.59 (br s, 1H), 4.41 (d, J = 5.7 Hz, 2H), 4.13 (br s, 1H), 3.96 (ddd, J = 11.6, 4.3, 2.2 Hz, 3H), 3.51 (tq, J = 11.8, 2.8 Hz, 2H), 3.15 – 2.89 (m, 2H), 2.69 – 2.48 (m, 2H), 1.99 – 1.68 (m, 5H), 1.61 (ddt, J = 10.7, 4.0, 2.3 Hz, 2H), 1.35 – 1.23 (m, 1H), 1.21 (d, J = 6.7 Hz, 3H), 1.19 – 1.09 (m, 1H), 0.98 (dd, J = 7.0, 1.5 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H). HRMS(B) (M+H) 446.2748 Calc'd (M+H) 446.2767

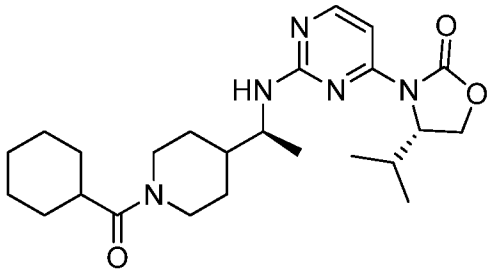
Example 468



Purified by column chromatography (50% to 100% EtOAc/Heptane follwed by 0% to 20% MeOH/CH_2Cl_2) to give (S)-4-isopropyl-3-(2-((S)-1-(1-(morpholine-4-carbonyl)piperidin-4-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one (21mg, 0.047mmol).

^{1}H NMR (400 MHz, MeOD) δ 8.11 (d, J = 5.8 Hz, 1H), 7.36 (d, J = 5.8 Hz, 1H), 4.81 (td, J = 5.8, 3.4 Hz, 1H), 4.41 (d, J = 5.7 Hz, 2H), 3.95 (p, J = 6.8 Hz, 1H), 3.84 – 3.70 (m, 2H), 3.68 – 3.65 (m, 4H), 3.26 – 3.23 (m, 4H), 2.80 (tt, J = 12.9, 3.1 Hz, 2H), 2.60 (ddq, J = 10.4, 7.0, 3.5 Hz, 1H), 1.88 – 1.73 (m, 2H), 1.67 (ddt, J = 18.5, 10.4, 3.5 Hz, 1H), 1.37 – 1.23 (m, 2H), 1.21 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H). HRMS(B) (M+H) 447.2690 Calc'd (M+H) 447.2720

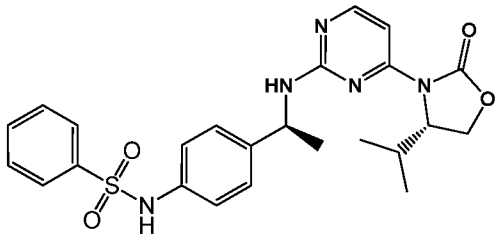
Example 469



Purified by column chromatography to give (S)-3-(2-((S)-1-(1-(cyclohexanecarbonyl) piperidin-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one

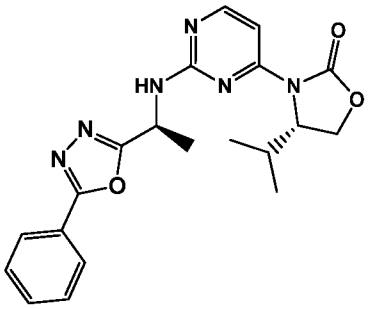
^{1}H NMR (400 MHz, MeOD) δ 8.12 (d, J = 5.7 Hz, 1H), 7.36 (d, J = 5.6 Hz, 1H), 4.80 (dt, J = 5.8, 2.9 Hz, 1H), 4.59 (br s, 1H), 4.40 (d, J = 5.6 Hz, 2H), 4.18 – 4.03 (m, 1H), 3.95 (p, J = 6.8 Hz, 1H), 3.05 (ddd, J = 14.1, 10.1, 6.6 Hz, 1H), 2.58 (td, J = 25.1, 23.5, 13.0 Hz, 3H), 1.97 – 1.63 (m, 8H), 1.54 – 1.08 (m, 7H), 1.21 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H). HRMS(B) (M+H) 444.2953 Calc'd (M+H) 444.2975

Examples 470



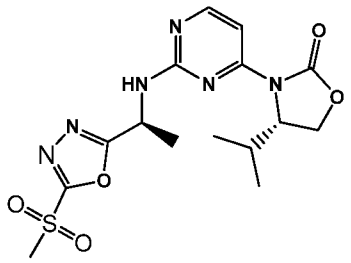
A solution of (S)-3-(2-(((S)-1-(4-aminophenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (100 mg, 0.30 mmol), benzenesulfonyl chloride (65 mg, 0.36 mmol, 1.2 equiv) and pyridine (35 mg, 0.45 mmol, 1.5 equiv) in DCM (5 mL) was stirred at room temperature for 15 h. The reaction mixture was quenched with MeOH, the solvent was removed to yield the crude product, which was purified by silica gel column chromatography (EA:MeOH=1:0 to 9:1), the solvent was removed to afford the pure product (46.8mg, white solid) in a 31.5% yield. N-(4-((S)-1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)ethyl)phenyl)benzenesulfonamide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 7.90 (m, 2H), 7.74 (d, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.41 (s, 1H), 4.99 – 4.79 (m, 1H), 4.62 – 4.39 (m, 1H), 4.28 – 3.99 (m, 2H), 1.91 – 1.65 (b, 1H), 1.40 (d, *J* = 7.0 Hz, 3H), 0.53 (b, *J* = 21.1 Hz, 6H). HRMS(B) *m/z* 482.1847 $(M + H)^+$. RT=2.60 min.

Examples 471



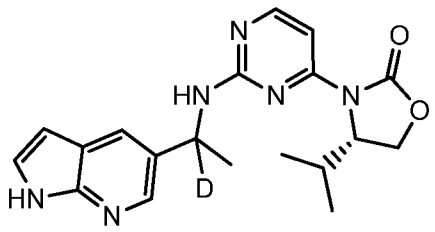
A solution of (triethoxymethyl)benzene (360 mg, 1.6 mmol, 5.0 equiv. in 5 mL of benzene and 0.5 mL of glacial AcOH) was added to (S)-2-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)propanehydrazide (99 mg, 0.30 mmol, 1.0 equiv.), the reaction mixture was stirred at reflux for 1.5 hours, the solvent was removed to yield the crude product. Silica gel column chromatography (ethyl acetate in heptane 10 to 90%) to yield (S)-4-isopropyl-3-(2-(((S)-1-(5-phenyl-1,3,4-oxadiazol-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one (21.2 mg, white solid) in 15.9% yield. HRMS(B) m/z 395.1820, (M+H)+, RT=2.42 min

Examples 472



To a solution of (S)-4-isopropyl-3-(2-(((S)-1-(5-(methylthio)-1,3,4-oxadiazol-2-yl)ethyl) amino)pyrimidin-4-yl)oxazolidin-2-one (102 mg, 0.28 mmol in 1.5 ml of CH_3COOH), was added a solution of $KMnO_4$ (66.4 mg, 0.42 mmol, 1.5 eq in 2.5 ml of water) dropwise. The solution was stirred at room temperature for 25 min, the mixture was decolorized with sodium bisulfite, the resulting solution was extracted with DCM, washed with sat. $NaHCO_3$, dried over Na_2SO_4, the solvent was removed to yield the pure desired product as a white solid. (S)-4-isopropyl-3-(2-(((S)-1-(5-(methylsulfonyl)-1,3,4-oxadiazol-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one (83 mg, white solid) in 71 % yield. HRMS(B) *m/z* 397.1281 $(M + H)^+$. RT=1.80 min.

Example 473 & 474



1-(1H-Pyrrolo[2,3-b]pyridin-5-yl)-ethanone (75 mg, 0.468 mmol), ammonium acetate (722 mg, 9.36 mmol, 20.0 eq) and sodium cyanoborodeuteride (131 mg, 1.999 mmol, 4.25 eq) were combined in propan-2-ol (5 ml) and heated under infrared irradiation at 130°C for 4 min. The reaction was diluted with EtOAc (15 ml) and water (15 ml) and treated with 6M NaOH solution (1 ml) to ~10 pH. The product, 1-deutero-1-(1H-pyrrolo[2,3-b]pyridin-5-yl)ethanamine, was carried to the next step without further purification.

A solution of 3-(2-fluoropyrimidin-4-yl)oxazolidin-2-one (99 mg, 0.441 mmol), 1-deutero-1-(1H-pyrrolo[2,3-b]pyridin-5-yl)ethanamine (72 mg, 0.441 mmol, 1.0 equiv), and DIEA (0.154 mL, 0.882 mmol, 2.0 equiv) in DMSO (1 mL) was heated at 130 °C for 120 min. The reaction mixture was diluted with EtOAc (20 mL) and washed with water (10 mL)

and concentrated in vacuo. Resolution of (4S)-3-(2-((1-deutero-1-(1H-pyrrolo[2,3-b]pyridin-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one via chiral SFC chromatography on a Al column (75 g/min, 120 bar, 20 x 250 mm) eluting 40-50% MeOH/0.2% DEA/CO2 (v/v) to give (4S)-3-(2-(((R)-1-deutero-1-(1H-pyrrolo[2,3-b]pyridin-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one and (4S)-3-(2-(((S)-1-deutero-1-(1H-pyrrolo[2,3-b]pyridin-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one

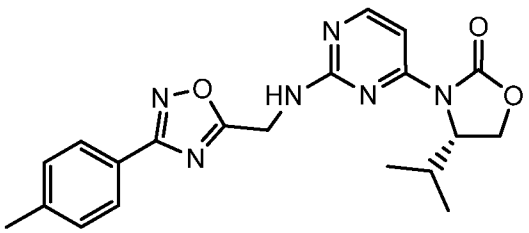
1st peak 473

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.33 (d, J = 2.2 Hz, 1H), 8.21 (d, J = 5.7 Hz, 1H), 7.92 (d, J = 2.3 Hz, 1H), 7.46 (d, J = 5.7 Hz, 1H), 7.35 (dd, J = 3.5, 2.0 Hz, 1H), 6.47 (dd, J = 3.4, 1.7 Hz, 1H), 5.82 (s, 1H), 1.66 – 1.58 (m, 3H), 4.59 (dt, J = 7.7, 3.2 Hz, 1H), 4.28 (t, J = 8.8 Hz, 1H), 4.19 (dd, J = 9.2, 3.1 Hz, 1H), 3.51 (s, 1H), 1.78 (d, J = 28.5 Hz, 2H), 1.30 – 1.15 (m, 1H), 0.57 (s, 6H). LCMS m/z 368.1 (M+H) RT=2.36 min.

2nd peak 474

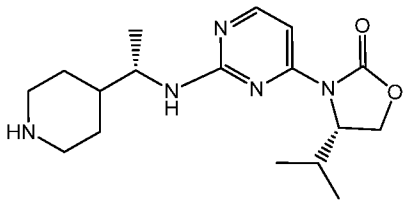
LCMS m/z 368.1 (M+H) RT=2.66 min.

Example 475



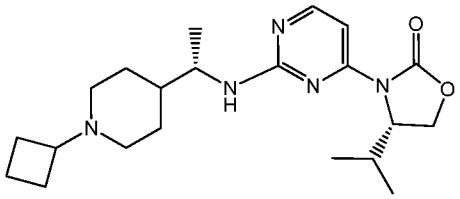
A solution of 3-(2-fluoropyrimidin-4-yl)oxazolidin-2-one (100 mg, 0.444 mmol), (3-(p-tolyl)-1,2,4-oxadiazol-5-yl)methanamine (84 mg, 0.444 mmol, 1.0 equiv), and TEA (0.186 mL, 1.332 mmol, 3.0 equiv) in butan-1-ol (2 mL) was heated at 100 °C for 90 min. Addition of propan-1-ol (1 ml) and heated at 150 °C for 60 min. The reaction mixture was concentrated in vacuo. Flash column (silica, 24 g) eluting w/ 0 - 30% EtOAc/DCM afforded (S)-4-Isopropyl-3-{2-[(3-p-tolyl-[1,2,4]oxadiazol-5-ylmethyl)-amino]-pyrimidin-4-yl}-oxazolidin-2-one (95 mg, white foam) in 54.2% yield. HRMS(B) m/z 394.1753 2.38 Min.

Example 476



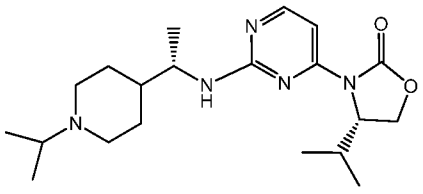
To a solution of 4-{(S)-1-[4-((S)-4-Isopropyl-2-oxo-oxazolidin-3-yl)-pyrimidin-2-ylamino]-ethyl}-piperidine-1-carboxylic acid benzyl ester (22 mg) in methanol (5 mL) was added palladium hydroxide on carbon (7 mg, 0.05 mmol). The reaction was then stirred at room temperature for 16 hours. The reaction is then filtered and then concentrated under vacuum. The crude material was then purified using reverse phase C18 ODB column water-acetonitrile 0.1% TFA modifier to give (S)-4-isopropyl-3-[2-((S)-1-piperidin-4-yl-ethylamino)-pyrimidin-4-yl]-oxazolidin-2-one (11 mg) in 70% yield.
HRMS(B) m/z 333.2165 (M + H)+; RT.: 1.09 min.

Example 477



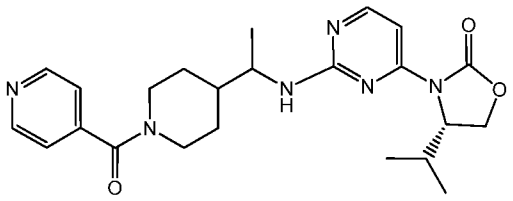
A solution of (S)-4-Isopropyl-3-[2-((S)-1-piperidin-4-yl-ethylamino)-pyrimidin-4-yl]-oxazolidin-2-one (28 mg, 0.084 mmol) in THF (2 mL) was added cyclobutanone (14 mg, 0.20 mmol) and sodium triacetoxyborohydride (28 mg, 0.13 mmol). The reaction was stirred at room temperature for 18 hours. The solvent is then removed under vacuum. The crude material was then purified using reverse phase C18 ODB column water-acetonitrile 0.1% TFA modifier to give (S)-3-{2-[(S)-1-(1-Cyclobutyl-piperidin-4-yl)-ethylamino]-pyrimidin-4-yl}-4-isopropyl-oxazolidin-2-one (20 mg) in 62% yield.
HRMS(B) m/z 388.2717 (M + H)+; RT.: 2.32 min.

Example 478



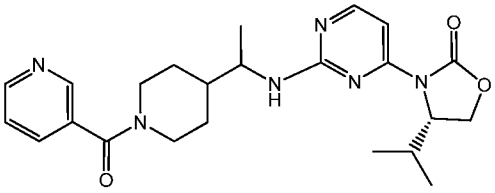
A solution of (S)-4-Isopropyl-3-[2-((S)-1-piperidin-4-yl-ethylamino)-pyrimidin-4-yl]-oxazolidin-2-one (20 mg, 0.060 mmol) in THF (2 mL) was added cyclobutanone (10 mg, 0.17 mmol) and sodium triacetoxyborohydride (20 mg, 0.09 mmol). The reaction was stirred at room temperature for 18 hours. The solvent is then removed under vacuum. The crude material was then purified using reverse phase C18 ODB column water-acetonitrile 0.1% TFA modifier to give (S)-4-Isopropyl-3-{2-[(S)-1-(1-isopropyl-piperidin-4-yl)-ethylamino]-pyrimidin-4-yl}-oxazolidin-2-one (20 mg) in 62% yield.
HRMS(B) m/z 376.2705 (M + H)+; RT.: 1.24 min.

Example 479



To a solution of S)-4-Isopropyl-3-[2-((S)-1-piperidin-4-yl-ethylamino)-pyrimidin-4-yl]-oxazolidin-2-one (20 mg, 0.48 mmol) in dichloromethane (1 mL) and DMF (1 mL) was added HATU (23 mg, 0.06 mmol) and DIPEA (0.03 mL, 0.18 mmol) The reaction was stirred at room temperature for 18 hours. The solvent is then removed under vacuum. The crude material was then purified using reverse phase C18 ODB column water-acetonitrile 0.1% TFA modifier to give (S)-4-Isopropyl-3-(2-{(S)-1-[1-(pyridine-4-carbonyl)-piperidin-4-yl]-ethylamino}-pyrimidin-4-yl)-oxazolidin-2-one (2 mg) in 8% yield.
HRMS(B) m/z 438.2379 (M + H)+; RT.: 1.82 min.

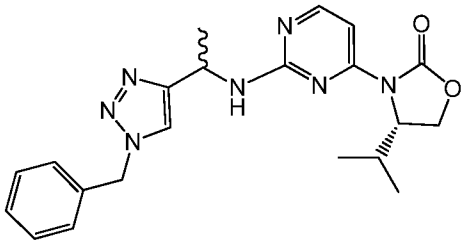
Example 480



To a solution of S)-4-Isopropyl-3-[2-((S)-1-piperidin-4-yl-ethylamino)-pyrimidin-4-yl]-oxazolidin-2-one (16 mg, 0.48 mmol) in dichloromethane (1 mL) and DMF (1 mL) was added HATU (20 mg, 0.05 mmol) and DiPEA (0.03 mL, 0.15 mmol) The reaction was stirred at room temperature for 18 hours. The solvent is then removed under vacuum. The crude material was then purified using reverse phase C18 ODB column water-acetonitrile 0.1% TFA modifier to give (S)-4-Isopropyl-3-(2-{(S)-1-[1-(pyridine-4-carbonyl)-piperidin-4-yl]-ethylamino}-pyrimidin-3-yl)-oxazolidin-2-one (2 mg) in 8% yield.

HRMS(B) m/z 438.2379 (M + H)+; RT.: 1.83 min.

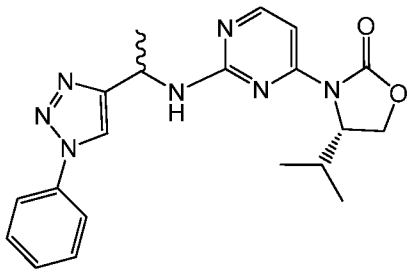
Example 481 & 482



To a solution of (S)-4-Isopropyl-3-[2-((S)-1-methyl-prop-2-ynylamino)-pyrimidin-4-yl]-oxazolidin-2-one (60 mg, 0.22 mmol) and benzyl azide (30 mg, 0.23 mmol) in water (0.5 mL) and DMSO (3 mL) was added copper sulfate pentahydrate (56 mg, 0.23 mmol) and L-ascorbic acid sodium salt (45 mg, 0.23 mmol). The reaction was stirred for 48 hours at room temperature. The reaction mixture was diluted with EtOAc (75 mL) and washed with water (15 mL) and 1N solution sodium bicarbonate (15 mL) . The organic layer was dried over MgSO4, filtered and concentrated. The crude material was then purified on reverse phase using a C18 columnn water-acetonitrile TFA as a modifier, which also effected separation of the two diastereomer products (S)-3-{2-[(S)-1-(1-benzyl-1H-[1,2,3]triazol-4-yl)-ethylamino]-pyrimidin-4-yl}-4-isopropyl-oxazolidin-2-one and (S)-3-{2-[(R)-1-(1-benzyl-1H-[1,2,3]triazol-4-yl)-ethylamino]-pyrimidin-4-yl}-4-isopropyl-oxazolidin-2-one

First Peak 481: HRMS(B) m/z 407.2070 (M + H)+; RT.: 2.26 min.
Second Peak 482: HRMS(B) m/z 407.2070 (M + H)+; RT.: 2.32 min.

Example 483 & 484



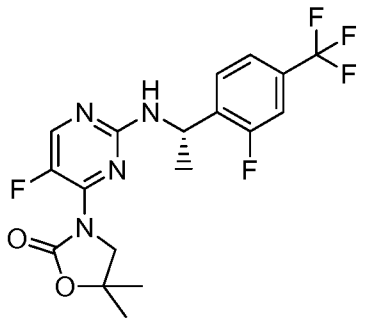
To a solution of (S)-4-Isopropyl-3-[2-((S)-1-methyl-prop-2-ynylamino)-pyrimidin-4-yl]-oxazolidin-2-one (82 mg, 0.30 mmol) and azidobenzene (36 mg, 0.30 mmol) in water (0.5 mL) and DMSO (3 mL) was added copper sulfate pentahydrate (75 mg, 0.23 mmol) and L-ascorbic acid sodium salt (60 mg, 0.23 mmol). The reaction was stirred for 48

hours at room temperature. The reaction mixture was diluted with EtOAc (75 mL) and washed with water (15 mL) and 1N solution sodium bicarbonate (15 mL) . The organic layer was dried over MgSO4, filtered and concentrated. The crude material was then purified on reverse phase using a C18 columnn water-acetonitrile TFA as a modifier , which also effected separation of the two diastereomer products (S)-4-isopropyl-3-{2-[(S)-1-(1-phenyl-1H-[1,2,3]triazol-4-yl)-ethylamino]-pyrimidin-4-yl}-oxazolidin-2-one and (S)-4-isopropyl-3-{2-[(R)-1-(1-phenyl-1H-[1,2,3]triazol-4-yl)-ethylamino]-pyrimidin-4-yl}-oxazolidin-2-one

First Peak 483: HRMS(B) m/z 393.1913 (M + H)+; RT.: 2.31 min.

Second Peak 484: HRMS(B) m/z 393.1913 (M + H)+; RT.: 2.40 min.

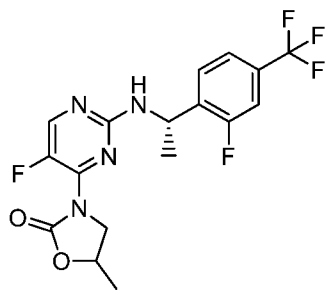
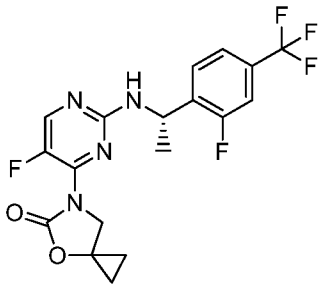
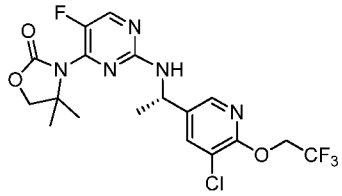
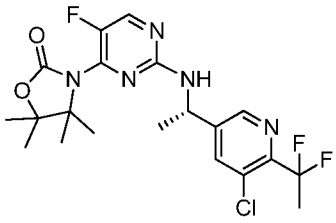
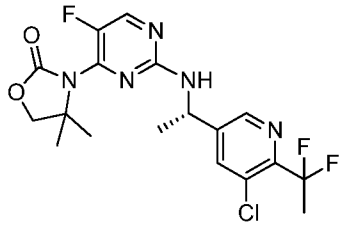
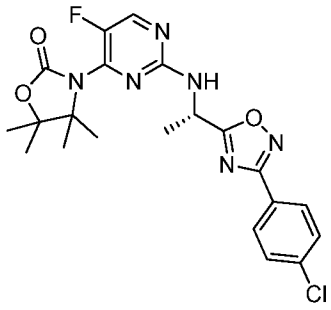
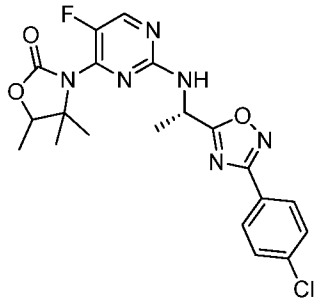
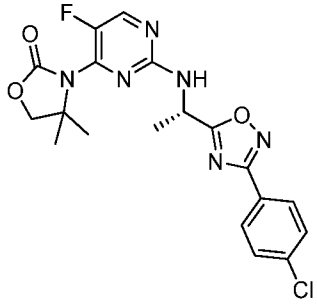
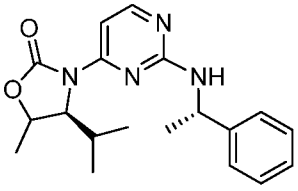
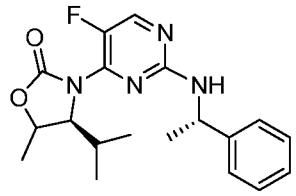
Example 485



To a room temperature solution of 3-(2-chloro-5-fluoropyrimidin-4-yl)-5,5-dimethyloxazolidin-2-one (30 mg, 0.122 mmol) in DMSO (300 µL) was treated with DIPEA (68 µL, 0.366 mmol) followed by addition of (S)-1-(2-fluoro-4-(trifluoromethyl)phenyl)ethanamine (41.4 mg, 0.2 mmol). The reaction was sealed, heated at 95°C for ~18 hr. . Purification by reverse phase HPLC provided the trifluoroacetate salt of (S)-3-(5-fluoro-2-(1-(2-fluoro-4-(trifluoromethyl) phenyl) ethylamino)pyrimidin-4-yl)-5,5-dimethyloxazolidin-2-one. (6.0 mg, white solid). ^{1}H NMR (400 MHz, METHANOL-*d*4) δ ppm 1.44 - 1.58 (m, 12 H) 3.50 - 3.74 (m, 1 H) 3.88 (d, *J*=9.8 Hz 1 H) 5.29 (d, *J*=7.04 Hz, 1 H) 7.38 - 7.45 (m, 2 H) 7.6 (t, *J*=8.22 Hz 1 H) 8.16 (d, *J*=3.13 Hz, 1 H); HRMS(A) *m/z* 417.1360 $(M + H)^+$, Rt 2.29 min.

The compounds in Table 11 were prepared using methods similar to those described for the preparation of Example 485.

Table 11.

486	487	
		
488	489	
		
490	491	492
		
493	494	495
		

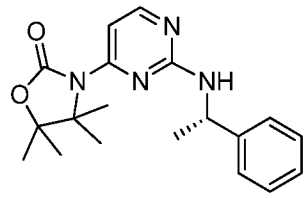
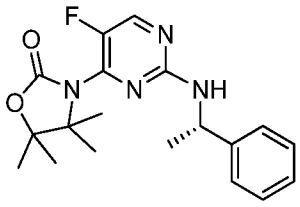
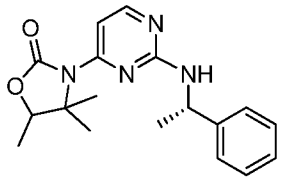
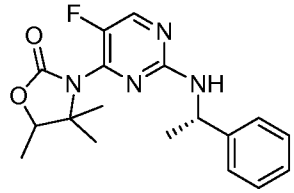
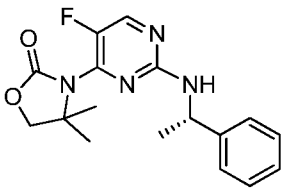
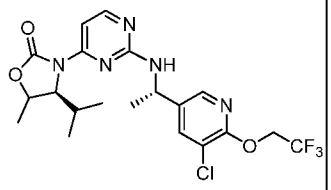
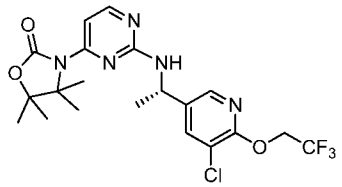
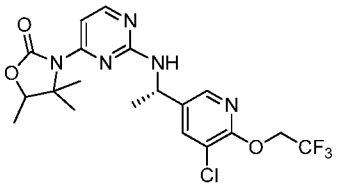
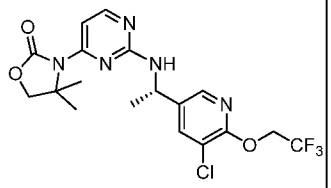
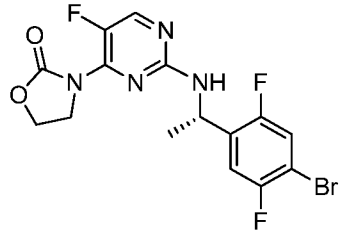
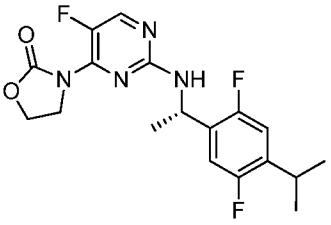
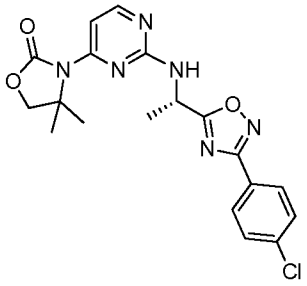
496	497	498
		
499	500	501
		
502	503	504
		
505	506	507
		

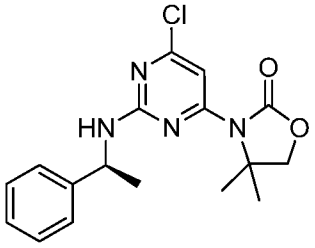
Table 12. Chemical name, NMR chemical shifts and LCMS signal for each compound listed in Table 11.

Example: Name	^{1}H NMR (400 MHz) ppm	LCMS
486: 3-(5-fluoro-2-((S)-1-(2-fluoro-4-(trifluoromethyl)phenyl)ethylamino)pyrimidin-4-yl)-5-methyloxazolidin-2-one	(CD_3OD) 1.41 - 1.58 (m, 8 H) 3.55 (br. s., 1 H) 3.74 - 3.80 (m, 1 H) 4.17 (dd, *J*=9.59, 7.63 Hz, 1 H) 5.26 - 5.33 (m, 1 H) 7.39 - 7.45 (m, 2 H) 7.60 (t, *J*=7.83 Hz, 1 H) 8.15 (d, *J*=3.52 Hz, 1 H)	HRMS(A) *m/z* 403.1198 $(M + H)^+$, Rt 2.20 min
487: (S)-6-(5-fluoro-2-(1-(2-fluoro-4-(trifluoromethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-oxa-6-azaspiro[2.4]heptan-5-one	(CD_3OD) 0.90 (m, 2 H) 1.18 - 1.27 (m, 2 H) 1.53 (d, *J*=7.04 Hz, 3 H) 4.21 (d, *J*=9.39 Hz, 1 H) 5.30 (d, *J*=7.04 Hz, 1 H) 7.38 - 7.45 (m, 2 H) 7.60 (t, *J*=7.83 Hz 1 H) 8.17 (d, *J*=3.52 Hz, 1 H)	HRMS(A) *m/z* 415.1204 $(M + H)^+$, Rt 2.31 min
488: (S)-3-(2-(1-(5-chloro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethylamino)-5-fluoropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	(CD_3OD) 8.22 (d, *J*=3.13 Hz, 1 H) 8.08 (d, *J*=1.96 Hz, 1 H) 7.84 (d, *J*=1.96 Hz, 1 H) 5.26 - 5.27 (m, 1 H) 4.90 (q, *J*=8.61 Hz, 3 H) 4.13 - 4.22 (m, 2 H) 1.47 - 1.59 (m, 9 H)	HRMS(A) *m/z* 464.1125 $(M + H)^+$, Rt 2.28 min
489: (S)-3-(2-(1-(5-chloro-6-(1,1-difluoroethyl)pyridin-3-yl)ethylamino)-5-fluoropyrimidin-4-yl)-4,4,5,5-tetramethyloxazolidin-2-one	(CD_3OD) 8.51 (d, J=1.57 Hz, 1 H) 8.23 (d, J=2.35 Hz, 1 H) 7.93 (d, J=1.56 Hz, 1 H) 4.99 (q, J=6.52 Hz, 1 H) 2.02 (t, J=18.78 Hz, 3 H) 1.57 (d, J=7.43 Hz, 3 H) 1.34 - 1.42 (m, 12 H)	HRMS(A) *m/z* 458.1573 $(M + H)^+$, Rt 2.02 min
490: (S)-3-(2-(1-(5-chloro-6-(1,1-difluoroethyl)pyridin-3-yl)ethylamino)-5-fluoropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	(CD_3OD) 8.50 (d, J=1.17 Hz, 1 H) 8.24 (d, J=2.35 Hz, 1 H) 7.93 (d, J=1.57 Hz, 1 H) 4.99 (q, J=6.65 Hz, 1 H) 4.12 - 4.21 (m, 2 H) 2.01 (t, J=18.78 Hz, 3 H) 1.57 (d, J=7.04 Hz, 3 H) 1.47 (s, 6 H)	HRMS(A) *m/z* 430.1265 $(M + H)^+$, Rt 2.05 min
491: (S)-3-(2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)-5-fluoropyrimidin-4-yl)-4,4,5,5-tetramethyloxazolidin-2-one	(CD_3OD) 8.27 (br. s., 1 H) 8.00 (d, *J*=8.61 Hz, 3 H) 7.52 (d, *J*=8.61 Hz, 4 H) 5.29 (d, *J*=7.04 Hz, 1 H) 1.73 (s, 3 H) 1.44 (s, 3 H) 1.38 (s, 3 H) 1.28 (s, 3 H)	HRMS(A) *m/z* 461.1512 $(M + H)^+$, Rt 2.37 min
492: 3-(2-((S)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)-5-fluoropyrimidin-4-yl)-4,4,5-trimethyloxazolidin-2-one (1:1 mixture of diastereomers)	(CD_3OD) 8.27 (d, *J*=1.57 Hz, 1 H) 8.00 (d, *J*=8.61 Hz, 2 H) 7.52 (d, *J*=8.61 Hz, 2 H) 5.29 (m, 1 H) 4.44(m, 1 H) 1.73 (d, *J*=7.43 Hz, 3 H) 1.44 (br. s., 3 H) 1.26 - 1.35 (m, 6 H)	HRMS(A) *m/z* 477.1349 $(M + H)^+$, Rt 2.3 min
493: (S)-3-(2-(1-(3-(4-chlorophenyl)-1,2,4-	(CD_3OD) 8.28 (d, J=2.35 Hz, 1 H) 8.00 (d, J=8.61 Hz, 2 H) 7.51 (d, J=8.61 Hz, 2 H)	HRMS(A) *m/z*

oxadiazol-5-yl)ethylamino)-5-fluoropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	5.29 (m, 1 H) 4.11 -4.24 (m, 2 H) 1.73 (d, J=7.04 Hz, 3 H) 1.53 (s, 3 H) 1.30 (br.s., 3 H)	433.1201 $(M + H)^+$, Rt 2.21 min
494: (4S)-4-isopropyl-5-methyl-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one (1:1 mixture of diastereomers)	(CD_3OD) 8.11 (d, *J*=6.26 Hz, 1 H) 7.71 (d, *J*=7.43 Hz, 1 H) 7.29 - 7.40 (m, 4 H) 7.22 - 7.28 (m, 1 H) 5.23 (br. s., 1 H) 4.82 - 4.91 (m, 1 H) 4.78 (br. s., 1 H) 2.01 (br. s., 1 H) 1.59 (d, *J*=7.04 Hz, 3 H) 1.54 (d, *J*=6.65 Hz, 3 H) 0.76 (br. s., 6 H)	HRMS(A) *m/z* 341.1985 $(M + H)^+$, Rt 1.78 min
495: (4S)-3-(5-fluoro-2-((S)-1-phenylethylamino)pyrimidin-4-yl)-4-isopropyl-5-methyloxazolidin-2-one (1:1 mixture of diastereomers)	(CD_3OD) 7.87 (d, *J*=3.13 Hz, 1 H) 6.95 - 7.02 (m, 2 H) 6.91 (t, *J*=7.63 Hz, 2 H) 6.75 - 6.85 (m, 1 H) 4.52 - 4.61 (m, 2H) 4.00 (br. s., 1 H) 1.49 (br. s., 1 H) 1.11 (dd, *J*=9.59, 6.85 Hz, 6 H) 0.38 (d, *J*=4.30 Hz, 6 H)	HRMS(A) *m/z* 359.1891 $(M + H)^+$, Rt 2.19 min
496: (S)-4,4,5,5-tetramethyl-3-(2-(1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 8.08 (d, *J*=6.26 Hz, 1 H) 7.28 - 7.40 (m, 5 H) 7.18 - 7.25 (m, 1 H) 5.05 (q, *J*=7.04 Hz, 1 H) 1.55 - 1.62 (m, 6H) 1.37 (s, 3 H) 1.32 (s, 3 H)	HRMS(A) *m/z* 341.1984 $(M + H)^+$, Rt 1.73 min
497: (S)-3-(5-fluoro-2-(1-phenylethylamino)pyrimidin-4-yl)-4,4,5,5-tetramethyloxazolidin-2-one	(CD_3OD) 8.18 (d, *J*=2.74 Hz, 1 H) 7.30 - 7.39 (m, 2 H) 7.23 - 7.30 (m, 2 H) 7.12 - 7.21 (m, 1 H) 4.90 (q, *J*=6.91 Hz, 1H) 1.50 (d, *J*=7.04 Hz, 3 H) 1.42 (s, 3 H) 1.36 (s, 3 H) 1.33 (s, 3 H)	HRMS(A) *m/z* 359.1891 $(M + H)^+$, Rt 2.16 min
498: 4,4,5-trimethyl-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one (1:1 mixture of diastereomers)	(CD_3OD) 8.09 (d, *J*=6.65 Hz, 1 H) 7.53 (d, *J*=7.04 Hz, 1 H) 7.45 (d, *J*=7.04 Hz, 1 H) 7.30 - 7.40 (m, 8 H) 7.20 - 7.28(m, 2 H) 5.09 (t, *J*=7.04 Hz, 2 H) 4.27 - 4.42 (m, 2 H) 1.52 - 1.69 (m, 12 H) 1.32 (dd, *J*=11.15, 6.46 Hz, 6 H) 0.82 - 1.20 (m, 6 H)	HRMS(A) *m/z* 327.1826 $(M + H)^+$, Rt 1.66 min
499: 3-(5-fluoro-2-((S)-1-phenylethylamino)pyrimidin-4-yl)-4,4,5-trimethyloxazolidin-2-one (1:1 mixture of diastereomers)	(CD_3OD) 8.18 (d, *J*=2.74 Hz, 1 H) 7.30 - 7.37 (m, 2 H) 7.24 - 7.30 (m, 2 H) 7.11 - 7.21 (m, 1 H) 4.87 - 4.97 (m, 1 H) 4.31 - 4.46 (m, 1 H) 1.50 (d, *J*=7.04 Hz, 3 H) 1.41 (d, *J*=10.96 Hz, 3 H) 1.29 (dd, *J*=6.46, 3.33 Hz, 3 H) 0.84 - 1.16 (br. s, 3 H)	HRMS(A) *m/z* 345.1735 $(M + H)^+$, Rt 2.09 min
500: (S)-3-(5-fluoro-2-(1-phenylethylamino)pyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	(CD_3OD) 8.19 (d, *J*=2.35 Hz, 1 H) 7.30 - 7.37 (m, 2 H) 7.24 - 7.30 (m, 2 H) 7.13 - 7.21 (m, 1 H) 4.91 (q, *J*=7.30 Hz, 1H) 4.12 (q, *J*=8.22 Hz, 2 H) 1.45 - 1.55 (m, 6 H) 1.08 (br. s., 3 H)	HRMS(A) *m/z* 331.1573 $(M + H)^+$, Rt 1.98 min
501: (4S)-3-(2-((S)-1-(5-chloro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethylamino)pyrimidin-4-yl)-4-isopropyl-5-	^1H NMR (400 MHz, CD_3OD) δ ppm 8.14 (d, *J*=6.65 Hz, 1 H) 8.10 (d, *J*=1.96 Hz, 1 H) 7.86 (d, *J*=2.35 Hz, 1 H) 7.57 (d, *J*=6.26 Hz, 1 H) 5.17 (d, *J*=6.65 Hz, 1 H) 4.92 (q, *J*=8.87 Hz, 1 H) 4.80 - 4.84 (m, 1H) 2.04	HRMS(A) *m/z* 474.1523 $(M + H)^+$, Rt 2.18

methyloxazolidin-2-one (1:1 mixture of diastereomers)	(br. s., 2 H) 1.55 (dd, *J*=15.85, 6.85 Hz, 6 H) 0.79 (br.s., 6 H)	min
502: (S)-3-(2-(1-(5-chloro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethylamino)pyrimidin-4-yl)-4,4,5,5-tetramethyloxazolidin-2-one	(CD_3OD) 8.07 - 8.16 (m, 1 H) 7.89 (d, *J*=1.96 Hz, 1 H) 7.32 (d, *J*=6.26 Hz, 1 H) 5.08 (q, *J*=6.78 Hz, 1 H) 1.55 - 1.65 (m, 8 H) 1.37 (d, *J*=11.35 Hz, 6 H) 1.20 (d, *J*=11.35 Hz, 3 H)	HRMS(A) *m/z* 474.1534 $(M + H)^+$, Rt 2.16 min
503: 3-(2-((S)-1-(5-chloro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethylamino)pyrimidin-4-yl)-4,4,5-trimethyloxazolidin-2-one (1:2 mixture of diastereomers)	(CD_3OD) 8.47 (d, *J*=5.87 Hz, 1 H) 8.11 (d, *J*=2.35 Hz, 3H) 7.99 (d, *J*=6.26 Hz, 1 H) 7.88 (d, *J*=1.96 Hz, 3 H) 7.39 (d,*J*=6.26 Hz, 2 H) 7.32 (d, *J*=6.65 Hz, 2 H) 5.04 - 5.13 (m, 1 H) 4.87 - 4.98 (m, 2 H) 4.45 (d, *J*=6.65 Hz, 1 H) 4.35 (dd, *J*=13.69, 6.65 Hz, 2 H) 1.67(d, *J*=4.70 Hz, 9 H) 1.59 (d, *J*=7.04 Hz, 12 H) 1.39 (d, *J*=6.65 Hz, 3 H) 1.33 (t, *J*=6.06 Hz, 6 H) 0.99 - 1.27 (m, 9 H)	HRMS(A) *m/z* 460.1375 $(M + H)^+$, Rt 2.08, 2.11 min
504: (S)-3-(2-(1-(5-chloro-6-(2,2,2-trifluoroethoxy)pyridin-3-yl)ethylamino)pyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	(CD_3OD) 8.09 - 8.17 (m, 1 H) 7.88 (d, *J*=2.35 Hz, 1 H) 7.38 (d, *J*=6.26 Hz, 1 H) 4.91 (q, *J*=8.61 Hz, 1 H) 4.06 - 4.16(m, 2 H) 1.71 (m, 5 H) 1.58 (d, *J*=7.04 Hz, 3 H) 1.28 (br. s., 3 H)	HRMS(A) *m/z* 446.1219 $(M + H)^+$, Rt 2.01 min
505: (S)-3-(2-(1-(2,5-difluoro-4-isopropylphenyl)ethylamino)-5-fluoropyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 8.15 (d, *J*=3.13 Hz, 1 H) 6.92 - 7.08 (m, 2 H) 5.21 (q, *J*=6.78 Hz, 1 H) 4.44 - 4.58 (m, 2 H) 4.10 - 4.22 (m, 1H) 3.96 (m, 1 H) 3.07 - 3.23 (m, 1 H) 1.48 (d, *J*=7.04 Hz, 5 H) 1.21 (m, 6 H)	HRMS(A) *m/z* 381.1544 $(M + H)^+$, Rt 2.26 min
506: (S)-3-(2-(1-(4-bromo-2,5-difluorophenyl)ethylamino)-5-fluoropyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 8.15 (d, *J*=3.52 Hz, 1 H) 7.39 (dd, *J*=9.00, 5.48 Hz, 1 H) 7.24 (dd, *J*=9.19, 6.46 Hz, 1 H) 5.19 (q, *J*=7.04 Hz,1 H) 4.44 - 4.58 (m, 2 H) 4.09 - 4.23 (m, 1 H) 3.94 (br. s., 1 H) 1.48 (d, *J*=7.04 Hz, 3 H)	HRMS(A) *m/z* 417.018 $(M + H)^+$, t 2.07 min
507: (S)-3-(2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)pyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	(CD_3OD) 8.09 (d, *J*=6.26 Hz, 1 H) 7.91 (d, *J*=8.61 Hz, 2 H) 7.43 (d, *J*=8.61 Hz, 3 H) 5.35 (q, *J*=7.30 Hz, 1 H) 3.97 -4.09 (m, 2 H) 1.69 (d, *J*=7.43 Hz, 3 H) 1.62 (s, 3 H) 1.14 - 1.45 (m, 3 H)	HRMS(A) *m/z* 415.1287 $(M + H)^+$, Rt 2.14 min

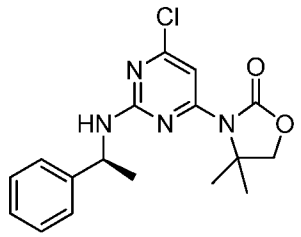
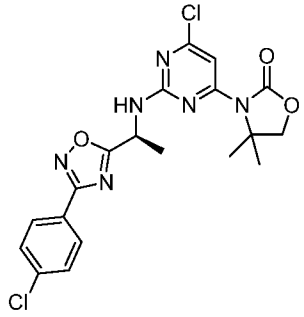
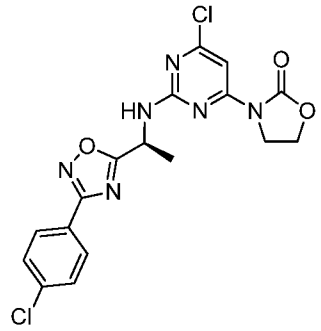
Example 508



A solution of 3-(2,6-dichloropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one (70.0 mg, 0.267 mmol), (*S*)-(-)-1-phenylethanamine (0.034 mL, 0.267 mmol, 1.0 equiv), and N-ethyl-N-isopropylpropan-2-amine (0.070 mL, 0.401 mmol, 1.5 equiv) in DMSO (1.5 mL) was heated at 85 °C for 2-4 h. Purification by reverse phase HPLC provided the trifluoroacetate salt of (S)-3-(6-chloro-2-(1-phenylethylamino)pyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one (20.0 mg, white solid) in 16% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.33 – 7.31 (m, 4H),7.26 – 7.21 (m, 1H), 5.48 (br m, 1H), 4.02 – 3.94 (m, 2H), 1.65 (s, 3H), 1.55 (d, J = 6.9 Hz, 3H), 1.26 (s, 3H); HRMS(A) *m/z* 347.1274 $(M + H)^+$, Rt 2.32 min.

The compounds in Table 13 were prepared using methods similar to those described for the preparation of Example 508.

Table 13.

509	510	511
		
512	513	

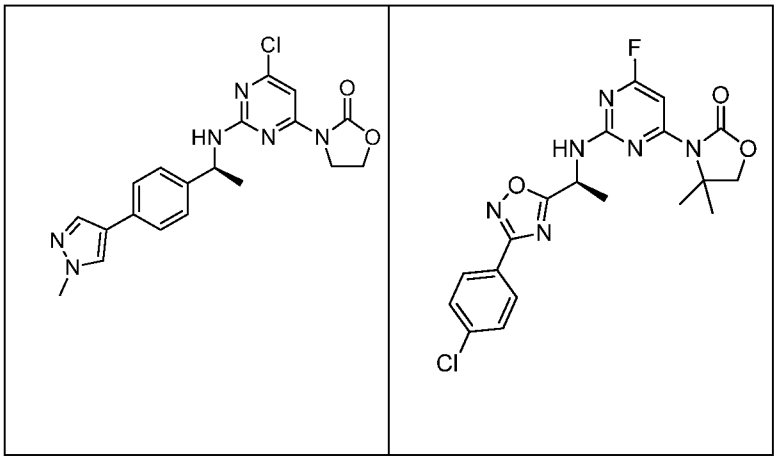
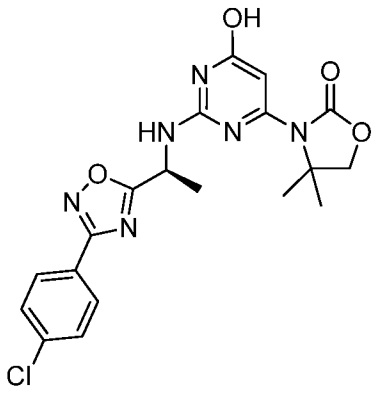


Table 14. Chemical name, NMR chemical shifts and LCMS signal for each compound listed in Table 13.

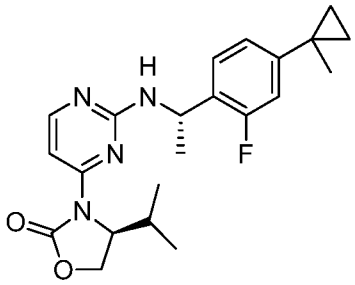
Example: Name	^{1}H NMR **(400 MHz) δ ppm**	**LCMS**
509: (S)-3-(6-chloro-2-(1-phenylethylamino)pyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	($CDCl_3$) 7.36 (s, 1H), 7.33 – 7.31 (m, 4H),7.26 – 7.21 (m, 1H), 5.48 (br m, 1H), 4.02 – 3.94 (m, 2H), 1.65 (s, 3H), 1.55 (d, J = 6.9 Hz, 3H), 1.26 (s, 3H)	HRMS(A) *m/z* 347.1274 $(M + H)^+$, Rt 2.32 min
510: (S)-3-(6-chloro-2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)pyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	($CDCl_3$) 8.00 (d, J = 8.4 Hz, 2 H), 7.53 (s, 1H), 7.47 (d, J = 8.4 Hz, 2H), 5.44 – 5.29 (br m, 1H), 4.09 – 4.02 (m, 2H), 1.78 (d, J = 7.1 Hz, 3H), 1.72 (s, 3H), 1.40 (br s, 3H)	HRMS(A) *m/z* 449.0905 $(M + H)^+$, Rt 2.51 min
511: (S)-3-(6-chloro-2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.00 (d, J = 8.7 Hz, 2H), 7.62 (s, 1H), 7.47 (d, J = 8.7 Hz, 2H), 5.32 (br m, 1H), 4.49 – 4.43 (m, 2H), 4.17 – 4.14 (m, 1H), 3.95 – 3.60 (br m, 1H), 1.77 (d, J = 7.1 Hz, 3H)	HRMS(A) *m/z* 421.0585 $(M + H)^+$, Rt 2.32 min
512: (S)-3-(6-chloro-2-(1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 7.76 (s, 1H), 7.60 (s, 1H), 7.50 (s, 1H), 7.34 – 7.28 (m, 1H), 7.20 (dd, J = 7.8, 1.6 Hz, 1H), 7.15 – 7.09 (m, 1H), 5.30 (br m, 1H), 4.49 – 4.42 (m, 2H), 4.28 – 4.23 (m, 1H), 3.97 (s, 3H), 3.92 (br m, 1H), 1.56 (d, J = 6.7 Hz, 3H)	LCMS m/z 417.2 (M+H)+
513: (S)-3-(2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)-6-fluoropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	($CDCl_3$) 7.99 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.11 (s, 1H), 5.38 (br m, 1H), 4.08 – 4.03 (m, 2H), 1.78 (d, J = 7.0 Hz, 3H), 1.73 (s, 3H), 1.38 (br s, 3H)	HRMS(A) *m/z* 433.1201 $(M + H)^+$, Rt 2.42 min

Example 514:



A solution of (S)-3-(2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)-6-fluoropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one (29.0 mg, 0.053 mmol) and 1 N aqueous hydrochloric acid (0.70 mL) in 1,4-dioxane (0.7 mL) was heated at 100 °C for 4 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (10 mL), washed with saturated aqueous sodium bicarbonate solution (10 mL), dried over Na_2SO_4, filtered and concentrated. Purification by reverse phase HPLC provided the trifluoroacetate salt of (S)-3-(2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)-6-hydroxypyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one (16 mg, white solid) in 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 6.71 (br s, 1H), 5.33 (br m, 1H), 4.02 – 3.99 (m, 2H), 1.83 (d, J = 7.1 Hz, 3H), 1.68 (s, 3H), 1.31 (s, 3H); HRMS(A) *m/z* 431.1245 $(M + H)^+$, Rt 1.80 min.

Example 515



Step 1

To round bottom flask containing (R)-N-((S)-1-(2-fluoro-4-(1-methylcyclopropyl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (87 mg, 0.29 mmol) was added dioxane (2 mL). To this solution was added hydrochloric acid in dioxane (4.0M, 0.15 ml, 0.59 mmol) and the solution allowed to stir 10 min at room temperature.

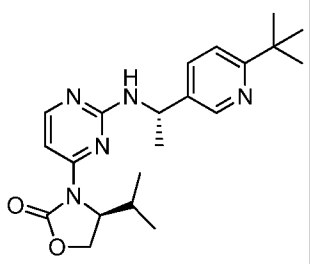
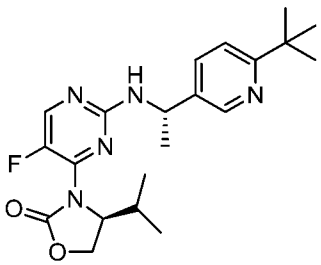
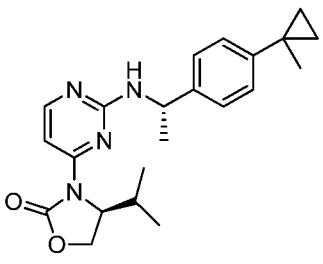
Volatiles were removed. Et_2O (10 mL) was added and the reaction mixture sonnicated. The volatiles were removed again. Et_2O (10 ml) was again added and the suspension sonnicated. Solid material was collected and washed with Et_2O to afford an HCl salt of (S)-1-(2-fluoro-4-(1-methylcyclopropyl)phenyl)ethanamine (42 mg, 0.18 mmol, 63 % yield) as a white solid. LCMS *m/z* 194.1 $(M + H)^+$, Rt 0.60 min.

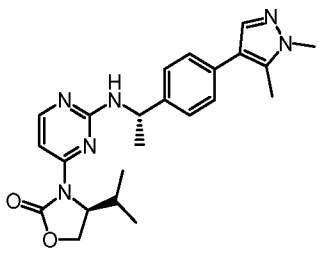
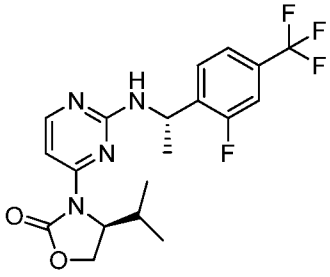
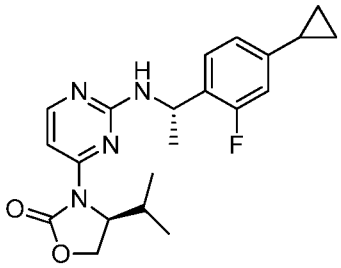
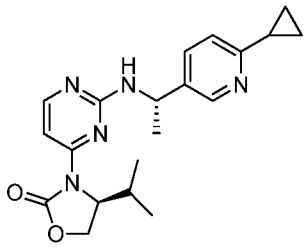
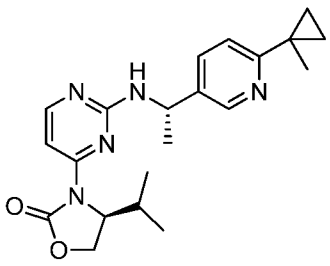
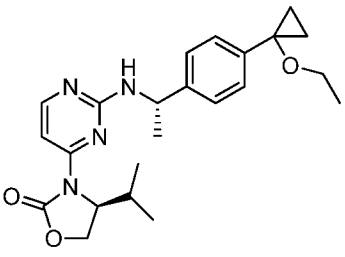
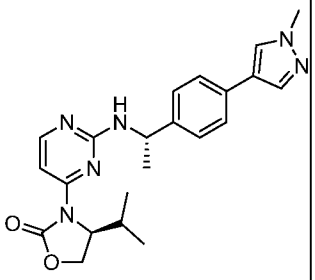
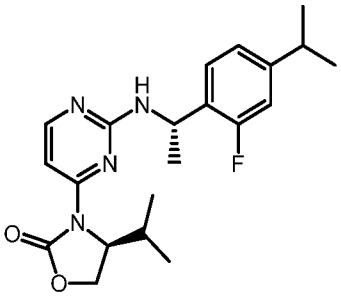
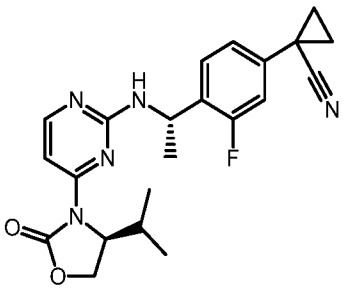
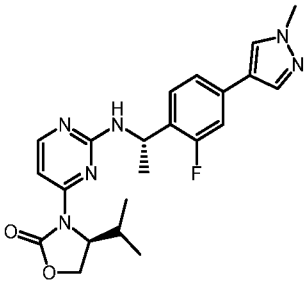
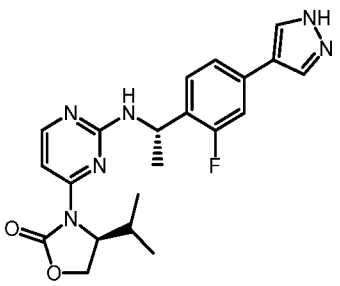
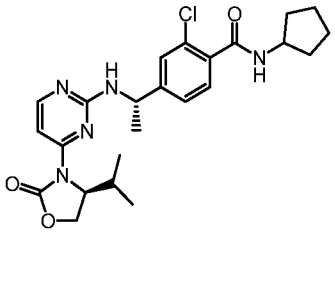
Step 2

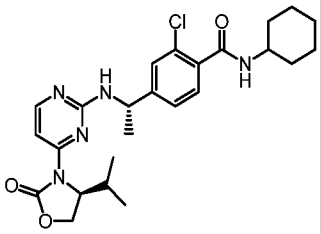
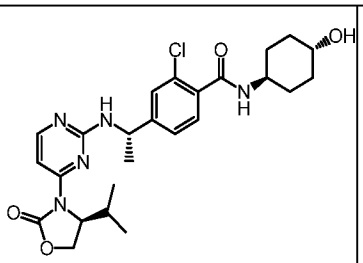
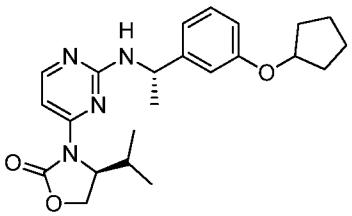
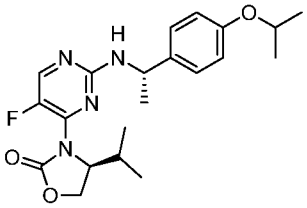
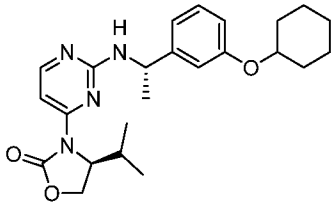
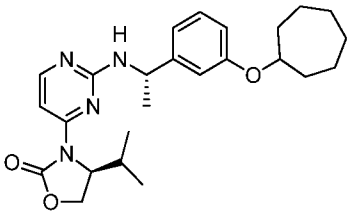
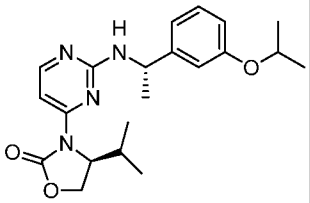
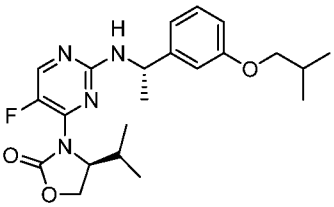
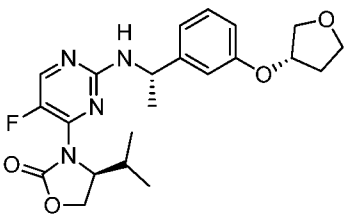
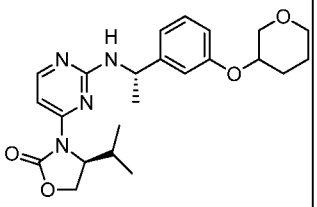
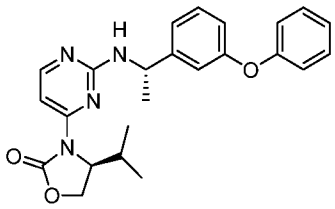
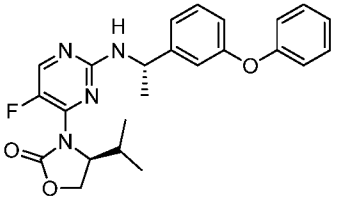
To a microwave vial with stir bar was added (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (30 mg, 0.12 mmol) and DMSO (1 mL). To this reaction mixture was added (S)-1-(2-fluoro-4-(1-methylcyclopropyl) phenyl)ethanamine (51 mg, 0.22 mmol) and DIEA (0.09 ml, 0.50 mmol). The vial was capped and the reaction mixture was heated in a preheated oil bath at 110 °C for 18 hr. Solution was purified by reverse phase HPLC. Product fractions combined, frozen and lyophilized to afford (S)-3-(2-((S)-1-(2-fluoro-4-(1-methylcyclopropyl) phenyl) ethylamino) pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (3.3 mg, 6.3 µmol, 5 % yield) as a TFA salt. ^1H NMR (400 MHz, CD_3OD) δ 0.58 (br. s., 3 H) 0.77 (td, *J*=5.23, 1.76 Hz, 5 H) 0.80 - 0.86 (m, 2 H) 1.38 (s, 3 H) 1.57 (d, *J*=6.94 Hz, 3 H) 4.34 - 4.41 (m, 2 H) 4.67 (br. s., 1 H) 5.33 (d, *J*=7.97 Hz, 1 H) 6.95 - 7.05 (m, 2 H) 7.22 (t, *J*=7.97 Hz, 1 H) 7.67 (d, *J*=6.85 Hz, 1 H) 8.14 (d, *J*=6.65 Hz, 1 H). LCMS *m/z* 399.4 $(M + H)^+$, Rt 0.93 min. HRMS(A) *m/z* 399.2202 $(M + H)^+$, Rt 2.23 min.

The compounds in Table 15 were prepared using methods similar to those described for the preparation of Examples 515.

Table 15.

516	517	518
		
519	520	521

		
522	523	524
		
525	526	527
		
528	529	530
		
531	532	533

		
534	535	536
		
537	538	539
		
540	541	542
		
543	544	545

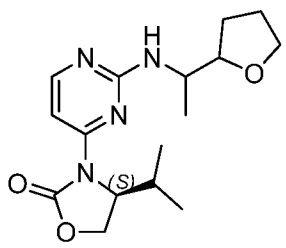
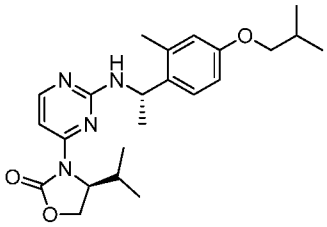
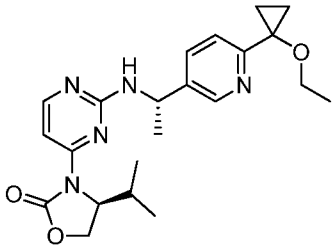
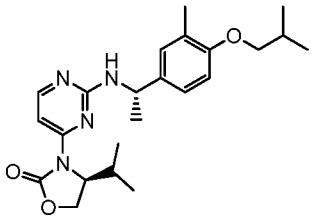
		
546		
		

Table 16. Chemical name, NMR chemical shifts and LCMS signal for each compound listed in Table 15.

Table 16.

Example: Name	^{1}H NMR **(400 MHz)** δ **ppm**	**LCMS**
516: (S)-3-(2-((S)-1-(6-tert-butylpyridin-3-yl) ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO) 0.46 (br. s., 3 H) 0.63 (br. s., 3 H) 1.35 (s, 9 H) 1.50 (d, *J*=6.99 Hz, 3 H) 4.34 (d, *J*=7.92 Hz, 2 H) 4.59 (br. s., 1 H) 5.14 (br. s., 1 H) 7.32 (d, *J*=5.92 Hz, 1 H) 7.70 (br. s., 1 H) 8.03 (br. s., 1 H) 8.24 (br. s., 2 H) 8.59 (br. s., 1 H)	HRMS(A) *m/z* 384.2410 $(M + H)^+$, Rt 1.34
517: (S)-3-(2-((S)-1-(6-tert-butylpyridin-3-yl)ethylamino)-5-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO) 0.55 (br. s., 6 H) 1.25 - 1.38 (s, 9 H) 1.47 (d, *J*=7.04 Hz, 3 H) 4.26 (br. s., 1 H) 4.45 - 4.59 (m, 2 H) 4.98 (br. s., 1 H) 7.66 (br. s., 1 H) 8.11 (br. s., 2 H) 8.41 (br. s., 1 H) 8.60 (br. s., 1 H)	HRMS(A) *m/z* 402.2314 $(M + H)^+$, Rt 1.45
518: (S)-4-isopropyl-3-(2-((S)-1-(4-(1-methyl cyclopropyl) phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one		HRMS(A) *m/z* 381.2295 $(M + H)^+$, Rt 2.10
519: (S)-3-(2-((S)-1-(4-(1,5-dimethyl-1H-pyrazol-4-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO) 0.49 (br. s., 3 H) 0.68 (br. s., 3 H) 1.48 (d, *J*=7.04 Hz, 6 H) 2.33 (s, 3 H) 3.76 (s, 3 H) 4.63 (br. s., 1 H) 4.75 - 4.82 (m, 1 H) 5.03 (br. s., 2 H) 7.30 - 7.37 (m, 4 H) 7.50 (s, 1 H) 8.22 (br. s., 1 H) 8.36 (br. s., 1 H)	HRMS(A) *m/z* 421.2362 $(M + H)^+$, Rt 1.58

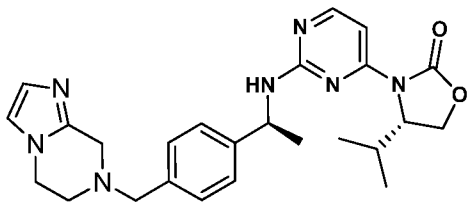
520: (S)-3-(2-((S)-1-(2-fluoro -4-(trifluoromethyl) phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO) 0.40 (br. s., 3 H) 0.57 (br. s., 3 H) 1.40 (br. s., 1 H) 1.47 (d, *J*=7.04 Hz, 3 H) 4.24 - 4.37 (m, 2 H) 4.49 (br. s., 1 H) 5.23 (br. s., 1 H) 7.30 (d, *J*=5.82 Hz, 1 H) 7.48 - 7.59 (m, 2 H) 7.65 (d, *J*=10.56 Hz, 1 H) 8.21 (d, *J*=18.58 Hz, 2 H)	HRMS(A) *m/z* 413.1602 $(M + H)^+$, Rt 2.16
521: (S)-3-(2-((S)-1-(4-cyclopropyl-2-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 0.61 (br. s., 3 H) 0.64 - 0.69 (m, 3 H) 0.77 (br. s., 3 H) 0.96 - 1.04 (m, 2 H) 1.57 (d, *J*=6.99 Hz, 3 H) 1.88 - 1.95 (m, 1 H) 4.39 (d, *J*=5.97 Hz, 2 H) 4.69 (br. s., 1 H) 5.33 (br. s., 1 H) 6.82 (dd, *J*=12.08, 1.71 Hz, 1 H) 6.88 (d, *J*=7.97 Hz, 1 H) 7.19 (t, *J*=8.31 Hz, 1 H) 7.70 (d, *J*=6.90 Hz, 1 H) 8.14 (d, *J*=7.04 Hz, 1 H)	HRMS(A) *m/z* 385.2042 $(M + H)^+$, Rt 2.06
522: (S)-3-(2-((S)-1-(6-cyclopropylpyridin-3-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 0.65 - 0.83 (m, 6 H) 1.14 - 1.20 (m, 2 H) 1.37 - 1.43 (m, 2 H) 1.64 (d, *J*=7.09 Hz, 3 H) 2.26 - 2.37 (m, 1 H) 4.36 - 4.39 (m, 2 H) 4.68 (br. s., 1 H) 5.25 (q, *J*=6.75 Hz, 1 H) 7.57 (d, *J*=8.51 Hz, 1 H) 7.63 (br. s., 1 H) 8.18 (d, *J*=5.92 Hz, 1 H) 8.33 (d, *J*=7.24 Hz, 1 H) 8.57 (d, *J*=2.10 Hz, 1 H)	HRMS(A) *m/z* 368.2097 $(M + H)^+$, Rt 1.12
523: (S)-4-isopropyl-3-(2-((S)-1-(6-(1-methylcyclopropyl)pyridin-3-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 0.59 - 0.84 (m, 6 H) 1.08 - 1.15 (m, 2 H) 1.22 - 1.28 (m, 2 H) 1.56 (s, 3 H) 1.64 (d, *J*=7.09 Hz, 3 H) 4.35 - 4.39 (m, 2 H) 4.69 (br. s., 1 H) 5.21 - 5.32 (m, 1 H) 7.62 (br. s., 1 H) 7.79 (d, *J*=8.46 Hz, 1 H) 8.18 (d, *J*=6.11 Hz, 1 H) 8.33 (d, *J*=7.14 Hz, 1 H) 8.57 (d, *J*=2.20 Hz, 1 H)	HRMS(A) *m/z* 382.2247 $(M + H)^+$, Rt 1.30
524: (S)-3-(2-((S)-1-(4-(1-ethoxycyclopropyl)-2-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 0.60 (br. s., 3 H) 0.78 (br. s., 3 H) 0.92 - 0.98 (m, 2 H) 1.15 (t, *J*=7.07 Hz, 3 H) 1.19 - 1.26 (m, 2 H) 1.59 (d, *J*=6.99 Hz, 3 H) 1.78 (br. s., 1 H) 3.43 (q, *J*=7.09 Hz, 2 H) 4.40 (d, *J*=5.72 Hz, 2 H) 4.70 (d, *J*=3.91 Hz, 1 H) 5.38 (br. s., 1 H) 7.06 (s, 1 H) 7.07 - 7.12 (m, 1 H) 7.31 (t, *J*=7.95 Hz, 1 H) 7.73 (d, *J*=7.04 Hz, 1 H) 8.15 (d, *J*=6.90 Hz, 1 H)	HRMS(A) *m/z* 429.2310 $(M + H)^+$, Rt 2.08
525: (S)-4-isopropyl-3-(2-((S)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	(DMSO) 0.47 (br. s., 3 H) 0.69 (br. s., 3 H) 1.45 (d, *J*=6.99 Hz, 3 H) 1.81 (br. s., 1 H) 3.84 (s, 3 H) 4.33 (d, *J*=13.45 Hz, 2 H) 4.62 (br. s., 1 H) 4.99 (br. s., 1 H) 7.24 - 7.33 (m, 3 H) 7.46 (d, *J*=8.27 Hz, 2 H) 7.79 (d, *J*=0.73 Hz, 1 H) 8.06 (s, 1 H) 8.18 (br. s., 1 H)	HRMS(B) *m/z* 407.2179 $(M + H)^+$, Rt 2.44min
526: (S)-3-(2-((S)-1-(2-fluoro-4-isopropylphenyl)ethylamin	(CD_3OD) 0.59 (br. s., 3 H) 0.78 (br. s., 3 H) 1.23 (dd, *J*=6.90, 1.03 Hz, 6 H) 1.58 (d, *J*=6.99 Hz, 3 H) 2.91 (dt, *J*=13.78, 6.93 Hz,	HRMS(A) *m/z* 387.2207

o)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	1 H) 4.39 (d, *J*=5.97 Hz, 2 H) 4.69 (br. s., 1 H) 5.35 (br. s., 1 H) 6.97 - 7.06 (m, 2 H) 7.20 - 7.28 (m, 1 H) 7.73 (d, *J*=6.99 Hz, 1 H) 8.15 (d, *J*=6.90 Hz, 1 H)	$(M + H)^+$, Rt 2.20
527: 1-(3-fluoro-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)phenyl)cyclopropanecarbonitrile	(CD_3OD) 0.61 (br. s., 3 H) 0.75 (br. s., 3 H) 1.40 - 1.50 (m, 2 H) 1.57 (d, *J*=6.94 Hz, 3 H) 1.71 - 1.79 (m, 2 H) 4.37 (d, *J*=6.50 Hz, 2 H) 4.66 (br. s., 1 H) 5.34 (d, *J*=6.55 Hz, 1 H) 7.07 - 7.18 (m, 2 H) 7.36 (t, *J*=8.19 Hz, 1 H) 7.64 (d, *J*=6.65 Hz, 1 H) 8.15 (d, *J*=6.60 Hz, 1 H)	HRMS(A) *m/z* 410.1999 $(M + H)^+$, Rt 1.82
528: (S)-3-(2-((S)-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 0.58 (br. s., 3 H) 0.78 (br. s., 3 H) 1.62 (d, *J*=7.04 Hz, 3 H) 1.82 (br. s., 1 H) 3.92 (s, 3 H) 4.40 (d, *J*=6.26 Hz, 2 H) 4.70 (br. s., 1 H) 5.39 (br. s., 1 H) 7.29 - 7.39 (m, 3 H) 7.78 (d, *J*=7.04 Hz, 1 H) 7.82 (s, 1 H) 7.99 (s, 1 H) 8.16 (d, *J*=7.04 Hz, 1 H)	HRMS(A) *m/z* 425.2112 $(M + H)^+$, Rt 1.64
529: (S)-3-(2-((S)-1-(2-fluoro-4-(1H-pyrazol-4-yl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 0.59 (br. s., 3 H) 0.79 (br. s., 3 H) 1.63 (d, *J*=6.94 Hz, 3 H) 1.84 (br. s., 1 H) 4.40 (d, *J*=6.26 Hz, 2 H) 4.71 (br. s., 1 H) 5.40 (br. s., 1 H) 7.29 - 7.36 (m, 1 H) 7.37 - 7.43 (m, 2 H) 7.78 (d, *J*=7.09 Hz, 1 H) 7.99 (s, 2 H) 8.17 (dd, *J*=6.36, 1.86 Hz, 1 H)	HRMS(A) *m/z* 411.1949 $(M + H)^+$, Rt 1.52
530: 2-chloro-N-cyclopentyl-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide	(DMSO) 0.55 (br. s., 3 H) 0.78 (br. s., 3 H) 1.42 (d, *J*=7.09 Hz, 3 H) 1.50 (d, *J*=4.65 Hz, 4 H) 1.64 (br. s., 2 H) 1.83 (d, *J*=6.46 Hz, 3 H) 4.14 (dd, *J*=12.72, 6.60 Hz, 1 H) 4.34 (br. s., 2 H) 4.64 (br. s., 1 H) 5.03 (br. s., 1 H) 7.25 (d, *J*=5.77 Hz, 1 H) 7.31 (s, 2 H) 7.42 (s, 1 H) 8.19 (br. s., 1 H) 8.27 (br. s., 1 H)	HRMS(A) *m/z* 472.2117 $(M + H)^+$, Rt 1.82
531: 2-chloro-N-cyclohexyl-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide	(DMSO) 0.55 (br. s., 3 H) 0.78 (br. s., 4 H) 1.18 - 1.34 (m, 4 H) 1.42 (d, *J*=7.04 Hz, 3 H) 1.56 (d, *J*=12.08 Hz, 1 H) 1.69 (d, *J*=12.86 Hz, 3 H) 1.81 (br. s., 3 H) 4.34 (br. s., 2 H) 4.63 (br. s., 1 H) 5.03 (br. s., 1 H) 7.26 (d, *J*=5.82 Hz, 1 H) 7.31 (s, 2 H) 7.43 (s, 1 H) 8.03 (br. s., 1 H) 8.18 (br. s., 2 H)	HRMS(A) *m/z* 486.2275 $(M + H)^+$, Rt 1.94
532: 2-chloro-N-((1r,4S)-4-hydroxycyclohexyl)-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide	(DMSO) 0.54 (br. s., 3 H) 0.77 (br. s., 3 H) 1.18 - 1.30 (m, 5 H) 1.36 (s, 1 H) 1.42 (d, *J*=7.04 Hz, 3 H) 1.81 (d, *J*=9.19 Hz, 5 H) 3.36 (br. s., 1 H) 4.33 (br. s., 2 H) 4.63 (br. s., 1 H) 5.02 (br. s., 1 H) 7.25 (d, *J*=5.77 Hz, 1 H) 7.30 (s, 2 H) 7.42 (s, 1 H) 8.17 (br. s., 2 H)	HRMS(A) *m/z* 502.2226 $(M + H)^+$, Rt 1.40
533: (S)-3-(2-((S)-1-(3-(cyclopentyloxy)phenyl)ethylamino)pyrimidin-4-yl)-	(DMSO) 0.40 - 0.73 (m, 6 H) 1.40 (d, *J*=6.99 Hz, 3 H) 1.47 - 1.70 (m, 6 H) 1.83 (dd, *J*=16.80, 6.72 Hz, 3 H) 4.31 (d,*J*=8.75	HRMS(A) *m/z* 411.2402

4-isopropyloxazolidin-2-one	Hz, 2 H) 4.58 (br. s., 1 H) 4.71 (br. s., 1 H) 4.94 (br. s., 1 H) 6.69 (dd, *J*=7.95, 2.03 Hz, 1 H) 6.81 (d, *J*=8.31 Hz, 2 H) 7.09 - 7.19 (m, 1 H) 7.27 (d, *J*=6.06 Hz, 1 H) 8.16 (br. s., 2 H)	$(M + H)^+$, Rt 2.15 min
534: (S)-3-(2-((S)-1-(3-(cyclohexyloxy)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO) 0.47 (br. s., 3 H) 0.65 (br. s., 3 H) 1.14 - 1.36 (m, 5 H) 1.40 (d, *J*=7.04 Hz, 3 H) 1.44 - 1.54 (m, 1 H) 1.65 (d, *J*=9.34 Hz, 2 H) 1.72 - 1.91 (m, 3 H) 4.11 - 4.39 (m, 3 H) 4.57 (br. s., 1 H) 4.94 (br. s., 1 H) 6.71 (dd, *J*=7.85, 1.88 Hz, 1 H) 6.80 (br. s., 2 H) 7.14 (t, *J*=8.07 Hz, 1 H) 7.26 (d, *J*=6.02 Hz, 1 H) 8.16 (br. s., 2 H)	HRMS(A) *m/z* 425.2565 $(M + H)^+$, Rt 2.26 min
535: (S)-3-(2-((S)-1-(3-(cycloheptyloxy)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO) 0.50 (br. s., 3 H) 0.68 (br. s., 3 H) 1.43 (d, *J*=7.04 Hz, 5 H) 1.53 (d, *J*=2.98 Hz, 4 H) 1.58 - 1.71 (m, 4 H) 1.73 - 1.97 (m, 3 H) 4.34 (d, *J*=8.46 Hz, 2 H) 4.38 - 4.46 (m, 1 H) 4.60 (br. s., 1 H) 4.98 (br. s., 1 H) 6.70 (dd, *J*=8.14, 2.03 Hz, 1 H) 6.76 - 6.89 (m, 2 H) 7.18 (t, *J*=7.87 Hz, 1 H) 7.30 (d, *J*=6.02 Hz, 1 H) 8.20 (br. s., 2 H)	HRMS(A) *m/z* 439.2712 $(M + H)^+$, Rt 2.41 min
536: (S)-3-(2-((S)-1-(3-isopropoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO) 0.49 (br. s., 3 H) 0.67 (br. s., 3 H) 1.09 - 1.28 (m, 7 H) 1.32 - 1.50 (m, 3 H) 4.23 - 4.39 (m, 2 H) 4.52 (dt, *J*=12.04, 6.08 Hz, 1 H) 4.60 (br. s., 1 H) 4.96 (br. s., 1 H) 6.71 (dd, *J*=8.00, 1.98 Hz, 1 H) 6.82 (br. s., 2H) 7.15 (t, *J*=8.09 Hz, 1 H) 7.30 (d, *J*=6.02 Hz, 1 H) 8.18 (br. s., 1 H) 8.28 (br. s., 1 H)	HRMS(A) *m/z* 385.2248 $(M + H)^+$, Rt 1.92 min
537: (S)-3-(5-fluoro-2-((S)-1-(3-isobutoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO) 0.49 (br. s., 6 H) 0.92 (d, *J*=6.7 Hz, 6 H) 1.37 (d, *J*=7.04 Hz, 3 H) 1.93 (dquin, *J*=13.25, 6.60, 6.60, 6.60, 6.60 Hz, 1 H) 3.59 - 3.70 (m, 2 H) 3.94 - 4.31 (m, 3 H) 4.45 (br. s., 1 H) 6.69 (dd, *J*=8.17, 1.76 Hz, 1 H) 6.80 - 6.89 (m, 2 H) 7.13 (t, *J*=7.83 Hz, 1H) 7.92 (br. s., 1 H) 8.34 (br. s., 1 H)	HRMS(A) *m/z* 417.231 $(M + H)^+$, Rt 2.53 min
538: (S)-3-(5-fluoro-2-((S)-1-(3-((S)-tetrahydrofuran-3-yloxy)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO) 1.41 (d, *J*=7.04 Hz, 6 H) 1.83 - 1.93 (m, 1 H) 2.11 - 2.23 (m, 1 H) 3.68 - 4.04 (m, 8 H) 4.25 (br. s., 1 H) 4.49 (br. s., 2 H) 4.80 (br. s., 1 H) 4.95 (dd, *J*=6.06, 4.65 Hz, 1 H) 6.72 (dd, *J*=8.02, 2.10 Hz, 1 H) 6.83 - 6.94 (m, 2 H) 7.19 (t, *J*=7.87 Hz, 1 H) 7.96 (br. s., 1 H) 8.38 (br. s., 1 H)	HRMS(A) *m/z* 431.2098 $(M + H)^+$, Rt 2.01 min
539: (4S)-4-isopropyl-3-(2-((1S)-1-(3-(tetrahydro-2H-pyran-3-yloxy)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	(DMSO) 0.47 (br. s., 3 H) 0.66 (br. s., 3 H) 1.39 (d, *J*=6.99 Hz, 3 H) 1.44 - 2.00 (m, 5 H) 3.32 - 3.50 (m, 2 H) 3.54 - 3.88 (m, 3 H) 4.23 - 4.37 (m, 2 H) 4.61 (br. s., 1H) 4.90 (br. s., 1H) 6.74 (d, *J*=8.36 Hz, 1 H) 6.85 (d, *J*=13.55 Hz, 2 H) 7.15 (t, *J*=7.87 Hz, 1 H) 7.25 (d, *J*=5.97 Hz, 1 H) 8.06 (br. s.,1 H) 8.16 (br. s., 1 H)	HRMS(A) *m/z* 427.2353 $(M + H)^+$, Rt 1.75 min
540: (S)-4-isopropyl-3-(2-((S)-1-(3-phenoxyphenyl)ethylamin	(DMSO) 0.50 (br. s., 3 H) 0.66 (br. s., 3 H) 1.42 (d, *J*=7.04 Hz, 3 H) 1.75 (br. s., 1 H) 4.27 - 4.37 (m, 2 H) 4.55 - 4.62 (m, 1 H)	HRMS(A) *m/z* 419.2092

o)pyrimidin-4-yl)oxazolidin-2-one	4.97 -5.07 (m, 1 H) 6.78 (dd, *J*=8.02, 1.81 Hz, 1 H) 6.87 (d, *J*=7.53 Hz, 2 H) 6.96 (br. s., 1 H) 7.04 - 7.14 (m, 2 H) 7.25 - 7.37 (m, 4 H) 8.17 (d, *J*=4.99 Hz, 1 H) 8.36 (br. s., 1 H)	$(M + H)^+$, Rt 2.12 min
541: (S)-3-(5-fluoro-2-((S)-1-(3-phenoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO) 0.44 - 0.65 (m, 6 H) 1.37 (d, *J*=6.99 Hz, 3 H) 4.08 - 4.40 (m, 2 H) 4.45 (br. s., 1 H) 4.82 (br. s., 1 H) 6.75 (dd, *J*=8.07, 1.37 Hz, 1 H) 6.86 (d, *J*=7.48 Hz, 2 H) 6.95 (br. s., 1 H) 7.03 - 7.11 (m, 2 H) 7.28 (dt, *J*=19.78, 7.86 Hz, 3 H) 7.94 (br. s., 1 H) 8.33 (br. s.,1 H)	HRMS(A) *m/z* 437.1992 $(M + H)^+$, Rt 2.45 min
542: (S)-3-(5-fluoro-2-((S)-1-(4-isopropoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO) 0.56 (br. s., 6 H) 1.18 (d, *J*=2.35 Hz, 3 H) 1.20 (d, *J*=2.30 Hz, 3 H) 1.36 (d, *J*=7.04 Hz, 3 H) 4.21 (br. s., 1H) 4.36 - 4.58 (m, 3 H) 4.75 (br. s., 1H) 6.77 (d, *J*=8.71 Hz, 2 H) 7.18 (d, *J*=8.56 Hz, 2 H) 7.87 (br. s., 1 H) 8.33 (d, *J*=2.74 Hz, 1 H)	HRMS(A) *m/z* 403.2156 $(M + H)^+$, Rt 2.30 min
543: (4S)-4-isopropyl-3-(2-((1-(tetrahydrofuran-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 8.00 - 8.17 (m, 1H), 7.71 (d, J = 7.04 Hz, 1H), 4.78 - 4.85 (m, 1H), 4.41 - 4.55 (m, 2H), 3.98 - 4.14 (m, 1H), 3.84 - 3.97 (m, 1H), 3.67 - 3.82 (m, 1H), 2.55 - 2.70 (m, 1H), 1.86 - 2.13 (m, 3H), 1.56 - 1.82 (m, 1H), 1.24 - 1.34 (m, 3H), 1.00 - 1.06 (m, 3H), 0.91 (t, J= 6.06 Hz, 3H)	HRMS(A) *m/z* 321.1935 (M + H)+, Rt 1.32 min
544: (S)-3-(2-((S)-1-(4-isobutoxy-3-methylphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(400 MHz, DMSO) δ ppm 0.54 (br. s., 3 H) 0.72 (br. s., 3 H) 0.96 (d, J=6.70 Hz, 6 H) 1.41 (d, J=6.99 Hz, 3 H) 1.89 (br. s., 1 H) 1.99 (dt, J=13.24, 6.61 Hz, 1 H) 2.11 (s, 3 H) 3.68 (d, J=6.41 Hz, 2 H) 4.31 - 4.41 (m, 2 H) 4.62 (dd, J=6.99, 3.72 Hz, 1 H) 4.94 (quin, J=6.94 Hz, 1 H) 6.80 (d, J=8.31 Hz, 1 H) 7.00 - 7.13 (m, 2 H) 7.34 (d, J=6.06 Hz, 1 H) 8.19 (d, J=4.94 Hz, 1 H) 8.42 (br. s., 1 H)	HRMS(A) m/z 413.2561 (M + H)+, Rt 2.34 min
545: (S)-3-(2-((S)-1-(6-(1-ethoxycyclopropyl)pyridin-3-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	^1H NMR (400 MHz, CD_3OD) d 0.65 (br. s., 3 H) 0.75 (br. s., 3 H) 1.23 (t, J=7.04 Hz, 3 H) 1.28 - 1.45 (m, 4 H) 1.64 (d, J=7.09 Hz, 3 H) 3.55 (q, J=7.04 Hz, 2 H) 4.36 - 4.43 (m, 2 H) 4.70 (br. s., 1 H) 5.20 - 5.28 (m, 1 H) 7.66 (d, J=8.41 Hz, 2 H) 8.04 (br. s., 1 H) 8.16 (d, J=6.41 Hz, 1 H)	HRMS(A) m/z 412.2349 (M + H)+, Rt 1.55 min
546: (S)-3-(2-((S)-1-(4-isobutoxy-3-methylphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	^1H NMR (400 MHz, DMSO) d ppm 0.54 (br. s., 3 H) 0.72 (br. s., 3 H) 0.96 (d, J=6.70 Hz, 6 H) 1.41 (d, J=6.99 Hz, 3 H) 1.89 (br. s., 1 H) 1.99 (dt, J=13.24, 6.61 Hz, 1 H) 2.11 (s, 3 H) 3.68 (d, J=6.41 Hz, 2 H) 4.31 - 4.41 (m, 2 H) 4.62 (dd, J=6.99, 3.72 Hz, 1 H) 4.94 (quin, J=6.94 Hz, 1 H) 6.80 (d, J=8.31 Hz, 1 H) 7.00 - 7.13 (m, 2 H) 7.34 (d, J=6.06 Hz, 1 H) 8.19 (d, J=4.94 Hz, 1 H) 8.42 (br. s., 1 H)	HRMS m/z 413.2561 (M + H)+; Rt-2.34 min.

Example 547

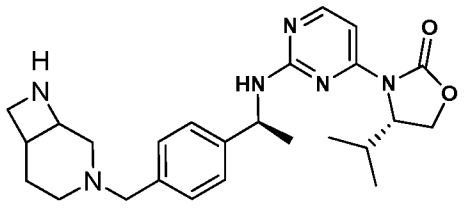


A solution of (S)-3-(2-((S)-1-(4-(chloromethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (75 mg, 0.2 mmol) and 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (25 mg, 0.2 mmol) in DMSO (2 mL) was heated at 80 °C for 16 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with water (20 mL). After separation, the aqueous phase was washed with EtOAc (2 x 15 mL). Combined organics were dried over Na2SO4, filtered and concentrated. Silica gel column chromatography (MeOH in CH_2Cl_2 0 to 10%) provided (S)-3-(2-((S)-1-(4-((5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (58 mg, white solid) in 62.8% yield.

^{1}H NMR (400 MHz, MeOD) δ 8.12 (d, J = 6.0 Hz, 1H), 7.34 (d, J = 5.9 Hz, 1H), 7.33 (s, 4H), 6.99 (d, J = 1.3 Hz, 1H), 6.89 (d, J = 1.4 Hz, 1H), 5.07 (q, J = 7.0 Hz, 1H), 4.68 (br s, 1H), 4.37 – 4.25 (m, 2H), 4.02 (t, J = 5.5 Hz, 2H), 3.72 (s, 2H), 3.63 (s, 2H), 2.90 (td, J = 5.4, 2.6 Hz, 2H), 1.84 (br s, 1H), 1.51 (d, J = 7.0 Hz, 3H), 0.72 (br s, 3H), 0.57 (br s, 3H); HRMS m/z 462.2606 (M + H)+.

The following compounds were prepared using methods similar to those described for the preparation of **Example 205.**

Example 548

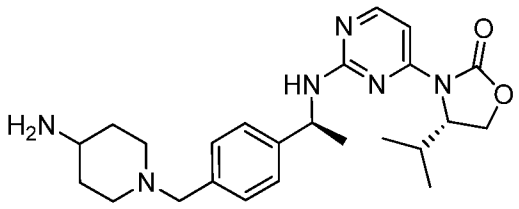


(4S)-3-(2-((1S)-1-(4-(3,8-diazabicyclo[4.2.0]octan-3-ylmethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

^{1}H NMR (400 MHz, MeOD) δ 8.12 – 8.08 (m, 1H), 7.37 – 7.22 (m, 5H), 5.10 – 5.01 (m, 1H), 4.66 (br s, 1H), 4.37 – 4.23 (m, 2H), 3.92 – 3.89 (m, 1H), 3.63 – 3.54 (m, 1H), 3.54 – 3.47 (m, 1H), 3.24 – 3.20 (m, 1H), 3.11 – 2.95 (m, 1H), 2.95 – 2.73 (m, 1H), .2.67 – 2.59

(m, 2H), 2.49 (ddd, J = 16.2, 12.8, 5.3 Hz, 1H), 2.20 – 2.08 (m, 1H), 1.99 – 1.68 (m, 3H), 1.50 (d, J = 7.0 Hz, 3H), 0.72 (br s, 1H), 0.56 (br s, 1H) ; HRMS m/z 451.2810 (M + H)+.

Example 549

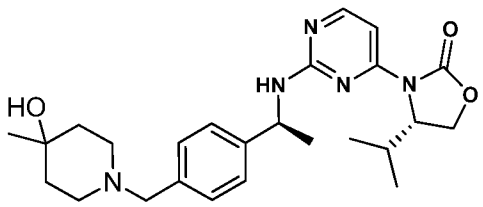


(S)-3-(2-((S)-1-(4-((4-aminopiperidin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

^{1}H NMR (400 MHz, MeOD) d 8.12 (d, J = 5.8 Hz, 1H), 7.34 (d, J = 5.8 Hz, 1H), 7.27 (q, J = 8.2 Hz, 4H), 5.05 (q, J = 7.0 Hz, 1H), 4.67 (s, 1H), 4.38 - 4.25 (m, 2H), 3.48 (s, 2H), 2.86 (br d, J = 11.8 Hz, 2H), 2.71 (tt, J = 10.9, 4.2 Hz, 1H), 2.05 (tt, J = 12.0, 2.5 Hz, 2H), 1.90 - 1.75 (m, 3H), 1.54 - 1.37 (m, 5H), 0.72 (br s, 4H), 0.55 (br s, 3H); HRMS m/z 439.2805 (M + H)+.

The following compounds were prepared using methods similar to those described for the preparation of **Example 210**.

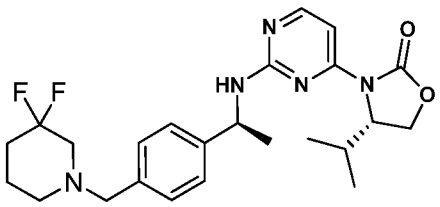
Example 550



(S)-3-(2-((S)-1-(4-((4-hydroxy-4-methylpiperidin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

^{1}H NMR (400 MHz, MeOD) δ 8.12 (d, J = 5.7 Hz, 1H), 7.34 (d, J = 5.9 Hz, 1H), 7.27 (t, J = 6.6 Hz, 4H), 5.06 (q, J = 6.8 Hz, 1H), 4.67 (br s, 1H), 4.37 – 4.25 (m, 2H), 3.51 (d, J = 3.2 Hz, 2H), 2.52 (br s, 2H), 2.44 (br s, 2H), 1.81 (br s, 1H), 1.59 (br s, 4H), 1.50 (d, J = 7.0 Hz, 3H), 1.19 (s, 3H), 0.72 (br s, 3H), 0.56 (br s, 3H); HRMS m/z 454.2816 (M + H)+.

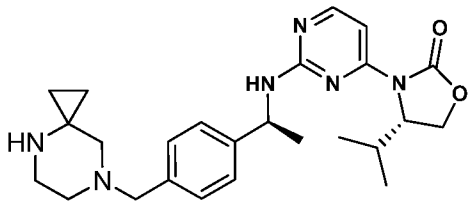
Example 552



(S)-3-(2-((S)-1-(4-((3,3-difluoropiperidin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

^{1}H NMR (400 MHz, MeOD) δ 8.12 (d, J = 5.8 Hz, 1H), 7.35 (d, J = 5.8 Hz, 1H), 7.28 (q, J = 8.2 Hz, 4H), 5.06 (q, J = 7.0 Hz, 1H), 4.67 (br s, 1H), 4.39 – 4.25 (m, 2H), 3.55 (d, J = 2.2 Hz, 2H), 2.56 (t, J = 11.5 Hz, 2H), 2.51 – 2.40 (m, 2H), 1.91 – 1.81 (m, 3H), 1.78 – 1.70 (m, 2H), 1.50 (d, J = 7.0 Hz, 3H), 0.71 (br s, 3H), 0.56 (br s, 3H) ; HRMS m/z 460.2537 (M + H)+.

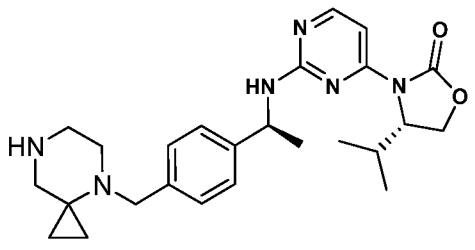
Example 553



(S)-3-(2-((S)-1-(4-(4,7-diazaspiro[2.5]octan-7-ylmethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one

^{1}H NMR (400 MHz, MeOD) δ 8.12 (d, J = 5.8 Hz, 1H), 7.34 (d, J = 5.8 Hz, 1H), 7.32 – 7.24 (m, 4H), 5.06 (q, J = 7.0 Hz, 1H), 4.68 (br s, 1H), 4.37 – 4.26 (m, 2H), 3.49 (s, 2H), 2.89 (t, J = 5.0 Hz, 2H), 2.47 (br s, 2H), 2.28 (br s, 2H), 1.86 (br s, 1H), 1.49 (d, J = 7.0 Hz, 3H), 0.72 (br s, 3H), 0.64 – 0.49 (m, 5H), 0.45 (t, J = 3.2 Hz, 2H) ; HRMS m/z 451.2809 (M + H)+.

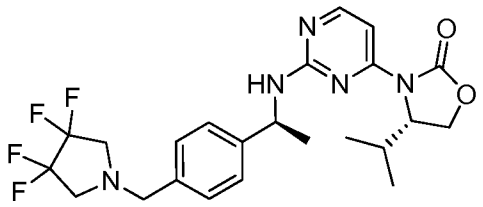
Example 554



(S)-3-(2-((S)-1-(4-(4,7-diazaspiro[2.5]octan-4-ylmethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

^{1}H NMR (400 MHz, MeOD) δ 8.11 (d, J = 5.8 Hz, 1H), 7.33 (d, J = 5.8 Hz, 1H), 7.24 (q, J = 8.3 Hz, 4H), 5.03 (q, J = 7.0 Hz, 1H), 4.67 (br s, 1H), 4.37 – 4.25 (m, 2H), 3.85 (s, 2H), 2.85 – 2.65 (m, 6H), 1.87 (br s, 1H), 1.48 (d, J = 7.0 Hz, 3H), 0.85 – 0.63 (m, 5H), 0.63 – 0.46 (m, 5H) ; HRMS m/z 451.2810 (M + H)+.

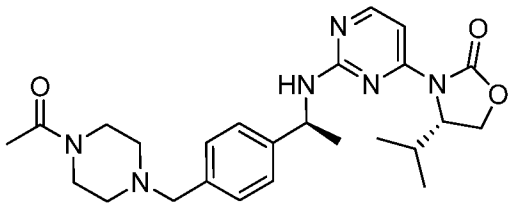
Example 555



(S)-4-isopropyl-3-(2-((S)-1-(4-((3,3,4,4-tetrafluoropyrrolidin-1-yl)methyl)phenyl) ethylamino)pyrimidin-4-yl)oxazolidin-2-one.

HRMS m/z 482.2161 (M + H)+; RT=2.78 min.

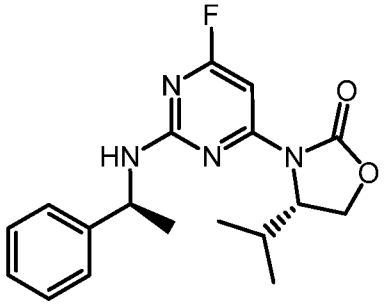
Example 556



(S)-3-(2-((S)-1-(4-((4-acetylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.

HRMS m/z 467.2752 (M + H)+; RT=1.92 min.

Example 557



(S)-4,6-difluoro-N-(1-phenylethyl)pyrimidin-2-amine (48.8 mg, 0.21 mmol) was added to NaH (95 %, 6.1 mg, 0.25 mmol, 1.2 equiv) in DMF (2 mL) at 0 °C. After 5 min, (S)-4-isopropyl-2-oxazolidinone (27.9 mg, 0.22 mmol, 1.0 equiv) was added. The reaction was stirred for 10 min at 0 °C and then warmed to room temperature. After 4h, the reaction mixture was quenched with water and poured into dilute brine (1:1 sat. brine:water) and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with diluted brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to a pink oil. Purification by reverse phase HPLC followed by lyopholization of the fractions containing product provided (S)-3-(6-fluoro-2-(((S)-1-phenylethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one as a white solid (22.5 mg TFA salt) in 31% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.27 - 7.39 (m, 4H), 7.17 - 7.26 (m, 1H), 6.92 (s, 1H), 5.05 (q, *J* = 7.04 Hz, 1H), 4.63 (br. s., 1H), 4.19 - 4.41 (m, 2H), 1.77 (br. s., 1H), 1.51 (d, *J* = 7.04 Hz, 3H), 0.44 - 0.78 (m, 6H); LCMS *m/z* 345.1 $(M + H)^+$., R_t 1.00 min; UPLC R_t 5.038 min.

The compounds in Table 17 were prepared using methods similar to those described for the preparation of Example 557.

Table 17.

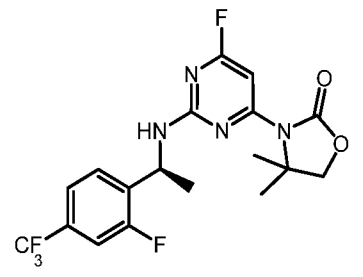
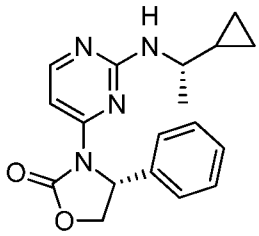
558


Table 18: Chemical name, NMR chemical shifts and LCMS signal for each compound listed in Table **17**.

Example: Name	^{1}H NMR (400 MHz) δ ppm	LCMS
558: (*S*)-5,5-dimethyl-4-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 8.06 (d, J = 5.8 Hz, 1 H), 7.43 (d, J = 5.8 Hz, 1 H), 7.31 – 7.24 (m, 3 H), 7.19 – 7.11 (m, 5 H), 7.01 (br s 2 H), 5.48 (s, 1 H), 4.86 – 4.80 (m, 1 H), 1.65 (s, 3 H), 1.43 (d, J = 7.0 Hz, 3 H), 0.98 (s, 3 H)	HRMS(A) *m/z* 389.1987 $(M + H)^+$

Example 559



A mixture of (R)-3-(2-chloropyrimidin-4-yl)-4-phenyloxazolidin-2-one (55.3 mg, 0.20 mmol), (S)-1-cyclopropylethylamine (40 μL, 0.26 mmol, 1.3 equiv) and *i*Pr_2Net (0.20 mL, 1.15 mmol, 5.7 equiv) in NMP (1 mL) was heated in the microwave at 180 °C for 20min. The reaction mixture was filtered and purified by reverse phase HPLC to give (R)-3-(2-(((S)-1-cyclopropylethyl)amino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one as a white solid (8.8 mg) in 10 % yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, J = 6.26 Hz, 1H), 7.29 - 7.43 (m, 6H), 5.76 (dd, J = 4.11, 8.80 Hz, 1H), 4.28 (dd, J = 4.30, 8.61 Hz, 1H), 3.06 - 3.19 (m, 1H), 1.39 (dd, J = 3.52, 6.65 Hz, 1H), 0.88 - 0.97 (m, 1H), 0.83 (br. s., 3H), 0.53 - 0.62 (m, 1H), 0.50 (dt, J = 4.11, 8.51 Hz, 1H), 0.33 (qd, J = 4.78, 9.54 Hz, 1H), 0.26 (td, J = 4.60, 9.59 Hz, 1H); HRMS(A) *m/z* 325.1667 $(M + H)^+$, Rt 1.54 min; UPLC 2.807 min.

The compounds in Table 19 were prepared using methods similar to those described for the preparation of Example 559.

Table 19.

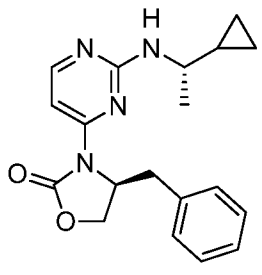
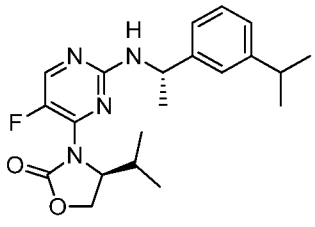
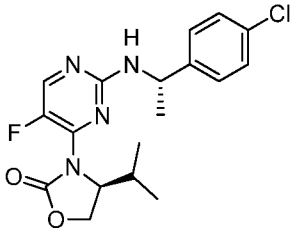
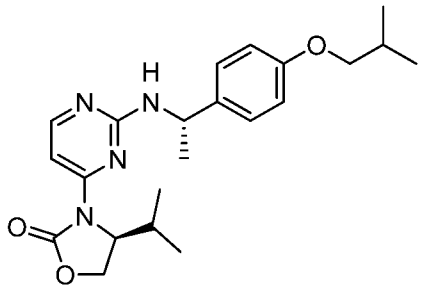
560	561	562
		

Table 20. Chemical name, NMR chemical shifts and LCMS signal for each compound listed in Table 19.

Example: Name	^{1}H NMR (400 MHz) δ ppm	LCMS
560: (S)-4-benzyl-3-(2-(((S)-1-cyclopropylethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 8.13 (d, J = 7.04 Hz, 1H), 7.71 (d, J = 7.04 Hz, 1H), 7.22 - 7.38 (m, 5H), 5.11 (tt, J = 3.03, 8.12 Hz, 1H), 4.23 -4.53 (m, 2H), 3.08 (dd, J = 8.41, 13.50 Hz, 1H), 1.42 (d, J = 6.65 Hz, 3H), 1.04 - 1.23 (m, 1H), 0.47 - 0.73 (m, 2H), 0.17 - 0.47 (m, 2H).	HRMS(A) *m/z* 339.1822 $(M + H)^+$, Rt 1.64 min
561: (S)-3-(5-fluoro-2-(((S)-1-(3-isopropylphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one		HRMS(A) *m/z* 387.2203 $(M + H)^+$, Rt 2.52 min
562: (S)-3-(2-(((S)-1-(4-chlorophenyl)ethyl)amino)-5-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one		HRMS(A) *m/z* 379.1341 $(M + H)^+$, Rt 2.30 min

Example 563



A mixture of (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (43.2 mg, 0.18 mmol), (1S)-1-[4-(2-Methylpropoxy)phenyl]ethan-1-amine (84.0 mg, 0.37 mmol, 2.0 equiv) and *i*Pr_2Net (0.30 mL, 1.72 mmol, 4.7 equiv) in NMP (1 mL) was heated at 105 °C for 24 h. The reaction mixture was filtered and purified by reverse phase HPLC to give (S)-3-(2-(((S)-1-(4-isobutoxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one as a white solid (5.3 mg, TFA salt) in 4 % yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.68 (d, J = 6.65 Hz, 1H), 7.25 (d, J = 8.61 Hz, 2H), 6.90 (d, J = 8.61 Hz, 2H), 4.41 (d, J = 5.87 Hz, 2H), 3.74 (d, J = 6.26 Hz, 2H), 1.96 - 2.15 (m, 1H), 1.58 (d, J = 7.04 Hz, 3H), 1.03 (d, J = 6.65 Hz, 6H); HRMS(A) *m/z* 399.2399 $(M + H)^+$, Rt 2.60 min; UPLC 4.223 min.

The compounds in Table 21 were prepared using methods similar to those described for the preparation of Example 563.

Table 21.

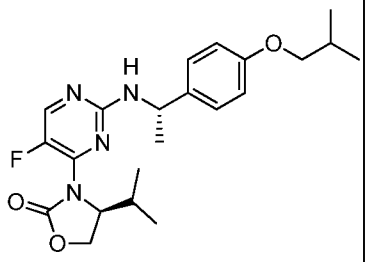
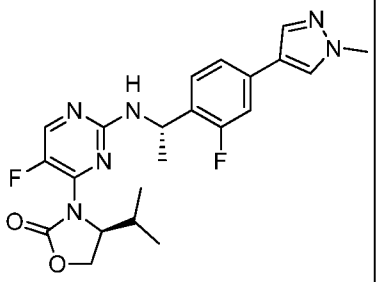
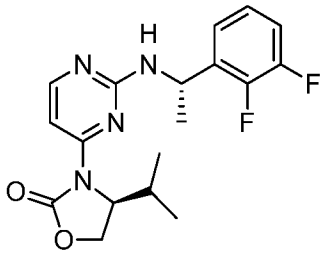
564	565
	

Table 22. Chemical name, NMR chemical shifts and LCMS signal for each compound listed in Table 21.

Example: Name	^{1}H NMR (400 MHz) δ ppm	LCMS
564: (S)-3-(5-fluoro-2-(((S)-1-(4-isobutoxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one		HRMS(A) *m/z* 417.2314 $(M + H)^+$, Rt 2.53 min
565: (S)-3-(5-fluoro-2-(((S)-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one		HRMS(A) *m/z* 443.2012 $(M + H)^+$, Rt 1.92 min

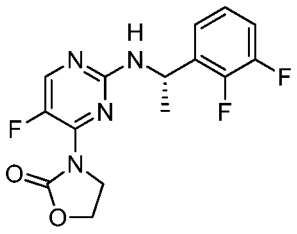
Example 566



To a microwave vial with stir bar was added (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (24.96 mg, 0.103 mmol) in DMSO (1653 µL). To this reaction mixture was added (S)-1-(2,3-difluorophenyl)ethanamine (40 mg, 0.207 mmol) and DIEA (144 µL, 0.826 mmol). The vial capped and heated at 110 °C over the weekend. The solution was filtered, then purified by reverse phase HPLC. Product fractions combined, frozen and lyopholyzed to afford ((S)-3-(2-((S)-1-(2,3-difluorophenyl)ethylamino) pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (10.2 mg, 0.021 mmol, 10.26 % yield) as a

TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 0.59 (br. s., 3 H) 0.75 (br. s., 3 H) 1.59 (d, *J*=6.99 Hz, 3 H) 1.69 (br. s., 1 H) 4.37 (d, *J*=5.67 Hz, 2 H) 4.66 (br. s., 1 H) 5.40 (d, *J*=7.38 Hz, 1 H) 7.06 - 7.23 (m, 3 H) 7.70 (d, *J*=6.90 Hz, 1 H) 8.14 (d, *J*=6.46 Hz, 1 H); LCMS *m/z* 363.3 $(M + H)^+$, Rt 0.77 min.; HRMS(A) *m/z* 363.1642 $(M + H)^+$, Rt 1.89 min.

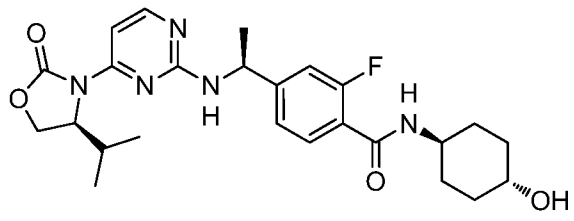
Example 567



(S)-3-(2-(1-(2,3-difluorophenyl)ethylamino)-5-fluoropyrimidin-4-yl)oxazolidin-2-one was prepared using a method similar to that described for the preparation of Example 566. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.50 (d, J=7.04 Hz, 3 H) 3.91 (br. s., 1 H) 4.09 - 4.20 (m, 1 H) 4.42 - 4.56 (m, 2 H) 5.26 (q, J=6.68 Hz, 1 H) 6.99 - 7.12 (m, 2 H) 7.16 (t, J=7.48 Hz, 1 H) 8.13 (d, J=3.37 Hz, 1 H). HRMS(A) m/z 339.1075 (M + H)+, Rt 1.86 min.

Example 568

2-fluoro-N-(*trans*-4-hydroxycyclohexyl)-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide



Step 1: Preperation of (S)-4-(1-(tert-butoxycarbonylamino)ethyl)-2-fluorobenzoic acid:

To (S)-4-(1-aminoethyl)-2-fluorobenzoic acid (900 mg, 4.10 mmol) was added, DCM (11 ml), Hunig's Base (2.147 ml, 12.29 mmol) and BOC-Anhydride (1.998 ml, 8.61 mmol). Then NMP (11.00 ml) was added to help solubility. The reaction was sonicated for 10 minutes and was stirred at room temperature for 22 hours, followed by LCMS. The DCM was mostly concentrated off. Then to the crude reaction was added 120 ml of water and basified with 10 ml of 5M NaOH. The basic aqueous solution was extracted with 2 x 50 ml of (15% ethyl acetate in heptane) solution. Then to the basic aqueous solution (with

the product) was added 150 ml of ethyl acetate and with stirring acidified with 2M aqueous HCl solution to about pH 3. Then the ethyl acetate was extracted, saved and the acidic water extracted again with 100 ml of ethyl acetate. The organic layers were combined and washed with 0.5M aqueous HCl solution 1 x 40 ml, with water 3 x 40 ml, and concentrated to constant mass to give 1104 mg of (S)-4-(1-(tert-butoxycarbonylamino)ethyl)-2-fluorobenzoic acid, used as is. LCMS *m/z* BOC pattern of 269.0 (M+H-15 fragment) and weak 228.0 (M+H-56 fragment) compared to expected 284.0 $(M + H)^+$, Rt 0.72 min.

Step 2: Preperation of tert-butyl (S)-1-(3-fluoro-4-(*trans*-4-hydroxycyclohexylcarbamoyl)phenyl)ethylcarbamate:
To (S)-4-(1-(tert-butoxycarbonylamino)ethyl)-2-fluorobenzoic acid (40.8 mg, 0.144 mmol) was added NMP (0.5 ml), *trans*-4-aminocyclohexanol (41.5 mg, 0.360 mmol), Hunig's Base (0.101 ml, 0.576 mmol) and HATU (110 mg, 0.288 mmol) The reaction was stirred at room temperature for 6 hours, followed by LCMS. To the reaction was added 0.5 ml of NMP, filtered, purified by prep LC and lyophilized to give 33 mg of tert-butyl (S)-1-(3-fluoro-4-(*trans*-4-hydroxycyclohexylcarbamoyl)phenyl)ethylcarbamate as the TFA Salt. LCMS *m/z* 381.1 (M + H)+, Rt 0.70 min.

Step 3: Preperation of 4-((S)-1-aminoethyl)-2-fluoro-N-(*trans*-4-hydroxycyclohexyl)benzamide:
To tert-butyl (S)-1-(3-fluoro-4-(*trans*-4-hydroxycyclohexylcarbamoyl)phenyl)ethylcarbamate (33 mg, 0.087 mmol) was added, HCl 4M in Dioxane (2 mL, 8.00 mmol) and MeOH (0.2 ml). The reaction was stirred at room temperature for 1 hour, followed by LCMS. The solvent was concentrated off to residue to give 4-((S)-1-aminoethyl)-2-fluoro-N-(*trans*-4-hydroxycyclohexyl)benzamide in quantitative yield (0.087 mmol) as HCl salt. LCMS *m/z* 281.1 $(M + H)^+$, Rt 0.33 min.

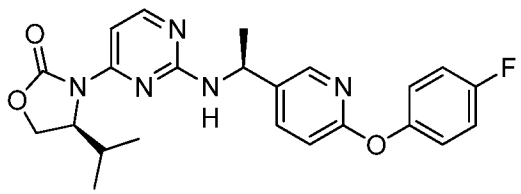
Step 4: Preperation of 2-fluoro-N-(*trans*-4-hydroxycyclohexyl)-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide:
To 4-((S)-1-aminoethyl)-2-fluoro-N-((1r,4S)-4-hydroxycyclohexyl)benzamide (0.024 g, 0.087 mmol) was added (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (0.034 g, 0.139 mmol), DMSO (0.6 ml) and Hunig's Base (0.053 ml, 0.305 mmol). The reaction was heated at 100-105 °C for 16 hours or until done by LCMS. The reaction was let cool, 0.5 ml of DMSO added, filtered, purified by prep LC and lyophilized to give 10.1 mg of 2-fluoro-N-(*trans*-4-hydroxycyclohexyl)-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-

yl)pyrimidin-2-ylamino)ethyl)benzamide as the TFA Salt. LCMS *m/z* 486.2 $(M + H)^+$, Rt 0.57 min.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.13 (d, J = 6.7 Hz, 1H), 7.70 (d, J = 6.7 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.13 - 7.28 (m, 2H), 5.16 (br. s., 1H), 4.67 (br. s., 1H), 4.37 (d, J = 5.5 Hz, 2H), 3.82 (br. s., 1H), 3.53 (d, J = 3.9 Hz, 1H), 1.97 (dd, J = 5.1, 3.1 Hz, 4H), 1.57 (d, J = 7.0 Hz, 3H), 1.38 (t, J = 8.6 Hz, 4H), 0.50 - 0.88 (m, 6H); HRMS(A) *m/z* 486.2523 $(M + H)^+$.

Example 569

(S)-3-(2-((S)-1-(6-(4-fluorophenoxy)pyridin-3-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one

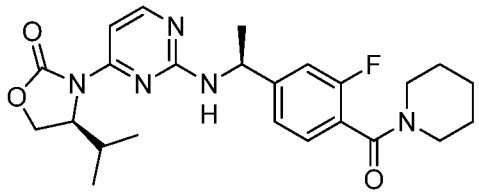


To (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (28 mg, 0.116 mmol) was added (S)-1-(6-(4-fluorophenoxy)pyridin-3-yl)ethanamine (46.7 mg, 0.174 mmol), DMSO (0.6 ml) and Hunig's Base (0.071 ml, 0.406 mmol). The reaction was heated at 105-110 °C for 24 hours or until done by LCMS. The reaction was let cool, 0.5 ml of DMSO was added, filtered, purified by prep LC and lyophilized to give 7.1 mg of (S)-3-(2-((S)-1-(6-(4-fluorophenoxy)pyridin-3-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one as the TFA Salt. LCMS *m/z* 438.2 $(M + H)^+$, Rt 0.82 min.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.04 (d, J = 6.3 Hz, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.73 (dd, J = 8.6, 2.3 Hz, 1H), 7.53 (d, J = 6.3 Hz, 1H), 6.94 - 7.10 (m, 4H), 6.84 (d, J = 8.6 Hz, 1H), 5.05 (d, J = 7.0 Hz, 1H), 4.61 (d, J = 3.9 Hz, 1H), 4.28 (d, J = 5.5 Hz, 2H), 1.49 (d, J = 7.0 Hz, 3H), 0.51 - 0.78 (m, 6H); HRMS(A) *m/z* 438.1946 $(M + H)^+$.

Example 570

(S)-3-(2-((S)-1-(3-fluoro-4-(piperidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one

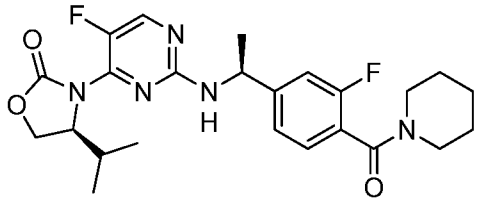


To (S)-(4-(1-aminoethyl)-2-fluorophenyl)(piperidin-1-yl)methanone (0.019 g, 0.076 mmol) was added (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (0.028 g, 0.114 mmol), NMP (0.5 ml) and Hunig's Base (0.033 ml, 0.190 mmol). The reaction was heated at 105-110 °C for 16 hours or until done by LCMS. The reaction was let cool, 0.5 ml of NMP was added, filtered, purified by prep LC and lyophilized to give 4.0 mg of (S)-3-(2-((S)-1-(3-fluoro-4-(piperidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one as TFA Salt. LCMS *m/z* 456.1 $(M + H)^+$, rt 0.74 min.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.13 (d, J = 6.7 Hz, 1H), 7.69 (d, J = 7.0 Hz, 1H), 7.30 - 7.38 (m, 1H), 7.23 - 7.28 (m, 1H), 7.20 (d, J = 10.6 Hz, 1H), 5.18 (br. s., 1H), 4.63 - 4.74 (m, 1H), 4.33 - 4.42 (m, 2H), 3.61 - 3.79 (m, 2H), 1.61 - 1.76 (m, 5H), 1.57 (d, J = 7.0 Hz, 3H), 1.51 (br. s., 2H), 0.77 (br. s., 3H), 0.62 (br. s., 3H); HRMS(A) *m/z* 456.2416 $(M + H)^+$.

Example 571

(S)-3-(5-fluoro-2-((S)-1-(3-fluoro-4-(piperidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one



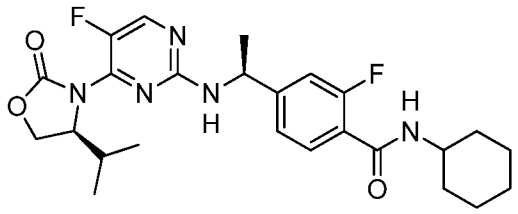
To (S)-(4-(1-aminoethyl)-2-fluorophenyl)(piperidin-1-yl)methanone (0.019 g, 0.076 mmol) was added (S)-3-(2-chloro-5-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (0.030 g, 0.114 mmol), NMP (0.5 ml) and Hunig's Base (0.033 ml, 0.190 mmol). The reaction was heated at 105-110 °C for 8 hours or until done by LCMS. The reaction was let cool, 0.5 ml of NMP added, filtered, purified by prep LC and lyophilized to give 4.5 mg of (S)-3-(5-fluoro-2-((S)-1-(3-fluoro-4-(piperidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one as TFA Salt. LCMS *m/z* 474.2 $(M + H)^+$, Rt 0.91 min.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.21 (d, J = 2.7 Hz, 1H), 7.22 - 7.33 (m, 2H), 7.17 (d, J = 11.0 Hz, 1H), 4.97 (q, J = 7.0 Hz, 1H), 4.59 (br. s., 1H), 4.47 (t, J = 8.8 Hz, 1H), 4.20

- 4.32 (m, 1H), 3.68 (br. s., 2H), 1.57 - 1.75 (m, 5H), 1.48 (d, J = 7.0 Hz, 5H), 0.69 (br. s., 3H), 0.62 (br. s., 3H) ; HRMS(A) *m/z* 474.2330 $(M + H)^+$.

Example 572

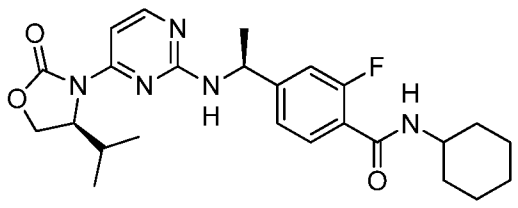
N-cyclohexyl-2-fluoro-4-((S)-1-(5-fluoro-4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide



To (S)-4-(1-aminoethyl)-N-cyclohexyl-2-fluorobenzamide (16 mg, 0.061 mmol) was added (S)-3-(2-chloro-5-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (31.4 mg, 0.121 mmol), NMP (0.5 ml) and Hunig's Base (0.032 ml, 0.182 mmol). The reaction was heated at 125 °C for 4 hours or until done by LCMS. The reaction was let cool, 0.5 ml of NMP added, filtered, purified by prep LC and lyophilized to give 2.5 mg of N-cyclohexyl-2-fluoro-4-((S)-1-(5-fluoro-4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide as the TFA Salt. LCMS *m/z* 488.2 $(M + H)^+$, Rt 0.99 min. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.21 (br. s., 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.24 (dd, J = 8.0, 1.4 Hz, 1H), 7.16 (d, J = 12.1 Hz, 1H), 4.39 - 4.54 (m, 2H), 4.23 (t, J = 7.2 Hz, 1H), 3.83 (t, J = 10.4 Hz, 1H), 1.86 - 1.97 (m, 2H), 1.76 (d, J = 12.9 Hz, 2H), 1.64 (d, J = 12.9 Hz, 1H), 1.48 (d, J = 7.0 Hz, 3H), 1.12 - 1.42 (m, 6H), 0.61 (br. s., 6H); HRMS(A) *m/z* 488.2484 $(M + H)^+$

Example 573

N-cyclohexyl-2-fluoro-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide



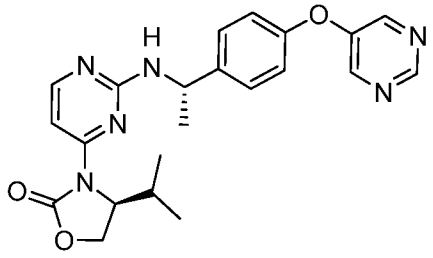
To (S)-4-(1-aminoethyl)-N-cyclohexyl-2-fluorobenzamide (16 mg, 0.061 mmol) was added (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (29.3 mg, 0.121 mmol),

NMP (0.5 ml) and Hunig's Base (0.032 ml, 0.182 mmol). The reaction was heated at 125 °C for 4 hours or until done by LCMS. The reaction was let cool, 0.5 ml of NMP added, filtered, purified by prep LC and lyophilized to give 5.6 mg of N-cyclohexyl-2-fluoro-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide as the TFA Salt. LCMS *m/z* 470.2 (M + H)+, Rt 0.83 min.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.12 (br. s., 1H), 7.57 - 7.73 (m, 2H), 7.13 - 7.27 (m, 2H), 5.15 (br. s., 1H), 4.66 (br. s., 1H), 4.36 (d, J = 5.5 Hz, 2H), 3.76 - 3.94 (m, 1H), 1.87 - 1.99 (m, 2H), 1.77 (d, J = 12.9 Hz, 2H), 1.65 (d, J = 13.7 Hz, 1H), 1.57 (d, J = 7.0 Hz, 3H), 1.12 - 1.50 (m, 6H), 0.73 (br. s., 3H), 0.62 (br. s., 3H); HRMS(A) *m/z* 470.2572 (M + H)$^+$

Example 574

(S)-4-Isopropyl-3-(2-(((S)-1-(4-(pyrimidin-5-yloxy)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one



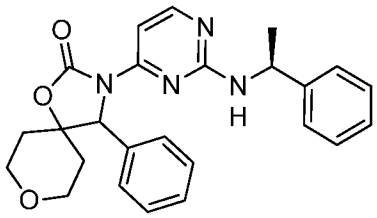
To the solution of (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (43 mg, 0.169 mmol) in NMP (0.7 mL) was added (S)-1-(4-(pyrimidin-5-yloxy)phenyl)ethanamine (41 mg, 0.169 mmol) and DIEA (88 µL, 0.507 mmol). The brown reaction mixture was stirred at 110 °C for 2 days. The reaction mixture was diluted with ethyl acetate and aqueous sodium bicarbonate solution. The separated organic layer was washed with saturated aqueous sodium bicarbonate solution, water and brine. The organic phase was dried over sodium sulfate, filtered off and concentrated under reduced pressure. The residue was purified by reverse phase column chromatography [C-18] to provide (S)-4-isopropyl-3-(2-(((S)-1-(4-(pyrimidin-5-yloxy)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one (7 mg) as its trifluoroacetic acid salt.

MS *m/z* 421.3 (M + H)$^+$, Rt 0.68 min.

HRMS(A) *m/z* 421.1996 (M + H)$^+$, Rt 1.54 min.

Example 575

4-Phenyl-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)-1,8-dioxa-3-azaspiro[4.5]decan-2-one

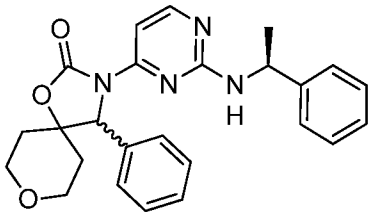


A mixture of crude 3-(2-chloropyrimidin-4-yl)-4-phenyl-1,8-dioxa-3-azaspiro[4.5]decan-2-one (330 mg, 0.954 mmol), (S)-1-phenylethanamine (810 mg, 6.68 mmol), Hunig's base (1.17 mL, 6.68 mmol) in DMA (3.5 mL) was heated in a sealed tube at 80 °C for ~16 hours. The mixture was allowed to cool to room temperature, diluted with DMSO and purified by reverse phase HPLC. Selected fractions were combined and lyophilized, providing 4-phenyl-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)-1,8-dioxa-3-azaspiro[4.5]decan-2-one as its trifluoroacetic acid salt as a white solid. LCMS *m/z* 431.2 $(M + H)^+$, Rt 0.83 min.

The solid was dissolved in ethyl acetate/saturated aqueous $NaHCO_3$ solution. The separated organic layer was washed with saturated aqueous $NaHCO_3$ solution (2x), brine, dried over sodium sulfate, filtered off and concentrated under reduced pressure providing 4-phenyl-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)-1,8-dioxa-3-azaspiro[4.5]decan-2-one (120 mg).

Examples 576 & 577

(S)-4-phenyl-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)-1,8-dioxa-3-azaspiro[4.5]decan-2-one and (R)-4-phenyl-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)-1,8-dioxa-3-azaspiro[4.5]decan-2-one



120 mg of 4-phenyl-3-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)-1,8-dioxa-3-azaspiro[4.5]decan-2-one were dissolved in EtOH (10 mL).

Analytical separation:

Column: CHIRALPAK AD-H (5 um) 100 x 4.6 mm (Daicel Chemical Industries, LTD.).

Solvent: n-heptane : ethyl alcohol = 70 : 30

Flow rate: 1.0 mL/min; detection: UV = 220 nm.

Fraction 1: Retention time: 5.84 min.

Fraction 2: Retention time: 10.18 min.

Preparative separation:

Column: CHIRALPAK AD-prep (10 um) 2 x 25 cm.

Solvent: n-heptane : ethyl alcohol = 70 : 30

Flow rate: 20 mL/min; 530 psi; injection: 4 mL; detection: UV = 210 nm.

Fractions were concentrated under reduce pressure. The residue was dissolved in acetonitrile and filtered through a syringe filter, diluted with water and lyophilized.

Example 576: Peak 1: white powder. Yield: 52.0 mg; de = 99% (UV, 220 nm).

LCMS *m/z* 431.3 $(M + H)^+$, Rt 0.81 min.

Example 577: Peak 2: white powder. Yield: 47.8 mg; de = 99% (UV, 220 nm).

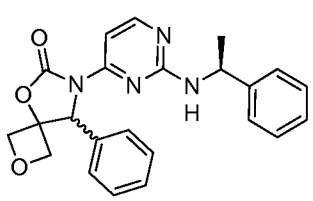
LCMS *m/z* 431.3 $(M + H)^+$, Rt 0.81 min.

Examples 578 and 579

(R)-8-phenyl-7-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)-2,5-dioxa-7-azaspiro[3.4]octan-6-one and

(S)-8-phenyl-7-(2-((S)-1-phenylethylamino)pyrimidin-4-yl)-2,5-dioxa-7-azaspiro[3.4]octan-6-one were prepared using methods similar to those described for the preparation of Example 576 & 577.

Table 23.

Example No.	Structure	Chiral column for separation/ conditions	Chiral column for quality control/ conditions	Retention time
578 (Peak 1)		AD column; 56 mg/ 6 mL EtOH; heptane:EtOH 75:25; 20 mL/min, 400 psi	AD-H column; heptane:EtOH 75:25; 1 mL/min	5.4 min
579 (Peak 2)			AD-H column; heptane:EtOH 75:25; 1 mL/min	8.9 min

The compounds in Table 24 were prepared using methods similar to those described for the preparation of Example 569

Table 24.

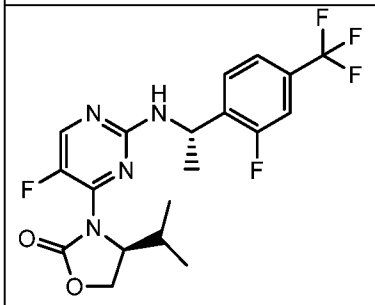
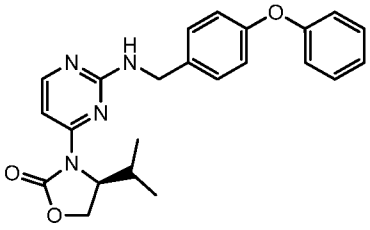
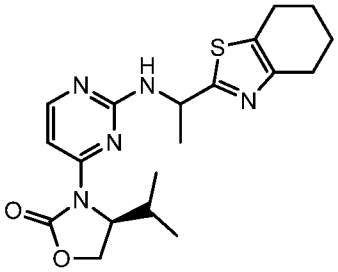
580	581	582
		

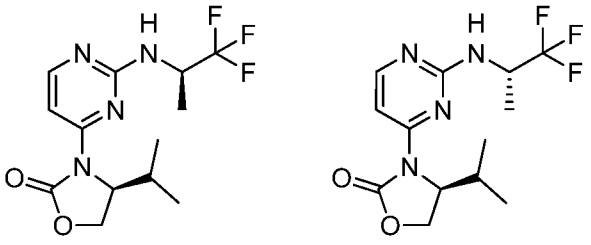
Table 25. Chemical name, NMR chemical shifts and LCMS signal for each compound listed in Table 24.

Example: Name	^{1}H NMR (400 MHz) δ ppm	LCMS
580: (S)-3-(5-fluoro-2-((S)-1-(2-fluoro-4-(trifluoromethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 0.46 - 0.69 (m, 6 H) 0.81 - 0.91 (m, 1 H) 1.53 (d, J=3.00 Hz, 3 H) 4.21 - 4.29 (m, 1 H) 4.43 - 4.53 (m, 2 H) 5.25 (m, J=7.00, 7.00, 7.00 Hz, 1 H) 7.43 (m, J=7.40 Hz, 2 H) 7.52 - 7.59 (m, 1 H) 8.21 - 8.27 (m, 1 H)	HRMS(A) m/z 431.1516 (M + H)+; Rt-2.40 min
581: (S)-4-isopropyl-3-(2-(4-phenoxybenzylamino)pyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 0.63 - 1.00 (m, 7 H) 4.37 - 4.49 (m, 2 H) 4.58 - 4.65 (m, 1 H) 4.66 - 4.78 (m, 2 H) 6.95 - 7.02 (m, 4 H) 7.10 - 7.16 (m, 1 H) 7.32 - 7.40 (m, 4 H) 7.75 (d, J=7.04 Hz, 1 H) 8.16 (d, J=6.65 Hz, 1 H)	HRMS(A) m/z 405.1935 (M + H)+; Rt-2.02 min
582: (4S)-4-isopropyl-3-(2-(1-(4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one		HRMS(A) m/z 388.1814 (M + H)+; Rt-1.82/1.88 min

Examples 583 & 584

(S)-4-isopropyl-3-(2-((R)-1,1,1-trifluoropropan-2-ylamino)pyrimidin-4-yl)oxazolidin-2-one

(S)-4-isopropyl-3-(2-((S)-1,1,1-trifluoropropan-2-ylamino)pyrimidin-4-yl)oxazolidin-2-one



To a solution of (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (40 mg, 0.166 mmol) in 2-butanol was added 1,1,1-trifluoropropan-2-amine (74.9 mg, 0.662 mmol) and para-toluenesulfonic acid monohydrate (74.9 mg, 0.662 mmol). The mixture was heated under argon in a sealed vial for ~7 days at 115 °C. Independently, to a solution of (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (100 mg, 0.414 mmol) in 2-butanol was added 1,1,1-trifluoropropan-2-amine (187 mg, 1.655 mmol) and para-toluenesulfonic acid monohydrate (157 mg, 0.828 mmol). The mixture was heated under argon in a sealed vial at 115 °C for ~4 days. The two reaction mixtures was combined and concentrated under reduced pressure. The residue was diluted with DMSO and water (~10 vol.% of DMSO), filtered through a syringe filter and purified by reverse phase HPLC. Selected fractions were collected and lyophilized providing two isomers as white solids as their trifluoroacetic acid salts.

1st Peak 583: Yield: 29.1mg.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 0.90 (d, *J*=7.04 Hz, 3 H) 0.98 - 1.02 (m, 3 H) 1.45 (d, *J*=7.04 Hz, 3 H) 2.59 (dtd, *J*=13.89, 6.95, 6.95, 3.52 Hz, 1 H) 4.43 - 4.47 (m, 2 H) 4.76 - 4.83 (m, 2 H) 7.70 (d, *J*=5.87 Hz, 1 H) 8.20 (d, *J*=6.26 Hz, 1 H)

LCMS *m/z* 319.3 $(M + H)^+$, Rt 0.73 min. HRMS(A) *m/z* 319.1391 (M + H)+, Rt 1.89 min

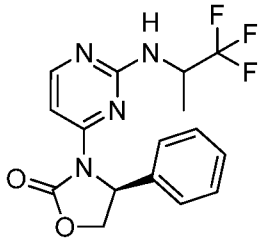
2nd Peak 584: Yield: 38.5 mg.

^{1}H NMR (400 MHz, CD_3OD) δ ppm 0.87 (d, *J*=7.04 Hz, 3 H) 0.98 (d, *J*=7.04 Hz, 3 H) 1.45 (d, *J*=7.04 Hz, 3 H) 2.48 - 2.60 (m, 1 H) 4.40 - 4.49 (m, 2 H) 4.88 - 4.95 (m, 2 H) 7.69 (d, *J*=5.87 Hz, 1 H) 8.20 (d, *J*=6.65 Hz, 1 H)

LCMS *m/z* 319.3 $(M + H)^+$, Rt 0.73 min. HRMS(A) *m/z* 319.1385 (M + H)+, Rt 1.88 min

Example 585

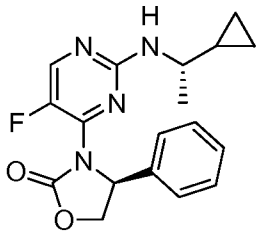
(4S)-4-phenyl-3-(2-(1,1,1-trifluoropropan-2-ylamino)pyrimidin-4-yl)oxazolidin-2-one



A mixture of (S)-3-(2-chloropyrimidin-4-yl)-4-phenyloxazolidin-2-one (40 mg, 0.145 mmol), 1,1,1-trifluoropropan-2-amine (82 mg, 0.725 mmol), Hunig's Base (0.038 mL, 0.218 mmol) in DMSO (0.4 mL) was heated under argon at 115 °C for ~3 days. Then mixture was allowed to cool to room temperature. The mixture was diluted with DMSO and water (~10 vol.% of DMSO), filtered through a syringe filter and purified by reverse phase HPLC. Selected fractions were collected and lyophilized providing (4S)-4-phenyl-3-(2-(1,1,1-trifluoropropan-2-ylamino)pyrimidin-4-yl)oxazolidin-2-one (ratio of two isomers: 7/3) as white solid as its trifluoroacetic acid salt. LCMS *m/z* 353.2 (M + H)+, Rt 0.78 min. HRMS(A) *m/z* 353.1231 (M + H)+, Rt 1.92/1.96 min.

Example 586

(S)-3-(2-((S)-1-cyclopropylethylamino)-5-fluoropyrimidin-4-yl)-4-phenyloxazolidin-2-one



A mixture of (S)-3-(2-chloro-5-fluoropyrimidin-4-yl)-4-phenyloxazolidin-2-one (40 mg, 0.136 mmol), (S)-1-cyclopropylethanamine (34.8 mg, 0.409 mmol), Hunig's Base (0.119 mL, 0.681 mmol) in DMSO (0.4 mL) was heated under argon at 105-115 °C for ~18 hrs (alternative: 120-135 °C for ~90 min). Then mixture was allowed to cool to room temperature. The mixture was diluted with DMSO and water (~10 vol.% of DMSO), filtered through a syringe filter and purified by reverse phase HPLC. Selected fractions were collected and lyophilized providing (S)-3-(2-((S)-1-cyclopropylethylamino)-5-fluoropyrimidin-4-yl)-4-phenyloxazolidin-2-one (26 mg) as a white solid as its trifluoroacetic acid salt.

^{1}H NMR (400 MHz, CD_3OD) δ ppm -0.14 - -0.05 (m, 1 H) 0.01 - 0.08 (m, 1 H) 0.23 - 0.31 (m, 1 H) 0.36 - 0.44 (m, 1 H) 0.78 - 0.86 (m, 1 H) 1.19 (d, J=6.65 Hz, 3 H) 3.05 - 3.14 (m,

1 H) 4.25 - 4.32 (m, 1 H) 4.89 - 4.90 (m, 1 H) 5.77 (t, J=8.61 Hz, 1 H) 7.32 - 7.39 (m, 5 H) 8.15 (d, J=3.52 Hz, 1 H).

LCMS *m/z* 343.1 $(M + H)^+$, Rt 0.88 min. HRMS(A) *m/z* 343.1577 $(M + H)^+$, Rt 2.09 min

The compounds in Table 26 were prepared using methods similar to those described for the preparation of Example **586.**

Table 26.

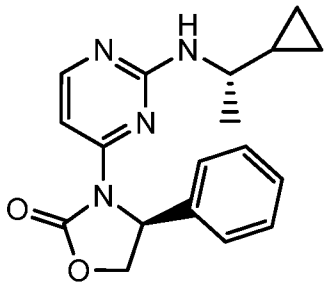
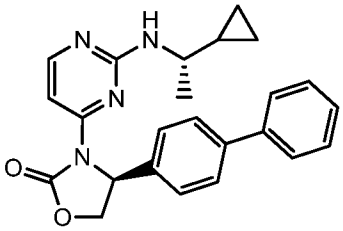
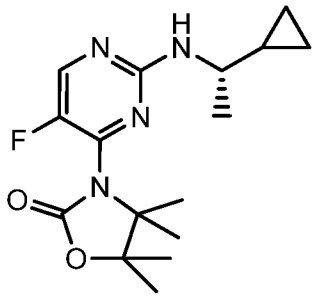
587	588	589
		

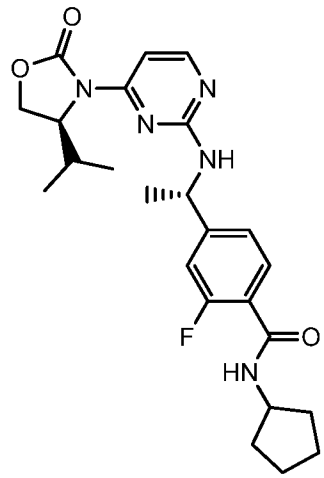
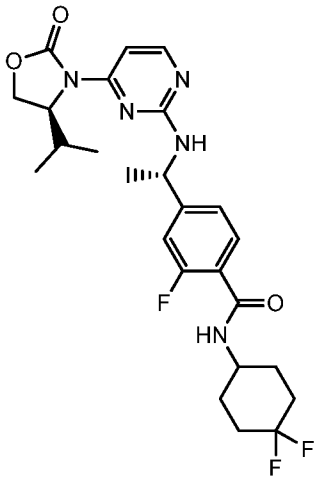
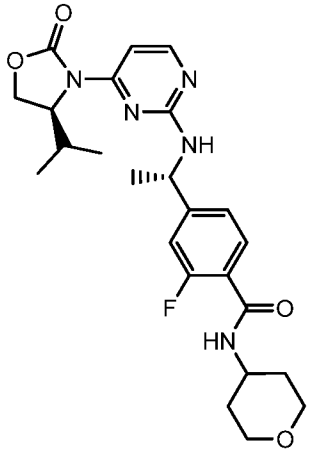
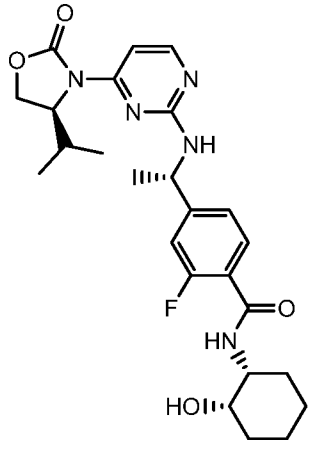
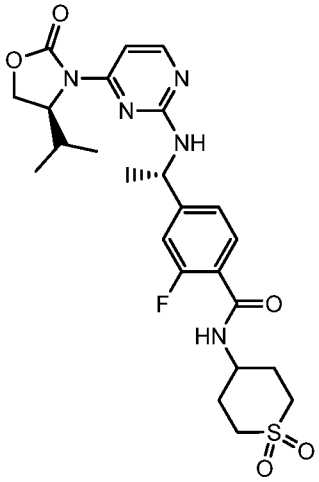
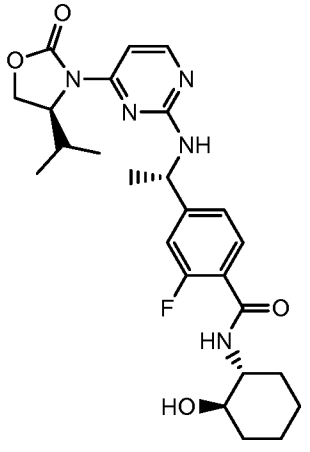
Table 27. Chemical name, NMR chemical shifts and LCMS signal for each compound listed in Table 26.

Example: Name	^{1}H NMR (400 MHz) δ ppm	LCMS
587: (S)-3-(2-((S)-1-cyclopropylethylamino)pyrimidin-4-yl)-4-phenyloxazolidin-2-one	(CD_3OD) -0.55 - -0.27 (m, 1 H), -0.01 (m, J=9.00, 4.30 Hz, 1 H), 0.12 - 0.32 (m, 1 H) 0.35 - 0.50 (m, 1 H) 0.64 - 0.93 (m, 1 H) 1.28 (d, J=1.00 Hz, 3 H) 2.77 - 3.00 (m, 1 H) 4.26 (dd, J=1.00 Hz, 1 H) 4.76 - 4.95 (m, 1-2 H; overlay with solvent) 5.75 (dd, J=1.00 Hz, 1 H) 7.17 - 7.52 (m, 5 H) 7.78 (d, J=1.00 Hz, 1 H) 8.08 (d, J=7.04 Hz, 1 H)	MS m/z 325.2 (M + H)+; Rt-0.77 min. HRMS(A) m/z 325.1664 (M + H)+; Rt-1.53 min
588: (S)-4-(biphenyl-4-yl)-3-(2-((S)-1-cyclopropylethylamino)pyrimidin-4-yl)oxazolidin-2-one	(CD_3OD) 0.01 (m, J=4.30 Hz, 1 H) 0.14 - 0.26 (m, 1 H) 0.33 - 0.45 (m, 1 H) 0.73 - 0.85 (m, 1 H) 1.28 (d, J=6.65 Hz, 3 H) 2.91 - 3.02 (m, 1 H) 4.32 (dd, J=9.00, 4.30 Hz, 1 H) 4.89 - 4.96 (m, 1 H) 5.81 (dd, J=9.00, 4.30 Hz, 1 H) 7.34 - 7.42 (m, 3 H) 7.45 (t, J=7.63 Hz, 2 H) 7.59 - 7.64 (m, 2 H) 7.67 (m, J=8.20 Hz, 2 H) 7.79 (d, J=7.04 Hz, 1 H) 8.10 (d, J=7.04 Hz, 1 H)	MS m/z 401.3 (M + H)+; Rt-0.89 min. HRMS(A) m/z 401.1988 (M + H)+; Rt-1.89 min
589: (S)-3-(2-(1-cyclopropylethylamino)-5-fluoropyrimidin-4-yl)-	(CD_3OD) 0.17 - 0.24 (m, 1 H) 0.31 (dq, J=9.34, 4.71 Hz, 1 H) 0.41 - 0.55 (m, 2 H) 0.93 - 1.04 (m, 1 H) 1.26 (d, J=6.65 Hz, 3	HRMS(A) *m/z* 464.1125

4,4,5,5-tetramethyloxazolidin-2-one	H) 1.42 (s, 6 H) 1.49 (s, 6 H) 3.34 - 3.42 (m, 1 H) 8.17 (d, J=3.13 Hz, 1 H) MS m/z 323.6 (M + H)+; Rt-0.89 min. HRMS m/z 323.1891 (M + H)+; Rt-2.10 min	$(M + H)^+$, Rt 2.28 min

The compounds in Table 28 were prepared using methods similar to those described for the preparation of Example 568

Table 28.

590	591	592
		
593	594	595
		
596	597	598

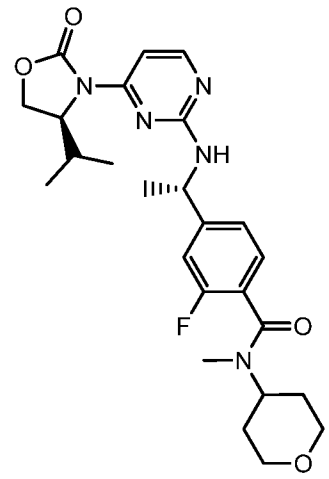
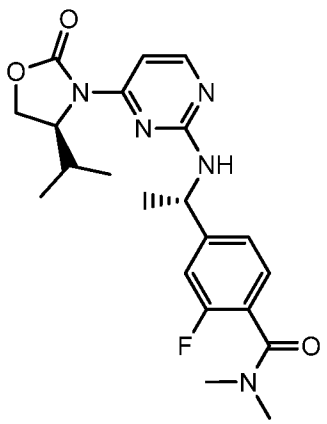
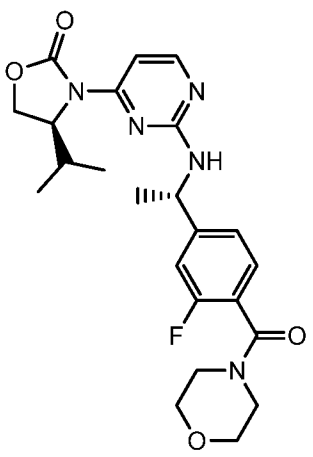
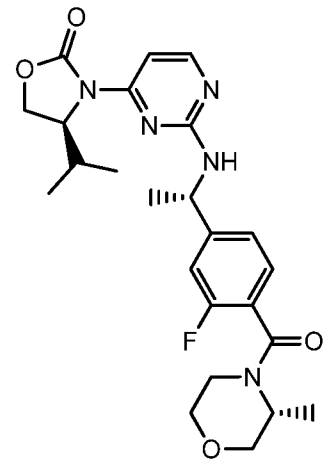
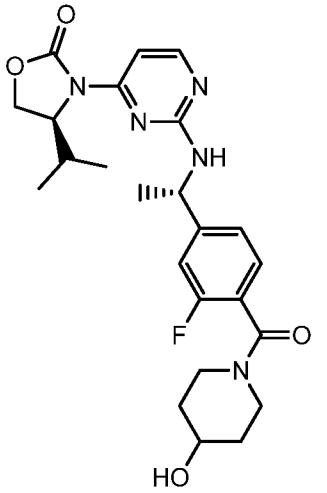
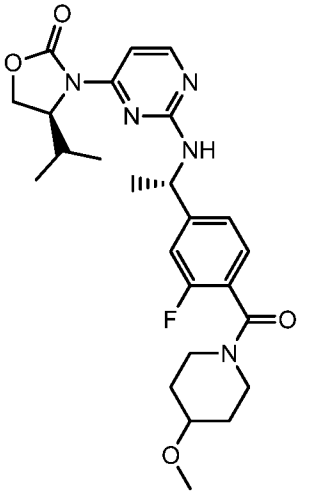
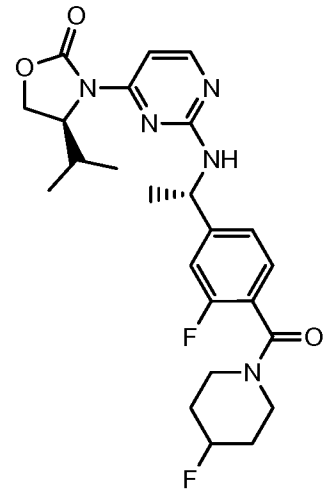
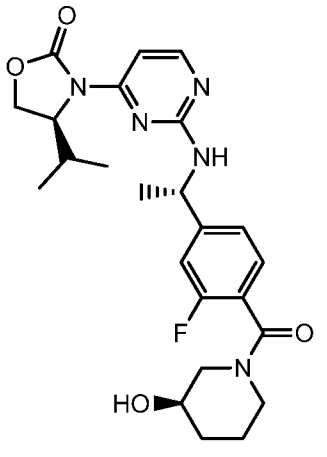
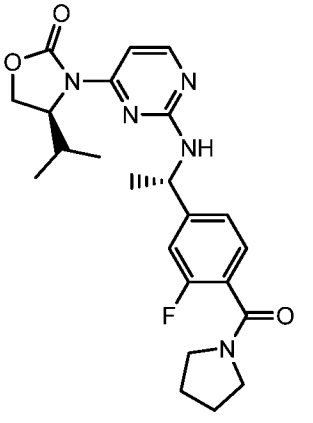
		
599	600	601
		
602	603	604
		

Table 29. Chemical name, NMR chemical shifts and LCMS signal for each compound listed in Table 28.

Example: Name	^{1}H NMR (400 MHz) δ ppm	LCMS
590: N-cyclopentyl-2-fluoro-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide	(CD_3OD) 8.14 (d, J = 6.3 Hz, 1H), 7.72 (d, J = 7.0 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.13 - 7.31 (m, 2H), 5.17 (br. s., 1H), 4.67 (br. s., 1H), 4.34 - 4.41 (m, 2H), 4.24 - 4.33 (m, 1H), 1.99 (dt, J = 11.7, 5.9 Hz, 2H), 1.73 (d, J = 6.7 Hz, 2H), 1.49 - 1.66 (m, 8H), 0.74 (br. s., 3H), 0.61 (br. s., 3H)	HRMS(A) m/z (M + H)+ 456.2422
591: N-(4,4-difluorocyclohexyl)-2-fluoro-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide	(CD_3OD) 8.14 (d, J = 6.3 Hz, 1H), 7.70 (d, J = 7.0 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.12 - 7.32 (m, 2H), 5.16 (br. s., 1H), 4.67 (br. s., 1H), 4.37 (d, J = 5.9 Hz, 2H), 4.00 (t, J = 10.0 Hz, 1H), 1.82 - 2.13 (m, 6H), 1.61 - 1.77 (m, 2H), 1.57 (d, J = 7.0 Hz, 3H), 0.73 (br. s., 3H), 0.61 (br. s., 3H)	HRMS(A) m/z (M + H)+ 506.2388
592: 2-fluoro-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)-N-(tetrahydro-2H-pyran-4-yl)benzamide	(CD_3OD) 8.13 (d, J = 5.9 Hz, 1H), 7.58 - 7.71 (m, 2H), 7.13 - 7.29 (m, 2H), 5.16 (br. s., 1H), 4.67 (br. s., 1H), 4.36 (d, J = 5.5 Hz, 2H), 4.01 - 4.16 (m, 1H), 3.94 (d, J = 11.3 Hz, 2H), 3.50 (td, J = 11.7, 2.0 Hz, 2H), 1.82 - 1.94 (m, 2H), 1.59 - 1.69 (m, 2H), 1.57 (d, J = 7.0 Hz, 3H), 0.73 (br. s., 3H), 0.61 (br. s., 3H)	HRMS(A) m/z (M + H)+ 472.2366
593: 2-fluoro-N-((1R,2S)-2-hydroxycyclohexyl)-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide	(CD_3OD) 8.14 (d, J = 6.3 Hz, 1H), 7.83 (t, J = 7.8 Hz, 1H), 7.69 (d, J = 7.0 Hz, 1H), 7.14 - 7.36 (m, 2H), 5.15 (d, J = 6.3 Hz, 1H), 4.65 (br. s., 1H), 4.36 (d, J = 5.5 Hz, 2H), 3.96 - 4.05 (m, 1H), 3.94 (d, J = 2.3 Hz, 1H), 1.79 (dd, J = 10.4, 4.5 Hz, 1H), 1.69 (d, J = 5.9 Hz, 4H), 1.54 - 1.64 (m, 5H), 1.28 - 1.48 (m, 2H), 0.70 (br. s., 3H), 0.60 (br. s., 3H)	HRMS(A) m/z (M + H)+ 486.2526
594: N-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-2-fluoro-4-((S)-1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)ethyl)benzamide	(CD_3OD) 8.14 (d, J = 6.3 Hz, 1H), 7.69 (d, J = 7.0 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.15 - 7.31 (m, 2H), 5.16 (br. s., 1H), 4.67 (br. s., 1H), 4.36 (d, J = 5.9 Hz, 2H), 4.13 - 4.27 (m, 1H), 3.08 (d, J = 13.7 Hz, 2H), 2.25 - 2.36 (m, 2H), 2.07 - 2.24 (m, 2H), 1.57 (d, J = 7.0 Hz, 3H), 0.73 (br. s., 3H), 0.61 (br. s., 3H)	HRMS(A) m/z (M + H)+ 520.203
595: 2-fluoro-N-((1R,2R)-2-hydroxycyclohexyl)-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide	(CD_3OD) 8.13 (d, J = 6.3 Hz, 1H), 7.63 - 7.78 (m, 2H), 7.14 - 7.30 (m, 2H), 5.15 (br. s., 1H), 4.67 (br. s., 1H), 4.36 (d, J = 5.5 Hz, 2H), 3.67 - 3.83 (m, 1H), 3.38 - 3.51 (m, 1H), 2.01 (d, J = 9.0 Hz, 2H), 1.64 - 1.81 (m, 3H), 1.57 (d, J = 7.0 Hz, 3H), 1.17 - 1.46 (m, 4H), 0.74 (br. s., 3H), 0.61 (br. s., 3H)	HRMS(A) m/z (M + H)+ 486.2521
596: 2-fluoro-4-((S)-1-(4-	(CD_3OD) 8.14 (d, J = 6.7 Hz, 1H), 7.76 (d,	HRMS(A)

((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)-N-methyl-N-(tetrahydro-2H-pyran-4-yl)benzamide	J = 7.4 Hz, 1H), 7.32 - 7.42 (m, 1H), 7.17 - 7.31 (m, 2H), 5.22 (br. s., 1H), 4.60 - 4.76 (m, 2H), 4.33 - 4.44 (m, 2H), 4.02 (dd, J = 11.3, 4.3 Hz, 1H), 3.91 (d, J = 8.6 Hz, 1H), 3.45 - 3.65 (m, 2H), 3.07 - 3.21 (m, 1H), 2.99 (s, 1H), 2.80 (s, 2H), 1.81 - 2.05 (m, 3H), 1.52 - 1.71 (m, 5H), 0.78 (br. s., 3H), 0.63 (br. s., 3H)	m/z (M + H)+ 486.2528
597: 2-fluoro-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)-N,N-dimethylbenzamide	(CD_3OD) 8.14 (d, J = 7.0 Hz, 1H), 7.75 (d, J = 7.0 Hz, 1H), 7.32 - 7.43 (m, 1H), 7.13 - 7.31 (m, 2H), 5.20 (br. s., 1H), 4.70 (br. s., 1H), 4.33 - 4.45 (m, 2H), 3.09 (s, 3H), 2.92 (d, J = 0.8 Hz, 3H), 1.76 (br. s., 1H), 1.59 (d, J = 7.0 Hz, 3H), 0.78 (br. s., 3H), 0.62 (br. s., 3H)	HRMS(A) m/z (M + H)+ 416.2106
598: (S)-3-(2-((S)-1-(3-fluoro-4-(morpholine-4-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 8.14 (d, J = 6.7 Hz, 1H), 7.73 (d, J = 6.7 Hz, 1H), 7.35 - 7.43 (m, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 10.6 Hz, 1H), 5.18 (br. s., 1H), 4.69 (br. s., 1H), 4.30 - 4.42 (m, 2H), 3.73 (d, J = 3.1 Hz, 4H), 3.59 (t, J = 4.7 Hz, 2H), 1.58 (d, J = 7.0 Hz, 3H), 0.76 (br. s., 3H), 0.62 (br. s., 3H)	HRMS(A) m/z (M + H)+ 458.2209
599: (S)-3-(2-((S)-1-(3-fluoro-4-((R)-3-methylmorpholine-4-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 8.14 (d, J = 6.7 Hz, 1H), 7.76 (d, J = 7.0 Hz, 1H), 7.36 (d, J = 6.7 Hz, 1H), 7.14 - 7.31 (m, 2H), 5.20 (br. s., 1H), 4.70 (br. s., 1H), 4.65 (br. s., 1H), 4.34 - 4.45 (m, 2H), 4.29 (d, J = 13.3 Hz, 1H), 3.96 (d, J = 10.6 Hz, 1H), 3.75 (d, J = 11.3 Hz, 1H), 3.51 - 3.67 (m, 2H), 3.43 - 3.51 (m, 1H), 3.07 - 3.19 (m, 1H), 1.76 (br. s., 1H), 1.59 (d, J = 7.0 Hz, 3H), 1.36 (d, J = 6.7 Hz, 2H), 1.28 (br. s., 1H), 0.77 (br. s., 3H), 0.62 (br. s., 3H)	HRMS(A) m/z (M + H)+ 472.2366
600: (S)-3-(2-((S)-1-(3-fluoro-4-(4-hydroxypiperidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 8.14 (d, J = 6.7 Hz, 1H), 7.73 (d, J = 7.0 Hz, 1H), 7.31 - 7.40 (m, 1H), 7.16 - 7.29 (m, 2H), 5.18 (br. s., 1H), 4.70 (br. s., 1H), 4.31 - 4.45 (m, 2H), 4.16 (dd, J = 12.9, 5.5 Hz, 1H), 3.87 (br. s., 1H), 3.48 (d, J = 14.1 Hz, 1H), 3.35 (d, J = 3.5 Hz, 1H), 3.05 - 3.22 (m, 1H), 1.85 - 1.98 (m, 1H), 1.70 - 1.83 (m, 2H), 1.58 (d, J = 7.0 Hz, 3H), 1.49 - 1.55 (m, 1H), 1.43 (br. s., 1H), 0.76 (br. s., 3H), 0.62 (br. s., 3H)	HRMS(A) m/z (M + H)+ 472.2369
601: (S)-3-(2-((S)-1-(3-fluoro-4-(4-methoxypiperidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 8.13 (d, J = 6.7 Hz, 1H), 7.70 (d, J = 6.7 Hz, 1H), 7.31 - 7.41 (m, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 10.6 Hz, 1H), 5.17 (br. s., 1H), 4.69 (br. s., 1H), 4.33 - 4.42 (m, 2H), 3.98 (dd, J = 10.8, 6.5 Hz, 1H), 3.40 - 3.60 (m, 3H), 3.34 (s, 3H), 3.18 (d, J = 8.6 Hz, 1H), 1.88 - 2.03 (m, 1H), 1.79 (br. s., 1H), 1.62 (br. s., 1H), 1.58 (d, J = 7.0 Hz, 3H), 1.49 (br. s., 1H), 0.76 (br. s., 3H), 0.62 (br. s., 3H)	HRMS(A) m/z (M + H)+ 486.2523
602: (S)-3-(2-((S)-1-(3-fluoro-4-(4-	(CD_3OD) 8.14 (d, J = 6.7 Hz, 1H), 7.73 (d, J = 7.0 Hz, 1H), 7.34 - 7.44 (m, 1H), 7.16 -	HRMS(A) m/z (M +

fluoropiperidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	7.31 (m, 2H), 5.18 (br. s., 1H), 4.93 (br. s., 1H), 4.70 (br. s., 1H), 4.29 - 4.43 (m, 2H), 3.91 (d, J = 11.3 Hz, 1H), 3.70 (br. s., 1H), 3.40 - 3.53 (m, 1H), 1.93 - 2.06 (m, 1H), 1.83 - 1.93 (m, 2H), 1.77 (dd, J = 10.2, 4.7 Hz, 2H), 1.58 (d, J = 7.0 Hz, 3H), 0.76 (br. s., 3H), 0.62 (br. s., 3H)	H)+ 474.2324
603: (S)-3-(2-((S)-1-(3-fluoro-4-((R)-3-hydroxypiperidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 8.13 (d, J = 6.7 Hz, 1H), 7.72 (d, J = 7.0 Hz, 1H), 7.36 (t, J = 7.4 Hz, 1H), 7.14 - 7.30 (m, 2H), 5.19 (br. s., 1H), 4.70 (br. s., 1H), 4.30 - 4.44 (m, 2H), 3.71 (br. s., 1H), 3.38 - 3.52 (m, 1H), 3.08 - 3.19 (m, 1H), 3.02 (br. s., 1H), 1.96 (br. s, 1H), 1.87 (br. s., 1H), 1.66 - 1.81 (m, 1H), 1.49 - 1.62 (m, 5H), 1.43 (br. s., 1H), 0.78 (br. s., 3H), 0.63 (br. s., 3H)	HRMS(A) m/z (M + H)+ 472.2362
604: (S)-3-(2-((S)-1-(3-fluoro-4-(pyrrolidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(CD_3OD) 8.13 (d, J = 6.3 Hz, 1H), 7.71 (d, J = 7.0 Hz, 1H), 7.34 - 7.43 (m, 1H), 7.14 - 7.30 (m, 2H), 5.18 (br. s., 1H), 4.70 (br. s., 1H), 4.28 - 4.43 (m, 2H), 3.57 (t, J = 6.8 Hz, 2H), 1.93 - 2.07 (m, 2H), 1.83 - 1.93 (m, 2H), 1.58 (d, J = 7.0 Hz, 3H), 0.77 (br. s., 3H), 0.63 (br. s., 3H)	HRMS(A) m/z (M + H)+ 442.2263

Biological Data

Mutant IDH1 biochemical assay: LC-MS detection of 2-HG.

Mutant IDH1 R132H catalytic activity was monitored using the quantitative liquid chromatography/mass spectrometry (LC-MS) detection of 2-HG, a product of the NADPH-dependent alpha-KG reduction reaction.

More specifically, the biochemical reactions were performed at room temperature in 384-well Greiner flat-bottom plates (Costar, Cat. No. 781201) using a final reaction volume of 30 μL and the following assay buffer conditions: 50 mM HEPES pH 7.4, 10 mM $MgCl_2$, 50 mM KCl, 1 mM DTT, 0.02% BSA, 5 uM NADPH and 100 uM alpha-KG.

The final reaction mixture contained 3.3% DMSO and inhibitors with concentrations ranging 0.02 – 50 μM. The IDH1 enzyme was used at a final concentration of 0.25 nM. Following 45 minutes incubation, the reaction mixtures were quenched by the addition of 10 μL of 16% formic acid containing 800 nM of 5-carbon labeled ^{13}C-2-HG). The protein was then precipitated by the addition of 2.5 volumes of acetonitrile followed by centrifugation (3000 x g, 20 minutes). The concentration of 2-HG in the resulting supernatants was measured by LC-MS (see below).

LC-MS method. Reaction mixture supernatants were submitted to chromatographic separation on a BiobasicAX column (2.1 mm x 20 mm, 5 μm particle,

Thermo Scientific Inc.). The chromatographic mobile phases were A) 25 mM ammonium biocarbonate and B) acetonitrile (0.1% ammonium hydroxide). Nicotinamide was eluted at 1 ml/min using a 85-5% B gradient over 0.9 minutes (Agilent 1200SL LC system, Thermofisher LX-4 autosampler) and analyzed by multiple reaction monitoring (MRM) on a API4000 QTrap mass spectrometer (ABSciex, Framingham, MA) in the positive electrospray ionization (ESI+) mode. The mass transition for 2-HG and ^{13}C-2-HG were 147→129 and 152→134, respectively. The relative responses (2-HG/^{13}C-2-HG) were measured at varied inhibitor concentrations and used to calculate inhibitory IC50 values (normalized IC50 regression curves).

R132 protein expression and purification.

IDH1 R132H was cloned into the pET47b vector using the restriction sites XmaI/XhoI which yields an in frame, N-terminal His_6 site cleavable with Prescission protease. This plasmid was transformed into Rosetta™ 2(DE3) (Novagen) cells. In shake flasks, 8L of cells were grown in Terrific Broth (Teknova) (plus kanamycin 50µg/mL and chloramphenicol 34µg/mL) at 37°C to an OD_{600} of 0.8 and protein expression was induced by addition of IPTG to a concentration of 0.20mM. The cells were subsequently grown for 18 hours at 18°C.

His_6-IDH1 (R132H) Uncut protein

MAHHHHHHSAALEVLFQGPGMSKKISGGSVVEMQGDEMTRIIWELIKEKLIFPYVELDL
HSYDLGIENRDATNDQVTKDAAEAIKKHNVGVKCATITPDEKRVEEFKLKQMWKSPNGT
IRNILGGTVFREAIICKNIPRLVSGWVKPIIIGHHAYGDQYRATDFVVPGPGKVEITYTPSD
GTQKVTYLVHNFEEGGGVAMGMYNQDKSIEDFAHSSFQMALSKGWPLYLSTKNTILKK
YDGRFKDIFQEIYDKQYKSQFEAQKIWYEHRLIDDMVAQAMKSEGGFIWACKNYDGDV
QSDSVAQGYGSLGMMTSVLVCPDGKTVEAEAAHGTVTRHYRMYQKGQETSTNPIASIF
AWTRGLAHRAKLDNNKELAFFANALEEVSIETIEAGFMTKDLAACIKGLPNVQRSDYLNT
FEFMDKLGENLKIKLAQAKL (stop) (SEQ ID NO: 1)

IDH1 (R132H) Prescission Cut Protein (N-term gpg is cloning artifact)

*GPG*MSKKISGGSVVEMQGDEMTRIIWELIKEKLIFPYVELDLHSYDLGIENRDATNDQVT
KDAAEAIKKHNVGVKCATITPDEKRVEEFKLKQMWKSPNGTIRNILGGTVFREAIICKNIP
RLVSGWVKPIIIGHHAYGDQYRATDFVVPGPGKVEITYTPSDGTQKVTYLVHNFEEGGG
VAMGMYNQDKSIEDFAHSSFQMALSKGWPLYLSTKNTILKKYDGRFKDIFQEIYDKQYK
SQFEAQKIWYEHRLIDDMVAQAMKSEGGFIWACKNYDGDVQSDSVAQGYGSLGMMTS
VLVCPDGKTVEAEAAHGTVTRHYRMYQKGQETSTNPIASIFAWTRGLAHRAKLDNNKE

LAFFANALEEVSIETIEAGFMTKDLAACIKGLPNVQRSDYLNTFEFMDKLGENLKIKLAQA KL (stop) (SEQ ID NO: 2)

Purification

The cells were homogenized in Lysis Buffer with protease inhibitors (cOmplete EDTA-free protease inhibitor tablets (Roche), 1 tablet per 50mL of buffer), DNAse, and to 200 µM PMSF and lysed in a Microfluidizer. After lysis, Triton X-100 was added to 0.1% and stirred at 4ºC for 30 minutes.

The cleared lysate was loaded onto 2 x 5mL HisTrap FF crude columns (GE), washed extensively with Lysis Buffer until the A_{280} stabilized and eluted with Ni Elution Buffer. Peak eluted fractions were concentrated to 30mL, EDTA was added to 1mM and GST-Prescission protease was added to 3U/100µg of protein. The sample was dialyzed against 2L Dialysis Buffer I (MWCO 50kDa) for 6 hours at 4°C then dialyzed against 2L of Dialysis Buffer II for at least 6 more hours. GST-Prescission cleaved sample was rocked with Glutathione Agarose Beads, spun down and then the supernatant was loaded through a 5mL HisTrap HP column and the flow through was collected.

Flow through was then diluted with ice cold 20mM Tris pH 7.4 and 1mM TCEP until the conductivity dropped to less than 5 mS/cm (a roughly three fold dilution). This sample was then flowed through a HiTrap Q column and the flow through was concentrated to 10mL and loaded onto an equilibrated 26/60 Superdex 200 column using SEC Buffer as the mobile phase. Peak fractions were collected, concentrated and aliquoted.

Lysis Buffer: 50mM Tris pH=7.4, 500mM NaCl, 20mM Imidazole, and 1mM TCEP

Ni Elution Buffer: 50mM Tris pH=7.4, 150mM NaCl, 200mM Imidazole, and 1mM TCEP

Dialysis Buffer I: 20mM Tris pH=7.4, 150mM NaCl, 1mM TCEP, and 50mM Imidazole

Dialysis Buffer II:20mM Tris pH=7.4, 150mM NaCl, and 1mM TCEP

SEC Buffer: 20mM Tris pH=7.4, 150mM NaCl, and 1mM TCEP

The results of the mutant IDH1 biochemical assay (mIDH R132H) are given in Table 30. Some of the examples were run in the assay multiple times and therefore the IC_{50} values are expressed as a range of activity.

Fluorescence biochemical assay

The IDH1 (R132H) mutant catalyzes the reduced form of NADP+ (NADPH) and α-ketoglutarate (α-KG) to form nicotinamide adenine dinucleotide phosphate (NADP+) and R (-)-2-hydroxyglutarate (2HG). The reaction can be monitored kinetically by following the oxidation of NADPH to NADP+ which is measured using fluorescence, excitation at 355 nm and emission at 530 nm. Reactions were monitored using the Perkin-Elmer Envision, Model 2101. More specifically, the biochemical reactions were performed at room temperature in 384-well Greiner flat-bottom plates (Cat. No. 781076) using a final reaction volume of 20 μL and the following assay buffer conditions: 50 mM HEPES pH 7.5, 10 mM $MgCl_2$, 1 mM DTT, 0.02% BSA, 0.02% Tween-20, 10 μM NADPH and 100 μM α-KG. The final reaction mixture contained 2.5% DMSO and test compounds with concentrations ranging 0.0000008 – 25 μM. The IDH1 (R132H) enzyme was used at a final concentration of 10 nM. Curve fitting for dose response IC50 determinations was done in the Helios module of the software package DAVID. The 4-parameter logistic model was used: $y = min + ((max - min) / 1 + (x / IC_{50})^{slope})$

Table 30. Results of the LC-MS and fluorescence biochemical assays.

Example Number	**LC-MS biochemical assay IC_{50} (μM)**	**Fluorescence biochemical assay IC50 (μM)**
1	0.084 – 0.236	
2	>50	
3	0.086 – 0.575	0.091-0.501
4	4.612	
5	0.410-0.600	
6	12.175	
7	2.527	
8	13.011	
9	6.444	
10	0.355-0.419	
11	0.770 – 4.552	
12	1.990 – 2.391	9.55
13	18.344 – 29.100	
14	2.333 – 2.814	

15	5.383	
16	>50	
17	7.625	
18	>50	
19	>50	
20	>50	
21	4.169	
22	19.671	
23	0.502 –0.591	
24	3.564	
25	18.182 – >50	
26	>50	
27	2.486 – 2.730	
28	4.427 – 4.625	
29	4.630 – 11.566	
30	1.072	
31	1.721	
32	9.797	
33	3.483	
34	7.588	
35	0.222 – 0.273	
36	17.576	
37	4.595	
38	>50	
39	8.806	
40	20.34	
41	0.291 – 0.581	
42	0.584	
43	7.686	
44	0.125	
45	>50	
46	0.234	
47	7.481	
48	2.090 – 2.601	1.91
49	2.803	
50	0.076 – 0.100	

51	19.457	
52	23.847	
53	3.852	
54	0.141	
55	3.494	
56	9.502	
57	1.393-3.153	7.58
58	>50	
59	0.575	
60	0.052	0.094
61	12.729	
62	0.117 – 0.178	
63	0.085 – 0.124	
64	6.79	
65	0.25	
66	0.073	
67	5.342	
68	6.302	
69	0.127 – 0.390	
70	0.195 – 0.230	
71	20.503	
72	37.361	
73	0.316	
74	2.569	
75	1.338	4.27
76	8.008	
77	11.26	
78	28.611	
79	0.09	
80	0.679	
81	0.103	
82	0.163 – 0.217	
83	0.238 – 0.462	
84	0.075	
85	1.061	17.9
86	9.767	

87	0.126	0.245
88	0.148 – 0.344	
89	0.203	0.308
90	0.272	0.275
91	2.875	
92	0.211 – 0.544	0.598
93	0.405 – 0.905	
94	4.487	
95	0.655	0.571
96	>50	
97	0.195	0.166
98	0.628	
99	0.184	
100	0.169	
101	2.382	
102	0.401	
103	3.184	
104	0.207	
105	0.352	0.352
106	1.918	
107	3.445	
108	>50	
109	0.542	0.939
110	0.188	0.284
111	0.125	
112	7.768	
113	1.925	
114	0.697	1.14
115	0.092	0.126
116	2.038	
117	0.163 – 0.217	
118	1.302 – 2.152	
119	0.117	0.149
120	0.258-0.847	
121	0.081-0.448	
122	0.157-0.379	

123	0.112	0.162
124	0.081 – 0.298	0.791
125	1.012	
126	0.118	
127	0.158	0.215
128	0.565	
129	0.467	
130	0.549 – 0.615	
131	14.319	
132	31.016	
133	7.115	
134	3.102	
135	11.6	
136	6.455	
137	3.14	
138	1.061	
139	1.252	2.5
140	0.089	0.114-0.181
141	0.095	
142	0.390 – 0.512	
143	>50	
144	>50	
145	6.807	
146	11.362	
147	6.445	
148	3.544	
149	0.647	
150	0.53	0.538
151	1.363	
152	0.385	0.598
153	0.759	0.582
154	0.049	0.091
155	0.04	
156	0.232	0.248
157	>50	
158	0.873	1.41

159	0.287	
160	6.078	
161	6.502	
162	0.009-0.035	0.020-0.043
163	0.149	
164	0.067	0.0339
165	0.183	0.143
166	0.637	1.56
167	0.254	
168	0.102	
169	0.195	
170	1.083	
171	6.161	
172	0.245 – 0.274	
173	2.908	
174	0.056 – 0.118	0.283
175	8.156	
176	0.125	0.138
177	4.333	
178	0.097	0.0687
179	5.973	
180	0.194	
181	10.232	
182	0.309-0.370	
183	36.818	
184	0.696	
185	6.066	
186	0.04	
187	3.899	
188	0.089	0.17
189	0.117	
190	2.134	
191	6.969	
192	0.221	0.294
193	0.097	
194	4.333	

195	5.748	
196	0.083	
197	15.05	
198	0.173	0.179
199	2.435	
200	0.08	0.0665
201	0.927	
202	0.025	0.0541
203	1.856	
204	0.062	0.0955
205	0.199	0.219
206	1.458	0.81
207	0.069	0.0169
208	0.085	0.108-0.183
209	0.088	0.0881
210	0.576	0.343
211		0.439
212	0.132	0.024
213	2.913	
214	0.298	0.791
215	0.390	0.419
216	0.031	0.0206
217	0.177 - 0.206	0.079-0.146
218	1.373	0.625
219	0.613	
220	0.529	0.247
221	0.098	0.0476
222	0.505	0.296
223	0.293	0.14
224	<0.022	0.0166
225	0.026	0.0173
226	0.114	0.0832
227	0.065	0.0339
228	0.067	0.0463
229	0.113	0.0662
230	0.072	0.0415

231	0.327	0.242
232	0.251	0.755
233	0.147	0.0684
234	> 50	> 25
235	0.039	0.0141
236	0.372	0.338
237	0.877	0.219
238		9.8
239	0.038	0.073
240	0.030	0.0506
241	0.155	0.213
242	0.048	0.242
243	0.260 - 0.914	1.21-1.6
244	0.863	0.774
245	0.184	0.103
246	0.497 - 0.589	0.236-0.316
247	1.373	1.79
248	0.687	0.842
249	0.585	0.616
250	0.031	0.0468
251	0.064	0.0878
252	0.033	0.0608
253		0.559
254	0.656	1.12
255	10.369	
256	0.197	
257	0.242 - 0.282	0.221-0.27
258	0.378	
259	2.569	
260	0.186	
261	0.040	0.0639
262	0.058	0.0991
263		0.679
264	0.108	
265	<0.022	0.0232
266	0.152	

267	3.308	
268	20.567	
269	0.467	
270	0.463	
271	0.100	0.108
272	1.717	2.28
273	0.202	0.143
274	0.104	0.0524
275	0.261	0.273
276	0.298	0.175
277	0.094	0.0899
278	0.241	0.29
279	0.312	
280	7.823	
281	<0.022	
282	0.180	
283	0.538	0.635
284	2.023	1.38
285	0.390	0.375
286	1.807	2.54
287	34.794	> 25
288	0.053	0.269
289	0.316	0.19
290	2.222	0.414-0.975
291		4.64
292	0.049	0.0645
293	2.696	
294	0.095	0.648
295	0.342	0.252
296	0.085	
297		0.848
298	0.188	1.04
299	4.052	10.4
300	1.639	1.84
301		0.0887
302	0.131	

303		0.326
304	2.107	
305	0.065	0.0413
306	4.043	12.5
307		0.225
308	0.259	0.703
309	0.868	1.66
310	36.281	> 25
311	4.139	
312	0.051	0.024
313	0.073	0.0799
314	1.311	1.59
315	5.916	
316	0.131	
317	0.050	
318	5.007	
319	0.705	
320	2.410	
321	1.214	
322	0.026	0.0666
323		17.1
324		0.483
325	15.718	18.5-21.4
326	0.115	0.268-0.369
327		19.2
328	0.329 - 1.144	0.558-0.843
329	2.164	5.62
330	0.026	0.0545
331	6.083	7.65
332	0.052 - 0.072	0.0693
333	0.128	0.335
334	0.646	
335		6.53
336		0.236
337		7.22
338	0.148	0.145

339	3.101	4.4
340	<0.022	0.0276
341		2.13
342	0.029	0.0278
343		4.08
344		0.265
345	> 50	
346	32.256	
347	> 50	
348	> 50	
349	4.010	24.2
350	0.583	0.731
351	> 50	
352	> 50	
353	> 50	
354	> 50	
355	33.589	> 25
356	1.642	4.53
357	13.229	
358	0.864	1.53
359	> 50	> 25
360	3.035	4.37-11.9
361	0.781	0.736
362	0.063	0.0621
363	14.441	23.3
364	0.964	1.06
365	> 50	> 25
366	2.602	20.2-21.7
367	20.809	> 25
368	0.706	0.862
369	> 50	> 25
370	6.649	3.01
371	25.036	> 25
372		4.19
373	39.696	> 25
374	1.617	1.89-2.42

375	> 50	> 25
376	2.321	3.27-4.33
377		>25
378		4.19
379		> 25
380		0.839
381		20
382	0.203	0.349
383		5.16
384	0.068	0.107
385		22.5
386		4.74
387		20.6
388		4.37
389		1.83
390	0.140	0.213
391		2.35-5.33
392	0.694	0.355-0.697
393		12.1
394	0.268	0.34
395		9.36
396	0.189	0.224
397		7.14
398	0.094 - 0.123	0.189
399		> 25
400		0.648
401		19
402	0.362	0.39
403		> 25
404		0.964
405		21.1
406		1.82
407		6.39
408	0.237	0.349
409		1.35
410	0.340 - 0.440	0.098-0.521

411	2.907	
412	0.190	
413	21.616	
414	6.026 - 7.675	5.47-8.32
415	26.674	
416	1.592	
417	20.287	
418	0.808	
419	2.833	
420	> 50	
421	27.999	> 25
422	2.136	3.81
423	7.595	14.8
424	0.162	0.491-0.747
425	0.909	2.45
426	<0.022 - 0.038	0.019-0.058
427	1.229	2.09
428	> 50	> 25
429	6.407	9.78
430	0.133	0.0908
431	0.568	0.811
432	0.040	0.0448
433	6.675	5.31
434	0.153	2.19-3.96
435		> 25
436	0.291	0.364-0.373
437		2.69-3.18
438		> 25
439		6.155
440	0.125	0.105-0.122
441	4.229	1.63-10.6
442	0.136	0.225
443	0.063 - 0.077	0.0414
444	0.040	0.0266
445	2.526	2.46
446	0.079 - 0.081	0.039

447	3.876	
448	0.034	0.0373
449		5.43
450	0.062	0.0518
451	0.207	0.386
452	0.063 - 0.065	0.134
453	11.400	14.5
454	0.401	0.601
455	6.218	> 25
456	0.082	0.041
457	<0.022	0.013
458	0.069	0.0588
459	0.991	1.16
460		
461	2.275	
462	1.924	2.87
463	> 50	
464	<0.022	0.020-0.055
465		0.164
466	0.665	0.821
467		9.82
468		3.03-11.8
469	0.077	0.185-0.198
470	0.075	0.172
471	0.925	0.78
472		14.8
473		0.0986
474		7.1
475	0.341	0.355
476	> 50	
477	> 50	
478	> 50	
479	> 50	
480	> 50	
481	0.780	2.52
482	>50	>25

483	0.096	0.202
484	5.160	21.3
485		2.12
486		0.873
487		1
488	0.311	0.437
489		4.15
490		2.61
491		0.821
492		0.249
493	0.067	0.139
494	1.649	0.595
495	0.712	0.734
496	0.751	0.723
497		1.13
498		5.27
499		2.39
500		1.45
501		0.494
502		0.305
503	0.546	0.96
504	0.268	0.243
505		0.275
506		0.46
507		0.0773
508	0.553	0.484
509	0.553	0.484
510		0.0294
511	0.062	
512	0.450	0.38
513		0.0336
514		
515		0.0287
516	0.082	0.0592
517		1.58
518		0.0785

519	0.123	0.363
520	0.080	0.053-0.321
521		0.23
522		0.745
523		0.165
524	0.026	0.0211
525	0.085	0.108-0.183
526	0.088	0.0427
527		0.0851
528	0.077	0.0613
529	0.117	0.0622
530	<0.022	0.00835
531		0.00812
532		0.0727
533	0.307	0.227
534	0.188	0.331
535		0.183
536		0.104
537	0.400	0.257
538	0.416	0.268
539		2.66
540	0.878	0.573
541	0.266	0.0899
542	0.090	0.0877
543		> 25
544	0.075	0.0477
545		0.0943
546	0.059	0.0423
547	0.158	0.146
548	0.184	
549	1.840	
550	0.791	0.276
552	<0.022	0.0199
553	0.521	0.41
554	0.075	0.217
555	<0.022	

556	<0.072	
557	0.246	0.237
558		0.283
559		17.6
560		25
561		0.552
562		0.364
563		0.04
564		0.0501
565		0.309
566	0.135	0.13
567		5.41
568	0.086 - 0.141	0.067-0.161
569		0.0575
570		0.0446
571		0.0742
572		0.0781
573		0.00786
574	0.204	0.324
575		1.91
576		2.37
577		1.65
578		1.07
579	0.911	0.591
580	0.153	0.193
581	0.260	0.432
582		0.204
583		> 25
584		10.6
585		6.7
586	2.797	1.02
587		1.95
588	0.764	0.85
589		2.92
590	<0.022	0.006-0.009
591	<0.022	0.018

592	0.138	0.077
593	0.077	0.036
594	0.257	0.178
595	0.121	0.053
596	0.161	0.154
597	0.457	0.741
598	0.519	0.715
599	0.155	0.265
600	0.488	0.729
601	0.042	0.042
602	0.049	0.034
603	0.244	0.336
604	0.112	0.161

IDH Cellular Assay

The IDH cellular assay consists of two side-by-side comparator assays: 1) 2HG oncometabolite detection assay using LC-MS (See Mutant IDH1 biochemical assay for LC-MS detection details) and 2) Cell proliferation assay to monitor off-target killing of cells and to normalize 2HG level change. IDH1 cellular screens were run with the HCT-116 cell line (express endogenous level of IDH1mut R132H, available from Horizon Discoveries X-Man isogenic human cell lines, catalog # HD104-013). The cells were grown in DMEM (LONZA Cat# 12-540F) with 10% Fetal bovine serum (Gibco cat# 10099) and 1X non-essential amino acids (NEAA LONZA cat# 13-114E). Panel assays were run periodically to test compound activity in cell lines with different endogenous mutations – HT1080 (IDH1mut R132C, EMEM + 10% FBS), SNU-1079 (IDH1mut R132C, RPMI + 10%FBS + 1% sodium pyruvate), and SW1353 (IDH2mut R172S, RPMI + 10%FBS + 1% sodium pyruvate).

The assay process is as follows:

Day 1: cells were seeded in 384-well plates (Corning Cat# 3707) in triplicates for both the cell proliferation and 2HG assay, and incubated at 37C, 95% Rh, 5% CO2 overnight.

Day 2: compounds were serially diluted 1:3 (10 point dilution from 10mM solutions in DMSO) and delivered to the cell assay plates via acoustic dispenser, with final concentration ranging from 30uM to 1.5nM. The plates were returned to the incubator after treatment and incubated for 48 hours.

Day 4 Proliferation assay: CTG (cell titer-glo, Promega part # G755B) was added to the assay plates and luminescence signal was read on the plate reader.

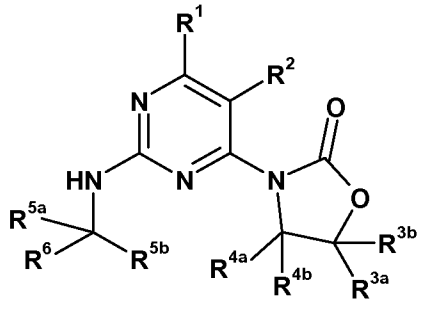
Day 4 2HG assay : Extraction sample preparation consisted of aspirating all media from the assay plates, adding 70 ul of 90% methanol in water, dry ice incubation for 15 minutes, centrifuging at 2000 rpm for 30 min to ensure all particulates have settled, and transferring 30 ul of the supernatant into LC-MS ready plates. LC-MS analysis follows.

Certain compounds of the invention have been tested in the IDH Cellular Assay.

CLAIMS

What is claimed is:

1. A compound of formula (I)



(I)

wherein:

R^1 and R^2 are each independently hydrogen, deuterium, halo, hydroxyl, NH_2, aryl, heteroaryl, or optionally substituted C_{1-4} alkyl,

wherein said C_{1-4} alkyl is optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, and NH_2;

R^{3a} is hydrogen, deuterium, C_{1-6} alkyl, phenyl, or benzyl and

R^{3b} is hydrogen, deuterium, or C_{1-6} alkyl; or

R^{3a} and R^{3b} are joined together forming an optionally substituted 3-7 membered cycloalkyl ring or an optionally substituted 4-7 membered heterocyclic ring,

wherein said cycloalkyl and heterocyclic rings are each optionally substituted with one or two substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl;

R^{4a} is hydrogen, C_{1-6} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted heteroaryl, or methylene-dibenzene,

wherein said phenyl, benzyl, and heteroaryl rings are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-4} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $-COOR^b$, $-SO_2R^b$, $-NHC(O)R^b$, and $-NR^bR^b$ and

R^{4b} is hydrogen, deuterium, or C_{1-3} alkyl; or

R^{4a} and R^{4b} are joined together forming an optionally substituted 3-7 membered cycloalkyl ring or an optionally substituted 4-7 membered heterocyclic ring,

wherein said cycloalkyl and heterocyclic rings are optionally substituted with one or two substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl,

provided that only one of R^{3a} and R^{3b} and R^{4a} and R^{4b} are joined together forming a ring;

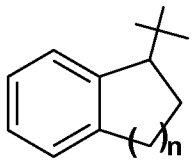
R^{5a} is hydrogen or deuterium;

R^{5b} is hydrogen, deuterium, methyl, ethyl, CD_3, CF_3, CH_2F, or CHF_2 and

R^6 is optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted C_{3-10} cycloalkyl,

wherein said C_{1-6} alkyl is optionally substituted with one substituent selected from the group consisting of hydroxyl, C_{1-3} alkoxy and $-OR^a$,

wherein said aryl, heteroaryl, heterocyclic and C_{3-10} cycloalkyl are optionally substituted with one to three substituents each independently selected from the group consisting of: halo; hydroxyl; cyano; nitro; C_{1-4} alkoxy; C_{1-3} haloalkyl; C_{1-3} haloalkoxy; C_{1-6} alkyl; C_{3-6} cycloalkyl optionally substituted with one to three substituents each independently selected from the group consisting of: hydroxyl, cyano, C_{1-3} alkyl, C_{1-3} alkoxy, and C_{1-3} haloalkyl; phenyl optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $-COOR^b$, $-SO_2R^b$, $-NHC(O)R^b$, and NR^bR^b; 5-6 membered heteroaryl optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, C_{1-3} alkyl, C_{1-3} alkoxy; 5-6 membered heterocyclic optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl; $-CH_2R^a$; $-OR^a$; $-C(O)R^a$; $-NR^aR^b$; $-COOR^a$; $-SO_2R^a$; $-SO_2R^b$; $-NHC(O)R^a$; $-NHC(O)R^b$; $-C(O)NR^aR^b$; $-C(O)NHR^b$; and $-SO_2NR^bR^b$; or

R^{5b} and R^6 are joined together forming an optionally substituted C_{3-7} cycloalkyl group or an optionally substituted group of formula (a):  (a),

wherein n is 1, 2, or 3 and

said C_{3-7} cycloalkyl and group of formula (a) are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, benzyloxy, $-COOR^b$, $-SO_2R^b$, $-NHC(O)R^b$, and $-NR^bR^b$;

each R^a is independently optionally substituted phenyl, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted C_{3-7} cycloalkyl,

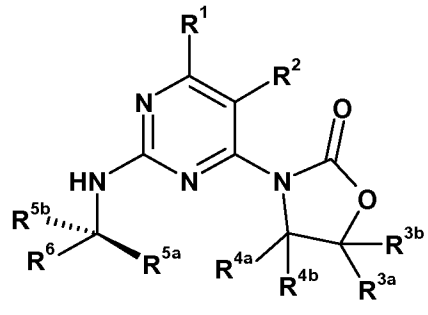
wherein said phenyl and heteroaryl are optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, and C_{1-3} alkyl,

wherein said heterocyclic is optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, oxo, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-4} alkyl, C_{3-5} cycloalkyl, $-C(O)R^b$, and $-NR^bR^b$, and

wherein said C_{3-7} cycloalkyl is optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, oxo, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, and C_{1-3} alkyl; and

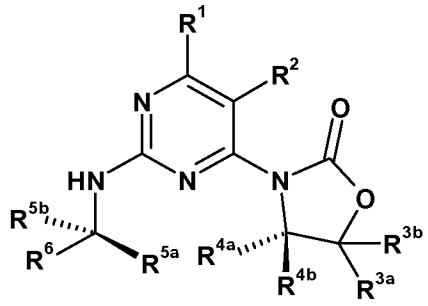
each R^b is independently hydrogen or C_{1-6} alkyl; or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 of the formula (III)



(III); or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 2 of the formula (IV)



(IV); or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 3 wherein R^{3a} and R^{3b} are both hydrogen; or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 4 wherein R^{5a} is hydrogen and R^{5b} is hydrogen, methyl, ethyl, or CF_3; or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 5 wherein R^{5b} is methyl; or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 6 wherein R^1 is hydrogen, fluoro or chloro and R^2 is hydrogen, fluoro, chloro, or methyl; or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 7 wherein R^1 and R^2 are both hydrogen; or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 8 wherein R^{4a} is hydrogen, C_{1-6} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted heteroaryl, or methylene-dibenzene,

wherein said phenyl, benzyl, and heteroaryl rings are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $-COOR^b$, $-SO_2R^b$,- $NHC(O)R^b$, and- NR^bR^b and

R^{4b} is hydrogen or C_{1-3} alkyl; or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 9 wherein R^{4b} is hydrogen or methyl; or a pharmaceutically acceptable salt thereof.

11. The compound according claim 10 wherein R^{4b} is hydrogen; or a pharmaceutically acceptable salt thereof.

12. The compound according to claim 11 R^{4a} is hydrogen, methyl, ethyl, isopropyl, phenyl, 4-fluorophenyl, 4-methoxyphenyl, biphenyl, benzyl, or pyridinyl; or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 12 wherein R^{4a} is isopropyl; or a pharmaceutically acceptable salt thereof.

14. The compound according to any one of claims 1-13 wherein R^6 is methyl, C_{5-10} cycloalkyl, optionally substituted phenyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted pyridazinyl, optionally substituted pyrazinyl, optionally substituted triazolyl, optionally substituted pyrazolyl, optionally substituted thiazolyl, optionally substitued 1,3,4-oxadiazolyl, optionally substituted 1,2,4-oxadiazolyl, optionally substitued isoxazolyl, thienyl, oxazolyl, quinolinyl, optionally substituted benzimidazolyl, benzthiazolyl, benzoxazolyl, tetrazolo[1,5-a]pyridinyl, imidazo[2,1-b][1,3,4]thiadiazolyl, optionally substituted piperidinyl, optionally substituted piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, optionally substituted tetrahydro-thiopyran1,1-dioxide, 1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydro-benzo[1,4]dioxinyl, 5,6,7,8-tetrahydro-[1,2,4]trazolo[4,3-a]pyrazinyl, 4,5,6,7-tetrahydro-benzothiazolyl, indolizinyl, cyclopropyl, cyclopentyl, or cyclohexyl, wherein said phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazolyl, pyrazolyl, thiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, isoxazolyl, benzimidazolyl, piperidinyl, piperazinyl, and tetrahydro-thiopyran1,1-dioxide are each optionally substituted with one or two substituents as defined in formula (I).

15. The compound according to claim 14 wherein R^6 is optionally substituted with one or two substituents each independently selected from the group consisting of: halo; hydroxy; nitro; C_{1-4} alkoxy; C_{1-3} haloalkyl; C_{1-3} haloalkoxy; C_{1-6} alkyl; C_{3-6} cycloalkyl optionally substituted with one substituent selected from the group consisting of: cyano, C_{1-3} alkyl, and C_{1-3} alkoxy; phenyl optionally substituted with one or two substituents each independently selected from the group consisting of: fluoro, chloro, methyl, cyano, and methoxy; and 5-6 membered heteroaryl optionally substituted with one or two methyl groups; or a pharmaceutically acceptable salt thereof.

16. The compound according to claim 15 wherein R^6 is optionally substituted 1,3,4-oxadiazolyl or optionally substituted 1,2,4-oxadiazolyl; or a pharmaceutically acceptable salt thereof.

17. The compound according to claim 14 wherein R^6 is substituted with one $-CH_2R^a$, $-C(O)R^a$, $-NHC(O)R^a$, $-NHC(O)R^b$, $-C(O)NHR^a$, $C(O)NHR^b$, $-OR^a$, $-NR^aR^b$, $-SO_2NR^bR^b$, $-SO_2R^a$, or $-SO_2R^b$ group; or a pharmaceutically acceptable salt thereof.

18. The compound according to claim 17 wherein R^a is

(a) phenyl optionally substituted with one or two substituents each independently selected from the group consisting of fluoro, chloro and bromo;

(b) optionally substituted 5-6 membered heteroaryl;

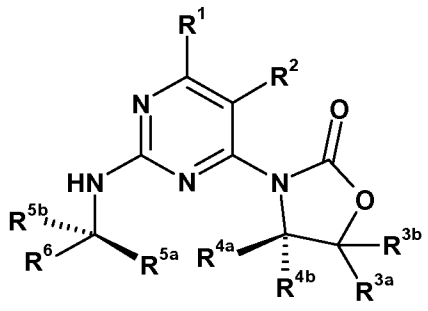
(c) C_{5-7} cycloalkyl optionally substituted with one or two substituents each independently selected from the group consisting of fluoro, hydroxy, methyl, and C_{1-3} haloalkoxy; or

(d) a heterocyclic group selected from the group consisting of: piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, tetrahydro-thiopyran1,1-dioxide, 1,4-diazepanyl, 4,7-diaza-spiro[2.5]octanyl, 3,8-diaza-bicyclo[3.2.1]octanyl, 3,8-diaza-bicyclo[4.2.0]octanyl, octahydro-pyrrolo[1,2-a]pyrazinyl, octahydro-pyrido[1,2-a]pyrazinyl, octahydro-pyrrolo[3,4-c]pyrrolyl, and 5,6,7,8-tetrahydro-imidazo[1,2-a]pyrazinyl each of which is optionally substituted with one to three substituents each independently selected from the group consisting of: hydroxy, fluoro, amino, dimethylamino, C_{1-3} haloalkoxy, C_{1-3} alkyl, and C_{3-5} cycloalkyl; or a pharmaceutically acceptable salt thereof.

19. The compound according to claim 18 wherein R^6 is optionally substituted phenyl; or a pharmaceutically acceptable salt thereof.

20. The compound according to claim 19 wherein the phenyl is substituted with one $-CH_2R^a$, -C(O)R^a, or -C(O)NHR^a group in the para position; or a pharmaceutically acceptable salt thereof.

21. The compound according to claim 2 of the formula (V)



(V);

wherein R^{4a} is phenyl and R^{4b} is hydrogen; or a pharmaceutically acceptable salt there

22. The compound according to claim 1 selected from the group consisting of:
(S)-4-isopropy-3-(2-(((S)-1-(4-(2-yl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one;
N-(4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)phenyl)cyclohexanecarboxamide;
(S)-3-(2-(((S)-1-(3-fluoro-4-((4-methylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-isopropyl-3-(2-(((S)-1-(4-((3,3,4-trimethylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one;
2-fluoro-N-(4-hydroxy-4-methylcyclohexyl)-4-((S)-1-((4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-yl)amino)ethyl)benzamide;
(S)-3-(2-((S)-1-(4-((4-amino-4-methylpiperidin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(4-((4-(dimethylamino)piperidin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-isopropyl-3-(2-((S)-1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-4-isopropyl-4-methyl-3-(2-((S)-1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-4-isopropyl-3-(2-((S)-1-(6-phenylpyridin-3-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;

(S)-3-(2-((S)-1-(4-benzoylphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-isopropyl-3-(2-(((S)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)ethyl) amino) pyrimidin-4-yl)oxazolidin-2-one;
(4S)-4-isopropyl-3-(2-(1-(5-phenylpyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
3-(5-fluoro-2-((1-(5-(4-fluoro-3-methylphenyl)pyridin-2-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-4-isopropyl-3-(2-(((S)-1-(1-(3-methoxyphenyl)-1H-pyrazol-4-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-3-(2-(((S)-1-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-isopropyl-3-(2-(((S)-1-(3-(m-tolyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-3-(2-(((S)-1-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(5-(4-fluoro-2-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-Isopropyl-3-{2-[(3-p-tolyl-[1,2,4]oxadiazol-5-ylmethyl)-amino]-pyrimidin-4-yl}-oxazolidin-2-one;
(S)-4-isopropyl-3-(2-((S)-1-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-3-(2-((S)-1-(2-fluoro-4-isopropylphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(4-isobutoxy-3-methylphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(4-isobutoxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(5-fluoro-2-(((S)-1-(4-isobutoxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
2-fluoro-N-(*trans*-4-hydroxycyclohexyl)-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide;
(S)-3-(5-fluoro-2-((S)-1-(3-fluoro-4-(piperidine-1-carbonyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
N-cyclohexyl-2-fluoro-4-((S)-1-(5-fluoro-4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide;

N-cyclohexyl-2-fluoro-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide; and
(S)-3-(5-fluoro-2-((S)-1-(2-fluoro-4-(trifluoromethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one; or a pharmaceutically acceptable salt thereof.

23. The compound according to claim 1 selected from the group consisting of:
(S)-3-(2-(((S)-1-(3-fluoro-4-((3,3,4-trimethylpiperazin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(4-((4,4-difluoropiperidin-1-yl)methyl)phenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(5-fluoro-2-(1-(4-phenoxyphenyl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-3-(2-((S)-1-(4-(4-fluorophenoxy)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(4-(((2S,6R)-2,6-dimethylmorpholino)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(5-(4-fluoro-3-methylphenyl)pyridin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(5-(4-fluorophenoxy)pyrazin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-4-isopropyl-3-(2-((S)-1-(5-(3-(trifluoromethyl)phenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one; and
(S)-3-(2-((S)-1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one; or a pharmaceutically acceptable salt thereof.

24. The compound according to claim 1 selected from the goup consisting of:
(S)-3-(2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)-5-fluoropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one;
(S)-3-(6-chloro-2-(1-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one;
(S)-3-(2-((S)-1-(2-fluoro-4-(1-methylcyclopropyl) phenyl) ethylamino) pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;

(S)-3-(2-((S)-1-(2-fluoro -4-(trifluoromethyl) phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
2-chloro-N-cyclopentyl-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide;
(S)-3-(2-((S)-1-(4-((3,3-difluoropiperidin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(4-(4,7-diazaspiro[2.5]octan-4-ylmethyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-((S)-1-(4-((4-acetylpiperazin-1-yl)methyl)phenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(2-(((S)-1-(4-isobutoxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one;
(S)-3-(5-fluoro-2-(((S)-1-(4-isobutoxyphenyl)ethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one; and
2-fluoro-N-(trans-4-hydroxycyclohexyl)-4-((S)-1-(4-((S)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzamide; or a pharmaceutically acceptable salt thereof.

25. The compound according to claim 1 wherein

each R^1 and R^2 is independently hydrogen, deuterium, halo, hydroxyl, NH_2, aryl, heteroaryl, or optionally substituted C_{1-4} alkyl,

wherein said C_{1-4} alkyl is optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, and NH_2;

R^{3a} is hydrogen, deuterium, C_{1-6} alkyl, phenyl, or benzyl and

R^{3b} is hydrogen, deuterium, or C_{1-6} alkyl; or

R^{3a} and R^{3b} are joined together forming an optionally substituted 3-7 membered cycloalkyl ring or an optionally substituted 4-7 membered heterocyclic ring,

wherein said cycloalkyl and heterocyclic rings are each optionally substituted with one or two substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl;

R^{4a} is hydrogen, C_{1-6} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted heteroaryl, or methylene-dibenzene,

wherein said phenyl, benzyl, and heteroaryl rings are optionally substituted with one to three substituents each independently selected from the group consisting of:

halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $COOR^b$, SO_2R^b, $NHC(O)R^b$, and NR^bR^b and

R^{4b} is hydrogen, deuterium, or C_{1-3} alkyl; or

R^{4a} and R^{4b} are joined together forming an optionally substituted 3-7 membered cycloalkyl ring or an optionally substituted 4-7 membered heterocyclic ring,

wherein said cycloalkyl and heterocyclic rings are optionally substituted with one or two substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl,

provided that only one of R^{3a} and R^{3b} and R^{4a} and R^{4b} are joined together forming a ring;

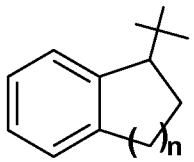
R^{5a} is hydrogen or deuterium;

R^{5b} is hydrogen, deuterium, methyl, ethyl, CD_3, CF_3, CH_2F, or CHF_2 and

R^6 is optionally substituted C_{1-6} alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclic, or optionally substituted C_{5-10} cycloalkyl,

wherein said C_{1-6} alkyl is optionally substituted with one substituent selected from the group consisting of hydroxyl, C_{1-3} alkoxy and $–OR^a$;

wherein said aryl, heteroaryl, heterocyclic and C_{5-10} cycloalkyl are optionally substituted with one to three substituents each independently selected from the group consisting of: halo; hydroxyl; cyano; nitro; C_{1-3} alkoxy; C_{1-3} haloalkyl; C_{1-3} haloalkoxy; C_{1-6} alkyl; C_{3-6} cycloalkyl; phenyl optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, phenoxy, $COOR^b$, SO_2R^b, $NHC(O)R^b$, and NR^bR^b; 5-6 membered heteroaryl; 5-6 membered heterocyclic optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, oxo, NH_2, and C_{1-3} alkyl; $-CH_2R^a$; $-OR^a$; $-C(O)R^a$; $-NR^aR^b$; $-COOR^a$; $–SO_2R^a$; $NHC(O)R^a$; and $-SO_2NR^bR^b$; or

R^{5b} and R^6 are joined together forming an optionally substituted C_{3-7} cycloalkyl group or an optionally substituted group of formula (a):  (a),

wherein n is 1, 2, or 3 and

said C_{3-7} cycloalkyl and group of formula (a) are optionally substituted with one to three substituents each independently selected from the group consisting of: halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, C_{1-6} alkyl, C_{3-6} cycloalkyl, 5-6 membered heteroaryl, 5-6 membered heterocyclic, benzyloxy, $COOR^b$, SO_2R^b, $NHC(O)R^b$, and NR^bR^b;

each R^a is independently optionally substituted phenyl, optionally substituted heteroaryl, or optionally substituted 4-7 membered heterocyclic,

wherein said phenyl and heteroaryl are optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, cyano, nitro, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, and C_{1-3} alkyl,

wherein said 4-7 membered heterocyclic is optionally substituted with one to three substituents each independently selected from the group consisting of halo, hydroxyl, oxo, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, and C_{1-3} alkyl; and

each R^b is independently hydrogen or C_{1-6} alkyl; or a pharmaceutically acceptabble salt thereof.

26. The compound according to claim 25 wherein

R^1 is hydrogen, fluoro, chloro, or methyl;

R^2 is hydrogen;

R^{3a} is hydrogen, methyl, or phenyl;

R^{3b} is hydrogen or methyl;

R^{4a} is hydrogen, C_{1-4} alkyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted heteroaryl, or methylene-dibenzene;

R^{4b} is hydrogen or methyl;

R^{5a} is H; and

R^{5b} is hydrogen, methyl, ethyl, or CF_3; or a pharmaceutically acceptable salt thereof.

27. The compound according to claim 26 wherein wherein R^6 is isopropyl, optionally substituted aryl, optionally substituted pyrazolyl, optionally substituted pyridinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, or optionally substituted C_{5-10} cycloalkyl; or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

29. A method for the treatment of a disease or disorder associated with a mutant IDH protein having a neomorphic activity comprising administration of a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, to subject in need of thereof.

30. A method for the treatment of a disease or disorder associated with a mutant IDH protein having a neomorphic activity comprising administration of a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and another therapeutic agent to subject in need of thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/055133

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 C07D413/14 C07D417/14 C07D471/04 C07D487/04
C07D498/10 C07D513/04 A61K31/506 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/080937 A1 (BASF SE [DE]; NAVE BARBARA [DE]; HARMSEN SVEN [DE]; MUELLER BERND [DE]) 10 July 2008 (2008-07-10) page 44; claims 1-4, 12, 14; table B	1-30
A	WO 01/60816 A1 (AMGEN INC [US]) 23 August 2001 (2001-08-23) page 3, line 29; example 5; compound 25	1-30
A	WO 2010/090290 A1 (NIPPON SHINYAKU CO LTD [JP]; FUJIHARA HIDETAKA [JP]; ASAKI TETSUO [JP]) 12 August 2010 (2010-08-12) use against cancer mentioned in some claims; page 204; example 67	1-30

☐ 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
12 December 2012	19/12/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Stroeter, Thomas

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/055133

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008080937 A1	10-07-2008	AR 064571 A1	08-04-2009
		CL 38472007 A1	18-04-2008
		TW 200833342 A	16-08-2008
		WO 2008080937 A1	10-07-2008
WO 0160816 A1	23-08-2001	AU 3704101 A	27-08-2001
		AU 2001237041 B2	21-07-2005
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		CN 1429222 A	09-07-2003
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		CA 2751695 A1	12-08-2010
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		US 2011288065 A1	24-11-2011
		WO 2010090290 A1	12-08-2010

3- PIRMIDIN- 4- IL- OXAZOLIDIN- 2- ONAS COMO INHIBIDORES DE LA IDH MUTANTE

CAMPO DE LA INVENCION

La presente invención se refiere a compuestos novedosos de 3- pirimidinil- 4- il- oxazolidin- 2- ona, composiciones que contienen estos compuestos, el uso de tales compuestos en la inhibición de las proteínas IDH mutantes que tienen una actividad neomórfica y en el tratamiento de enfermedades o trastornos asociados con tales proteínas IDH mutantes incluyendo, pero sin limitar a, trastornos de proliferación celular, como el cáncer.

FUDAMENTO DE LA INVENCION

La isocitrato deshidrogenasa (IDH) es una familia clave de enzimas que se encuentran en el metabolismo celular. Son oxidoreductasas metal-dependientes y dependientes de las coenzimas $NADP^+$ y NAD^+ del sistema enzimático EC 1.1.1.42. Las proteínas tipo silvestre catalizan la descarboxilación oxidativa de isocitrato a alfa-00cetoglutarato generando dióxido de carbono y NADPH/NADH en el proceso. Se sabe también que convierten el oxalosuccinato en alfa- cetoglutarato. Las mutaciones en IDH1 (citosólico) y IDH2 (mitocondriales) se han identificado en varios tipos de cáncer que incluyen, pero no se limitan a glioma, glioblastoma multiforme, paraganglioma, tumores neuroectodérmicos primitivos supratentoriales, leucemia mieloide aguda (LMA), cáncer de próstata, cáncer de tiroides, cáncer de colon, condrosarcoma, colangiocarninoma, linfoma de células T periféricas y melanoma. (Véase L. Deng, Trends Mol. Med, 2010, 16, 387; T. Shibata, Am. J. Pathol, 2011, 178 (3), 1395; Gaal, J. Clin Endocrinol Metab 2010;. Hayden , Cell Cycle, 2009;. Balss, Acta Neuropathol, 2008). Las mutaciones se han encontrado en o cerca de los principales residuos en el sitio activo: G97D, R100, R132, H133Q, y A134D para IDH1, y R140 y R172 para IDH2. (Véase L. Deng, Nature, 2009, 462, 739; L. Sellner, Eur. J. Haematol, 2011, 85, 457).

Se ha mostrado que estas formas mutantes de la IDH tienen actividad neomorfica (también conocida como una actividad de ganancia de función), reduciendo alfa-cetoglutarato a 2- hidroxiglutarato (2- HG). (Ver PS Ward., Cancer Cell, 2010, 17, 225).

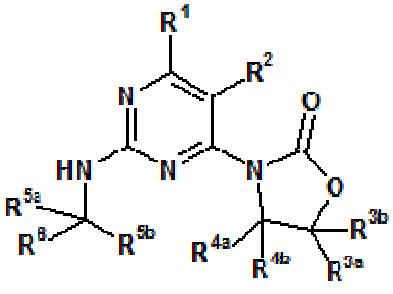
En general, la producción de 2- HG es enantioespecífica, lo que resulta en la generación del enantiómero - D (también conocido como enantiómero R o R- 2- HG). Las células normales tienen bajos niveles nativos de 2- HG, mientras que las células que albergan estas mutaciones en IDH1 o IDH2 muestran niveles significativamente elevados de 2- HG. Niveles altos de 2- HG se han detectado en los tumores que albergan las mutaciones. Por ejemplo, niveles altos de 2- HG se han detectado en el plasma de pacientes con IDH mutante que contienen LMA. (Véase S. Gross., J. Exp.. Med., 2010, 207 (2), 339). Los altos niveles de 2- HG están altamente relacionados con la tumorigénesis.

La IDH2 mutante también está asociada con el inusual trastorno neurometabólico, la aciduria D- 2- hidroxiglutárica tipo II (D- 2- HGA tipo II). Las mutaciones de línea germinal se encontraron en R140 en IDH2 en 15 pacientes con D- 2- HGA tipo II. Los pacientes con este trastorno también tenían niveles aumentados de manera constante de D- 2- HG en la orina, plasma y líquido cefalorraquídeo. (Ver Kranendijk, M. Science, 2010, 330, 336). Finalmente, pacientes con la enfermedad de Ollier y el síndrome Mafucci (dos trastornos raros que predisponen a tumores cartilaginosos) han sido mostrados por ser somáticamente mosaicos para mutaciones IDH1 y 2 y exhiben altos niveles de D-2-HG. (Ver Amary et al., Nature Genetics, 2011 y Pansuriva et al., Nature Genetics, 2011).

Por lo tanto, hay una necesidad de inhibidores de moléculas pequeñas de las proteínas IDH mutantes que tengan una actividad neomórfica para el tratamiento de enfermedades y trastornos asociados con estas proteínas.

RESUMEN DE LA INVENCIÓN

En un aspecto, esta invención proporciona un compuesto de la Fórmula (I)



(I)

ó una sal farmacéuticamente aceptable del mismo, en donde R^1-R^6 son como se definen en la presente.

En un segundo aspecto, la presente invención proporciona una composición farmacéutica que comprende un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo y un vehículo ó excipiente farmacéuticamente aceptable.

En un tercer aspecto, esta invención proporciona el uso de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, como un inhibidor de una proteína mutante IDH que tiene una actividad neomórfica como la reducción de alfa-cetoglutarato a 2-hidroxiglutarato (actividad neomórfica 2-HG). Convenientemente, esta invención proporciona el uso de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, como un inhibidor de IDH1 mutante que tiene una actividad neomórfica, tal como la actividad neomórfica 2-HG, y/o IDH2 mutante que tiene una actividad neomórfica, como la actividad neomórfica 2-HG. Esta invención proporciona además el uso de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, como un inhibidor de IDH1 que tiene una mutación en el residuo 97, 100 o 132, por ejemplo G97D, R100Q, R132H, R132C, R132S, R132G , R132L, y R132V; y/o un inhibidor de la IDH2 que tiene una mutación en el residuo 140 o 172, por ejemplo R172K, R172M, R172S, R172G, y R172W.

En un cuarto aspecto, esta invención proporciona un método para tratar una enfermedad o trastorno asociado con una proteína IDH mutante que tiene un actividad neomórfica que comprende administración de una cantidad eficaz de un compuesto según la fórmula (I), o una sal farmacéuticamente aceptable del mismo, a un sujeto en necesidad del mismo. En una realización, la enfermedad o trastorno es un trastorno de proliferación celular, tal como cáncer. En otra realización, el cáncer es cáncer cerebral, tal como el glioma, el glioblastoma multiforme, paraganglioma, y tumores neuroectodérmicos primordiales supratentoriales (pNET), leucemia, tal como leucemia mieloide aguda (LMA), síndrome mielodisplásico y leucemia mielógena crónica (LMC); cáncer de piel, incluyendo melanoma, tumores de próstata, de tiroides, de colon, de pulmón, condrosarcoma central, tumores de condroma central y periostio, y fibrosarcoma. En otra realización, la enfermedad o trastorno es aciduria D-2-hidroxiglutárica.

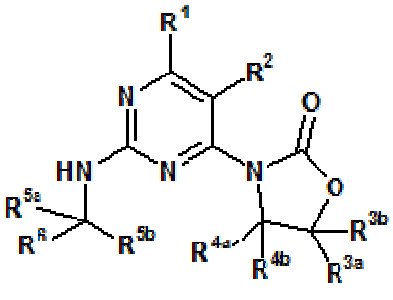
En un quinto aspecto, la invención proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en combinación con otro agente terapéutico.

Estos y otros aspectos de la presente invención se describen adicionalmente en la siguiente descripción detallada de la invención.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención se refiere a un compuesto de la fórmula (I)

Un compuesto de la Fórmula (I):



(I)

en donde:

R^1 y R^2 son cada uno independientemente hidrógeno, deuterio, halo, hidroxilo, NH_2, arilo, heteroarilo, o opcionalmente sustituido alquilo C_{1-4},

en donde dicho alquilo C_{1-4} es opcionalmente sustituido por uno a tres sustituyentes seleccionados cada uno independientemente a partir del grupo que consta de: halo, --hidroxilo, y NH_2;

R^{3a} es hidrógeno, deuterio, alquilo C_{1-6}, fenilo, o bencilo y

R^{3b} es hidrógeno, deuterio, o alquilo C_{1-6}; o

R^{3a} y R^{3b} se unen juntos formando un anillo cicloalquilo de 3-7 miembros opcionalmente sustituido o un anillo heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dicho cicloalquilo y anillo heterocíclico son cada uno opcionalmente sustituido por uno o dos sustituyentes cada uno independientemente seleccionado del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3};

R^{4a} es hidrógeno, alquilo C_{1-6}, fenilo opcionalmente sustituido, bencilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o metileno-dibenceno,

en donde dicho fenilo, bencilo, y anillos de heteroarilo son opcionalmente sustituidos con uno a tres sustituyentes cada uno independientemente seleccionados del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-4}, haloalquilo C_{1-3},

haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, fenilo, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, fenoxilo, $-COOR^b$, $-SO_2R^b$, $-NHC(O)R^b$, y $-NR^bR^b$ y

R^{4b} es hidrógeno, deuterio, o alquilo C_{1-3}; o

R^{4a} y R^{4b} se unen juntos formando un anillo cicloalquilo de 3-7 miembros opcionalmente sustituido o un anillo heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dicho cicloalquilo y anillo heterocíclico son opcionalmente sustituidos por uno o dos sustituyentes cada uno independientemente seleccionado del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3},

siempre y cuando solo uno entre R^{3a} y R^{3b} y R^{4a} y R^{4b} se unan juntos formando un anillo;

R^{5a} es hidrógeno o deuterio;

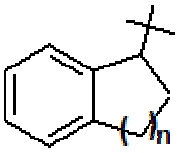
R^{5b} es hidrógeno, deuterio, metilo, etilo, CD_3, CF_3, CH_2F, o CHF_2 y

R^6 alquilo C_{1-6} es opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heterocíclico opcionalmente sustituido, o cicloalquilo C_{3-10} opcionalmente sustituido,

en donde dicho alquilo C_{1-6} es opcionalmente sustituido por un sustituyente selecionado del grupo que consta de hidroxilo, alcoxilo C_{1-3} y $–OR^a$,

en donde dicho arilo, heteroarilo, heterocíclico y cicloalquilo C_{3-10} son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado del grupo que consta de: halo; hidroxilo; ciano; nitro; alcoxilo C_{1-4}; haloalquilo C_{1-3}; haloalcoxilo C_{1-3}; alquilo C_{1-6}; cicloalquilo C_{3-6} opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionados del grupo que consta de: hidroxilo, ciano, alquilo C_{1-3}, alcoxilo C_{1-3}, y haloalquilo; fenil opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, fenoxilo, $-COOR^b$, $-SO_2R^b$, $-NHC(O)R^b$, y

□NR^bR^b; heteroarilo de 5-6 miembros opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionados del grupo que consta de: halo, hidroxilo, ciano, alquilo C_{1-3}, alcoxilo C_{1-3}; heterocíclico de 5-6 miembros opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3}; -CH_2R^a; -OR^a; -$C(O)R^a$; -NR^aR^b; -$COOR^a$; –SO_2R^a; –SO_2R^b; $NHC(O)R^a$; -$NHC(O)R^b$; □$C(O)NR^aR^b$; -$C(O)NHR^b$; y -$SO_2NR^bR^b$; o

R^{5b} y R^6 se unen juntos formando un grupo cicloalquilo C_{3-7} opcionalmente sustituido o un grupo opcionalmente sustituido de la Fórmula (a):  (a),

en donde n es 1, 2, o 3 y

dicho cicloalquilo C_{3-7} y grupo de la Fórmula (a) son opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, bencilooxilo, -$COOR^b$, □SO_2R^b, -$NHC(O)R^b$, y -NR^bR^b;

cada R^a es independientemente fenilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heterocíclico opcionalmente sustituido, o cicloalquilo C_{3-7} opcionalmente sustituido,

en donde dicho fenilo y heteroarilo son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionados del grupo que consta de halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, y alquilo C_{1-3},

en donde dicho heterocíclico es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado del grupo que consta de halo, hidroxilo, oxo, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-4}, cicloalquilo C_{3-5}, -$C(O)R^b$, y –NR^bR^b; y

en donde dicho cicloalquilo C_{3-7} es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado del grupo que consta de halo, hidroxilo, oxo, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, y alquilo C_{1-3}; y

cada R^b es independientemente hidrógeno o alquilo C_{1-6}.

"Alquilo" se refiere a una cadena de hidrocarbono saturada monovalente que tiene el número especificado de átomos de carbono. Por ejemplo, C_{1-6} alquilo se refiere a un grupo alquilo que tiene de 1 a 6 átomos de carbono. Los grupos alquilo pueden ser opcionalmente sustituidos por uno o más sustituyentes como se define en la fórmula (I). Los grupos alquilo pueden ser lineales ó ramificados. Grupos alquilo ramificados representativos tienen uno, dos, ó tres ramificaciones. Ejemplos de grupos alquilo incluyen, pero no están limitados a, metilo, etilo, propilo (n-propilo e isopropilo), butilo (n-butilo, isobutilo, sec-butilo, y t-butilo), pentil (n-pentilo, isopentilo, y neopentilo), y hexilo.

"Alcoxilo" se refiere a cualquier fracción alquilo fijada a través de un puente de oxigeno (es decir un grupo –O-C_{1-3} alquilo en donde C_{1-3} alquilo es como se define en la presente. Ejemplos de tales grupos incluyen, pero no se limitan a, metoxilo, etoxilo, y propoxilo.

"Arilo" se refiere a un sistema de anillo de hidrocarbono que tiene un anillo aromático. Grupos arilo son sistemas de anillo monocíclico o sistemas de anillo bicíclico. Anillo de arilo monocíclico se refiere a fenilo. Anillos de arilo bicíclico se refieren a naftilo y a anillos en donde el fenilo está fusionado con un anillo de C_{5-7} cicloalquilo ó C_{5-7} cicloalquenilo. Los grupos arilo pueden ser opcionalmente sustituidos por uno o más sustituyentes como se define en la fórmula (I).

"Cicloalquilo" se refiere a un sistema de anillo de hidrocarbono saturado que tiene el número especificado de átomos de carbono. Los grupos cicloalquilo son sistemas de anillo monocíclico ó bicíclico. Por ejemplo, $C5_{-10}$ cicloalquilo se refiere a un grupo cicloalquilo que tiene de 1 a 10 átomos de carbono. Los grupos cicloalquilo pueden ser opcionalmente sustituidos por uno o más sustituyentes como se define en la fórmula (I). Ejemplos de grupos cicloalquilo incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y adamantanilo.

"Cicloalquenilo" se refiere a un sistema de anillo de hidrocarbono no saturado que tiene el número especificado de átomos de carbono y que tiene un enlace doble carbono-

carbono dentro del anillo. Por ejemplo, C_{5-7} cicloalquenilo se refiere a un grupo cicloalquenilo que tiene de 5 a 7 átomos de carbono. En ciertas realizaciones, los grupos cicloalquenilo tienen un enlace doble carbono-carbono dentro del anillo. En otras realizaciones, los grupos cicloalquenilo tienen más de un enlace doble carbono-carbono dentro del anillo. Los anillos de cicloalquenilo no son aromáticos. Los grupos cicloalquenilo pueden ser opcionalmente sustituidos por uno o más sustituyentes como se define en la fórmula (I).

"Halo" se refiere a radicales de haógeno, flúor, cloro, bromo y yodo.

"Haloalquilo" se refiere a un grupo alquilo en donde al menos un átomo de hidrógeno fijado a un átomo de carbono dentro del grupo alquilo es reemplazado por halo. El número de sustituyentes de halo incluye pero no está limitado a 1, 2, 3, 4, 5, ó 6 sustituyentes. Haloalquilo incluye, pero no está limitado a, monofluorometilo, difluoroetilo, y trifluorometilo.

"Haloalcoxilo" se refiere a cualquier fracción haloalquilo fijada a través de un puente de oxigeno (es decir un grupo $–O-C_{1-3}$ haloalquilo en donde C_{1-3} haloalquilo es como se define en la presente). Un ejemplo de un grupo haloalcoxilo es trifluorometoxilo.

"Heteroarilo" se refiere a un sistema de anillo aromático que contiene de 1 a 5 heteroátomos. Los grupos heteroarilo que contienen más de un heteroátomo pueden contener diferentes heteroátomos. Los grupos heteroarilo pueden ser opcionalmente sustituidos por uno o más sustituyentes como se define en la fórmula (I). Los grupos heteroarilo son sistemas de anillo monocíclico o sistemas de anillo bicíclico. Los anillos de heteroarilo monocíclicos tienen de 5 a 6 átomos de anillo. Los anillos de heteroarilo bicíclicos tienen de 8 a 10 átomos de anillo. Los anillos heteroarilo bicíclicos incluyen los sistemas de anillo en donde un anillo de heteroarilo está condensado a un anillo de fenilo. Heteroarilo incluye, pero no se limita a, pirrolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, oxadiazolilo (incluyendo 1,3,4-oxadiazolilo y 1,2,4-oxadiazolilo), tiazolilo, isotiazolilo, tiadiazolilo, furanilo, furanzanilo, tienilo, triazolilo, piridinilo (incluyendo 2, 3, y 4-piridinilo), pirimidinilo, piridazinilo, pirazinilo, trazinilo, tetrazinilo, tetrazolilo, indonilo, isoindolilo, indolizinilo, indazolilo, purinilo, quinolinilo, isoquinolinilo, quinoxalinilo, quinazolinilo, bencimidazolilo, benzopiranilo, benzopiranilo, benzoxazolilo, benzoisoxazolilo, benzofuranilo, benzotiazolilo, benzotienilo, naftiridinilo, 1H-pirrolo [2,3-b] piridinilo, tetrazolo [1,5-a] piridinilo, imidazo [2,1-b] [1,3 , 4] tiadiazolilo y similares.

"Heteroátomo" se refiere a un átomo de nitrógeno, oxigeno ó azufre.

"Heterocíclico" se refiere a un anillo saturado o no saturado monocíclico o bicíclico de 3 a 11 miembros. Los sistemas de anillo heterocíclico no son aromáticos. Los grupos heterocíclicos que contienen más de un heteroátomo pueden contener diferentes heteroátomos. Heterocíclico incluye sistemas de anillo en donde un átomo de azufre se oxida para formar SO ó SO_2. Los grupos heterocíclicos pueden ser opcionalmente sustituidos por uno o más sustituyentes como se define en la fórmula (I). Los grupos heterocíclicos son sistemas de anillo monocíclicos, espiro, ó fusionados ó puenteados. Los anillos monocíclicos heterocíclicos tienen de 3 a 7 átomos de anillo. Ejemplos de grupos heterocíclicos monocíclicos incluyen oxtanilo, tetrahidrofuranilo, dihidrofuranilo, 1,4-dioxanilo, morfolinilo, 1,4-ditianilo, piperazinilo, piperidinilo, 1,3-dioxolanilo, imidazolidinilo, imidazolinilo, pirrolinilo, pirrolidinilo, tetrahidropiranilo, dihidropiranilo, oxatiolanilo, ditiolanilo, 1,3-dioxanilo, 1,3-ditianilo, oxatianilo, tiomorfolinilo, tetrahidro-tiopiran1,1-dióxido, 1,4-diazepanilo, y similares. Los sistemas de anillo heterocíclicos fusionados tienen de 8 a 11 átomos de anillo e incluyen grupos en donde un anillo heterocíclico es fusionado a un anillo de fenilo, un anillo de heteroarilo u otro anillo heterocíclico. Ejemplos de anillos heterocíclicos condensados incluyen 2,3-dihidrobenzo [b] [1,4] dioxinilo, octahidro-pirrolo [1,2-a] pirazinilo, octahidro-pirido [1,2-a] pirazinilo, octahidro-pirrolo [3 ,4-c] pirrolilo, 5,6,7,8-tetrahidro-[1,2,4] triazolo [4,3-a] pirazinilo, 5,6,7,8-tetrahidro-imidazo [1,2 - a] pirazinilo y similares. Ejemplos de grupos heterocíclicos puenteados incluyen 3,8-diaza-biciclo [3.2.1] octanilo, 3,8-diaza-biciclo [4.2.0] octanilo y similares. Ejemplos de grupos espiro heterocíclicos incluyen 4,7-diaza-espiro[2.5]octanilo y similares.

"Heterocíclico de 4 a 7 miembros" se refiere a un grupo heterocíclico como se definió anteriormente, que tiene de 4 a 7 átomos de anillo y que contiene de 1 a 4 heteroátomos.

"Heterocíclico de 5 a 6 miembros" se refiere a un grupo heterocíclico como se definió anteriormente, que tiene de 5 a 6 átomos de anillo y que contiene de 1 a 4 heteroátomos.

"Opcionalmente sustituido" indica que un grupo, tal como un alquilo, cicloalquilo, heteroarilo, heterocílico, fenilo, y bencilo puede ser no sustituido o el grupo puede ser sustituido con uno o más sustituyentes como se definió en la fórmula (I).

"Oxo" se refiere a un grupo C=O.

"Farmacéuticamente aceptable" significa un compuesto el cual es apropiado para uso farmacéutico. Sales y solvatos (ej., hidratos e hidratos de sales) de compuestos de la invención que son apropiados para utilizar en medicina son aquellos donde en el contraión ó solvente asociado es farmacéuticamente aceptable. Sin embargo, sales y solvatos que tienen contraiones no farmacéuticamente aceptables ó solventes asociados están dentro del alcance de la presente invención, por ejemplo, para utilizar como intermedios en la preparación de otros compuestos de la invención y sus sales y solvatos farmacéuticamente aceptables.

"Sustituidos" en referencia a un grupo tal como alquilo, fenilo, bencilo, heteroarilo, y heterocíclico, indica que uno ó más átomos de hidrógeno fijados a un átomo dentro del grupo es reemplazado por un sustituyente seleccionado del grupo de sustituyentes definidos. Se entendería que el término "sustituido" incluye la provisión implícita que tal sustitución estaría según la valencia permitida del átomo sustituido y el sustituyente; y que la sustitución resulta en un compuesto estable (es decir, un compuesto que no experimenta transformaciones espontáneas, por ejemplo, mediante hidrolisis, reconfiguración, ciclización, ó eliminación y que es suficientemente robusto para sobrevivir al aislamiento desde una mezcla de reacción. Cuando se afirma que un grupo puede contener uno ó más sustituyentes, uno ó más átomos (según lo apropiado) dentro del grupo pueden ser sustituidos. Además, un único átomo dentro del grupo puede ser sustituido por más de un sustituyente siempre y cuando tal sustitución sea según la valencia permitida del átomo. Sustituyentes apropiados son definidos para cada grupo sustituido u opcionalmente sustituido.

Los expertos apreciarán que las sales, incluyendo sales farmacéuticamente aceptables de los compuestos según la fórmula (I) pueden prepararse. Estas sales pueden prepararse *in situ* durante el aislamiento y la purificación final del compuesto, ó haciendo reaccionar de manera separada el compuesto purificado en su forma de ácido libre o de base libre con una base ó ácido apropiados, respectivamente.

Sales de adición ácida farmacéuticamente aceptables pueden formarse con ácidos inorgánicos y ácidos orgánicos, ej., acetato, aspartato, benzoato, besilato, bromuro/hidrobromuro, bicarbonato/carbonato, bisulfato/sulfato, canforsulfornato, cloruro/hidrocloruro, clorteofilonato, citrato, etanodisulfonato, fumarato, gluceptato, gluconato, glucuronato, hipurato, hidroyoduro/yoduro, isetionato, lactato, lactobionato, laurilsulfato, malato, maleato, malonato, mielato, misilato, metilsulfato, naftoato, napsilato, nicotinato, nitrato, octadecanoato, oleato, oxalato, palmitato, pamoato,

fosfato/fosfato de hidrógeno/fosfato de dihidrógeno, poligalacturonato, propionato, estearato, succinato, sulfosalicilato, tartrato, tosilato y sales de trifluoroacetato.

Ácidos inorgánicos a partir de los cuales las sales pueden derivarse incluyen, por ejemplo, ácido clorhídrico, ácido hidrobrómico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y similares.

Ácidos orgánicos de tales sales pueden derivarse incluyendo, por ejemplo, ácido acético, ácido propiónico, ácido glicólico, ácido oxálico, ácido maléico, ácido manólico, ácido succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzóico, ácido mandélico, ácido metanosulfónico, ácido etanosulfónico, ácido toluensulfónico, ácido sulfosalicílico, y similares. Las Sales de adición alcalina farmacéuticamente aceptables pueden formarse con bases inorgánicas y orgánicas.

Bases inorgánicas a partir de las cuales las sales pueden derivarse incluyen, por ejemplo, sales y metales de amonio de las columnas I a XII de la tabla periódica. En ciertas realizaciones, las sales se derivan a partir de sodio, potasio, amonio, calcio, magnesio, hierro, plata, zinc, y cobre; sales particularmente apropiadas incluyen sales de amonio, potasio, sodio, calcio y magnesio.

Bases orgánicas a partir de las cuales pueden derivarse las sales incluyen, por ejemplo, aminas primarias, secundarias y terciarias, aminas sustituidas incluyendo aminas sustituidas de ocurrencia natural, aminas cíclicas, resinas de intercambio de iones alcalinos, y similares. Ciertas aminas orgánicas incluyen esopropilamina, benzatina, colinato, dietanolamina, dietilamina, lisina, meglumina, piperazina y trometamina.

Las sales farmacéuticamente aceptables del presente invento pueden sintetizarse a partir de una fracción alcalina o ácida, mediante métodos químicos convencionales. Generalmente, tales sales pueden prepararse al reaccionar formas ácidas libres 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 al reaccionar formas alcalinas libres de estos compuestos con una cantidad estequiométrica del ácido apropiado. Típicamente, tales reacciones se realizan en agua o en un solvente orgánico, o en una mezcla de los dos. Generalmente, el uso de medios no acuosos tipo éter, acetato de etilo, etanol, isopropanol, o acetonitrilo es deseable, donde pueda realizarse. Listas de sales apropiadas adicionales pueden encontrarse, ej., en "*Remington's Farmaceutical Sciences*", 20th ed., Mack Publishing Company, Easton, Pa., (1985); y en "*Handbook of Farmaceutical Salts: Properties, Selection, and Use*" de Stahl y Wermuth (Wiley- VCH, Weinheim, Alemania, 2002).

Solvatos, incluyendo solvatos farmacéuticamente aceptables, de los compuestos de la fórmula (I) también pueden prepararse. "Solvato" se refiere a un complejo de esteiquiometría variable formado por un soluto y un solvente Tales solventes para el propósito de la invención pueden no interferir con la actividad biológica del soluto. Ejemplos de solventes adecuados incluyen, pero no están limitados a, agua, MeOH, EtOH, y AcOH Los solvatos en donde el agua es la molecula de solvente típicamente se conocen como hidratos. Loa hidratos incluyen composiciones que contienen cantidades estequiométricas de agua, así como también composiciones que contienen cantidades variables de agua.

Los compuestos de la fórmula (I), incluyendo sales y solvatos de los mismos, pueden existir en formas cristalinas, formas no cristalinas, ó mezclas de las mismas. El compuesto o sal o solvato del mismo también pueden exhibir polimorfismo, es decir la capacidad de ocurrir en diferentes formas cristalinas. Estas diferentes formas cristalinas típicamente se conocen como "polimorfos". Los polimorfos tienen la misma composición química pero difieren en el empaquetado, disposición geométrica, y otras propiedades descriptivas del estado sólido cristalino. Por lo tanto, los polimorfos pueden tener diferentes propiedades físicas tales como forma, densidad, dureza, deformabilidad, y disolución. Típicamente los polimorfos exhiben diferentes puntos de fusión, espectros IR, y patrones de difracción de rayos-X de polvos, todos éstos utilizados para identificación. Los expertos en la técnica apreciarán que diferentes polimorfos pueden producirse, por ejemplo, al cambiar o ajustar las condiciones utilizadas en la cristalización/recristalización de un compuesto de la fórmula (I).

La invención también incluye varios isómeros de los compuestos de la fórmula (I). Ïsómero" se refiere a compuestos que tienen la misma composición y peso molecular pero difieren en las propiedades físicas y/o químicas. La diferencia estructural puede estar en la constitución (isómeros geométricos) ó en la capacidad para girar el plano de la luz polarizada (estereoisómeros). Con respecto a los estereoisómeros, los compuestos de la fórmula (I) pueden tener uno ó más átomos de carbono asimétricos y pueden ocurrir como racematos, mezclas racémicas y como enantiomeros o diastereomeros individuales. Todas éstas formas isoméricas están incluidas dentro de la presente invención, incluyendo mezclas de las mismas. Si el compuesto contiene un enlace doble, el sustituyente puede ser de configuración E o Z. Si el compuesto contiene un cicloalquilo disustituido, el sustituyente cicloalquilo puede tener una configuración cis- o - trans. Todas las formas tautoméricas también son incluidas.

Cualquier átomo asimétrico (ej., carbono o similares) de un compuesto de la fórmula (I) puede presentarse en la configuración racémica o enantioméricamente enriquecida, por ejemplo (*R*)-, (*S*)- o (*R,S*)-. En ciertas realizaciones, cada átomo asimétrico tiene al menos 50 % de exceso enantiomérico, al menos 60 % de exceso enantiomérico, al menos 70 % de exceso enantiomérico, al menos 80 % de exceso enantiomérico, al menos 90 % de exceso enantiomérico, al menos 95 % de exceso enantiomérico, o al menos 99 % de exceso enantiomérico en la configuración (*R*)- o (*S*)- . Los sustituyentes en átomos con enlaces no saturados pueden, si es posible, estar presentes en la forma *cis*- (*Z*)- o *trans*- (*E*)- .

En consecuencia, como se utiliza en la presente un compuesto de la fórmula (I) puede estar en la forma de uno de los posibles isómeros, rotámeros, atropisómeros, tautómeros o mezclas de los mismos, por ejemplo, como isómeros geométricos sustancialmente puros (*cis* o *trans*), diastereomeros, isómeros ópticos (antípodas), racematos o mezclas de los mismos.

Cualquier mezcla resultante de isómeros puede ser separada sobre la base de las diferencias fisicoquímicas de los constituyentes, en isómeros geométricos u ópticos puros o sustancialmente puros, diastereoisómeros, racematos, por ejemplo, mediante cromatografía y/o cristalización fraccional.

Los racematos resultantes de los productos finales o intermedios pueden ser resueltos en los antípodos ópticos mediante métodos conocidos, *ej.*, mediante separación de las sales diastereoisoméricas de los mismos, obtenidas con un ácido o base óptimamente activos, y liberando el compuesto ácido o alcalino ópticamente activo. En particular, una fracción alcalina puede emplearse para separar los compuestos del presente invento en sus antípodos ópticos, *ej.*, mediante cristalización fraccional de una sal formada con un ácido ópticamente activo, *ej.*, 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 pueden separarse mediante cromatografía quiral, *ej.*, cromatografía líquida de alta presión (HPLC) utilizando un absorbente quiral.

La invención incluye formas no rotuladas así como también formas isotópicamente rotuladas de los compuestos de la fórmula (I). Los compuestos isotopicamente rotulados tienen estructuras representadas por las fórmulas dadas en la presente excepto que uno o más átomos son reemplazados por un átomo que tiene un número de masa o masa atómica seleccionados. Ejemplos de isótopos que pueden

incorporarse en compuestos del invento incluyen isótopos de hidrógeno, carbono, nitrógeno, oxigeno, 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. El invento incluye diferentes compuestos isotópicamente rotulados como se definen en la presente, por ejemplo aquellos en los cuales isótopos radioactivos, tales como ^{3}H, y ^{14}C, o aquellos en los cuales isotopos no radioactivos, tales como ^{2}H y ^{13}C están presentes. Tales compuestos rotulados isotópicamente son útiles en estudios metabólicos (con ^{14}C), estudios cinéticos de reacción (con, por ejemplo ^{2}H o ^{3}H), técnicas de detección o visualización, tales como tomografía de emisión de positrones (PET) o tomografía computarizada de emisión de fotones individuales (SPECT) incluyen ensayo de distribución tisular de sustratos o fármacos, o tratamientos radioactivos de pacientes. En particular, un ^{18}F o un compuesto rotulado pueden ser particularmente deseados para estudios PET o SPECT. Compuestos isotópicamente rotulados de la fórmula (I) pueden generalmente prepararse mediante técnicas convencionales conocidas por aquellos con experiencia en el estado de la técnica o mediante procesos análogos a aquellos descritos en los Ejemplos y Preparaciones anexos utilizando un reactivo isotópicamente rotulado apropiado en cambio del reactivo no rotulado previamente empleado.

Además, la sustitución con isótopos más pesados, particularmente deuterio (es decir,., ^{2}H o D) puede proporcionar ciertas ventajas terapéuticas que resultan a partir de la mayor estabilidad metabólica, por ejemplo vida media *in vivo* aumentada o requerimientos de dosificación reducidos o una mejora en el índice terapéutico. Se entiende que deuterio en este contexto es considerado como un sustituyente de un compuesto de la fórmula (I). La concentración de tal isótopo más pesado, específicamente deuterio, será definida por el factor de enriquecimiento isotópico. El término "factor de enriquecimiento isotópico" como se utiliza en la presente se refiere a la relación entre la abundancia isotópica y la abundancia natural de un isótopo específico. Si un sustituyente en un compuesto de este invento se denota deuterio, tal compuesto tiene un factor de enriquecimiento isotópico para cada átomo de deuterio designado de al menos 3500 (52.5% de incorporación de deuterio en cada átomo de deuterio designado), al menos 4000 (60% de incorporación de deuterio), al menos 4500 (67.5% de incorporación de deuterio), al menos 5000 (75% de incorporación de deuterio), al menos 5500 (82.5% de incorporación de deuterio), al menos 6000 (90% de incorporación de deuterio), al menos 6333.3 (95% de incorporación de deuterio), al menos 6466.7 (97% de incorporación de

deuterio), al menos 6600 (99% de incorporación de deuterio), o al menos 6633.3 (99.5% de incorporación de deuterio).

Realizaciones Representativas

Varias realizaciones de la invención se describen en la presente. Se reconocerá que las características especificadas en cada realización pueden combinarse con otras características especificadas para proporcionar realizaciones adicionales.

Una realización de la presente invención es un compuesto según la fórmula (I) en donde:

cada R^1 y R^2 es independientemente hidrógeno, deuterio, halo, hidroxilo, NH_2, arilo, heteroarilo, o alquilo C_{1-4} opcionalmente sustituido,

en donde dicho alquilo C_{1-4} es opcionalmente sustituido por uno a tres sustituyentes seleccionados cada uno independientemente a partir del grupo que consta de: halo, hidroxilo, y NH_2;

R^{3a} es hidrógeno, deuterio, alquiloC_{1-6}, fenilo, o bencilo y

R^{3b} es hidrógeno, deuterio, o C_{1-6} alquilo; o

R^{3a} y R^{3b} se unen juntos formando un anillo de cicloalquilo de 3-7 miembros opcionalmente sustituido o un anillo heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dichos anillos cicloalquilo y heterocíclicos son opcionalmente sustituidos por uno o dos sustituyentes cada uno independientemente seleccionados a partir del grupo que consta de: halo, hidroxilo, oxo, NH_2, y C_{1-3} alquilo;

R^{4a} es hidrógeno, alquilo C_{1-6}, fenil opcionalmente sustituido, bencilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o metileno-dibenceno,

en donde dicho fenilo, bencilo, y anillos de heteroarilo son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3} , haloalcoxiloC_{1-3}, alquilo C_{1-6} , cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros fenoxilo, $COOR^b$, SO_2R^b, $NHC(O)R^b$, y NR^bR^b y

R^{4b} es hidrógeno, deuterio, o alquilo C_{1-3}; o

R^{4a} y R^{4b} se unen juntos formando un anillo cicloalquilo de 3-7 miembros opcionalmente sustituido o un anillo heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dichos anillos cicloalquilo y heterocíclicos son opcionalmente sustituidos por uno o dos sustituyentes cada uno independientemente seleccionados a partir del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3};

Siempre y cuando solamente uno de R^{3a} y R^{3b} y R^{4a} y R^{4b} estén unidos juntos formando un anillo;

R^{5a} es hidrógeno o deuterio;

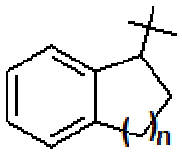
R^{5b} es hidrógeno, deuterio, metilo, etilo, CD_3, CF_3, CH_2F, o CHF_2 y

R^6 es alquilo C_{1-6} opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heterocíclico opcionalmente sustituido, o cicloalquilo C_{5-10} opcionalmente sustituido,

en donde dicho alquilo C_{1-6} es opcionalmente sustituido por un sustituyente seleccionado a partir del grupo que consta de hidroxilo, alcoxilo C_{1-3} y $–OR^a$;

en donde dicho arilo, heteroarilo, heterocíclico y cicloalquilo C_{5-10} son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo; hidroxilo; ciano; nitro; alcoxilo C_{1-3}; haloalquilo C_{1-3}; haloalcoxilo C_{1-3}; alquilo C_{1-6}; cicloalquilo C_{3-6}; fenil opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, fenoxilo, $COOR^b$, SO_2R^b, $NHC(O)R^b$, y NR^bR^b; heteroarilo de 5-6 miembros; heterocíclico de 5-6 miembros opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que

consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3}; $-CH_2R^a$; $-OR^a$; $-C(O)R^a$; $-NR^aR^b$; $-COOR^a$; $-SO_2R^a$; $NHC(O)R^a$; y $-SO_2NR^bR^b$; o

R^{5b} y R^6 se unen juntos formando un grupo cicloalquilo C_{3-7} opcionalmente sustituido o un grupo opcionalmente sustituido de la Fórmula (a):  (a),

en donde n es 1, 2, o 3 y

dicho cicloalquilo C_{3-7} y grupo de la Fórmula (a) son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionados a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, benciloxilo, $COOR^b$, SO_2R^b, $NHC(O)R^b$, y NR^bR^b;

cada R^a es independientemente fenilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dicho fenilo y heteroarilo son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, y alquilo C_{1-3},

en donde dicho heterocíclico de 4-7 miembros es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de halo, hidroxilo, oxo, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, y alquilo C_{1-3}; y

cada R^b es independientemente hidrógeno o alquilo C_{1-6}.

En otra realización de la presente invención R^1 es hidrógeno, halo, o alquilo C_{1-4} opcionalmente sustituido. De manera adecuada R^1 es hidrógeno, flúor, cloro, o metilo. En otra realización R^1 es hidrógeno, flúor o cloro. De manera adecuada R^1 es hidrógeno.

En otra realización de la presente invención R^2 es hidrógeno, halo o alquilo C_{1-4} opcionalmente sustituido. De manera adecuada R^2 es hidrógeno, flúor, cloro, o metilo. En otra realización R^2 es hidrógeno o fluoro. En otra realización de la presente invención R^2 es hidrógeno.

En otra realización de la presente invención R^1 y R^2 son ambos hidrógeno.

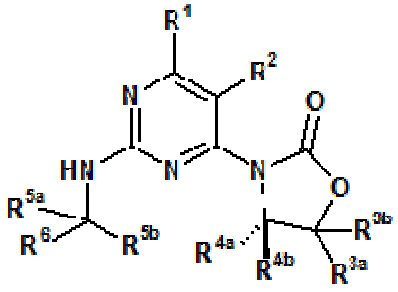
En otra realización de la presente invención R^{3a} es hidrógeno, alquilo C_{1-6}, o fenilo. Apropidamente R^{3a} es hidrógeno, metilo, o fenilo. De manera adecuada R^{3a} es hidrógeno o metilo. De manera adecuada R^{3a} es hidrógeno.

En otra realización de la presente invención R^{3b} es hidrógeno o metilo. De manera adecuada R^{3b} es hidrógeno.

En otra realización R^{3a} y R^{3b} son ambos hidrógeno.

En otra realización de la presente invención R^{3a} y R^{3b} se unen juntos formando oxetanilo o tetrahidro-2H-piranilo.

Otra realización de la presente invención es un compuesto según la Fórmula (II).



(II)

En otra realización de la presente invención R^{4a} es hidrógeno, alquilo C_{1-6}, fenilo opcionalmente sustituido, bencilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o metileno-dibenceno,

en donde dicho fenilo, bencilo, y anillos de heteroarilo son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, fenoxilo, □$COOR^b$, $-SO_2R^b$,- $NHC(O)R^b$, y- NR^bR^b .

En otra realización de la presente invención R^{4a} es hidrógeno, alquilo C_{1-4}, fenilo opcionalmente sustituido, bencilo opcionalmente sustituido, heteroarilo opcionalmente

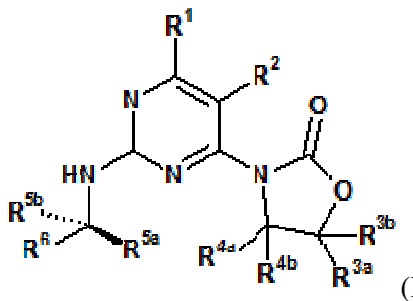
sustituido, o metileno-dibenceno. De manera adecuada R^{4a} es hidrógeno, alquilo C_{1-4}, fenilo opcionalmente sustituido, bencilo opcionalmente sustituido, piridinilo opcionalmente sustituido, o metileno-dibenceno. De manera más adecuada R^{4a} es hidrógeno, metilo, isopropilo, isobutilo, t-butilo, fenilo, 4-metoxifenilo, 4-fluorofenilo, bencilo, o metileno-dibenceno. En otra realización R^{4a} es hidrógeno, metilo, etilo, isopropilo, fenilo, 4-fluorofenilo, 4-metoxifenilo, bifenilo, bencilo, o piridinilo. De manera adecuada R^{4a} es isopropilo.

En otra realización de la presente invención R^{4b} es hidrógeno o metilo. De manera adecuada R^{4b} es hidrógeno.

En otra realización R^{4a} es isopropilo y R^{4b} es metilo. En otra realización R^{4a} es isopropilo y R^{4b} es hidrógeno.

En otra realización de la presente invención R^{4a} y R^{4b} se unen juntos formando ciclopentilo.

Otra realización de la presente invención es un compuesto según la Fórmula (III).



(III)

En otra realización de la presente invención R^{5a} es hidrógeno. En otra realización R^{5a} es deuterio.

En otra realización de la presente invención R^{5b} es hidrógeno, metilo, etilo, o CF_3. De manera adecuada R^{5b} es metilo.

En otra realización de la presente invención R^6 es isopropilo, arilo opcionalmente sustituido, pirazolilo opcionalmente sustituido, piridinilo opcionalmente sustituido, 2,3-dihidrobenzofuranilo, 2,3-dihidrobenzo[b][1,4]dioxinilo, o cicloalquilo C_{5-10} opcionalmente sustituido. De manera adecuada R^6 es isopropilo, fenilo opcionalmente sustituido, naftilo opcionalmente sustituido, pirazolilo, piridinilo, 2,3-dihidrobenzofuranilo, 2,3-dihidrobenzo[b][1,4]dioxinilo, o cicloalquilo C_{5-10}, en donde

dicho fenilo y naftilo son cada uno opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: flúor, cloro, bromo, hidroxilo, ciano, metoxilo, trifluorometilo, metilo, t-butilo, fenilo, pirrolilo, piperidinilo, 4-metilpiperazinilo, morfolinilo, fenoxilo, y $-SO_2NH_2$.

En otra realización de la presente invención R^6 es heteroarilo opcionalmente sustituido, heterocíclico opcionalmente sustituido o cicloalquilo C_{5-10} opcionalmente sustituido.

En otra realización de la presente invención R^6 es metilo, cicloalquilo C_{5-10}, fenilo opcionalmente sustituido, piridinilo opcionalmente sustituido, pirimidinilo opcionalmente sustituido, piridazinilo opcionalmente sustituido, pirazinilo opcionalmente sustituido, triazolilo opcionalmente sustituido, pirazolilo opcionalmente sustituido, tiazolilo opcionalmente sustituido, 1,3,4-oxadiazolilo opcionalmente sustituido, 1,2,4-oxadiazolilo opcionalmente sustituido, isoxazolilo opcionalmente sustituido, tienilo, oxazolilo, quinolinilo, bencimidazolilo opcionalmente sustituido, benztiazolilo, benzoxazolilo, tetrazolo[1,5-a]piridinilo, imidazo[2,1-b][1,3,4]tiadiazolilo, piperidinilo opcionalmente sustituido, piperazinilo opcionalmente sustituido, tetrahidrofuranilo, tetrahidropiranilo, tetrahidro-tiopiran1,1-dióxido opcionalmente sustituido, 1H-pirrolo[2,3-b]piridinilo, 2,3-dihidro-benzo[1,4]dioxinilo, 5,6,7,8-tetrahidro-[1,2,4]trazolo[4,3-a]pirazinilo, 4,5,6,7-tetrahidro-benzotiazolilo, o indolizinilo, en donde dicho fenilo, piridinilo, pirimidinilo, piridazinilo, pirazinilo, triazolilo, pirazolil, tiazolilo, 1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, isoxazolilo, bencimidazolilo, piperidinilo, piperazinil, y tetrahidro-tiopiran1,1-dióxido son cada uno opcionalmente sustituidos por uno o dos sustituyentes como se define en la Fórmula (I). De manera adecuada R^6 es fenilo opcionalmente sustituido por uno o dos sustituyentes. De manera adecuada R^6 es 1,3,4-oxadiazolilo opcionalmente sustituido o 1,2,4-oxadiazolilo opcionalmente sustituido. De manera adecuada R^6 es pirimidinilo opcionalmente sustituido por un sustituyente.

En otra realización R^6 es opcionalmente sustituido por uno o dos sustituyentes cada uno independientemente seleccionados a partir del grupo que consta de: halo; hidroxilo; nitro; alcoxilo C_{1-4}; haloalquilo C_{1-3}; haloalcoxilo C_{1-3}; alquilo C_{1-6}; cicloalquilo C_{3-6} opcionalmente sustituido por un sustituyente seleccionado a partir del grupo que consta de: ciano, alquilo C_{1-3}, y alcoxilo C_{1-3}; fenilo opcionalmente sustituido

por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: flúor, cloro, metilo, ciano, y metoxilo; y heteroarilo de 5-6 miembros (por ejemplo, imidazolilo, pirazolilo, trazolilo, y piridinilo) opcionalmente sustituido por uno o dos grupos metilo.

En otra realización R^6 es sustituido con un grupo $-CH_2R^a$, $-C(O)R^a$, $-NHC(O)R^a$, $-NHC(O)R^b$, $-C(O)NHR^a$, $-C(O)NHR^b$, $-OR^a$, $-NR^aR^b$, $-SO_2NR^bR^b$, $-SO_2R^a$, o $-SO_2R^b$. De manera adecuada R^6 es sustituido por un grupo $-CH_2R^a$, $-C(O)R^a$, o $-OR^a$.

En otra realización R^6 es fenilo sustituido por un flúor o grupo de cloro y un grupo $-CH_2R^a$, $-C(O)R^a$, o $-C(O)NHR^a$ en donde el grupo $-CH_2R^a$, $-C(O)R^a$, o $-C(O)NHR^a$ en la posición para del anillo de fenilo. De manera adecuada R^6 es fenilo sustituido por un grupo flúor y un grupo $-CH_2R^a$, $-C(O)R^a$, o $-C(O)NHR^a$ en donde el grupo $-CH_2R^a$, $-C(O)R^a$, o $-C(O)NHR^a$ en la posición para del anillo de fenilo. En otra realización R^6 es fenilo sustituido por un grupo $-CH_2R^a$, $-C(O)R^a$, o $-C(O)NHR^a$ en la posición para. En otra realización R^6 es fenilo sustituido por $-CH_2R^a$ en la posición para.

En otra realización R^a es fenilo opcionalmente sustituido por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de flúor, cloro y bromo.

En otra realización R^a es un heteroarilo de 5-6 miembros opcionalmente sustituido. De manera adecuada R^a es piridinilo opcionalmente sustituido o pirimidinilo opcionalmente sustituido. De manera adecuada R^a es piridinilo o pirimidinilo opcionalmente sustituido por un trifluorometilo.

En otra realización R^a es cicloalquilo C_{5-7} cada uno de los cuales es opcionalmente sustituido por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de flúor, hidroxilo, metilo, y haloalcoxilo C_{1-3}.

En otra realización R^a es heterocíclico opcionalmente sustituido. De manera adecuada R^a es piperidinilo, piperazinil, morfolinilo, tetrahidropiranilo, tetrahidro-tiopiran1,1-dióxido, 1,4-diazepanilo, 4,7-diaza-spiro[2.5]octanili, 3,8-diaza-biciclo[3.2.1]octanil, 3,8-diaza-biciclo[4.2.0]octanilo, octahidro-pirrolo[1,2-a]pirazinilo, octahidro-pirido[1,2-a]pirazinilo, octahidro-pirrolo[3,4-c]pirrolilo, y 5,6,7,8-tetrahidro-

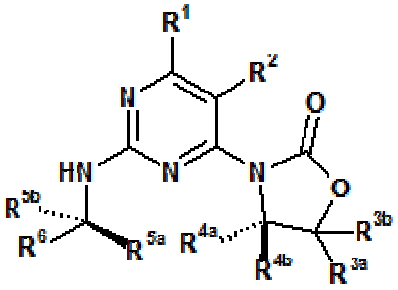
imidazo[1,2-a]pirazinilo cada uno de los cuales es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: hidroxilo, flúor, amino, dimetilamino, haloalcoxilo C_{1-3}, alquilo C_{1-3}, y cicloalquilo C_{3-5}. De manera adecuada R^a es piperidinilo, piperazinilo, o morfolinilo cada uno de los cuales es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: hidroxilo, flúor, amino, dimetilamino, haloalcoxilo C_{1-3}, alquilo C_{1-3}, y cicloalquilo C_{3-5}.

En otra realización de la presente invención R^{5b} y R^6 se unen juntos formando un grupo cicloalquilo C_{3-7} opcionalmente sustituido o un grupo opcionalmente sustituido de la Fórmula (a).

En otra realización de la presente invención cada R^b es independientemente hidrógeno o metilo.

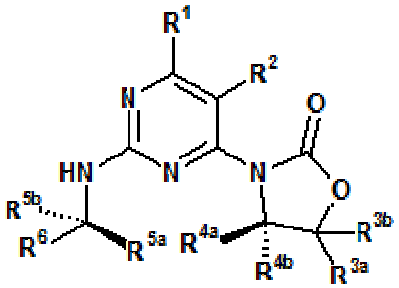
En otra realización R^1 es hidrógeno, R^2 es fluoro y R^{3a}, R^{3b}, R^{4a} y R^{4b} son cada uno hidrógeno.

Otra realización de la presente invención es un compuesto según la Fórmula (IV).



(IV)

Otra realización de la presente invención es un compuesto según la Fórmula (V):



(V), en donde R^{4a} es fenil y R^{4b} es hidrógeno.

Compuestos seleccionados de la presente invención incluyen:

(S)-4-isopropi-3-(2-(((S)-1-(4-(2-il)fenil)etil)amino)pirimidin-4-il)oxazolidin-2-ona;

N-(4-((S)-1-(4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)fenil)ciclohexanocarboxamida;

(S)-3-(2-(((S)-1-(3-fluoro-4-((4-metilpiperazin-1-il)metil)fenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-4-isopropil-3-(2-(((S)-1-(4-((3,3,4-trimetilpiperazin-1-il)metil)fenil)etil)amino)pirimidin-4-il)oxazolidin-2-ona;

2-fluoro-N-(4-hidroxi-4-metilciclohexil)-4-((S)-1-((4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-il)amino)etil)benzamida;

(S)-3-(2-((S)-1-(4-((4-amino-4-metilpiperidin-1-il)metil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(2-((S)-1-(4-((4-(dimetilamino)piperidin-1-il)metil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-4-isopropil-3-(2-((S)-1-(4-((4-metilpiperazin-1-il)metil)fenil)etilamino)pirimidin-4-il)oxazolidin-2-ona;

(S)-4-isopropil-4-metil-3-(2-((S)-1-(4-((4-metilpiperazin-1-il)metil)fenil)etilamino)pirimidin-4-il)oxazolidin-2-ona;

(S)-4-isopropil-3-(2-((S)-1-(6-fenilpiridin-3-il)etilamino)pirimidin-4-il)oxazolidin-2-ona;

(S)-3-(2-((S)-1-(4-benzoilfenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-4-isopropil-3-(2-(((S)-1-(5-fenil-1,3,4-tiadiazol-2-il)etil) amino) pirimidin-4-il)oxazolidin-2-ona;

(4S)-4-isopropil-3-(2-(1-(5-fenilpirimidin-2-il)etilamino)pirimidin-4-il)oxazolidin-2-ona;

3-(5-fluoro-2-((1-(5-(4-fluoro-3-metilfenil)piridin-2-il)etil)amino)pirimidin-4-il)oxazolidin-2-ona;

(S)-4-isopropil-3-(2-(((S)-1-(1-(3-metoxifenil)-1H-pirazol-4-il)etil)amino)pirimidin-4-il)oxazolidin-2-ona;

(S)-3-(2-(((S)-1-(5-(4-fluorofenil)-1,3,4-oxadiazol-2-il)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(2-(((S)-1-(3-(4-clorofenil)-1,2,4-oxadiazol-5-il)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-4-isopropil-3-(2-(((S)-1-(3-(m-tolil)-1,2,4-oxadiazol-5-il)etil)amino)pirimidin-4-il)oxazolidin-2-ona;

(S)-3-(2-(((S)-1-(3-(4-fluorofenil)-1,2,4-oxadiazol-5-il)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(2-((S)-1-(5-(4-fluoro-2-metilfenil)pirimidin-2-il)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-4-Isopropil-3-{2-[(3-p-tolil-[1,2,4]oxadiazol-5-ilmetil)-amino]-pirimidin-4-il}-oxazolidin-2-ona;

(S)-4-isopropil-3-(2-((S)-1-(4-(1-metil-1H-pirazol-4-il)fenil)etilamino)pirimidin-4-il)oxazolidin-2-ona;

(S)-3-(2-((S)-1-(2-fluoro-4-isopropilfenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(2-((S)-1-(4-isobutoxi-3-metilfenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(2-(((S)-1-(4-isobutoxifenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(5-fluoro-2-(((S)-1-(4-isobutoxifenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

2-fluoro-N-(*trans*-4-hidroxiciclohexil)-4-((S)-1-(4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)benzamida;

(S)-3-(5-fluoro-2-((S)-1-(3-fluoro-4-(piperidina-1-carbonil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

N-ciclohexil-2-fluoro-4-((S)-1-(5-fluoro-4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)benzamida;

N-ciclohexil-2-fluoro-4-((S)-1-(4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)benzamida; y

(S)-3-(5-fluoro-2-((S)-1-(2-fluoro-4-(trifluorometil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona.

Compuestos seleccionados de la presente invención incluyen:

(S)-3-(2-(((S)-1-(3-fluoro-4-((3,3,4-trimetilpiperazin-1-il)metil)fenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(2-(((S)-1-(4-((4,4-difluoropiperidin-1-il)metil)fenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(5-fluoro-2-(1-(4-fenoxifenil)etilamino)pirimidin-4-il)oxazolidin-2-ona;

(S)-3-(2-((S)-1-(4-(4-fluorofenoxi)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(2-((S)-1-(4-(((2S,6R)-2,6-dimetilmorfolino)metil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(2-(((S)-1-(3-(4-clorofenil)-1,2,4-oxadiazol-5-il)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-(((S)-1-(5-(4-clorofenil)-1,2,4-oxadiazol-3-il)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(5-(4-fluoro-3-metilfenil)piridin-2-il)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(5-(4-fluorofenoxi)pirimidin-2-il)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(5-(4-fluorofenoxi)pirazin-2-il)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-4-isopropil-3-(2-((S)-1-(5-(3-(trifluorometil)fenil)pirimidin-2-il)etilamino)pirimidin-4-il)oxazolidin-2-ona; y
(S)-3-(2-((S)-1-(5-(4-fluoro-3-metilfenil)pirimidin-2-il)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona.

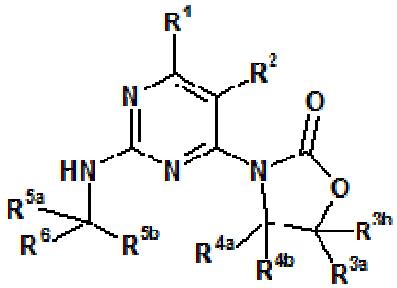
Compuestos seleccionados de la presente invención incluyen:
(S)-3-(2-(1-(3-(4-clorofenil)-1,2,4-oxadiazol-5-il)etilamino)-5-fluoropirimidin-4-il)-4,4-dimetiloxazolidin-2-ona;
(S)-3-(6-cloro-2-(1-(3-(4-clorofenil)-1,2,4-oxadiazol-5-il)etilamino)pirimidin-4-il)oxazolidin-2-ona;
(S)-3-(2-((S)-1-(2-fluoro-4-(1-metilciclopropil) fenil) etilamino) pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(2-fluoro -4-(trifluorometil) fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
2-cloro-N-ciclopentil-4-((S)-1-(4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)benzamida;
(S)-3-(2-((S)-1-(4-((3,3-difluoropiperidin-1-il)metil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(4-(4,7-diazaspiro[2.5]octan-4-ilmetil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(4-((4-acetilpiperazin-1-il)metil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-(((S)-1-(4-isobutoxifenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(5-fluoro-2-(((S)-1-(4-isobutoxifenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona; y

2-fluoro-N-(trans-4-hidroxiciclohexil)-4-((S)-1-(4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)benzamida.

Realizaciones Enumeradas

Realización 1. Un compuesto de la Fórmula (I)



(I)

en donde:

cada R^1 y R^2 es independientemente hidrógeno, deuterio, halo, hidroxilo, NH_2, arilo, heteroarilo, o alquilo C_{1-4} opcionalmente sustituido,

en donde dicho alquilo C_{1-4} es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, y NH_2;

R^{3a} es hidrógeno, deuterio, alquilo C_{1-6} , fenilo, o bencilo y

R^{3b} es hidrógeno, deuterio, o alquilo C_{1-6}; o

R^{3a} y R^{3b} se unen juntos formando un anillo cicloalquilo de 3-7 miembros opcionalmente sustituido o un anillo heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dichos anillos cicloalquilo y heterocíclico son cada uno opcionalmente sustituidos por uno o dos sustituyentes cada uno independientemente seleccionados a partir del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3};

R^{4a} es hidrógeno, alquilo C_{1-6}, fenilo opcionalmente sustituido, bencilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o metileno-dibenceno,

en donde dicho fenilo, bencilo, y anillos de heteroarilo son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionados a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, fenoxilo, $COOR^b$, SO_2R^b, $NHC(O)R^b$, y NR^bR^b y

R^{4b} es hidrógeno, deuterio, o alquilo C_{1-3}; o

R^{4a} y R^{4b} se unen juntos formando un anillo cicloalquilo de 3-7 miembros opcionalmente sustituido o un anillo heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dichos anillos cicloalquilo y heterocíclico son opcionalmente sustituidos por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3},

siempre que solo uno entre R^{3a} y R^{3b} y R^{4a} y R^{4b} se unan juntos formando un anillo;

R^{5a} es hidrógeno o deuterio;

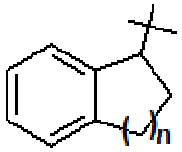
R^{5b} es hidrógeno, deuterio, metilo, etilo, CD_3, CF_3, CH_2F, o CHF_2 y

R^6 es opcionalmente sustituido alquilo C_{1-6}, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heterocíclico opcionalmente sustituido, o cicloalquilo C_{5-10} opcionalmente sustituido,

en donde dicho alquilo C_{1-6} es opcionalmente sustituido por un sustituyente seleccionado a partir del grupo que consta de hidroxilo, alcoxilo C_{1-3} y $–OR^a$;

en donde dicho arilo, heteroarilo, heterocíclico y cicloalquilo C_{5-10} son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo; hidroxilo; ciano; nitro; alcoxilo C_{1-3}; haloalquilo C_{1-3}; haloalcoxilo C_{1-3}; alquilo C_{1-6}; cicloalquilo C_{3-6}; fenilo opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6

miembros, heterocíclico de 5-6 miembros, fenoxilo, $COOR^b$, SO_2R^b, $NHC(O)R^b$, y NR^bR^b; heteroarilo de 5-6 miembros; heterocíclico de 5-6 miembros opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, oxo, NH_2, y C_{1-3} alquilo; $-CH_2R^a$; $-OR^a$; $-C(O)R^a$; $-NR^aR^b$; $-COOR^a$; SO_2R^a; $NHC(O)R^a$; y $-SO_2NR^bR^b$; o

R^{5b} y R^6 se unen juntos formando un grupo cicloalquilo C_{3-7} opcionalmente sustituido o un grupo opcionalmente sustituido de la Fórmula (a):  (a),

en donde n es 1, 2, o 3 y

dicho cicloalquilo C_{3-7} y grupo de la Fórmula (a) son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, benciloxilo, $COOR^b$, SO_2R^b, $NHC(O)R^b$, y NR^bR^b;

cada R^a es independientemente fenilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dicho fenilo y heteroarilo son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, y alquilo C_{1-3},

en donde dicho heterocíclico de 4-7 miembros es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de halo, hidroxilo, oxo, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, y alquilo C_{1-3}; y

cada R^b es independientemente hidrógeno o alquilo C_{1-6}; o una sal farmacéuticamente aceptable del mismo.

Realización 2. El compuesto según la realización 1 en donde R^2 es hidrógeno; o una sal farmacéuticamente aceptable del mismo.

Realización 3. El compuesto según la realización 2 en donde R^1 es hidrógeno, halo, o alquilo C_{1-4} opcionalmente sustituido; o una sal farmacéuticamente aceptable del mismo.

Realización 4. El compuesto según la realización 3 en donde R^1 es hidrógeno, flúor, cloro, o metilo; o una sal farmacéuticamente aceptable del mismo.

Realización 5. El compuesto según la realización 4 en donde R^{3a} es hidrógeno, C_{1-6} alquilo, fenilo, o bencilo y R^{3b} es hidrógeno o C_{1-6} alquilo; o una sal farmacéuticamente aceptable del mismo.

Realización 6. El compuesto según la realización 5 en donde R^{3b} es hidrógeno o metilo; o una sal farmacéuticamente aceptable del mismo.

Realización 7. El compuesto según la realización 6 en donde R^{3a} es hidrógeno, metilo, o fenilo; o una sal farmacéuticamente aceptable del mismo.

Realización 8. El compuesto según la realización 7 en donde R^{4a} es hidrógeno, alquilo C_{1-6}, fenilo opcionalmente sustituido, bencilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o metileno-dibenceno,

en donde dicho fenilo, bencilo, y anillos de heteroarilo son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, fenoxilo, $COOR^b$, SO_2R^b, $NHC(O)R^b$, y NR^bR^b y R^{4b} es hidrógeno o alquilo C_{1-3}; o una sal farmacéuticamente aceptable del mismo.

Realización 9. El compuesto según la realización 8 en donde R^{4b} es hidrógeno o metilo; o una sal farmacéuticamente aceptable del mismo.

Realización 10. El compuesto según la realización 9 en donde R^{4a} es hidrógeno, alquilo C_{1-4}, fenilo opcionalmente sustituido, bencilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o metileno-dibenceno; o una sal farmacéuticamente aceptable del mismo.

Realización 11. El compuesto según la realización 10 en donde R^{4a} es hidrógeno, metilo, isopropilo, isobutilo, t-butilo, fenilo, 4-metoxifenilo, 4-fluorofenilo, bencilo, o metileno-dibenceno; o una sal farmacéuticamente aceptable del mismo.

Realización 12. El compuesto según la realización 11 en donde R^{5a} es H; o una sal farmacéuticamente aceptable del mismo.

Realización 13. El compuesto según la realización 12 en donde R^{5b} es hidrógeno, metilo, etilo, o CF_3.

Realización 14. El compuesto según la realización 13 en donde R^6 es isopropilo, arilo opcionalmente sustituido, pirazolilo opcionalmente sustituido, piridinilo opcionalmente sustituido, 2,3-dihidrobenzofuranil, 2,3-dihidrobenzo[b][1,4]dioxinilo, o cicloalquilo C_{5-10} opcionalmente sustituido; o una sal farmacéuticamente aceptable del mismo.

Realización 15. Una composición farmacéutica que comprende un compuesto según la realización 1, o una sal farmacéuticamente aceptable del mismo y un vehículo o excipiente farmacéuticamente aceptable.

Realización 16. Un método para el tratamiento de una enfermedad o trastorno asociado con una proteína IDH mutante que tiene una actividad neomorfica que comprende la administración de una cantidad terapéuticamente eficaz de un compuesto según la

realización 1, o una sal farmacéuticamente aceptable del mismo, a un sujeto en necesidad de tratamiento de la misma.

Realización 17. Un método para el tratamiento de una enfermedad o trastorno asociado con una proteína IDH mutante que tiene una actividad neomorfica que comprende la administración de una cantidad terapéuticamente eficaz de un compuesto según la realización 1, o una sal farmacéuticamente aceptable del mismo, y otro agente terapéutico a un sujeto en necesidad del mismo.

Procedimientos Sintéticos Generales

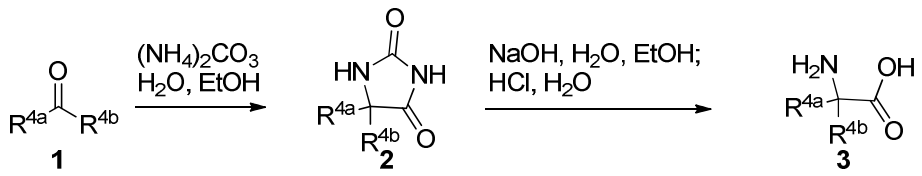
Los compuestos de la presente invención pueden prepararse mediante una variedad de métodos incluyendo la química estándar. Rutas sintéticas apropiadas se ilustran en los Esquemas dados a continuación.

Los compuestos de la fórmula (I) pueden prepararse mediante métodos conocidos en el estado de la técnica de síntesis orgánica como se expone en parte por los siguientes esquemas sintéticos. En los esquemas descritos a continuación, se entiende bien que los grupos protectores para grupos sensibles o reactivos son empleados donde sea necesario según principios o química general. Los grupos protectores son manipulados según métodos estándar de síntesis orgánica (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Tercera Edición, Wiley, New York 1999). Estos grupos son retirados en una etapa conveniente de la síntesis del compuesto utilizando métodos que son fácilmente evidentes para los expertos en la técnica. Los procesos de selección, así como las condiciones de reacción y el orden de su ejecución, serán consistentes con la preparación de los compuestos de la fórmula (I).

Los expertos en la técnica reconocerán si existe un estereocentro en los compuestos de la fórmula (I). Por consiguiente, la presente invención incluye ambos estereoisómeros posibles e incluye no solo los compuestos racémicos sino los enantiomeros individuales y/o diastereomeros también. Cuando se desea un compuesto como un único enantiomero o diastereomero, éste se puede obtener mediante síntesis estereoespecífica o por resolución del producto final o cualquier intermedio conveniente. La resolución del producto final, un intermedio, ó un material de inicio puede realizarse mediante cualquier método adecuado conocido en el estado de la técnica. Ver, por ejemplo, “Stereochemistry of Organic Compounds” de E. L. Eliel, S. H. Wilen, y L. N. Mander (Wiley-Interscience, 1994).

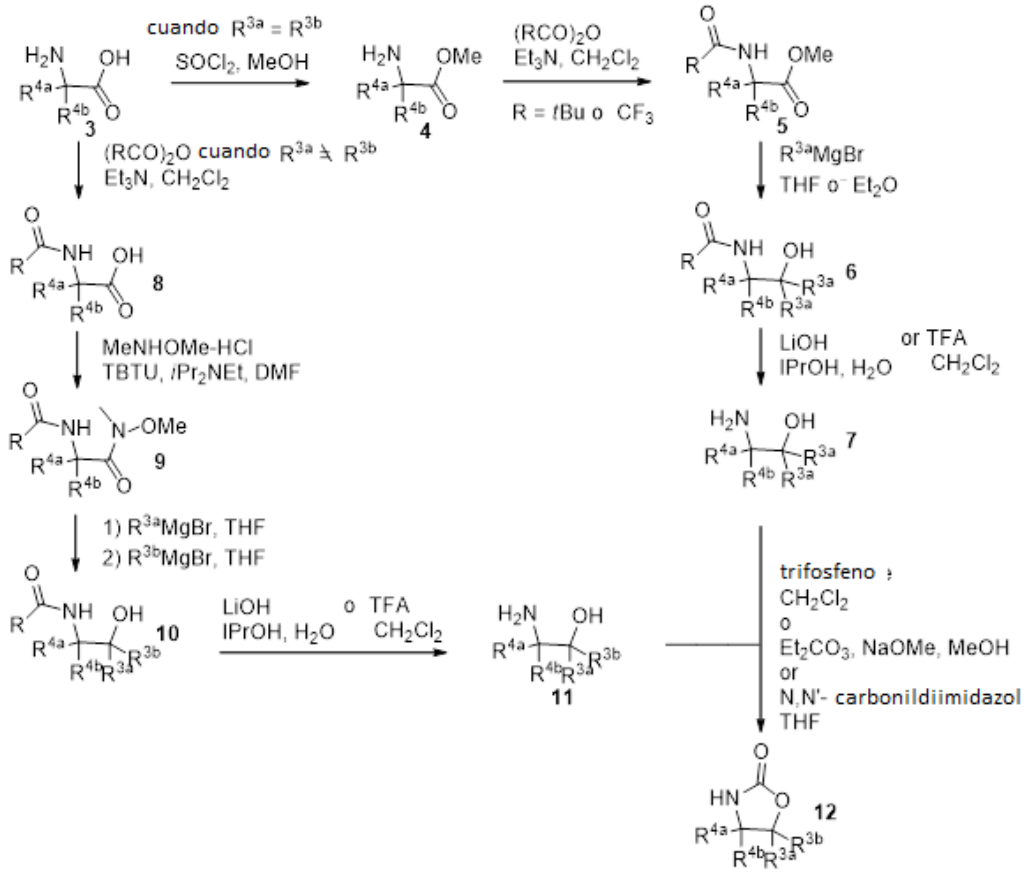
Los compuestos descritos en la presente pueden prepararse a partir de materiales de inicio comercialmente disponibles o pueden sintetizarse utilizando procesos orgánicos, inorgánicos y/o enzimáticos conocidos.

Esquema 1



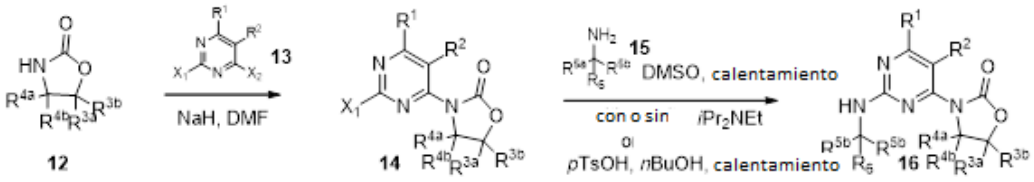
Los aminoácidos no comerciales pueden prepararse siguiendo los procedimientos del Esquema 1. La conversión de la cetona 1 a la correspondiente imidazolidina-2,4-diona 2 seguida por hidrólisis proporciona el aminoácido 3.

Esquema 2



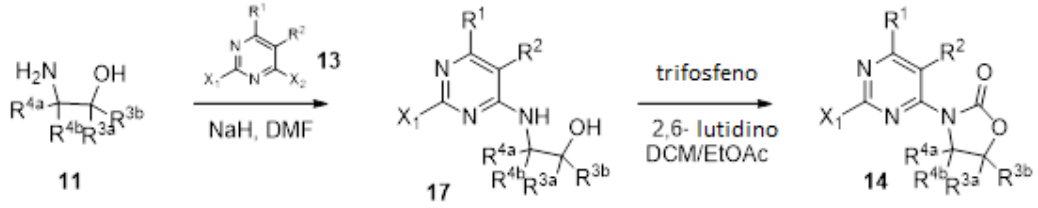
Cuando un aminoalcohol, precursor de oxazolidinona, no está disponible comercialmente, se puede preparar a partir del aminoácido 3 siguiendo los procedimientos del Esquema 2. Cuando R3a = R3b, el aminoéster protegido 5 se trata con un reactivo de Grignard apropiado para proporcionar el aminoalcohol protegido 6 que pasa a través del paso de desprotección alcalina o ácida. Cuando $R^3 \neq R^4$, aminoácido protegido 8 se convierte en la amida Weinreb 9 que se trata con diferentes reactivos de Grignard secuencialmente para proporcionar el aminoalcohol 10 protegido. Cualquiera entre desprotección alcalina o ácida de 10 da 11. La inserción de la unidad de CO en 7 o 11 para proporcionar oxazolidinona 12 se lleva a cabo con varios reactivos, incluyendo (pero no limitado a) trifosgeno, Et2CO3 o N-N'-darbonildiimidazol, como se muestra en el Esquema 2.

Esquema 3



La oxazolidinona 12 se acopla con dihalogen-pirimidina 13 en presencia de NaH y el 14 resultante se trata con la amina primaria 15 bajo diferentes condiciones de reacción como se muestra en el Esquema 3 para proporcionar 16.

Esquema 4



Alternativamente el intermedio 14 se puede preparar por acoplamiento del amino alcohol 11 y dihalógeno-pirimidina 13 en presencia de una base tal como diisopropiletilamina resultante en el compuesto intermedio 17 que se puede tratar con trifosgeno en presencia de una base tal como 2,6-lutidina resultante en el compuesto intermedio 14.

Métodos de Uso

Los compuestos de la presente invención son inhibidores de una proteína IDH mutante que tiene actividad neomórfica y por lo tanto son útiles en el tratamiento de enfermedades o trastornos asociados con tales proteínas incluyendo, pero sin limitar a, trastornos de proliferación celular, tales como cáncer.

Ejemplos de una proteína IDH mutante que tiene una actividad neomórfica son IDH1 mutante y IDH2 mutante. Una actividad neomórfica asociada con el IDH1 mutante y IDH2 mutante es la capacidad para producir 2-hidroxiglutarato (actividad neomórfica 2-HG), específicamente R-2-HG (actividad neomórfica R-2-HG). Las mutaciones en IDH1 asociados con la actividad neomórfica 2-HG, específicamente actividad neomórfica R-2-HG, incluyen las mutaciones en los residuos 97, 100 y 132, por ejemplo, G97D, R100Q,

R132H, R132C, R132S, R132G, R132L, y R132V. Las mutaciones en IDH2 asociadas con neoactividad 2-HG, específicamente actividad neomórfica R-2-HG, incluyen las mutaciones en los residuos 140 y 172, por ejemplo, R140Q, R140G, R172K, R172M, R172S, R172G, y R172W.

Los trastornos de proliferación celular asociados con una proteína IDH mutante que tiene una actividad neomórfica IDH incluyen, pero no se limitan a, cáncer. Ejemplos de tales cánceres incluyen Leucemia Linfoblástica Aguda, Adulto, leucemia linfoblástica aguda, Infantil, leucemia mieloide aguda, Adulto, Carcinoma de la corteza suprarrenal, carcinoma de la corteza suprarrenal, Infantil,; linfoma relacionado con el SIDA, neoplasias relacionadas con SIDA, Cáncer Anal; Astrocitoma, Cerebeloso Infantil; Astrocitoma, Cerebral Infantil; Cáncer del Conducto Biliar, Extrahepático; Cáncer de Vejiga, Cáncer de Vejiga, Infantil, Cáncer Óseo, Osteosarcoma/Histiocitoma Fibroso Maligno; Glioma del Tallo Encefálico, Infantil, Tumor Cerebral, Adulto, Tumor Cerebral, Glioma del Tallo Encefálico, Infantil, Tumor Cerebral, Astrocitoma Cerebeloso, Infantil; Tumor Cerebral, Astrocitoma Cerebral/Glioma Maligno, Infantil, Tumor Cerebral, Ependimoma, Infantil, Tumor Cerebral, Meduloblastoma, Infantil, Tumor Cerebral, Tumores Neuroectodérmicos Primitivos Supratentoriales, Infantil, Tumor Cerebral, Glioma de Vias Optícas e Hipotalámico, Infantil, Tumor Cerebral, Infantil (Otros); Cáncer de Mama, Cáncer de Mama y Embarazo, Cáncer de Mama, Infantil, Cáncer de mama, Masculino; Adenomas Bronquiales/Carcinoides, Infantil, Tumor Carcinoide, Infantil, Tumor Carcinoide, Gastrointestinal, Carcinoma, de la Corteza Suprarrenal; Carcinoma de Células Islote; Carcinoma de Origen Primario Desconocido; Linfoma del Sistema Nervioso Central, Primario; Astrocitoma cerebeloso, Infantil; Astrocitoma Cerebral/Glioma Maligno, Infantil, Cáncer de cuello uterino; Cánceres Infantiles, Leucemia Linfocítica Crónica, Leucemia Mielógena Crónica, Trastornos Mieloproliferativos Crónicos; Sarcoma de Células Claras de Tendones y Aponeurosis, Cáncer de Colon ; Cáncer Colorrectal, Infantil, Linfoma Cutáneo de Células T, Cáncer Endometrial, Ependimoma, Infantil, Cáncer Epitelial, Ovario, cáncer de Esófago, Cáncer de Esófago, Infantil, Familia de Tumores de Ewing; Tumor de Células Germinales Extracraneales, Infantil; Tumor Extragonadal de Células Germinales; Cáncer del Conducto Biliar Extrahepático, Cancer Ocular, Melanoma Intraocular, Cáncer Ocular, Retinoblastoma, Cáncer de la Vesícula Biliar, Cáncer Gástrico (estómago); Cáncer Gástrico (estómago), Infantil, Tumor Carcinoide Gastrointestinal, Tumor de Células Germinales, Extracraneal, Infantil, Tumor de Células Germinales, Extragonadales; Tumor

de Células Germinales, Ovario, Tumor Trofoblástico Gestacional, Glioma, Tallo Encefálico Infantil, Glioma, Ruta Visual Infantil e Hipotalámica, Leucemia de Células Pilosas; Cáncer de Cabeza y Cuello; Cáncer Hepatocelular (Hígado), Adulto (Primarip); Cáncer Hepatocelular (Hígado), Infantil (Primario); Linfoma de Hodgkin, Adulto, Linfoma de Hodgkin, Infantil, Linfoma de Hodgkin Durante el Embarazo, Cáncer de la Hipofaringe; Glioma de las Vías Hipotalámicas y Visuales, Infantil, Melanoma Intraocular; Carcinoma de Células de Islotes (Páncreas Endocrino), Sarcoma de Kaposi, Cáncer de Riñón, Cáncer de la Laringe, Cáncer de la Laringe, Infantil; Leucemia Linfoblástica Aguda, Adulto, Leucemia Linfoblástica Aguda Infantil,; Leucemia Mieloide Aguda, Adulto, Leucemia Mieloide Aguda, Infantil, Leucemia linfocítica Crónica, Leucemia Mielógena Crónica; Leucemia de Células Pilosas; Cáncer de Labios y Cavidad Oral, Cáncer de Hígado, Adulto (Primario), Cáncer de Hígado, Infantil (Primario); Cáncer de Pulmón, de Células no Pequeñas, Cáncer de Pulmón de Células Pequeñas, Leucemia Linfoblástica Aguda en Adultos, Leucemia Linfoblástica, Aguda Infantil, Leucemia Linfocítica, Crónica, Linfoma Relacionado con el SIDA, Linfoma, del Sistema Nervioso Central (Primario); Linfoma Cutáneo de Células T, Linfoma, Enfermedad de Hodgkin, Adulto, Linfoma, enfermedad de Hodgkin, Infantil, Linfoma de Hodgkin durante el embarazo, Linfoma, No Hodgkin, Adulto; Linfoma No Hodgkin, Infantil; Linfoma No Hodgkin durante el embarazo; Linfoma Primario del Sistema Nervioso Central; Macroglobulinemia, de Waldenstrom, Cáncer de Mama Masculino, Mesotelioma Maligno, Adulto, Mesotelioma Maligno, Infantil, Timoma Maligno, Meduloblastoma, Infantil; Melanoma, Melanoma, Intraocular, Carcinoma de Células de Merkel, Mesotelioma, Maligno, Cáncer Escamoso Metastásico del Cuello con Tumor Primario Oculto; Síndrome de Neoplasia Endocrina Múltiple, Infantil, Mieloma Múltiple/Neoplasma de Células Plasmáticas, Micosis Fungoide, Síndrome Mielodisplásico, Leucemia Mieloide Crónica; Leucemia Mieloide Aguda Infantil, Mieloma, Múltiple, Trastornos Mieloproliferativos, Crónicos, Cáncer de Cavidad Nasal y del Seno Paranasal, Cáncer de la Nasofaringe, Cáncer de la Nasofaringe, Infantil, Neuroblastoma, Linfoma No Hodgkin, Adulto, Linfoma no Hodgkin, Infantil, Linfoma no Hodgkin Durante el Embarazo; Cáncer de Pulmonar de Células no Pequeñas, Cáncer Oral, Infantil, Cáncer de Labios y de la Cavidad Oral y Cáncer de Labios, Cáncer de la Orofaringe; Esteosarcoma/Histiocitoma Fibroso Maligno Óseo, Cáncer de Ovario, Infantil, Cáncer Epitelial de los Ovarios, Tumores de Células Germinales del Ovario; Tumor de Ovario de Bajo Potencial Maligno; Cáncer Pancreático, Cáncer Pancreático,

Infantil, Cáncer Pancreático de Células Islote; Cáncer del Seno Paranasal y de la Cavidad Nasal, Cáncer de la Paratiroides, Cáncer de Pene, Feocromocitoma, Tumores Neuroectodérmicos Primitivos Pineales y Supratentoriales, Infantil, Tumor de la Glándula Pituitaria; Neoplasia de Células Plasmáticas/Mieloma Múltiple; Blastoma Pleuropulmonar; Embarazo y Cáncer de Mama, Embarazo y Linfoma de Hodgkin, Embarazo y Linfoma No Hodgkin, Linfoma Primario del Sistema Nervioso Central, Cáncer Primario del Hígado, Adulto, Cáncer Primario del Hígado, Infantil, Cáncer de Próstata, Cáncer del Recto, Cáncer Renal (Células Renales), Cáncer de Células Renales, Infantil, Pelvis Renal y Uréter, Cáncer de Células de Transición; Retinoblastoma, Rabdomiosarcoma, Infantil, Cáncer de Glándulas Salivales, Cáncer de Glándulas Salivales, Infantil, Sarcoma, Familia de Tumores de Ewing, Sarcoma, de Kaposi, Sarcoma (Osteosarcoma)/Histiocitoma Fibroso Maligno Óseo; Sarcoma, Rabdomiosarcoma, Infantil, Sarcoma de Tejidos Blandos, Adulto, Sarcoma de Tejidos Blandos Infantil; Síndrome de Sézary, Cáncer de Piel, Cáncer de Piel, Infantil, Cáncer de Piel (Melanoma), Carcinoma de Piel, Células de Merkel, Cáncer Pulmonar de Células Pequeñas, Cáncer del Intestino Delgado, Sarcoma de Tejidos Blandos, Adulto, Sarcoma de Tejidos Blandos, Infantil, Cáncer Escamoso de Cuello con Tumor Primario Oculto, Metastásico, Cáncer de Estómago (gástrico) Cáncer; Cáncer de Estómago (Gástrico), Infantil, Tumores Neuroectodérmicos Primitivos Supratentoriales, Infantil, Linfoma de Células T, Cutáneo; Cáncer Testicular, Timoma, Infantil, Timoma, Maligno, Cáncer de Tiroides, Cáncer de Tiroides, Infantil, Cáncer de Células de Transición de la Pelvis Renal y del Uréter, Tumor Trofoblástico, Gestacional, Cáncer de Sitio Primario Desconocido, Infantil, Cánceres Poco Comunes Infantiles; Uréter y Pelvis Renal, Cáncer de Células de Transición; Cáncer de la Uretra; Sarcoma Uterino, Cáncer Vaginal, Glioma de Vías Ópticas y del Hipotálamo, Infantil; Cáncer de la vulva; Globulinemia Waldenstrom Macro, y Tumor de Wilms.

En otra realización, el cáncer asociado con una proteína IDH mutante que tiene una acitvity neomórfica es cáncer cerebral, tales como tumor astrocítico (por ejemplo, astrocitoma pilocítico, astrocitoma subependimaria de células gigantes, astrocitoma difuso, xantoastrocitoma pleomórfico, astrocitoma anaplásico, astrocitoma, glioblastoma de células gigantes, glioblastoma, glioblastoma secundario, glioblastoma primario adulto, y glioblastoma primaria pediátrico); tumor oligodendroglial (por ejemplo, oligodendroglioma y oligodendroglioma anaplásico); tumor oligoastrocítico (por ejemplo, oligoastrocitoma y oligoastrocitoma anaplásico); ependimoma (por ejemplo, ependimoma

mixopapilar y ependimoma anaplásico), meduloblastoma, el tumor neuroectodérmico primitivo, schwannoma, meningioma, meningioma meatípico, meningioma anaplásico, y adenoma pituitario. En otra realización, el cáncer de cerebro es glioma, glioblastoma multiforme, paraganglioma, o tumores neuroectodérmicos supratentoriales primordiales (TNEPS).

En otra realización, el cáncer asociado con una proteína IDH mutante que tiene una actividad neomórfica es leucemia, tal como leucemia mieloide aguda (LMA), síndrome mielodisplásico (MDS), leucemia mielógena crónica (CML), neoplasias mieloproliferativas (MPN), MDS.MPN incluyendo leucemia mielomonocítica crónica, pos- MDS LMA, pos- NMP LMA, pos- SMD/NMP LMA, LMA o SMD de alto riesgo asociado con del(5q), leucemia mieloide crónica de fase blástica, linfoma angioinmunoblástico y leucemia linfoblástica aguda.

En otra realización, el cáncer asociado con una proteína IDH mutante que tiene actividad neomórfica es cáncer de piel, incluyendo melanoma.

En otra realización, el cáncer asociado con una proteína IDH mutante que tiene actividad neomórfica es cáncer de próstata, cáncer de tiroides, cáncer de colon o cáncer de pulmón.

En otra realización, el cáncer asociado con una proteína IDH mutante que tiene actividad neomórfica es sarcoma, incluyendo condrosarcoma central, condroma central y periostio y fibrosarcoma.

En otra realización, el cáncer asociado con una proteína IDH mutante que tiene actividad neomórfica es colangiocarcinoma

Otra enfermedad o trastorno asociado con una proteína IDH mutante que tiene actividad neomórfica R-2-HG es aciduria hidroxiglutárica D-2.

Otra enfermedad o trastorno asociado con una proteína IDH mutante que tiene actividad neomórfica R-2-HG es la enfermedad de Oiller y el síndrome de Mafucci.

Tal como se utiliza en la presente, el término "actividad neomórfica" se refiere a una ganancia de actividad novedosa de una proteína que la proteína de tipo salvaje no tiene o no exhibe en un grado significativo. Por ejemplo, una actividad neomórfica asociada con una forma mutante de IDH1 y IDH2 es la capacidad para reducir el alfa-cetoglutarato a 2-hidroxiglutarato (decir, 2-HG, específicamente R-2-HG). La forma de tipo salvaje de IDH1 y IDH2 no tiene la capacidad de reducir el alfa-cetoglutarato a 2-hidroxiglutarato (decir, 2-HG, específicamente R-2-HG) o si tiene esta capacidad, no

produce cantidades significativas (es decir cantidades perjudiciales o causantes de enfermedades) de 2-HG.

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 a por ejemplo, primates (*ej.*, humanos, hombres o mujeres), vacas, ovejas, cabras, caballos, perros, gatos, conejos, ratas, ratones, peces, aves y similares. En ciertas realizaciones, el sujeto es un primate. En aún otras realizaciones, el sujeto es un humano.

Como se utiliza en la presente, el término “cantidad terapéuticamente efectiva” en referencia a un compuesto de la invención se refiere a la cantidad de un compuesto suficiente para tratar la enfermedad o condición del sujeto, pero suficientemente baja para evitar serios efectos secundarios (a una tasa beneficio/riesgo razonable) dentro del alcance del sano criterio médico. Una cantidad terapéuticamente efectiva de un compuesto variará con el compuesto particular elegido (ej., considerar la potencia, eficacia, y vida media del compuesto); la ruta de administración elegida; la condición tratada; la severidad de la condición tratada; la edad, tamaño, peso, y condición física del sujeto tratado; la historia química del sujeto tratado; la duración del tratamiento; la naturaleza de la terapia concurrente; el efecto terapéutico deseado; y factores similares y puede determinarse de manera rutinaria por el experto en el estado de la técnica.

Como se utiliza en la presente, el término “tratar”, o "tratamiento" de cualquier enfermedad o trastorno se refiere en una realización, a mejorar la enfermedad o trastorno (es decir, retardar o detener o reducir el desarrollo de la enfermedad o al menos uno de los síntomas clínicos de la misma). En otra realización “tratar” o “tratamiento” se refiere a aliviar o mejorar al menos parámetro físico incluyendo aquellos los cuales pueden ser no discernibles por el paciente. En aún otra realización, “tratar” o “tratamiento” se refiere a modular la enfermedad o trastorno, bien sea físicamente, (*ej.*, estabilización de un síntoma discernible), fisiológicamente, (*ej.*, estabilización de un parámetro físico), o ambos. En aún otra realización, “tratar” o “tratamiento” se refiere a prevenir o retardar el comienzo o desarrollo o progresión de la enfermedad o trastorno.

Como se utiliza en la presente, un sujeto esta “en necesidad de” un tratamiento si tal sujeto se beneficia biológicamente, médicamente o mejora su calidad de vida a partir de tal tratamiento.

Los compuestos de la presente invención pueden administrarse mediante cualquier ruta adecuada incluyendo administración oral y parenteral. La administración parenteral

es típicamente por inyección o infusión, e incluye inyección intravenosa, intramuscular, y subcontaneous o infusión.

Los compuestos de la invención se pueden administrar una vez o según un régimen de dosificación en donde un número de dosis se administran a diferentes intervalos de tiempo durante un período de tiempo dado. Por ejemplo, las dosis pueden administrarse una, dos, tres, o cuatro veces por día. Las dosis pueden administrarse hasta que el efecto terapéutico deseado se logra o indefinidamente para mantener el efecto terapéutico deseado. Regímenes de dosificación adecuados para un compuesto de la invención dependerán de las propiedades farmacocinéticas de ese compuesto, tales como absorción, distribución y vida media las cuales pueden determinarse por el experto en la técnica. Además, los regímenes de dosificación adecuados, incluyendo la duración de tales regímenes, para un compuesto de la invención, dependerán de la enfermedad o condición que se está tratando, la gravedad de la enfermedad o condición, la edad y la condición física del sujeto a tratar, la historia médica del sujeto a tratar, la naturaleza de la terapia concurrente, el efecto terapéutico deseado, y factores similares dentro del conocimiento y experiencia del experto en la técnica. Se entenderá además por dichos expertos en la técnica que los regímenes de dosificación adecuados pueden requerir un ajuste dada la respuesta de un sujeto al régimen de dosificación o en el tiempo a medida que cambian las necesidades del sujeto individual. Las dosis diarias típicas pueden variar dependiendo de la ruta de administración particular elegida. Dosificaciones diarias típicas para administración oral, a un ser humano con un peso aproximado de 70 kg estarían en el rango entre 5 mg y 500 mg aproximadamente de un compuesto de la fórmula (I).

Una realización de la presente invención proporciona un método para tratar una enfermedad o trastorno asociado con una forma mutante de IDH que tiene una actividad neomórfica que comprende la administración de una cantidad terapéuticamente eficaz de un compuesto de la fórmula (I) a un sujeto en necesidad de tal tratamiento. En una realización, la enfermedad o trastorno asociado con una forma mutante de IDH que tiene una actividad neomórfica es un trastorno de proliferación celular. En otra realización, el trastorno de proliferación celular es cáncer. En otra realización, el cáncer es un cáncer asociado con IDH1 mutante que tiene actividad neomórfica 2-HG o IDH2 mutante que tiene actividad neomórfica 2-HG. En otra realización, la actividad neomórfica es actividad neomórfica R-2-HG. En otra realización, el cáncer está asociado con IDH1 mutante que tiene actividad neomórfica 2-HG o R-2-HG que tiene una mutación en los

residuos 97, 100 o 132, tal como G97D, R100Q, R132H, R132C, R132S, R132G, R132L, y R132V. En otra forma de realización el cáncer se asocia con IDH2 mutante que tiene actividad neomórfica 2-HG o R-2-HG que tiene una mutación en los residuos 140 o 172, por ejemplo, R140Q, R140G, R172K, R172M, R172S, R172G, y R172W. En otra realización, el cáncer es cáncer cerebral, leucemia, cáncer de piel, cáncer de próstata, cáncer de tiroides, cáncer de colon, cáncer de pulmón o sarcoma. En otra realización, el cáncer es glioma, glioblastoma multiforme, paraganglioma, tumores neuroectodérmicos suprantentoriales primordiales, leucemia mieloide aguda, síndrome mielodisplásico, leucemia mielógena crónica, melanoma, tumores de próstata, de tiroides, de colon, de pulmón, condrosarcoma central, tumores de condroma central y periostio, fibrosarcoma y colangiocarcinoma.

Otra realización de la presente invención proporciona un método para tratar una enfermedad o trastorno asociado con una forma mutante de IDH que tiene actividad neomórfica R-2-HG que comprende la administración de una cantidad terapéuticamente eficaz de un compuesto según la fórmula (I) a un sujeto en necesidad del mismo en el que la enfermedad o trastorno es aciduria D-2-hidroxiglutárica, enfermedad de Ollier, o síndrome de Mafucci.

Otra realización de la presente invención proporciona el uso de un compuesto de la fórmula (I) en terapia. En una realización adicional la terapia es una enfermedad o trastorno asociado con una forma mutante de IDH que tiene una actividad neomórfica. En otra realización, la terapia es un trastorno de proliferación celular asociado con una forma mutante de IDH que tiene una actividad neomórfica. En otra realización, la terapia es cáncer. En otra realización, la terapia es un cáncer asociado a una proteína IDH mutante que tiene actividad neomórfica, tal como IDH1 mutante que tiene actividad neomórfica 2-HG o IDH2 mutante que tiene actividad neomórfica 2-HG. En otra realización, la actividad neomórfica es actividad neomórfica R-2-HG. En otra realización, el cáncer está asociado con IDH1 mutante que tiene actividad neomórfica 2-HG o R-2-HG que tiene una mutación en los residuos 97, 100 o 132, tal como G97D, R100Q, R132H, R132C, R132S, R132G, R132L, y R132V. En otra realización el cáncer se asocia con IDH2 mutante que tiene actividad neomórfica 2-HG o R-2-HG que tiene una mutación en los residuos R140 o 172, por ejemplo, R140Q, R140G, R172K, R172M, R172S, R172G, y R172W. En otra realización, el cáncer es cáncer cerebral, leucemia, cáncer de piel, cáncer de próstata, cáncer de tiroides, cáncer de colon, cáncer de pulmón o sarcoma. En otra realización, el cáncer es glioma, glioblastoma multiforme, paraganglioma, tumores

neuroectodérmicos supratentoriales primordiales, leucemia mieloide aguda, síndrome mielodisplásico, leucemia mielógena crónica, melanoma, tumores de próstata, de tiroides, de colon, de pulmón, condrosarcoma central, tumores de condroma central y periostio, fibrosarcoma y colangiocarcinoma.

Otra realización de la presente invención proporciona el uso de un compuesto de la fórmula (I) en terapia en donde la terapia es aciduria hidroxiglutárica D-2, enfermedad de Ollier o síndrome de Mafucci.

Otra realización de la presente invención proporciona el uso de un compuesto según la fórmula (I) en la fabricación de un medicamento para el tratamiento de una enfermedad o trastorno asociado con una forma mutante de IDH que tiene una actividad neomórfica. En una realización, la enfermedad o trastorno asociado con una forma mutante de IDH que tiene una actividad neomórfica es un trastorno de la proliferación celular. En otra realización, el trastorno de proliferación celular es cáncer. En otra realización, el cáncer es un cáncer asociado a una proteína IDH mutante actividad neomórfica, tales como IDH1 mutante que tiene actividad neomórfica 2-HG o IDH2 mutante que tiene actividad neomórfica 2-HG. En otra realización, la actividad neomórfica es actividad neomórfica R-2-HG. En otra realización, el cáncer está asociado con IDH1 mutante que tiene actividad neomórfica 2-HG o R-2-HG que tiene una mutación en los residuos 97, 100 o 132, tal como G97D, R100Q, R132H, R132C, R132S, R132G, R132L, y R132V. En otra realización el cáncer se asocia con IDH2 mutante que tiene actividad neomórfica 2-HG o R-2-HG que tiene una mutación en los residuos 140 o 172, por ejemplo, R140Q, R140G, R172K, R172M, R172S, R172G, y R172W. En otra realización, el cáncer es cáncer cerebral, leucemia, cáncer de piel, cáncer de próstata, cáncer de tiroides, cáncer de colon, cáncer de pulmón o sarcoma. En otra realización, el cáncer es glioma, glioblastoma multiforme, paraganglioma, tumores neuroectodérmicos supratentoriales primordiales, leucemia mieloide aguda, síndrome mielodisplásico, leucemia mielógena crónica, melanoma, tumores de próstata, de tiroides, de colon, de pulmón, condrosarcoma central, tumores de condroma central y periostio, fibrosarcoma y colangiocarcinoma.

Otra realización de la presente invención proporciona el uso de un compuesto según la fórmula (I) en la fabricación de un medicamento para el tratamiento de una enfermedad o trastorno asociado con una forma mutante de IDH que tiene actividad neomórfica R-2-HG en donde la enfermedad o trastorno es aciduria hidroxiglutárica D-2, enfermedad de Ollier, o síndrome de Mafucci.

Composiciones

En otro aspecto, la presente invención proporciona una composición farmacéutica que comprende a compuesto de la fórmula (I) y un vehículo ó excipiente farmacéuticamente aceptable.

Las composiciones farmacéuticas de la invención pueden prepararse y empacarse en a granel en donde una cantidad terapéuticamente eficaz de un compuesto de la invención puede ser extraída y, a continuación dada a un sujeto, tal como con polvos o jarabes. Alternativamente, las composiciones farmacéuticas de la invención pueden prepararse y empacarse en forma de dosificación unitaria en donde cada unidad físicamente discreta contiene una cantidad terapéuticamente eficaz de un compuesto de la invención. Cuando se preparan en forma de dosificación unitaria, las composiciones farmacéuticas de la invención contienen normalmente entre 5 mg y 500 mg aproximadamente de un compuesto de la fórmula (I).

Tal como se utiliza en la presente, el término "vehículo o excipiente farmacéuticamente aceptable" significa un material farmacéuticamente aceptable, composición o vehículo que, por ejemplo, están implicados en dar forma o consistencia a la composición farmacéutica. Cada excipiente debe ser compatible con los otros ingredientes de la composición farmacéutica al mezclarse de tal manera que las interacciones que sustancialmente reducirían la eficacia del compuesto de invento se evitarían al administrarse en un sujeto y también se evitarían las interacciones que resultarían en composiciones farmacéuticas que no fuesen farmacéuticamente aceptables. Además, cada excipiente debe, por supuesto, ser de pureza suficientemente alta para que sea farmacéuticamente aceptable.

El compuesto de la invención y el vehículo o excipiente farmacéuticamente aceptable (s) típicamente se formularán en una forma de dosificación adaptada para la administración al sujeto por la ruta de administración deseada. Por ejemplo, formas de dosificación incluyen las adaptadas para (1) administración oral tales como comprimidos, cápsulas, comprimidos, oblongos, píldoras, trociscos, polvos, jarabes, elixires, suspensiones, soluciones, emulsiones, sachets y cápulas (cachets), y (2) administración parenteral tales como soluciones estériles, suspensiones y polvos para la reconstitución. Excipientes farmacéuticamente aceptables adecuados variarán dependiendo de la forma de dosificación particular elegida. Además, los excipientes farmacéuticamente aceptables adecuados pueden ser elegidos para una función particular que pueden desempeñar en la

composición. Por ejemplo, ciertos excipientes farmacéuticamente aceptables pueden ser elegidos por su capacidad para facilitar la producción de formas de dosificación uniformes. Ciertos excipientes farmacéuticamente aceptables pueden ser elegidos por su capacidad para facilitar la producción de formas de dosificación estables. Ciertos excipientes farmacéuticamente aceptables pueden ser elegidos por su capacidad para facilitar el transporte del compuesto o compuestos de la invención, una vez administrados al sujeto, desde un órgano o parte del cuerpo hacia otro órgano u otra parte del cuerpo. Ciertos excipientes farmacéuticamente aceptables pueden ser elegidos por su capacidad para mejorar adherencia del paciente.

Los excipientes farmacéuticamente aceptables incluyen los siguientes tipos de excipientes: diluyentes, lubricantes, aglutinantes, desintegrantes, rellenos, deslizantes, agentes de granulación, agentes de revestimiento, agentes humectantes, disolventes, codisolventes, agentes de suspensión, emulsionantes, edulcorantes, agentes saborizantes, agentes enmascarantes de sabor, agentes colorantes, agentes antiaglomerantes, humectantes, agentes quelantes, plastificantes, agentes mejoradores de la viscosidad, antioxidantes, conservantes, estabilizantes, surfactantes, y agentes amortiguantes.

Los expertos en la técnica poseen el conocimiento y habilidad para seleccionar vehículos y excipientes farmacéuticamente aceptables apropiados y excipientes en cantidades apropiadas para el uso en la invención. Además, hay un número de recursos disponibles para el experto en la técnica, que describen vehículos y excipientes farmacéuticamente aceptables y pueden ser útiles en la selección de vehículos y excipientes farmacéuticamente aceptables adecuados. Ejemplos incluyen Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), y The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association y The Pharmaceutical Press).

Las composiciones farmacéuticas de la invención se preparan usando técnicas y métodos conocidos por los expertos en la técnica. Algunos métodos comúnmente utilizados en la técnica se describen en Remington Pharmaceutical Sciences (Mack Publishing Company).

En un aspecto, la invención se refiere a una forma sólida de dosificación oral tal como un comprimido o cápsula que comprende una cantidad terapéuticamente eficaz de un compuesto de la invención y un diluyente o relleno. Diluyentes y rellenos adecuados incluyen lactosa, sacarosa, dextrosa, manitol, sorbitol, almidón (por ejemplo almidón de maíz, almidón de patata, y almidón pre-gelatinizado), celulosa y sus derivados, (por

ejemplo, celulosa microcristalina), sulfato de calcio, y fosfato de calcio dibásico. La forma de dosificación sólida oral puede comprender además un aglutinante. Aglutinantes adecuados incluyen almidón (por ejemplo almidón de maíz, almidón de patata, y almidón pre-gelatinizado), gelatina, goma arábiga, alginato de sodio, ácido algínico, tragacanto, goma guar, povidona y celulosa y sus derivados (por ejemplo, celulosa microcristalina). La forma oral de dosificación sólida puede comprender además un desintegrante. Desintegrantes adecuados incluyen crospovidona, glicolato de almidón de sodio, croscarmelosa, ácido algínico, y carboximetilcelulosa de sodio. La forma de dosificación sólida oral puede comprender además un lubricante. Lubricantes adecuados incluyen ácido esteárico, estearato de magnesio, estearato de calcio y talco.

Donde sea apropiado, las formulaciones unitarias de dosificación para administración oral pueden ser microencapsuladas. La composición también se puede preparar para prolongar o mantener la liberación como, por ejemplo, por revestimiento o incrustación de material particulado en polímeros, cera, o similares.

Los compuestos de la invención también pueden acoplarse con polímeros solubles como vehículos farmacológicos sobre los cuales se puede actuar. Tales polímeros pueden incluir polivinilpirrolidona, pirancopolímero, polihidroxipropilmetacrilamidafenol, polihidroxietilaspartamidafenol o polietilenoxidopolilisina sustituida con residuos de palmitoilo. Además, los compuestos de la invención pueden ser acoplados a una clase de polímeros biodegradables útiles para conseguir la liberación controlada de un fármaco, por ejemplo, ácido poliláctico, polepsilon caprolactona, ácido polihidroxi butírico, poliortoésteres, poliacetales, polidihidropiranos, policianocrilatos y copolímeros de bloque entrecruzados o anfipáticos de hidrogeles.

En otro aspecto, la invención está dirigida a una forma de dosificación oral líquida. Líquidos orales tales como soluciones, jarabes y elixires pueden prepararse en forma de dosificación unitaria de manera que una cantidad dada contenga una cantidad predeterminada de un compuesto de la invención. Los jarabes se pueden preparar disolviendo el compuesto de la invención en una solución acuosa convenientemente aromatizada, mientras que los elixires se preparan mediante el uso de un vehículo alcohólico no tóxico. Las suspensiones pueden formularse dispersando el compuesto de la invención en un vehículo no tóxico. Solubilizantes y emulsionantes tales como alcoholes isoestearílicos etoxilados y éteres de polioxietilen sorbitol, conservantes, aditivos aromatizantes tales como aceite de menta u otros edulcorantes naturales o sacarina u otros edulcorantes artificiales y similares también se pueden añadir.

En otro aspecto, la invención está dirigida a la administración parenteral. Las composiciones farmacéuticas adaptadas para administración parenteral incluyen soluciones de inyección estéril acuosas y no acuosas que pueden contener anti-oxidantes, buffers, bacteriostáticos y solutos que hacen la formulación isotónica con la sangre del receptor previsto, y suspensiones estériles acuosas y no acuosas que pueden incluir agentes de suspensión y agentes espesantes. Las composiciones pueden presentarse en recipientes de dosis unitaria o de múltiples dosis, por ejemplo ampollas selladas y viales, y pueden almacenarse en una condición secada por congelación (liofilizada) que requiere sólo la adición del vehículo líquido estéril, por ejemplo agua para inyecciones, inmediatamente antes de su uso. Soluciones y suspensiones inyectables extemporáneas se pueden preparar a partir de polvos, gránulos y comprimidos estériles.

Combinaciones

El compuesto del presente invento puede administrarse bien sea simultáneamente con, o antes de o después de, uno o más de otros agentes terapéuticos. El compuesto de la presente invención puede administrarse de manera separada, mediante la ruta de administración igual o diferente, o juntas en la misma composición farmacéutica que los otros agentes.

En una realización, la invención proporciona un producto que comprende un compuesto de la fórmula (I) y al menos otro agente terapéutico como una preparación combinada para uso simultaneo, separado o secuencial en terapia. En una realización, la terapia es el tratamiento de una enfermedad o trastorno asociado con una forma mutante de IDH. Los productos proporcionados como una preparación combinada incluyen una composición que comprende el compuesto de la fómrula (I) y los otros agentes terapéuticos en la misma composición farmacéutica, o el compuesto de la fórmula (I) y los otros agentes terapéuticos en forma separada, *ej.,* en forma de un kit.

En una realización, el invento proporciona una composición farmacéutica que comprende un compuesto de la fórmula (I) y otros agentes terapéuticos. Opcionalmente, la composición farmacéutica puede comprender un excipiente farmacéuticamente aceptable, como se describió anteriormente.

En una realización, el invento proporciona un kit que comprende dos o más composiciones farmacéuticas separadas, al menos una de las cuales contiene un compuesto de la fórmula (I). En una realización, el kit comprende medios para retener de manera separada dichas composiciones, tales como un recipiente, botella dividida, o

empaque dividido en aluminio. Un ejemplo de tal kit es paquete blister, como el que típicamente se utiliza para empacar tabletas, cápsulas y similares.

El kit del invento puede utilizarse 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 diferentes composiciones entre sí. Para ayudar en el cumplimiento terapéutico, el kit del invento típicamente comprende pautas para administración.

En las terapias de combinación del invento, el compuesto del invento y el otro agente terapéutico pueden fabricarse y/o formularse por los mismos o diferentes fabricantes. Además, el compuesto de la invención y el otro agente terapéutico serán llevados juntos en una terapia de combinación: (i) antes de entregar el producto de combinación a los médicos (*ej.* en el caso de un kit que comprende el compuesto del invento y el otro agente terapéutico); (ii) por los médicos mismos (o bajo la pauta del médico) poco antes de administración; (iii) en los pacientes mismos, *ej.* durante administración secuencial del compuesto del invento y el otro agente terapéutico.

Por consiguiente, la invención proporciona el uso de un compuesto de la fórmula (I) para tratar una enfermedad o condición asociada con una forma mutante de IDH, en donde el medicamento es preparado para administración con otro agente terapéutico. La invención también proporciona el uso de otro agente terapéutico para tratar una enfermedad o condición asociada con una forma mutante de IDH, en donde el medicamento se administra con un compuesto de la fórmula (I).

La invención también proporciona un compuesto de la fórmula (I) para utilizar en un método para tratar una enfermedad o condición asociada con una forma mutante de IDH, en donde el compuesto de la fórmula (I) es preparado para administración con otro agente terapéutico. La invención también proporciona otro agente terapéutico para utilizar en un método para tratar una enfermedad o condición asociada con una forma mutante de IDH, en donde el otro agente terapéutico es preparado para administración con un compuesto de la fórmula (I). La invención también proporciona un compuesto de la fórmula (I) para utilizar en un método para tratar una enfermedad o condición asociada con una forma mutante de IDH, en donde el compuesto de la fórmula (I) es preparado con otro agente terapéutico. La invención también proporciona otro agente terapéutico para utilizar en un método para tratar una enfermedad o condición asociada con una forma mutante de IDH, en donde el otro agente terapéutico se administra con un compuesto de la fórmula (I).

La invención proporciona el uso de un compuesto de la fórmula (I) para tratar una enfermedad o condición asociada con una forma mutante de IDH, en donde el paciente ha sido previamente tratado (ej., dentro de las 24 horas) con otro agente terapéutico. La invención proporciona el uso de otro agente terapéutico para tratar una enfermedad o condición asociada con una forma mutante de IDH, en donde el paciente ha sido previamente tratado (ej., dentro de las 24 horas) con un compuesto de la fórmula (I).

En una realización, el otro agente terapéutico es seleccionado a partir de inhibidores del receptor del factor de crecimiento endotelial vascular (VEGF), inhibidores de la topoisomerasa II, inhibidores suavizados, agentes alquilantes, antibióticos anti-tumorales, anti-metabolitos, retinoides, y otros agentes citotóxicos.

Ejemplos del factor de crecimiento endotelial vascular (VEGF) Inhibidores de los receptores incluyen pero no se limitan a, bevacizumab (comercializados bajo la marca Avastin® por Genentech/Roche), axitinib, (N-metil-2-[[3-[(E)-2-piridin-2-iletenil]-1 H-indazol-6-il]sulfanil]benzamida, también conocido como AG013736, y descritos en la Publicación PCT No. WO 01/002369), Alaninato de Brivanib ((S)-((R)-1-(4-(4-Fluoro-2-metil-1H-indol-5-iloxi)-5-metilpirrolo[2,1-f][1,2,4]triazin-6-iloxi)propan-2-il)2-aminopropanoato, también conocido como BMS-582664), motesanib (N-(2,3-dihidro-3,3-dimetil-1H-indol-6-il)-2-[(4-piridinilmetil)amino]-3-piridinacarboxamida, y descritos en la Publicación PCT No. WO 02/066470), pasireotida (también conocido como SOM230, y descritos en la Publicación PCT No. WO 02/010192), y sorafenib (comercializado bajo la marca Nexavar®).

Ejemplos de inhibidores de la topoisomerasa II incluyen pero no están limitados a etoposida (también conocido como VP-16 y fosfato de Etoposida, comercializados bajo las marcas Toposar®, VePesid® y Etopophos®), y teniposida (también conocidos como VM-26, comercializados bajo la marca Vumon®);

Ejemplos de agentes alquilantes, incluyen pero no están limitados aTemozolomida (comercializado bajo las marcas Temodar® y Temodal® por Schering-Plough/Merck), dactinomicino (también conocido como actinomicina-D y comercializado bajo la marca Cosmegen®), melfalan (también conocido como L-PAM, L-sarcolisina, y mostaza de fenilalanina, comercializado bajo la marca Alkeran®), altretamina (también conocido como hexametilmelamina (HMM), comercializado bajo la marca Hexalen®), carmustina (comercializado bajo la marca BiCNU®), bendamustina (comercializado bajo la marca Treanda®), busulfan (comercializado bajo las marcas Busulfex® y Mileran®), carboplatino (comercializados bajo la marca Paraplatin®), lomustina (también conocido

como CCNU, comercializado bajo la marca CeeNU®), cisplatino (también conocido como CDDP, comercializado bajo las marcas Platinol® y Platinol®-AQ), clorambucil (comercializados bajo la marca Leukeran®), ciclofosfamida (comercializado bajo la marcas Cytoxan® y Neosar®), dacarbazina (también conocidos como DTIC, DIC y carboxamida de imidazol, comercializado bajo la marca DTIC-Dome®), altretamina (también conocido como hexametilmelamina (HMM) comercializado bajo la marca Hexalen®), ifosfamida (comercializados bajo la marca Ifex®), procarbazina (comercializado bajo la marca Matulane®), mecloretamina (también conocido como mostaza de nitrógeno, mustina y hidrocloruro de mecloroetamina, comercializados bajo la marca Mustargen®), estreptozocina (comercializados bajo la marca Zanosar®), y tiotepa (también conocidos como tiofosfoamida, TESPA y TSPA, comercializados bajo la marca Tioplex®;

Ejemplos de antibióticos anti-tumorales incluyen, pero no están limitados a doxorubicina (comercializados bajo las marcas Adriamycin® y Rubex®), bleomicina (comercializados bajo la marca lenoxane®), daunorubicina (también conocido como hidrocloruro de dauorubicina, daunomicina, y hidrocloruro de rubidomicina, comercializado bajo la marca Cerubidina®), daunorubicina liposomal (liposomas de citrato de daurorubicina, comercializada bajo la marca DaunoXome®), mitoxantrona (también conocido como DHAD, comercializado bajo la marca Novantrone®), epirubicina (comercializado bajo la marca Ellence™), idarubicina (comercializado bajo las marcas Idamycin®, Idamycin PFS®), y mitomicina C (comercializado bajo la marca Mutamycin®);

Ejemplos de antimetabolitos incluyen, pero no se limitan a, claribina (2-clorodeoxiadenosina, vendido bajo el nombre comercial Leustatin®), 5-fluorouracil (vendido bajo el nombre comercial ® Adrucil), 6-tioguanina-(vendido bajo el nombre comercial Purinethol®) , pemetrexed (vendido bajo el nombre comercial Alimta ®), citarabina (también conocido como arabinosilcitosina (Ara-C), que se vende bajo el nombre comercial Cytosar-U ®), citarabina liposomal (también conocido como liposomal Ara-C, vendido bajo el nombre comercial DepoCyt ™), decitabina (vendido bajo el nombre comercial Dacogen®), hidroxiurea (vendido bajo el nombres comerciales Hydrea®, Droxia ™ y Mylocel ™), fludarabina (vendido bajo el nombre comercial ® Fludara), floxuridina (vendido bajo el nombre comercial FUDR®), cladribina (también conocido como 2-clorodesoxiadenosina (2-CdA) vendido bajo el nombre comercial Leustatin ™), metotrexato (también conocido como ametopterina, metotrexato sodim

(MTX), que se vende bajo los nombres comerciales Rheumatrex ® y Trexall™) y pentostatina (vendido bajo el nombre comercial Nipent ®).

Los ejemplos de retinoides incluyen, pero no se limitan a, alitretinoina (vendido bajo el nombre comercial ®Panretin), tretinoína (ácido all-*trans* retinoico, también conocido como ATRA, que se vende bajo el nombre comercial Vesanoid ®), isotretinoína (ácido 13-cis-retinoico, que se vende bajo los nombres comerciales Accutane®, Amnesteem ®, Claravis®, Clarus®, Decutan®, Isotane ®, Izotech ®, Oratane ®, Isotret®, y Sotret ®), y bexaroteno (vendido bajo el nombre comercial Targretin®).

Ejemplos de otros agentes citotóxicos incluyen, pero no se limitan a, trióxido de arsénico (vendido bajo el nombre comercial Trisenox®), asparaginasa (también conocido como L-asparaginasa, y Erwinia L-asparaginasa, vendido bajo el nombres comerciales Elspar® y Kidrolase®).

Intermedios y Ejemplos

Los siguientes ejemplos pretenden ser solamente ilustrativos y no limitativos en forma alguna. A menos que se indique lo contrario, los siguientes Intermedios y Ejemplos, se purificaron a través de cromatografía en columna de gel de sílice utilizando columnas RediSep ® RF de Teledyne Isco, Inc. Las abreviaturas usadas son las convencionales en la técnica o las siguientes:

ACN	acetonitrilo
BSA	albúmina de suero bovino
C	Centígrado
CDI	1,1'-carbonildiimidazol
d	doblete
dd	Doblete de dobletes
DAST	trifluoruro de dietilaminoazufre
DEAD	azodicarboxilato de dietilo
DIPEA	NN-diisopropiletilamina
DMF	*N,N*-dimetilformamida
DMSO	dimetilsulfóxido
DTT	ditiotreitol
EtOAc	acetato de etilo
EtOH	etanol
g	gramos

h	Horas (s)
HATU	Hexafluorofosfato de 2-(1H-7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio
HEPES	ácido 4-(2-hidroxietil)-1-piperazinaetilanosulfónico
HPLC	Cromatografía líquida de alta presión
Base de Hunig	NN-diisopropiletilamina
kg	kilogramos
L	litro
LC	cromatografía líquida
LCMS	cromatografía líquida y espectrometría de masas
MeOH	metanol
MS	espectrometría de masas
m	multiplete
min	minutos
mL	mililitros(s)
µM	micromolar
m/z	relación masa a carga
nm	nanometros
nM	nanomolar
N	normal
NADPH	Nicotinamida adenina dinucleotido fosfato
NMP	N-metilpirrolidona
NMR	resonancia magnética nuclear
$PdCl_2(dppf).CH_2Cl_2$	Complejo 1,1'-bis(difenilfosfino)ferroceno-paladio(II)dicloruro diclorometano
pTsOH	ácido p-toluensulfónico
rac	racémico
Rt	tiempo de retención
S	singulete
sat.	saturado
t	tripleta
TBTU	tetrafluoroborato de O-(benzotriazol-1-il-) -N,N,N',N'-tetrametiluronio
TCEP	tris(2-carboxietil)fosfina
TEA	trietilamina

TFA	ácido trifluoroacético
THF	tetrahidrofurano
TLC	cromatografía de capa delgada
TMS-CN	Cianuro de trimetilsililo

Instrumentación

LCMS

Los datos LCMS (también reportados en el presente documento simplemente como MS) se registraron usando un sistema Waters (Acuity UPLC y un espectrómetro de masas Micromass ZQ; Columna: Acuity HSS C18 1.8-micras, 2.1 x 50 mm; gradiente: 5-95% acetonitrilo en agua con TFA al 0,05 % durante un período de 1,8 min, tasa de flujo 1.2 ml/min, rango de peso molecular 200-1500; voltaje de cono de 20 V; temperatura de columna 50 º C). Todas las masas reportadas son aquellas de iones precursores protonados a menos que se registre lo contrario.

Espectroscopia de Masas de Alta Resolución (HRMS)

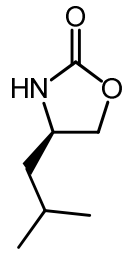
HRMS Método A: Los datos de ESI-MS se registraron utilizando un SYNAPT G2 HDMS (espectrómetro de masas TOF, Waters) con fuente de ionización por electrospray. La resolución del sistema MS fue de aproximadamente 15.000. La leucina encefalina fue utilizada como masa de bloqueo (normas internas) infundida desde la sonda LockSpray. El compuesto se infundió en el espectrómetro de masas por UPLC (Acquity, Waters) desde la sonda de muestra. La separación se realizó en una columna ACQUITY UPLC BEH C18 1x50 mm a 0,2 ml / min de tasa de flujo con el gradiente de 5% a 95% en 3 min. El disolvente A fue agua con 0,1% ácido fórmico y disolvente B fue acetonitrilo con Ácido Fórmico al 0.1%. La exactitud de la masa del sistema se ha encontrado como <5 ppm con masa de bloqueo.

HRMS Mıtodo B: Los datos LC-MS/ESI-MS se registraron en un Acquity G2 Xevo QTof - Rs (FWHM)> 20.000 Precisión <5 ppm. La separación se realizó en una columna Acquity CSH 1.7µm 2.1x50mm - 50 °C Eluyente A: Agua + acetato de amonio 3,75 mM. Eluyente B: Acetonitrilo Gradiente: de 2 a 98% B en 4. min - flujo de 1,0 ml / min.

Los métodos HRMS A and B se conocen a lo largo de la presente como HRMS(A) o HRMS(B), respectivamente.

Intermedios

Intermedio A: (*R*)- 4- isobutiloxazolidin- 2- ona



A una solución enfriada (4 ºC) de (*R*)- 2- amino- 4- metilpentan- 1- ol (2.98 g, 25.4 mmol) y se añadió por goteo trietilamina (7.6 ml, 54 mmol, 2.1 equiv) en CH_2Cl_2 (80 ml) una solución de trifosgeno (2.52 g, 8.49 mmol, 0.334 equiv) en 10 ml de CH_2Cl_2 más de 30 min. La mezcla de reacción se agitó a 4 °C durante 15 min, se calentó hasta temperatura ambiente y se agitó durante 1 h adicional. La mezcla se trató con NH_4Cl saturado (25 ml), seguido de CH_2Cl_2 (50 ml) y la mezcla resultante se agitó durante 20 min. Las capas se separaron y la capa orgánica se lavó con agua. Las capas acuosas combinadas se extrajeron con CH_2Cl_2 (50 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron para proporcionar (*R*)- 4- isobutiloxazolidin- 2- ona (3.22 g) en un rendimiento del 88%. El producto crudo se usó para la siguiente reacción sin purificación. ^{1}H RMN (400 MHz, CD_3OD) δ 4,53- 4,47 (m, 1 H), 4,00- 3,92 (m, 2 H), 1,67 (ddq, J = 13, 8,0, 6,5 Hz, 1H), 1,56- 1,48 (m, 1 H), 1,40- 1,32 (m, 1 H), 0,95 (d, J = 6,1 Hz, 3 H), 0,93 (d, J = 6,1 Hz, 3 H).

Los compuestos intermedios de la Tabla 1 se prepararon por un método similar al descrito para la preparación del Intermedio A.

Tabla 1.

Intermedio B	Intermedio C	Intermedio D

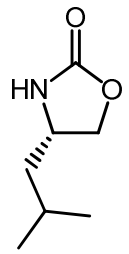
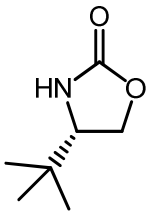
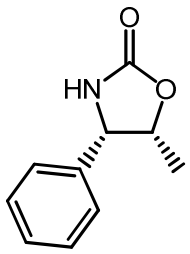
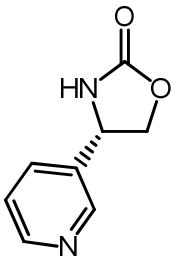
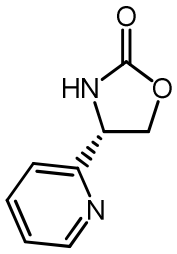
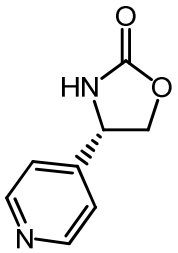
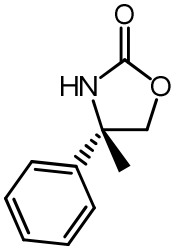
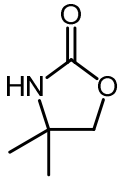
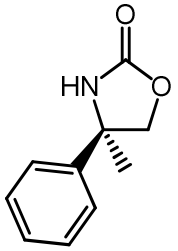
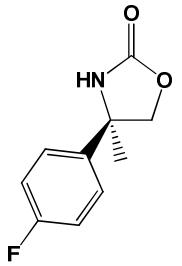
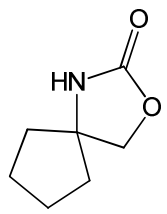
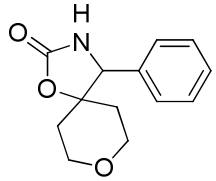
		
Intermedio E	Intermedio F	Intermedio T
		
Intermedio H	Intermedio I	Intermedio J
		
Intermedio K	Intermedio L	
		

Tabla 2. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada intermedio enumerado en la Tabla 1.

Intermedio: Nombre	^{1}H RMN (**400 MHz**) **δ ppm**	**LCMS**
B: (*S*)- 4- isobutiloxazolidin- 2- ona	($CDCl_3$) 6,59 (br s, 1H), 4,53- 4,48 (m, 1 H), 4,01- 3,92 (m, 2 H), 1,71- 1,54 (m, 2 H), 1,42- 1,35 (m, 1 H), 0,94 (d, J = 6,5 Hz, 3 H), 0,93 (d, J = 6,5 Hz, 3	ninguna señal UV

	H).	
C: (*S)* - 4- terc- Butiloxazolidin- 2- ona	(CD3OD) 4,37 (t, J = 9,1 Hz, 1 H), 4,23 (dd, J = 9,1, 5,6 Hz, 1 H), 3,61 (dd, J = 9,1, 5,6 Hz, 1 H), 0,90 (s, 9 H)	ninguna señal UV
D: (4S, 5R)- 5- metil- 4- feniloxazolidin- 2- ona	(CD_3OD) □ 7,42- 7,32 (m, 3 H), 7.27 a 7.24 (m, 2 H), 5,05 (q, J = 8,0, 6,4 Hz, 1 H), 4,98 (d, J = 8,0 Hz, 1 H), 0,89 (d, J = 6,5 Hz, 3 H)	ninguna señal UV
E: (*S*) - 4 - (Piridin- 3- il) oxazolidin- 2- ona		MS m/z 165,1 (M+H)+
F: (*S*) - 4 - (Piridin- 2- il) oxazolidin- 2- ona	($CDCl_3$) 8,62 (dt, J = 5,4, 1,1 Hz, 1 H), 7,80 (td, J = 7,8, 1,5 Hz, 1 H), 7,45 (d, J = 7,5 Hz, 1H), 7,33- 7,28 (m, 1 H), 6,40 (br s, 1H), 5,12 (dd, J = 8,8, 5,8 Hz, 1 H), 4,86 (t, J = 9,0 Hz, 1 H), 4,43 (dd, J = 8,5 , 5,5 Hz, 1 H)	HRMS (B) *m/z* 165.0663 (M+H)+
G: (S) - 4 - (piridin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,67- 8,66 (m, 2 H), 7,36- 7,34 (m, 2 H), 6,50 (br s, 1H), 5,04 - 5.00 (m, 1 H), 4,80 (t, J = 8,8 Hz , 1 H), 4,16 (dd, J = 8,5, 6,5 Hz, 1 H)	HRMS (B) *m/z* 165.0664 (M+H)+
H: (*S*)- 4- metil- 4- feniloxazolidin- 2- ona	($CDCl_3$) 7,45- 7,33 (m, 5 H), 6,10 (br s, 1H), 4,39 (q, J = 8,4 Hz, 2 H), 1,79 (s, 3 H)	HRMS (B) *m/z* 178.0871 (M+H)+
I: 4,4- dimetiloxazolidin- 2- ona	($CDCl_3$) 4,96 (br s, 1H), 4,12 (s, 2 H), 1,40 (s, 6 H)	ninguna señal UV
J: (*S*)- 4- metil- 4- feniloxazolidin- 2- ona	($CDCl_3$) 7,33- 7,19 (m, 5 H), 6,86 (br s, 1H), 4,32- 4,27 (m, 2 H), 1,67 (s, 3 H)	MS m/z 177,9 (M+H)+
K: (R) - 4 - (4- fluorofenil)- 4- metiloxazolidin- 2- ona	(CDCl3) δ 7,41- 7,36 (m, 2 H), 7.14 a 7.8 (m, 2 H), 6,06 (br s, 1H), 4,39 (d, J = 8,3 Hz, 1 H), 4,33 (d, J = 8,3 Hz, 1 H), 1,78 (s, 3 H)	MS m/z 195,9 (M+H)+
L: 3- oxa- 1- azaespiro [4.4] nonan- 2- ona	($CDCl_3$) δ 5,62 (br s, 1H), 4,25 (s, 2H), 1,90- 1,65 (m, 8 H)	ninguna señal UV

Intermedio M: 4- fenil- 1 ,8- dioxa- 3- azaespiro[4.5] decan- 2- ona



Paso 1: Preparación de 4 - (amino (fenil) metil) tetrahidro- 2H- piran- 4- ol

A dihidro- 2H- piran- 4 (3H)- ona (1.001 mg, 10 mmol) y trietilamina (0.279 ml, 2.00 mmol) se añadió lentamente TMS- CN (1.190 mg, 12.00 mmol) [Precaución: reacción

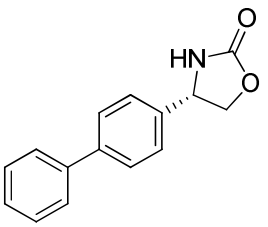
exotérmica]. Después de agitar durante 1 hora, la mezcla se concentró bajo presión reducida. El residuo, se disolvió en éter dietílico (10 ml), se añadió por goteo a bromuro de fenilmagnesio (solución 3 M en éter dietílico, 4.33 ml, 13.00 mmol). Se añadió adicional ~ 5 ml de éter dietílico y la suspensión se agitó durante ~ 4 horas. A la mezcla de reacción se añadió muy lentamente MeOH (3.0 ml), seguido por las adiciones cuidadosas y lentas de $NaBH_4$ (454 mg, 12.00 mmol) y MeOH (12 ml) en porciones (se observó desarrollo de gas). La mezcla de reacción se agitó durante la noche y se añadió cuidadosamente agua (~ 6 ml), seguido por una solución de HCl acuoso al 10% (~ 20 ml). La mezcla se agitó vigorosamente durante 4 horas y se añadió éter dietílico. La capa orgánica separada se extrajo con solución de HCl acuoso al 10% (1x ~ 20 ml). Las capas acuosas combinadas se lavaron con éter dietílico (2x). Las capas ácidas se hicieron básicas mediante la adición de solución acuosa de NaOH 6N. La mezcla blanca lechosa se extrajo con DCM (1x), acetato de etilo/THF (1:1; 1x) y acetato de etilo (2x). Las capas orgánicas (DCM y soluciones de acetato de etilo de forma independiente) se lavaron con solución acuosa saturada de $NaHCO_3$, se secaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida proporcionando ácido 4 - (amino(fenil)metil)tetrahidro- 2H- piran- 4- ol , que se usó directamente en la siguiente reacción sin purificación adicional.

Líquido amarillento. Rendimiento: 451 mg. LCMS m/z 208.2 (M+H)+, Rt 0.29 min.

Paso 2: Preparación de 4- fenil- 1 ,8- dioxa- 3- azaespiro [4.5]decan- 2- ona

A una mezcla de CDI (388 mg, 2.394 mmol) en THF (1.5 ml) se añadió lentamente una solución de 4 - (amino (fenil) metil) tetrahidro- 2H- piran- 4- ol (451 mg, 2.176 mmol) en THF (3 ml). La mezcla se agitó bajo argón durante ~ 5 horas. La mezcla se diluyó con solución de $NaHCO_3$ acuoso saturado y DCM. La capa acuosa separada se extrajo con DCM (2x) y las capas orgánicas combinadas se lavaron con solución acuosa de HCl 0.5 N y salmuera, se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en columna [SiO_2, 12 g, 0 - 100% de heptano/acetato de etilo] proporcionando 4- fenil- 1 ,8- dioxa- 3- azaespiro [4.5] decan- 2- ona como un sólido blanco. Rendimiento: 330 mg. LCMS m/z 234.1 (M+H)+; Rt 0.52 min.

Intermedio N: (S) - 4 - (bifenil- 4- il) oxazolidin- 2- ona



Paso 1: Preparación de vinilbifenilo

A una suspensión de bromuro de metiltrifenilfosfonio (5.10 g, 14.27 mmol) en THF (26 ml) se añadió lentamente terc- butóxido potásico (solución 1 M en THF, 14.27 ml) durante ~ 20 min a 0 ° C. La mezcla de reacción se dejó calentar hasta temperatura ambiente y se agitó durante 10 min. La mezcla se enfrió a 0 °C y se añadió una solución de 4- bifenilcarbaldehido (2.0 g, 10.98 mmol) en THF (9 ml) durante 20 min. La mezcla de reacción se dejó calentar hasta temperatura ambiente y se agitó durante ~ 19 horas. La mezcla se filtró y el filtrado se concentró bajo presión reducida. El residuo se disolvió/suspendió en DCM y se filtró a través de una almohadilla de sílice y el filtrado se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en columna [SiO_2, 80 g, EtOAc/heptano] para proporcionar vinilbifenilo (1.845 g) como un sólido blanco. LCMS Rt 0.79 min.

Paso 2: Preparación de 1 - (bifenil- 4- il)- 2- hidroxietilcarbamato de (S)- terc- butilo

A una solución de carbamato de terc- butilo (2.82 g, 24.08 mmol) en 1- propanol (30 ml) se añadió solución acuosa de NaOH (0.38 m, 61,5 ml, 23.36 mmol). La mezcla se agitó durante 5 min y 1,3- dicloro- 5 ,5- dimetilimidazolidina- 2 ,4- diona (2.351 g, 11.93 mmol). La mezcla se agitó se agitó durante 10 min y $(DHQ)_2PHAL$ (0.303 g, 0.388 mmoles), disuelto en se añadió 1- propanol (30 ml), seguido de una solución de vinilbifenilo (1.4 g, 7.77 mmol) en 1- propanol (60 ml). Se añadió una suspensión de dihidrato de osmiato de potasio (0.114 g, 0.311 mmol) en solución acuosa de NaOH, (0.38 m, 0.613 ml, 0.233 mmol) y la mezcla se agitó durante ~ 16 horas. La mezcla de reacción se diluyó con agua (200 ml) y se extrajo con EtOAc (3 x 200 ml). Las capas orgánicas combinadas se lavaron con salmuera (2x 400 ml), se secaron sobre sulfato de sodio, filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía en columna [SiO_2, 80 g, EtOAc/heptano] para proporcionar 1 - (bifenil- 4- il)- 2- hidroxietilcarbamato de (S)- terc- butilo (609 mg). LCMS m/z 258.2 (M+H; pérdida de *t*- Bu)$^+$, Rt 0,97 min.

^{1}H RMN (400 MHz, CD_3OD) δ ppm 7,62- 7,56 (m, 4 H), 7,45- 7,37 (m, 4 H), 7,34- 7,2 (m, 1 H), 4,69 (t, *J*= 5,8 Hz, 1 H), 3,76 - . 3,63 (m, 2H), 1,44 (br s, 9 H)

Paso 3: Preparación de (S)- 2- amino- 2- (bifenil- 4- il) etanol

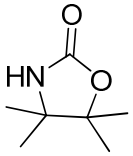
A una solución de 1 - (bifenil- 4- il)- 2- hidroxietilcarbamato de (S)- terc- butilo (608 mg, 1,940 mmol) en MeOH (3 ml) se añadió HCl (4 M en dioxano, 8 ml) a temperatura ambiente. La mezcla se agitó durante 1 hora y se concentró bajo presión reducida. El residuo se disolvió en DCM (10 ml)/agua (1.0 ml) y se agitó con $NaHCO_3$ durante 1 hora. La mezcla se separó mediante filtración y se enjuagó con DCM. El filtrado se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida proporcionando (S)- 2- amino- 2- (bifenil- 4- il) etanol (171 mg) como un sólido blanco. LCMS m/z 214.2 (M+H)+, Rt 0.58 min.

Paso 4: Preparación de (S) - 4 - (bifenil- 4- il) oxazolidin- 2- ona

A una solución de (S)- 2- amino- 2- (bifenil- 4- il) etanol (171 mg, 0.802 mmol) en THF (12 ml) bajo atmósfera de argón se añadió CDI (132 mg, 0.814 mmol). La solución se agitó a temperatura ambiente durante 2 horas. La mezcla se diluyó con solución acuosa saturada de $NaHCO_3$ (40 ml) y se extrajo con EtOAc (2x 30 ml). Las capas orgánicas combinadas se lavaron con solución acuosa de HCl 0.5 M (30 ml), salmuera (40 ml), se secaron sobre sulfato de sodio, se filtraron y se concentraron bajo presión reducida. El residuo se disolvió en DCM y se concentró bajo presión reducida para proporcionar (S) - 4 - (bifenil- 4- il) oxazolidin- 2- ona cruda (156 mg) como un sólido de color beige, que se usó sin purificación adicional. LCMS m/z 240.1 (M+H)+, Rt 0.80 min.

^{1}H RMN (400 MHz, CD_3OD) δ ppm 4,19 (dd, *J*= 8,61, 6,50 Hz, 1 H) 4,80 (t, *J*= 8,73 Hz, 1 H) 5,05 (dd, *J*= 8,78, 6,48 Hz, 1 H) 7,31- 7,38 (m, 1 H) 7,39- 7,54 (m, 4 H) 7,55- 7,71 (m, 4 H).

Intermedio P: 4,4,5,5- tetrametiloxazolidin- 2- ona



Paso 1: Preparación de 2 - (terc- butoxicarbonilamino)- 2- metilpropanoato de metilo

A una solución del ácido 2 - (terc- butoxicarbonilamino)- 2- metilpropanoico (10.03 g, 49.4 mmol) en MeOH/DCM (60mL/140mL) a temperatura ambiente se añadió por goteo (trimetilsilil)diazometano (37.0 ml, 74.0 mmol) . La mezcla de reacción se agitó durante 30 minutos. Se añadió por goteo ácido acético para inactivar (trimetilsilil) diazometano. La mezcla de reacción se concentró bajo presión reducida para proporcionar el producto deseado como un sólido blanco (10.56 g). LCMS m/z 240.2 (M+Na)+, Rt 0.71 min.

Paso 2: Preparación de 3- hidroxi- 2 ,3- dimetilbutan- 2- ilcarbamato de terc- butilo

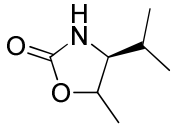
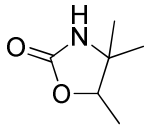
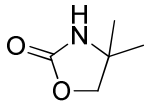
A una solución de 2 - (terc- butoxicarbonilamino)- 2- metilpropanoato de metilo (10.56 g, 48.6 mmol) en THF (300 ml) a 0 ºC se añadió por goteo bromuro de metilmagnesio (64.8 ml, 194 mmoles). el baño frío se retiró después de 1 hora. La reacción se agitó a 20 °C durante 4 horas. La reacción se enfrió de nuevo a 0 °C y se inactivó con solución saturada de NH_4Cl (10 ml). La mezcla de reacción se dejó calentar a temperatura ambiente, y se diluyó con EtOAc (100 ml) y agua (50 ml). Las fases se separaron y la capa acuosa se extrajo con EtOAc (2x100 mL). Los orgánicos combinados se secaron (Na_2SO_4) y se concentraron. El residuo se purificó a través de cromatografía ultrarrápida en gel de sílice (0- 20% de EtOAc- hexanos) para proporcionar el producto deseado como un sólido blanco (9.02 g). LCMS m/z 240.1 (M+Na)+, Rt 0.78 min.

Paso 3: Preparación de 4,4,5,5- tetrametiloxazolidin- 2- ona

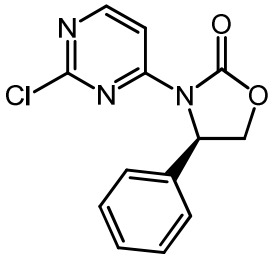
A 3- hidroxi- 2 ,3- dimetilbutan- 2- ilcarbamato de terc- butilo (10.02 g, 46.1 mmol) en THF (300 ml) se añadió en porciones de potasio de 2- metilpropan- 2- olato (7.24 g, 64.6 mmoles). La reacción se agitó durante cinco horas y se inactivó con HCl (1M, 66 ml) a pH = 2. La mezcla de reacción se concentró al vacío a aproximadamente un tercio del volumen, y se diluyó con agua (50 ml). Después, la capa acuosa se extrajo con DCM (3x100 ml). La capan orgánica combinada se lavó con salmuera (50 ml), se secó (Na_2SO_4) y se concentró para proporcionar el producto crudo como un aceite de color canela claro (6.25 g). LCMS m/z 144.1 (M+H)+, Rt 0.42 min.

Los compuestos intermedios de la Tabla 2b se prepararon por un método similar al descrito para la preparación del Intermedio P.

Tabla 2b.

Intermedio: Nombre	**Estructura**	**LCMS**
Q: (4S)- 4- isopropil- 5- metiloxazolidin- 2- ona		MS m/z (M+H)+ 144.4, Rt 0.47 min
R: 4,4,5- trimetiloxazolidin- 2- ona		MS m/z (M+H)+ 130.4, Rt 0.36 min
S: 4,4- dimetiloxazolidin- 2- ona		MS m/z (M+H)+ 116.0, Rt 0.28 min

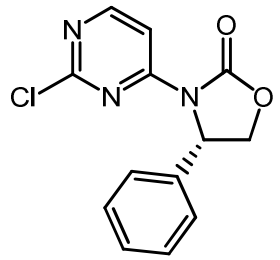
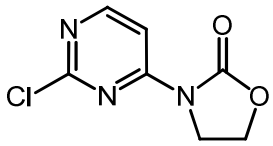
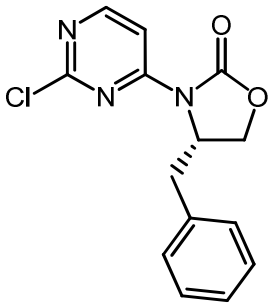
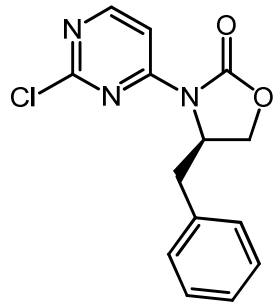
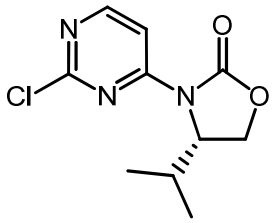
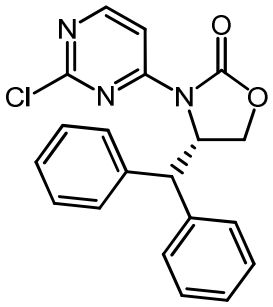
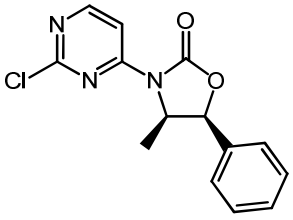
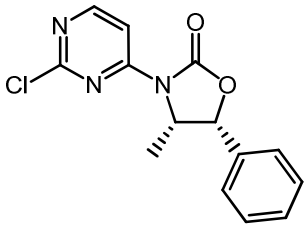
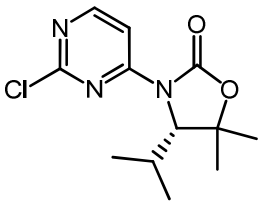
Intermedio 1: (*R*) - 3 - (2- cloropirimidin- 4- il)- 4- feniloxazolidin- 2- ona

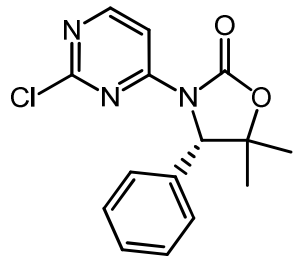
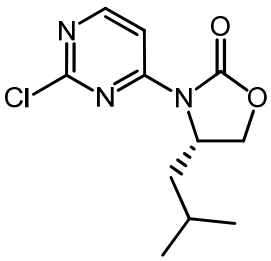
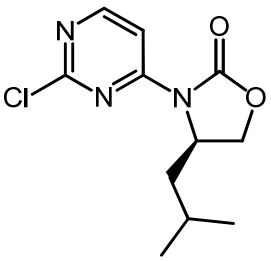
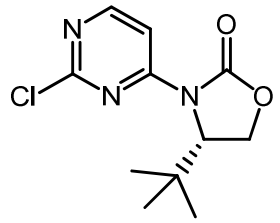
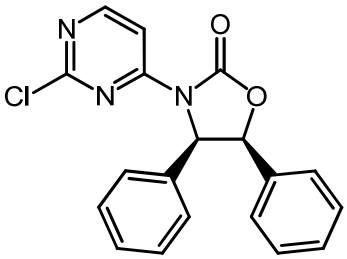
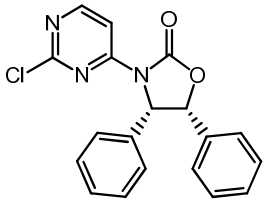
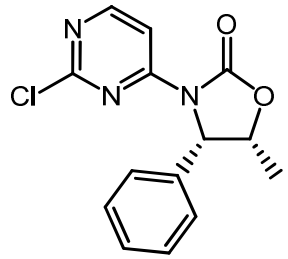
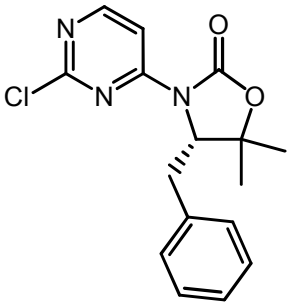
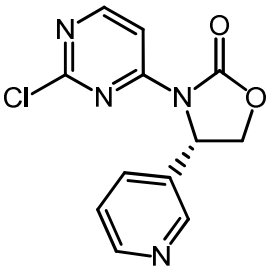
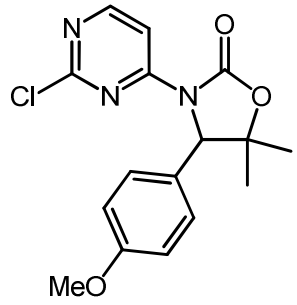
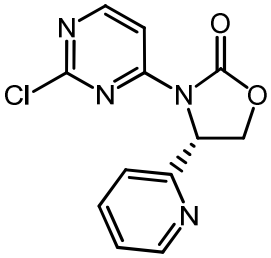
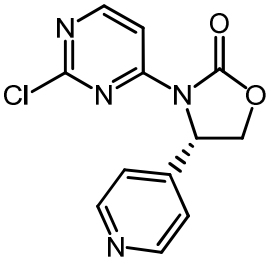


Una solución de (*R*)- 4- feniloxazolidin- 2- ona (2.9484 g, 18.07 mmol) y 2,4- dicloropirimidina (3.1872 g, 21.39 mmol, 1.184 equiv) en DMF (30 ml) se trató con NaH (95%, 0.4773 g, 18.89 mmol, 1.046 equiv), después la mezcla resultante (de color amarillo a rojo turbio) se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con EtOAc (200 ml), se lavó con una solución saturada de NH_4Cl (75 ml) y NaCl acuoso al 4% (2 x 100 ml), se secó sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano 0 a 40%) proporcionó (*R*) - 3 - (2- cloropirimidin- 4- il)- 4- feniloxazolidin- 2- ona (2.7020 g, rendimiento del sólido blanco pegajoso) en 46,9%. ^{1}H RMN (400 MHz, CD_3OD) □ 8,47 (d, J = 5,6 Hz, 1 H), 8,18 (d, J = 6,1 Hz, 1H), 7,38- 7,30 (m, 5 H), 5,81 (dd, J = 8,6, 3,5 Hz, 1 H), 4,88 (t, J = 8,6 Hz, 1 H), 4,37 (dd, J = 8,6, 3,5 Hz, 1 H), MS m/z 276,4 (M+H)+.

Los compuestos intermedios de la Tabla 3 se prepararon por un método similar al descrito para la preparación del intermedio 1.

Tabla 3.

Intermedio 2	Intermedio 3	Intermedio 4
		
Intermedio 5	Intermedio 6	Intermedio 7
		
Intermedio 8	Intermedio 9	Intermedio 10
		
Intermedio 11	Intermedio 12	Intermedio 13

		
Intermedio 14	Intermedio 15	Intermedio 16
		
Intermedio 17	Intermedio 18	Intermedio 19
		
Intermedio 20	Intermedio 21	Intermedio 22
		
Intermedio 23	Intermedio 24	Intermedio 25

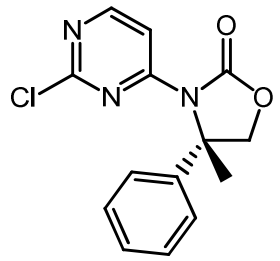
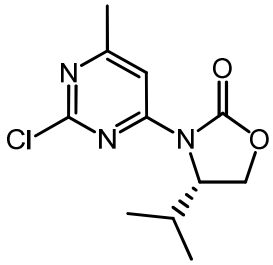
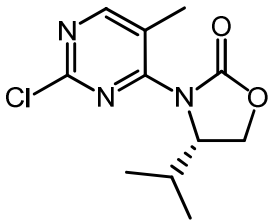
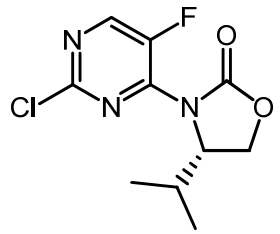
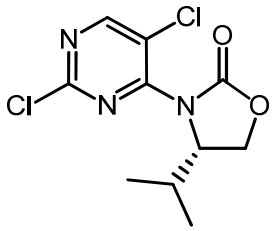
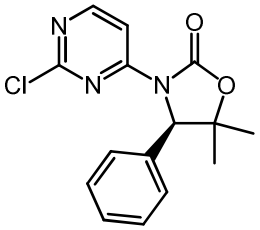
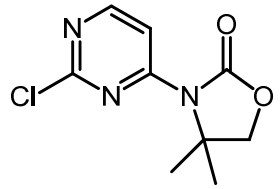
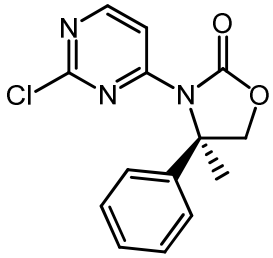
		
Intermedio 26	Intermedio 27	Intermedio 28
		
Intermedio 29	Intermedio 30	
		

Tabla 4. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada intermedio enumerado en la Tabla 3.

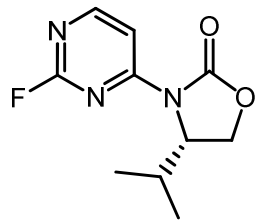
Intermedio: Nombre	**^{1}H RMN (400 MHz) δ ppm**	**LCMS**
2: (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- feniloxazolidin- 2- ona	($CDCl_3$) 8,47 (d, J = 6,1 Hz, 1 H), 8,18 (d, J = 5,7 Hz, 1H), 7,39- 7,29 (m, 5 H), 5,81 (dd, J = 8,6, 3,5 Hz, 1 H) , 4,88 (t, J = 8,8 Hz, 1 H), 4,37 (dd, J = 8,8, 3,8 Hz, 1 H)	MS m/z 276,5 (M+H)+
3: 3 - (2- cloropirimidin- 4- il) oxazolidin- 2- ona	(CD_3OD) 8,48 (d, J = 6,1 Hz, 1 H), 8,16 (d, J = 6,1 Hz, 1 H), 4,54 (t, J = 7,8 Hz, 2 H), 4,22 (t, J = 8,1 Hz , 2 H)	MS m/z 200,4 (M+H)+
4: (*S*)- 4- bencil- 3- (2- cloropirimidin- 4- il) oxazolidin- 2- ona	(CD_3OD) 8,52 (d, J = 6,1 Hz, 1 H), 8,15 (d, J = 6,1 Hz, 1H), 7,32- 7,22 (m, 5 H), 5.7- 5.2 (m, 1 H), 4,46 - 4,37 (m, 2 H), 3.30- 3.27 (m, 1 H), 3,06 (dd, J = 13, 8,1 Hz, 1 H)	MS m/z 290,3 (M+H)+
5: (*R*)- 4- bencil- 3- (2-	(CD_3OD) 8,51 (d, J = 5,6 Hz, 1 H),	MS m/z

cloropirimidin- 4- il) oxazolidin- 2- ona	8,13 (d, J = 5,6 Hz, 1 H), 7.31- 7.21 (m, 5 H), 5,06- 4,98 (m, 1 H), 4,45 - 4,34 (m, 2 H), 3.30- 3.25 (m, 1 H), 3,04 (dd, J = 14, 8,1 Hz, 1 H)	290,3 (M+H)+
6: (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(CD_3OD) 8,50 (d, J = 5,9 Hz, 1 H), 8,17 (d, J = 5,8 Hz, 1H), 4,83- 4,76 (m, 1 H), 4,48- 4,43 (m, 2 H), 2,56 (dtd, J = 14, 7,0, 3,8 Hz, 1 H), 0,99 (d, J = 7,1 Hz, 3 H), 0,87 (d, J = 7,1 Hz, 3 H)	MS m/z 242,6 (M+H)+
7: (*S*)- 4- benzhidrilo- 3- (2- cloropirimidin- 4- il) oxazolidin- 2- ona	(CD_3OD) 8,41 (d, J = 5,8 Hz, 1 H), 8,01 (d, J = 5,8 Hz, 1H), 7,35- 7,26 (m, 3 H), 7.24- 7.12 (m, 7 H), 5,86 - 5,70 (m, 1 H), 4,74 (d, J = 7,1 Hz, 1 H), 4,64 (t, J = 8,5 Hz, 1 H), 4,45 (dd, J = 9,1, 2,0 Hz, 1 H)	MS m/z 366,1 (M+H)+
8: (*4R, 5S*) - 3 - (2- cloropirimidin- 4- il)- 4- metil- 5- feniloxazolidin- 2- ona	(CD_3OD) 8,52 (d, J = 6,1 Hz, 1 H), 8,20 (d, J = 6,1 Hz, 1H), 7,48- 7,38 (m, 5 H), 5,92 (d, J = 7,6 Hz, 1 H), 5,15 (quintuplete, J = 6,8 Hz, 1 H), 0,98 (d, J = 6,6 Hz, 3 H)	MS m/z 290,3 (M+H)+
9: (*4S, 5R*) - 3 - (2- cloropirimidin- 4- il)- 4- metil- 5- feniloxazolidin- 2- ona	(CD_3OD) 8,52 (d, J = 6,1 Hz, 1 H), 8,20 (d, J = 6,1 Hz, 1H), 7,48- 7,38 (m, 5 H), 5,92 (d, J = 7,6 Hz, 1 H), 5,15 (quintuplete, J = 6,7 Hz, 1 H), 0,98 (d, J = 6,6 Hz, 3 H)	MS m/z 290,3 (M+H)+
10: (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropil- 5 ,5- dimetiloxazolidin- 2- ona	(CD_3OD) 8,48 (d, J = 5,8 Hz, 1 H), 8,20 (d, J = 5,8 Hz, 1 H), 4,63 (d, J = 3,1 Hz, 1 H), 2,29 (dtd, J = 14, 7,0, 3,1, 1 H), 1,60 (s, 3H), 1,47 (s, 3H), 1,05 (d, J = 7,1 Hz, 3 H), 0,99 (d, J = 7,1 Hz, 3 H)	MS m/z 270,1 (M+H)+
11: (*S*) - 3 - (2- cloropirimidin- 4- il) - 5,5- dimetil- 4- feniloxazolidin- 2- ona	(CD_3OD) 8,48 (d, J = 5,8 Hz, 1 H), 8,25 (d, J = 5,8 Hz, 1H), 7,39- 7,30 (m, 3 H), 7,22 (br s, 2 H), 1,67 (s, 3 H), 1,04 (s, 3 H)	MS m/z 304,3 (M+H)+
12: (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isobutiloxazolidin- 2- ona	(CD_3OD) 8,49 (d, J = 5,9 Hz, 1 H), 8,13 (d, J = 5,9 Hz, 1 H), 4,83 (ddt, J = 10, 7,6, 2,9 Hz, 1H), 4,58- 4,54 (m, 1 H), 4,31 (dd, J = 8,8, 2,8 Hz, 1H), 1,87- 1,81 (m, 1 H), 1,75- 1,65 (m, 1 H), 1,62- 1,55 (m, 1 H) , 1,05 (d, J = 6,5 Hz, 3 H), 0,99 (d, J = 6,5 Hz, 3 H)	MS m/z 256,3 (M+H)+
13: (*R*) - 3 - (2- cloropirimidin- 4- il)- 4- isobutiloxazolidin- 2- ona	(CD_3OD) 8,48 (d, J = 5,8 Hz, 1 H), 8,12 (d, J = 6,0 Hz, 1H), 4,87- 4,79 (m, 1 H), 4,57 (t, J = 8,6 Hz, 1 H), 4,31 (dd, J = 8,6, 2,5 Hz, 1H), 1,87- 1,81 (m, 1 H), 1,75- 1,65 (m, 1 H), 1,62- 1,56 (m, 1 H), 1,05 (d , J = 6,6 Hz, 3 H), 0,99 (d, J = 6,6 Hz, 3 H)	MS m/z 256,3 (M+H)+
14: (*S*)- 4- terc- butil- 3- (2-	(CD_3OD) 8,50 (d, J = 5,9 Hz, 1 H),	MS m/z

cloropirimidin- 4- il) oxazolidin- 2- ona	8,12 (d, J = 5,9 Hz, 1 H), 4,94 (dd, J = 7,6, 1,5 Hz, 1 H), 4,54 (dd, J = 9,1, 1,5 Hz, 1H), 4,46- 4,42 (m, 1 H), 0,95 (s, 9H)	256,4 (M+H)+
15: (*4R, 5S*) - 3 - (2- cloropirimidin- 4- il) - 4,5- difeniloxazolidin- 2- ona	(CD_3OD) 8,52 (d, J = 5,9 Hz, 1 H), 8,33 (d, J = 5,9 Hz, 1 H), 7.14- 7.5 (m, 8 H), 6,93- 6,91 (m, 2 H), 6,18 - 6,11 (m, 2 H)	MS m/z 352,4 (M+H)+
16: (*4S, 5R*) - 3 - (2- cloropirimidin- 4- il) - 4,5- difeniloxazolidin- 2- ona	(CD_3OD) 8,52 (d, J = 5,9 Hz, 1 H), 8,33 (d, J = 5,9 Hz, 1 H), 7.14- 7.5 (m, 8 H), 6,93- 6,91 (m, 2 H), 6,18 - 6,11 (m, 2 H)	MS m/z 352,3 (M+H)+
17: (*4S, 5R*) - 3 - (2- cloropirimidin- 4- il)- 5- metil- 4- feniloxazolidin- 2- ona	(CD_3OD) 8,47 (d, J = 5,9 Hz, 1 H), 8,25 (d, J = 5,9 Hz, 1H), 7,40- 7,31 (m, 3 H), 7,21 (d, J = 7,0 Hz, 2H), 5,80 (d, J = 7,5 Hz, 1 H), 5.18- 5.12 (m, 1 H), 1,02 (d, J = 6,5 Hz, 3 H);	MS m/z 290,4 (M+H)+
18: (*S*)- 4- bencil- 3- (2- cloropirimidin- 4- il) - 5,5- dimetiloxazolidin- 2- ona	($CDCl_3$) 8,45 (d, J = 5,8 Hz, 1 H), 8,16 (d, J = 5,8 Hz, 1H), 7,37- 7,28 (m, 4 H), 7.25- 7.21 (m, 1 H), 4,87 (dd, J = 9,0, 4,5 Hz, 1 H), 3,24 (dd, J = 15, 4,5 Hz, 1 H), 2,97 (dd, J = 14, 9,0 Hz, 1 H), 1,51 (s, 3 H), 1,45 (s, 3 H)	MS m/z 318,1 (M+H)+
19: (*S*) - 3 - (2- cloropirimidin- 4- il) - 4 - (piridin- 3- il) oxazolidin- 2- ona	($CDCl_3$) 8,76- 8,75 (m, 1 H), 8,62 (d, J = 3,5 Hz, 1 H), 8,47 (d, J = 5,8 Hz, 1 H), 8,16 (d, J = 5,8 Hz, 1 H), 7,74 (dt, J = 8,0, 2,0 Hz, 1 H), 7,35 (dd, J = 7,8, 4,8 Hz, 1 H), 5,83 (dd, J = 8,8, 3,8 Hz, 1 H), 4,90 (t , J = 9,0 Hz, 1 H), 4,50 (dd, J = 9,0, 3,5 Hz, 1 H)	MS m/z 277,4 (M+H)+
20: 3 - (2- cloropirimidin- 4- il) - 4 - (4- metoxifenil) - 5,5- dimetiloxazolidin- 2- ona	($CDCl_3$) 8,44 (d, J = 5,8 Hz, 1 H), 8,25 (d, J = 5,8 Hz, 1 H), 7,13 (br d, J = 7,0 Hz, 2 H), 6,89 (d, J = 9,0 Hz, 2 H), 5,39 (s, 1 H), 3,82 (s, 3H), 1,67 (s, 3H), 1,11 (s, 3 H)	HRMS (B) *m/z* 334.0954 (M+H)+
21: (*S*) - 3 - (2- cloropirimidin- 4- il) - 4 - (piridin- 2- il) oxazolidin- 2- ona	($CDCl_3$) 8,62- 8,60 (m, 1 H), 8,45 (d, J = 5,8 Hz, 1 H), 8,22 (d, J = 5,8 Hz, 1 H), 7,73 (td, J = 7,7, 1,8 Hz, 1 H), 7,43 (d, J = 7,5 Hz, 1 H), 7.29- 7.26 (m, 1 H), 5,85 (dd, J = 8,5, 3,5 Hz, 1 H), 4,82 (t, J = 8,8 Hz , 1 H), 4,64 (dd, J = 8,8, 3,8 Hz, 1 H)	MS m/z 277,0 (M+H)+
22: (*S*) - 3 - (2- cloropirimidin- 4- il) - 4 - (piridin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,72- 8,70 (m, 1 H), 8,52 (d, J = 5,8 Hz, 1 H), 8,20 (d, J = 5,8 Hz, 1H), 7,43- 7,42 (m, 1 H), 5,81 (dd, J = 8,8, 3,8 Hz, 1 H), 4,91 (t, J = 9,0 Hz, 1 H), 4,44 (dd, J = 9,3, 3,8 Hz, 1 H)	MS m/z 276,9 (M+H)+
23: (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- metil- 4- feniloxazolidin- 2- ona	($CDCl_3$) 8,44 (d, J = 5,8 Hz, 1 H), 8,13 (d, J = 5,8 Hz, 1H), 7,41- 7,28 (m, 5 H), 4,46 (d, J = 8,5 Hz, 1 H), 4,38 (d, J	MS m/z 289,9 (M+H)+

	= 8,5 Hz, 1 H), 2,23 (s, 3 H)	
24: (*S*) - 3 - (2- cloro- 6- metilpirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	($CDCl_3$) 8,06 (s, 1H), 4,83- 4,77 (m, 1 H), 4,44- 4,34 (m, 2 H), 2,65- 2,55 (m, 1 H), 2,53 (s, 3H), 1,00 (d, J = 8 Hz, 3 H), 0,88 (d, J = 8 Hz, 3 H)	MS m/z 255,8 (M+H)+
25: (*S*) - 3 - (2- cloro- 5- metilpirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	($CDCl_3$) 8,50 (s, 1H), 5,01- 4,96 (m, 1 H), 4,53 (t, J = 9,0 Hz, 1 H), 4,28 (t, J = 8,8 Hz, 1 H), 2,35 (s , 3 H), 2,16 (td, J = 7,0 Hz, J = 4,5 Hz, 1 H), 0,93 (d, J = 7,0 Hz, 3 H), 0,84 (d, J = 6,5 Hz, 3 H)	MS m/z 255,9 (M+H)+
26: (*S*) - 3 - (2- cloro- 5- fluoropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO- d_6) 8,95 (d, J = 3,0 Hz, 1H), 4,79- 4,73 (m, 1 H), 4,58 (t, J = 9,0 Hz, 1 H), 4,41 (dd, J = 8,5 Hz, J = 6,5 Hz, 1 H), 2.24 - 2.16 (m, 1 H), 0,86 (d, J = 7,0 Hz, 3 H), 0,78 (d, J = 6,5 Hz, 3 H)	MS m/z 259,9 (M+H)+
27: (*S*) - 3 - (2,5- dicloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO- d_6) 9,01 (s, 1 H), 4,81 (ddd, J = 9,1 Hz, J = 7,8 Hz, J = 4,3 Hz, 1 H), 4,59 (t, J = 8,8 Hz, 1 H), 4,38 - 4,33 (m, 1H), 2,06 (td, J = 7,0 Hz, J = 4,3 Hz, 1 H), 0,84 (d, J = 6,8 Hz, 3 H), 0,78 (d, J = 6,8 Hz, 3 H)	MS m/z 274,2 (M - H) -
28: (*R*) - 3 - (2- cloropirimidin- 4- il) - 5,5- dimetil- 4- feniloxazolidin- 2- ona	($CDCl_3$) 8,20 (d, J = 5,8 Hz, 1 H), 8,01 (d, J = 5,8 Hz, 1 H), 7.16 - 7.7 (m, 3 H), 6,98- 6,96 (m, 2 H), 5,19 (s, 1 H), 1,46 (s, 3H), 0,87 (s, 3 H)	MS m/z 303,9 (M+H)+
29: 3 - (2- cloropirimidin- 4- il) - 4,4- dimetiloxazolidin- 2- ona	($CDCl_3$) 8,47 (d, J = 5. 8 Hz, 1 H), 8,06 (d, J = 5,8 Hz, 1 H), 4,17 (s, 2 H), 1,77 (s, 6 H)	MS m/z 228,3 (M+H)+
30: (*R*) - 3 - (2- cloropirimidin- 4- il)- 4- metil- 4- feniloxazolidin- 2- ona	($CDCl_3$) 8,43 (d, J = 5,8 Hz, 1 H), 8,13 (d, J = 5,8 Hz, 1H), 7,40- 7,36 (m, 4 H), 7,35- 7,28 (m, 1 H), 4,45 (d, J = 8,6 Hz, 1 H), 4,38 (d, J = 8,6 Hz, 1 H), 2,22 (s, 3 H)	MS m/z 289,9 (M+H)+

Intermedio 31: (S) - 3 - (2- fluoropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona

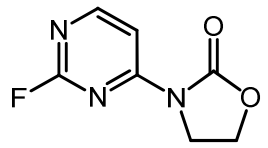
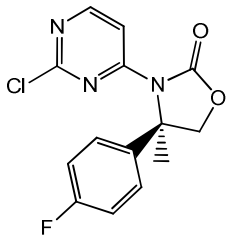
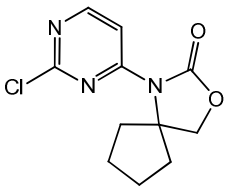
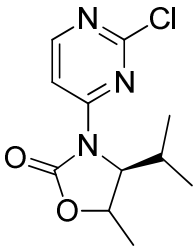
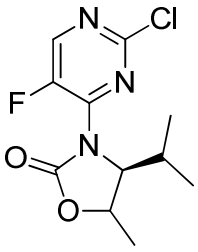
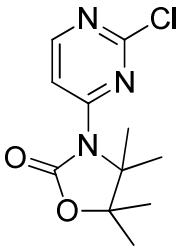


Una solución de 2,4- difluoropirimidina (3.5 ml, 41 mmol) y (S)- 4- isopropiloxazolidin- 2- ona (5,3 g 41 mmol) en 30 ml de DMF se enfrió a 0 °C bajo atmósfera de N_2. Se añadió lentamente NaH (2.1 g de suspensión al 60%, 53 mmol). Se observó exoterma de burbujeo. La temperatura interna se mantuvo por debajo de 5 °C. Después de 5 minutos,

se retiró el baño frío. La mezcla de reacción (una suspensión de arena) se dejó calentar a la temperatura ambiente y se agitó 18 h. La mezcla de reacción se diluyó con agua (100 ml) y se extrajo con (3 x 75 ml) de EtOAc. La capa orgánica se lavó con 50 ml de agua, y salmuera. Se secó sobre Na_2SO_4, y se concentró sobre gel de sílice al vacío. La cromatografía en columna (EtOAc/heptano 10 a 100% de gradiente) proporcionó 3,1 g de (S) - 3 - (2- fluoropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (IV) como un sólido cristalino blanco (33%) . ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,50 (dd, J = 5,8, 2,2 Hz, 1H), 8,19 (dd, J = 5,8, 3,8 Hz, 1H), 4,79 (dt, J = 8,1, 3,5 Hz, 1H) , 4,48- 4,34 (m, 2H), 2,64 (heptd, J = 7,0, 3,6 Hz, 1H), 1,01 (d, J = 7,0 Hz, 3H), 0,90 (d, J = 6,9 Hz, 3H). MS m/z 471,8 y 471,8 (M+H)+.

Los compuestos intermedios de la Tabla 4b se prepararon por un método similar al descrito para la preparación del Intermedio 1 y 31.

Tabla 4b.

Intermedio 32	Intermedio 33	Intermedio 34
		
Intermedio 35	Intermedio 36	Intermedio 37
		
Intermedio 38	Intermedio 39	Intermedio 40

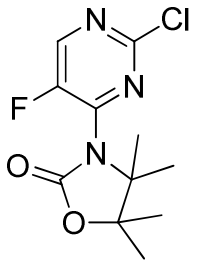
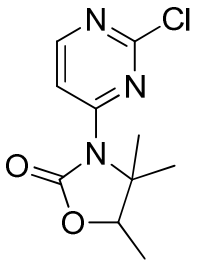
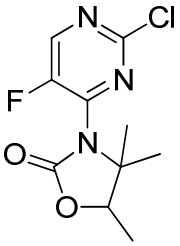
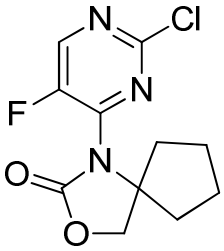
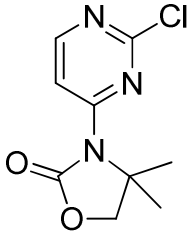
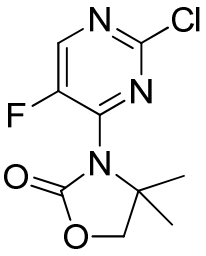
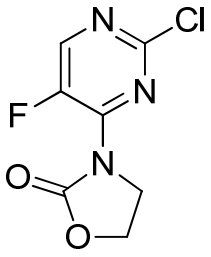
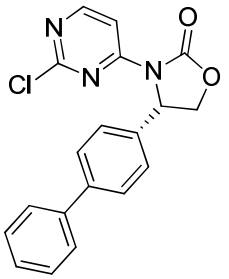
		
Intermedio 41	Intermedio 42	Intermedio 43
		
Intermedio 44		
		

Tabla 4c. Nombre químico, desplazamientos RMN químicos y señal LCMS para cada intermedio enumerado en la Tabla 4b.

Intermedio: Nombre	**^{1}H RMN (400 MHz) δ ppm**	**LCMS**
32: 3 - (2- fluoropirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,51 (dd, J = 5,8, 2,0 Hz, 1 H), 8,17 (dd, J = 5,8, 2,0 Hz, 1H), 4,61- 4,57 (m, 2 H), 4.31- 4.27 (m, 2 H)	MS m/z 184,0 (M+H)
33: (R) - 3 - (2- cloropirimidin- 4- il) - 4 - (4- fluorofenil)- 4- metiloxazolidin- 2- ona	($CDCl_3$) 8,45 (d, J = 5,8 Hz, 1 H), 8,12 (d, J = 5,8 Hz, 1H), 7,40- 7,35 (m, 2 H), 7.10 - 7.4 (m, 2 H), 4,40 - 4,37 (m, 2 H), 2,22 (s, 3 H)	MS m/z 308,0 (M+H)+
34: 1 - (2- cloropirimidin- 4- il)- 3- oxa- 1- azaespiro [4.4] nonan- 2- ona	(CDCl3) 8,48 (d, J = 5,8 Hz, 1 H), 8,12 (d, J = 5,8 Hz, 1 H), 4,22 (s, 2H), 2,66- 2,59 (m, 2 H), 2.22- 2.14 (m, 2 H), 1,75- 1,62 (m, 4 H)	MS m/z 254,1 (M+H)+

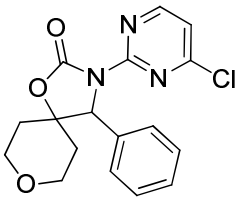
35: (4S) - 3 - (2-cloropirimidin- 4- il)- 4-isopropil- 5- metiloxazolidin-2- ona		MS m/z (M+H)+ 256,2, Rt 0,87 min
36: (4S) - 3 - (2- cloro- 5-fluoropirimidin- 4- il)- 4-isopropil- 5- metiloxazolidin-2- ona		MS m/z (M+H)+ 274,1, Rt 0,82 min
37: 3 - (2- cloropirimidin- 4- il) 4,4,5,5- tetrametiloxazolidin- 2-ona		MS m/z (M+H)+ 256,1, Rt 0,85 min
38: 3 - (2- cloro- 5-fluoropirimidin- 4- il) 4,4,5,5-tetrametiloxazolidin- 2- ona		MS m/z (M+H)+ 274,1, Rt 0,83 min
39: 3 - (2- cloropirimidin- 4- il) - 4,4,5- trimetiloxazolidin- 2-ona		MS m/z (M+H)+ 242,1, Rt 0,81 min
40: 3 - (2- cloro- 5-fluoropirimidin- 4- il) - 4,4,5-trimetiloxazolidin- 2- ona		MS m/z (M+H)+ 260,1, Rt 0,77 min
41: 1 - (2- cloro- 5-fluoropirimidin- 4- il)- 3- oxa-1- azaespiro [4.4] nonan- 2-ona	($CDCl_3$) 8,47 (d, J = 2 Hz, 1 H), 4,28 (s, 2H), 2,54- 2,44 (m, 2 H), 2,11- 1,99 (m, 2 H), 1,90- 1,82 (m, 2 H), 1,72-1,61 (m, 42 H)	MS m/z (M+H)+ 272,4
42: 3 - (2- cloropirimidin- 4- il) - 4,4- dimetiloxazolidin- 2- ona		MS m/z (M+H)+ 228,0, Rt 0,73 min
43: 3 - (2- cloro- 5-fluoropirimidin- 4- il) - 4,4-dimetiloxazolidin- 2- ona		MS m/z (M+H)+ 246,0, Rt 0,70 min
44: 3 - (2- cloro- 5-fluoropirimidin- 4- il) oxazolidin- 2- ona		MS m/z (M+H)+ 218,0, Rt 0,47 min

Intermedio 46: (S) - 4 - (bifenil- 4- il) - 3 - (2- cloropirimidin- 4- il) oxazolidin- 2- ona



A una solución de 2,4- dicloropirimidina (46.5 mg, 0.312 mmol) y (S) - 4 - (bifenil- 4- il) oxazolidin- 2- ona (74.7 mg, 0.312 mmol) en DMF (700 l) se añadió NaH (60% por peso, 10.49 mg, 0.437 mmol) en dos porciones dentro de ~ 5 min [Precaución: exotérmica; desarrollo de gas] a temperatura ambiente (baño de agua). La mezcla de reacción se agitó durante 1.5 horas. La mezcla se diluyó con EtOAc (25 ml), se agitó durante 5 min y después se diluyó lentamente con salmuera diluida (10 ml; salmuera/agua 1:1). La mezcla se vertió en salmuera diluida (40 ml) y EtOAc (25 ml). La fase orgánica separada se lavó con salmuera diluida (3 x 40 ml), se secó sobre Na_2SO_4, se filtró y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en columna [SiO_2, 40 g, EtOAc/heptano] para proporcionar (S) - 4 - (bifenil- 4- il) - 3 - (2- cloropirimidin- 4- il) oxazolidin- 2- ona (49,5 mg). LCMS m/z 352,2 (M+H)+, Rt 1,06 min.

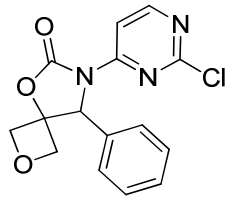
Intermedio 47: 3 - (2- cloropirimidin- 4- il)- 4- fenil- 1 ,8- dioxa- 3- azaespiro [4.5] decan- 2- ona



A una mezcla de 4- fenil- 1 ,8- dioxa- 3- azaespiro [4.5] decan- 2- ona (300 mg, 1,286 mmol) y 2,4- dicloropirimidina (192 mg, 1,286 mmol) en DMF (7 ml) en atmósfera de argón se añadió NaH (60% por peso., 67.9 mg, 2.83 mmol) en dos porciones. La mezcla se agitó durante ~ 1 hora. La mezcla de reacción se vertió cuidadosamente en solución acuosa de HCl 0.25 N enfriado con hielo. Se añadieron DCM y solución acuosa de $NaHCO_3$. La capa acuosa separada se extrajo con DCM (3x) y acetato de etilo (1x). Las capas orgánicas (DCM y acetato de etilo que contiene capas de forma independiente) se

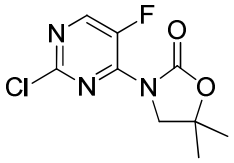
lavaron con salmuera, se secaron sobre Na_2SO_4 y se filtraron. Las capas orgánicas se combinaron y se concentraron bajo presión reducida proporcionando ácido 3 - (2- cloropirimidin- 4- il)- 4- fenil- 1 ,8- dioxa- 3- azaespiro [4.5] decan- 2- ona (330 mg) como un líquido amarillento, que se utilizó directamente en la siguiente reacción sin purificación adicional. LCMS m/z 346,1 (M+H)+, Rt 0,83 min.

Intermedio 48: 7 - (2- cloropirimidin- 4- il)- 8- fenil- 2 ,5- dioxa- 7- azaespiro [3.4] octan- 6- ona



Preparado usando métodos similares a los descritos anteriormente para 3 - (2- cloropirimidin- 4- il)- 4- fenil- 1 ,8- dioxa- 3- azaespiro [4.5] decan- 2- ona, pero a partir de oxetan- 3- ona .
LCMS m/z 318.1 (M+H)+, Rt 0.78 min.

Intermedio 50: 3 - (2- cloro- 5- fluoropirimidin- 4- il) - 5,5- dimetiloxazolidin- 2- ona



Paso 1
Una solución de 2,4- dicloro- 5- fluoropirimidina (2 g, 11.98 mmol) en acetonitrilo (10 ml) se enfrió a - 40 ºC, evitando la congelación. A esta solución se añadió diisopropilamina (3.82 ml, 21,88 mmol) seguido de 1- amino- 2- metil- 2- ol (1.5 g, 16.83 mmol). La mezcla de reacción se retiró del baño de enfriamiento, se calentó a temperatura ambiente y se dejó agitar durante la noche (~ 18 horas). Los disolventes se retiraron al vacío y el residuo se absorbió en un mínimo de diclorometano (~ 1,5- 2 ml) y se diluyó con heptano hasta se levemente turbio. Esta mezcla se cargó en un cartucho de gel de sílice de 40 gramos de BioRad. La purificación mediante cromatografia ultrarrápida (. Sistema Analogix, gradiente de 20 min, 0- 25% metanol/diclorometano, 40 ml/min)

proporcionó 1 - (2- cloro- 5- fluoropirimidin- 4- ilamino)- 2- metil- 2- ol como un sólido blanco. LCMS m/z 220.1, 221.8 (M+H)+, Rt 0.49 min.

Paso 2

A una suspensión de 1 - (2- cloro- 5- fluoropirimidin- 4- ilamino)- 2- metil- 2- ol (400 mg, 1.82) en DCM/acetato de etilo (5 ml) se añadió 2,6- lutidina (1 ml, 8.59 mmol). La reacción se enfrió a - 78 °C y se añadió en una sola porción trifosgeno (292 mg, 0.983 mmol). La reacción se retiró del baño de enfriamiento y se dejó calentar a temperatura ambiente. La reacción tenía una coloración rosada en este momento. LCMS indicó el consumo del material de partida y la conversión del intermedio aducto de cloroformiato de acilo de 1 - (2- cloro- 5- fluoropirimidin- 4- ilamino)- 2- metil- 2- ol. La reacción se selló y se agitó durante la noche. La reacción se agitó a temperatura ambiente durante la noche para proporcionar el cierre parcial del intermedio formiato de acilo a carbamato cíclico. Después, la reacción (sellado) se calentó a 60 °C durante ~ 4 horas hasta que se consumióel intermedio cloroformiato de aciclo. La reacción se enfrió a temperatura ambiente, se diluyó con DCM (~ 50 ml) y se lavó con agua (1x50 ml) y $NaHCO_3$saturado (1x50 ml). Las capas acuosas se volvieron a extraer con DCM (~ 50 ml). Los orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron al vacío. El sólido se disolvió en DCM (~ 15 ml) y se añadió Celite (~ 4 gramos). La mezcla se concentró y se secó al vacío para proporcionar un sólido de pre- carga para la purificación posterior. La purificación mediante cromatografía ultrarrápida (. Sistema Analogix, en columna de gel de sílice de 80 gramos, gradiente de 25 min, 0- 25% de metanol/diclorometano, 40 ml/min) proporcionó 3 - (2- cloro- 5- fluoropirimidin- 4- il) - 5 ,5- dimetiloxazolidin- 2- ona como un sólido blanco. ^{1}H RMN (400 MHz, Metanol- d_4) □□ ppm 1,58 (s, 8 H) 4,02 (s, 2 H) 8,59 (d, *J*= 3,13 Hz, 1 H): LCMS m/z (M+H)+ 246,1, 247.8.0, Rt 0,61 min

Los compuestos intermedios de la Tabla 4d se prepararon por métodos similares a los descritos para la preparación del Intermedio 50.

Tabla 4d.

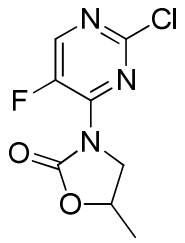
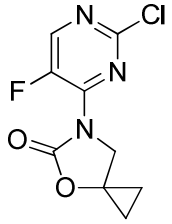
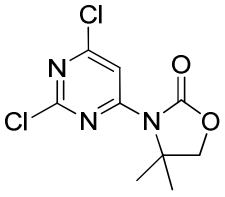
Intermedio 51	Intermedio 52
	

Tabla 4e. Nombre químico, desplazamientos químicos RMN y señal LCMS para cada intermedio que aparece en la Tabla 4d.

Intermedio: Nombre	^{1}H RMN (400 MHz, Metanol- d_4) δ ppm	LCMS
51: 3 - (2- cloro- 5- fluoropirimidin- 4- il)- 5- metiloxazolidin- 2- ona	1,52 (d, *J*= 6,26 Hz, 3 H) 3,89 (dd, *J*= 9,78, 7,43 Hz, 1 H) 4,26 (dd, *J*= 9,78, 7,43 Hz, 1 H) 4,90- 4,98 (m, 1 H) 8,58 (d, *J*= 2,74 Hz, 1 H)	MS m/z (M+H)+ 232,0, 233,9, Rt 0,52 min
52: 6 - (2- cloro- 5- fluoropirimidin- 4- il)- 4- oxa- 6- azaespiro [2,4] heptan- 5- ona	0,90- 1,08 (m, 2 H) 1,18- 1,37 (m, 2 H) 4,31 (s, 2 H) 8,61 (d, *J*= 3,13 Hz, 1 H)	MS m/z (M+H)+ 244,0, 245,8, Rt 0,61 min

Intermedio 53: 3 - (2,6- dicloropirimidin- 4- il) - 4,4- dimetiloxazolidin- 2- ona



Una solución de 4,4- dimetiloxazolidin- 2- ona (0.103 g, 0.895 mmol) y 2,4,6- tricloropirimidina (0.181 g, 0.984 mmoles, 1.10 equiv) en DMF (3 ml) se trató con NaH (60% , 0.0429 g, 1.07 mmol, 1,2 equiv), después la mezcla resultante (de color amarillo) se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con EtOAc (20 ml), se lavó con NaCl acuoso saturado (2 x 20 ml), se secó sobre Na_2SO_4, se filtró y se concentró. La cromatografía en columna de gel de sílice (EtOAc/heptano 0 a 40%) proporcionó 3- (2,6- dicloropirimidin- 4- il) - 4,4- dimetiloxazolidin- 2- ona (0.146 g,

sólido blanco) con un rendimiento 62.3%. ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,14 (s, 1 H), 4,16 (s, 2 H), 1,74 (s, 9H); LCMS m/z 261,9 (M+H)+, Rt 0,91 min.

Los intermedios de la Tabla 4f se prepararon por un método similar al descrito para la preparación del Intermedio 53.

Tabla 4f.

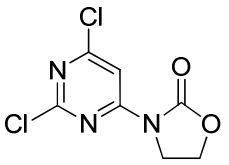
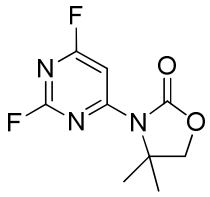
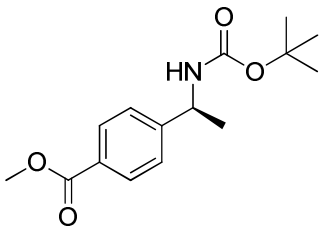
Intermedio 54	Intermedio 55
	

Tabla 4G. Nombre químico, desplazamientos RMN químicos y señal LCMS para cada intermedio que aparece en la Tabla 4f.

Intermedio: Nombre	**^{1}H RMN (400 MHz) δ ppm**	**LCMS**
54: 3 - (2,6- dicloropirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,20 (s, 1 H), 4,59 (t, J = 8,0 Hz, 2 H), 4,29 (t J = 8,0 Hz, 2 H)	MS m/z 234,0 (M+H)+, Rt 0,67 min
55: 3 - (2,6- difluoropirimidin- 4- il) - 4,4- dimetiloxazolidin- 2- ona	($CDCl_3$) 7,68 (d, J = 2,0 Hz, 1 H), 4,16 (s, 2 H), 1,74 (s, 6 H)	MS m/z 230,1 (M+H)+, Rt 0,79 min

Intermedio 56: 4 - (1 - (terc- butoxicarbonilamino) etil) benzoato de (S)- metilo

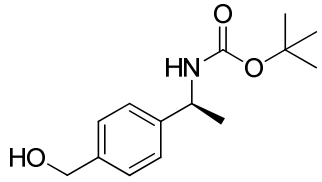


A una solución de 4 - (1- aminoetil) benzoato de (S)- metilo (4.9 g, 22.7 mmoles) en DCM (114 ml) se añadió dicarbonato de di- terc- butilo (5.95 g, 27.3 mmol) y trietilamina (6.97 ml , 50 mmol). La solución se agitó durante 16 h a temperatura ambiente después se

lavó con agua y salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. La cromatografía en columna de gel de sílice (EtOAc/heptano 0 a 80%) proporcionó 4 - (1 - (terc- butoxicarbonilamino) etil)benzoato de (S)- metilo como un sólido blanco (6.35 g, rendimiento del 100%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 8,04- 7,96 (m, 2H), 7,40- 7,33 (m, 2H), 4,83 (s, 1H), 3,91 (s, 3H), 1,43- 1,23 (m, 12H); MS m/z 224,0 (M - 56 + H).

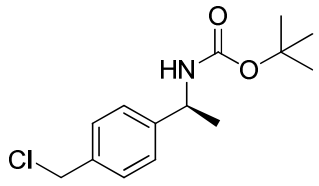
Intermedio 57: 1 - (4 - (hidroximetil) fenil) etilcarbamato de (S)- terc- butilo



A una solución enfriada (0 ºC) de 4 - (1 - (terc- butoxicarbonilamino) etil) benzoato de (S)- metilo (6.35 g, 22.7 mmoles) en THF (114 ml) se añadió una solución de LAH en THF (2.0 M, 13.64 ml, 27.3 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 40 min. La mezcla de reacción se inactivó mediante la adición de una solución de NaOH 1 N hasta que cesó la evolución de gas. La mezcla de reacción se filtró, se lavó con EtOAc. Después de la separación, la fase acuosa se lavó con EtOAc (2 x 150 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 0 al 100%) proporcionó 1 - (4 - (hidroximetil) fenil) etilcarbamato de (S)- terc- butilo como un sólido blanco (5.01 g, rendimiento del 84%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,35- 7,23 (m, 4H), 4,80- 4,71 (m, 1H), 4,67 (s, 2H), 2,04 (br s, 1H), 1,47- 1,37 (m, 12H); MS m/z 196,0 (M - 56 + H).

Intermedio 58: 1 - (4 - (clorometil) fenil) etilcarbamato de (S)- terc- butilo

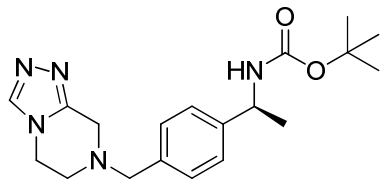


A una solución de 1 - (4 - (hidroximetil) fenil) etilcarbamato de (S)- terc- butilo (503 mg, 2 mmol) en DCM (10 ml) se añadió cloruro de metanosulfonilo (275 mg, 2.4 mmol) y

trietilamina (0.56 ml, 4 mmoles). La solución se agitó durante 16 h a temperatura ambiente después se lavó con agua y salmuera. Después de la separación, la fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró. La cromatografía en columna de gel de sílice (EtOAc/heptano 0 a 80%) proporcionó 1 - (4 - (clorometil) fenil)etilcarbamato de (S)- terc- butilo como un sólido blanco (254 g, rendimiento del 47.1%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,40- 7,24 (m, 4H), 4,79 (s, 1H), 4,58 (s, 2H), 1,50- 1,30 (br m, 12H), MS m/z 214.0 (M - 56 + H).

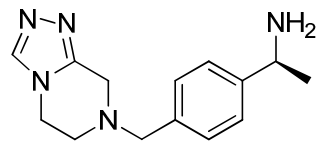
Intermedio 59: 1 - (4 - ((5,6- dihidro- [1,2,4] triazolo [4,3- a] pirazin- 7 (8H)- il) metil) fenil) etilcarbamato de (S)- terc- butilo



Una solución de 1 - (4 - (clorometil) fenil) etilcarbamato de (S)- terc- butilo (127 mg, 0.47 mmoles), 5,6,7,8- tetrahidro- [1,2,4] triazolo [4, 3- a] pirazina (91 mg, 0,56 mmol) y DIPEA (183 mg, 1.41 mmol) en DMSO (2,3 ml) se calentó a 80 °C durante 16 h. La mezcla de reacción se diluyó con EtOAc (20 ml) y se lavó con agua (20 ml). Después de la separación, la fase acuosa se lavó con EtOAc (2 x 15 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El producto crudo se usó para la siguiente etapa sin purificación adicional.

MS m/z 358,3 (M+H)

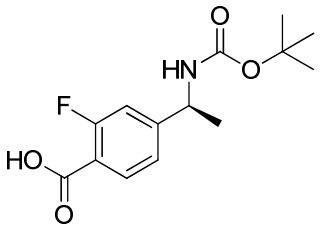
Intermedio 60: (S) - 1 - (4 - ((5,6- dihidro- [1,2,4] triazolo [4,3- a] pirazin- 7 (8H)- il) metil) fenil)etanamina



A una solución de 1 - (4 - ((5,6- dihidro- [1,2,4] triazolo [4,3- a] pirazin- 7 (8H)- il) metil) fenil) etilcarbamato de (S)- terc- butilo (168 mg, 0.47 mmoles) en DCM (2 ml) se añadió lentamente TFA (2 ml, 26 mmol) a - 78 ° C. La reacción se agitó a temperatura ambiente durante 1 h, después se concentró y se diluyó con DCM (10 ml). La solución se agitó con

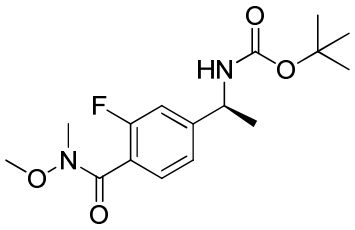
3 eq. de resina de MP- carbonato (3.28 mmol/g, Biotage) durante 1 hora a temperatura ambiente. La resina se separó por filtración y se lavó (2 x 5 ml) con DCM. El filtrado se concentró y el residuo crudo se utilizó para la siguiente etapa sin purificación adicional. MS m/z 258,2 (M+H).

Intermedio 61: ácido (S) - 4 - (1 - (terc- butoxicarbonilamino) etil)- 2- fluorobenzoico



A una solución de ácido (S) - 4 - (1- aminoetil)- 2- fluorobenzoico (5 g, 22.76 mmol) en agua (66 ml) y THF (66 ml) se añadió dicarbonato de di- terc- butilo (6.95 g , 31.9 mmol) y carbonato de sodio (5,74 g, 68,3 mmoles). La solución se agitó durante 16 h a temperatura ambiente y después se eliminó el THF bajo presión reducida. La solución acuosa se acidificó con HCl 1 N a pH 3- 4 y se extrajo con EtOAc (3 x 60 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron para proporcionar un sólido blanco (1.94 g, rendimiento del 30.1%). El producto crudo se usó para la siguiente etapa sin purificación adicional.
^{1}H RMN (400 MHz, MeOD) δ 7,89 (t, J = 7,8 Hz, 1H), 7,20 (dd, J = 8,2, 1,7 Hz, 1H), 7,13 (dd, J = 12,0, 1,6 Hz, 1H), 4,70 (d, J = 7,1 Hz, 1H), 1,47- 1,35 (m, 12H), MS m/z 282,0 (M - H).

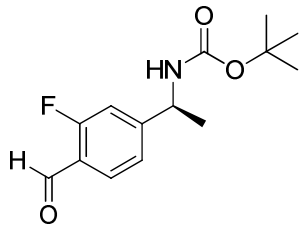
Intermedio 62: 1 - (- (3- fluoro- 4 metoxi (metil) carbamoil) fenil) etilcarbamato de (S)- terc- butilo



Una solución del ácido (S) - 4 - (1 - (terc- butoxicarbonilamino) etil)- 2- fluorobenzoico (1,416 g, 5 mmol), clorhidrato de N, O- dimetilhidroxilamina (732 mg, 7.5 mmol), HATU (2.85 g, 7.5 mmol) y DIPEA (3.49 ml, 20 mmoles) en DMF (25 ml) se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se diluyó con EtOAc y se lavó con agua. Después de la separación, la fase acuosa se lavó con EtOAc (2 x 75 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano 12 a 100%) proporcionó 1 - (3- fluoro- 4- (metoxi (metil) carbamoil) fenil) etilcarbamato de (S)- terc- butilo como un sólido blanco (1,5 g, 92% de rendimiento).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,40 (t, J = 7,4 Hz, 1H), 7,13 (dd, J = 7,8, 1,6 Hz, 1H), 7,04 (dd, J = 10,7, 1,6 Hz, 1H), 4,80 (br s, 1H), 3,56 (s, 3H), 3,34 (s, 3H), 1,50- 1,29 (m, 12H), MS m/z 327,1 (M+H).

Intermedio 63: 1 - (3- fluoro- 4- formilfenil)etilcarbamato de (S)- terc- butilo



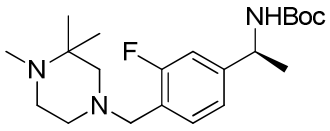
Procedimiento 1: A una solución enfriada (0 º C) de 1 - 4- (3- fluoro-)(metoxi(metil) carbamoil)fenil)etilcarbamato de (1.175 g, 3.6 mmol) en THF (36 ml) se añadió una solución de LAH en THF (1.0 M, 18 ml, 18 mmol) y la mezcla resultante se agitó a 0 ° C durante 20 min. La mezcla de reacción se inactivó mediante la adición de una solución saturada de Na_2SO_4 hasta que cesó la evolución de gas. La mezcla de reacción se extrajo con EtOAc (2 x 100 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano 12 a 100%) proporcionó 1 - (3- fluoro- 4- formilfenil) etilcarbamato de (S)- terc- butilo como un sólido blanco (760 mg, rendimiento del 79%).

Procedimiento 2: Una solución de 1 - (4- bromo- 3- fluorofenil) carbamato de (S)- terc- butilo (318 mg, 1 mmol) en THF seco (5 ml) se enfrió a - 78 ºC. Se añadió BuLi (2.5 M, 840 l, 2.1 mmol) por goteo y la solución resultante se agitó a - 78 ºC durante 1 h. Entonces DMF (232 l, 3,00 mmol) se añadió en una porción. La reacción se agitó durante

otros 30 min a - 78 º C después se inactivó con una solución saturada de NH_4Cl. La reacción se agitó a temperatura ambiente durante otros 30 min, después se diluyó con EtOAc, se lavó con agua y salmuera. La capa orgánica separada se secó sobre Na_2SO_4, se filtró y se concentró. La cromatografía en columna de gel de sílice (EtOAc/heptano 0 a 80%) proporcionó 1 - (3- fluoro- 4- formilfenil) etilcarbamato de (S)- terc- butilo como un sólido blanco (70 mg, rendimiento del 26.2%).

^1H RMN (400 MHz, $CDCl_3$) δ 10,31 (s, 1H), 7,87- 7,80 (m, 1H), 7,20 (dd, J = 8,2, 1,3 Hz, 1H), 7,11 (dd, J = 11,5, 1,4 Hz, 1H), 4,80 (br s, 1H), 1,45 (br s, 12H), MS m/z 212,1 (M - 56 + H).

Intermedio 64: 1 - (3- fluoro- 4- ((3,3,4- trimetilpiperazin- 1- il) metil) fenil) etilcarbamato de (S)- terc- butilo

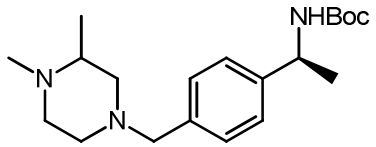


(Procedimiento general A para aminación reductiva)

Una solución de 1 - (3- fluoro- 4- formilfenil)etilcarbamato de (S)- terc- butilo (267 mg, 1 mmol) y dihidrocloruro de 1,2,2- trimetilpiperazina (402 mg, 2 mmol) en THF (5 ml) se agitó a temperatura ambiente durante 1 h y se trató con triacetoxiborohidruro de sodio (848 mg, 4 mmol). La mezcla resultante se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se inactivó con solución acuosa saturada de $NaHCO_3$ (15 ml) y se extrajo con EtOAc (3 x 25 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice ($MeOH/CH_2Cl_2$ al 0 a 10%) proporcionó 1 - (3- fluoro- 4- ((3,3,4- trimetilpiperazin- 1- il) metil) fenil)etilcarbamato de (S)- terc- butilo como de un sólido blanco (186 mg, rendimiento del 49%).

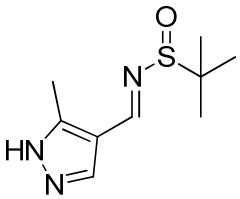
^1H RMN (400 MHz, $CDCl_3$) δ 7,35 (t, J = 7,7 Hz, 1H), 7,03 (dd, J = 7,9, 1,9 Hz, 1H), 6,95 (dd, J = 11,1, 1,8 Hz, 1H), 4,77 (s, 1H), 3,49 (s, 2H), 2,56 (br s, 4H), 2,24 (br s, 5H), 1,42 (br s, 12H), 1,04 (s, 6H); MS m/z 380,4 (M + H).

Intermedio 65: (1S) - 1 - (4 - ((3,4- dimetilpiperazin- 1- il) metil) fenil) etilcarbamato de terc- butilo



Una solución de 1 - (4- formilfenil) etilcarbamato de (S)- terc- butilo (84.1 mg, 0.337 mmoles) [obtenido a partir de (S) - 1 - (4- bromofenil) etanamina de acuerdo con el procedimiento de Hashihayata, Takashi PCT Int.. Appl., 2008081910, 10 Jul 2008] y 1,2- dimetilpiperazina (86.3 mg, 0.756 mmoles, 2.24 equiv) en THF (1,5 ml) se agitó a temperatura ambiente durante 65 min y se trató con triacetoxiborohidruro de sodio (277.2 mg, 1.308 mmoles , 3.88 equiv). La mezcla resultante se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se inactivó con solución acuosa saturada de $NaHCO_3$ (15 ml) y se extrajo con EtOAc (5 x 15 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice ($MeOH/CH_2Cl_2$ al 0 a 20%) proporcionó (1S) - 1 - (4 - ((3,4- dimetilpiperazin- 1- il) metil) fenil) carbamato de terc- butilo (90.7 mg) en 34.5 % de rendimiento. ^1H RMN (400 MHz, CD_3OD) δ 7,29 (s, 4 H), 4,68 (br s, 1H), 3,54- 3,47 (m, 2 H), 3,37 (s, 1H), 2,84- 2,74 (m, 3 H), 2,38 (td, J = 12, 2,5 Hz, 1 H), 2,31 (s, 3 H), 2.28 - 2.22 (m, 2 H), 1,94- 1,89 (m, 1 H), 1,40 (br s, 9 H), 1,38 (d, J = 6,9 Hz, 3 H), 1,06 (d, J = 6,3 Hz, 3 H); MS m/z 348,2 (M+H)

Intermedio 66: (R, E)- 2- metil- N- ((3- metil- 1H- pirazol- 4- il) metileno) propano- 2- sulfinamida

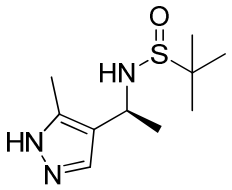


Se disolvió 3- metil- 1H- pirazol- 4- carbaldehído (2.03 g, 18.44mmol) en THF (30 ml) y (R)- 2- metilpropano- 2- sulfinamida (2.35, 19.39mmol) se añadió seguido de Ti (OEt) 4 (8.41mmol, 36.90mmol). La mezcla de reacción resultante se agitó a 80ºC durante 18 h. LCMS muestra la mayor parte del producto. La mezcla de reacción se diluyó con EtOAc (300 ml), se lavó con NaCl acuoso 4% (2 x 150, 2x50 ml). Las capas acuosas combinadas se extrajeron de nuevo con EtOAc (100 ml). Las capas orgánicas combinadas se lavaron

con salmuera (100 ml), se secaron sobre Na_2SO_4, se filtraron y se concentraron. Se purificó mediante cromatografía en columna (REDI 80 g, EtOAc/heptano 20- 100% durante 33 min 100% para 7min.) Para proporcionar el compuesto del título (2,25 g, 10.55mmol).

^{1}H RMN (400 MHz, MeOD) δ 8,55 (s, 1H), 2,53 (s, 3H), 1,25 (s, 9H). EM 214,2 m/z (M+H)

Intermedio 67: (R)- 2- metil- N- ((S) - 1 - (3- metil- 1H- pirazol- 4- il) etil) propano- 2- sulfinamida

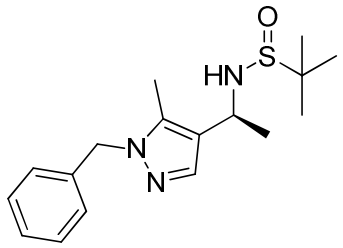


Se disolvió (R, E)- 2- metil- N- ((3- metil- 1H- pirazol- 4- il) metileno) propano- 2- sulfinamida (2.25 g, 10.55mmol) en THF y se enfrió a 0 º C. Se añadió por goteo bromuro de metilmagnesio (3M, 12.5 ml, 37.5 mmol) y la solución resultante se agitó durante 1 h. El baño de hielo se retiró y la reacción se agitó durante otras 15 h. Se añadió Otros 2,5 eq. de bromuro de metilmagnesio MeMgBr (a 0 °C). No se obervó mucho cambio según LCMS.

La mezcla de reacción se inactivó con NH_4Cl saturado y la capa acuosa se lavó con THF (2X). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtró y se concentró para proporcionar el compuesto del título (1.79 g, 7.80mmol)

^{1}H RMN (400 MHz, MeOD) δ 7,48 (s, 1H), 4,49 (qd, J = 6,7, 4,7 Hz, 1H), 2,26 (s, 3H), 1,57 (dd, J = 6,5, 1,3 Hz, 3H) , 1,23 (s, 9H). EM 230,2 m/z (M+H)

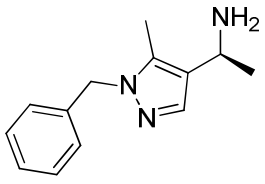
Intermedio 68: (R)- N- ((S) - 1 - (1- bencil- 3- metil- 1H- pirazol- 4- il) etil)- 2- metilpropano- 2- sulfinamida



Se disolvió (R)- 2- metil- N- ((S) - 1 - (3- metil- 1H- pirazol- 4- il) etil) propano- 2- sulfinamida (290 mg, 1,26 mmol) en DMF (5 ml) y se añadió por goteo a una solución de Cs2CO3 (458 mg, 1.41 mmol) en DMF (4 ml). La mezcla de reacción resultante se agitó a temperatura ambiente durante 15 min. Se añadió bromuro de benciclo (216 mg, 1.26 mmol) y la reacción se agitó a temperatura ambiente durante 2 h. LCMS muestra la mayor parte del producto con un poco de pirazol de partida. Se añadio 0.1 ml de BnBr y 135mg de Cs_2CO_3. Se agitó 24 h más a 50 ºC. La mezcla de reacción se diluyó con EtOAc (300 ml), se lavó con NaCl acuoso 4% (2 x 150, 2x50 ml). Las capas acuosas combinadas se extrajeron de nuevo con EtOAc (100 ml). Las capas orgánicas combinadas se lavaron con salmuera (100 ml), se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía de gel de sílice, EtOAc/heptano 20- 80% para proporcionar el compuesto del título (mezcla de regioisómeros, 150mg, 0.470mmol). ^{1}H RMN (400 MHz, MeOD) δ 7,54 (s, 0,6 H), 7,46 (s, 0,4 H), 7,36- 6,99 (m, 5H), 5,31 (s, 0,8 H), 5,21 (s, 1,2 H), 4,44 (t, J = 6,9 Hz, 1H), 2,21 (2s, 3H), 1,54 (2dt, 3H), 1,17 (s, 9H). MS 320.2 m/z (M+H)

Intermedio 69:

Hidrocloruro de (S) - 1 - (1- bencil- 3- metil- 1H- pirazol- 4- il) etanamina



Se disolvió (R)- N- ((S) - 1 - (1- bencil- 3- metil- 1H- pirazol- 4- il) etil)- 2- metilpropano- 2- sulfinamida en dioxano (5 ml) y se añadió HCl 4N en dioxano (1.2 ml, 10 eq.). Se agitó 1H a termperatura ambiente. Se eliminaron los solventes y se co-evaporaron dos veces con CH_2Cl_2. Se observó algo de t- butilo por RMN. Se sometió

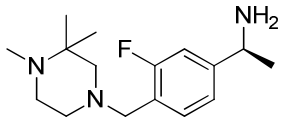
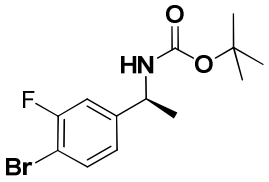
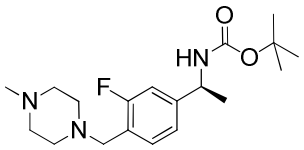
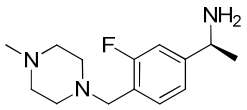
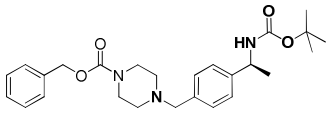
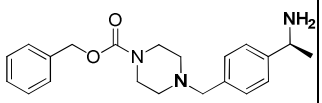
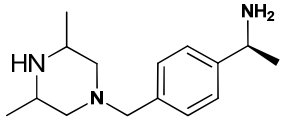
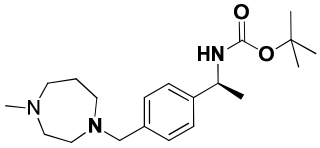
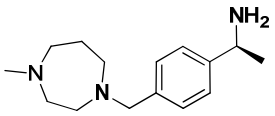
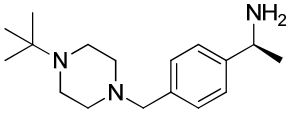
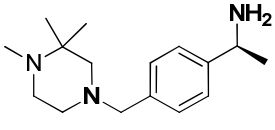
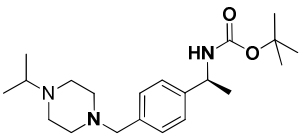
nuevamente a condicones de reacción y se proceso adiconalmente para proporcionar el compuesto del título.

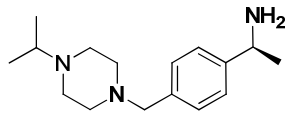
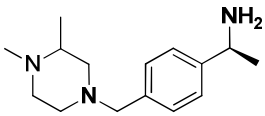
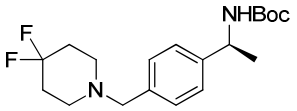
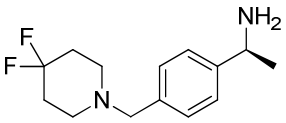
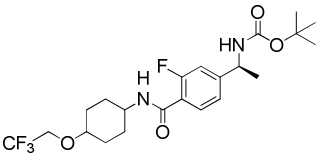
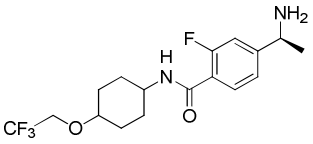
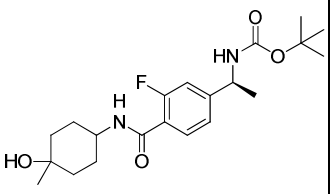
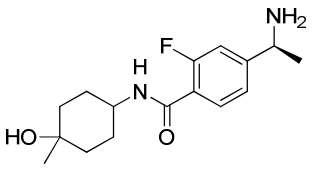
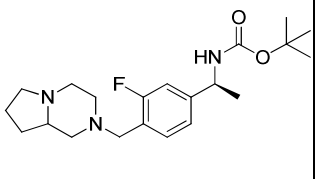
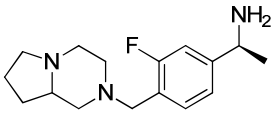
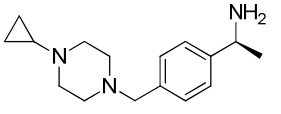
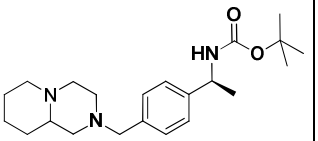
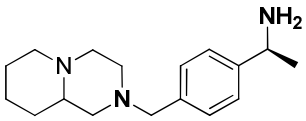
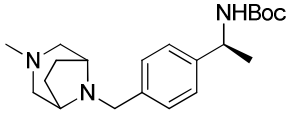
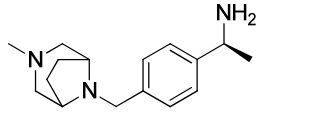
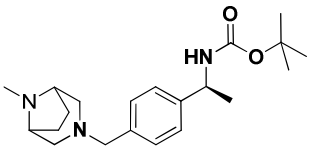
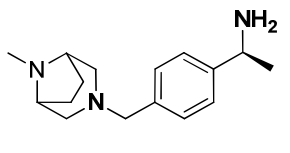
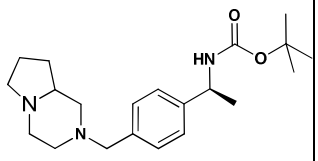
^{1}H RMN mezcla de regioisómeros (400 MHz, MeOD) δ 8,00 (s, 0,7 H), 7,80 (s, 0,3 H), 7,52- 6,96 (m, 5H), 5,40 (s, 0,6 H), 5,36 (s, 1,4 H), 4,47 (q, J = 6,9 Hz, 1H), 2,34 (s, 2,1 H), 2,32 (s, 0,9 H), 1,62 (2d, J = 6,9 Hz, 3H).

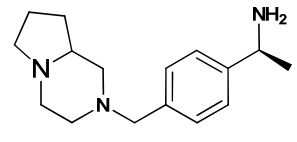
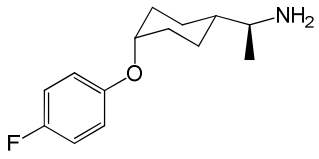
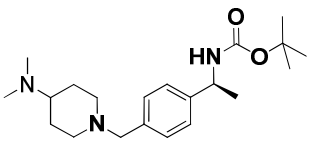
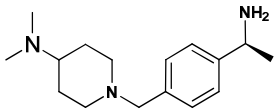
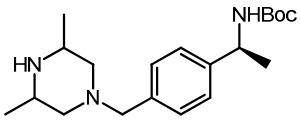
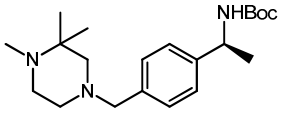
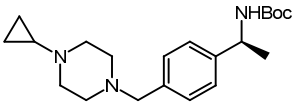
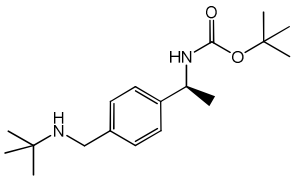
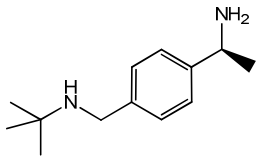
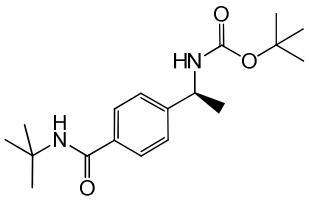
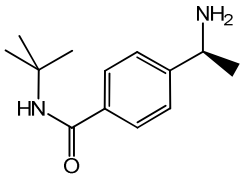
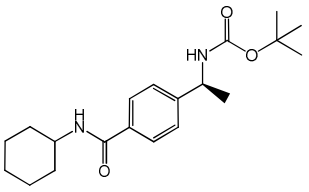
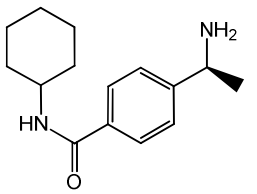
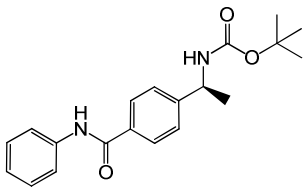
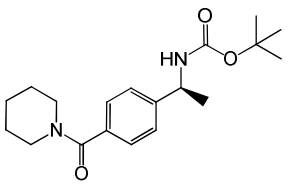
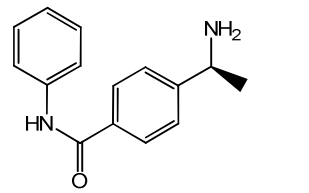
EM 216,3 m/z (M+H)

Los compuestos intermedios en 4h Tabla se prepararon por métodos sustancialmente similares a los descritos para la preparación de los intermedios 56 a 69.

Tabla 4 h.

Intermedio 70	Intermedio 71	Intermedio 72
		
Intermedio 73	Intermedio 74	Intermedio 75
		
Intermedio 76	Intermedio 77	Intermedio 78
		
Intermedio 79	Intermedio 80	Intermedio 81
		
Intermedio 82	Intermedio 83	Intermedio 84

		
Intermedio 85	Intermedio 86	Intermedio 87
		
Intermedio 88	Intermedio 89	Intermedio 90
		
Intermedio 91	Intermedio 92	Intermedio 93
		
Intermedio 94	Intermedio 95	Intermedio 96
		
Intermedio 97	Intermedio 98	Intermedio 99
		
Intermedio 100	Intermedio 101	Intermedio 102

		
Intermedio 103	Intermedio 104	Intermedio 105
		
Intermedio 106	Intermedio 107	Intermedio 108
		
Intermedio 109	Intermedio 110	Intermedio 111
		
Intermedio 112	Intermedio 113	Intermedio 114
		
Intermedio 115	Intermedio 116	Intermedio 117
		
Intermedio 118	Intermedio 119	Intermedio 120

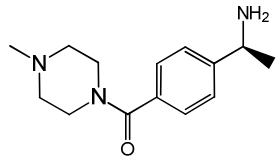
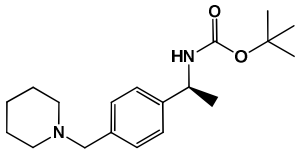
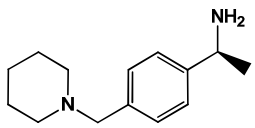
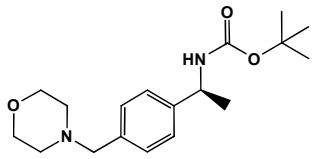
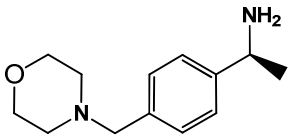
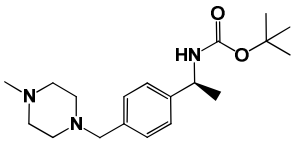
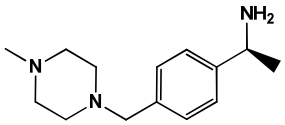
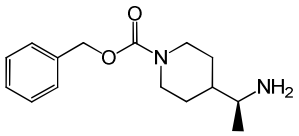
		
Intermedio 121	Intermedio 122	Intermedio 123
		
Intermedio 124	Intermedio 125	
		

Tabla 4i. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada intermedio enumerado en la Tabla 4 h.

Intermedio: Nombre	^{1}H RMN (**400 MHz**) **δ ppm**	**LCMS**
70: (S) - 1 - etanamina (3- fluoro- 4- ((3,3,4- trimetilpiperazin- 1- il) metil) fenil)		MS m/z 280,2 (M+H).
71: 1 - (4- bromo- 3- fluorofenil) etilcarbamato de (S)- terc- butilo	($CDCl_3$) 7,51- 7,45 (m, 1H), 7,07 (dd, J = 9,8, 2,0 Hz, 1H), 6,98 (dd, J = 8,4, 2,1 Hz, 1H), 4,67 (br s, 1H),, 1,41 (br s, 12H)	MS m/z 317,9 (M+H).
72: 1 - (- (3- fluoro- 4 (4- metilpiperazin- 1- il) metil) fenil) etilcarbamato de (S)- terc- butilo	($CDCl_3$) 7,28 (t, J = 7,7 Hz, 1H), 7,01 (dd, J = 7,7, 1,8 Hz, 1H), 6,94 (dd, J = 10,8, 1,9 Hz, 1H), 4,86 (br s, 1H) , 4,74 (br s, 1H), 3,54 (s, 2H), 2,67- 2,29 (m, 8H), 2,25 (s, 3H), 1,51- 1,26 (m, 12H)	MS m/z 353,2 (M+H)
73: (S) - 1 - etanamina (3- fluoro- 4- ((4- metilpiperazin- 1- il) metil) fenil)		MS m/z 252,1 (M+H)
74: 4 - (4 - (1 - (terc- butoxicarbonilamino) etil) bencil) piperazina- 1- carboxilato de (S)- benciclo	($CDCl_3$) 7,43- 7,19 (m, 9H), 5,12 (s, 2H), 4,78 (br s, 2H), 3,95- 3,20 (m, 6H), 2,43 (br s, 4H), 1,43 (br s, 12H)	MS m/z 454,3 (M+H)

75: 4 - (4 - (1- aminoetil) bencil) piperazina- 1- carboxilato de (S)- benciclo		MS m/z 354,3 (M+H)
76: (1S) - 1 - (4 - ((3,5- dimetilpiperazin- 1- il) metil) fenil) etanamina		MS m/z 248,2 (M+H)
77: 1 - (4 - ((4- metil- 1 ,4- diazepan- 1- il) metil) fenil) etilcarbamato de (S)- terc- butilo	($CDCl_3$) 7.31 - 7.20 (m, 4H), 4,78 (s, 1H), 3,61 (s, 2H), 2,81- 2,69 (m, 8H), 2,44 (s, 3H), 1,94- 1,85 (m, 2H) , 1,43 (br s, 12H)	MS m/z 349,4 (M+H)
78: (S) - 1 - (4 - ((4- metil- 1 ,4- diazepan- 1- il) metil) fenil) etanamina		MS m/z 248,1 (M+H)
79: (S) - 1 - (4 - ((butilpiperazin- 4- terc- 1- il) metil) fenil) etanamina		MS m/z 276,2 (M+H)
80: (S) - 1 - (4 - ((3,3,4- trimetilpiperazin- 1- il) metil) fenil) etanamina		MS m/z 262,2 (M+H)
81: 1 - (4 - ((4- isopropilpiperazin- 1- il) metil) fenil) etilcarbamato de (S)- terc- butilo	($CDCl_3$) 7.28 - 7.22 (m, 4H), 4,78 (s, 1H), 3,49 (s, 2H), 2,88- 2,22 (m, 9H), 1,42 (br s, 12H), 1,05 (d, J = 6,5 Hz, 6H)	MS m/z 363,4 (M+H)
82: (S) - 1 - (4 - ((4- isopropilpiperazin- 1- il) metil) fenil) etanamina		MS m/z 262,2 (M+H)
83: (1S) - 1 - (4 - ((3,4- dimetilpiperazin- 1- il) metil) fenil) etanamina		MS m/z 248,2 (M+H)
84: 1 - (4 - ((1- il 4,4- difluoropiperidin-) metil) fenil) etilcarbamato de (S)- terc- butilo		MS m/z 356,2 (M+H)
85: (S) - 1 - (4 - ((4,4- difluoropiperidin- 1- il) metil) fenil) etanamina		MS m/z 255,2 (M+H)
86: 1 - (- (3- fluoro- 4 4 - (2,2,2- trifluoroetoxi) ciclohexilcarbamoil) fenil) etilcarbamato de (S)- terc- butilo	($CDCl_3$) 8,01 (t, J = 8,1 Hz, 1H), 7,16 (d, J = 7,9, 1H), 7,04 (d, J = 13,2, 1H), 6,67 - 6,63 (m, 1H), 4,96 (br s, 1H), 4,76 (br s, 1H), 4,06 (br s, 1H), 3,85- 3,77 (m, 2H), 3,64 (br s, 1H), 1,92- 1,74 (m, 4H), 1,73- 1,59 (m, 4H), 1,40 (br s, 12H)	MS m/z 463,3 (M+H)
87: (S) - 4 - (1- aminoetil)- 2- fluoro- N- (4 - (2,2,2- trifluoroetoxi) ciclohexil) benzamida		MS m/z 363,2 (M+H)
88: 1 - (3- fluoro- 4- (4- hidroxi- 4- metilciclohexilcarbamoil) fenil) etilcarbamato de (S)- terc- butilo	($CDCl_3$) 8,04 (t, J = 8,1 Hz, 1H), 7,19 (d, J = 8,3, 1H), 7,05 (dd, J = 13,2, 1,7 Hz, 1H), 6,65 (br dd, J = 12,1, 6,6 Hz, 2H),	MS m/z 395,1 (M+H)

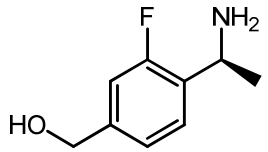
	4,84 (br s, 1H), 4,77 (br s, 1H), 4.17 a 4.6 (m, 1H), 2,09- 2,00 (m, 2H), 1,61- 1,59 (m, 4H), 1,55- 1,47 (m, 2H), 1,42 (br s, 12H), 1,30 (s, 3H)	
89: (S) - 4 - (1- aminoetil)- 2- fluoro- N- (4- hidroxi- 4- metilciclohexilo) benzamida		MS m/z 295,2 (M+H)
90: (1S) - 1 - (3- fluoro- 4- ((hexahidropirrolo [1,2- a] pirazin- 2 (1H)- il) metil) fenil) etilcarbamato de terc- butilo		MS m/z 376,1 (M - H)
91: (1S) - 1 - etanamina (3- fluoro- 4- ((hexahidropirrolo [1,2- a] pirazin- 2 (1H)- il) metil) fenil)		MS m/z 278,1 (M+H)
92: (S) - 1 - (4 - ((4- ciclopropilpiperazin- 1- il) metil) fenil) etanamina		MS m/z 260,2 (M+H)
93: (1S) - 1 - (4 - ((dihidro- 1H- pirido [1,2- a] pirazin- 2 (6H, 7H, 8H, 9H, 9aH)- il) metil) fenil) etilcarbamato de terc- butilo	($CDCl_3$) 7.30 - 7.20 (m, 4H), 4,78 (s, 2H), 3,46 (s, 2H), 2,89- 2,61 (m, 4H), 2,39- 2,21 (m, 2H), 2,10- 1,93 (m, 2H), 1,86 (t, J = 10,7 Hz, 1H), 1,79- 1,68 (m, 1H), 1,62 (br s, 2H), 1,43 (br s, 13H), 1,32- 1,19 (m, 2H)	MS m/z 372,4 (M - H)
94: (1S) - 1 - (4 - ((dihidro- 1H- pirido [1,2- a] pirazin- 2 (6H, 7H, 8H, 9H, 9aH)- il) metil) fenil) etanamina		MS m/z 274,2 (M+H)
95: (1S) - 1 - (4 - ((3- metil- 3 ,8- diazabiciclo [3.2.1] octan- 8- il) metil) fenil) etilcarbamato de terc- butilo		MS m/z 361,3 (M+H)
96: (1S) - 1 - (4 - ((3- metil- 3 ,8- diazabiciclo [3.2.1] octan- 8- il) metil) fenil) etanamina		MS m/z 260,2 (M+H)
97: (1S) - 1 - (4 - ((8- metil- 3 ,8- diazabiciclo [3.2.1] octan- 3- il) metil) fenil) etilcarbamato de terc- butilo	($CDCl_3$) 7.28 - 7.19 (m, 4H), 4,77 (br s, 2H), 3,44 (s, 2H), 3,03 (br s, 2H), 2,55 (dd, J = 10,8, 2,9 Hz, 2H), 2,29 (d, J = 10,3 Hz, 2H), 2,25 (s, 3H), 1,93- 1,78 (m, 4H), 1,64 (br s, 1H), 1,43 (br s, 12H)	MS m/z 360,6 (M+H)
98: (1S) - 1 - (4 - ((8- metil- 3 ,8- diazabiciclo [3.2.1] octan- 3- il) metil) fenil) etanamina		MS m/z 260,2 (M+H).
99: (1S) - 1 - (4 - ((hexahidropirrolo [1,2- a] pirazin- 2 (1H)- il) metil) fenil) etilcarbamato de terc- butilo	($CDCl_3$) 7.30 - 7.21 (m, 4H), 4,78 (br s, 1H), 3,61- 3,44 (m, 2H), 3,05 (td, J = 8,6, 1,9 Hz, 1H), 3,00- 2,93 (m, 2H), 2,86-	MS m/z 361,3 (M+H)

	2,76 (m, 1H), 2,33- 2,19 (m, 2H), 2,17- 2,00 (m, 2H), 1,87- 1,65 (m, 4H), 1,43 (br s, 12H)	
100: (1S) - 1 - (4 - ((hexahidropirrolo [1,2- a] pirazin- 2 (1H)- il) metil) fenil) etanamina		MS m/z 260,2 (M+H)
101: (S) - 1 - [4 - (4- fluoro- fenoxi)- ciclohexil]- etilamina		CL- MS m/z 237.4 (M+H)+; RT: 1,08 min..
102: 1 - (4 - ((4 - (dimetilamino) piperidin- 1- il) metil) fenil) etilcarbamato de (S)- terc- butilo	($CDCl_3$) 7.28- 7.20 (m, 4H), 4,79 (br s, 2H), 3,46 (s, 2H), 2,91 (br d, J = 12,1 Hz, 2H), 2,26 (s, 6H), 2.17 a 2.9 (m, 1H), 1,94 (td, J = 11,8, 2,4 Hz, 2H), 1,85 (br s, 1H), 1,81- 1,71 (m, 2H), 1,53 (td, J = 12,1, 3,7 Hz, 2H) , 1,44- 1,42 (m, 12H)	MS m/z 361,8 (M+H)
103: (S) - 1 - (4 - (1- aminoetil) bencil)- N, N- dimetil- piperidin- 4- amina		MS m/z 262,1 (M+H)
104: (1S) - 1 - (4 - ((3,5- dimetilpiperazin- 1- il) metil) fenil) etilcarbamato de terc- butilo	(CD_3OD) 7,29 (s, 4 H), 4,68 (br s, 1H), 3,52 (s, 2H), 2,96- 2,88 (m, 2 H), 2,82- 2,79 (m, 2 H), 1,69 (t, J = 11 Hz, 2 H), 1,44 (br s, 9 H), 1,40 (d, J = 7,1 Hz, 3 H), 1,06 (d, J = 6,5 Hz, 6 H);	MS m/z 348,3 (M+H)
105: 1 - (4 - ((3,3,4- trimetilpiperazin- 1- il) metil) fenil) etilcarbamato de (S)- terc- butilo	(CD_3OD) δ 7,35- 7,25 (m, 4 H), 4,67 (br s, 1H), 4,59 (s, 1 H), 3,45 (s, 2 H), 3,31 (s, 1 H), 2,62 (br s, 2 H), 2,51 (br s, 1H), 2,24 (s, 3H), 2,18 (br s, 1H), 1,43 (br s, 9 H), 1,40 (d, J = 7,1 Hz, 3 H), 1,07 (s, 6 H);	MS m/z 362,3 (M+H)
106: 1 - (4 - ((4- ciclopropilpiperazin- 1- il) metil) fenil) etilcarbamato de ((S)- terc- butilo	($CDCl_3$) δ 7.21- 7.16 (m, 4 H), 5,23 (s, 1 H), 4,72 (br s, 1 H), 3,42 (s, 2 H), 2,58 (br s, 4 H), 2,38 (br s, 4 H), 1,57- 1,51 (m, 1 H), 1,41- 1,30 (br m, 12 H), 0,39 a 0,33 (m, 4 H);	MS m/z 359,8 (M+H)
107: 1 - (4 - ((terc- butilamino) metil) fenil) etilcarbamato de (S)- terc- butilo	($CDCl_3$) 7,32 (d, J = 8,0 Hz, 1H), 7,25 (d, J = 8,2 Hz, 1H), 4,77 (s, 1H), 3,72 (s, 1H), 1,43 (d, J = 5,4 Hz, 6H), 1,18 (s, 4H)	MS m/z 308,2 (M+H)+
108: (S)- N- (4 - (1- aminoetil) bencil)- 2- metil- 2- amina		MS m/z 207,2 (M+H)+
109: 1 - (4 - (terc- butilcarbamoil) fenil) etil carbamato de (S)- terc- butilo	($CDCl_3$) 7,71- 7,62 (m, 2H), 7,33 (d, J = 8,1 Hz, 2H), 5,90 (s, 1H), 4,80 (br s, 2H), 1,46- 1,41 (m, 21H)	MS m/z 321,2 (M+H)+

110: Clorhidrato de (S) - 4 - (1-aminoetil)- N- terc- butilbenzamida		MS m/z 221,3 (M+H)+
111: 1 - (4 - (ciclohexilcarbamoil) fenil) etil carbamato de (S)- terc-butilo	($CDCl_3$) 7,71 (dd, J = 8,3, 1,8 Hz, 2H), 7,35 (d, J = 7,8 Hz, 2H), 5,91 (d, J = 8,3 Hz, 1H), 4,94- 4,59 (m, 2H), 3,97 (ddt, J = 10,8, 6,5, 2,9 Hz, 1H), 2,02 (dt, J = 12,6, 3,7 Hz, 2H), 1,75 (dp, J = 11,8, 3,9 Hz, 2H), 1,66-1,56 (m, 3H), 1,49- 1,30 (m, 12H), 1,23 (m, 3H)	MS m/z 347,2 (M+H)+
112: clorhidrato de (S) - 4 - (1-aminoetil)- N- ciclohexilbenzamida		MS m/z 247,3 (M+H)+
113: 1 - (4 - (fenilcarbamoil) fenil) etil carbamato de (S)- terc- butilo	($CDCl_3$) 7,90- 7,83 (m, 2H), 7,81- 7,62 (m, 3H), 7,49- 7,36 (m, 4H), 7,18 (td, J = 7,4, 1,2 Hz, 1H), 4,87 (br s, 2H), 1,58 (s, 3H), 1,46 (m, 9H)	MS m/z 340,6 (M+H)+
114: clorhidrato de (S) - 4 - (1-aminoetil)- N- fenilbenzamida		MS m/z 241,2 (M+H)+
115: 1 - (4 - (piperidina- 1- carbonil) fenil) etilcarbamato de (S)- terc-butilo	($CDCl_3$) 7,33 (q, J = 8,3 Hz, 4H), 4,80 (br s, 2H), 3,70 (br s, 2H), 3,47- 3,22 (m, 2H), 1,70-1,63 (m, 4H), 1,53 - 1,26 (m, 14H)	MS m/z 333,2 (M+H)+
116: (S) - (4 - (1- aminoetil) fenil) (piperidin- 1- il) metanona		MS m/z 233,2 (M+H)+
117: 1 - (4 - (4- metilpiperazina- 1-carbonil) fenil) etilcarbamato de (S)-terc- butilo	($CDCl_3$) 7,35 (q, J = 8,2 Hz, 4H), 4,81 (br s, 1H), 3,79 (br s, 2H), 3,45 (br s, 2H), 2,50- 2,32 (m, 7H), 1,61 (s , 1H), 1,51-1,29 (m, 12H)	MS m/z 348,2 (M+H)+
118: (S) - (4 - (1- aminoetil) fenil) (4- metilpiperazin- 1- il) metanona		MS m/z 248,2 (M+H)+
119: 1 - (4 - (piperidin- 1- ilmetil) fenil) etilcarbamato de (S)- terc-butilo	($CDCl_3$) 7,27 (q, J = 7,9 Hz, 4H), 4,80 (br s, 2H), 3,49 (s, 2H), 2,60- 2,28 (m, 4H), 1,60 (t, J = 5,5 Hz, 4H) , 1,52- 1,31 (m, 15H)	MS m/z 319,0 (M+H)+
120: (S) - 1 - (4 - (piperidin- 1-ilmetil) fenil) etanamina		MS m/z 219,1 (M+H)+
121: 1 - (4 - (morfolinometil) fenil) etil carbamato de (S)- terc- butilo	($CDCl_3$) 7,48- 7,10 (m, 4H), 4,82 (d, J = 25,7 Hz, 2H), 3,80-3,62 (m, 3H), 3,48 (s, 2H), 2,61- 2,24 (m, 3H), 1,44 (m, 13H)	MS m/z 321,2 (M+H)+
122: (S) - 1 - (4 - (morfolinometil) fenil) etanamina		MS m/z 220,9 M + H) +
123: 1 - ((4 - (4- metilpiperazin- 1-il) metil) fenil) etilcarbamato de	($CDCl_3$) 7,39- 7,15 (m, 7H), 4,79 (br s, 2H), 3,51 (s, 2H),	MS m/z 321,2 (M+H)+

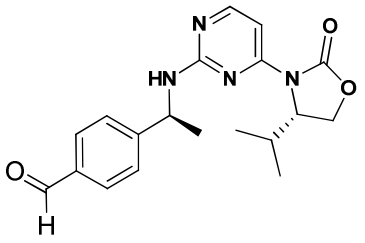
(S)- terc- butilo	2,41 (m, 9H), 1,46 (m, 11H)	
124: (S) - 1 - (4 - ((4- metilpiperazin- 1- il) metil) fenil) etanamina		MS m/z 234,2 (M+H)+
125: éster benciclo del ácido 4 - ((S)- 1- amino- etil) - piperidina- 1- carboxílico		LC- MS (M+H) = 263,1 RT:. 0.91 min.

Intermedio 126: (S) - (4 - (1- aminoetil)- 3- fluorofenil) metanol



A una (0 ° C) suspensión enfriada de clorhidrato de 4 - (1- aminoetil)- 3- fluorobenzoato de (S)- metilo (0.109 g, 0.468 mmol) en THF (15 ml) se añadió una solución de LAH en THF (2.0 M, 1.05 ml, 2.10 mmol, 4.49 equiv) y la mezcla resultante se agitó a 0 ºC durante 2 h 20 min y a temperatura ambiente durante 2 1/2 horas. La mezcla de reacción se inactivó mediante la adición de una mezcla de Na_2SO_4 decahidrato y Celite (1:1 por peso) hasta que la evolución de gas cesó. La mezcla de reacción se filtró, se lavó con EtOAc. El filtrado se concentró y se utilizó para la siguiente reacción sin purificación. ^{1}H RMN (400 MHz, CD_3OD) δ 7,43 (t, J = 7,7 Hz, 1 H), 7,15 (d, J = 8,1 Hz, 1 H), 7,08 (d, J = 12 Hz, 1 H), 4,60 (s, 2 H), 4,32 (q, J = 6,6 Hz, 1H), 1,42- 1,40 (m, 3 H).

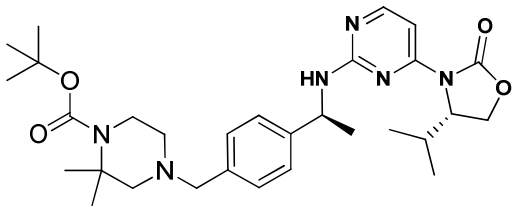
Intermedio 127: 4 - ((S) - 1 - (4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- ilamino) etil) benzaldehído



Una solución de (S) - 3 - (2 - ((S) - 1 - (4 - (hidroximetil) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (285 mg, 0.8 mmoles) y dióxido de manganeso (2.78 g, 32 mmol, 40 equiv) en DCM (16 ml) se agitó a temperatura ambiente durante 30 min. La

solución se filtró a través de una almohadilla de celite y se lavó con DCM. El filtrado se concentró y se usa para la siguiente etapa sin purificación adicional.

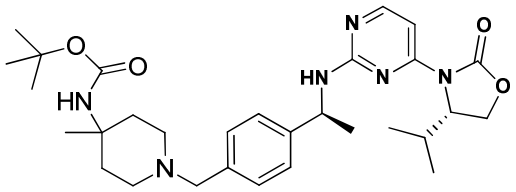
Intermedio 128: 4- (4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzil)- 2,2- dimetilpiperazina- 1- carboxílato de terc- butilo



Una solución de 4 - ((S) - 1 - (4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)) etil pirimidin- 2- ilamino)benzaldehído (71 mg, 0,2 mmol) y 2,2- dimetil- 1- carboxilato de terc - butilo (47.1 mg, 0.22 mmol) en MeOH (4 ml) se añadió ácido acético (14.4 mg, 0.24 mmol) y complejo de borano de 5- etil- 2- metilpiridina (27 mg, 0.2 mmol, Sigma Aldrich). La solución se agitó a 50 °C durante 4 h, después se añadieron 5 gotas de agua. La solución se agitó a temperatura ambiente durante otras 2 h, después se diluyó con EtOAc (10 ml) y se lavó con agua (10 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se purificó a través de cromatografía en columna de gel de sílice (MeOH/ EtOAc al 0 a 10%) para proporcionar el 4- (4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzil)- 2,2- dimetilpiperazina- 1- carboxílato de ter- butilo como un sólido blanco (80 mg, rendimiento del 72.4%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 8,18 (br s, 1H), 7,44 (d, J = 5,7 Hz, 1H), 7.24 a 7.29 (m, 4H), 5,46 (br s, 1H), 5,03 (br s, 1H), 4,59- 4,63 (m, 1H), 4,29 (t, J = 8,7 Hz, 1H), 4,22 (dd, J = 9,1, 3,1 Hz, 1H), 3,44 (br s, 4H), 2,40 (s , 2H), 2,16 (s, 2H), 1,54 (d, J = 6,9 Hz, 3H), 1,45 (s, 9H), 1,36 (s, 6H), 0,80- 0,57 (m, 6H); MS m/z 252,1 (M+H).

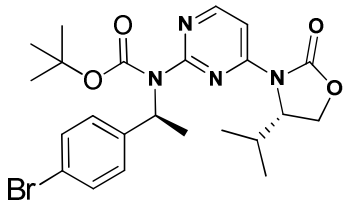
Intermedio 129: 1- (4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzil)- 4- metilpiperidin- 4- ilcarbamato de terc- butilo



Preparado por un método similar al descrito para la preparación del Intermedio 128.

^{1}H RMN (400 MHz, $CDCl_3$) 8,17 (d, J = 5,7 Hz, 1H), 7,43 (d, J = 5,7 Hz, 1H), 7,26 (br s, 4H), 5,40 (br s, 1H), 5,02 (br s, 1H), 4,60 (dt, J = 8,2, 3,1 Hz, 1H), 4,34- 4,19 (m, 3H), 3,47 (br s, 2H), 2,54 (br s, 2H), 2,26 (br s, 2H), 1,95 (br s, 3H), 1,60 (br s, 2H), 1,53 (d, J = 6,9 Hz, 3H), 1,43 (s, 9H), 1,33 (s, 3H), 0,69 (br s, 3H), 0,63 (br s, 3H). MS m/z 553,6 (M+H).

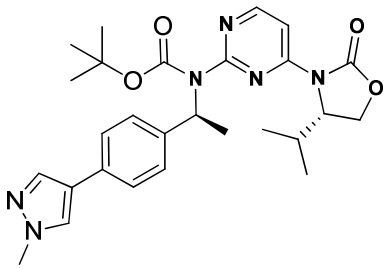
Intermedio 130: (S) - 1 - (4- bromofenil) etil (4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- il) carbamato de terc- butilo



A una solución de (S) - 3 - (2 - ((S) - 1 - (4- bromofenil) etilamino) pirimidin- 4- il)- 2- ona- 4- isopropiloxazolidin (1.62 g, 4 mmol) en THF (20 ml) se añadió dicarbonato de di-terc- butilo (1.31 g, 6 mmol), DMAP (49 mg, 0.4 mmol) y DIPEA (1.40 ml, 8 mmol). La solución se agitó a 50 °C durante 7 días y después se concentró bajo presión reducida. El residuo se diluyó con EtOAc (40 ml) y se lavó con agua y salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. La cromatografía en columna de gel de sílice (EtOAc/heptano 0 a 80%) proporcionó (S) - 1 - (4- bromofenil) etil (4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin - 2- il) carbamato de terc- butilo como un sólido blanco (1.03 g, rendimiento del 50.9%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 8,57 (d, J = 5,8 Hz, 1H), 7,99 (d, J = 5,8 Hz, 1H), 7,44- 7,39 (m, 2H), 7,33- 7,28 (m, 2H) , 5,63 (q, J = 7,2 Hz, 1H), 4,63 (dt, J = 8,0, 3,3 Hz, 1H), 4,39- 4,26 (m, 2H), 2,47- 2,39 (m, 1H), 1,66 (d, J = 7,1 Hz, 3H), 1,30 (s, 9H), 0,84 (d, J = 7,0, 3H), 0,83 (d, J = 7,0, 3H); MS m/z 507,0 (M+H).

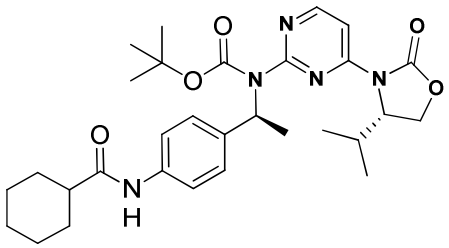
Intermedio 131: 4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il((S)- 1- (4- (1- metil- 1H- pirazol- 4- il)fenil)etil)carbamato de terc- butilo



En un vial de 5 ml de microondas se añadió una solución de (S) - 1 - (4- bromofenil) etil (4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- il) carbamato de terc- butilo (101 mg, 0.2 mmoles), 1- metil- 4- (4,4,5,5- tetrametil- 1, 3,2- dioxaborolan- 2- il)- 1H- pirazol (50 mg, 0.24 mmol), El bicarbonato de sodio (0.2 ml, 0.4 mmol, 2 M de solución acuosa) en dioxano (2 ml) se burbujeó N_2 durante 3 min y después se añadió $Cl_2Pd(dppf)CH_2Cl_2$ (16 mg, 0.02 mmol). El tubo tapado se calentó a 100 °C durante 16 h. Después de enfriar la mezcla de reacción se diluyó con EtOAc (10 ml) y se lavó con agua (10 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se purificó a través de cromatografía en columna de gel de sílice (EtOAc en heptano 12 a 100%) para proporcionar un sólido blanco (50 mg, rendimiento del 49,3%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 8,57 (d, J = 5,7 Hz, 1H), 7,97 (d, J = 5,8 Hz, 1H), 7,74 (s, 1H), 7,59 (s, 1H), 7,39 (s , 4H), 5,71 (q, J = 7,0 Hz, 1H), 4,65 (dt, J = 8,1, 3,2 Hz, 1H), 4,36- 4,24 (m, 2H), 3,94 (s, 3H), 2,50- 2,42 (m, 1H), 1,71 (d, J = 7,0 Hz, 3H), 1,29 (s, 9H), 0,82 (d, J = 7,0 Hz, 3H), 0,80 (d, J = 7,0 Hz, 3H); MS m/z 507,1 (M+H).

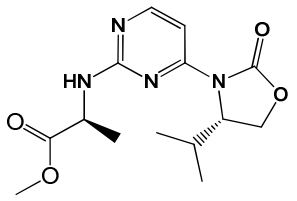
Intermedio 132: (S)- 1- (4- (ciclohexanecarboxamido)fenil)etil(4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il)carbamato de terc- butilo



En un vial de reacción de microondas de 5 ml se añadió (S) - 1 - (4- bromofenil) etil (4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- il) carbamato de terc- butilo(101 mg, 0.2 mmoles), ciclohexanocarboxamida (30 mg, 0.24 moles), carbonato de cesio (91 mg, 0.28 mmol), fosfato de xanteno (7 mg, 0.012 mmol, Strem Chemicals), y $Pd_2(dba)_3$ (4 mg, 0.02 mmoles). El vial se selló, se evacuó y se purgó con nitrógeno seco tres veces antes de añadir dioxano (1,6 ml). La mezcla de reacción se calentó a 100 °C durante 16 horas en un baño de aceite. Después de enfriar la reacción se diluyó con EtOAc (10 ml) y se lavó con agua (10 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se purificó a través de cromatografía en columna de gel de sílice (EtOAc en heptano 12 a 100%) para proporcionar un sólido blanco (65 mg, rendimiento del 58,9%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 8,55 (d, J = 5,8 Hz, 1H), 7,95 (d, J = 5,8 Hz, 1H), 7,48-7,43 (m, 2H), 7,38- 7,32 (m, 2H) , 7,13 (br s, 1H), 5,66 (q, J = 7,1 Hz, 1H), 4,64 (dt, J = 8,2, 3,2 Hz, 1H), 4,38- 4,26 (m, 2H), 2,51- 2,43 (m, 1H), 2,20 (tt, J = 11,8, 3,5 Hz, 1H), 1,95 (d, J = 13,2, 2H), 1,87- 1,81 (m, 2H), 1,71- 1,68 (m, 4H), 1,60- 1,47 (m, 2H), 1,33-1,25 (m, 12H), 0,85 (d, J = 6,9 Hz, 3H), 0,82 (d, J = 6,9 Hz, 3H); MS m/z 552,1 (M+H).

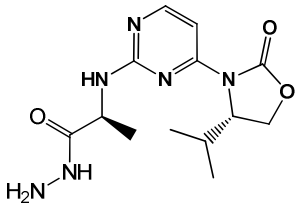
Intermedio 133: 2 - ((4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- il) amino) propanoato de (S)- metilo



A una solución de 2- aminopropanoato de (S)- metilo (270 mg, 2.0 mmoles, 1.2 equv.in 10 ml de DMSO) y (S) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2 - ona (430 mg, 1,8 mmol, 1,0 equv.) se añadió DIPEA (805 mg, 6.23 mmol, 3.5 equiv), y la mezcla de reacción se calentó a 110 °C durante 120 min. La mezcla de reacción se vertió en agua (40 ml) y se extrajo con EtOAc (2x30 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (acetato de etilo en heptano del 10 al 80%) para proporcionar 2 -

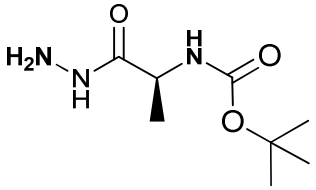
((4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- il) amino) propanoato de (S)- metilo (260 mg, rendimiento sólido) de color blanco en el 47,4%. LCMS m/z 309.1 (M+H)+ RT = 1.53 min.

Intermedio 134: (S) - 2 - ((4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- il) amino) propanohidrazida



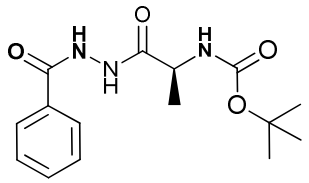
A una solución de 2 - ((4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- il) amino) propanoato de (S)- metio (120 mg, 0.39 mmol en 5 ml de MeOH) se añadió 99% de hidrato de hidrazina, la solución de reacción se agitó a temperatura ambiente durante la noche (24 horas), se eliminó el disolvente para proporcionar el producto deseado (99 mg) con un rendimiento del 78%, y se usó para la siguiente etapa sin purificación . LCMS m/z 309.1 (M+H)+ RT = 1.25 min.

Intermedio 135: (1- hidrazinilo- 1- oxopropan- 2- il) carbamato de (S)- terc- butilo



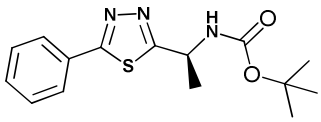
Una solución de hidrazina (234 mg, 7.31 mmoles, en 8 ml de THF 1.5 equv.) Se añadió a 2 - (terc- butoxicarbonilamino) propanoato de (S)- metilo (1.000 mg, 4.88 mmol, 1.0 equv), que se agitó en un tubo sellado y se calentó a reflujo (72 °C) durante la noche (18 horas), se eliminó el disolvente para proporcionar el producto deseado (880 mg, sólido blanco) de rendimiento en 84%.

Intermedio 136: (1 - (2- benzoilhidrazinil)- 1- oxopropan- 2- il) carbamato de (S)- terc- butilo



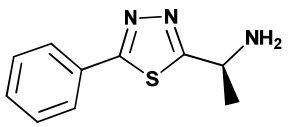
A una solución de (1- hidrazinilo- 1- oxopropan- 2- il) carbamato de (S)- terc- butilo (293 mg, 1.44 mmol, 1.0 equvalente en 3 ml de DCM) se añadió fluoruro de benzoilo (179 mg, 1.44 mmol en 2 ml de DCM), la solución de reacción se agitó a temperatura ambiente durante 50 minutos se eliminó el disolvente para proporcionar el producto deseado. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,89- 7,78 (m, 2H), 7,54 (t, *J* = 7,4 Hz, 1H), 7,43 (t, *J* = 7,6 Hz, 2H), 5,32 (b, 1H), 4,45 (b, 1H), 1,46 (s, 9H).

Intermedio 137: (1 - (5- fenil- 1 ,3,4- tiadiazol- 2- il) etil) carbamato de (S)- terc- butilo



A una solución de (1 - (2- benzoilhidrazinil)- 1- oxopropan- 2- il) carbamato de (S)- terc-butilo (155 mg, 0.5 mmol, 1.0 equv. en 5 ml de THF) se añadió reactivo de Lawesson (36.4 mg, 0.5 mmol, 1.0 equv.) la mezcla de reacción se agitó a reflujo durante 3 horas, la mezcla de reacción se filtró y el disolvente se eliminó para proporcionar el producto crudo. La cromatografía en columna de gel de sílice (acetato de etilo en heptano de 10 a 50%) para proporcionar (1 - (5- fenil- 1 ,3,4- tiadiazol- 2- il) etil) carbamato de (S)- terc-butilo (114.6 mg, sólido) de color blanco en el 70.7% de rendimiento. ^{1}H RMN (400 MHz, CD_2Cl_2) δ 7,94- 7,72 (m, 2H), 7,52- 7,26 (m, 3H), 5,59 (b, 1H), 5,11 (b, 1H), 1,57 (d, *J* = 7,0 Hz, 3H), 1,34 (s, 9H).

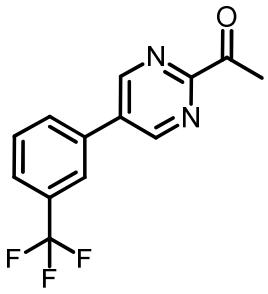
Intermedio 138: (S) - 1 - (5- fenil- 1 ,3,4- tiadiazol- 2- il) etanamina



A una solución de (1 - (5- fenil- 1 ,3,4- tiadiazol- 2- il) etil) carbamato de (S)- terc- butilo (110 mg, 0.4 mmoles, en 5 ml de DCM) se añadió 1 ml de TFA, la mezcla de reacción se agitó a temperatura ambiente durante 3 horas, se eliminó el disolvente para proporcionar

el producto deseado (52 mg) con un rendimiento del 66,8%. LCMS m/z 206,0 (M+H)+ RT = 0.97min.

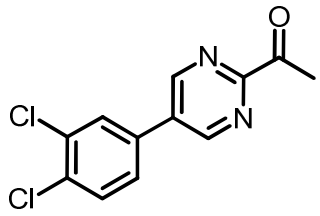
Intermedio 139: 1 - (5 - (3 - (trifluorometil) fenil) pirimidin- 2- il) etanona



Una solución turbia de 1 - (5- bromopirimidin- 2- il) etanona (300 mg, 1,49 mmol), ácido 3 - (trifluorometil) fenilborónico (567 mg, 2,98 mmol), K_3PO_4 (950 mg, 4,48 mmoles), DavePhos [2- diciclohexilfosfino- 2'- (N, N- dimetilamino) bifenil] ligando (59 mg, 0.15 mmoles), y Pd (OAc) 2 (17 mg, 0.075 mmol) en 6 ml de tolueno se calentó a 100 ºC durante 1 h. La mezcla se enfrió a temperatura ambiente, y se filtró a través de Celite. La torta de filtro se aclaró con 30 ml de EtOAc. El filtrado se vertió en 20 ml de agua. Las capas se separaron, y la fase acuosa se extrajo adicionalmente con EtOAc (20 ml). Las fases orgánicas combinadas se lavaron con agua (20 ml) y salmuera (20 ml), se secaron sobre Na_2SO_4, se filtraron y se concentraron directamente sobre gel de sílice. La cromatografía en columna (10 - 100% de EtOAc / heptano) dio 0,26 g de 1 - (5 - (3 - (trifluorometil) fenil) pirimidin- 2- il) etanona (V) como sólido de color canela. MS m/z 267,1 (M+H)+. ^{1}H RMN (400 MHz, $CDCl_3$) δ 9,16 (s, 2H), 7,93- 7,69 (m, 4H), 2,87 (s, 3H).

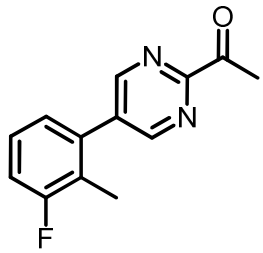
Los compuestos intermedios siguientes se prepararon usando un método similar al descrito para la preparación de **Intermedio 139**. Usando anal. Columna RP- HPLC = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm. Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de amonio formiato, 2% ACN), B: ACN. Tasa de flujo = 2 ml/min. Gradiente = 0 min 5% de B; 5% a 95% de B en 1.70 min; 0.3 min 95% de B; 2.1 min 1% de B.)

Intermedio 140: 1 - (5 - (3,4- diclorofenil) pirimidin- 2- il) etanona.



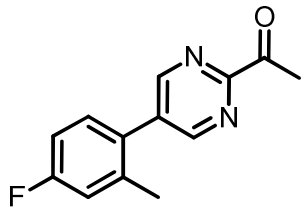
Anal. RP- HPLC tR = 1,17 min. MS m/z 266.9 (M + H)+.

Intermedio 141: 1 - (5 - (3- fluoro- 2- metilfenil) pirimidin- 2- il) etanona.



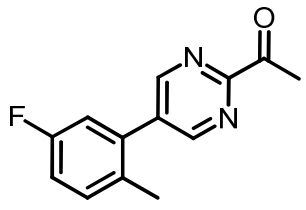
Anal. RP- HPLC tR = 1,07 min. MS m/z 231,1 (M + H)+.

Intermedio 142: 1 - (5 - (4- fluoro- 2- metilfenil) pirimidin- 2- il) etanona.



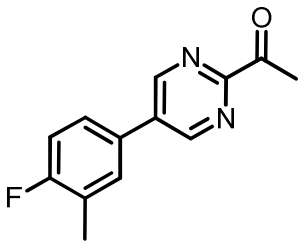
Anal. RP- HPLC tR = 1,18 min.MS m/z 231,1 (M + H)+.

Intermedio 143: 1 - (5 - (5- fluoro- 2- metilfenil) pirimidin- 2- il) etanona



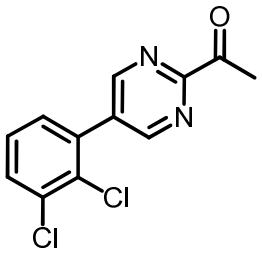
Anal. RP- HPLC tR = 1.16 min. MS m/z 231.2 (M + H)+.

Intermedio 144: 1 - (5 - (4- fluoro- 3- metilfenil) pirimidin- 2- il) etanona



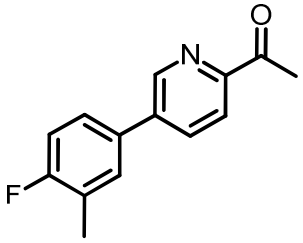
^{1}H RMN (400 MHz, $CDCl_3$) δ 9,09 (s, 2H), 7,52- 7,41 (m, 2H), 7.24- 7.16 (m, 1H), 2,85 (s, 3H), 2,41 (d, J = 2,0 Hz, 3H). Anal. RP- HPLC tR = 1,20 min.MS m/z 231,0 (M + H)+.

Intermedio 145: 1 - (5 - (2,3- diclorofenil) pirimidin- 2- il) etanona



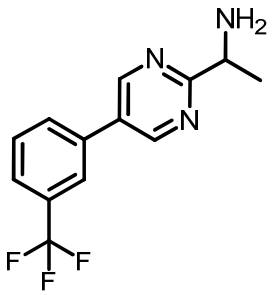
Anal. RP- HPLC tR = 1,15 min. MS m/z 267.9 (M + H)+.

Intermedio 146: 1 - (5 - (4- fluoro- 3- metilfenil) piridin- 2- il) etanona.



^{1}H RMN (400 MHz, $CDCl_3$) δ 8,88 (dd, J = 2,3, 0,8 Hz, 1H), 8,13 (dd, J = 8,1, 0,8 Hz, 1H), 7,98 (dd, J = 8,1, 2,3 Hz, 1H) , 7,50- 7,39 (m, 2H), 7.21- 7.12 (m, 1H), 2,78 (s, 3H), 2,42- 2,36 (m, 3H). Anal. RP- HPLC tR = 1,40 min. MS m/z 230,8 (M + H)+.

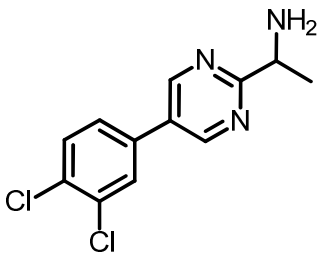
Intermedio 147: 1 - (5 - (3 - (trifluorometil) fenil) pirimidin- 2- il) etanamina



Se absorbió 1 - (5 - (3 - (trifluorometil) fenil) pirimidin- 2- il) etanona (260 mg, 0.977 mmol), NH_4OAc (1.13 g, 14.6 mmoles), y $NaBH_3CN$ (245 mg, 3.91 mmol) en 8 ml 200 a prueba de EtOH, y se calentó a 120 ºC durante 5 minutos en un aparato de microondas. La mezcla se concentró para eliminar el EtOH. El crudo se absorbió en 30 ml de agua + 25 ml de EtOAc. Se añadió NaOH 6N hasta que el pH acuoso fue de ~ 10. Las capas se separaron, y se extrajo acuosa con EtOAc (25 ml). La capa orgánica combinada se lavó con 25 ml de salmuera y se secó con Na_2SO_4. Filtró y se concentró bajo presión reducida para proporcionar 262 mg de aceite crudo de color amarillo, que se llevó adelante sin purificación adicional. Anal. RP- HPLC tR = 0,90 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C. Los eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN. tasa de flujo = Gradiente 2 ml/min = 0 min 5% de B; 5% a 95% de B en 1.70 min; 0.3 min 95% de B; 2.1 min 1% de B.) MS m/z 268,1 (M + H)+.

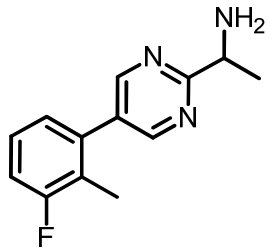
Los intermedios siguientes se prepararon usando un método similar al descrito para la preparación de **Intermedio 147**.

Intermedio 148: 1 - (5 - (3,4- diclorofenil) pirimidin- 2- il) etanamina.



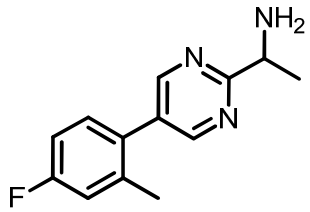
Anal. RP- HPLC tR = 1.09 min (gradiente: 2 a 98% de B en 1.7 min - flujo 1 ml/min Eluyente A: agua + 3.75 mM de NH4Ac + 2% de ACN Columna: Acquity CSH 1.7µm 2.1x50mm - 50 ° C.) MS m/z 268.4 (M + H)+.

Intermedio 149: 1 - (5 - (3- fluoro- 2- metilfenil) pirimidin- 2- il) etanamina.



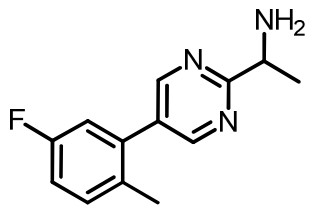
Anal. RP- HPLC tR = 0,99 min. (Gradiente: 2 a 98% B en 1.7 min - flujo de 1 mL/min Eluyente A: agua + 3.75 mM NH4Ac + 2% de ACN Columna: Acquity CSH 1.7µm 2.1x50mm - 50 ° C.). MS m/z 232.4 (M + H)+.

Intermedio 150: 1 - (5 - (4- fluoro- 2- metilfenil) pirimidin- 2- il) etanamina.



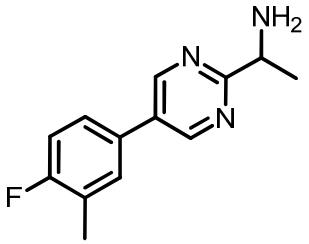
Anal. RP- HPLC tR = 0,87 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% B; 5% a 95% B en 1.70 min; 0,3 min 95% B; 2,1 min 1% B.) MS m/z 231.0 (M) - .

Intermedio 151: 1 - (5 - (5- fluoro- 2- metilfenil) pirimidin- 2- il) etanamina



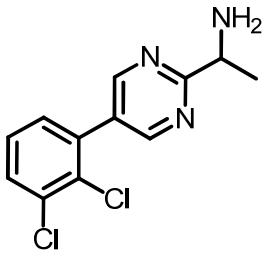
Anal. RP- HPLC tR = 0,79 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 ºC. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% B; 5% a 95% B en 1,70 min; 0,3 min 95% B; 2,1 min 1% B.) MS m/z 232.0 (M + H)+.

Intermedio 152: 1 - (5 - (4- fluoro- 3- metilfenil) pirimidin- 2- il) etanamina



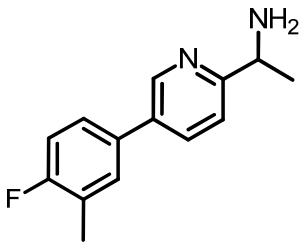
Anal. RP- HPLC tR = 0,81 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 ºC. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% de B; 5% a 95% B en 1,70 min; 0,3 min 95% de B; 2,1 min 1% de B.) MS m/z 231,9 (M + H)+.

Intermedio 153: 1 - (5 - (2,3- diclorofenil) pirimidin- 2- il) etanamina



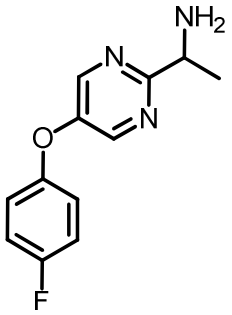
Anal. RP- HPLC tR = 1,01 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% de B; 5% a 95% B en 1,70 min; 0,3 min 95% B; 2,1 min 1% de B.) MS m/z 269,0 (M + H)+.

Intermedio 154: 1 - (5 - (4- fluoro- 3- metilfenil) piridin- 2- il) etanamina



Anal. RP- HPLC tR = 0,92 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% B; 5% a 95% B en 1.70 min; 0.3 min 95% B; 2,1 min 1% de B.) MS m/z 230.9 (M + H)+.

Intermedio 155: 1 - (5 - (4- fluorofenoxi) pirimidin- 2- il) etanamina



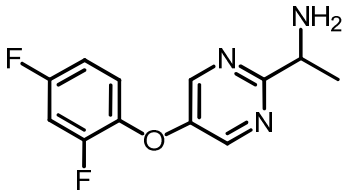
Paso 1: Una solución de 1 - (5- fluoropirimidin- 2- il) etanona (700 mg, 5,0 mmol) y 4-fluorofenol (616 mg, 5.50 mmol) en 6 ml de DMF se trató con carbonato de potasio (829 mg 6,0 mmol) y se calentó a 50 º C durante 3.5 h. La mezcla de reacción se vertió en 20 ml de agua, y se extrajo con EtOAc (2 x 20 ml). Los orgánicos se lavaron con 20 ml de agua, salmuera, y se secaron sobre Na_2SO_4. La mezcla se filtró y se concentró sobre gel de sílice. La cromatografía en columna (10 - 100% de EtOAc/hept) dio 295 mg (25%) 1 - (5 - (4- fluorofenoxi) pirimidin- 2- il) etanona en forma de un sólido blanco que se utilizó directamente en la siguiente etapa. MS m/z 233,2 (M + H)+. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,55 (s, 2H), 7.23 - 7.7 (m, 4H), 2,78 (s, 3H).

Paso 2: 1 - (5 - (4- fluorofenoxi) pirimidin- 2- il) etanona (290 mg, 1.25 mmol), NH_4OAc (1.9 g, 24.6 mmoles), y $NaBH_3CN$ (314 mg, 5.00 mmol) se absorbió en 20 ml 200 a prueba de EtOH, y se calentó a 130 ºC durante 3 minutos en un aparato de microondas. La mezcla se concentró para eliminar el EtOH. El crudo se absorbió en 30 ml de agua +

25 ml de EtOAc. Se añadió NaOH 6N hasta que el pH acuoso fue de ~ 10. Las capas se saparon, y se extrajo acuosa con EtOAc (25 ml). La capa orgánica combinada se lavó con 25 ml de salmuera y se secó con Na_2SO_4. Filtró y se concentró bajo presión reducida para proporcionar 275 mg de aceite de color canela crudo, que se llevó adelante sin purificación adicional. El producto principal Anal. RP- HPLC tR = 1,26 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% B; 5% a 95% B en 1,70 min; 0,3 min 95% B; 2,1 min 1% B.) MS m/z 234,1 (M + H)+.

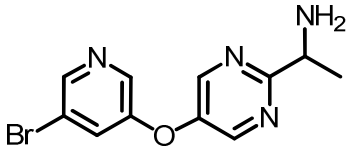
Los intermedios siguientes se prepararon usando métodos similares a los descritos para la preparación de **Intermedio 155**.

Intermedio 156: 1 - (5 - (2,4- difluorofenoxi) pirimidin- 2- il) etanamina



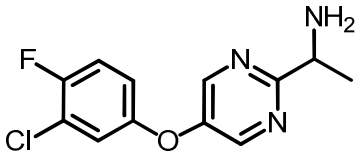
Anal. RP- HPLC tR = 0,81 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C.Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% B; 5% a 95% B en 1,70 min; 0,3 min 95% B; 2,1 min 1% de B.) MS m/z 252.1 (M + H)+.

Intermedio 157: 1 - (5 - (5- bromopiridin- 3- iloxi) pirimidin- 2- il) etanamina



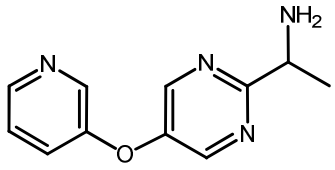
Anal. RP- HPLC tR = 1.29 min. (Columna = Columna Inertsil C8, 3.0 m, 3.0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% B; 5% a 95% B en 1.70 min; 0.3 min 95% de B; 2.1 min 1% de B.) MS m/z 297.3 (M + H)+.

Intermedio 158: 1 - (5 - (3- cloro- 4- fluorofenoxi) pirimidin- 2- il) etanamina



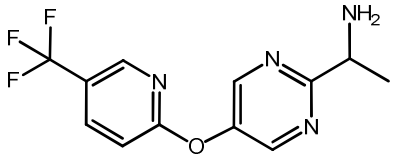
Anal. RP- HPLC tR = 1,40 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasade flujo = 2 ml/min Gradiente = 0 min 5% B; 5% a 95% B en 1.70 min; 0,3 min 95% B; 2,1 min 1% B.) MS m/z 268,0 (M + H)+.

Intermedio 159: 1 - (5 - (piridin- 3- iloxi) pirimidin- 2- il) etanamina



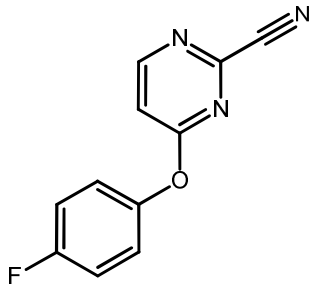
Anal. RP- HPLC tR = 1,21 min. (Columna = Columna Inertsil C8, 3.0 m, 3.0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% B; 5% a 95% B en 1,70 min; 0,3 min 95% B; 2,1 min 1% B.) MS m/z 218.4 (M + H)+.

Intermedio 160: 1 - (5 - (5 - (trifluorometil)) pirimidin- 2- il piridin- 2- iloxi) etanamina



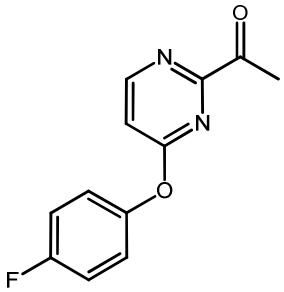
Anal. RP- HPLC tR = 1.16 min. (Columna = Columna Inertsil C8, 3.0 m, 3.0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% B; 5% a 95% B en 1,70 min; 0.3 min 95% B; 2,1 min 1% B.) MS m/z 285.4 (M + H)+.

Intermedio 161: 4 - (4- fluorofenoxi) pirimidina- 2- carbonitrilo



Una solución de 4- cloro- pirimidina- 2- carbonitrilo (0,63 g, 4,51 mmol) y 4- fluorofenol Se enfrió (0.51 g, 4.51 mmol) en 5 ml de DMF a 0 ºC bajo atmósfera de N_2. Se añadió lentamente NaH (0.217 g de suspensión al 60%, 5.42 mmol). Se observó exoterma de burbujeo. La temperatura interna se mantuvo por debajo de 5 ºC. Después de 15 minutos, se retiró el baño frío. La mezcla de reacción se dejó calentar a la temperatura ambiente y se agitó 1 h. La mezcla de reacción se diluyó con agua (40 ml) y se extrajo con (3 x 25 ml) de EtOAc. La capa orgánica se lavó con 40 ml de agua, y salmuera. Se secó sobre Na_2SO_4, y se concentró sobre gel de sílice al vacío. La cromatografía en columna (EtOAc/heptano 10 a 100% de gradiente) dio 0.72 g (74%) de (4- fluorofenoxi) pirimidina- 2- carbonitrilo en forma de sólido cristalino blanco. Anal. RP- HPLC tR = 1.38 min, gradiente: 2- 98% B en 1.7 min - flujo 1 ml/min. Eluyente A: agua + 3.75 mM NH4Ac + 2% ACN. Columna: Acquity CSH 1.7µm 2.1x50mm - 50 °C. MS m/z 216,1 (M + H)+.

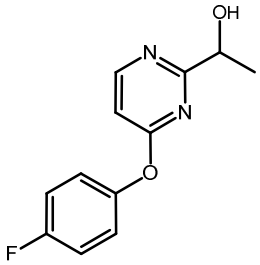
Intermedio 162: 1 - (4 - (4- fluorofenoxi) pirimidin- 2- il) etanona



Se suspendió 4 - (4- fluorofenoxi) pirimidina- 2- carbonitrilo (450 mg, 2,09 mmol) en 12 ml de éter anhidro bajo atmósfera de N_2. Recipiente se enfrió a 0 ºC. Se añadió MeMgBr (3.1 ml de solución 1.0 M en éter de butilo, 3.10 mmol) durante 5 min. La suspensión de color amarillo- verde se agitó 30 minutos, después se inactivó con 50 ml de solución saturada de NH_4Cl. Se ajustó el pH a ~ 6 con HCl conconcentrado. La mezcla se extrajo

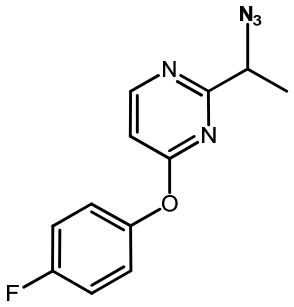
con (2 x 40 ml) de EtOAc. Los orgánicos se lavaron con 30 ml de salmuera, y se secaron sobre Na_2SO_4. Se filtraron y se concentraron en gel de sílice. La cromatografía en columna (10 - 100% de EtOAc en hept) dio 157 mg (32%) 1 - (4 - (4- fluorofenoxi) pirimidin- 2- il) etanona en forma de un aceite de color amarillo. Anal. RP- HPLC tR = 1,44 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% B; 5% a 95% B en 1,70 min; 0,3 min 95% B; 2,1 min 1% B.) MS m/z 233,2 (M + H)+.

Intermedio 163: 1 - (4 - (4- fluorofenoxi) pirimidin- 2- il) etanol



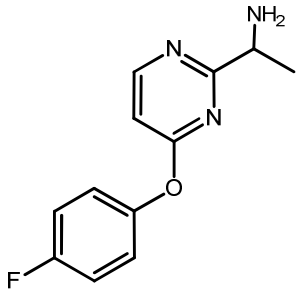
Se absorbió1 - (4 - (4- fluorofenoxi) pirimidin- 2- il) etanona (0,150 g 0,646 mmoles) en 2.5 ml 4:01 MeOH: DCM, y se enfrió a 0 ºC. Se añadió $NaBH_4$ (49 mg 1,30 mmol). Se observó efervescencia. Después de 10 min, se retiró el baño frío, y la reacción se agitó 1 h. El disolvente se eliminó al vacío. El residuo blanco se absorbió en 10 ml de agua, y se extrajo con (2 x 10 ml) de EtOAc. Los orgánicos se lavaron con 10 ml de salmuera. Se secó sobre Na_2SO_4. Se filtró y se concentró para proporcionar 143 mg (95%) 1 - (4 - (4- fluorofenoxi) pirimidin- 2- il) etanol como un aceite incoloro. Anal. RP- HPLC tR = 1,38 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% ACN), B: ACN Tasa de flujo = 2 ml/min Gradiente = 0 min 5% de B; 5% a 95% B en 1,.0 min; 0,3 min 95% B; 2,1 min 1% B.) MS m/z 235,1 (M + H)+.

Intermedio 164: 2 - (1- azidoetil) - 4 - (4- fluorofenoxi) pirimidina



Bajo atmósfera de N_2, se disolvió 1 - (4 - (4- fluorofenoxi) pirimidin- 2- il) etanol (140 mg, 0,598 mmoles) en 3 ml de DCM anhidro. Se añadió trietilamina (0.175 ml, 1.26 mmol), y la mezcla se enfrió a 0 º C. Se añadió MsCl (0.070 ml, 0.897 mmol), y la mezcla se agitó 15 minutos. El mantenimiento de 0 °C, DCM disolvente se eliminó bajo corriente de N_2. El residuo se absorbió en 2 ml de DMF seca. Se añadió NaN_3 (78 mg, 1.19 mmoles), y la reacción se agitó a temperatura ambiente durante 24 h. La mezcla se vertió en 20 ml de agua, y se extrajo con 20 ml de EtOAc. La capa orgánica se lavó con 20 ml de salmuera y se secó sobre Na_2SO_4. Se filtró y se concentró para proporcionar 120 mg (77%) 2 - (1- azidoetil) - 4 - (4- fluorofenoxi) pirimidina en forma de un aceite de color amarillo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,49 (d, J = 5,7 Hz, 1H), 7,16- 6,90 (m, 4H), 6,70 (d, J = 5,7 Hz, 1H), 4,34 (q, J = 6,9 Hz , 1H), 1,55- 1,46 (m, 3H).

Intermedio 165: 1 - (4 - (4- fluorofenoxi) pirimidin- 2- il) etanamina

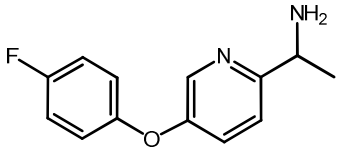


Se disolvió 2 - (1- azidoetil) - 4 - (4- fluorofenoxi) pirimidina (120 mg, 0.463 mmoles) en 2 ml de EtOH puro. Se añadió 24.6 mg (0,023 mmol) de paladio al 10% sobre catalizador de carbono. Con agitación vigorosa, el vial de reacción se evacuó y se purgó 3 veces con H_2. El recipiente de reacción se equipó con un globo de H_2 y se agitó durante 2 h. La mezcla se filtró a través de Celite y se concentró al vacío para proporcionar 75 mg (69%) 1 - (4 - (4- fluorofenoxi) pirimidin- 2- il) etanamina como un aceite marrón. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,45 (d, J = 5,7 Hz, 1H), 7,13- 6,92 (m, 4H), 6,59 (d, J = 5,7 Hz,

1H), 4,00 (q, J = 6,8 Hz , 1H), 1,34- 1,30 (m, 3H). Anal. RP- HPLC tR = 1,18 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasa de flujo = 2 ml/min. Gradiente = 0 min 5% B; 5% a 95% B en 1.70 min; 0.3 min 95% B; 2.1 min 1% de B.) MS m/z 234.2 (M + H)+.

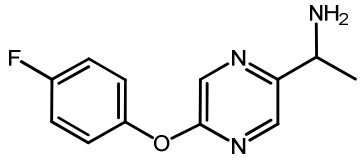
Los intermedios siguientes se prepararon usando métodos similares a los descritos para la preparación de los **Intermediarios del 161 a 165**.

Intermedio 166: 1 - (5 - (4- fluorofenoxi) piridin- 2- il) etanamina



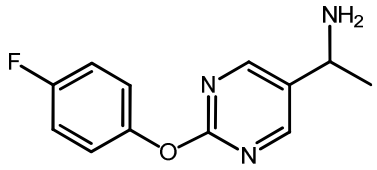
Anal. RP- HPLC tR = 0,91 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN Tasa de flujo = 2 ml/min. Gradiente = 0 min 5% B; 5% a 95% B en 1,70 min; 0,3 min 95% B; 2,1 min 1% B.) MS m/z 233.1 (M + H)+.

Intermedio 167: 1 - (5 - (4- fluorofenoxi) pirazin- 2- il) etanamina



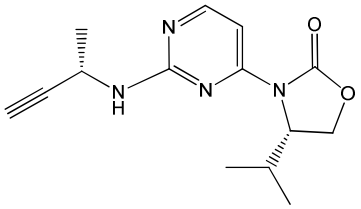
Anal. RP- HPLC tR = 1.39 min. (Columna = Columna Inertsil C8, 3.0 m, 3.0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% ACN), B: ACN. Tasa de flujo = 2 ml/min. Gradiente = 0 min 5% B; 5% a 95% B en 1.70 min; 0.3 min 95% B; 2,1 min 1% B.) MS m/z 217.1 (Fragmento principal + H)+.

Intermedio 168: 1 - (2 - (4- fluorofenoxi) pirimidin- 5- il) etanamina



Anal. RP- HPLC tR = 1.20 min. (Columna = Columna Inertsil C8, 3,0 m, 3,0 x 30 mm Temperatura de la columna = 50 º C. Eluyentes = A: Agua (5 mM de formiato de amonio, 2% de ACN), B: ACN. Tasa de flujo = 2 ml/min. Gradiente = 0 min 5% B; 5% a 95% B en 1,70 min; 0,3 min 95% de B; 2,1 min 1% B.) MS m/z 233.9 (M + H)+.

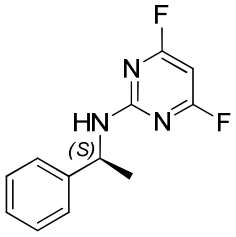
Intermedio 169: (S)- 4- isopropil- 3- [2 - ((S)- 1- metil- prop- 2- inilamino)- pirimidin- 4- il]- oxazolidin- 2- ona



A una solución del compuesto (S) - 3 - (2- cloro- pirimidin- 4- il)- 4- isopropil- oxazolidin- 2- ona (1.03 g, 4,3 mmol) en DMSO (12 ml) se añadió sal de HCl de metil- prop - 2- inilamina (450 mg, 4.3 mmol) y diisopropiletilamina (2.2 ml, 12.6 mmol). La reacción se calentó a 110 º C durante 18 horas. La mezcla de reacción se diluyó con EtOAc (50 ml) y se lavó con agua (25 ml) y salmuera (25 ml). La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El material crudo se purificó en cromatografía en columna de gel de sílice (EtOAc/heptano 0 a 75%) proporcionó (S)- 4- isopropil- 3- [2 - ((S)- 1- metil- prop- 2- inilamino)- pirimidin - 4- il]- oxazolidin- 2- ona (360 mg) con un rendimiento del 31%.

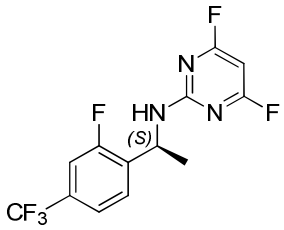
CL- MS m/z: 275.1 (M - Boc) +; RT: 1.33 min..

Intermedio 170: (S) - 4,6- difluoro- N- (1- feniletil) pirimidin- 2- amina



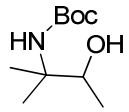
Una solución de 2,4,6- trifluoropirimidina (128,4 mg, 0,96 mmol) y diisopropiletilamina (0,50 ml, 2,9 mmol, 3 equiv) en dioxano (5 ml) se enfrió a 0 °C con un baño de hielo. Después de 30 min, se retiró el baño de hielo, y la reacción se dejó calentar a temperatura ambiente. Después de agitar durante la noche, la reacción se concentró a un aceite de color marrón claro y se purificó mediante cromatografía en columna de gel de sílice (EtOAc/heptano 0 a 100%) para proporcionar (S) - 4,6- difluoro- N- (1- feniletil) pirimidin- 2- amina (151.2 mg, sólido blanco) el rendimiento en un 45%. ^{1}H RMN (400 MHz, CD_3OD) □ 7,35- 7,40 (m, 2H), 7,29- 7,34 (m, 2H), 7.20- 7.26 (m, 1H), 5,84 (s, 1H), 5,08 (q, *J*= 6,91 Hz, 1H), 1,52 (d, *J*= 7,04 Hz, 3H); LCMS m/z 236,1 (M + H)+, Rt 0,95 min.

Intermedio 171: (S) - 4,6- difluoro- N- (1 - (- (2- fluoro- 4 trifluorometil) fenil) etil) pirimidin- 2- amina



El Intermedio 171 se preparó por un método similar al descrito para la preparación del Intermedio 170. ^{1}H RMN (400 MHz, CD_3OD) 7,58 (t, J = 7,63 Hz, 1H), 7,34- 7,48 (m, 2H), 5,84 (br s, 1H.), 5,35 (q, J = 6,91 Hz, 1H) , 1,54 (d, J = 7,04 Hz, 3H). MS m/z 321,9 (M + H)+, Rt 1,11 min.

Intermedio 172: 3- hidroxi- 2- metilbutan- 2- ilcarbamato de terc- butilo



Paso 1: Preparación de 1 - (metoxi (metil) amino)- 2- metil- 1- oxopropan- 2- ilcarbamato de terc- butilo

Se combinó ácido 2 - (terc- butoxicarbonilamino)- 2- metilpropanoico (6.62 g, 32.6 mmoles), clorhidrato de O, N- dimetilhidroxilamina (3.50 g, 35.8 mmoles), y HATU (14.86 g, 39.1 mmol) en DMF (100 ml). A esta solución se añadió base Hunig (17.07 ml, 98 mmol). La reacción se agitó durante toda la noche (17 horas). Después, la reacción se concentró al vacío y el residuo se diluyó con EtOAc (300 ml) y se lavó con agua (2x80mL). La capa orgánica se lavó con salmuera, se secó (Na_2SO_4), y se concentró bajo presión reducida. El residuo se purificó a través de cromatografía ultrarrápida en gel de sílice (10- 50 por ciento de EtOAc- hexanos) para proporcionar el producto deseado como un sólido blanco (6.36 g). LCMS m/z 247.2 (M + H)+, Rt 0.61 min.

Paso 2: Preparación de 2- metil- 3- oxobutan- 2- ilcarbamato de terc- butilo

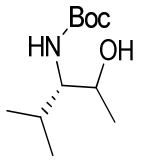
A una solución de 1 - (metoxi (metil) amino)- 2- metil- 1- oxopropan- 2- ilcarbamato de terc- butilo (4.26 g, 17.30 mmol) en THF (100 ml) a - 70 º C se añadió por goteo metil-litio (32.4 ml, 51,9 mmol). El baño frío fue reemplazado con - 40 °C baño y la reacción se agitó durante 4 horas. Después se añadió cuidadosamente solución saturada de NH_4Cl (10 ml) para interrumpir la reacción. La mezcla de reacción se dejó calentar a temperatura ambiente, y se diluyó con EtOAc (100 ml) y agua (50 ml). Las fases se separaron y la capa acuosa se extrajo con EtOAc (2x100 mL). Los orgánicos combinados se secaron (Na_2SO_4) y se concentraron bajo presión reducida. El residuo se purificó a través de cromatografía ultrarrápida en gel de sílice (10- 50% EtOAc- hexanos) para proporcionar el producto deseado como un sólido blanco (2.36 g). LCMS m/z 224.2 (M+Na)+, Rt 0.7 min.

Paso 3: Preparación de 3- hidroxi- 2- metilbutan- 2- ilcarbamato de terc- butilo

A una solución de 2- metil- 3- oxobutan- 2- ilcarbamato de terc- butilo (2.36 g, 11.73 mmol) en MeOH (30 ml) a 0 º C se añadió en porciones $NaBH_4$ (0.887 g, 23.45 mmol). El

baño frío se retiró y la reacción se agitó durante 1 hora. Luego se añadió cuidadosamente solución de HCl (1 M, 0.2 ml) para interrumpir la reacción. La mezcla de reacción se concentró y se diluyó con EtOAc (50 ml) y agua (10 ml). Las fases se separaron y la capa acuosa se extrajo con EtOAc (2x20 ml). Los orgánicos combinados se secaron ($Na_{2SO}4$) y se concentraron bajo presión reducida. El residuo se purificó a través de cromatografía ultrarrápida en gel de sílice (10- 50% EtOAc- hexanos) para proporcionar el producto deseado como un sólido blanco (2.12 g). LCMS m/z 204.1 (M + H)+, Rt 0,69 min.

Intermedio 173: ((3S)- 2- hidroxi- 4- metil- 3- il) carbamato de terc- butilo



Paso 1: Preparación de 1 - (metoxi (metil) amino)- 2- metil- 1- oxopropan- 2- ilcarbamato de terc- butilo

A una solución del ácido (S) - 2 - (terc- butoxicarbonilamino)- 3- metilbutanoico (5.86 g, 27.0 mmoles) en DCM (100 ml) a 0 ºC se añadió por porciones di(1H- imidazol- 1- il) metanona (4.81 g, 29.7 mmoles). El baño frío se retiró y la reacción se agitó a 20 °C durante 30 minutos. Luego se añadió hidrocloruro de O,N- dimetilhidroxilamina (3.16 g, 32.4 mmol) y seguido por la adición lenta de trietilamina (3.28 g, 32.4 mmoles). La mezcla de reacción se agitó a 20 ºC durante toda la noche (18 h), y se diluyó con DCM (200 ml) y se lavó con HCl (1 M, 2x50 ml) y solución saturada de $NaHCO_3$ (2x50 ml), H_2O (50 ml) y salmuera (50 ml). A continuación, la orgánica se secó (Na_2SO_4) y se concentró bajo presión reducida para proporcionar el producto crudo (6.61 g). LCMS m/z 261.2 (M + H)+, Rt 0.77 min.

Paso 2: Preparación de 2- metil- 4- oxopentan- 3- ilcarbamato de (S)- terc- butilo

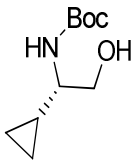
A una solución de 1 - (metoxi (metil) amino)- 3- metil- 1- oxobutan- 2- ilcarbamato de (S)- terc- butilo (4.23 g, 16.25 mmol) en THF (100 ml) a - 70 ºC se añadió por goteo metil- litio (1.071 g, 48.7 mmol). El baño frío fue reemplazado por un baño - 40 °C (MeCN en hielo seco) retiró y la reacción se agitó durante 4 horas. Después se añadió

cuidadosamente solución saturada de NH_4Cl (10 ml) para interrumpir la reacción. La mezcla de reacción se dejó calentar a temperatura ambiente, y se diluyó con EtOAc (100 ml) y agua (50 ml). Las fases se separaron y la capa acuosa se extrajo con EtOAc (2x100 mL). Los orgánicos combinados se secaron (Na_2SO_4) y se concentraron bajo presión reducida. El residuo se purificó a través de cromatografía ultrarrápida en gel de sílice (10-50% EtOAc- hexanos) para proporcionar el producto deseado como un sólido blanco (3.01 g). LCMS m/z 238.2 (M+Na)+, Rt 0,78 min.

Paso 3: Preparación de 3- hidroxi- 2- metilbutan- 2- ilcarbamato de terc- butilo

A una solución del ácido 2- metil- 4- oxopentan- 3- ilcarbamato del (S)- terc- butílico (2.65 g, 12.31 mmol) en MeOH (30 ml) a 0 ° C se añadió en porciones $NaBH_4$ (0.931 g, 24.62 mmoles) . El baño frío se retiró y la reacción se agitó durante 1 hora. Después se añadió cuidadosamente solución de HCl (1 M, 0.3 ml) para interrumpir la reacción. La mezcla de reacción se concentró y se diluyó con EtOAc (50 ml) y agua (10 ml). Las fases se separaron y la capa acuosa se extrajo con EtOAc (2x20 ml). Los orgánicos combinados se secaron (Na_2SO_4) y se concentraron. El residuo se purificó a través de cromatografía ultrarrápida en gel de sílice (10- 50% EtOAc- hexanos) para proporcionar el producto deseado como un sólido blanco (2.05 g). LCMS m/z 240.2 (M+Na)+, Rt 0,69 min.

Intermedio 174: (1- ciclopropil- 2- hidroxietil)carbamato de (S)- terc- butilo



Paso 1: Preparación de 1 - (metoxi (metil) amino)- 2- metil- 1- oxopropan- 2- ilcarbamato de terc- butilo

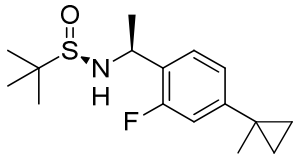
A ácido (S) - 2 - (terc- butoxicarbonilamino)- 2- ciclopropilacético (5.01 g, 23.28 mmol) en MeOH (50 ml) se añadió por goteo trimetilsilildiazometano (18.62 ml, 37.2 mmoles) hasta que no hay burbujas. La reacción se agitó durante 30 minutos y se inactivó con gotas de HOAc (0,1 ml). La mezcla de reacción se concentró bajo presión reducida para

proporcionar el producto crudo como un aceite de color canela claro (5,35 g). LCMS m/z 252.1 (M+Na)+, Rt 0.77 min.

Paso 2: Preparación de (1- ciclopropil- 2- hidroxietil)carbamato de (S)- terc- butilo

A una solución de 2 - (terc- butoxicarbonilamino)- 2- ciclopropilacetato de (S)- metilo (5.35 g, 23.33 mmol) en Et_2O (100 ml) se añadió $LiBH_4$ (0.762 g, 35.0 mmol), seguido por goteo adicional de metanol (1.420 ml, 35.0 mmoles). La reacción se calentó a reflujo a 40 °C durante una hora. La mezcla de reacción se enfrió a 0 °C, y se inactivó con HCl (1 M) hasta pH = 2 para la capa acuosa. Las fases se separaron y la capa acuosa se extrajo con DCM (3x100 ml). A continuación, la capa orgánica se secó (Na_2SO_4) y se concentró bajo presión reducida para proporcionar el producto crudo final (4.16 g). LCMS m/z 224.1 (M+Na)+, Rt 0.62 min.

Intermedio 175: (R)- N- ((S) - 1 - (2- fluoro- 4- (1- metilciclopropil) fenil) etil)- 2- metilpropano- 2- sulfinamida



Paso 1

A un matraz secado en horno de fondo redondo con barra de agitación se añadió 4- bromo- 2- fluorobenzaldehído (5 g, 24.6 mmoles), (R)- 2- metilpropano- 2- sulfinamida (3.28 g, 27.1 mmol) y DCE (49 ml). Luego a esta mezcla se añadió sulfato de cobre (II) (5.90 g, 36.9 mmoles). La mezcla de reacción se calentó en un baño de aceite precalentado a 55 °C durante 18 horas. La mezcla de reacción se filtró a través de un lecho de Celite, lavando los sólidos con CH_2Cl_2. El filtrado se concentró para proporcionar un aceite amarillo viscoso de (R, E)- N- (4- bromo- 2- fluorobenciliden)- 2- metilpropano- 2- sulfinamida (7.73 g, 25.2 mmol, rendimiento del 103%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,27 (s, 9 H) 7,31- 7,42 (m, 2 H) 7,87 (t, *J*= 7,87 Hz, 1 H) 8,83 (s, 1 H). LCMS m/z 307,9 (M + H)+, Rt 1,01 min.

Paso 2

A una solución de (R, E)- N- (4- bromo- 2- fluorobenciliden)- 2- metilpropano- 2- sulfinamida (7.73 g, 25.2 mmoles) en CH_2Cl_2 (252 ml), se enfrió a 0 °C (agua/baño de hielo) en atmósfera de nitrógeno, se añadió 3M metil bromuro de magnesio (33.7 ml, 101 mmol) en Et_2O. La mezcla de reacción se dejó agitar durante 30 min a 0 º C, después se dejó calentar gradualmente a temperatura ambiente y se agitó durante 1 hora a temperatura ambiente. La mezcla de reacción se enfrió a 0 ºC después se inactivó con la adición lenta de una solución saturada de NH_4Cl. La mezcla acuosa se extrajo con EtOAc. Las fases orgánicas combinadas, se lavaron con agua, salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron sobre gel de sílice. La cromatografía en columna de gel de sílice (EtOAc/Heptano 40 a 100%) proporcionó (R)- N- ((S) - 1 - (4- bromo- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida (4.93 g, 15.3 mmol, rendimiento del 60%) como un sólido cristalino blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,20 (s, 9 H) 1,56 (d, *J*. = 6,70 Hz, 3 H) 3,34 (br s, 1 H) 4,77- 4,87 (m, 1 H) 7.19 - 7.31 (m, 3 H). LCMS m/z 324,0 (M + H)+, Rt 0,90 min.

Paso 3

A un vial de microondas con una barra de agitación se añadió (R)- N- ((S) - 1 - (4- bromo- 2- fluorofenil) etil)- 2- metilpropano- 2- (1 g, 3,10 mmol), éster de pinacol del ácido isopropenilo borónico (1.51 ml, 8.07 mmol), DME (8 ml), carbonato de sodio (7.76 ml, 15.5 mmoles) (acuoso 2.0 M) y aducto $PdCl_2$(dppf).CH_2Cl_2 (0.127 g, 0.155 mmol). El recipiente se tapó y se calentó por irradiación de microondas durante 20 min a 100 °C. La mezcla de reacción se diluyó con una solución saturada de NH_4Cl. La mezcla acuosa se extrajo con EtOAc. Las fases orgánicas combinadas, se lavaron con agua, salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron sobre gel de sílice. La cromatografía en columna de gel de sílice (EtOAc/heptano 50 al 100%) proporcionó (R)- N- ((S) - 1 - (2- fluoro- 4- (prop- 1- en- 2- il) fenil) etil) - 2- metilpropano- 2- sulfinamida (830 mg, 2.93 mmol, rendimiento del 94%) como un sólido cristalino de color marrón pálido. ^{1}H RMN (400 MHz, DMSO) 1.8 - 1.11 (m, 9 H) 1,47 (d, *J*= 6,80 Hz, 3 H) 2,09 (d, *J*= 0,54 Hz, 3 H) 4,61- 4,71 (m, 1 H) 5,14 (t, *J*= 1,32 Hz, 1 H) 5,43 (d, *J*= 5,58 Hz, 1 H) 5,49 (s, 1 H) 7.24 - 7.30 (m, 1 H) 7,31- 7,36 (m, 1 H) 7,41- 7,47 (m, 1 H). LCMS m/z 284,0 (M + H)+, Rt 0,93 min.

Paso 4

A un matraz de fondo redondo que contenía (R)- N- ((S) - 1 - (2- fluoro- 4- (prop- 1- en- 2- il) fenil) etil)- 2- metilpropano- 2- (0.37 g, 1.31 mmol) en DCE (13 ml) a 0 º C se añadió bajo argón dietilzinc (1.0 M en hexanos) (13.1 ml, 13.1 mmol) seguido de la adición por goteo de cloroyodometano (0.95 ml, 13.1 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se enfrió a 0 °C después de lo cual una segunda adición de dietilzinc (1.0 M en hexanos) (13.1 ml, 13.1 mmol) se llevó a cabo, seguido de la adición de cloroyodometano (0.95 ml, 13.1 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó 18 horas en atmósfera de argón. La mezcla de reacción se enfrió a 0 °C en un baño de hielo y a la mezcla de reacción fría se añadió lentamente una solución saturada de NH_4Cl. La mezcla acuosa se extrajo con EtOAc. Las fases orgánicas combinadas, se lavaron con agua, salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron sobre gel de sílice. La cromatografía en columna de gel de sílice (EtOAc/heptano del 20 al 100%) proporcionó un blanco cristalino de (R)- N- ((S) - 1 - (2- fluoro- 4- (1- metilciclopropil) fenil) etil) - 2 - metilpropano- 2- sulfinamida (89 mg, 0.299 mmol, rendimiento del 22,92%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,75- 0,79 (m, 2 H) 0.85 - 0.90 (m, 2 H) 1,20 (s, 9 H) 1,55 (s, 3 H) 1,57 (d, *J*= 6,80 Hz, 1 H) 3,34 (d, *J*= 5,23 Hz, 1 H) 4,75- 4,85 (m, 1 H) 6,90 (dd, *J*= 12,30, 1,74 Hz, 1H) 6,97 (dd, *J*= 8,05, 1,78 Hz, 1 H) 7,22 (t, *J*= 7,97 Hz, 1 H). LCMS m/z 298,1 (M + H)+, Rt 1,01 min.

Los compuestos intermedios de la Tabla 4k se prepararon por un método similar al descrito para la preparación del Intermedio 175.

Tabla 4k

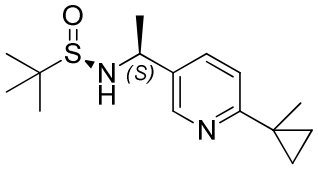
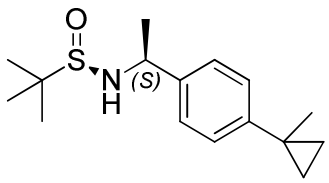
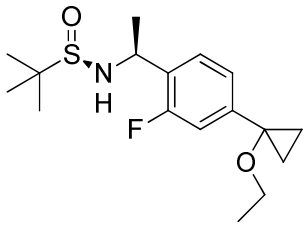
Intermedio 176	Intermedio 177
	

Tabla 4 m. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada intermedio que aparece en la Tabla 4 k.

Intermedio: Nombre	^{1}H RMN (400 MHz) δ ppm	LCMS
176: (R)- 2- metil- N- ((S) - 1 - (6 - (1- metilciclopropil) piridin- 3- il) etil) propano- 2- sulfinamida		MS m/z 282,1 (M + H)+, Rt 0,48 min.
177: (R)- 2- metil- N- ((S) - 1 - (4 - (1- metilciclopropil) fenil) etil) propano- 2- sulfinamida	($CDCl_3$) 0,71- 0,76 (m, 2 H) 0,85- 0,89 (m, 2 H) 1.20 - 1.22 (m, 9 H) 1,41 (s, 3 H) 1,53 (d, *J*= 6,65 Hz, 3 H) 3,29 (d, *J*= 3,57 Hz, 1 H) 4,50- 4,57 (m, 1 H) 7,21 (s, 2 H) 7,23 (s, 2 H)	MS m/z 280,1 (M + H)+, Rt 0,98 min.

Intermedio 178: (R)- N- ((S) - 1 - (4 - (1- etoxiciclopropil)- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida



Paso 1

Se añadió a un vial de microondas con una barra de agitación (R)- N- ((S) - 1 - (4- bromo- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida (500 mg, 1.55 mmol) seguido de la adición de tributil (1- etoxivinil)estanano (1.12 g, 3.10 mmol), trietilamina (0.65 ml, 4.65 mmol) y aducto de $PdCl_2(dppf).CH_2Cl_2$ (63 mg, 0,078 mmol). A los sólidos se añadió tolueno (10 ml). El vial tapado y se calentó en un baño de arena precalentado a 100 °C durante 1 hora. La mezcla de reacción se cargó en columna de gel de sílice. La cromatografía en columna de gel de sílice ($MeOH/CH_2Cl_2$ 0 a 10% con buffer de NH_4OH al 1%) proporcionó (R)- N- ((S) - 1 - (4 - (1- etoxivinil)- 2- fluorofenil) etil) - 2 - metilpropano- 2- sulfinamida (498 mg, 1.59 mmol, rendimiento del 102%) como un aceite viscoso de color marrón que cristalizó al dejarlo en reposo. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,20 (s, 9 H) 1,43 (t, *J*= 6,97 Hz, 3 H) 1,58 (d, *J*= 6,75 Hz, 3 H) 3,35 (d, *J*= 4,74 Hz, 1 H) 3,92 (q, *J*= 6,96 Hz, 2H) 4,23 (d, *J*= 2,79 Hz, 1 H) 4,65 (d, *J*= 2,79 Hz, 1 H) 4,79- 4,89 (m, 1 H) 7.16 - 7.20 (m, 1 H) 7,29- 7,34 (m, 1 H) 7,39 (dd, *J*= 8,07, 1,66 Hz, 1 H).

Paso 2

A un matraz de fondo redondo que contenía (R)- N- ((S) - 1 - (4 - (1- etoxivinil)- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida (0.49 g, 1.56 mmol) y cloroyodometano (1.14 ml, 15.6 mmol) en tolueno (15 ml) a 0 °C en atmósfera de argón se añadió dietilzinc (1,0 M en hexanos) (15.6 ml, 15.6 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora. La mezcla de reacción se enfrió a 0 °C en un baño de hielo y a la mezcla de reacción fría se añadió lentamente una solución saturada de NH_4Cl. La mezcla acuosa se extrajo con EtOAc. Las fases orgánicas combinadas, se lavaron con agua, salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron sobre gel de sílice. La cromatografía en columna de gel de sílice ($MeOH/CH_2Cl_2$ al 0 a 10%) proporcionó (R)- N- ((S) - 1 - (4 - (1- etoxiciclopropil)- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida (145 mg, 0.44 mmol, rendimiento del 28%) como un aceite viscoso de color marrón. ^{1}H RMN (300 MHz, $CDCl_3$) δ 0,93- 0,99 (m, 2 H) 1.14 - 1.20 (m, 3 H) 1,21 (s, 9 H) 1.22 - 1.27 (m, 2 H) 1,57- 1,61 (m, 4 H) 3,35 (d, *J*= 4,98 Hz, 1 H) 3,45 (q, *J*= 7,07 Hz, 2 H) 4,77- 4,87 (m, 1 H) 6,98 (dd, *J*= 7,58, 1,43 Hz, 3 H) 7,00- 7,03 (m, 4 H) 7,28- 7,32 (m, 1 H). LCMS m/z 328,1 (M + H)+, Rt 0,95 min.

El Intermedio en Tabla 4n se prepararó por un método similar al descrito para la preparación del Intermedio 178.

Tabla 4n.

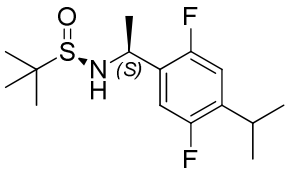
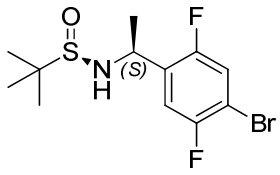
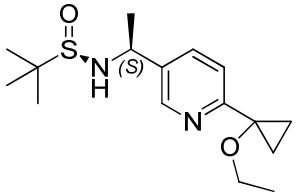
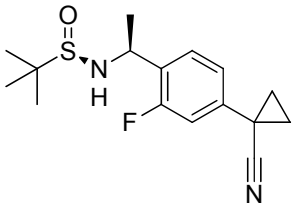
Intermedio 179	Intermedio 180	Intermedio 181
		

Tabla 4p. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada intermedio enumerado en la Tabla 4n.

Intermedio: Nombre	^{1}H RMN (400 MHz) δ ppm	LCMS
179: (R)- N- ((S) - 1 - (2,5- difluoro- 4- isopropilfenil) etil)- 2- metilpropano- 2- sulfinamida		MS m/z 304,2 (M + H)+, Rt 1,04 min.

180: (R)- N- ((S) - 1 - (4- bromo- 2 ,5- difluorofenil) etil)- 2- metilpropano- 2- sulfinamida		MS m/z 340,1, 342,1 (M + H)+, Rt 0,96 min.
181: (R)- N- ((S) - 1 - (6 - (1- etoxiciclopropil) piridin- 3- il) etil)- 2- metilpropano- 2- sulfinamida		MS m/z 311,1 (M + H)+, Rt 0,52 min.

Intermedio 182: (R)- N- ((S) - 1 - (4 - (1- cianociclopropil)- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida



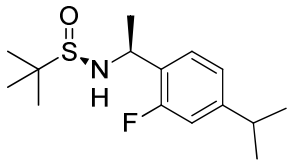
Paso 1

Se añadió a un vial de microondas con una barra de agitación (R)- N- ((S) - 1 - (4- bromo- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida (300 mg, 0.93 mmoles), éster de pinacol de ácido 4- isoxazolborónico (218 mg, 1.12 mmol), aducto de $PdCl_2(dppf).CH_2Cl_2$ (76 mg, 0,09 mmoles), fluoruro de potasio (2.7 ml, 1.0 M en agua, 2.79 mmol) y, finalmente, DMSO (9 ml) . La mezcla de reacción se desgasificó con nitrógeno burbujeante (3 min) y el vial tapado y se calentó en un baño de aceite precalentado a 130 °C durante 18 horas. La mezcla de reacción se diluyó con una solución saturada de NH_4Cl y se extrajo con EtOAc. Las fases orgánicas combinadas, se lavaron con agua, salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron sobre gel de sílice. La cromatografía en columna de gel de sílice (EtOAc /heptanos 40 a 100%) proporcionó (R)- N- ((S) - 1 - (4 - (cianometil)- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida (136 mg, 0.48 mmol, rendimiento del 52%) como un aceite viscoso de color marrón. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,19 (s, 9 H) 1,57 (d, *J*= 6,80 Hz, 3 H) 3,39 (d, *J*= 4,35 Hz, 1 H) 3,74 (s, 2 H) 4,81- 4,88 (m, 1 H) 7,04 (d, *J*= 10,66 Hz, 1 H) 7,11 (d, *J*= 7,97 Hz, 1 H) 7,38 (t, *J*= 7,73 Hz, 1 H). LCMS m/z 283,0 (M + H)+, Rt 0,72 min.

Paso 2

Para un vial de centelleo que contiene (R)- N- ((S) - 1 - (4 - (cianometil)- 2- fluorofenil) etil)- 2- metilpropano- 2- (86 mg, 0.31 mmol) y una barra de agitación se añadido tolueno (2 ml). Luego a esta mezcla se añadió bromuro de tetrabutilamonio (19 mg, 0.06 mmol) seguido de la adición de NaOH (1.52 ml, 1.0 M (ac), 1.52 mmol) y 1,2- dibromoetano (0.11 ml, 1.22 mmol). El vial tapado y la mezcla de reacción se agitó vigorosamente a temperatura ambiente durante 18 horas. Después de lo cual, se añadió 1,2- dibromoetano (0,11 ml, 1,22 mmol) y bromuro de tetrabutilamonio (19 mg, 0,06 mmol) y la mezcla de reacción se dejó agitar 18 horas adicionales. Se añadió una tercera adición de 1,2- dibromoetano (0.11 ml, 1.22 mmol) y la mezcla de reacción se calentó a 50 °C durante 18 horas adicionales en una bandeja de aluminio precalentado. La mezcla de reacción se inactivó con una solución saturada de NH_4Cl y la mezcla acuosa se extrajo con EtOAc. Los organicos se combinaron y se lavaron dos veces con agua, salmuera, se secaron (Na_2SO_4), se filtró y se concentraron. El material crudo se pasó a través de un pequeño conector de gel de sílice usando 10% MeOH: 90% DCM para eluir el producto. La solución se concentró para proporcionar un aceite viscoso de color naranja de (R)- N- ((S) - 1 - (4 - (1- cianociclopropil)- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida (23 mg , 0,08 mmol, rendimiento del 24%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,20 (s, 9 H) 1,38- 1,44 (m, 2 H) 1,56 (d, *J*= 6,75 Hz, 3 H) 1,73- 1,79 (m, 2 H) 3,37 (d, *J*= 4,45 Hz, 1 H) 4,78- 4,88 (m, 1 H) 6,94 (dd, *J*= 11,35, 1,91 Hz, 1 H) 7,09 (dd, *J*= 8,07, 1,91 Hz, 1 H) 7,34 (t, *J*= 7,90 Hz, 1 H). LCMS m/z 309,2 (M + H)+, Rt 0,83 min.

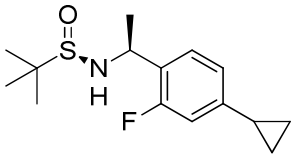
Intermedio 183: (R)- N- ((S) - 1 - (2- fluoro- 4- isopropilfenil) etil)- 2- metilpropano- 2- sulfinamida



A un matraz de fondo redondo que contenía (R)- N- ((S) - 1 - (2- fluoro- 4- (prop- 1- en- 2- il) fenil) etil)- 2- metilpropano- 2- sulfinamida (204 mg, 0.72 mmol) y una barra de agitación se añadió MeOH (7,2 ml). A esta solución se añadió paladio sobre carbono (77 mg, 10%, 0.07 mmol) en MeOH (1 ml). Se insertó una atmósfera de hidrógeno y la mezcla de reacción resultante se agitó a temperatura ambiente durante 18 horas, momento

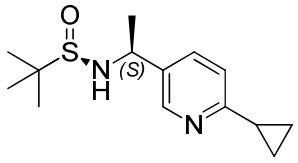
en el que se añadió más paladio sobre carbono (300 mg) en MeOH (5 ml). Una atmósfera de hidrógeno se inserta de nuevo y la mezcla de reacción se dejó agitar 18 horas adicionales a temperatura ambiente. La mezcla de reacción se filtró a través de un filtro de jeringa y se concentró para proporcionar un aceite viscoso de color marrón claro de (R)- N- ((S) - 1 - (2- fluoro- 4- isopropilfenil) etil)- 2- metilpropano- 2- sulfinamida (149 mg, 0.52 mmol, rendimiento del 73%) que se cristalizó al dejarlo reposar. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,20 (s, 9 H) 1,24 (d, *J*= 5,87 Hz, 6 H) 1,58 (d, *J*= 6,70 Hz, 3 H) 2,89 (dt, *J*= 13,79, 6,90 Hz, 1 H) 3,35 (d, *J*= 5,04 Hz, 1 H) 4,76- 4,85 (m, 1 H) 6,90 (dd, *J*= 12,03, 1,52 Hz, 1 H) 6,98 (dd, *J*= 7,90, 1,54 Hz, 1 H) 7,24 (t, *J*= 7,97 Hz, 1 H). LCMS m/z 286,3 (M + H)+, Rt 1,01 min.

Intermedio 184: (R)- N- ((S) - 1 - (4- ciclopropil- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida



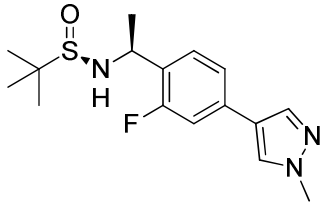
Se añadió a un vial de microondas que contiene una barra de agitación (R)- N- ((S) - 1 - (4- bromo- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida (100 mg, 0.31 mmol) seguido por la adición de ciclopropiltrifluoroborato de potasio (459 mg, 3.10 mmol), carbonato de cesio (506 mg, 1.55 mmol) y Pd (OAc) 2(7 mg, 0.03 mmol) y di (1- adamantil)- n- butilfosfina (22 mg , 0.06 mmol), tolueno (2.6 ml) y finalmente agua (0.5 ml). El vial tapado y calentado por irraditation microondas durante 20 min a 100 °C, seguido de calentamiento térmico a 100 °C en una bandeja de aluminio precalentada durante 18 horas. La mezcla de reacción se diluyó con una solución saturada de NH_4Cl. La mezcla acuosa se extrajo con EtOAc. Las fases orgánicas combinadas, se lavaron con agua, salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron para proporcionar un sólido cristalino de color amarillo de (R)- N- ((S) - 1 - (4- ciclopropil- 2- fluorofenil) etil) - 2 - metilpropano- 2- sulfinamida (116 mg, 0.33 mmol, rendimiento del 106%). LCMS m/z 284.0 (M + H)+, Rt 0.90 min.

Intermedio 185: (R)- N- ((S) - 1 - (6- ciclopropilpiridin- 3- il) etil)- 2- metilpropano- 2- sulfinamida



(R)- N- ((S) - 1 - (6- ciclopropilpiridin- 3- il) etil)- 2- metilpropano- 2- sulfinamida se preparó con un método similar al que se utilizó para evaluar el Intermedio 184. MS m/z 267.1 (M + H)+, Rt 0.44 min.

Intermedio 186: (R)- N- ((S) - 1 - (2- fluoro- 4- (1- metil- 1H- pirazol- 4- il) fenil) etil)- 2- metilpropano- 2- sulfinamida



A dos viales de microondas con barras de agitación se añadió (R)- N- ((S) - 1 - (4- bromo- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida (1.5 g, 4.65 mmol), éster pinacol del ácido 1- metil- 4- 1H- pirazolboronico (2.91 g, 13.9 mmol), DME (20 ml), carbonato de sodio (11.6 ml, 23.3 mmoles, solución acuosa 2.0 M) y aducto de $PdCl_2$(dppf). CH_2Cl_2 (190 mg , 0.23 mmol), dividido entre los dos viales. Los viales se taparon y se calentaron por irradiación de microondas durante 20 min a 100 °C, respectivamente. Las mezclas de reacción combinadas, se diluyeron con una solución saturada de NH_4Cl y EtOAc. Las fases se particionaron y la fase acuosa se extrajo con EtOAc. Las fases orgánicas combinadas, se lavaron con agua, salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron sobre gel de sílice. La cromatografía en columna de gel de sílice (EtOAc/Heptano 40 a 100%) proporcionó un sólido cristalino de color naranja de (R)- N- ((S) - 1 - (2- fluoro- 4- (1- metil- 1H- pirazol- 4- il) fenil) etil)- 2- metilpropano- 2- sulfinamida (1.07 g, 3.31 mmol, rendimiento del 71%. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,21 ppm (s, 9 H) 1,60 (d, *J*= 6,80 Hz, 3 H) 3,36 (d, *J*= 4,25 Hz, 1 H) 3,96 (s, 3 H) 4,79- 4,91 (m, 1 H) 7,13 (dd, *J*= 11,69, 1,61 Hz, 1 H) 7,23 (dd, *J*= 8,00, 1,64 Hz, 1 H) 7,30- 7,37 (m, 1 H) 7,60 (s, 1 H) 7,74 (s, 1 H). LCMS m/z 324,0 (M + H)+, Rt 0,74 min.

Los compuestos intermedios en Tabla 4q se prepararon por un método similar al descrito para la preparación del Intermedio 186.

Tabla 4q.

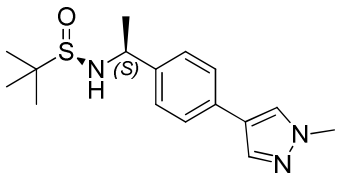
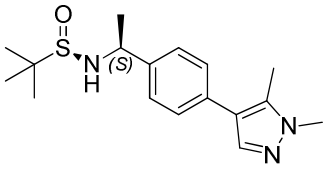
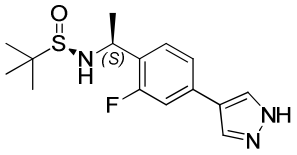
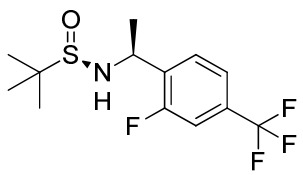
Intermedio 187	Intermedio 188	Intermedio 189
		

Tabla 4r. Nombre químico, desplazamientos químicos RMN y señal LCMS para cada intermedio que aparece en la Tabla 4q.

Intermedio: Nombre	^{1}H RMN (400 MHz) □ ppm	LCMS
187: (R)- 2- metil- N- ((S) - 1 - (4 - (1- metil- 1H- pirazol- 4- il) fenil) etil) propano- 2- sulfinamida		MS m/z 306,0 (M + H)+, Rt 0,71 min.
188: (R)- N- ((S) - 1 - (4 - (1,5- dimetil- 1H- pirazol- 4- il) fenil) etil)- 2- metilpropano- 2- sulfinamida		MS m/z 320,0 (M + H)+, Rt 0,72 min.
189: (R)- N- ((S) - 1 - (2- fluoro- 4- (1H- pirazol- 4- il) fenil) etil)- 2- metilpropano- 2- sulfinamida	(DMSO) 1,10 (s, 9 H) 1,47 (d, *J*= 6,75 Hz, 3 H) 4,60- 4,70 (m, 1 H) 5,41 (d, *J*= 5,48 Hz, 1 H) 7,38 - 7,44 (m, 3 H) 7,96 (br s, 1 H) 8,23 (br s, 1 H) 12,97 (br s, 1 H)	MS m/z 310,0 (M + H)+, Rt 0,67 min.

Intermedio 190: (R)- N- ((S) - 1 - (2- fluoro- 4- (trifluorometil) fenil) etil)- 2- metilpropano- 2- sulfinamida



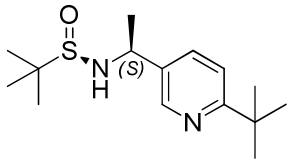
Paso 1

A un matraz de fondo redondo secado en horno con barra de agitación se añadió 2- fluoro- 4- (trifluorometil) benzaldehído (5 g, 26,0 mmoles), (R)- 2- metilpropano- 2- sulfinamida (3,47 g, 28.6 mmol) y DCE (52 ml). Luego a esta mezcla se añadió sulfato de cobre(II) (6.23 g, 39.0 mmoles). La mezcla de reacción se calentó en un baño de aceite precalentado a 55 °C durante 18 horas. La mezcla de reacción se filtró a través de un almohadilla de Celite, lavando los sólidos con DCE. El filtrado se concentró para proporcionar un aceite viscoso verde de (R, E)- N- (- (2- fluoro- 4 trifluorometil) bencilideno)- 2- metil propano- 2- sulfinamida (7.3 g, 24,7 mmol, rendimiento del 95%). El material se suspendió en la siguiente etapa sin purificación adicional. ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1,29 (s, 9 H) 7,44 (d, *J*= 10,08 Hz, 1 H) 7,51 (d, *J*= 8,27 Hz, 1 H) 8,13 (t, *J*= 7,46 Hz, 1 H) 8,92 (s, 1 H). LCMS m/z 296,0 (M + H)+, Rt 1,02 min.

Paso 2

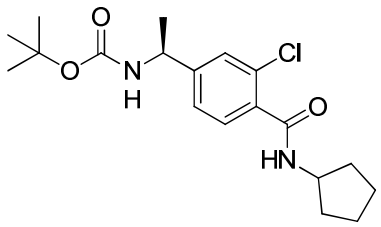
A una solución de (R, E)- N- (2- fluoro- 4- (trifluorometil) benciliden)- 2- metilpropano- 2- sulfinamida (7.3 g, 24.7 mmoles) en CH_2Cl_2 (247 ml) enfriada a 0 °C (baño de agua/hielo) en atmósfera de nitrógeno, se añadió bromuro de metilo 3M (33 ml, 99 mmol) en Et_2O. La mezcla de reacción se dejó agitar durante 30 min a 0 ºC, después se dejó calentar gradualmente a temperatura ambiente y se agitó durante 1 hora a temperatura ambiente. La mezcla de reacción se enfrió a 0 ºC después se inactivó con la adición lenta de una solución saturada de NH_4Cl. La mezcla acuosa se extrajo con EtOAc. Las fases orgánicas combinadas, se lavaron con agua, salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron sobre gel de sílice. La cromatografía en columna de gel de sílice (EtOAc/ Heptano 40 a 100%) proporcionó (R)- N- ((S) - 1 - (- (2- fluoro- 4 trifluorometil) fenil) etil)- 2- metilpropano- 2- sulfinamida (4.68 g, 15.0 mmol, rendimiento del 61%) como un sólido cristalino blanco. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,22 (s, 9 H) 1,60 (d, *J*= 6,80 Hz, 3 H) 3,38 (d, *J*= 4,01 Hz, 1 H) 4,87- 4,97 (m, 1 H) 7,33 (d, *J*= 10,32 Hz, 1 H) 7,39- 7,45 (m, 1 H) 7,49- 7,55 (m, 1 H). LCMS m/z 312,0 (M + H)+, Rt 0,92 min.

Intermedio 191: (R)- N- ((S) - 1 - (6- terc- butilpiridin- 3- il) etil)- 2- metilpropano- 2- sulfinamida



(R)- N- ((S) - 1 - (6- terc- 3- butilpiridin- il) etil)- 2- metilpropano- 2- sulfinamida se preparó con métodos similares a los utilizados para preparar el Intermedio 190. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,22 (s, 9 H) 1,37 (s, 9 H) 1,57 (d, *J*= 6,75 Hz, 3 H) 3,31 (d, *J*= 3,37 Hz, 1 H) 4,56- 4,65 (m, 1 H) 7,32 (d, *J*= 8,22 Hz, 1 H) 7,57 (dd, *J*= 8,24, 2,23 Hz, 1 H) 8,54 (d, *J*= 2,05 Hz, 1 H). MS m/z 283,1 (M + H)+, Rt 0,51 min.

Intermedio 192: 1 - (3- cloro- 4- (ciclopentilcarbamoil) fenil)etilcarbamato de (S)- terc- butilo



Paso 1

A un matraz de fondo redondo con barra de agitación se añadió sal de HCl de 4 - (ácido (S)- 1aminoetil- 2- clorobenzoico (1.05 g, 4.45 mmol) seguido de la adición de THF (40 ml) A esta solución se añadió DIEA (1.86 ml, 10.7 mmoles). La mezcla de reacción se volvió de color blanco turbio seguido de la adición de dicarbonato de di- terc- butilo (1.07 g, 4.89 mmoles). La mezcla de reacción resultante se dejó en agitación durante 18 horas a temperatura ambiente. Tiempo en el que la mezcla de reacción se calentó entonces a 60 °C durante 2 horas en un baño de aceite. Luego se añadió dicarbonato de di- terc- butilo (1.07 g, 4.89 mmol) y NMP (20 ml) y la mezcla de reacción resultante se dejó en agitación durante 2 horas a 60 °C. Los volátiles se eliminaron. El aceite resultante se diluyó con una solución saturada de NH_4Cl y la mezcla acuosa se extrajo con EtOAc. Las fases orgánicas combinadas, se lavaron dos veces con agua, salmuera, se secaron (Na_2SO_4), se filtró y se concentró hasta un aceite viscoso de color amarillo del ácido (S) - 4 - (1- (terc- butoxicarbonilamino) etil)- 2- clorobenzoico (2.32 g, 6.19 mmol, rendimiento del 139%) que contiene algún exceso de dicarbonato de di- terc- butilo y

NMP. LCMS m/z 284.9 (M + H)+ (fragmento de ácido carboxílico + aducto de CH_3CN), Rt 0.75 min.

Paso 2

A un matraz de fondo redondo con barra de agitación se añadió ácido (S) - 4 - (1 - (terc-butoxicarbonilamino) etil)- 2- clorobenzoico (450 mg, 1.20 mmol), ciclopentilamina (355 µl, 3.60 mmol), HCl EDC (460 mg, 2.40 mmoles), 1- hidroxi- 7- aza- benzotriazol (229 mg, 1.68 mmoles) y DMF (6 ml). A esta mezcla se añadió DIEA (629 µl, 3.60 mmoles). La mezcla de reacción se dejó en agitación a temperatura ambiente durante 18 horas. La mezcla de reacción se diluyó con agua y se extrajo con EtOAc. Las fases orgánicas se combinaron, se lavaron dos veces con agua, salmuera, se secaron (Na_2SO_4), se filtraron y se concentraron a un cristalino de color marrón de 1 - (3- cloro- 4- (ciclopentilcarbamoil) fenil) etilcarbamato de (S)- terc- butilo (476 mg, 1.17 mmol, rendimiento del 97%). LCMS m/z 367.0 (M + H)+, Rt 0,90 min.

Los intermedios en la Tabla 4s se prepararon por un método similar al descrito para la preparación del Intermedio 192.

Tabla 4s.

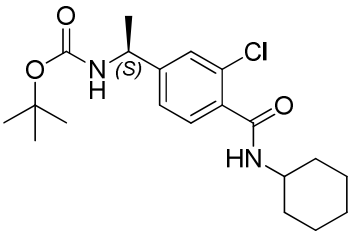
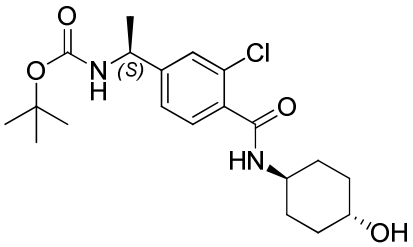
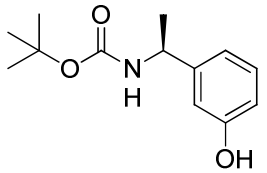
Intermedio 193	Intermedio 194
	

Tabla 4t. Nombre químico y señal de LCMS para cada intermedio listado en la Tabla 4s.

Intermedio: Nombre	LCMS
193: 1 - (3- cloro- 4- (ciclohexil carbamoil) fenil) etilcarbamato de (S)- terc- butilo	MS m/z 381,1 (M + H)+, Rt 0,96 min.
194: (S) - 1 - (3- cloro- 4- ((1R, 4S)- 4- hidroxiciclohexil carbamoil) fenil) etilcarbamato	MS m/z 391,1 (M + H)+, Rt 0,71

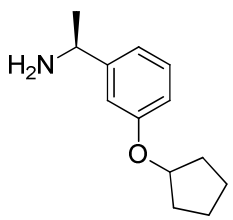
de terc- butilo	min.

Intermedio 195: 1 - (3- hidroxifenil) etilcarbamato de (S)- terc- butilo



Una suspensión de (S) - 3 - (1- aminoetil)fenol (1.188 g, 6.84 mmol) y Boc_2O (1.747 ml, 7.53 mmoles) en DCM (17.10 ml) se agitó a temperatura ambiente en atmósfera de N_2 mientras se adiocionó lentamente DIEA (1.434 ml, 8.21 mmol). Los materiales de partida inicialmente insolubles se disolvieron lentamente. La solución se agitó a temperatura ambiente durante 16 horas y después se concentró. El residuo aceitoso se volvió a disolver en EtOAc y se lavó con Na_2CO_3 saturado, seguido por salmuera. La capa acuosa original fue se extrajo nuevamente con EtOAc, que después se lavó con salmuera y se combinó con el lote anterior de EtOAc. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron al crudo 2,4 g aceite amarillento claro que se purificó mediante cromatografía en columna de gel de sílice (EtOAc/heptano del 0 al 30%), proporcionando 1 - (3- hidroxifenil) etilcarbamato de (S)- terc- butilo como un aceite incoloro claro, que se solidifica al sentarse (1.79 g, 7.55 mmol, rendimiento del 110%). ^{1}H NMR (400 MHz, $CDCL_3$) □ 1.44 (br. s., 12 H) 4.08 - 4.18 (m, 1 H) 4.76 (br. s., 1 H) 6.72 (dd, *J*=7.46, 1.83 Hz, 1 H) 6.78 (br. s., 1 H) 6.88 (br. s., 1 H) 7.16 - 7.24 (m, 1 H). LCMS *m/z* 223.0/182.0 (no se observa el precursor, sólo los fragmentos Boc) (M + H)+, Rt 0.71 min.

Intermedio 196: hidrocloruro de (S) - 1 - (3 - (ciclopentiloxi) fenil) etanamina



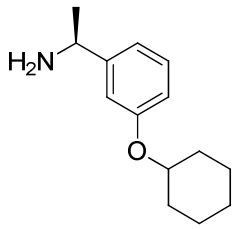
Paso 1: Mitsunobu A

A una solución de 1 - (3- hidroxifenil)etilcarbamato de (S)- terc- butilo (107.5 mg, 0.453 mmol), PPh_3(238 mg, 0.906 mmol) y ciclopentanol (0.164 ml, 1.812 mmol) en THF (2 ml) a temperatura ambiente se añadió por goteo DEAD (0.143 ml, 0.906 mmol) en atmósfera de N_2. La solución amarilla resultante se agitó durante 4 horas y después se concentró. El aceite viscoso de color amarillo se volvió a disolver en DMSO y se purificó mediante HPLC de fase inversa. Las fracciones del producto combinadas se desalinaron mediante la adición de la misma cantidad de EtOAc y alrededor de 250 mg de Na_2CO_3 en un embudo de separación. Las fases se separaron y la fase orgánica se lavó con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron *al vacío* para proporcionar 1 - (3 - (ciclopentiloxi) fenil) etilcarbamato de (S)- terc- butilo (75.1 mg, 0.246 mmol, rendimiento 54.3%) como una película sólida de color blanco. LCMS m/z 291.1/250.0 (no se observa el precursor, sólo los fragmentos Boc) (M + H)+, Rt 1,07 min.

Paso 2

1 - (3 - (ciclopentiloxi) fenil) etilcarbamato de (S)- terc- butilo (75.1 mg, 0.246 mmol) se disolvió en HCl 4 M en dioxano (1 ml, 4,00 mmol) y la mezcla resultante se dejó reposar durante 1 hora, después se concentró para proporcionar (S) - 1 - (3 - (ciclopentiloxi) fenil) etanamina como una sal de HCl (se supone rendimiento cuantitativo). LCMS m/z 206.1 (M + H)+, Rt 0.61 min.

Intermedio 197: hidrocloruro de (S) - 1 - (3 - (ciclohexiloxi) fenil) etanamina



Paso 1: Mitsunobu B

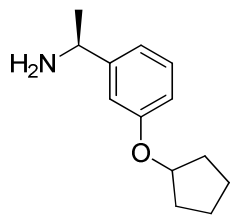
A una solución de 1 - (3- hidroxifenil)etilcarbamato de (S)- terc- butilo (100 mg, 0.421 mmol), ciclohexanol (0.180 ml, 1.686 mmol) y PPh_3(221 mg, 0.843 mmol) en THF (2 ml), se añadió por goteo DEAD (0.133 ml, 0.843 mmol), bajo N_2, a temperatura ambiente. La solución amarilla resultante se agitó durante 3 horas, momento en el que se añadió otro lote de ciclohexanol (0.180 ml, 1.686 mmol), PPh_3(221 mg, 0.843 mmoles), y 10 minutos más tarde se añadió DEAD (0.133 ml, 0.843 mmol), a temperatura ambiente. La mezcla de reacción se agitó durante 16 horas y después se concentró. El aceite claro crudo se volvió a disolver en DMSO y se purificó mediante HPLC de fase inversa. Las fracciones de producto combinadas se desalinizaron mediante la adición de la misma cantidad de EtOAc y alrededor de 250 mg de Na_2CO_3 en un embudo de separación. Las fases se separaron y la orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtraron y se concentraron *al vacío* para proporcionar 1 - (3 - (ciclohexiloxi) fenil) etilcarbamato de (S)- terc- butilo (74.1 mg, 0.232 mmol, rendimiento 55,0%) como una película incolora transparente. LCMS m/z 305.0/264.0 (no se observó precursor, sólo los fragmentos Boc) (M + H)+, Rt 1,12 min.

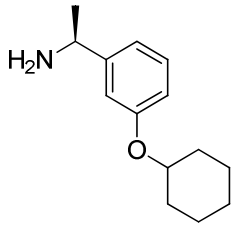
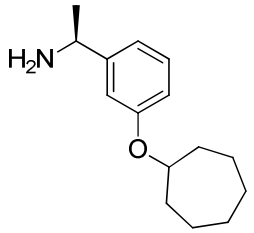
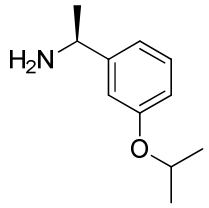
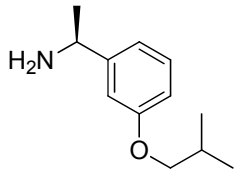
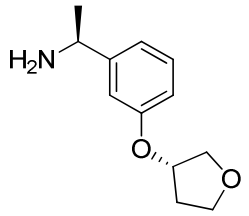
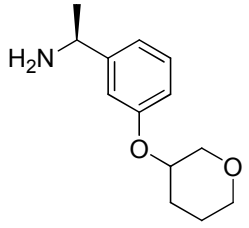
Paso 2

1 - (3 - (ciclohexiloxi) fenil) etilcarbamato de (S)- terc- butilo (74.1 mg, 0.232 mmol) se disolvió en HCl 4 M en dioxano (1 ml, 4,00 mmol) y la mezcla resultante se dejó reposar durante 1 hora , después se concentró para proporcionar (S) - 1 - (3 - (ciclohexiloxi) fenil) etanamina como una sal de HCl (se supone rendimiento cuantitativo). LCMS m/z 220.1 (M + H)+, Rt 0.66 min.

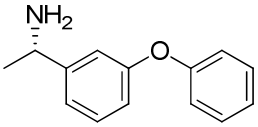
Los intermedios en Tabla 4v se prepararon usando el método descrito para la preparación de los Intermedios 196 o 197.

Tabla 4v.

Intermedio: Nombre	Estructura	LCMS
198: (S) - 1 - (3 - (ciclopentiloxi) fenil) etanamina		MS m/z 206,1 (M + H)+, Rt 0,61 min.

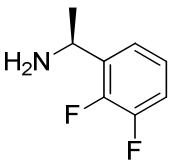
199: (S) - 1 - (3 - (ciclohexiloxi) fenil) etanamina		MS m/z 220,1 (M + H)+, Rt 0,66 min.
200: (S) - 1 - (3 - (cicloheptiloxi) fenil) etanamina		MS m/z 234,1 (M + H)+, Rt 0,73 min.
201: (S) - 1 - (3- isopropoxi- fenil) etanamina		MS m/z 180,1 (M + H)+, Rt 0,50 min.
202: (S) - 1 - (3- isobutoxifenil) etanamina		MS m/z 194,1 (M + H)+, Rt 0,61 min.
203: (S) - 1 - (3 - ((S)- tetrahidrofurano- 3- iloxi) fenil) etanamina		MS m/z 208,1 (M + H)+, Rt 0,41 min.
204: (1S) - 1 - (3 - (tetrahidro- 2H- piran- 3- iloxi) fenil) etanamina		MS m/z 222,1 (M + H)+, Rt 0,46 min.

Intermedio 205: (S) - 1 - (3- fenoxifenil)etanamina



En un vial de microondas de 20 ml se pesó ligando de 1 - (piridin- 2- il) propan- 2- ona (90 mg, 0.665 mmol), fenol (407 mg, 4.32 mmoles), CuBr (47.7 mg, 0.332 mmol) y Cs_2CO_3 (2.166 mg, 6.65 mmol). A la mezcla se añadió DMSO (5 ml) y (S) - 1 - (3- bromofenil) etanamina (0.5 ml, 3.32 mmol). El tubo se purgó con N_2, se tapó, y la mezcla de color negro se calentó en el baño de aceite a 90 °C durante 18 horas. La mezcla heterogénea se diluyó con EtOAc y se filtró a través de un embudo de vidrio poroso, eluyendo con EtOAc y otros 5 ml de DMSO. Después se eliminaron los volátiles *al vacío* y el líquido de color marrón crudo se filtró a través de filtro 1 µm de PTFE y se purificó mediante HPLC de fase inversa. Las fracciones del producto combinadas se desalinazaron mediante la adición de la misma cantidad de EtOAc y alrededor de 250 mg de Na_2CO_3 en un embudo de separación. Las fases se separaron y la fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtraron y se concentraron *al vacío* para proporcionar (S) - 1 - (3- fenoxifenil) etanamina (361.5 mg, 1.678 mmol, rendimiento 50.5%) como un aceite de color ámbar. LCMS m/z 214.1 (M + H)+, Rt 0.61 min.

Intermedio 206: (S) - 1 - (2,3- difluorofenil) etanamina



Paso 1

A un matraz de fondo redondo secado en horno con barra de agitación se añadió 2,3- difluorobenzaldehído (0.5 g, 3.52 mmoles), (R)- 2- metilpropano- 2- sulfinamida (0.469 g, 3.87 mmol) y DCE (7.04 ml). Luego a esta mezcla se añadió sulfato de cobre (II) (0.842 g, 5.28 mmol). La mezcla de reacción se calentó en un baño de aceite precalentado a 55 °C durante 24 horas. La mezcla de reacción se filtró a través de una almohadilla de Celite lavando los solidos con DCE. El Filtrado combinado se concentró para proporcionar un aceite amarillo viscoso de (R, E)- N- (2,3- difluorobencilideno)- 2-

metilpropano- 2- sulfinamida (0.8007 g, 3.26 mmol, rendimiento del 93%). LCMS m/z 246.1 (M + H)+, Rt 0.91 min.

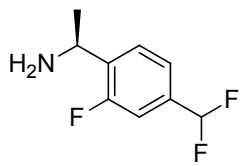
Paso 2

A una solución de (R, E)- N- (2,3- difluorobencilideno)- 2- metilpropano- 2- sulfinamida (0,800 g, 3.26 mmoles) en DCM (32,6 ml), se enfrió a 0 °C (agua/baño de hielo) bajo N_2, se añadió MeMgBr 3M (4.35 ml, 13.05 mmol) en éter dietílico. La mezcla de reacción se dejó agitar durante 30 min a 0 °C. Después se dejó calentar gradualmente a temperatura ambiente y se agitó durante 30 minutos a temperatura ambiente. La mezcla de reacción se enfrió a 0 ºC después se inactivó con la adición lenta de una solución saturada de NH_4Cl y se diluyó con EtOAc. Las fases se particionaron, la fase acuosa se extrajo con EtOAc y las capas orgánicas combinadas se lavaron con agua, salmuera, se secaron con $MgSO_4$, se filtraron y se concentró para proporcionar (R)- N- ((S) - 1 - (2,3- difluorofenil) etil) - 2- metilpropano- 2- sulfinamida (0.7868 g, 3.01 mmol, rendimiento del 92%) como un sólido amarillo. LCMS m/z 262.0 (M + H)+, Rt 0.70 min.

Paso 3

A un matraz de fondo redondo que contenía (R)- N- ((S) - 1 - (2,3- difluorofenil) etil)- 2- metilpropano- 2- sulfinamida (786.8 mg, 3.01 mmol) se añadió dioxano (10.000 ml) . A esta solución se añadió HCl 4.0 M en dioxano (1.505 ml, 6.02 mmol) y la solución se dejó en agitación 15 min a temperatura ambiente. La mezcla de reacción se concentró, se disolvió en Et_2O 10 ml, y se concentró de nuevo. Se añadió Et_2O de nuevo y mezcla resultante sonicó y un material sólido se filtró y se secó para proporcionar (S) - 1 - (2,3- difluorofenil) etanamina (0.4213 g, 2.176 mmol, rendimiento 72.3%) como una sal de HCl cristalina blanca. ^{1}H RMN (400 MHz, D_2O) d ppm 1,55 (d, J = 6,99 Hz, 3 H) 4,71 (q, J = 6,96 Hz, 1 H) 7.10 a 7.26 (m, 3 H); LCMS m/z 158,0 (M + H)+, Rt 0,37 min.

Intermedio 207: (S) - 1 - (4 - (difluorometil)- 2- fluorofenil) etanamina



Paso 1: Preparación de 1- bromo- 4- (difluorometil)- 2- fluorobenceno

Una mezcla de 4- bromo- 3- fluorobenzaldehído (2,03 g, 10 mmol) y trifluoruro de (dietilamino)azufre (DAST; 1.32 ml, 10 mmol) se calentó cuidadosamente hasta que se produce la reacción exotérmica, después se calentó a 60 °C durante 15 min, y se dejó enfriar a temperatura ambiente. La mezcla se diluyó con DCM (20 ml) y se vertió en hielo/agua (30 ml). La mezcla se neutralizó con $NaHCO_3$ a pH ~ 8. La capa acuosa separada se extrajo con DCM (20 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía en columna [SiO_2, 40 g, heptano/acetato de etilo], proporcionando 1- bromo- 4- (difluorometil)- 2- fluorobenceno (0,845 g) como un aceite incoloro transparente.

Paso 2: Preparación de 4 - (difluorometil)- 2- fluorobenzaldehído

A una solución de 1- bromo- 4- (difluorometil)- 2- fluorobenceno (311 mg, 1.382 mmol) en THF (2.99 ml) se añadió butil- litio (solución 1.6 M en hexanos; 0.881 ml, 1.410 mmol) durante ~ 5 min a - 78 °C. La mezcla de reacción se agitó durante 30 min a - 78 ºC y después se añadió por goteo DMF (0.161 ml, 2.073 mmol) durante ~ 1 min. Se continuó agitando durante 20 min. La mezcla de reacción se inactivó con solución acuosa de HCl 1 M/MeOH (2:1, 3 ml) y se dejó calentar a temperatura ambiente. La mezcla se diluyó con 5 ml de agua. La capa acuosa se separó con éter (5 ml). Las capas orgánicas combinadas se lavaron con solución acuosa de NaOH 1 M (10 ml) y salmuera saturada (10 ml), se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. La reacción se repitió con 420 mg de 1- bromo- 4- (difluorometil)- 2- fluorobenceno y materiales crudos combinados para la purificación. El material crudo se purificó mediante cromatografía en columna [SiO_2, 24 g, heptano/acetato de etilo], proporcionando 4 - (difluorometil)- 2- fluorobenzaldehído (162,8 mg) como un aceite de color amarillo.

Paso 3: Preparación de (R, E)- N- (4 - (difluorometil)- 2- fluorobenciliden)- 2- metilpropano- 2- sulfinamida

A una mezcla de 4 - (difluorometil)- 2- fluorobenzaldehído (162 mg, 0.930 mmol) y (R)- 2- metilpropano- 2- sulfinamida (124 mg, 1.023 mmol) en DCE (3 ml) se añadió sulfato de cobre (223 mg, 1.396 mmol). La mezcla de reacción se calentó en un baño de aceite precalentado a 55 °C durante 38 horas. La mezcla se dejó enfriar a temperatura ambiente, se filtró a través de una almohadilla de celites y se lavó con DCE. Los filtrados

combinados se concentraron bajo presión reducida para proporcionar (R, E)- N- (4 - (difluorometil)- 2- fluorobenciliden)- 2- metilpropano- 2- sulfinamida (266 mg) como un aceite amarillo, que se usó sin más purificación. LCMS m/z 278.1 (M + H)+, Rt 0.98 min.

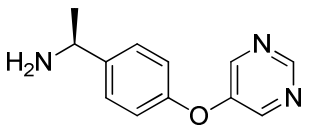
Paso 4: Preparación de (R)- N- ((S) - 1 - (4 - (difluorometil)- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida

A una solución de (R, E)- N- (4 - (difluorometil)- 2- fluorobenciliden)- 2- metilpropano- 2- sulfinamida (266 mg, 0.959 mmoles) en DCM (9,6 ml) se añadió bromuro de metilmagnesio (3M en éter dietílico, 1,20 ml) a 0 °C. La mezcla de reacción se dejó en agitación durante 30 min a 0 °C, se dejó calentar gradualmente a temperatura ambiente y se agitó durante 1 hora a temperatura ambiente. La mezcla se enfrió a 0 °C, y cuidadosamente se inactivó con una solución de NH_4Cl acuoso saturado (3 ml). La fase acuosa separada se extrajo con DCM. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio, filtraron y se concentraron bajo presión reducida. El material crudo se purificó mediante cromatografía en columna [SiO_2, 40 g, heptano/acetato de etilo], proporcionando (R)- N- ((S) - 1 - (4 - (difluorometil)- 2- fluorofenil) etil) - 2 - metilpropano- 2- sulfinamida (160.5 mg) como un sólido blanco. LCMS m/z 294.5 (M + H)+, Rt 0.85 min.

Paso 5: Preparación de (S) - 1 - (4 - (difluorometil)- 2- fluorofenil) etanamina

A (R)- N- ((S) - 1 - (4 - (difluorometil)- 2- fluorofenil) etil)- 2- metilpropano- 2- sulfinamida (160 mg, 0.545 mmol) se añadió HCl 4 M en dioxano (409 l) para proporcionar una solución de color amarillo. La mezcla resultante se agitó a temperatura ambiente durante ~ 1 hora. A la mezcla se añadió lentamente éter dietílico (~ 20 ml). Los sólidos se separaron por filtración, se suspendió en éter dietílico, se filtró y se aclararon con éter dietílico, se secó bajo presión reducida proporcionando (S) - 1 - (4 - (difluorometil)- 2- fluorofenil) etanamina (103 mg) como un sólido de color blanquecino, que se usó sin purificación adicional. LCMS m/z 190.1 (M + H)+, Rt 0.42 min.

Intermedio 208: (S) - 1 - (4 - (pirimidin- 5- iloxi) fenil) etanamina



Paso 1: Preparación de 4 - (pirimidin- 5- iloxi) benzaldehído

A una solución de pirimidin- 5- ol (500 mg, 5.20 mmoles) en DMF (5.20 ml) en atmósfera de argón se añadió 4- fluorobenzaldehído (0.558 ml, 5.20 mmol), metanosulfinato de sodio (133 mg, 1.30 mmol), y carbonato de potasio (1.079 g, 7.81 mmoles). La mezcla de reacción se calentó a 120 °C durante 3 horas. La mezcla se dejó enfriar a temperatura ambiente y se diluyó con agua (25 ml). La mezcla se extrajo con EtOAc (2x 25 ml). Las capas orgánicas combinadas se lavaron con salmuera (2x 50 ml), se secaron sobre sulfato de sodio, filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía en columna [SiO_2, 24 g, heptano/acetato de etilo], proporcionando 4 - (pirimidin- 5- iloxi)benzaldehído (666 mg) como un sólido de color amarillo. LCMS m/z 201.0 (M + H)+, Rt 0.52 min.

Paso 2: Preparación de (R, E)- metil- N- 2- (4 - (pirimidin- 5- iloxi) bencilideno) propano- 2- sulfinamida

Una mezcla de 4 - (pirimidin- 5- iloxi) benzaldehído (666 mg, 3,33 mmoles), (R) - (+)- terc- butanosulfinamida (450 mg, 3.71 mmol) y sulfato de cobre (796 mg, 4.99 mmol) en anhidro en dicloroetano (7.648 ml) en atmósfera de argón y se calentó a 55 °C durante ~ 21 horas. La mezcla de reacción se dejó enfriar a temperatura ambiente. La suspensión se filtró a través de una almohadilla de celite, se eluyó con DCM (5x 10 ml). Los filtrados combinados se concentraron bajo presión reducida y el aceite de color amarillento resultante se purificó mediante cromatografía en columna [SiO_2, 24 g, heptano/acetato de etilo] proporcionando (R, E)- 2- metil- N- (4 - (pirimidin- 5- iloxi) bencilideno) propano- 2- sulfinamida (836 mg) como un aceite viscoso pálido. LCMS m/z 304.0 (M + H)+, Rt 0.79 min.

Paso 3: Preparación de 2- metil- N- ((S) - 1 - (4 - (pirimidin- 5- iloxi) fenil) etil) propano- 2- sulfinamida

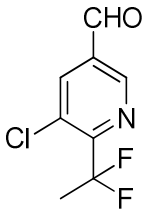
Una solución de (R, E)- 2- metil- N- (4 - (pirimidin- 5- iloxi) bencilideno) propano- 2- sulfinamida (830 mg, 2.74 mmoles) en DCM (6.72 ml) se enfrió a - 40 °C. A la solución se añadió por goteo bromuro de metilmagnesio (3M en éter dietílico; 1.81 ml) durante 10 min. se añadió DCM adicional (5 ml) para retener agitación. La suspensión de color amarillo se agitó a - 40 ° C durante ~ 30 min mientras se calienta a - 20 ° C. La mezcla se enfrió a - 40 °C y se añadió bromuro de metilmagnesio adicional (3M en éter dietílico; 1,8 ml). La suspensión se agitó durante ~ 3 horas mientras se calentaba lentamente a - 20 °C.

La mezcla se enfrió a - 40 ºC, y se añadió bromuro de metilmagnesio adicional (3 M en éter dietílico, 0,4 ml). La suspensión se agitó durante 30 min y se dejó calentar a - 10 °C. La mezcla se inactivó lentamente durante 10 min con una solución de NH_4Cl acuoso saturado (10 ml). La mezcla se diluyó con solución acuosa saturada de NH_4Cl (30 ml) y agua (15 ml). La fase acuosa separada se extracto con DCM (2x 75 ml). Las capas orgánicas combinadas se lavaron con salmuera (50 ml), se secaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía en columna [SiO_2, 40 g, heptano/acetato de etilo seguido de MeOH al 5% en EtOAc] proporcionando 2- metil- N- ((S) - 1 - (4 - (pirimidin- 5- iloxi) fenil) etil) propano- 2- sulfinamida (55 mg; pureza ~ 87%) como un sólido de color blanquecino. LCMS m/z 320.0 (M + H)+, Rt 0.69 min.

Paso 4: Preparación de (S) - 1 - (4 - (pirimidin- 5- iloxi) fenil) etanamina

Para 2- metil- N- ((S) - 1 - (4 - (pirimidin- 5- iloxi) fenil) etil) propano- 2- sulfinamida (55 mg, 0,172 mmol) se añadió HCl 4 M en dioxano (800 µl, 3.20 mmoles) para proporcionar una suspensión blanca. Esta mezcla resultante se agitó a temperatura ambiente durante ~ 35 min y se concentró bajo presión reducida para proporcionar (S) - 1 - (4 - (pirimidin- 5- iloxi) fenil) etanamina (44 mg) como su sal de HCl, que era utilizadá sin purificación adicional. LCMS m/z 217.1 (M + H)+, Rt 0.37 min.

Intermedio 209: 5- cloro- 6- (1,1- difluoroetil)nicotinaldehído



Paso 1: Preparación de 5,6- dicloronicotinato de etilo

A una solución del ácido 5,6- dicloronicotínico (20.01 g, 104 mmol) en EtOH (500 ml) a 20 ºC se añadió clorotrimetilsilano (132 ml, 1.042 mmol). La reacción se agitó durante 72 horas. La mezcla de reacción se concentró y se diluyó con EtOAc (500 ml), y se lavó con $NaHCO_3$ saturado (2x100 ml) y salmuera (100 ml). Luego la capa orgánica se secó

(Na_2SO_4) y se concentró bajo presión reducida para proporcionar el producto crudo final (21.25 g). LCMS m/z 220.1 (M + H)+, Rt 0.94 min.

Paso 2: Preparación de 6- acetil- 5- cloronicotinato etilo

A una suspensión de 5,6- dicloronicotinato de etilo (5.26 g, 23.90 mmol) y cloruro de tetraetilamonio (11.88 g, 71.7 mmoles) en MeCN (50 ml) se añadió tributil (1- etoxivinil) estannano (9.50 g, 26.3 mmoles) y $PdCl_2(PPh_3)_2$ (0.671 g, 0.956 mmol). La reacción se selló, se calentó a 80 °C durante 5 horas. Una solución resultante transparente de color oscuro. La mezcla de reacción se enfrió entonces a 20 °C, se concentró y se diluyó con EtOAc (200 ml), y se lavó con agua (50 ml) y salmuera (50 ml). Luego la capa orgánica se secó (Na_2SO_4) y se concentró para proporcionar 5- cloro- 6- (1- etoxivinil)nicotinato de etilo crudo. Después, el residuo se disolvió en THF (100 ml) y se añadió HCl (20 ml, 3 M en H_2O). La mezcla de reacción se agitó a 20 °C durante 5 horas, y una solución saturada de $NaHCO_3$ se añadió hasta pH = 8. Después, la mezcla se diluyó con EtOAc (200 ml) y agua (50 ml). Las fases se separaron y la capa acuosa se extrajo con EtOAc (2x50 ml). Los extractos orgánicos combinados se lavaron con salmuera (20 ml), se secaron (Na_2SO_4) y se concentraron para proporcionar el producto deseado (3,56 g). LCMS m/z 228.5 (M + H)+, Rt 0.83 min.

Paso 3: Preparación de 5- cloro- 6- (1,1- difluoroetil) nicotinato de etilo

A una solución de 6- acetil- 5- cloronicotinato de etilo (3.01 g, 13.22 mmol) en $CHCl_3$ (7 ml) se añadió DAST (5.20 ml, 39.7 mmol) y etanol (0.061 g, 1.32 mmol). La reacción se selló, se calentó a 60 ºC durante 24 horas. Una solución transparente de color oscuro resultante. La mezcla de reacción se enfrió entonces a 20 °C, y se añadió con precaución con solución fría se concentró $NaHCO_3$ acuoso (50 ml). La capa acuosa se extrajo con DCM (2x100 mL). A continuación, la capa orgánica combinada se secó (Na_2SO_4) y se concentró. El residuo se purificó a través de cromatografía ultrarrápida en gel de sílice (0-20 por ciento de EtOAc- hexanos) para proporcionar el producto deseado en forma de aceite de color amarillo (2.88 g). LCMS m/z 250.1 (M + H)+, Rt 0.99 min.

Paso 4: Preparación de (5- cloro- 6- (1,1- difluoroetil) piridin- 3- il) metanol

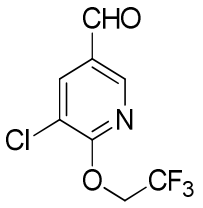
A una solución de acetato de 5- cloro- 6- (1,1- difluoroetil)nicotinato (2.68 g, 10.74 mmol) en Et_2O (40 ml) se añadió $LiBH_4$ (0.351 g, 16.10 mmoles), seguido de la adición por goteo de metanol (0.653 ml, 16.10 mmol). La reacción se calentó a reflujo a 40 °C

durante una hora. La mezcla de reacción se enfrió a 0 °C, y se inactivó con HCl (1 M) hasta pH = 2 para la capa acuosa. Las fases se separaron y la capa acuosa se extrajo con DCM (3x50 ml). A continuación, la capa orgánica se secó (Na_2SO_4) y se concentró bajo presión reducida para proporcionar el producto crudo final (2.12 g). LCMS m/z 208.0 (M + H)+, Rt 0.63 min.

Paso 5: Preparación de 5- cloro- 6- (1,1- difluoroetil)nicotinaldehído

A una solución de (5- cloro- 6- (1,1- difluoroetil) piridin- 3- il) metanol (2.12 g, 10.21 mmoles) en DCM (100 ml) se añadió PCC (3.30 g, 15.32 mmol). La reacción se agitó a 20 °C durante 3 horas. Una suspensión de color oscuro resultante. LCMS mostró una conversión limpia al producto. La mezcla de reacción se filtró a través de una almohadilla de celite, y se lavó con DCM (200 ml). Después, el filtrado se concentró para proporcionar el producto crudo (1.78 g). LCMS m/z 224.0 ($M+H_2O$ + H) +, Rt 0.72 min.

Intermedio 210: 5- cloro- 6- (2,2,2- trifluoroetoxi)nicotinaldehído



Paso 1: Preparación de 6- cloro- 5- (2,2,2- trifluoroetoxi)nicotinato de etilo

A una solución de 5,6- dicloronicotinato de etilo (6.28 g, 28.5 mmol) y 2,2,2- trifluoroetanol (2.71 ml, 37.1 mmol) en THF (90 ml) se añadió a- 73 ºC NaHMDS (37.1 ml, 37.1 mmol). La reacción se agitó a - 73 °C durante 30 minutos, después a 0 °C durante 5 horas. La reacción se inactivó con 30 ml de solución saturada de NH_4Cl. La mezcla de reacción se vertió en 50 ml de salmuera y las fases se separaron. La capa acuosa se extrajo con DCM (2x100 mL). Los orgánicos combinados se secaron (Na_2SO_4) y se concentraron. La cromatografía de gel de sílice con heptano al 100% a EtOAc al 30% en heptano proporcionó el producto final (7.51 g). LCMS m/z 284.1 (M + H)+, Rt 1.07 min.

Paso 2: Preparación de (5- cloro- 6- (2,2,2- trifluoroetoxi) piridin- 3- il) metanol

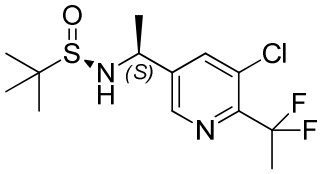
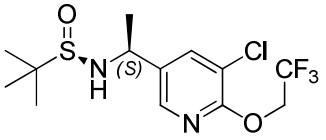
A una solución de 5- cloro- 6- (2,2,2- trifluoroetoxi)nicotinato de etilo (7,5µ1 g, 26.5 mmol) en Et_2O (200 ml) se añadió $LiBH_4$ (0.865 g, 39.7 mmol), seguido por adición por goteo de metanol (1.611 ml, 39.7 mmoles). La reacción se calentó a reflujo a 40 °C durante una hora. La mezcla de reacción se enfrió a 0 °C, y se inactivó con HCl (1 M) hasta pH = 2 para la capa acuosa. Las fases se separaron y la capa acuosa se extrajo con DCM (3x200 ml). A continuación, la capa orgánica se secó (Na_2SO_4) y se concentró bajo presión reducida para proporcionar el producto crudo final (6.31 g). LCMS m/z 242.1 (M + H)+, Rt 0.77 min.

Paso 3: Preparación de 5- cloro- 6- (2,2,2- trifluoroetoxi)nicotinaldehído

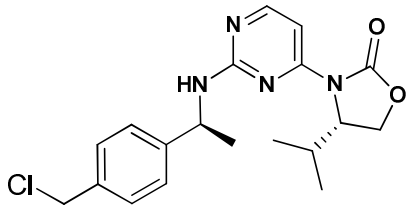
A una solución de (5- cloro- 6- (2,2,2- trifluoroetoxi) piridin- 3- il)metanol (4.00 g, 16.56 mmoles) en EtOAc (15 ml) se añadió óxido de manganeso(IV) (16.93 g , 166 mmol). La reacción se calentó con microondas a 120 °C durante 30 minutos. Después, la mezcla se filtró a través de una almohadilla de celite, y se aclaró con EtOAc. El filtrado se concentró para proporcionar el producto crudo (3.38 g).

Los intermedios de la Tabla 4w se prepararon con procedimientos similares a los usados para preparar los Intermedios 210 y 192.

Tabla 4w.

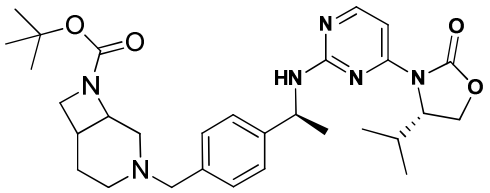
Intermedio: Nombre	**Estructura**	**LCMS**
211: (R)- N- ((S) - 1 - piridin- 3- il) acetato de (5- cloro- 6- (1,1- difluoroetil))- 2- metilpropano- 2- sulfinamida		MS m/z 325,2 (M + H)+, Rt 0,85 min.
212: (R)- N- ((S) - 1 - piridin- 3- il) acetato de (5- cloro- 6- (2,2,2- trifluoroetoxi))- 2- metilpropano- 2- sulfinamida		MS m/z 359,1 (M + H)+, Rt 0,95 min.

Intermedio 213: (S) - 3 - (2 - ((S) - 1 - (4 - (clorometil) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona



A una solución de (S) - 3 - (2 - ((S) - 1 - (4 - (hidroximetil) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (71 mg, 0.2 mmoles) en DCM (2 ml) se añadió cloruro de metanosulfonilo (27 mg, 0.24 mmol) y DIPEA (0.070 ml, 0.4 mmol). La solución se agitó durante 16 h a temperatura ambiente después se lavó con agua y salmuera. Después de la separación, la fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El producto crudo se usó para la siguiente etapa sin purificación adicional.
MS m/z 373.4 (M - H).

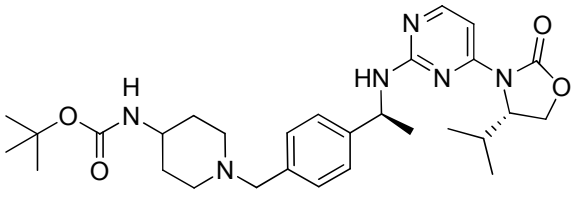
Intermedio 214: 3- (4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzil)- 3,8- diazabiciclo[4.2.0]octano- 8- carboxílato de terc- butilo



El compuesto del título se preparó como un sólido blanco (64 mg, rendimiento del 58.1%), con procedimientos similares a los usados para preparar el Intermedio 128, pero utilizando 4 - ((S) - 1 - (4 - ((S)- 4- isopropil - 2- oxooxazolidin- 3- il) pirimidin- 2- ilamino) etil) benzaldehído y 3,8- diazabiciclo [4.2.0] octano- 8- carboxilato de de terc- butilo

^{1}H RMN (400 MHz, $CDCl_3$) δ 8,17 (dd, J = 5,9, 0,9 Hz, 1H), 7,42 (d, J = 5,7 Hz, 1H), 7.28- 7.23 (m, 4H), 5,39 (br s, 1H), 5,02 (br s, 1H), 4,62- 4,59 (m, 1H), 4,28 (t, J = 8,7 Hz, 1H), 4,21 (dd, J = 9,0, 3,2 Hz, 2H), 3,89 (td, J = 7,7, 1,9 Hz, 1H), 3,54- 3,50 (m, 2H), 3,03 (d, J = 12,2 Hz, 1H), 2,65- 2,60 (m, 1H), 2,54- 2,40 (m, 2H), 2,10 (br s, 1H), 1,99- 1,88 (m, 1H), 1,79- 1,72 (m, 1H), 1,65 (br s, 1H), 1,52 (dd, J = 6,8, 1,9 Hz, 3H), 1,38 (t, J = 7,7 Hz, 9H), 0,71 (br s, 3H), 0,66 (br s, 3H). MS m/z 569,1 (M+H).

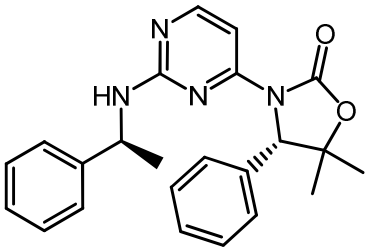
Intermedio 215: 1- (4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzil)piperidin- 4- ilcarbamato de terc- butilo



El compuesto del título se preparó como un sólido blanco (32 mg, rendimiento del 59%), con procedimientos similares a los usados para preparar el Intermedio 128, pero utilizando 4 - ((S) - 1 - (4 - ((S)- 4- isopropil - 2- oxooxazolidin- 3- il) pirimidin- 2- ilamino) etil) benzaldehído y piperidin- 4- ilcarbamato de terc- butilo. MS m/z 539.4 (M+H).

Ejemplos

Ejemplo 1: (*S*) - 5,5- Dimetil- 4- fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona

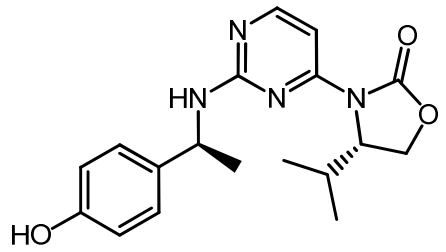


Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il) - 5,5- dimetil- 4- feniloxazolidin- 2- ona (33.9 mg, 0.112 mmol) y (*S*) - (-)- 1- feniletanamina (0.15 ml, 1.2 mmol, 10 equiv) en DMSO (1 ml) se calentó a 110 °C durante 140 min. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 10 a 50%) proporcionó (*S*) - 5,5- Dimetil- 4- fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona (37.0 mg, rendimiento del sólido blanco) en 85%. ^{1}H RMN (400 MHz, CD_3OD) δ 8,06 (d, J = 5,8 Hz, 1 H), 7,43 (d, J = 5,8 Hz, 1 H), 7.31- 7.24 (m, 3 H), 7.19- 7.11 (m , 5 H), 7,01 (br s 2 H), 5,48 (s, 1H), 4,86-

4,80 (m, 1 H), 1,65 (s, 3H), 1,43 (d, J = 7,0 Hz, 3 H), 0,98 (s, 3 H); HRMS (B) *m/z* 389.1987 (M + H)+.

Procedimiento alternativo

Ejemplo 113: (*S*) - 3 - (2 - ((*S*) - 1 - (4- hidroxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona

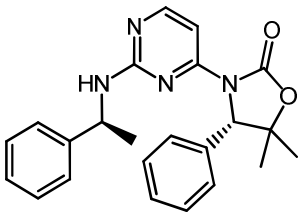
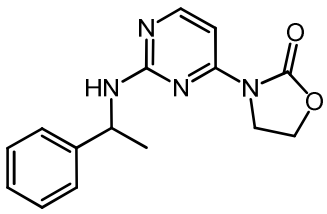
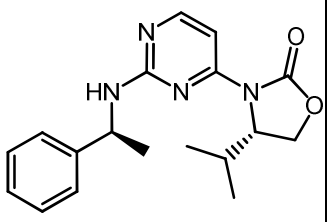
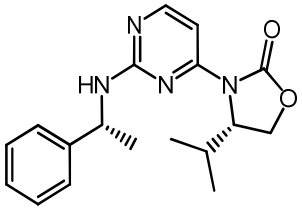
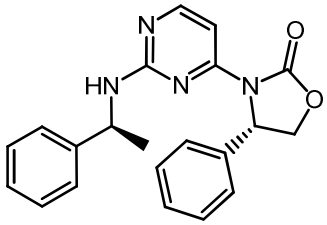
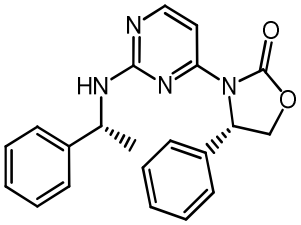
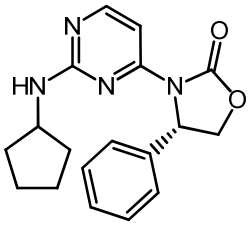
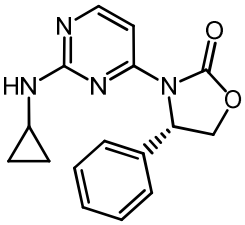
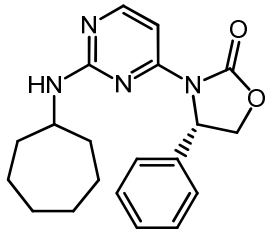
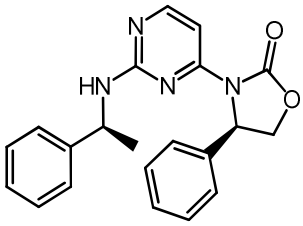
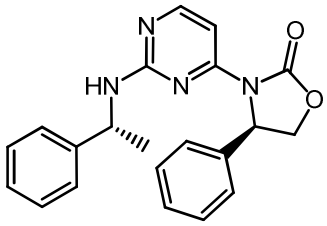
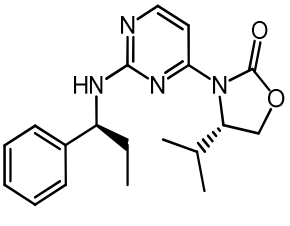
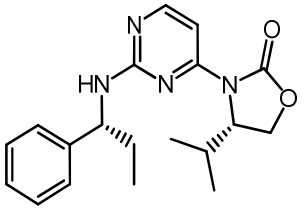
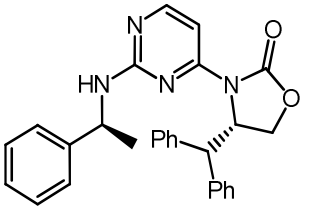
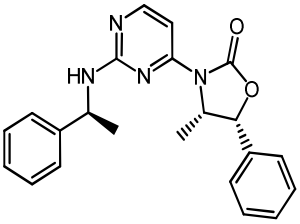


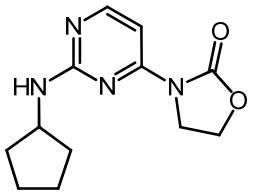
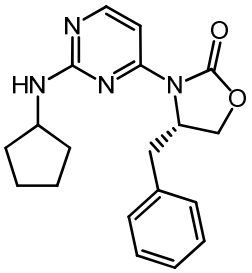
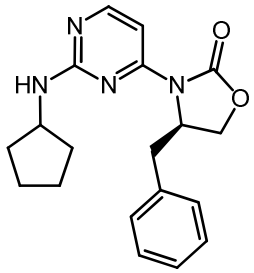
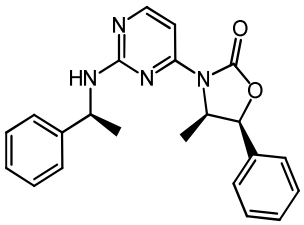
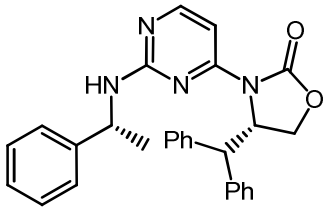
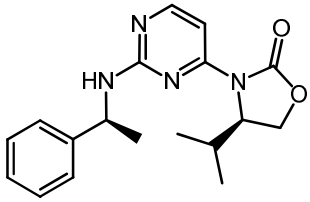
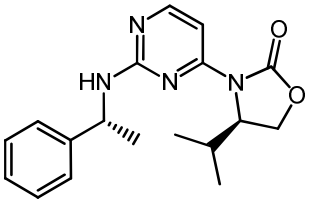
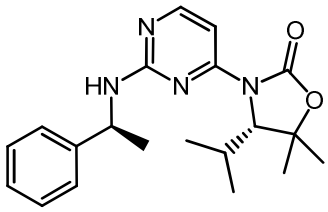
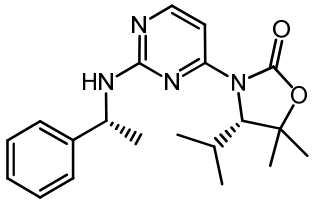
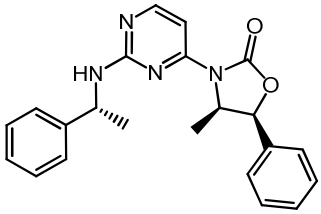
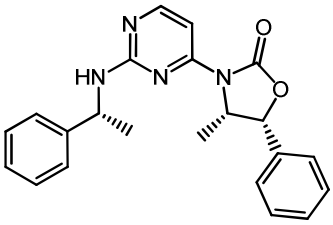
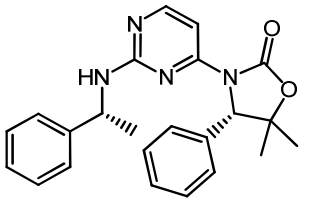
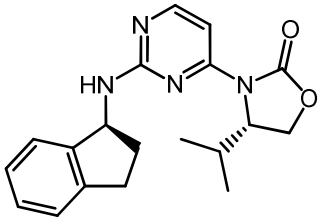
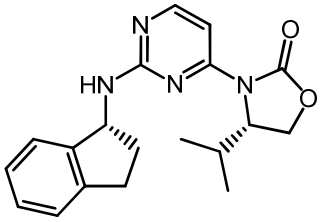
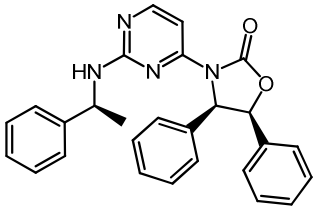
Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (42 mg, 0.17 mmoles), clorhidrato de (*S*) - 4 - (1- aminoetil)fenol (107 mg, 0.616 mmol, 3.5 equiv) y *i*Pr_2NEt (0.121 ml, 0.695 mmol, 4.0 equiv) en DMSO (1 ml) se calentó a 110 °C durante 3 h y a 130 ºC durante 2 h adicionales. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 10 a 80%) proporcionó (*S*) - 3 - (2 - ((*S*) - 1 - (4- hidroxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (3 mg) con un rendimiento del 5%. ^{1}H RMN (400 MHz, CD_3OD) δ 8,11 (d, J = 5,8 Hz, 1 H), 7,33 (d, J = 5,8 Hz, 1 H), 7,12 (d, J 8,1 Hz, 2H), 6,72- 6,68 (m, 2 H), 4,95 (q, J = 6,9 Hz, 1H), 4,69- 4,65 (m, 1 H), 4,35- 4,28 (m, 2 H), 1,47 (d, J = 7,1 Hz, 3 H), 0,75 (br s, 3 H), 0,62 (br s, 3 H); HRMS (B) *m/z* 343.1776 (M + H)+.

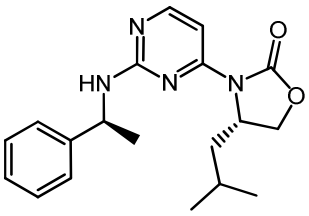
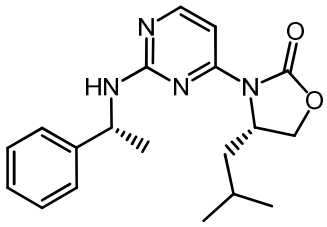
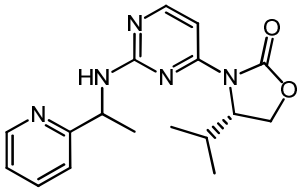
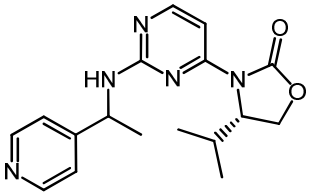
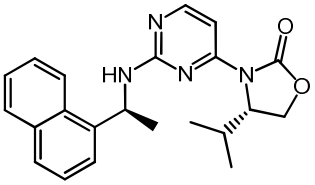
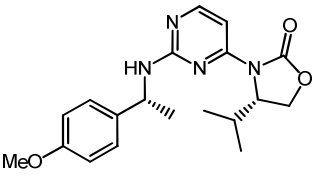
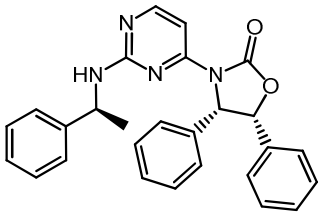
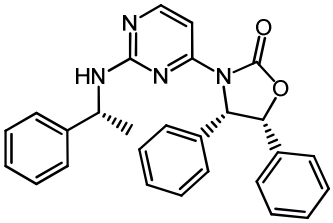
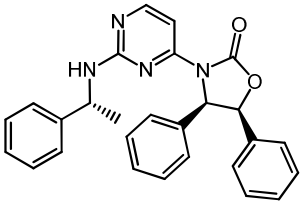
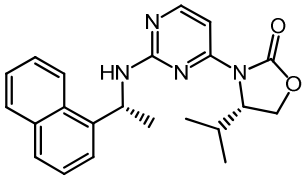
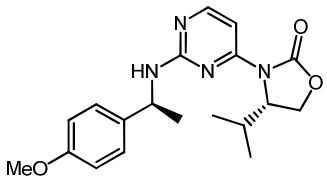
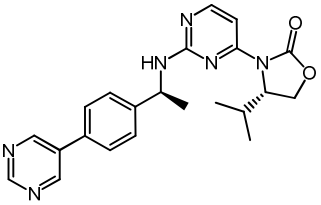
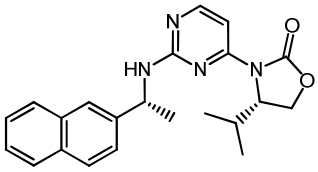
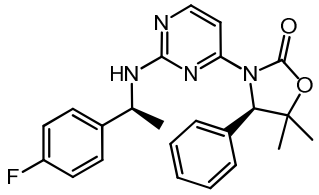
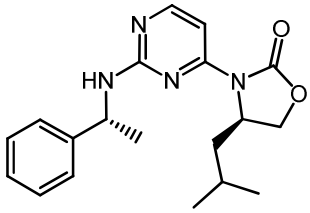
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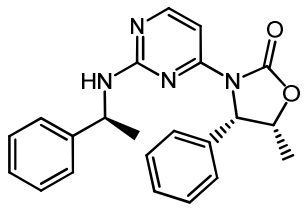
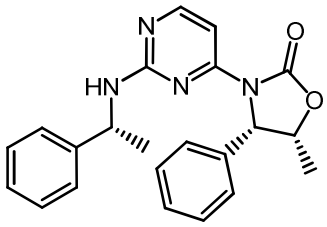
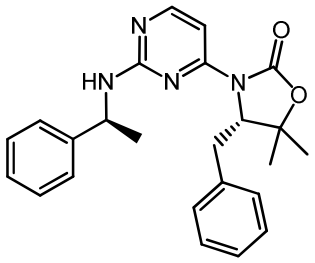
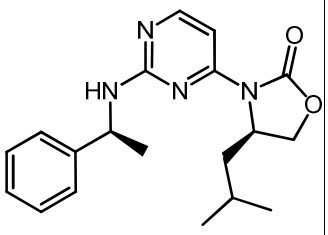
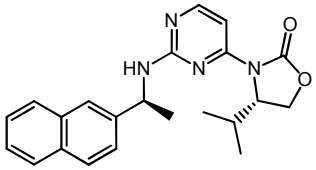
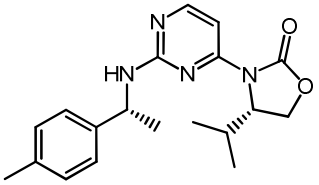
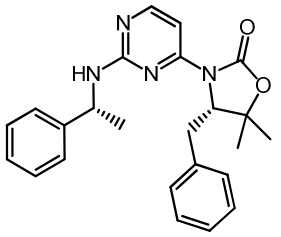
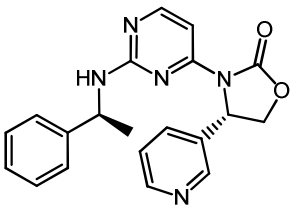
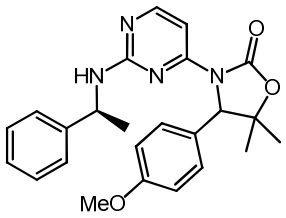
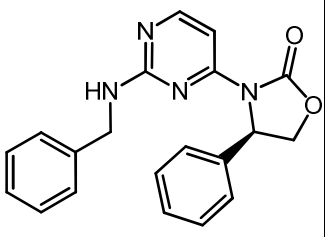
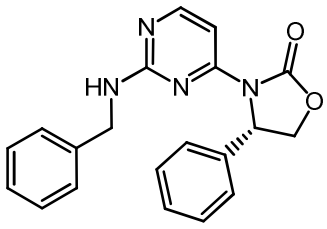
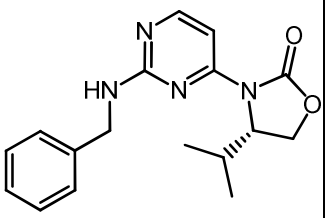
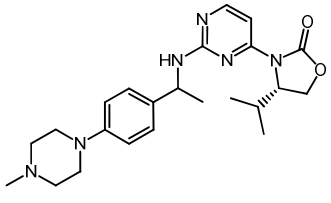
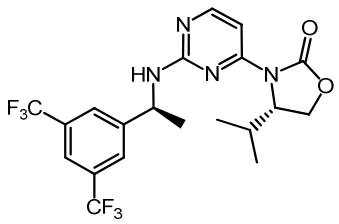
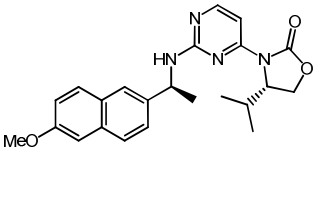
Tabla 5.

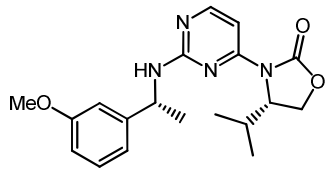
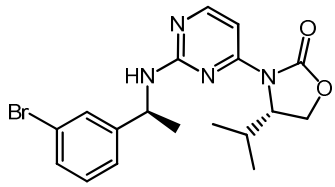
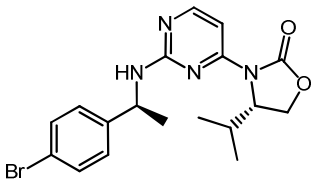
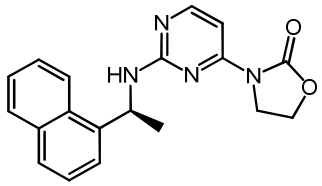
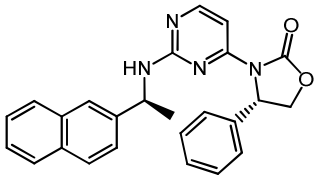
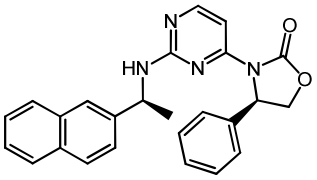
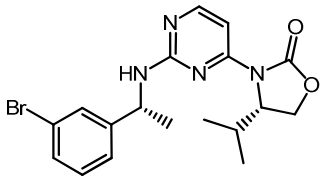
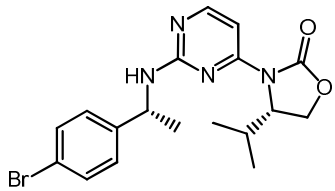
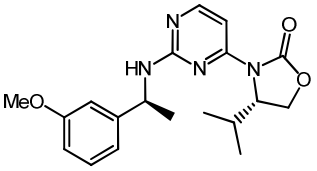
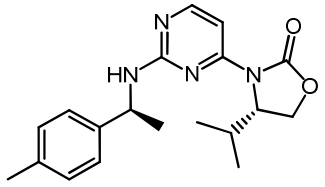
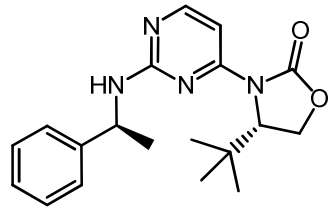
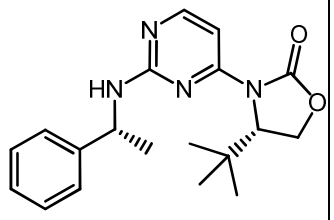
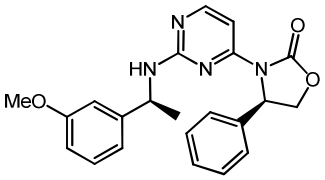
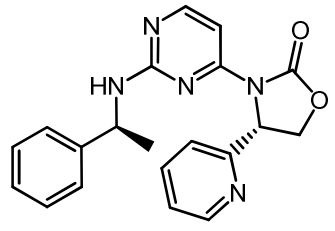
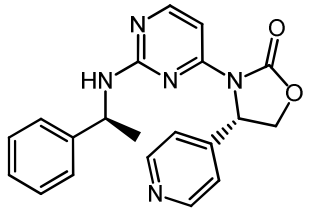
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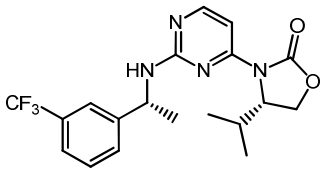
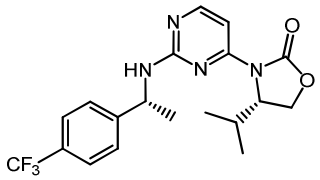
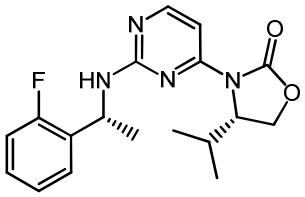
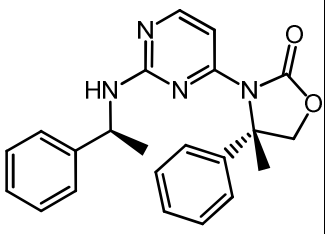
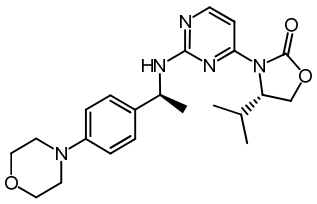
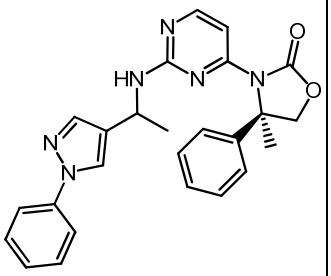
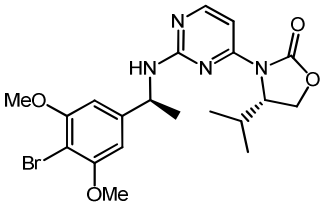
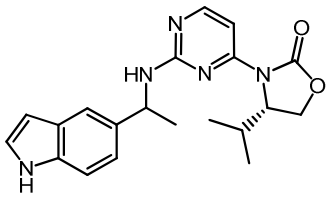
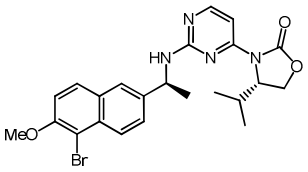
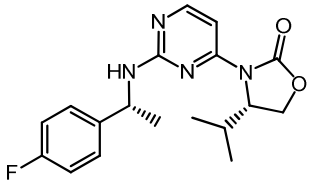
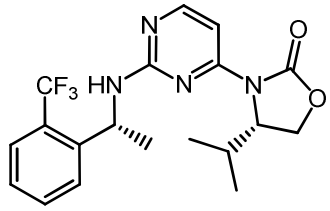
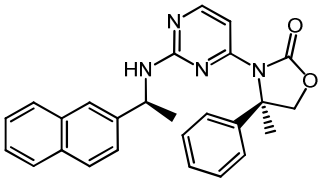
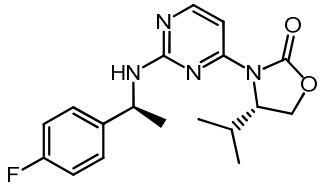
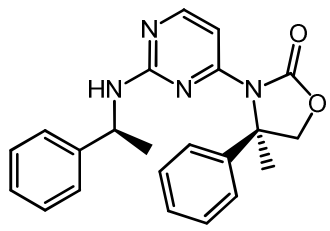
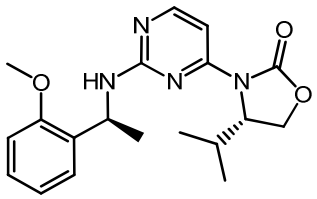
		
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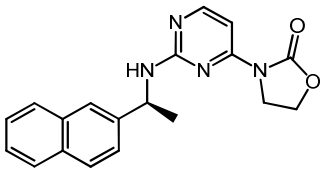
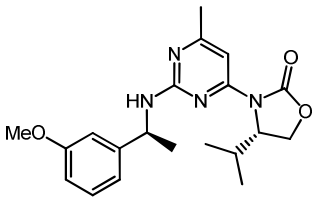
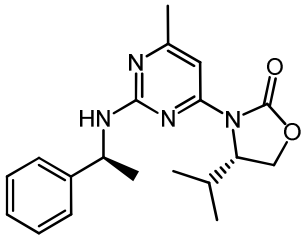
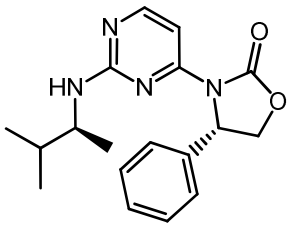
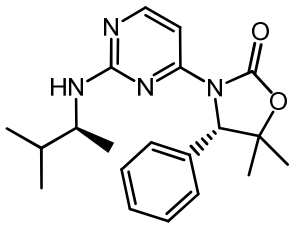
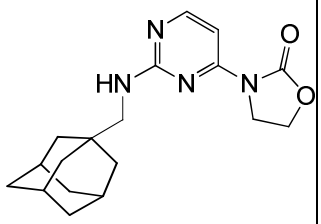
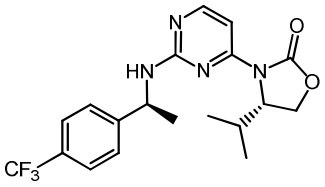
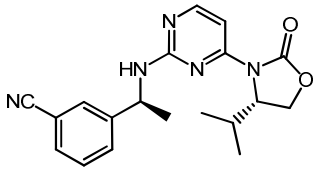
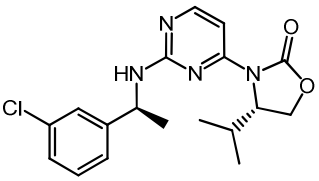
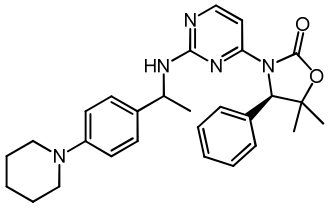
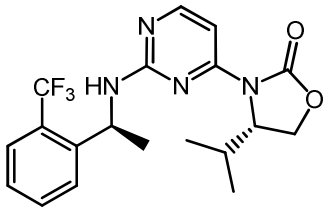
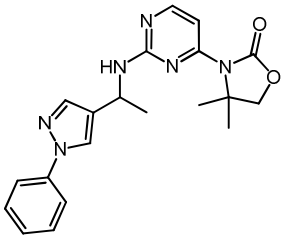
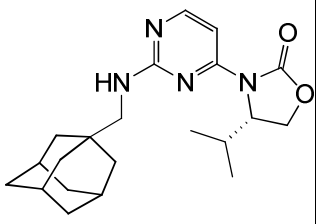
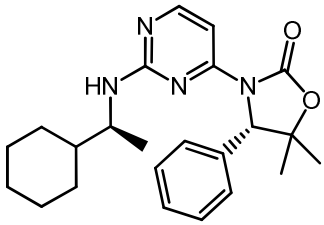
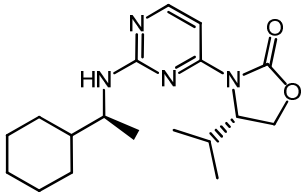
		
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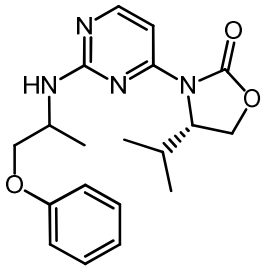
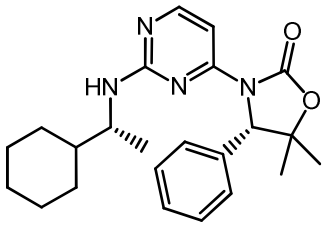
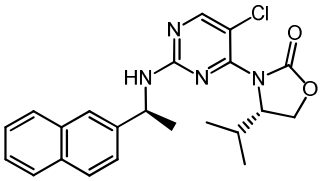
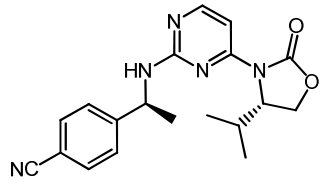
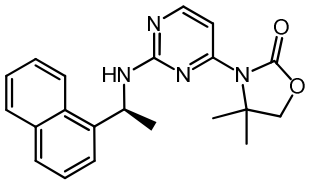
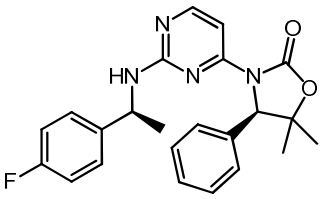
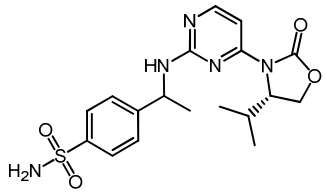
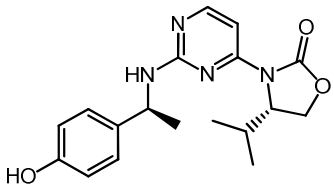
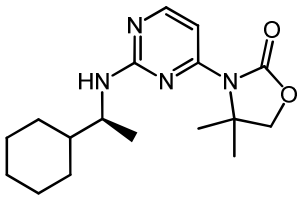
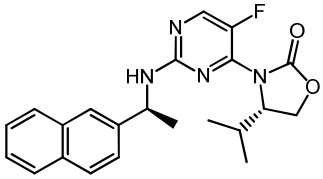
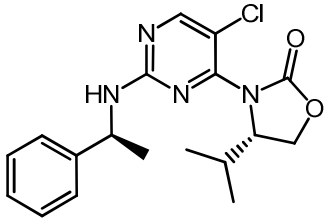
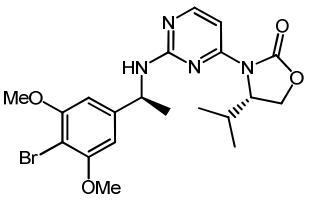
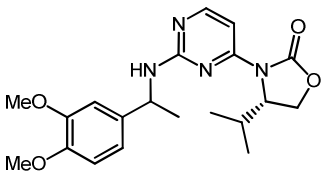
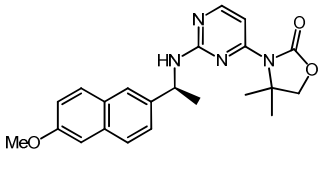
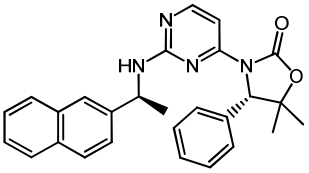
		
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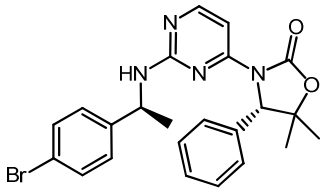
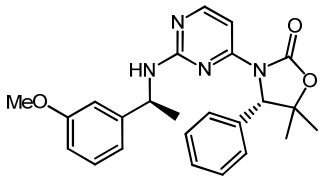
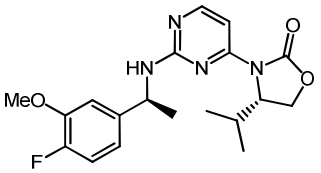
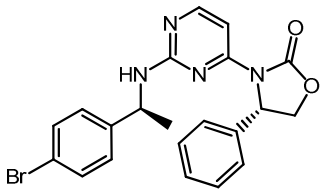
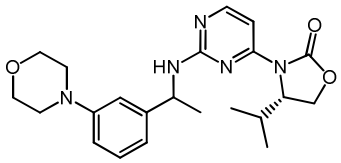
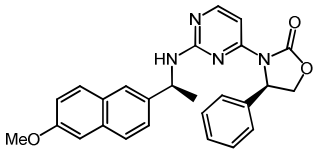
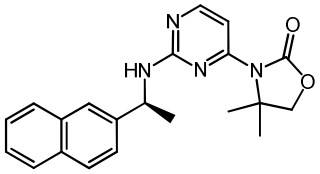
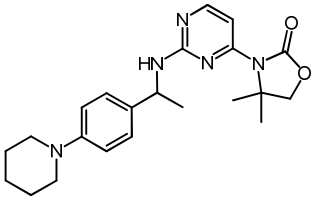
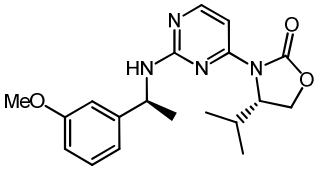
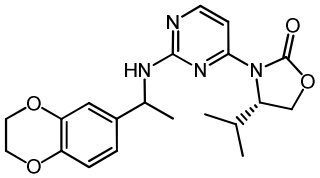
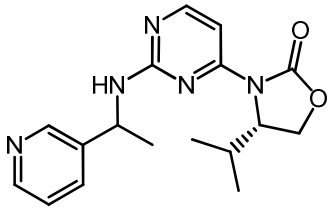
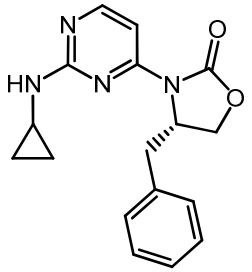
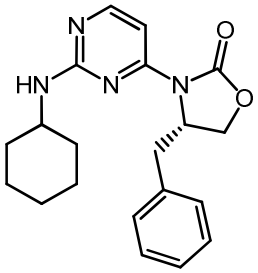
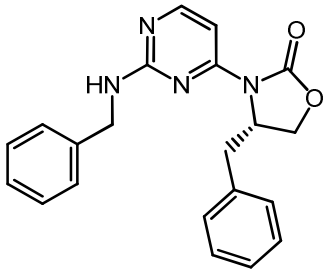
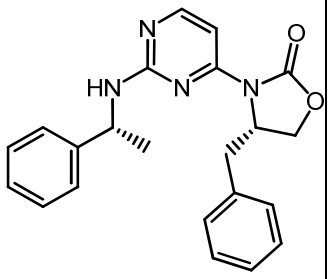
		
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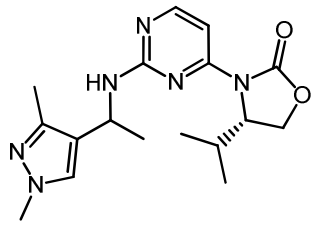
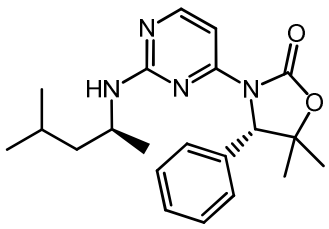
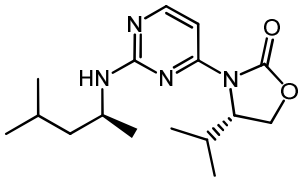
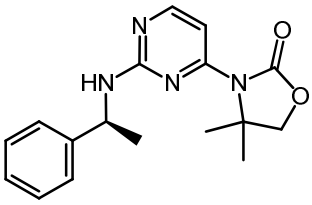
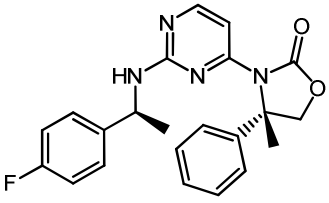
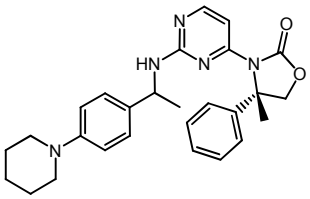
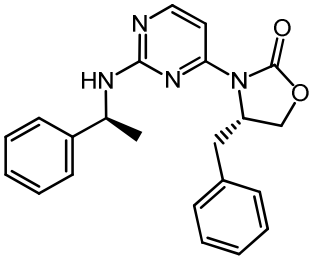
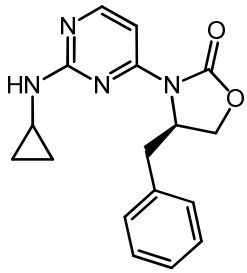
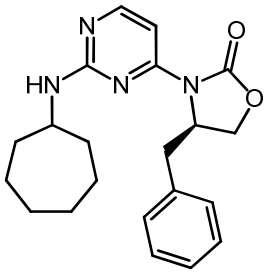
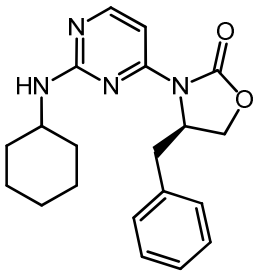
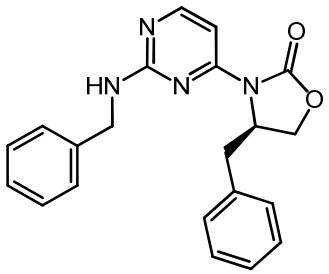
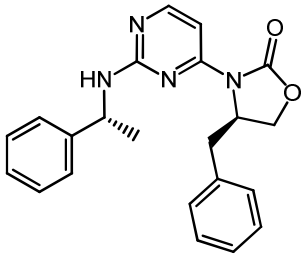
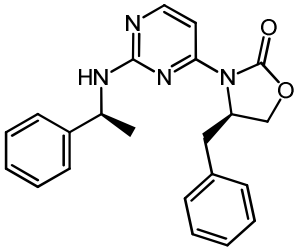
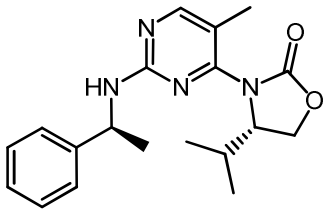
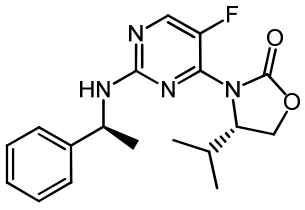
		
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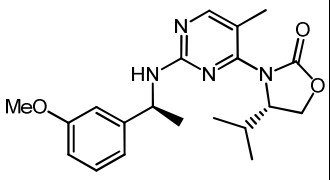
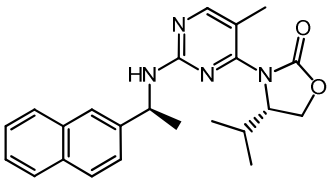
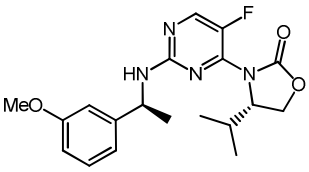
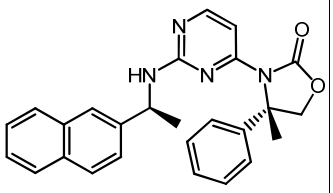
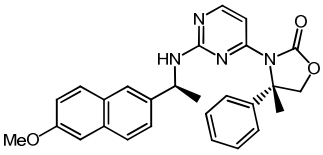
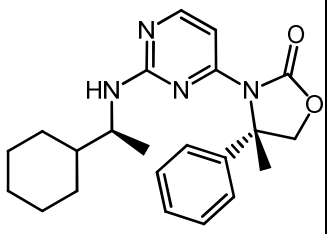
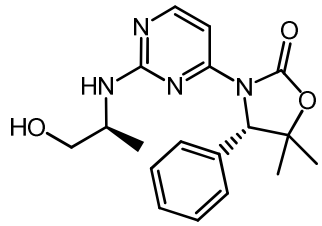
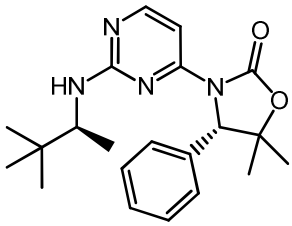
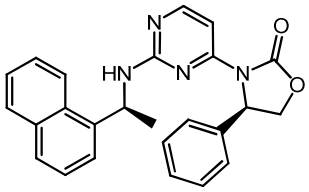
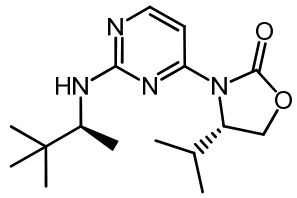
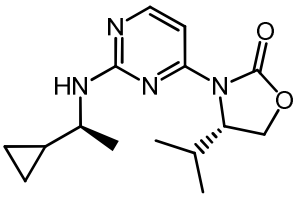
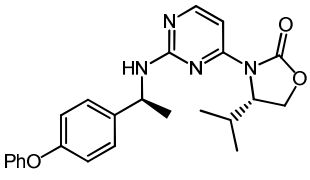
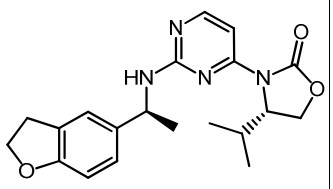
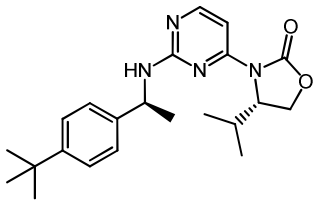
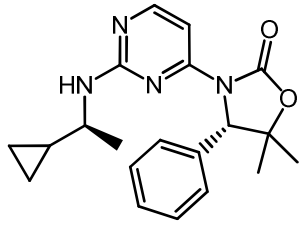
		
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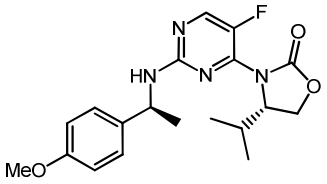
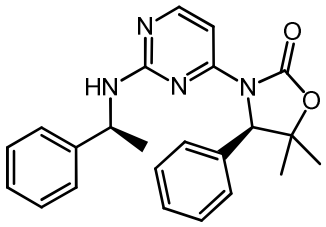
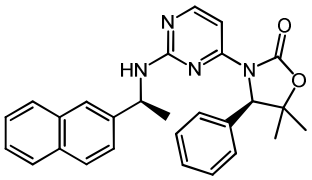
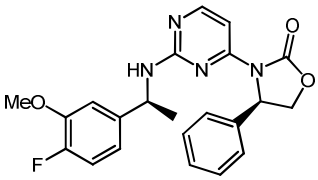
		
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Tabla 6. Nombre químico, desplazamientos químicos de RMN y señal LCMS señal para cada compuesto enumerado en la Tabla 5.

Ejemplo: Nombre	^{1}H RMN (**400 MHz,** CD_3OD) **δ ppm (otros solventes descritos)**	**LCMS**
1: (*S*) - 5,5- Dimetil- 4- fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,06 (d, J = 5,8 Hz, 1 H), 7,43 (d, J = 5,8 Hz, 1 H), 7.31- 7.24 (m, 3 H), 7.19- 7.11 (m, 5 H), 7,01 (br s 2 H), 5,48 (s, 1H), 4,86- 4,80 (m, 1 H), 1,65 (s, 3H), 1,43 (d, J = 7,0 Hz, 3 H), 0,98 (s, 3 H)	HRMS (B) *m/z* 389.1987 (M + H)+
2: 3 - (2 - (1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,06 (d, J = 6,1 Hz, 1H), 7,37- 7,26 (m, 5 H), 7.22- 7.15 (m, 1 H), 5,04 (q, J = 6,9 Hz, 1 H), 4,43 (sxt, J = 8,2 Hz, 2 H), 4,17 (td, J = 9,8, 7,1 Hz, 1 H), 3,92 (br s, 1H), 1,50 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 284.1275 M +
3: (*S*)- 4- isopropil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,12 (d, J = 5,6 Hz, 1H), 7,34- 7,26 (m, 5 H), 7.22- 7.13 (m, 1 H), 5,04 (q, J = 7,1 Hz, 1 H), 4,64 (br s , 1 H), 4,34- 4,26 (m, 2 H), 1,85 (br s, 1H), 1,50 (d, J = 7,1 Hz, 3 H), 0,70 (br s, 3 H), 0,57 (br s , 3 H)	HRMS (B) *m/z* 326.1745 M +
4: (*S*)- 4- isopropil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,10 (d, J = 5,8 Hz, 1H), 7,35- 7,27 (m, 5 H), 7.23- 7.15 (m, 1 H), 4,96 (q, J = 6,9 Hz, 1 H), 4,44 (br s , 1 H), 4,34- 4,23 (m, 2 H), 2,72- 2,58 (m, 1 H), 1,51 (d, J = 6,6 Hz, 3 H), 0,99 (d, J = 7,1 Hz, 3 H) , 0,85 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 326.1746 M +
5: (*S*)- 4- fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,07 (d, J = 5,6 Hz, 1 H), 7,38 (d, J = 5,6 Hz, 1 H), 7.28 a 7.5 (m, 10 H), 5,84 (dd, J = 8,6, 3,5 Hz, 2 H) , 4,88 (q, J = 6,8 Hz, 1H), 4,83- 4,79 (m, 1 H), 4,24 (dd, J =	HRMS (B) *m/z* 361.1666 (M + H)+

	8,6, 3,5 Hz, 1 H), 1,44 (d, J = 6,8 Hz, 3 H)	
6: (*S*)- 4- fenil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,08 (d, J = 5,8 Hz, 1H), 7,43- 7,18 (m, 11 H), 5,55 (br s, 1H), 4,74 (t, J = 8,6 Hz, 1 H), 4,63 (br s, 1 H), 4,18 (dd, J = 8,3, 3,8 Hz, 1 H), 1,19 (d, J = 6,7 Hz, 3 H)	HRMS (B) *m/z* 360.1591 M +
7: (*S*) - 3 - (2 - (ciclopentilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,06 (d, J = 6,1 Hz, 1H), 7,39- 7,28 (m, 6 H), 5,80 (dd, J = 8,8, 3,8 Hz, 1H), 4,83- 4,80 (m, 1 H), 4,20 (dd, J = 8,6, 4,0 Hz, 1 H), 3,79 (br m, 1 H), 1,90- 1,99 (m, 1 H), 1,72- 1,53 (m, 4 H), 1,49- 1,35 (m, 3 H)	HRMS (B) *m/z* 325.1671 (M + H)+
8: (*S*) - 3 - (2 - (ciclopropilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,10 (d, J = 5,6 Hz, 1 H), 7,44 (d, J = 5,6 Hz, 1H), 7,36- 7,26 (m, 5 H), 5,86 (dd, J = 8,6, 3,5 Hz, 1 H) , 4,83- 4,80 (m, 1 H), 4,26 (dd, J = 8,6, 3,5 Hz, 1 H), 2,40 (br s, 1H), 0,64- 0,71 (m, 1 H), 0,54 (br s, 1 H), 0,44- 0,37 (m, 1 H), 0,25 (br s, 1 H)	HRMS (B) *m/z* 297.1356 (M + H)+
9: (*S*) - 3 - (2 - (cicloheptilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,06 (d, J = 6,1 Hz, 1H), 7,38- 7,27 (m, 6 H), 5,82 (dd, J = 8,6, 3,5 Hz, 1H), 4,83- 4,80 (m, 1 H), 4,21 (dd, J = 8,6, 3,5 Hz, 1 H), 3,57 (br s, 1H), 1,90 (br s, 1H), 1,69- 1,42 (m, 8 H), 1,32- 1,18 (m, 3 H)	HRMS (B) *m/z* 353.1961 (M + H)+
10: (*R*)- 4- fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,08 (d, J = 5,8 Hz, 1H), 7,43- 7,18 (m, 11 H), 5,54 (br s, 1H), 4,74 (t, J = 8,6 Hz, 1 H), 4,62 (br s, 1 H), 4,18 (dd, J = 8,8, 3,8 Hz, 1 H), 1,19 (d, J = 6,6 Hz, 3 H)	HRMS (B) *m/z* 361.1712 (M + H)+
11: (*R*)- 4- fenil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,07 (d, J = 5,8 Hz, 1 H), 7,38 (d, J = 5,8 Hz, 1 H), 7.28 a 7.5 (m, 10 H), 5,84 (dd, J = 8,3, 3,3 Hz, 1 H) , 4,88 (q, J = 6,9 Hz, 1H), 4,82- 4,78 (m, 1 H), 4,24 (dd, J = 8,6, 3,5 Hz, 1 H), 1,44 (d, J = 6,9 Hz, 3 H)	HRMS (B) *m/z* 361.1661 (M + H)+
12: (*S*)- 4- isopropil- 3- (2 - ((*S*)- 1- fenilpropilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,11 (d, J = 5,6 Hz, 1H), 7,33- 7,26 (m, 5 H), 7.22- 7.15 (m, 1 H), 4,83- 4,79 (m, 1 H), 4,68 (br s, 1H), 4,36- 4,28 (m, 2 H), 1,84 (quintuplete, J = 7,3 Hz, 2 H), 0,99 (t, J = 7,3 Hz, 3 H), 0,76 (br s, 3 H), 0,59 (br s, 3 H)	HRMS (B) *m/z* 341.1974 (M + H)+
13: (*S*)- 4- isopropil- 3- (2 - ((*R*)- 1- fenilpropilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,09 (d, J = 5,8 Hz, 1H), 7,34- 7,27 (m, 5 H), 7.24- 7.16 (m, 1 H), 4,74 (t, J = 6,8 Hz, 1 H), 4,52 (br s , 1 H), 4,36- 4,26 (m, 2 H), 2,66 (td, J = 6,9, 3,8 Hz, 1H), 1,95- 1,75 (m, 2 H), 1,02 (d, J = 7,1 Hz, 3 H), 0,96 (t, J = 7,3 Hz, 3 H), 0,86 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 341.1976 (M + H)+
14: proporcionó (*S*)- 4- benzhidrilo- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il)	8,09 (d, J = 5,8 Hz, 1H), 7,32- 7,23 (m, 3 H), 7.20 - 7.16 (br m, 6 H), 7,00 (br s, 5 H), 6,72 (br s, 2 H), 5,76- 5,68 (m, 1 H), 5,04 (q, J = 7,1 Hz, 1 H), 4,59 (t, J = 8,8	HRMS (B) *m/z* 451.2126 (M + H)+

oxazolidin- 2- ona	Hz, 1 H), 4,50 (br s, 1H), 4,47 (dd, J = 9,1, 2,5 1H), 1,44 (d, J = 7,1 Hz, 3 H)	
15: (*4S, 5R*)- 4- metil- 5- fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,12 (d, J = 5,8 Hz, 1H), 7,45- 7,30 (m, 8 H), 7,20 (t, J = 7,6 Hz, 2 H), 7.10 a 7.7 (m, 1 H), 5,80 (d, J = 7,1 Hz, 1H), 5,10- 4,92 (m, 2 H), 1,49 (d, J = 7,0 Hz, 3 H), 0,37 (br s, 3 H)	HRMS (B) *m/z* 375.1823 (M + H)+
16: 3 - (2 - (ciclopentilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,07 (d, J = 5,7 Hz, 1 H), 7,32 (d, J = 5,8 Hz, 1 H), 4,48 (t, J = 8,1 Hz, 2 H), 4.22- 4.16 (m, 3 H), 2,02 (dq, J = 12, 6,1 Hz, 2H), 1,70- 1,80 (m, 2 H), 1,67- 1,47 (m, 4 H)	HRMS (B) *m/z* 248.1275 M +
17: (*S*)- 4- bencil- 3- (2 - (ciclopentilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,13 (d, J = 5,8 Hz, 1H), 7,35- 7,21 (m, 6 H), 5.14 a 5.4 (m, 1 H), 4,36 (t, J = 8,4 Hz, 1H), 4,33- 4,24 (m, 2 H), 3,37- 3,33 (m, 1 H), 3,06 (dd, J = 13, 8,3 Hz, 1H), 2,11- 1,98 (m, 2 H), 1,86- 1,71 (m, 2 H) , 1,70- 1,53 (m, 4 H)	HRMS (B) *m/z* 338.1749 M +
18: (*R*)- 4- bencil- 3- (2 - (ciclopentilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,13 (d, J = 5,6 Hz, 1H), 7,35- 7,21 (m, 6 H), 5.14 - 5.5 (m, 1 H), 4,36 (t, J = 8,5 Hz, 1H), 4,32- 4,26 (m, 2 H), 3,37- 3,33 (m, 1 H), 3,06 (dd, J = 13, 8,3 Hz, 1H), 2,13- 1,99 (m, 2 H), 1,85- 1,71 (m, 2 H) , 1,70- 1,51 (m, 4 H)	HRMS (B) *m/z* 338.1748 M +
19: (*4R, 5S*)- 4- metil- 5- fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 1H), 7,48- 7,28 (m, 10 H), 7.24- 7.21 (m, 1 H), 5,70 (d, J = 6,8 Hz, 1H), 4,96- 4,90 (m, 1 H), 4,65 (br s, 1 H) 1,49 (d, J = 7,1 Hz, 3 H), 0,97 (d, J = 6,6 Hz, 3 H)	HRMS (B) *m/z* 375.1824 (M + H)+
20: (*S*)- 4- benzhidrilo- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,13 (d, J = 5,8 Hz, 1H), 7,47- 7,40 (m, 2 H), 7,35- 7,22 (m, 5 H), 7.19- 7.10 (m, 5 H), 7,01- 6,99 (m, 2 H), 6,89 (br s, 2 H), 5,26 (br s, 1H), 5,09 (br s, 1H), 4,76 (br s, 1H), 4,54- 4,44 (m, 2 H), 1,37 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 451.2134 (M + H)+
21: (*R*)- 4- isopropil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,10 (d, J = 5,8 Hz, 1H), 7,35- 7,27 (m, 5 H), 7.20- 7.17 (m, 1 H), 4,96 (q, J = 6,7 Hz, 1 H), 4,44 (br s , 1 H), 4,32 (dd, J = 9,1, 2,5 Hz, 1 H), 4,25 (t, J = 8,6 Hz, 1 H), 2,65 (dtd, J = 14, 7,0, 3,5 Hz, 1 H), 1,51 (d, J = 7,1 Hz, 3 H), 0,99 (d, J = 7,1 Hz, 3 H), 0,85 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 327.1824 (M + H)+
22: (*R*)- 4- isopropil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,12 (d, J = 5,8 Hz, 1H), 7,37- 7,25 (m, 5 H), 7.19 - 7.16 (m, 1H), 5,04 (q, J = 6,9 Hz, 1 H), 4,64 (br s, 1 H), 4,35- 4,26 (m, 2 H), 1,88 (br s, 1H), 1,50 (d, J = 6,6 Hz, 3 H), 0,70 (br s, 3 H), 0,57 (br s, 3 H)	HRMS (B) *m/z* 327.1821 (M + H)+
23: (*S*)- 4- isopropil- 5 ,5- dimetil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin-	8,13 (d, J = 5,8 Hz, 1H), 7,35- 7,26 (m, 5 H), 7.19 - 7.16 (m, 1H), 5.8- 5.3 (m, 1 H), 4,45 (br s, 1 H) , 1,99 (br s, 1 H), 1,52	HRMS (B) *m/z* 355.2132

4- il) oxazolidin- 2- ona	(s, 3H), 1,50 (d, J = 7,1 Hz, 3 H), 1,41 (s, 3H), 0,73 (br s, 3 H), 0,58 (br s, 3 H)	(M + H)+
24: (*S*)- 4- isopropil- 5 ,5- dimetil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,10 (d, J = 5,8 Hz, 1H), 7,34- 7,25 (m, 5 H), 7.18- 7.15 (m, 1 H), 4,93 (br s, 1H), 4,32 (br s, 1 H) , 2,25 (td, J = 6,8, 3,5 Hz, 1 H), 1,50 (d, J = 7,1 Hz, 3 H), 1,49 (s, 3H), 1,09 (br s, 3 H), 1,03 (d, J = 7,1 Hz, 3 H), 0,95 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 355.2128 (M + H)+
25: (*4R, 5S*)- 4- metil- 5- fenil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,12 (d, J = 5,8 Hz, 1H), 7,45- 7,30 (m, 8 H), 7,20 (t, J = 7,3 Hz, 2 H), 7.10 - 7.6 (m, 1 H), 5,80 (d, J = 7,0 Hz, 1H), 5,01- 4,94 (m, 2 H), 1,49 (d, J 7,0 Hz, 3 H), 0,30 (br s, 3 H)	HRMS (B) *m/z* 375.1823 (M + H)+
26: (*4S, 5R*)- 4- metil- 5- fenil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,10 (d, J = 5,8 Hz, 1H), 7,48- 7,28 (m, 10 H), 7.24- 7.20 (m, 1 H), 5,69 (br s, 1H), 5,01- 4,93 (m, 1 H), 4,59 (br s, 1 H) 1,49 (d, J = 7,1 Hz, 3 H), 0,96 (d, J = 6,5 Hz, 3 H)	HRMS (B) *m/z* 375.1819 (M + H)+
27: (*S*) - 5,5- Dimetil- 4- fenil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	δ 8,08 (d, J = 5,9 Hz, 1H), 7,44- 7,39 (m, 3H), 7,36- 7,29 (m, 5 H), 7.22 a 7.17 (m, 3 H), 5,16 (br s, 1H), 4,55 (br s, 1H), 1,49 (s, 3H), 1,18 (d, J = 6,8 Hz, 3 H), 0,96 (s, 3 H)	HRMS (B) *m/z* 389.1974 (M + H)+
28: (*S*) - 3 - (2 - ((*S*) - 2,3- Dihidro- 1H- inden- 1- ilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,16 (d, J = 5,8 Hz, 1 H), 7,41 (d, J = 5,9 Hz, 1 H), 7.25- 7.13 (m, 4 H), 5,48 (t, J = 7,8 Hz, 1 H), 4,79 - 4,68 (m, 1 H), 4,36 (d, J = 6,1 Hz, 2 H), 3,01 (ddd, J = 16, 8,6, 3,0 Hz, 1H), 2,94- 2,81 (m, 1 H), 2,66 - 2,54 (m, 2 H), 2,01- 1,92 (m, 1 H), 0,86 (d, J = 6,9 Hz, 3 H), 0,85 (d, J = 6,9 Hz, 3 H)	HRMS (B) *m/z* 339.1825 (M + H)+
29: (*S*) - 3 - (2 - ((*R*) - 2,3- Dihidro- 1H- inden- 1- ilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,15 (d, J = 5,8 Hz, 1 H), 7,41 (d, J = 5,8 Hz, 1 H), 7.29 a 7.15 (m, 4 H), 5,48 (t, J = 7,6 Hz, 1 H), 4,83 - 4,79 (m, 1H), 4,41- 4,36 (m, 2 H), 3,03 (ddd, J = 16, 8,8, 3,3 Hz, 1 H), 2,86 (dt, J = 16, 8,0 Hz, 1 H) , 2,64- 2,50 (m, 2 H), 2,00- 1,91 (m, 1 H), 0,93 (d, J = 7,1 Hz, 3 H), 0,87 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 339.1830 (M + H)+
30: (*4R, 5S*) - 4,5- Difenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,12 (d, J = 5,8 Hz, 1 H), 7,48 (d, J = 5,8 Hz, 1H), 7,33- 7,20 (m, 5 H), 7.13 a 7.8 (m, 6 H), 7,03- 7,00 (m, 2 H), 6,88- 6,86 (m, 2 H), 5,99 (d, J = 8,0 Hz, 1 H), 5,76 (br s, 1H), 4,53 (br s, 1H), 1,11 (br s, 3 H)	HRMS (B) *m/z* 437.1982 (M + H)+
31: (*S*)- 4- isobutil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 1H), 7,36- 7,28 (m, 5 H), 7.21- 7.18 (m, 1 H), 5,18 (q, J = 6,9 Hz, 1H), 4,83- 4,79 (m, 1 H), 4,46 (t, J = 8,5 Hz, 1 H), 4,23 (dd, J = 9,0, 3,0 Hz, 1 H), 1,57 (br s, 2 H), 1,53 (d, J = 7,0 Hz, 3	HRMS (B) *m/z* 341.1974 (M + H)+

	H), 1,33 (br s, 1H), 0,82 (br s, 3 H), 0,73 (br s, 3 H)	
32: (*S*)- 4- isobutil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,09 (d, J = 5,8 Hz, 1H), 7,36- 7,27 (m, 5 H), 7.21- 7.18 (m, 1 H), 5,16 (q, J = 7,0 Hz, 1 H), 4,69 (br s , 1 H), 4,42 (t, J = 8,3 Hz, 1 H), 4,24 (dd, J = 8,8, 2,8 Hz, 1H), 1,92- 1,86 (m, 1 H), 1,80- 1,70 (m, 1 H), 1,58 (ddd, J = 13, 10, 4,8 Hz, 1 H), 1,52 (d, J = 7,0 Hz, 3 H), 1,07 (d, J = 6,5 Hz, 3 H), 0,98 (d, J = 6,5 Hz, 3 H)	HRMS (B) *m/z* 341.1972 (M + H)+
33: (4*S*)- 4- isopropil- 3- (2 - (1 - (piridin- 2- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,49- 8,48 (m, 1 H), 8,13 (dd, J = 10, 5,8 Hz, 1 H), 7,75 (td, J = 7,7, 1,8 Hz, 1H), 7,43- 7,36 (m, 2 H), 7.29- 7.23 (m, 1 H), 5,08- 4,99 (m, 1 H), 4,60 (br s, 0,5 H), 4,34- 4,22 (m, 2,5 H), 2,63- 2,56 (m, 0,5 H), 1,55 (d, J = 7,0 Hz, 1,5 H), 1,54 (d, J = 7,0 Hz, 1,5 H), 1,53 (br s, 0,5 H), 0,97 (d, J = 7,1 Hz, 1,5 H), 0,83 (d , J = 7,1 Hz, 1,5 H), 0,65 (br s, 1,5 H), 0,55 (br s, 1,5 H)	HRMS (B) *m/z* 328.1762 (M + H)+
34: (4*S*)- 4- isopropil- 3- (2 - (1 - (piridin- 4- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,45- 8,43 (m, 2 H), 8,14 (dd, J = 12, 5,6 Hz, 1H), 7,43- 7,37 (m, 2 H), 5,05 (q, J = 7,1 Hz, 0,5 H), 4,99 - 4,95 (br m, 0,5 H), 4,59 (br s, 0,5 H), 4,33- 4,26 (m, 2,5 H), 2,64- 2,59 (m, 0,5 H), 1,53 (d, J = 7,1 Hz, 3,5 H) , 0,97 (d, J = 7,1 Hz, 1,5 H), 0,84 (d, J = 7,1 Hz, 1,5 H), 0,62 (br s, 1,5 H), 0,57 (br s, 1,5 H)	HRMS (B) *m/z* 328.1772 (M + H)+
35: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (Naftalen- 1- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8.19 - 8.16 (m, 2 H), 7,88 (d, J = 8,1 Hz, 1 H), 7,72 (d, J = 8,1 Hz, 1H), 7,56- 7,45 (m, 3H), 7,40- 7,32 (m, 2 H), 5,80 (q, J = 6,6 Hz, 1 H), 4,32 (br s, 1 H), 4.17 - 4.13 (m, 1 H), 4,05 (br s, 1H), 1,64 (d , J = 7,1 Hz, 3 H), 1,15 (br s, 1H), 0,23 (br s, 3 H), - 0,31 (br s, 3 H)	HRMS (B) *m/z* 377.1969 (M + H)+
36: (*S*)- 4- isopropil- 3- (2 - ((*R*) - 1 - (4- metoxifenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,09 (d, J = 5,6 Hz, 1 H), 7,33 (d, J = 6,1 Hz, 1 H), 7.28- 7.24 (m, 2 H), 6,87- 6,83 (m, 2 H), 4,93 (q, J = 6,9 Hz, 1 H), 4,52 (br s, 1H), 4,35- 4,26 (m, 2 H), 3,75 (s, 3H), 2,65 (ddt, J = 10, 6,9, 3,5, 1 H), 1,48 (d, J = 7,1 Hz, 3 H), 0,99 (d, J = 7,1 Hz, 3 H), 0,83 (d, J = 6,8 Hz, 3 H)	HRMS (B) *m/z* 357.1928 (M + H)+
37: (*4S, 5R*) - 4,5- Difenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,10 (d, J = 5,8 Hz, 1 H), 7,50 (d, J = 5,8 Hz, 1 H), 7.12 - 7.9 (m, 6 H), 7.6- 7.3 (m, 2 H), 7,01- 6,97 (m, 5 H), 6,83- 6,81 (m, 2 H), 6,10 (s, 2H), 4,86- 4,81 (br m, 1 H), 1,42 (d, J = 6,5 Hz, 3 H)	HRMS (B) *m/z* 437.1984 (M + H)+
38: (*4S, 5R*) - 4,5- Difenil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin-	8.11 - 8.9 (m, 1 H), 7,47 (d, J = 5,8 Hz, 1H), 7,32- 7,20 (m, 5 H), 7.12 - 7.7 (m, 6 H), 7,02- 6,99 (m, 2 H), 6,86 (d, J = 6,5	HRMS (B) *m/z* 437.1970

4- il) oxazolidin- 2- ona	Hz, 2H), 5,98- 5,93 (br m, 1 H), 5,75 (br s, 1H), 4,53 (br s, 1H), 1,11 (br s, 3 H)	(M + H)+
39: (*4R, 5S*) - 4,5- Difenil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,09 (d, J = 5,9 Hz, 1 H), 7,50 (d, J = 5,8 Hz, 1 H), 7.11- 7.9 (m, 6 H), 7.5- 7.3 (m, 2 H), 7,00- 6,95 (m, 5 H), 6,82- 6,80 (m, 2 H), 6,09 (s, 2H), 4,87- 4,81 (br m, 1 H), 1,41 (d, J = 7,0 Hz, 3 H)	HRMS (B) *m/z* 437.1975 (M + H)+
40: (*S*)- 4- isopropil- 3- (2 - ((*R*) - 1 - (Naftalen- 1- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,16 (d, J = 8,4 Hz, 1 H), 8,12 (d, J = 5,8 Hz, 1 H), 7,73 (d, J = 8,2 Hz, 1H), 7,56- 7,45 (m, 3 H), 7,42 - 7,38 (m, 1 H), 7,33 (d, J = 5,8 Hz, 1 H), 5,81 (q, J = 6,6 Hz, 1 H), 4,15 (br s, 1H), 4,03 (br s, 1 H), 2,56 (td, J = 7,1, 3,5 Hz, 1 H), 1,65 (d, J = 7,1 Hz, 3 H), 0,78 (d, J = 6,6 Hz, 3 H), 0,74 (br s, 3 H)	HRMS (B) *m/z* 377.1981 (M + H)+
41: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (4- metoxifenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 1 H), 7,33 (d, J = 5,9 Hz, 1 H), 7,22 (d, J = 8,6 Hz, 2H), 6,85- 6,82 (m, 2 H), 4,98 (q, J = 6,9 Hz, 1H), 4,67- 4,63 (m, 1 H), 4,34- 4,27 (m, 2 H), 3,75 (s, 3H), 1,94 (br s, 1H), 1,48 (d, J = 7,1 Hz, 3 H), 0,73 (br s, 3 H), 0,61 (br s, 3 H)	HRMS (B) *m/z* 357.1922 (M + H)+
42: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (4 - (pirimidin- 5- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	9,11 (s, 1 H), 9,03 (s, 2 H), 8,14 (d, J = 5,8 Hz, 1H), 7,69- 7,66 (m, 2 H), 7,52 (d, J = 8,1 Hz, 2H), 7,35 (d, J = 5,8 Hz, 1 H), 5,11 (q, J = 6,9 Hz, 1 H), 4,65 (br s, 1H), 4,35- 4,26 (m, 2 H), 1,80 (br s, 1 H), 1,55 (d, J = 7,1 Hz, 3 H), 0,66 (br s, 3 H), 0,55 (br s, 3 H)	HRMS (B) *m/z* 405.2035 (M + H)+
43: (*S*)- 4- isopropil- 3- (2 - ((*R*) - 1 - (Naftalen- 2- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,10 (d, J = 5,9 Hz, 1H), 7,80- 7,75 (m, 4 H), 7,51- 7,48 (m, 1 H), 7,43- 7,36 (m, 2 H), 7,32 (d, J = 5,8 Hz, 1 H), 5.15 - 5.7 (m, 1 H), 4,36 (br s, 1H), 4,24 (dd, J = 9,1, 2,5 Hz, 1 H), 4.14 - 4.6 (br m, 1 H) , 2,67 (dtd, J = 14, 6,9, 3,5 Hz, 1 H), 1,60 (d, J = 7,1 Hz, 3 H), 0,99 (d, J = 7,1 Hz, 3 H), 0,83 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 377.1984 (M + H)+
44: (*R*) - 3 - (2 - ((*S*) - 1 - (4- fluorofenil) etilamino) pirimidin- 4- il) - 5,5- dimetil- 4- feniloxazolidin- 2- ona	8.9 - 8.7 (m, 1 H), 7,41- 7,18 (m, 8 H), 7.12 a 7.7 (m, 2 H), 5,21 (s, 1H), 4,99- 4,93 (m, 1 H), 1,50 (s, 3 H), 1,24 (d, J = 7,1 Hz, 3 H), 0,98 (s, 3 H)	HRMS (B) *m/z* 407,188 (M + H)+
45: (*R*)- 4- isobutil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,10 (d, J = 5,8 Hz, 1H), 7,36- 7,27 (m, 5 H), 7.22- 7.17 (m, 1 H), 5,18 (q, J = 6,9 Hz, 1H), 4,82- 4,78 (m, 1 H), 4,46 (t, J = 8,6 Hz, 1 H), 4,22 (dd, J = 8,6, 3,0 Hz, 1H), 1,62- 1,54 (m, 2 H), 1,53 (d, J = 7,0 Hz, 3H), 1,36- 1,30 (m, 1 H), 0,82 (br s, 3 H), 0,73 (br s, 3 H)	HRMS (B) *m/z* 341.1967 (M + H)+
46: (*4S, 5R*)- 5- metil- 4-	8,05 (d, J = 5,8 Hz, 1 H), 7,42 (d, J = 5,8	HRMS (B)

fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	Hz, 1 H), 7.31- 7.26 (m, 3 H), 7.19- 7.11 (m, 5 H), 7,02 (br s, 2 H), 5,80 (d, J = 7,5 Hz, 1 H), 5.11 - 5.4 (m, 1 H), 4,85 (q, J = 6,7 Hz, 1 H), 1,44 (d, J = 7,0 Hz, 3 H), 0,97 (d, J = 6,5 Hz, 3 H)	*m/z* 375.1828 (M + H)+
47: (*4S, 5R*)- 5- metil- 4- fenil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,06 (d, J = 5,8 Hz, 1H), 7,43- 7,40 (m, 3H), 7,37- 7,30 (m, 5 H), 7.23- 7.17 (m, 3 H), 5,51 (br d, J = 7,1 Hz, 1 H), 4,99 (quintuplete, J = 6,8 Hz, 1 H), 4,63 (br s, 1H), 1,16 (br d, J = 6,3 Hz, 3 H), 0,95 (d, J = 6,5 Hz, 3 H)	HRMS (B) *m/z* 375.1819 (M + H)+
48: (*S*)- 4- bencil- 5 ,5- dimetil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,18 (d, J = 5,7 Hz, 1 H), 7,43 (d, J = 5,7 Hz, 1 H), 7.31- 7.17 (m, 10 H), 5,34 (br s, 1H), 5,14 (quintuplete, J = 7,0 Hz, 1 H), 4,85 (dd, J = 10, 3,5 Hz, 1 H), 3,22 (br d, J = 14 Hz, 1 H), 2,72 (br s, 1H), 1,57 (d, J = 6,5 Hz, 3 H), 1,42 (s, 3H), 1,33 (s, 3 H)	HRMS (B) *m/z* 403.2133 (M + H)+
49: (*R*)- 4- isobutil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,09 (d, J = 6,1 Hz, 1H), 7,36- 7,27 (m, 5 H), 7.21- 7.17 (m, 1 H), 5,16 (q, J = 7,1 Hz, 1 H), 4,69 (t, J = 8,6 Hz, 1 H), 4,41 (t, J = 8,3 Hz, 1 H), 4,23 (dd, J = 8,6, 3,0 Hz, 1H), 1,92- 1,86 (m, 1 H), 1,79- 1,69 (m, 1 H), 1,57 (ddd, J = 13, 10, 4,8 Hz, 1 H), 1,52 (d, J = 7,1 Hz, 3 H), 1,07 (d, J = 6,6 Hz, 3 H), 0,98 (d, J = 6,6 Hz, 3 H)	HRMS (B) *m/z* 341.1973 (M + H)+
50: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (Naftalen- 2- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,15 (d, J = 5,7 Hz, 1H), 7,81- 7,73 (m, 4 H), 7,49- 7,38 (m, 3 H), 7,33 (d, J = 5,8 Hz, 1 H), 5,18 (q, J = 7,1 Hz, 1 H), 4,57 (br s, 1 H), 4.30 - 4.25 (m, 1 H), 4,20 (br s, 1H), 1,60 (d, J = 7,1 Hz, 3 H), 1,59 (br s, 1 H), 0,34 (br s, 6 H)	HRMS (B) *m/z* 377.1979 (M + H)+
51: (*S*)- 4- isopropil- 3- (2 - ((*R*)- 1- p- toliletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,08 (d, J = 5,6 Hz, 1 H), 7,32 (d, J = 5,6 Hz, 1 H), 7,22 (d, J = 8,1 Hz, 2 H), 7,10 (d, J = 8,1 Hz, 2H), 4,95- 4,90 (m, 1 H), 4,48 (br s, 1H), 4,32 (dd, J 9,1, 3,0 Hz, 1 H), 4,25 (t, J = 8,8 Hz, 1 H), 2,65 (dtd, J = 14, 7,1, 3,5 Hz, 1 H), 2,28 (s, 3H), 1,48 (d, J = 7,1 Hz, 3 H), 0,99 (d, J = 7,1 Hz, 3 H), 0,84 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 341.1972 (M + H)+
52: (*S*)- 4- bencil- 5 ,5- dimetil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	(CDCl3) 8,17 (d, J = 5,7 Hz, 1 H), 7,44 (d, J = 5,7 Hz, 1H), 7,38- 7,21 (m, 10 H), 5,32 (br s, 1H), 5,02 (br s, 1H), 4,69- 4,68 (br m, 1 H), 3,34 (dd, J = 15, 4,0 Hz, 1 H), 2,93 (dd, J = 15, 9,5 Hz, 1 H), 1,51 (d, J = 6,9 Hz, 3 H), 1,35 (s, 3H), 1,29 (s, 3 H)	HRMS (B) *m/z* 403.2133 (M + H)+
53: (*S*) - 3 - (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) - 4 - (piridin- 3- il)	($CDCl_3$) 8,56- 8,53 (br m, 2 H), 8,18 (d, J = 5,7 Hz, 1 H), 7,48 (d, J = 5,7 Hz, 1H), 7,45- 7,34 (m, 1 H), 7.30 - 7.16 (m, 6 H),	HRMS (B) *m/z* 362.1620

oxazolidin- 2- ona	5,77 (dd, J = 8,8, 3,8 Hz, 1 H), 5,26 (br s, 1H), 4,83 (br s, 1H), 4,81 (t, J = 8,8 Hz, 1 H), 4,31 (dd, J = 8,8, 3,8 Hz, 1 H), 1,51 (d, J = 6,8 Hz, 3 H)	(M + H)+
54: 4 - (4- metoxifenil) - 5,5- dimetil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,06 (d, J = 5,7 Hz, 1H), 7,55- 7,52 (m, 1 H), 7,37- 7,20 (m, 4 H), 7,13- 6,99 (m, 3 H), 6,91 (d, J = 8,0 Hz, 1 H), 6,78 (d, J = 8,0 Hz, 1 H), 5,87 (br s, 0,5 H), 5,67 (br s, 0,5 H), 5,01 (br s, 0,5 H), 4,82 (br s, 0,5 H), 4,64 (br s, 0,5 H), 3,83 (s, 1,5 H), 3,78 (s, 1,5 H), 3,36 (br s, 0,5 H), 1,66 (s, 1,5 H), 1,51 (d, J = 6,9 Hz, 1,5 H), 1,49 (s, 1,5 H), 1.29- 1.27 (m, 1,5 H), 1,04 (s, 1,5 H), 1,00 (s, 1 5 H).	HRMS (B) *m/z* 419.2093 (M + H)+
55: (*R*) - 3 - (2 - (bencilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,08 (d, J = 5,8 Hz, 1 H), 7,41 (d, J = 5,8 Hz, 1 H), 7.30- 7.17 (m, 8 H), 7,09 (br d, J = 7,1 Hz, 2 H), 5,69 (br dd, J = 8,1, 3,0 Hz, 1 H), 4,76 (t, J = 8,8 Hz, 1 H), 4,28 (dd, J = 44, 15 Hz, 2 H), 4,19 (dd, J = 8,8, 3,8 Hz, 1 H)	HRMS (B) *m/z* 347.1512 (M + H)+
56: (*S*) - 3 - (2 - (bencilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,10 (d, J = 5,7 Hz, 1 H), 7,42 (d, J = 5,9 Hz, 1 H), 7.31 a 7.16 (m, 8 H), 7,09 (br d, J = 7,1 Hz, 2 H), 5,71 (br m, 1 H), 4,78 (t, J = 8,8 Hz, 1 H), 4,28 (dd, J = 45, 15 Hz, 2 H), 4,21 (dd, J = 8,6, 3,5 Hz, 1 H)	HRMS (B) *m/z* 347.1499 (M + H)+
57: (*S*) - 3 - (2 - (bencilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,13 (d, J = 5,8 Hz, 1 H), 7,37 (d, J = 5,8 Hz, 1 H), 7,28 (d, J = 4,6 Hz, 4 H), 7,20 (dq, J = 8,5, 4,2 Hz, 1 H), 4,64 (br s, 1H), 4,56 (dd, J = 51, 16 Hz, 2 H), 4,35- 4,29 (m, 2 H), 2,31 (br s, 1H), 0,77 (br s, 3 H), 0,72 (br d, J = 6,6 Hz, 3 H)	HRMS (B) *m/z* 312.1584 M +
58: (4*S*)- 4- isopropil- 3- (2 - (1 - (4 - (4- metilpiperazin- 1- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,23 (d, J = 5,8 Hz, 1 H), 7,40 (d, J = 5,8 Hz, 1 H), 7.28- 7.24 (m, 2 H), 7,01- 6,98 (m, 2 H), 4,85- 4,82 (m, 1 H), 4,44- 4,39 (m, 2 H), 4,03- 3,98 (m, 1 H), 3,93- 3,90 (m, 4 H), 3,30 (s, 3H), 3.21- 3.18 (m, 4 H), 2,60 (dtt, J = 10, 6,9, 3,5 Hz, 1 H), 1,37 (d, J = 7,1 Hz, 3 H), 1,00 (d, J = 7,1 Hz, 3 H), 0,87 (d , J = 6,9 Hz, 3 H)	HRMS (B) *m/z* 425.2651 (M + H)+
59: (*S*) - 3 - (2 - ((*S*) - 1 - (3,5- bis (trifluorometil) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,17 (br d, J = 5,0 Hz, 1 H), 7,93 (s, 2 H), 7,82 (s, 1 H), 7,40 (d, J = 5,9 Hz, 1 H), 5,21 (q, J = 7,1 Hz, 1 H), 4,59 (br s, 1H), 4,33- 4,25 (m, 2 H), 1,69 (br s, 1H), 1,57 (d, J = 7,1 Hz, 3 H), 0,57 (br s, 6 H)	HRMS (B) *m/z* 463.1564 (M + H)+
60: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (6- metoxinaftalen- 2- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,14 (d, J = 5,8 Hz, 1 H), 7,71 (d, J = 8,6 Hz, 1H), 7,67- 7,64 (m, 2 H), 7,42 (dd, J = 8,3, 1,8 Hz, 1 H) , 7,33 (d, J = 5,8 Hz, 1 H), 7,19 (d, J = 2,5 Hz, 1 H), 7,08 (dd, J = 9,1, 2,5 Hz, 1 H), 5,15 (q, J = 7,1 Hz , 1	HRMS (B) *m/z* 407.2084 (M + H)+

	H), 4,59 (br s, 1H), 4,29 (t, J = 8,8 Hz, 1 H), 04.24 a 04.19 (br m, 1 H), 3,88 (s, 3H), 1,74 (br s , 1 H), 1,58 (d, J = 7,1 Hz, 3 H), 0,39 (br s, 6 H)	
61: (*S*)- 4- isopropil- 3- (2 - ((*R*) - 1 - (3- metoxifenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,09 (d, J = 5,8 Hz, 1 H), 7,33 (d, J = 5,9 Hz, 1 H), 7,20 (t, J = 7,8 Hz, 1H), 6,92- 6,90 (m, 2 H), 6,75 (ddd, J = 8,1, 2,5, 1,0 Hz, 1H), 4,94- 4,89 (m, 1 H), 4,46 (br s, 1H), 4,34- 4,23 (m, 2 H), 3,75 (s, 3 H), 2,65 (dtd, J = 14, 6,9, 3,5 Hz, 1 H), 1,49 (d, J = 7,1 Hz, 3 H), 0,99 (d, J = 7,1 Hz, 3 H), 0,85 (d, J = 6,9 Hz, 3 H)	HRMS (B) *m/z* 357.1927 (M + H)+
62: (*S*) - 3 - (2 - ((*S*) - 1 - (3- bromofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,14 (d, J 5,8 Hz, 1 H), 7,48 (s, 1H), 7,37- 7,28 (m, 3 H), 7,20 (t, J = 7,1 Hz, 1 H), 5,01 (q, J = 7,1 Hz, 1 H), 4,62 (br s, 1H), 4,34- 4,26 (m, 2 H), 1,83 (br s, 1H), 1,50 (d, J = 7,1 Hz, 3 H), 0,71 (br s, 3 H), 0,59 (br s, 3 H)	HRMS (B) *m/z* 405.0937 (M + H)+
63: (*S*) - 3 - (2 - ((*S*) - 1 - (4- bromofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,13 (d, J 5,8 Hz, 1H), 7,44- 7,41 (m, 2 H), 7,35 (d, J = 5,8 Hz, 1 H), 7.26- 7.22 (m, 2 H), 4,98 (q, J = 7,1 Hz, 1 H), 4,60 (br s, 1H), 4,33- 4,26 (m, 2 H), 1,73 (br s, 1 H), 1,49 (d, J = 7,1 Hz, 3 H), 0,68 (br s, 3 H), 0,58 (br s, 3 H)	HRMS (B) *m/z* 405.0912 (M + H)+
64: (*S*) - 3 - (2 - (1 - (naftalen- 1- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,23 (d, J = 8,1 Hz, 1 H), 8,07 (d, J = 5,8 Hz, 1H), 7,88- 7,86 (m, 1 H), 7,73 (d, J = 8,1 Hz, 1 H), 7,58 (d, J = 7,1 Hz, 1H), 7,54- 7,45 (m, 2 H), 7,42- 7,39 (m, 1 H), 7,29 (d, J = 5,8 Hz, 1 H), 5,90 (q, J = 6,7 Hz, 1 H), 4,32 (br s, 1H), 4,22 (br s, 1 H), 3,98 (br s, 1H), 3,37 (br s, 1H), 1,65 (d, J = 6,9 Hz, 3 H)	HRMS (B) *m/z* 335.1500 (M + H)+
65: (*S*) - 3 - (2 - ((*S*) - 1 - (Naftalen- 2- il) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 1H), 7,80- 7,77 (m, 1 H), 7,73- 7,68 (m, 2 H), 7,56 (s, 1H), 7,45- 7,40 (m, 2 H) , 7,37 (d, J = 5,8 Hz, 1 H), 7,23 (dd, J = 8,6, 1,5 Hz, 1H), 7,08- 7,00 (m, 5 H), 5,80 (dd, J = 8,8, 3,8 Hz, 1 H), 5,07 (q, J = 6,9 Hz, 1 H), 4,79 (t, J = 8,7 Hz, 1 H), 4,20 (dd, J = 8,6, 3,5 Hz, 1 H), 1,55 (d, J = 6,9 Hz, 3 H)	HRMS (B) *m/z* 411.1820 (M + H)+
66: (*R*) - 3 - (2 - ((*S*) - 1 - (Naftalen- 2- il) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,10 (d, J = 5,8 Hz, 1H), 7,82- 7,78 (m, 3 H), 7,69 (s, 1H), 7,47- 7,40 (m, 5 H), 7,38- 7,29 (m, 4 H) , 5,53 (dd, J = 8,8, 3,8 Hz, 1 H), 4,82 (q, J = 6,9 Hz, 1 H), 4,68 (t, J = 8,6 Hz, 1 H), 4,15 (dd, J = 8,6, 4,0 Hz, 1 H), 1,31 (d, J = 6,9 Hz, 3 H)	HRMS (B) *m/z* 411.1821 (M + H)+
67: (*S*) - 3 - (2 - ((*R*) - 1 - (3- bromofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2-	8,10 (d, J 5,8 Hz, 1H), 7,53- 7,50 (m, 1 H), 7,36- 7,31 (m, 3 H), 7,21 (t, J = 7,8 Hz, 1H), 4,94- 4,86 (m , 1 H), 4,42 (br s, 1H), 4,33 (dd, J = 9,1, 2,5, 1 H), 4,26 (t, J	HRMS (B) *m/z* 405.0930

ona	= 8,8 Hz, 1 H), 2,65 (dtd, J = 14, 7,0 , 3,8 Hz, 1 H), 1,50 (d, J = 7,1 Hz, 3 H), 1,00 (d, J = 7,1 Hz, 3 H), 0,85 (d, J = 7,1 Hz, 3 H)	(M + H)+
68: (*S*) - 3 - (2 - ((*R*) - 1 - (4- bromofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,10 (d, J 5,8 Hz, 1H), 7,45- 7,42 (m, 2 H), 7,35 (d, J = 5,9 Hz, 1 H), 7.29- 7.25 (m, 2 H), 4,95- 4,90 (m , 1 H), 4,44 (br s, 1H), 4,34- 4,25 (m, 2 H), 2,63 (dtd, J = 14, 6,9, 3,5 Hz, 1 H), 1,49 (d, J = 7,1 Hz, 3 H), 0,98 (d, J = 7,1 Hz, 3 H), 0,84 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 405.0934 (M + H)+
69: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (3- metoxifenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,12 (d, J = 5,8 Hz, 1 H), 7,34 (d, J = 6,0 Hz, 1 H), 7.20- 7.16 (m, 1 H), 6,89- 6,87 (m, 2 H), 6,75- 6,73 (m, 1 H), 4,99 (q, J = 6,7 Hz, 1 H), 4,63 (br s, 1H), 4,34- 4,25 (m, 2 H), 3,74 (s, 3H), 1,84 (br s , 1 H), 1,49 (d, J = 7,1 Hz, 3 H), 0,68 (br s, 3 H), 0,57 (br s, 3 H)	HRMS (B) *m/z* 357.1918 (M + H)+
70: (*S*)- 4- isopropil- 3- (2 - ((*S*)- 1- p- toliletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 1 H), 7,33 (d, J = 5,9 Hz, 1 H), 7,18 (d, J = 8,1 Hz, 2 H), 7,08 (d, J = 8,1 Hz, 2H), 4,99 (q, J = 7,1 Hz, 1 H), 4,63 (br s, 1H), 4,34- 4,26 (m, 2 H), 2,28 (s, 3H), 1,86 (br s, 1 H) , 1,48 (d, J = 7,1 Hz, 3 H), 0,69 (br s, 3 H), 0,58 (br s, 3 H)	HRMS (B) *m/z* 341.1977 (M + H)+
71: (*S*)- 4- terc- butil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,14 (d, J = 5,7 Hz, 1H), 7,37- 7,34 (m, 2 H), 7.30- 7.26 (m, 2 H), 7.19- 7.15 (m, 2 H), 5,00 (q, J = 6,9 Hz, 1 H), 4,76 (br s, 1H), 4,41 - . 4,33 (m, 2 H), 1,48 (d, J = 7,1 Hz 3 H), 0,55 (br s, 9 H)	HRMS (B) *m/z* 341.1979 (M + H)+
72: (*S*)- 4- terc- butil- 3- (2 - ((*R*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,09 (d, J = 5,7 Hz, 1H), 7,35- 7,32 (m, 2 H), 7.29- 7.24 (m, 3 H), 7.19- 7.15 (m, 1 H), 5,01- 4,96 (m, 1 H), 4,68 (br s, 1H), 4,39 (d, H = 9,2 Hz, 1 H), 4,15 (br s, 1H), 1,50 (d, J = 7,0 Hz. 3 H), 0,94 (s , 9 H)	HRMS (B) *m/z* 341.1974 (M + H)+
73: (*R*) - 3 - (2 - ((*S*) - 1 - (3- metoxifenil) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,09 (d, J = 5,8 Hz, 1H), 7,42- 7,37 (m, 3H), 7,34- 7,28 (m, 3 H), 7,21 (t, J = 7,8 Hz, 1H), 6,86- 6,83 (m, 2 H), 6,78- 6,76 (m, 1 H), 5,58 (dd, J = 8,6, 4,0 Hz, 1 H), 4,74 (t, J = 8,7 Hz, 1H), 4,66- 4,61 (m, 1 H), 4,18 (dd, J = 8,6, 4,0 Hz, 1 H), 3,77 (s, 3H), 1,20 (d, J = 6,9 Hz, 3 H)	HRMS (B) *m/z* 391.1768 (M + H)+
74: (*S*) - 3 - (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) - 4 - (piridin- 2- il) oxazolidin- 2- ona	8,55 (d, J = 4,5 Hz, 1 H), 8,10 (d, J = 6,0 Hz, 1 H), 7,64 (d, J = 6,0 Hz, 1 H), 7,43 (br s, 1H), 7,26 - 7,15 (m, 4 H), 7,06 (br s, 2 H), 6,92 (br s, 1H), 5,84 (dd, J = 8,7, 3,2 Hz, 1 H), 4,94 (br s, 1 H), 4,88- 4,78 (m, 2 H), 4,48 (dd, J = 8,7, 3,2 Hz, 1 H), 1,51 (d, J = 6,9 Hz, 3 H)	HRMS (B) *m/z* 362.1624 (M + H)+
75: (*S*) - 3 - (2 - ((*S*)- 1-	8,43 (br s, 2 H), 8,16 (br d, J = 5,0 Hz, 1	HRMS (B)

feniletilamino) pirimidin- 4- il) - 4 - (piridin- 4- il) oxazolidin- 2- ona	H), 7,65 (br s, 1H), 7,36- 7,09 (br m, 6 H), 6,90 (br s, 1H), 5,88 (br s, 1H), 4,83 (t, J = 8,8 Hz, 1 H), 4,78 (br s, 1H), 4,23 (br s, 1H), 1,34 (d, J = 7,0 Hz , 3 H)	*m/z* 362.1623 (M + H)+
76: (*S*)- 4- isopropil- 3- (2 - ((*R*) - 1 - (3 - (trifluorometil) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 1 H), 7,66 (s, 1H), 7,64- 7,61 (m, 1 H), 7,53- 7,49 (m, 2 H), 7,36 (d, J = 5,9 Hz, 1 H), 5,05- 4,99 (m, 1 H), 4,42 (br s, 1H), 4,33 (dd, J = 9,1, 3,0 Hz, 1 H), 4,24 (t, J = 8,6 Hz, 1 H) , 2,68- 2,60 (m, 1 H), 1,54 (d, J = 7,1 Hz, 3 H), 0,99 (d, J = 7,1 Hz, 3 H), 0,85 (d, J = 7,0 Hz, 3 H)	HRMS (B) *m/z* 395.1686 (M + H)+
77: (*S*)- 4- isopropil- 3- (2 - ((*R*) - 1 - (4 - (trifluorometil) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 1 H), 7,60 (d, J = 8,3 Hz, 2 H), 7,54 (d, J = 8,3 Hz, 2 H), 7,36 (d, J = 5,8 Hz, 1 H), 5,07 - 5.00 (m, 1 H), 4,39 (br s, 1H), 4,33- 4,30 (m, 1 H), 4.27- 4.23 (m, 1 H), 2,63 (dtd, J = 14, 7,1 , 3,5 Hz, 1 H), 1,54 (d, J = 7,0 Hz, 3 H), 0,98 (d, J = 7,1 Hz, 3 H), 0,84 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 395.1698 (M + H)+
78: (*S*) - 3 - (2 - ((*R*) - 1 - (2- fluorofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,10 (d, J = 5,8 Hz, 1H), 7,40- 7,34 (m, 2 H), 7.24- 7.18 (m, 1 H), 7.10 - 7.2 (m, 2 H), 5,28 (q, J = 7,1 Hz, 1 H), 4,42 (br s, 1H), 4,32 (dd, J = 9,1, 2,5 Hz, 1 H), 4,24 (t, J = 8,8 Hz, 1 H), 2,64 (dtd, J = 14 , 7,0, 3,8 Hz, 1 H), 1,50 (d, J = 7,1 Hz, 3 H), 0,98 (d, J = 7,1 Hz, 3 H), 0,84 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 345.1727 (M + H)+
79: (*S*)- 4- metil- 4- fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,15 (d, J = 5,8 Hz, 1H), 7,44- 7,38 (m, 3H), 7,36- 7,21 (m, 6 H), 7.15- 7.13 (m, 2 H), 5,40 (br s, 1H), 4.22- 4.17 (m, 2 H), 4,15 (br s, 1H), 1,63 (br s, 3 H), 1,15 (d, J 6,6 Hz, 3 H)	HRMS (B) *m/z* 375.1809 (M + H)+
80: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (4- morfolinofenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 1 H), 7,33 (d, J = 5,8 Hz, 1 H), 7.22- 7.19 (m, 2 H), 6,92- 6,89 (m, 2 H), 5,00- 4,95 (m, 1 H), 4,66 (br s, 1H), 4,58 (br s, 1H), 4,35- 4,27 (m, 2 H), 3,82- 3,80 (m, 4 H), 3.9- 3.7 (m, 4 H), 1,48 (d, J = 7,1 Hz, 3 H), 0,73 (br s, 3 H), 0,60 (br s, 3 H)	HRMS (B) *m/z* 412.2359 (M + H)+
81: (4*R*)- 4- metil- 4- fenil- 3- (2 - ((1 - (1- fenil- 1H- pirazol- 4- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona		HRMS (B) *m/z* 441.2049 (M + H)+
82: (*S*) - 3 - (2 - ((*S*) - 1 - (4- bromo- 3 ,5- dimetoxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2-	8,16 (d, J = 5,8 Hz, 1 H), 7,36 (d, J = 5,8 Hz, 1 H), 6,64 (s, 2H), 5,00- 4,95 (m, 1 H), 4,58 (br s, 1 H), 4,33- 4,23 (m, 2 H), 3,79 (s, 6 H), 1,54 (d, J = 7,0 Hz, 3 H), 0,55 (br s, 6 H)	HRMS (B) *m/z* 465.1134 (M + H)+

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83: (4*S*) - 3 - (2 - (1 - (1*H*- Indol- 5- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 0,5 H), 8,09 (d, J = 5,8 Hz, 0,5 H), 7,52 (s, 0,5 H), 7,46 (s, 0,5 H), 7,32- 7,29 (m, 2 H), 7.19- 7.18 (m, 1 H), 7,10 (ddd, J = 14, 8,6, 1,5 Hz, 1 H), 6,36 (dt, J = 4,0, 3,0 Hz, 1 H), 5,11 (q, J = 6,9 Hz, 0,5 H), 5,05 (q, J = 6,8 Hz, 0,5 H), 4,64 (br s, 0,5 H), 4,50 (br s, 0,5 H), 4,33- 4,19 (m, 2 H), 2,74 - 2,64 (m, 0,5 H), 1,86 (br s, 0,5 H), 1,55 (d, J = 7,1 Hz, 3 H), 1,02 (d, J = 7,1 Hz, 1,5 H), 0,86 (d, J = 7,1 Hz, 1,5 H), 0,57 (br s, 1,5 H), 0,46 (br s, 1,5 H)	HRMS (B) *m/z* 366.1928 (M + H)+
84: (*S*) - 3 - (2 - ((*S*) - 1 - (5- bromo- 6- metoxinaftalen- 2- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	δ 8.16 - 8.12 (m, 2 H), 7,80 (d, J = 9,1 Hz, 1 H), 7,72 (s, 1 H), 7,56 (dd, J = 8,8, 1,8 Hz, 1 H), 7,37 (d, J = 9,1 Hz, 1 H), 7,32 (d, J = 5,7 Hz, 1 H), 5,18 (q, J = 6,7 Hz, 1H), 4,60- 4,54 (m, 1 H), 4,28 (t, J = 8,8 Hz, 1 H), 4,19 (dd, J = 9,1, 3,0 Hz, 1 H), 3,99 (s, 3H), 1,72 (br s, 1H), 1,61 (d, J = 7,1 Hz, 3 H), 0,39 (br d, J = 6,6 Hz, 3 H), 0,43 (br d, J = 6,1 Hz, 3 H)	HRMS (B) *m/z* 485.1184 (M + H)+
85: (*S*) - 3 - (2 - ((*R*) - 1 - (4- fluorofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,09 (d, J = 5,9 Hz, 1H), 7,38- 7,33 (m, 3H), 7,04- 6,98 (m, 2 H), 4,96 (q, J = 6,7 Hz, 1 H), 4,48 (br s , 1 H), 4,35- 4,25 (m, 2 H), 2,64 (dtd, J = 14, 7,1, 3,5 Hz, 1 H), 1,50 (d, J = 6,6 Hz, 3 H), 0,98 (d, J = 7,1 Hz, 3 H), 0,85 (d, J = 7,0 Hz, 3 H)	HRMS (B) *m/z* 345.1725 (M + H)+
86: (S)- 4- isopropil- 3- (2 - ((R) - 1 - (2 - (trifluorometil) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,12 (d, J = 5,8 Hz, 1 H), 7,77 (d, J = 8,1 Hz, 1 H), 7,66 (d, J = 8,1 Hz, 1 H), 7,60 (t, J = 7,6 Hz, 1 H), 7,42- 7,36 (m, 2 H), 5,58 (q, J = 6,7 Hz, 1 H), 4,70 (dt, J = 7,8, 3,7 Hz, 1H), 4,38- 4,31 (m, 2 H), 2,58 (dtd, J = 14, 7,0, 3,8 Hz, 1 H), 1,50 (d, J = 6,9 Hz, 3 H), 0,98 (d, J = 7,0 Hz, 3 H), 0,85 (d, J = 6,9 Hz, 3 H)	HRMS (B) *m/z* 395.1706 (M + H)+
87: (*R*)- 4- metil- 3- (2 - ((*S*) - 1 - (Naftalen- 2- il) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona		HRMS (B) *m/z* 425.1967 (M + H)+
88: (*S*) - 3 - (2 - ((*S*) - 1 - (4- fluorofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,12 (d, J = 5,8 Hz, 1H), 7,35- 7,31 (m, 3H), 7,03- 6,97 (m, 2 H), 5,03 (q, J = 7,1 Hz, 1H), 4,66- 4,63 (br m, 1 H), 4,35- 4,27 (m, 2 H), 1,85 (br s, 1H), 1,49 (d, J = 7,0 Hz, 3 H), 0,71 (br s, 3 H), 0,60 (br s, 3 H)	HRMS (B) *m/z* 345.1724 (M + H)+
89: (*R*)- 4- metil- 4- fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin-	($CDCl_3$) 8,12 (d, J = 5,8 Hz, 1 H), 7,43 (d, J = 5,8 Hz, 1 H) 7,32- 7,20 (m, 8 H), 6,99 (br s, 2 H), 5,20 (br s, 1 H), 4,33 (br	HRMS (B) *m/z* 375.1822

4- il) oxazolidin- 2- ona	s, 1H), 4,32 - 4. 27 (m, 2 H), 2,20 (s, 3H), 1,41 (d, J = 6,8 Hz, 3 H)	(M + H)+
90: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (2- metoxifenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 1 H), 7,33 (d, J = 5,8 Hz, 3 H), 7.20- 7.16 (m, 2 H), 6,95 (d, J = 8,1 Hz, 1 H), 6,86 - 6,82 (m, 1 H), 5,28 (q, J = 7,1 Hz, 1 H), 4,63 (br s, 1H), 4,35- 4,26 (m, 2 H), 3,87 (s, 3H), 1,86 (br s, 1H), 1,46 (d, J = 6,9 Hz, 3 H), 0,69 (br s, 3 H), 0,56 (br s, 3 H)	HRMS (B) *m/z* 357.1924 (M + H)+
91: (*S*) - 3 - (2 - (1 - (naftalen- 2- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,08 (d, J = 5,8 Hz, 1H), 7,82- 7,78 (m, 4 H), 7,52 (dd, J = 8,6, 1,5 Hz, 1H), 7,45- 7,38 (m, 2 H), 7,29 (d, J = 5,8 Hz, 1 H), 5,23 (q, J = 6,9 Hz, 1H), 4,46- 4,33 (m, 2 H), 4.21 - 4.15 (m, 1 H), 3,93- 3,86 (m, 1 H), 1,61 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 335.1509 (M + H)+
92: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (3- metoxifenil) etilamino)- 6- metilpirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 15,12 (br s, 1H), 9,23 (br s, 1H), 7,67- 7,56 (m, 1 H), 7,24 (dd, J = 8, 8 Hz, 1H), 6,92- 6,72 (m, 3 H), 5,04- 4,86 (m, 1 H), 4,72- 4,51 (m, 1 H), 4,42- 4,25 (m, 2 H), 3,81 (s, 3H), 2,56 (s, 3 H), 1,90- 1,76 (m, 1 H), 1,64 (br s, 3 H), 0,73 (d, J = 8 Hz, 3 H), 0,64 (d, J = 8 Hz, 3 H)	HRMS (B) *m/z* 371.2082 (M + H)+
93: (*S*)- 4- isopropil- 3- (6- metil- 2- ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 7,57- 7,19 (m, 6 H), 5,05- 4,86 (m, 1 H), 4,63- 4,09 (m, 3 H), 2,561 / 2,49 (2 xs, 3H), 1,91- 1,70 (m, 1 H), 1,62 / 1,54 (2 xd, 3H), 0,75 - 0,45 (m, 6 H)	HRMS (B) *m/z* 341.1982 (M + H)+
94: (*S*) - 3 - (2 - (((*S*)- 3- metilbutan- 2- il) amino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	(DMSO- d_6) 8,11 (d, *J* = 5,5 Hz, 1H), 7,39- 7,32 (m, 2 H), 7.31- 7.19 (m, 4 H), 6,95- 6,82 (m, 1 H), 5,83- 5,73 (m, 1 H), 4,82 (t, *J* . = 8,5 Hz, 1 H), 4,15 (br s, 1H), 1,37- 1,21 (m, 1 H), 0,97 (d, *J* = 7,0 Hz, 3 H), 0,58 (br s., 3 H), 0,47 (br s., 3 H)	HRMS (B) *m/z* 327.1822 (M + H)+
95: (*S*) - 5,5- Dimetil- 3- (2 - (((*S*)- 3- metilbutan- 2- il) amino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	(DMSO- d_6) 8,10 (d, *J* = 5,5 Hz, 1H), 7,39- 7,32 (m, 2 H), 7.31- 7.23 (m, 2 H), 7,18 (br s, 1H), 6,93- 6,79 (m, 1 H), 5,43 (s, 1 H), 1,62 (s, 3H), 1.30- 1.14 (m, 1 H), 0,96 (d, *J* = 6,5 Hz, 3 H), 0,90 (s, 3H), 0,54 (d, *J* = 5,0 Hz, 3 H), 0,43 (d, *J* = 5,0 Hz, 3 H)	HRMS (B) *m/z* 355.2123 (M + H)+
96: 3 - (2 - (((3R, 5R, 7R)- adamantan- 1- ilmetil) amino) pirimidin- 4- il) oxazolidin- 2- ona	(DMSO- d_6) 8,11 (br s, 1H), 7,15 (br s, 1H), 4,52- 4,36 (m, 2 H), 4,09 (br s, 2 H), 3,03 (br s, 2 H), 1,92 (br s, 3 H), 1,74- 1,31 (m, 12 H)	HRMS (B) *m/z* 329.1971 (M + H)+
97: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (4 - (trifluorometil) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,14 (d, J = 5,8 Hz, 1 H), 7,59 (d, J = 8,1 Hz, 2 H), 7,51 (d, J = 8,1 Hz, 2 H), 7,36 (d, J = 5,8 Hz, 1 H), 5,08 (q, J = 6,9 Hz, 1 H), 4,59 (br s, 1H), 4,33- 4,25 (m, 2 H), 1,57 (br s, 1H), 1,54 (d, J = 7,1 Hz, 3 H), 0,60 (br s, 3 H), 0,53 (br s, 3 H)	HRMS (B) *m/z* 395.1686 (M + H)+

98: 3 - ((*S*) - 1 - (4 - ((*S*)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- ilamino) etil) benzonitrilo	8,14 (d, J = 5,8 Hz, 1H), 7,69- 7,65 (m, 2 H), 7,58- 7,56 (m, 1 H), 7,48 (t, J = 7,7 Hz, 1 H), 7,37 (d, J = 5,8 Hz, 1 H), 5,09 (q, J = 7,1 Hz, 1 H), 4,64 (br s, 1H), 4,35- 4,27 (m, 2 H), 1,74 (br s, 1 H), 1,52 (d, J = 7,1 Hz, 3 H), 0,71 (br s, 3 H), 0,60 (br s, 3 H)	HRMS (B) *m/z* 352.1764 (M + H)+
99: (*S*) - 3 - (2 - ((*S*) - 1 - (3- clorofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,14 (d, J = 5,8 Hz, 1 H), 7,36 (d, J = 5,8 Hz, 1 H), 7,32 (br s, 1H), 7.29- 7.23 (m, 2 H), 7.20- 7.17 (m , 1 H), 5,02 (q, J = 6,9 Hz, 1 H), 4,63 (br s, 1H), 4,34- 4,27 (m, 2 H), 1,82 (br s, 1H), 1,50 (d, J = 7,1 Hz, 3 H), 0,70 (br s, 3 H), 0,59 (br s, 3 H)	HRMS (B) *m/z* 361.1424 (M + H)+
100: (4*R*) - 5,5- Dimetil- 4- fenil- 3- (2 - (1 - (4 - (piperidin- 1- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,07 (d, J = 5,8 Hz, 0,5 H), 8,06 (d, J = 5,8 Hz, 0,5 H), 7,41- 7,37 (m, 2 H), 7,34- 7,26 (m, 2 H), 7.19- 7.14 (m, 3 H), 6,95- 6,89 (m, 2 H), 6,81- 6,78 (m, 1 H), 5,46 (s, 0,5 H), 5,25 (s, 0,5 H), 4,73- 4,68 (m, 0,5 H), 4,60- 4,55 (m, 0,5 H), 3.12 a 3.7 (m, 4 H), 1,73- 1,68 (m, 4 H), 1,65 (s, 1,5 H), 1,61- 1,57 (m, 2 H), 1,54 (s, 1,5 H), 1,41 (d, J = 6,9 Hz, 1,5 H), 1,14 (d, J = 6,9 Hz, 1,5 H), 0,99 (d, J = 4,7 Hz, 3 H)	HRMS (B) *m/z* 472.2715 (M + H)+
101: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (2 - (trifluorometil) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,15 (d, J = 5,8 Hz, 1 H), 7,74 (d, J = 8,1 Hz, 1 H), 7,69 (d, J = 8,1 Hz, 1 H), 7,58 (t, J = 7,6 Hz, 1 H), 7,42- 7,35 (m, 2 H), 5,35 (q, J = 6,6 Hz, 1 H), 4,65 (dt, J = 8,0, 3,8 Hz, 1H), 4,35- 4,26 (m, 2 H), 1,76 (br s, 1H), 1,52 (d, J = 6,6 Hz, 3 H), 0,64 (br d, J = 5,5 Hz, 3 H), 0,58 (br d, J = 6,3 Hz, 3 H)	HRMS (B) *m/z* 395.1682 (M + H)+
102: 4,4- dimetil- 3- (2 - (1 - (1- fenil- 1H- pirazol- 4- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,22 (d, J = 5,8 Hz, 1 H), 7,87 (s, 1H), 7,69- 7,65 (m, 3H), 7,48- 7,43 (m, 2 H), 7,35- 7,28 (m, 2 H), 5,34 (br s, 1H), 5.24- 5.17 (m, 1 H), 4.9- 4.5 (m, 2 H), 1,74 (s, 3H), 1,64 (d, J = 7,1 Hz, 3 H), 1,58 (s, 3 H)	HRMS (B) *m/z* 379.1890 (M + H)+
103: (*S*) - 3 - (2 - (((3*S*, 5*S*, 7*S*)- adamantan- 1- ilmetil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO- d_6) 8,13 (d, *J* = 5,5 Hz, 1 H), 7,20 (br s., 1 H), 7,17 (d, *J* = 5,5 Hz, 1H), 4,69- 4,63 (m, 1 H), 4,44- 4,33 (m, 2 H), 3,11- 2,85 (m, 2 H), 2,54 (br s, 1H), 1,92 (br . s, 3 H), 1,70 - . 1,53 (m, 6 H), 1,47 (br s, 6 H), 0,93 (d, *J* = 7,0 Hz, 3 H), 0,78 (d, *J* = 6,5 Hz, 3 H);	HRMS (B) *m/z* 371.2448 (M + H)+
104: (*S*) - 3 - (2 - (((*S*)- 1- ciclohexiletil) amino) pirimidin- 4- il) - 5,5- dimetil- 4- feniloxazolidin- 2- ona	(DMSO- d_6) 8,09 (d, *J* = 5,5 Hz, 1H), 7,40- 7,32 (m, 2 H), 7,32- 7,23 (m, 3 H), 6,83 (d, *J* = 9,0 Hz, 1 H), 5,42 (s, 1 H), 3,36 (br s, 1H), 1,72- 1,23 (m, 9 H), 1,02- 0,82 (m, 10 H), 0,62 (s, 1 H), 0,20 - 0,04 (m, 1 H)	HRMS (B) *m/z* 395.2446 (M + H)+

105: (*S*) - 3 - (2 - (((*S*)- 1-ciclohexiletil) amino) pirimidin- 4- il)- 4-isopropiloxazolidin- 2-ona	(DMSO- d_6) 8,13 (d, *J* = 5,8 Hz, 1 H), 7.19 - 7.9 (m, 2 H), 4,68 (br s, 1H), 4,41-4,33 (m, 2 H), 3,77 (br s, 1H), 2,47 (br s , 1 H), 1,76- 1,58 (m, 5 H), 1,43- 1,35 (m, 1 H), 1.15 - 1.4 (m, 6 H), 0,97 - 0,88 (m, 5 H), 0,77 (d, *J* = 6,8 Hz, 3 H);	HRMS (B) *m/z* 333.2288 (M + H)+
106: (4*S*)- 4- isopropil- 3-(2 - ((1- fenoxipropan- 2-il) amino) pirimidin- 4- il) oxazolidin- 2- ona	(DMSO- d_6) 8,19 (d, *J* = 5,6 Hz, 1 H), 7.30 - 7.24 (m, 3 H), 7,18 (br s, 1H), 6,96- 6,85 (m, 3H), 4,70- 4,52 (m, 1 H), 4,39- 4,19 (m, 3H), 4,12- 4,00 (m, 1 H), 3,92- 3,78 (m, 1 H), 2,46 (br s, 1H), 1.29-1.21 (m, 3H), 0,93- 0,58 (m, 6 H)	HRMS (B) *m/z* 357.1921 (M + H)+
107: (S) - 3 - (2 - (((R)- 1-ciclohexiletil) amino) pirimidin- 4- il) - 5,5-dimetil- 4-feniloxazolidin- 2- ona	(DMSO- d_6) 8,09 (d, *J* = 5,6 Hz, 1H), 7,38- 7,12 (m, 6 H), 6,71 (br s, 1H), 5,36 (s, 1H), 1,77- 1,56 (m, 9 H), 1.31 a 1.5 (m , 4 H), 0,92 (s, 6 H), 0,48 (br s., 2 H)	HRMS (B) *m/z* 395.2440 (M + H)+
108: (*S*) - 3 - (5- cloro- 2-((*S*) - 1 - (2- naftalen- il) etilamino) pirimidin- 4-il)- 4- isopropiloxazolidin-2- ona	($CDCl_3$) 8,29 (s, 1H), 7,84- 7,74 (m, 4 H), 7,49- 7,43 (m, 3 H), 5,76 (br s, 1H), 5.17- 5.10 (m, 1 H), 4,39- 4,30 (m, 1 H), 4,31 (t, J = 8,1 Hz, 1 H), 4.9- 4.5 (m, 1 H), 1,66 (d, J = 7,0 Hz, 3H), 1,40- 1,30 (m, 1 H), 0,52 (d, J = 6,1 Hz, 3 H), 0,27 (br s, 3 H)	HRMS (B) *m/z* 411.1588 (M + H)+
109: 4 - ((*S*) - 1 - (4 - ((*S*)-4- isopropil- 2-oxooxazolidin- 3- il) pirimidin- 2- ilamino) etil) benzonitrilo	8,14 (d, J = 5,8 Hz, 1H), 7,68- 7,66 (m, 2 H), 7,52 (d, J = 8,1 Hz, 3 H), 7,36 (d, J = 5,9 Hz, 1 H), 5,08 (q, J = 7,1 Hz, 1 H), 4,61 (br s, 1H), 4,34- 4,26 (m, 2 H), 1,60 (br s, 1H), 1,52 (d, J = 7,1 Hz, 3 H), 0,65 (br s, 3 H), 0,58 (br s, 3 H)	HRMS (B) *m/z* 352.1775 (M + H)+
110: (*S*) - 4,4- Dimetil- 3-(2 - (1 - (naftalen- 1- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,10 (d, J = 5,8 Hz, 1 H), 8,01 (d, J = 8,6 Hz, 1H), 7,81- 7,78 (m, 1 H), 7,66 (d, J = 8,1 Hz, 1 H), 7,52 (d, J = 6,6 Hz, 1H), 7,48- 7,39 (m, 2 H), 7,36- 7,32 (m, 1 H), 7.19- 7.18 (m, 1 H), 5,66 (br s, 2 H), 3,78- 3,69 (m, 2 H), 1,65 (s, 3H), 1,64 (s, 3H), 1,35 (br s, 3 H)	HRMS (B) *m/z* 363.1822 (M + H)+
111: (*R*) - 3 - (2 - ((*S*) - 1 - (4- fluorofenil) etilamino) pirimidin- 4- il) - 5,5-dimetil- 4-feniloxazolidin- 2- ona	8,09 (d, J = 5,7 Hz, 1H), 7,41- 7,07 (m, 10 H), 5,21 (s, 3H), 4,96 (q, J = 7,1 Hz, 1 H), 1,50 (s, 3 H), 1,24 (d, J = 7,1 Hz, 3 H), 0,98 (s, 3 H)	HRMS (B) *m/z* 407,188 (M + H)+
112: 4 - (1 - (4 - ((*S*)- 4-isopropil- 2-oxooxazolidin- 3- il) pirimidin- 2- ilamino) etil)bencenosulfonamida	8,13 (d, J = 5,8 Hz, 0,5 H), 8,11 (d, J = 5,8 Hz, 0,5 H), 7,85- 7,80 (m, 2 H), 7,51 (d, J = 8,6 Hz, 1 H), 7,49 (d, J = 8,6 Hz, 1 H), 7,36 (d, J = 5,7 Hz, 0,5 H), 7,35 (d, J = 5,7 Hz, 0,5 H), 5,09 (q, J = 6,9 Hz, 0,5 H) , 5,03- 4,97 (br m, 0,5 H), 4,61 (br s, 0,5 H), 4,33- 4,24 (m, 2,5 H), 2,66- 2,58 (m, 0,5 H), 1,62 (br s, 0,5 H), 1,532 (d, J	HRMS (B) *m/z* 406.1553 (M + H)+

	= 7,1 Hz, 1,5 H), 1,527 (d, J = 7,1 Hz, 1,5 H), 0,98 (d, J = 7,0 Hz, 1,5 H), 0,84 (d, J = 7,0 Hz, 1,5 H), 0,67 (br s, 1,5 H), 0,56 (br s, 1,5 H)	
113: (*S*) - 3 - (2 - ((*S*) - 1 - (4- hidroxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 1 H), 7,33 (d, J = 5,8 Hz, 1 H), 7,12 (d, J 8,1 Hz, 2H), 6,72- 6,68 (m, 2 H), 4,95 (q, J = 6,9 Hz, 1H), 4,69- 4,65 (m, 1 H), 4,35- 4,28 (m, 2 H), 1,47 (d, J = 7,1 Hz, 3 H), 0,75 (br s, 3 H), 0,62 (br s, 3 H)	HRMS (B) *m/z* 343.1776 (M + H)+
114: (*S*) - 3 - (2 - (1- ciclohexiletilamino) pirimidin- 4- il) - 4,4- dimetiloxazolidin- 2- ona	($CDCl_3$) 8,14 (d, J = 5,8 Hz, 1 H), 7,24 (d, J = 5,8 Hz, 1 H), 5,08 (br s, 1H), 4,10 (s, 2 H), 3,87 (q, J = 7,0 Hz, 1H), 1,83- 1,68 (m, 6 H), 1,75 (s, 3H), 1,74 (s, 3H), 1,48 (dddd, J = 12, 8,7, 5,7, 2,8 Hz, 1 H), 1.28 a 1.3 (m, 4 H), 1,17 (d, J = 6,8 Hz, 3 H)	HRMS (B) *m/z* 319.2132 (M + H)+
115: (*S*) - 3 - (5- fluoro- 2- ((*S*) - 1 - (2- naftalen- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	($CDCl_3$) 8,15 (d, J = 3,5 Hz, 1H), 7,83- 7,72 (m, 4 H), 7,49- 7,42 (m, 3 H), 5.6- 5.3 (m, 1 H), 4,35- 4,28 (m, 2 H), 4.10 a 4.8 (m, 1 H), 1,65 (d, J = 7,0 Hz, 3H), 1,33- 1,26 (m, 1 H), 0,38 (br s, 3 H), 0,14 (br s, 3 H)	HRMS (B) *m/z* 395.1884 (M + H)+
116: (*S*) - 3 - (5- cloro- 2- ((*S*)- 1- feniletilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO- d6) 8,39- 8,31 (m, 2 H), 7,35- 7,32 (m, 2 H), 7,28 (t, J = 7,8 Hz, 2 H), 7,17 (t, J = 7,8 Hz, 1 H) , 4,89 - 4,82 (m, 1 H), 4,49- 4,45 (m, 2 H), 4,16 (br s, 1H), 1,42 (d, J = 7,0 Hz, 3 H), 1,24 (br s, 1H), 0,86 hasta 0,78 (m, 3 H), 0,48 (br s, 3 H)	HRMS (B) *m/z* 361.1431 (M + H)+
117: (*S*) - 3 - (2 - ((*S*) - 1 - (4- bromo- 3 ,5- dimetoxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,16 (d, J = 5,8 Hz, 1 H), 7,36 (d, J = 5,8 Hz, 1 H), 6,64 (s, 2H), 5,00- 4,95 (m, 1 H), 4,58 (br s, 1 H), 4,33- 4,23 (m, 2 H), 3,79 (s, 6 H), 1,54 (d, J = 7,0 Hz, 3 H), 0,55 (br s, 6 H)	HRMS (B) *m/z* 465.1134 (M + H)+
118: (4*S*) - 3 - (2 - (1 - (3,4- dimetoxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,12 (d, J = 5,8 Hz, 0,5 H), 8,10 (d, J = 5,8 Hz, 0,5 H), 7,35- 7,32 (m, 1 H), 6,97- 6,85 (m, 3H), 5,00- 4,91 (m, 1 H), 4,65 (br s, 0,5 H), 4,55 (br s, 0,5 H), 4,36- 4,27 (m, 2 H), 3,80- 3,79 (m, 6 H), 2,69- 2,61 (m, 0,5 H), 1,87 (br s, 0,5 H), 1,50 (d, J = 7,1 Hz, 3 H), 1,00 (d, J = 7,1 Hz, 1,5 H), 0,86 (d, J = 7,0 Hz, 1,5 H), 0,69 (br s, 1,5 H), 0,60 (br s, 1,5 H)	HRMS (B) *m/z* 387.2035 (M + H)+
119: (*S*) - 3 - (2 - (1 - (6- metoxinaftalen- 2- il) etilamino) pirimidin- 4- il) - 4,4- dimetiloxazolidin- 2- ona	($CDCl_3$) 8,09 (d, J = 5,8 Hz, 1H), 7,64- 7,59 (m, 3 H), 7,36 (dd, J = 8,3, 1,8 Hz, 1 H), 7.20- 7.18 (m, 1 H) , 7.7 a 7.3 (m, 2 H), 5,56 (br s, 1 H), 5.7- 5.3 (br m, 1 H), 3,91- 3,82 (m, 5 H), 1,61 (s, 3H), 1,56 (d, J = 6,8 Hz, 3 H), 0,97 (br s, 3 H)	HRMS (B) *m/z* 393.1925 (M + H)+

120: (*S*) - 5,5- Dimetil- 3- (2 - ((*S*) - 1 - (Naftalen- 2- il) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,09 (d, J = 5,8 Hz, 1H), 7,81- 7,79 (m, 1 H), 7,74- 7,68 (m, 2 H), 7,52 (br s, 1H), 7,46- 7,41 (m, 3 H), 7,18 (br s, 1H), 7,02 (br s, 2 H), 6,99 (s, 3H), 5,43 (s, 1 H), 5,02 (q, 6,6 Hz, 1 H), 1,62 (s , 3 H), 1,53 (d, J = 6,6 Hz, 3 H), 0,93 (s, 3 H)	HRMS (B) *m/z* 439.2131 (M + H)+
121: (*S*) - 3 - (2 - ((*S*) - 1 - (4- bromofenil) etilamino) pirimidin- 4- il) - 5,5- dimetil- 4- feniloxazolidin- 2- ona	8,08 (d, J = 5,8 Hz, 1 H), 7,44 (d, J = 5,8 Hz, 1 H), 7.29- 7.24 (m, 5 H), 7,06 (br s, 2 H), 6,92 (br s, 2 H), 5,44 (s, 1H), 4,88- 4,84 (m, 1 H), 1,63 (s, 3H), 1,42 (d, J = 7,1 Hz, 3 H), 0,95 (s, 3 H)	HRMS (B) *m/z* 467.1088 (M + H)+
122: (*S*) - 3 - (2 - ((*S*) - 1 - (3- metoxifenil) etilamino) pirimidin- 4- il) - 5,5- dimetil- 4- feniloxazolidin- 2- ona	8,07 (d, J = 5,8 Hz, 1 H), 7,42 (d, J = 5,8 Hz, 1 H), 7.28- 7.21 (m, 3 H), 7.11 - 7.8 (m, 3 H), 6,72 (dd, J = 8,3, 1,8 Hz, 1 H), 6,66 (br s, 1H), 6,62 (br s, 1H), 5,46 (s, 1H), 4,80- 4,74 (m, 1 H), 3,73 (s , 3 H), 1,64 (s, 3H), 1,42 (d, J = 7,1 Hz, 3 H), 0,98 (s, 3 H)	HRMS (B) *m/z* 419.2067 (M + H)+
123: (*S*) - 3 - (2 - ((*S*) - 1 - (4- fluoro- 3- metoxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,14 (d, J = 6,6 Hz, 1 H), 7,57 (d, J = 6,6 Hz, 1H), 7,08- 6,99 (m, 2 H), 6,88 (ddd, J = 8,5, 4,2, 2,0 Hz, 1 H), 5,07 (q, J = 7,1 Hz, 1 H), 4,68 (dt, J = 7,8, 3,7 Hz, 1H), 4,40- 4,32 (m, 2 H), 3,86 (s, 3H), 1,99 (br s, 1 H), 1,57 (d, J = 7,1 Hz, 3 H), 0,75 (d, J = 7,1 Hz, 3 H), 0,66 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 375.1824 (M + H)+
124: (*S*) - 3 - (2 - ((*S*) - 1 - (4- bromofenil) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,10 (d, J = 5,8 Hz, 1 H), 7,39 (d, J = 5,8 Hz, 1 H), 7.29- 7.26 (m, 2 H), 7.25- 7.21 (m, 3 H), 7,12 (dd, J = 6,3, 2,8 Hz, 2 H), 6,96 (d, J = 8,6 Hz, 2 H), 5,80 (dd, J = 8,6, 3,5 Hz, 1 H), 4,87 (q, J = 7,1 Hz, 1 H), 4,79 (t, J = 8,6 Hz, 1 H), 4,20 (dd, J = 8,6, 3,5 Hz, 1 H), 1,43 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 439.0763 (M + H)+
125: (4*S*)- 4- isopropil- 3- (2 - (1 (- (3- morfolinofenil) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona	8,215 (d, J = 6,1 Hz, 0,5 H), 8,212 (d, J = 6,1 Hz, 0,5 H), 7,52 (t, J = 7,1 Hz, 2 H), 7,46 (dd, J = 5,8, 3,8 Hz, 1 H), 7,43- 7,34 (m, 3 H), 5,86 (qd, J = 8,2, 4,0 Hz, 1H), 4,83- 4,75 (m, 1 H), 4,42- 4,33 (m, 2 H), 2,62 (dtd, J = 14, 7,0, 3,8 Hz, 0,5 H), 2,28 (br s, 0,5 H), 1,02 (d, J = 7,1 Hz, 1,5 H), 0,91 (d, J = 7,1 Hz, 1,5 H) , 0,88 (d, J = 7,11 Hz, 1,5 H), 0,73 (d, J = 7,1 Hz, 1,5 H)	HRMS (B) *m/z* 412.2342 (M + H)+
126: (*R*) - 3 - (2 - ((*S*) - 1 - (6- metoxinaftalen- 2- il) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,10 (d, J = 5,6 Hz, 1 H), 7,69 (d, J = 9,1 Hz, 1 H), 7,72 (d, J = 8,6 Hz, 1 H), 7,62 (s, 1 H), 7,44- 7,29 (m, 7 H), 7,20 (d, J = 2,5 Hz, 1 H), 7,11 (dd, J = 9,1, 2,5 Hz, 1 H), 5,55 (dd, J = 8,8, 3,8 Hz, 1 H), 4,80 (q, J = 7,1 Hz, 1 H), 4,69 (t, J = 8,6 Hz, 1 H), 4,16 (dd, J = 8,6, 4,0 Hz, 1 H), 3,90	HRMS (B) *m/z* 441.1929 (M + H)+

	(s, 3H), 1,28 (d, J = 7,1 Hz, 3 H)	
127: (*S*) - 4,4- Dimetil- 3- (2 - (1 - (naftalen- 2- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,20 (d, J = 5,8 Hz, 1H), 7,84- 7,79 (m, 4 H), 7,51- 7,43 (m, 3 H), 7,29 (d, J = 5,8 Hz, 1 H), 5,65 (br s, 1H), 5.19- 5.16 (br m, 1 H), 3,98 (d, J = 8,1 Hz, 1 H), 3,91 (d, J = 8,1 Hz, 1 H), 1,70 (s, 3 H), 1,66 (d, J = 6,9 Hz, 3 H), 1,02 (br s, 3 H)	HRMS (B) *m/z* 363.1819 (M + H)+
128: 4,4- dimetil- 3- (2 - (1 - (4 - (piperidin- 1- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,17 (d, J = 5,8 Hz, 1 H), 7.26- 7.22 (m, 3 H), 6,91 (d, J = 8,6 Hz, 2 H), 5,39 (br s, 1H), 5,01 - 4,94 (m, 1H), 4,04- 3,99 (m, 2 H), 3.14- 3.12 (m, 4 H), 1,75- 1,69 (m, 8 H), 1,61- 1,57 (m, 2 H), 1,55 (d, J = 7,1 Hz, 3H), 1,34- 1,29 (br m, 2 H)	HRMS (B) *m/z* 396.2396 (M + H)+
129: (*S*) - 3 - (2 - ((*S*) - 1 - (3- metoxifenil) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,09 (d, J = 5,8 Hz, 1 H), 7,36 (d, J = 5,8 Hz, 1 H), 7.26- 7.16 (m, 5 H), 7,11 (t, J = 7,8 Hz, 3 H), 6,74 - 6,66 (m, 3 H), 5,81 (dd, J = 8,6, 3,5 Hz, 1H), 4,86- 4,79 (m, 2 H), 4,23 (dd, J = 8,8, 3,8 Hz, 1 H), 3,73 (s, 3 H), 1,44 (d, J 7,1 Hz, 3 H)	HRMS (B) *m/z* 391.1771 (M + H)+
130: (4*S*)- 3- (2- (1- (2,3- dihidrobenzo[b][1,4]dioxi n- 6- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,11 (d, J = 5,8 Hz, 0,5 H), 8,09 (d, J = 5,8 Hz, 0,5 H), 7,34- 7,33 (m, 1 H), 6,81- 6,71 (m, 3H), 4,93- 4,88 (m, 1 H), 4,65 (br s, 0,5 H), 4,52 (br s, 0,5 H), 4,36- 4,27 (m, 2 H), 4.20- 4.17 (m, 4 H), 2,66 (dtd, J = 14, 6,9, 3,5 Hz, 0,5 H), 1,99 (br s, 0,5 H), 1,456 (d, J = 7,1 Hz, 1,5 H), 1,454 (d, J = 7,1 Hz, 1,5 H), 1,00 (d, J = 7,1 Hz, 1,5 H), 0,85 (d, J = 7,1 Hz, 1,5 H), 0,75 (br s, 1,5 H), 0,63 (br s, 1,5 H)	HRMS (B) *m/z* 385.1854 (M + H)+
131: (4*S*)- 4- isopropil- 3- (2 - (1 - (piridin- 3- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,545 (d, J = 6,1 Hz, 0,5 H), 8,540 (d, J = 6,1 Hz, 0,5 H), 8,39 (dt, J = 4,9, 1,6 Hz, 1 H), 8,13 (dd, J = 11, 5,7 Hz, 1 H), 7,86- 7,80 (m, 1 H), 7,40- 7,36 (m, 2 H), 5,12 (q, J = 7,1 Hz, 0,5 H), 5,02 (m, 0,5 H), 4,65 (br s, 0,5 H), 4,42 (br s, 0,5 H), 4,35- 4,25 (m, 2 H), 2,67- 2,62 (m, 0,5 H), 1,76 (br s, 0,5 H), 1,56 (d, J = 7,1 Hz, 1,5 H), 1,55 (d, J = 7,1 Hz, 1,5 H), 0,99 (d, J = 7,1 Hz, 1,5 H), 0,85 (d, J = 7,1 Hz, 1,5 H), 0,70 (br s , 1,5 H), 0,60 (br s, 1,5 H)	HRMS (B) *m/z* 328.1771 (M + H)+
132: (*S*)- 4- bencil- 3- (2 - (ciclopropilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,17 (d, *J*= 5,5 Hz, 1 H), 7,46 (d, *J*= 6,0 Hz, 1H), 7,32- 7,18 (m, 4 H), 7,15 (d, *J*= 7,0 Hz, 2H), 5,04- 4,91 (m, 1 H) 5,39 (br s, 1H), 4.25- 4.11 (m, 2 H), 3,51 (d, *J*= 13,0 Hz, 1 H), 2,80 (dd, *J*= 13,3, 9,79 Hz, 1 H), 2,76- 2,69 (m, 1 H), 0,84 a 0,71 (m, 2 H), 0,60 a 0,47 (m, 2 H)	HRMS (B) *m/z* 311.1515 (M + H)+
133: (*S*)- 4- bencil- 3- (2 -	($CDCl_3$) 8,18 (d, *J*= 5,5 Hz, 1 H), 7,48 (d,	HRMS (B)

(ciclohexilamino) pirimidin- 4- il) oxazolidin- 2- ona	*J*= 6,0 Hz, 1H), 7,42- 7,31 (m, 3 H), 7,26 (d, *J*= 7,0 Hz, 2 H), 5,56 (br s, 1H), 5,02 (ddd, *J*= 9,9, 3,6, 3,5 Hz, 1H), 4,33- 4,22 (m, 2 H), 3,96- 3,83 (m, 1 H), 3,53 (d, *J*= 12,6 Hz, 1 H), 2,85 (dd, *J*= 13,3, 9,8 Hz, 1H), 1,89- 1,75 (m, 2 H), 2.16 a 2.5 (m, 2 H), 1,73- 1,63 (m, 1 H), 1,52- 1,26 (m, 7 H)	*m/z* 353.1979 (M + H)+
134: (*S*)- 4- bencil- 3- (2 - (bencilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,17 (d, *J*= 5,8 Hz, 1 H), 7,38 (d, *J*= 5,8 Hz, 1H), 7,36- 7,30 (m, 2 H), 7.30- 7.11 (m, 6 H), 7,02 (br s, 2 H), 4,95 (br s, 1H), 4,76- 4,65 (m, 1 H), 4,65- 4,55 (m, 1 H), 4,30 (t, *J*= 8,4 Hz, 1 H), 4.26- 4.18 (m, 1 H), 3,05 (br s, 1H), 2,84 (br s, 1 H)	HRMS (B) *m/z* 361.1669 (M + H)+
135: (*S*)- 4- bencil- 3- (2 - (((*R*)- 1- feniletil) amino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,22 (d, *J*= 5,5 Hz, 1 H), 7,48 (d, *J*= 5,5 Hz, 1H), 7,42- 7,29 (m, 8 H), 7,19 (d, *J*= 7,0 Hz, 2 H), 5,62 (br s, 1H), 5,15 (t, *J*= 6,8 Hz, 1 H), 4,77 (br s, 1H), 4.25- 4.16 (m, 2 H), 3,45 (dd, *J*= 13,8, 3,3 Hz, 1 H), 2,94 (dd, *J*= 13,6, 9,0 Hz, 1 H), 1,61 (d, *J*= 7,0 Hz, 3 H)	HRMS (B) *m/z* 375.1817 (M + H)+
136: (4*S*) - 3 - (2 - (1 - (1,3- dimetil- 1H- pirazol- 4- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,14 (d, J = 5,8 Hz, 0,5 H), 8,13 (d, J = 5,8 Hz, 0,5 H), 7,42 (s, 0,5 H), 7,35 (s, 0,5 H), 7,35 (d, J = 5,7 Hz , 0,5 H), 7,34 (d, J = 5,8 Hz, 0,5 H), 5,10 - 5.00 (m, 1 H), 4,75 (q, J = 7,8, 4,0 Hz, 1H), 4,41- 4,32 (m, 2 H), 3,76 (s, 1,5 H), 3,74 (s, 1,5 H), 2,64- 2,57 (m, 0,5 H), 2,41- 2,32 (m, 0,5 H), 2,18 (s, 3 H), 1.493 (d , J = 7,1 Hz, 1,5 H), 1,488 (d, J = 7,1 Hz, 1,5 H), 0,97 (d, J = 7,1 Hz, 1,5 H), 0,88 (d, J = 7,1 Hz, 3 H), 0,78 (d, J = 7,1 Hz, 1,5 H)	HRMS (B) *m/z* 345.2038 (M + H)+
137: (*S*) - 3 - [2 - ((*S*) - 1,3- Dimetil- butilamino)- pirimidin- 4- il] - 5,5- dimetil- 4- fenil- oxazolidin- 2- ona	(DMSO- d_6) 8,10 (m, 1 H), 7,34 (m, 2 H), 7,26 (m, 3 H), 7,17 (br s, 1H), 6,83 (s, 1 H), 5,39 (s, 1 H), 1,61 (s, 3H), 1,39 (s, 1 H), 1,26 (s, 1 H), 1,02 (m, 4 H), 0,90 (s, 3H), 0,81 (s, 1 H), 0,71 (s, 3 H), 0,41 (s, 3 H)	HRMS (B) *m/z* 369.2297 (M + H)+
138: (*S*) - 3 - [2 - ((*S*)- 2- hidroxi- 1- metil- etilamino)- pirimidin- 4- il] - 5,5- dimetil- 4- fenil- oxazolidin- 2- ona	(DMSO- d_6) 8,14 (d, *J* = 5,8 Hz, 1 H), 7,17 (d, *J* = 5,8 Hz, 1 H), 7,03 (br s, 1H), 4,67 (br s, 1H), 4,42- 4,34 (m, 2 H), 3,96 (br s, 1H), 2,46 (m, 1 H), 1,63 (m, 1 H), 1,47 (m, 1 H), 1,21 (m, 1 H), 1,09 (d, *J* = 6,3 Hz, 3 H), 0,89 (d, *J* = 7,3 Hz, 3 H), 0,87 (d, *J* = 6,5 Hz, 3 H), 0,84 (d, *J* = 6,5 Hz, 3 H), 0,77 (d, *J* = 6,8 Hz, 3 H)	HRMS (B) *m/z* 307.2141 (M + H)+
139: (*S*) - 4,4- Dimetil- 3- (2 - (1- feniletilamino) pirimidin- 4- il)	($CDCl_3$) 8,08 (d, J = 5,8 Hz, 1 H), 7.27- 7.20 (m, 4 H), 7,17 (d, J = 5,6 Hz, 1 H), 7.15- 7.11 (m, 1 H), 5,42 (br s, 1H), 4,94-	HRMS (B) *m/z* 313.1668

oxazolidin- 2- ona	4,87 (m, 1 H), 3,92- 3,86 (m, 2 H), 1,58 (s, 3H), 1,47 (d, J = 6,9 Hz, 3 H), 1,06 (br s, 3 H)	(M + H)+
140: (*S*) - 3 - (2 - ((*S*) - 1 - (4- fluorofenil) etilamino) pirimidin- 4- il)- 4- metil- 4- feniloxazolidin- 2- ona	($CDCl_3$) 8,17 (d, J = 5,8 Hz, 1H), 7,45- 7,31 (m, 4 H), 7.28- 7.24 (m, 2 H), 7.9- 7.6 (m, 2 H), 7,01- 6,95 (m, 2 H), 5,21 (br s, 1H), 4,20 (s, 2 H), 4,13 (br s, 1H), 1,65 (br s, 3 H), 1,13 (d, J = 6,8 Hz, 3 H)	HRMS (B) *m/z* 393.1729 (M + H)+
141: (4*S*)- 4- metil- 4- fenil- 3- (2 - (1 - (4 - (piperidin- 1- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,14 (d, J = 5,8 Hz, 0,35 H), 8,12 (d, J = 5,8 Hz, 0,65 H), 7,42- 7,27 (m, 6 H), 7,04 (d, J = 8,6 Hz, 0,65 H), 6,91- 6,82 (m, 3,35 H), 5,16 (br s, 0,35 H), 5,02 (br s, 0,65 H), 4,30 (s, 1,3 H), 4,22 (s, 0,7 H), 4,19 (br s , 1 H), 3.16- 3.13 (m, 4 H), 2,20 (s, 1,95 H), 1,79- 1,70 (br m, 5,05 H), 1,62- 1,56 (m, 2 H), 1,37 (d, J = 6,8 Hz, 1,95 H), 1,06 (d, J = 6,3 Hz, 1,05 H)	HRMS (B) *m/z* 458.2551 (M + H)+
142: (*S*)- 4- bencil- 3- (2 - (((*S*)- 1- feniletil) amino) pirimidin- 4- il) oxazolidin- 2- ona	8,15 (d, *J*= 5,77 Hz, 1 H), 7,40- 7,30 (m, 3 H), 7.25- 7.13 (m, 5 H), 7,07 (t, *J*= 7,0 Hz, 1 H), 6,91 (br s, 2 H), 5,13 (q, *J*= 7,0 Hz, 1 H), 5,01 (t, *J*= 7,4 Hz, 1 H), 4,34 (t, *J*= 8,5 Hz, 1 H), 4,20 (dd, *J*= 8,9, 2,4 Hz, 1 H), 2,64 (br s, 1H), 2,47 (br s, 1H), 1,54 (d, *J*= 7,3 Hz, 3 H)	HRMS (B) *m/z* 375.1817 (M + H)+
143: (*R*)- 4- bencil- 3- (2 - (ciclopropilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,19 (d, *J*= 5,0 Hz, 1 H), 7,62 (d, *J*= 6,0 Hz, 1H), 7,41- 7,29 (m, 4 H), 7.26- 7.19 (m, 2 H), 6,42 (br s, 1H), 5,07 (t, *J*= 8,3 Hz, 1 H), 4.30- 4.24 (m, 2 H), 3,60 (d, *J*= 12,6 Hz, 1 H), 2,97- 2,79 (m, 2 H), 0,95 a 0,81 (m, 2 H), 0,75 - 0,62 (m, 2 H)	HRMS (B) *m/z* 311.1516 (M + H)+
144: (*R*)- 4- bencil- 3- (2 - (cicloheptilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,12 (d, *J*= 6,0 Hz, 1H), 7,36- 7,28 (m, 3 H), 7.28- 7.19 (m, 3 H), 5.15- 5.5 (m, 1 H), 4,37 (t, *J*= 8,5 Hz, 1 H), 4,30 - . 4,24 (m, 1 H), 4,04 (br s, 1H), 3,09 (dd, *J*= 13,6, 8,0 Hz, 1H), 2,11- 1,94 (m, 2 H), 1,78- 1,48 (m, 11 H)	HRMS (B) *m/z* 367.2134 (M + H)+
145: (*R*)- 4- bencil- 3- (2 - (ciclohexilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,18 (d, *J*= 5,0 Hz, 1 H), 7,48 (d, *J*= 6,0 Hz, 1H), 7,42- 7,29 (m, 3 H), 7,26 (d, *J*= 7,0 Hz, 2 H), 5,55 (br s, 1H), 5,10- 4,94 (m, 1 H), 4,33- 4,22 (m, 2 H), 3,96- 3,82 (m, 1 H), 3,53 (d , *J*= 12,1 Hz, 1 H), 2,85 (dd, *J*= 13,3, 9,8 Hz, 1 H), 2.22 - 2.1 (m, 2 H), 1,81 (td, *J*= 13,6, 4,0 Hz, 2 H), 1,68 (dd, *J*= 9,0, 3,5 Hz, 1H), 1,51- 1,22 (m, 6 H)	HRMS (B) *m/z* 353.1981 (M + H)+
146: (*R*)- 4- bencil- 3- (2 - (bencilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,17 (d, *J*= 5,8 Hz, 1 H), 7,38 (d, *J*= 6,0 Hz, 1H), 7,35- 7,30 (m, 2 H), 7.29 a 7.18 (m, 5 H), 7,15 (t, *J*= 7,3 Hz, 1 H), 7,02	HRMS (B) *m/z* 361.1659

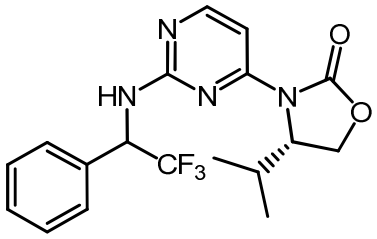
	(br s, 2 H), 4,95 (br s, 1H), 4,75- 4,65 (m, 1 H), 4,65- 4,56 (m, 1 H), 4,30 (t, *J*= 8,5 Hz, 1 H), 4.27- 4.20 (m, 1 H), 3,05 (br s, 1H), 2,82 (br s, 1 H)	(M + H)+
147: (*R*)- 4- bencil- 3- (2 - (((*R*)- 1- feniletil) amino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,21 (d, *J*= 5,5 Hz, 1 H), 7,50 (d, *J*= 6,0 Hz, 1H), 7,43- 7,29 (m, 5 H), 7,28 - . 7,12 (m, 4 H), 7,00 (br s, 2 H), 5,97 (br s, 1H), 5,17 (t , *J*= 6,8 Hz, 1H), 5,03- 4,89 (m, 1 H), 4,28 (t, *J*= 8,5 Hz, 1 H), 4,19 (dd, *J*= 9,0, 3,0 Hz, 1 H), 2,97 (br s, 1H), 2,53 (br s, 1H), 1,63 (d, *J*= 7,0 Hz, 3 H)	HRMS (B) *m/z* 375.1822 (M + H)+
148: (*R*)- 4- bencil- 3- (2 - (((*S*)- 1- feniletil) amino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,21 (d, *J*= 6,0 Hz, 1 H), 7,49 (d, *J*= 5,5 Hz, 1H), 7,44- 7,29 (m, 8 H), 7,19 (d, *J*= 6,5 Hz, 2 H), 5,69 (br s, 1 H),, 5,15 (t, *J*= 7,0 Hz, 1 H), 4,76 (br s, 1H), 4.24- 4.16 (m, 2 H), 3,45 (dd, *J*= 13,8, 3,3 Hz, 1 H), 2,94 (dd, *J*= 13,6, 9,5 Hz, 1 H), 1,61 (d, *J*= 7,0 Hz, 3 H)	HRMS (B) *m/z* 375.1816 (M + H)+
149: (*S*)- 4- isopropil- 3- (5- metil- 2- ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,13 (s, 1H), 7,35- 7,28 (m, 4 H), 7.24- 7.20 (m, 1 H), 5,73 (br s, 1H), 5,00- 4,92 (m, 1 H), 4,59- 4,51 (m, 1 H), 4,38 (t, J = 8,8 Hz, 1 H), 4,12 (t, J = 8,8 Hz, 1 H), 2,14 (s, 3H), 1,55 (d, J = 6,5 Hz, 3 H), 1,44 (br s, 1H), 0,59 (d, J = 6,5 Hz, 3 H), 0,53 (d, J = 5,0 Hz, 3 H)	HRMS (B) *m/z* 341.1974 (M + H)+
150: (*S*) - 3 - (5- fluoro- 2- ((*S*)- 1- feniletilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	($CDCl_3$) 8,18 (d, J = 3,0 Hz, 1H), 7,32- 7,28 (m, 4 H), 7.25- 7.20 (m, 1 H), 5,64 (br s, 1H), 4,92- 4,87 (m , 1 H), 4,47- 4,40 (m, 1 H), 4,39 (t, J = 8,5 Hz, 1 H), 4,17 (t, J = 8,6 Hz, 1 H), 1,86 (br s, 1 H), 1,54 (d, J = 7,0 Hz, 3 H), 0,68 a 0,56 (m, 6 H)	HRMS (B) *m/z* 345.1724 (M + H)+
151: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (3- metoxifenil) etilamino)- 5- metilpirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,11 (s, 1 H), 7.24- 7.20 (m, 1 H), 6,94- 6,89 (m, 2H), 6,76 (dd, J = 7,6 Hz, J = 2,5 Hz, 1 H), 5,99 (br s, 1H), 4,97 (quintuplete, J = 6,8 Hz, 1 H), 4,58 (td, J = 8,8 Hz, J = 5,1 Hz, 1 H), 4,39 (t, J = 8,8 Hz, 1 H) , 4,13 (t, J = 8,6 Hz, 1 H), 3,80 (s, 3H), 2,16 (s, 3H), 1,62- 1,56 (m, 1 H), 1,57 (d, J = 6,5 Hz, 3 H), 0,64 (d, J = 7,1 Hz, 3 H), 0,59 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 371.2083 (M + H)+
152: (*S*)- 4- isopropil- 3- (5- metil- 2- ((*S*) - 1 - (Naftalen- 2- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) 8,13 (s, 1H), 7,81- 7,74 (m, 4 H), 7,48- 7,40 (m, 3 H), 5,87 (br s, 1H), 5.17- 5.10 (m, 1 H), 4,42 (td, J = 8,7 Hz, J = 4,8 Hz, 1 H), 4,29 (t, J = 8,8 Hz, 1 H), 4,02 (t, J = 8,6 Hz, 1 H), 2,13 (s, 3 H), 1,64 (d, J = 7,0 Hz, 3H), 1,35- 1,28 (m, 1 H), 0,42 (d, J = 7,1 Hz, 3 H), 0,17 (d, J = 7,0 Hz, 3 H)	HRMS (B) *m/z* 391.2135 (M + H)+

153: (*S*) - 3 - (5- fluoro- 2- ((*S*) - 1 - (3- metoxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	($CDCl_3$) 8,16 (d, J = 2,5 Hz, 1 H), 7,23 (t, J = 7,8 Hz, 1H), 6,91- 6,83 (m, 2 H), 6,78- 6,74 (m, 1 H), 6,05 (br s, 1H), 4,86 (br s, 1H), 4,49- 4,38 (m, 2 H), 4,19 (t, J = 7,8 Hz, 1 H), 3,79 (s, 3H), 1,54 (d, J = 8,0 Hz, 3H), 1,32- 1,25 (m, 1 H), 0,66- 0,58 (m, 6 H)	HR- MS m/z (M + H)+
154: (*S*)- 4- metil- 3- (2 - ((*S*) - 1 - (Naftalen- 2- il) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	($CDCl_3$) 8,17 (d, J = 5,8 Hz, 1H), 7,84- 7,78 (m, 3 H), 7,55 (s, 1H), 7,51- 7,43 (m, 5 H), 7,39- 7,36 (m, 1 H), 7.29 - 7.25 (m, 3 H), 5,54 (br s, 1H), 4,31 (br s, 1H), 4.19- 4.12 (m, 2 H), 1,84 (br s, 3 H) , 1,24 (d, J = 6,8 Hz, 3 H)	HRMS (B) *m/z* 425.1972 (M + H)+
155: (*S*) - 3 - (2 - ((*S*) - 1 - (6- metoxinaftalen- 2- il) etilamino) pirimidin- 4- il)- 4- metil- 4- feniloxazolidin- 2- ona	($CDCl_3$) 8,18 (d, J = 5,8 Hz, 1 H), 7,69 (t, J = 7,8 Hz, 2H), 7,47- 7,41 (m, 4 H), 7,38- 7,34 (m, 1 H), 7,28 - 7,23 (m, 3 H), 7.17- 7.13 (m, 2 H), 5,31 (br s, 1H), 4,31 (br s, 1H), 4.19- 4.13 (m, 2 H), 3,94 (s , 3 H), 1,56 (br s, 3 H), 1,20 (d, J = 6,6 Hz, 3 H)	HRMS (B) *m/z* 455.2081 (M + H)+
156: (*S*) - 3 - (2 - ((*S*)- 1- ciclohexiletilamino) pirimidin- 4- il)- 4- metil- 4- feniloxazolidin- 2- ona	($CDCl_3$) 8,11 (d, J = 5,8 Hz, 1H), 7,38- 7,32 (m, 5 H), 7.29- 7.25 (m, 1 H), 4,81 (br s, 1H), 4.31- 4.26 (m , 2 H), 3,16 (br s, 1H), 2,17 (s, 3H), 1,77- 1,57 (m, 6 H), 1.28 a 1.9 (m, 4 H), 0,99 - 0,85 (m, 2 H), 0,55 (br s, 2 H)	HRMS (B) *m/z* 381.2280 (M + H)+
157: (*S*) - 3 - [2 - ((*S*)- 2- hidroxi- 1- metil- etilamino)- pirimidin- 4- il] - 5,5- dimetil- 4- fenil- oxazolidin- 2- ona	(DMSO- d_6) 8,13 (m, 1 H), 7,36 (m, 2 H), 7,29 (m, 3 H), 7,19 (br s, 1H), 6,65 (s, 1 H), 5,44 (s, 1 H), 4,30 (br s, 1 H), 2,95 (br s, 1H), 2,77 (br s, 3 H), 1,61 (s, 3H), 1,25 (s, 1 H), 1,04 (m, 3 H) , 0,92 (s, 3 H)	HRMS (B) *m/z* 343.1778 (M + H)+
158: (*S*) - 5,5- Dimetil- 4- fenil- 3- [2 - ((*S*) - 1,2,2- Trimetil- propilamino)- pirimidin- 4- il]- oxazolidin- 2- ona	(DMSO- d_6) 8,10 (d, *J* = 5,5 Hz, 1H), 7,37- 7,33 (m, 2 H), 7.29- 7.25 (m, 3 H), 7,20 (br s, 1H), 6,75 (d, *J* = 10 Hz, 1 H), 5,42 (s, 1 H), 3,47 (m, 1 H), 1,62 (s, 3H), 0,96 (d, *J* = 6,8 Hz, 3 H), 0,88 (s, 3H), 0,46 (s, 9H)	HRMS (B) *m/z* 369.2277 (M + H)+
159: (*R*) - 3 - (2 - ((*S*) - 1 - (Naftalen- 1- il) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,11 (d, J = 6,1 Hz, 1 H), 8,04 (d, J = 8,6 Hz, 1 H), 7,89 (d, J = 8,1 Hz, 1 H), 7,74 (d, J = 8,1 Hz, 1 H), 7,60- 7,56 (m, 1 H), 7,53- 7,49 (m, 1 H), 7,46- 7,44 (m, 1 H), 7,42- 7,31 (m, 5 H), 7.21- 7.18 (m, 2 H), 5,52 (q, J = 6,9 Hz, 1 H), 5,44 (dd, J = 8,8, 3,8 Hz, 1 H), 4,63 (t, J = 8,7 Hz, 1 H), 4,10 (dd, J = 8,6 , 4,0 Hz, 1 H), 1,33 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 411.1823 (M + H)+
160: (*S*)- 4- isopropil- 3- [2 - ((*S*)1,2,2- trimetil- propilamino)- pirimidin-	(DMSO- d_6) 8,14 (d, *J* = 5,5 Hz, 1 H), 7,16 (d, *J* = 5,5 Hz, 1 H), 7,00 (br s, 1H), 4,73- 4,66 (m, 1 H), 4,41- 4,34 (m, 2 H),	HRMS (B) *m/z* 307.2130

4- il]- oxazolidin- 2- ona	3,92 (br s, 1H), 2,46 (br s, 1 H), 1,05 (d, *J* = 6,8 Hz, 3 H), 0,91 (d, *J* = 7,3 Hz, 3 H), 0,87 (s, 9 H), 0,77 (d, *J* = 6,8 Hz, 3 H)	(M + H)+
161: (*S*) - 3 - [2 - ((*S*)- 1- ciclopropil- etilamino)- pirimidin- 4- il]- 4- isopropil- oxazolidin- 2- ona	(DMSO- d_6) 8,13 (d, *J* = 5,5 Hz, 1 H), 7,17 (d, *J* = 5,5 Hz, 1 H), 7,09 (br s, 1H), 4,67- 4,63 (m, 1 H), 4,37 (m, 2 H), 3,52- 3,43 (m, 1 H), 2,46 (br s, 1 H), 1,19 (d, *J* = 6,8 Hz, 3H), 1,01- 0,93 (m, 1 H), 0,89 (d, *J* = 7,0 Hz, 3 H), 0,77 (d, *J* = 6,8 Hz, 3 H), 0,41 (m, 1 H), 0,33 (m, 1 H), 0,22 (br s, 1H), 0,10 (br s, 1 H)	HRMS (B) *m/z* 291.1812 (M + H)+
162: (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (4- fenoxifenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,13 (d, J = 5,8 Hz, 1H), 7,34- 7,28 (m, 5 H), 7.9- 7.5 (m, 1 H), 6,96- 6,90 (m, 4 H), 5,06 (q, J = 7,1 Hz, 1 H), 4,71- 4,67 (m, 1 H), 4,37- 4,28 (m, 2 H), 2,08 (br s, 1H), 1,52 (d, J = 7,1 Hz, 3 H), 0,76 (d, J = 7,1 Hz, 3 H), 0,67 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 419.2081 (M + H)+
163: (*S*) - 3 - (2 - ((*S*) - 1 - (2,3- dihidro- benzofuran- 5- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,12 (d, J = 5,6 Hz, 1 H), 7,32 (d, J = 5,6 Hz, 1 H), 7,17 (s, 1 H), 7.4- 7.2 (m, 1 H), 6,63 (d, J = 8,1 Hz, 1 H), 4,98 (q, J = 7,1 Hz, 1H), 4,69- 4,65 (m, 1 H), 4,51- 4,47 (m, 2 H), 4,36- 4,27 (m, 2 H), 3.16 a 3.12 (m, 2 H), 2,09 (br s, 1H), 1,48 (d, J = 7,0 Hz, 3 H), 0,75 (d, J = 7,0 Hz, 3 H), 0,65 (d, J = 7,1 Hz, 3 H)	HRMS (B) *m/z* 369.1915 (M + H)+
164: (*S*) - 3 - (2 - ((*S*) - 1 - (4- terc- butilfenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,12 (d, J = 5,8 Hz, 1H), 7,34- 7,31 (m, 3 H), 7.24- 7.21 (m, 2 H), 5,02 (q, J = 7,1 Hz, 1H), 4,66- 4,63 (m, 1 H), 4,35- 4,25 (m, 2 H), 1,95 (br s, 1H), 1,50 (d, J = 7,0 Hz, 3 H), 1,29 (s, 9 H), 0,69 (d, J = 7,0 Hz, 3 H), 0,58 (d, J = 6,9 Hz, 3 H)	HRMS (B) *m/z* 383.2449 (M + H)+
165: (*S*) - 3 - [2 - ((*S*)- 1- ciclopropil- etilamino)- pirimidin- 4- il] - 5,5- dimetil- 4- fenil- oxazolidin- 2- ona	(DMSO- d_6) 8,10 (d, *J* = 5,5 Hz, 1H), 7,37- 7,33 (m, 2 H), 7.30- 7.24 (m, 3 H), 7,15 (br s, 1H), 7,00 (br s, 1H), 5,37 (s, 1 H), 2,82 (br s, 1H), 1,61 (s, 3H), 1,07 (d, *J* = 6,5 Hz, 3 H), 0,89 (s, 3H), 0,65 (br s, 1H), 0,17 (br s, 1H), 0,00 (br s, 1 H), - 0,23 (br s, 1 H), - 0,65 (br s, 1 H)	HRMS (B) *m/z* 353.1974 (M + H)+
166: (*S*) - 3 - (5- fluoro- 2- ((*S*) - 1 - (4- metoxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO- d_6) 8,36 (br s, 1H), 7,95 (br s, 1H), 7,24 (d, J = 8,5 Hz, 2 H), 6,82 (d, J = 9,0 Hz, 2 H), 6,05 (br s, 1 H), 4,77 (br s, 1H), 4,54- 4,45 (m, 2 H), 4,24 (br s, 1H), 3,70 (s, 3H), 1,38 (d, J = 7,0 Hz, 3 H), 1.26- 1.22 (m, 1 H), 0,66 a 0,47 (m, 6 H)	HRMS (B) *m/z* 375.1815 (M + H)+
167: (*R*) - 5,5- Dimetil- 4- fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,08 (d, J = 5,8 Hz, 1H), 7,42- 7,38 (m, 3H), 7,35- 7,27 (m, 5 H), 7.22 a 7.17 (m, 3 H), 5,18 (s, 1 H) , 4,62- 4,57 (m, 1 H), 1,51 (s, 3H), 1,19 (d, J = 7,0 Hz, 3 H), 0,98 (s, 3 H)	HRMS (B) *m/z* 389.1975 (M + H)+

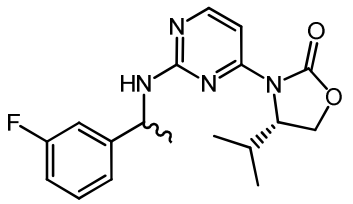
168: (*R*) - 5,5- Dimetil- 3- (2 - ((*S*) - 1 - (Naftalen- 2- il) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,10 (d, J = 5,8 Hz, 1 H), 7,82 (d, J = 8,1 Hz, 3 H), 7,73 (s, 1H), 7,48- 7,33 (m, 7 H), 7,19 (d, J = 7,1 Hz, 2 H), 5,07 (s, 1 H), 4,74 (q, J = 6,6 Hz, 1 H), 1,32 (d, J = 6,9 Hz, 3 H), 1,29 (s, 3H), 0,92 (s, 3 H)	HRMS (B) *m/z* 439.2132 (M + H)+
169: (*R*) - 3 - (2 - ((*S*) - 1 - (4- fluoro- 3- metoxifenil) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	□ 8,10 (d, J = 5,8 Hz, 1H), 7,41- 7,28 (m, 6 H), 7,02- 6,97 (m, 2 H), 6,82 (ddd, J = 8,2, 4,4, 2,0 Hz, 1 H), 5,61 (dd, J = 8,6, 4,0 Hz, 1 H), 4,77 (t, J = 8,6 Hz, 1 H), 4,65 (q, J = 7,1 Hz, 1 H), 4,19 (dd, J = 9,1, 4,0 Hz, 1 H), 3,83 (s, 3H), 1,20 (d, J = 7,9 Hz, 3 H)	HRMS (B) *m/z* 409.1677 (M + H)+

Ejemplo 170: (4*S*)- 4- isopropil- 3- (2 - (2,2,2- trifluoro- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona



Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (163 mg, 0.674 mmol), 2,2,2- trifluoro- 1- feniletanamina (624 mg, 3,56 mmol, 5.3 equiv) y *p*-monohidrato del ácido toluenosulfónico (321 mg, 1.69 mmol, 2.5 equiv) en n- BuOH (3 ml) se calentó a 110 °C durante 2 h y se trató con monohidrato de ácido *p*-Toluenosulfónico adicional (321 mg, 1.69 mmol, 2.5 equiv), luego se calentó a 110 °C durante 1 ½ h. Después de enfriar, la mezcla de reacción sólida se trató con MeCN, se sonicó y se filtró. El filtrado se concentró y se purificó mediante cromatografía en columna de gel de sílice (EtOAc/heptano del 0 al 30%) para proporcionar (4*S*)- 4- isopropil- 3- (2 - (2,2,2- trifluoro- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona (65 mg) con un rendimiento del 25%. ^{1}H RMN (400 MHz, CD_3OD) δ 8,215 (d, J = 6,1 Hz, 0,5 H), 8,212 (d, J = 6,1 Hz, 0,5 H), 7,52 (t, J = 7,1 Hz, 2 H), 7,46 (dd, J = 5,8, 3,8 Hz, 1H), 7,43- 7,34 (m, 3 H), 5,86 (qd, J = 8,2, 4,0 Hz, 1H), 4,83- 4,75 (m, 1 H), 4,42 - 4,33 (m, 2 H), 2,62 (dtd, J = 14, 7,0, 3,8 Hz, 0,5 H), 2,28 (br s, 0,5 H), 1,02 (d, J = 7,1 Hz, 1,5 H), 0,91 (d , J = 7,1 Hz, 1,5 H), 0,88 (d, J = 7,11 Hz, 1,5 H), 0,73 (d, J = 7,1 Hz, 1,5 H); HRMS (B) *m/z* 381.1545 (M + H)+.

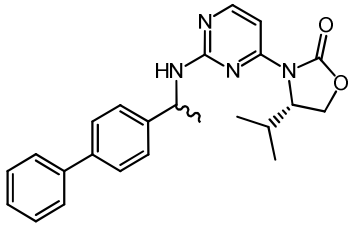
Ejemplos 171 y 172



Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (106 mg, 0.439 mmol) y 1 - (3- fluorofenil) etanamina (196 mg, 1.41 mmoles, 3.21 equiv) en DMSO (1 ml) se calentó a 110 ° C durante 1 ½ h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 10 a 50%) proporcionó (*S*) - 3 - (2 - ((*R*) - 1 - (3- fluorofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (*S*) - 3 - (2 - ((*S*) - 1 - (3- fluorofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

Ejemplo 171 primer producto eluido (28 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,11 (d, J = 5,8 Hz, 1H), 7,36- 7,27 (m, 2 H), 7,16 (d, J = 7,6 Hz, 1 H), 7,07 (dt, J = 10, 2,0 Hz, 1H), 6,92- 6,88 (m, 1 H), 4,98- 4,93 (m, 1 H), 4,42 (br s, 1H), 4,32 (dd, J = 9,1, 2,8 Hz, 1 H), 4,26 (t, J = 8,7 Hz, 1 H), 2,64 (dtd, J = 14, 7,1, 3,5 Hz, 1 H), 1,50 (d, J = 7,0 Hz, 3 H), 0,98 (d, J = 7,1 Hz, 3 H), 0,85 (d, J = 7,0 Hz, 3 H); HRMS (B) *m/z* 345.1729 (M + H)+.
Ejemplo 172 segundo producto eluido (22 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,13 (d, J = 5,7 Hz, 1 H), 7,36 (d, J = 5,8 Hz, 1 H), 7,29 (td, J = 8,1, 6,1 Hz, 1 H), 7,13 (d, J = 7,6 Hz, 1 H), 7.6- 7.4 (m, 1 H), 6,94- 6,87 (m, 1 H), 5,03 (q, J = 7,1 Hz , 1 H), 4,64 (br s, 1H), 4,34- 4,26 (m, 2 H), 1,79 (br s, 1H), 1,50 (d, J = 7,1 Hz, 3 H), 0,70 (br s , 3 H), 0,58 (br s, 3 H); HRMS (B) *m/z* 345.1727 (M + H)+.

Ejemplos 173 y 174

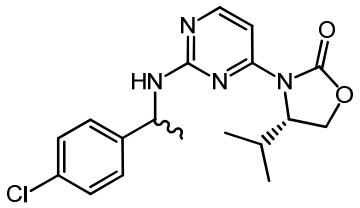


Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (90 mg, 0.37 mmol), *i*Pr$_2$NEt (0.455 ml, 2.61 mmol, 7.0 equiv) y 1 - (bifenil- 4- il) etanamina (87 mg, 0,37 mmol) en DMSO (1 ml) se calentó a 110 °C durante 2 h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 10 al 50%) proporcionó (*S*) - 3 - (2 - ((*R*) - 1 - (Bifenil- 4- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (*S*) - 3 - (2 - ((*S*) - 1 - (Bifenil- 4- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

Ejemplo 173 primer producto eluido (17 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,11 (d, J = 5,8 Hz, 1H), 7,59- 7,54 (m, 4 H), 7,43- 7,28 (m, 6 H) , 5,01 (q, J = 6,8 Hz, 1 H), 4,49 (br s, 1H), 4,32 (dd, J = 9,1, 3,0 Hz, 1 H), 4,26 (t, J = 8,6 Hz, 1 H) , 2,67 (dtd, J = 14, 7,0, 3,5 Hz, 1 H), 1,55 (d, J = 7,1 Hz, 3 H), 1,01 (d, J = 7,1 Hz, 3 H), 0,86 (d, J = 7,0 Hz, 3 H); HRMS (B) *m/z* 403.2141 (M + H)+.

Ejemplo 174 segundo producto eluido (21 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,14 (d, J = 5,8 Hz, 1H), 7,58- 7,52 (m, 4 H), 7,42- 7,28 (m, 6 H) , 5,06 (q, J = 7,1 Hz, 1 H), 4,63 (br s, 1H), 4,34- 4,25 (m, 2 H), 1,79 (br s, 1H), 1,55 (d, J = 7,1 Hz , 3 H), 0,65 (br s, 3 H), 0,53 (br s, 3 H); HRMS (B) *m/z* 403.2139 (M + H)+.

Ejemplos 175 y 176



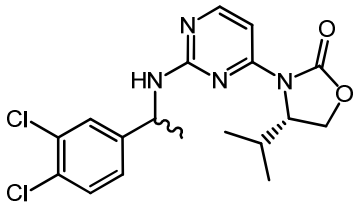
Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- ona- isopropiloxazolidin- 2 (96 mg, 0,40 mmol) y 1 - (4- clorofenil) etanamina (204 mg, 1.31 mmol, 3.3 equiv) en DMSO (1 ml) se calentó a 110 °C durante 3 h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 10 a 50%) proporcionó (*S*) - 3 - (2 - ((*R*) - 1 - (4- clorofenil) etilamino) pirimidin- 4- il)- 4-

isopropiloxazolidin- 2- ona y (*S*) - 3 - (2 - ((*S*) - 1 - (4- clorofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

Ejemplo 175 primer producto eluido (32 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,10 (d, J = 5,8 Hz, 1H), 7,36- 7,28 (m, 5 H), 4,95 (q, J = 6,7 Hz, 1 H), 4,45 (br s, 1H), 4,35- 4,26 (m, 2 H), 2,64 (dtt, J = 11, 7,0, 3,4 Hz, 1 H), 1,50 (d, J = 7,1 Hz, 3 H), 0,98 (d, J = 7,1 Hz, 3 H), 0,85 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 361.1430 (M + H)+.

Ejemplo 176 segundo producto eluido (40 mg) $_1$H RMN (400 MHz, CD_3OD) δ 8,13 (d, J = 5,7 Hz, 1H), 7,36- 7,26 (m, 5 H), 5,00 (q, J = 7,1 Hz, 1 H), 4,62 (br s, 1H), 4,34- 4,26 (m, 2 H), 1,77 (br s, 1H), 1,50 (d, J = 7,1 Hz, 3 H), 0,68 (br s, 3 H), 0,59 (br s, 3 H); HRMS (B) *m/z* 361.1431 (M + H)+.

Ejemplos 177 y 178

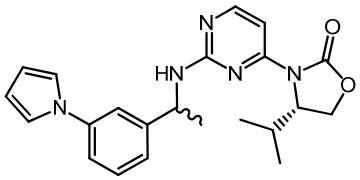


Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (93 mg, 0,38 mmol) y 1 - (3,4- diclorofenil) etanamina (73.1 mg, 0.385 mmol, 1.0 equiv) en DMSO (1 ml) se calentó a 110 °C durante 1 ½ h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 10 a 50%) proporcionó (*S*) - 3 - (2 - ((*R*) - 1 - (3,4- diclorofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (*S*) - 3 - (2 - ((*S*) - 1 - (3,4- diclorofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

Ejemplo 177 primer producto eluido (21 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,12 (d, J = 5,8 Hz, 1 H), 7,50 (d, J = 2,0 Hz, 1 H), 7,44 (d, J = 8,2 Hz, 1 H), 7,37 (d, J = 5,8 Hz, 1 H), 7,28 (dd, J = 8,6, 2,0 Hz, 1H), 4,94- 4,88 (m, 1 H), 4,43 (br s, 1 H), 4,35- 4,26 (m, 2 H), 2,68- 2,60 (m, 1 H), 1,50 (d, J = 7,1 Hz, 3 H), 0,99 (d, J = 7,1 Hz, 3 H), 0,85 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 395.1035 (M + H)+.

Ejemplo 178 segundo producto eluido (28 mg) 1H RMN (400 MHz, CD_3OD) δ 8,15 (d, J = 5,8 Hz, 1H), 7,47- 7,42 (m, 2 H), 7,37 (d, J = 5,8 Hz, 1 H), 7,25 (dd, J = 8,1, 2,0 Hz, 1H), 5,01- 4,96 (m, 1 H), 4,61 (br s, 1H), 4,34- 4,26 (m, 2 H), 1,72 (br s, 1H), 1,50 (d, J = 7,1 Hz, 3 H), 0,67 (br s, 3 H), 0,60 (br s, 3 H); HRMS (B) *m/z* 395.1044 (M + H)+.

Ejemplos 179 y 180

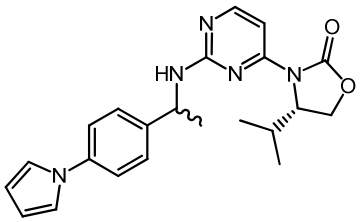


Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (86 mg, 0.36 mmol) y 1 - (3 - (1*H*- Pirrol- 1- il) fenil) etanamina (100 mg, 0.537 mmol, 1.5 equiv) en DMSO (1 ml) se calentó a 110 °C durante 1 ½ h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 10 a 50%) proporcionó (*S*) - 3 - (2 - ((*R*) - 1 - (3 - (1H- pirrol- 1- il) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (*S*) - 3 - (2 - ((*S*) - 1 - (3 - (1H- pirrol- 1- il) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

Ejemplo 179 primer producto eluido (14 mg) ^1H RMN (400 MHz, CD_3OD) δ 8. 11 (d, J = 5,8 Hz, 1 H), 7,45 (t, J = 1,8 Hz, 1H), 7,39- 7,29 (m, 3 H), 7,23 (d, J = 7,6 Hz, 1 H), 7,13 (t, J = 2,0 Hz, 2 H), 6,25 (t, J = 2,1 Hz, 2H), 5,03- 4,97 (m, 1 H), 4,46 (br s, 1H), 4.31- 4.20 (m, 2 H), 2,64 (dtd, J = 14, 7,0, 3,8 Hz, 1 H), 1,56 (d, J = 7,1 Hz, 3 H), 0,95 (d, J = 7,1 Hz, 3 H), 0,84 (d , J = 7,0 Hz, 3 H); HRMS (B) *m/z* 392.2092 (M + H)+.

Ejemplo 180 segundo producto eluido (10 mg) ^1H RMN (400 MHz, CD_3OD) δ 8,14 (d, J = 5,7 Hz, 1 H), 7,42 (br s, 1H), 7,38- 7,28 (m, 3 H), 7,20 (d, J = 7,6 Hz, 1 H), 7,12 (t, J = 2,3 Hz, 2 H), 6,25 (t, J = 2,0 Hz, 2 H), 5,09 (q, J = 6,9 Hz, 1 H), 4,64 (br s, 1H), 4,32- 4,23 (m, 2 H), 1,84 (br s, 1H), 1,55 (d, J = 7,1 Hz, 3 H), 0,54 (br s, 6 H); HRMS (B) *m/z* 392.2090 (M + H)+.

Ejemplos 181 y 182

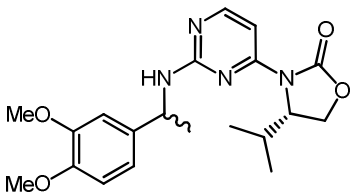


Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (44 mg, 0.18 mmol) y 1 - (4 - (1*H*- Pirrol- 1- il) fenil) etanamina (33.9 mg, 0.182 mmoles, 1 equiv) en DMSO (1 ml) se calentó a 110 °C durante 2 h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 10 a 50%) proporcionó (*S*) - 3 - (2 - ((*R*) - 1 - (4 - (1H- pirrol- 1- il) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (*S*) - 3 - (2 - ((*S*) - 1 - (4 - (1H- pirrol- 1- il) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

Ejemplo 181 primer producto eluido (18 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,11 (d, J = 5,8 Hz, 1H), 7,44- 7,39 (m, 4 H), 7,35 (d, J = 5,9 Hz, 1 H), 7,13 (t, J = 2,2 Hz, 2 H), 6,24 (t, J = 2,0 Hz, 2H), 5,02- 4,96 (m, 1 H), 4,49 (br s, 1H), 4,34 - 4,25 (m, 2 H), 2,66 (dtd, J = 14, 7,0, 3,3 Hz, 1 H), 1,53 (d, J = 7,1 Hz, 3 H), 1,00 (d, J = 7,1 Hz, 3 H), 0,86 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 392.2089 (M + H)+.

Ejemplo 182 segundo producto eluido (9 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,14 (d, J = 5,8 Hz, 1 H), 7,39 (s, 4 H), 7,35 (d, J = 5,9 Hz, 1 H), 7,12 (t, J = 2,2 Hz, 2 H), 6,25 (t, J = 2,0 Hz, 2 H), 5,05 (q, J = 7,1 Hz, 1 H), 4,64 (br s, 1 H), 4,34- 4,26 (m, 2 H), 1,87 (br s, 1H), 1,53 (d, J = 7,1 Hz, 3 H), 0,68 (br s, 3 H), 0,57 (br s, 3 H); HRMS (B) *m/z* 392.2082 (M + H)+.

Ejemplos 183 y 184



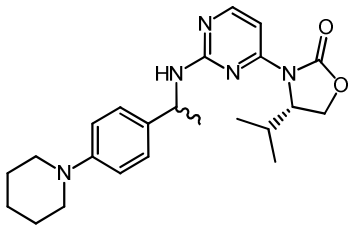
Una mezcla de (4*S*) - 3 - (2 - ((1 - (3,4- dimetoxifenil) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (ejemplo 118) Se separó en una columna (AS- H 4,6 x 100

mm) utilizando 30% *i*PrOH en CO_2 para proporcionar (*S*) - 3 - (2 - ((*R*) - 1 - (3,4- dimetoxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (*S*) - 3 - (2 - ((*S*) - 1 - (3,4- dimetoxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

Ejemplo 183 primer producto eluido (13 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,11 (d, J = 5,8 Hz, 1 H), 7,33 (d, J = 5,8 Hz, 1 H), 6,97 (br d, J = 1,5 Hz, 1H), 6,92- 6,88 (m, 2 H), 4,96 (q, J = 6,7 Hz, 1H), 4,61- 4,55 (m, 1 H), 4,35- 4,28 (m, 2 H) , 3,803 (s, 3 H), 3,800 (s, 3 H), 2,63 (dtd, J = 14, 7,0, 3,5 Hz, 1 H), 1,51 (d, J = 7,1 Hz, 3 H), 0,99 (d , J = 7,1 Hz, 3 H), 0,86 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 387.2031 (M + H)+.

Ejemplo 184 segundo producto eluido (10 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,13 (d, J = 5,8 Hz, 1 H), 7,32 (d, J = 5,7 Hz, 1 H), 6,94 (br d, J = 1,1 Hz, 1H), 6,89- 6,84 (m, 2 H), 4,99 (q, J = 7,1 Hz, 1H), 4,67- 4,63 (m, 1 H), 4,36- 4,26 (m, 2 H) , 3,79 (s, 6 H), 2,01 (br s, 1H), 1,51 (d, J = 7,1 Hz, 3 H), 0,71 (d, J = 7,1 Hz, 3 H), 0,63 (d, J = 7,0 Hz, 3 H); HRMS (B) *m/z* 387.2029 (M + H)+.

Ejemplos 185 y 186



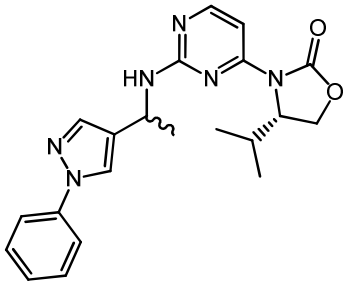
Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (93 mg, 0.38 mmol) y 1 - (4 - (piperidin- 1- il) fenil) etanamina (410 mg, 2.01 mmoles , 5.2 equiv) en DMSO (1 ml) se calentó a 110 °C durante 2 h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/Heptano 10 a 100%) proporcionó (4*S*)- 4- isopropil- 3- (2 - (4 - - (1 ((piperidin- 1- il) fenil) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona (57 mg) con un rendimiento del 36% . Una mezcla de (4*S*)- 4- isopropil- 3- (2 - (1 - (4 - (piperidin- 1- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona Se separó en una columna (AD- H 4.6 x 100 mm) utilizando 5 a 55% MeOH con 0.2% CO_2 en Et_2NH para proporcionar (*S*)- 4- isopropil- 3- (2 - ((*R*) - 1 - (4 - (piperidin- 1- il) fenil) etilamino) pirimidin- 4- il)

oxazolidin- 2- ona y (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (4 - (piperidin- 1- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona.

Ejemplo 185 primer producto eluido (16 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,10 (d, J = 5,8 Hz, 1 H), 7,31 (d, J = 5,8 Hz, 1 H), 7.24- 7.20 (m, 2 H), 6,94- 6,91 (m, 2 H), 4,93 (q, J = 7,1 Hz, 1H), 4,58- 4,54 (m, 1 H), 4,34- 4,27 (m, 2 H), 3.11 - 3.8 (m, 4 H), 2,63 (dtd, J = 14, 7,1, 3,5 Hz, 1H), 1,73- 1,67 (m, 4 H), 1,60- 1,54 (m, 2 H), 1,49 (d, J = 7,1 Hz, 3 H), 0,98 (d, J = 7,1 Hz, 3 H), 0,86 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 410.2555 (M + H)+.

Ejemplo 186 segundo producto eluido (16 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,11 (d, J = 5,8 Hz, 1 H), 7,31 (d, J = 5,8 Hz, 1 H), 7.20- 7.16 (m, 2 H), 6,93- 6,89 (m, 2 H), 4,98 (q, J = 6,9 Hz, 1H), 4,69- 4,65 (m, 1 H), 4,36- 4,26 (m, 2 H), 3.10 a 3.7 (m, 4 H), 2,07 (br s, 1H), 1,73- 1,67 (m, J = 4 H), 1,60- 1,54 (m, 2 H), 1,48 (d, J = 7,1 Hz, 3 H) , 0,75 (d, J = 7,0 Hz, 3 H), 0,63 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 410.2556 (M + H)+.

Ejemplos 187 y 188



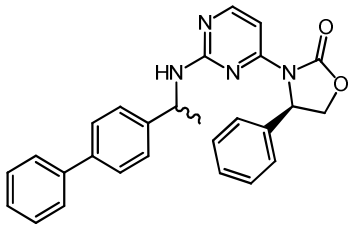
Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (96 mg, 0.40 mmol) y 1 - (1- fenil- 1*H*- Pirazol- 4- il) etanamina (387 mg, 2.97 mmol, 5.2 equiv) en DMSO (1,5 ml) se calentó a 110 °C durante 1 ½ h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 20 al 80%) proporcionó (*S*)- 4- isopropil- 3- (2 - ((*R*) - 1 - (1- fenil- 1H- pirazol- 4- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona y (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (1- fenil- 1H- pirazol- 4- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona.

Ejemplo 187 primer producto eluido (13 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,16 (d, J = 5,8 Hz, 1 H), 8,10 (s, 1H), 7,70- 7,66 (m, 3 H), 7,48 - 7,43 (m, 2 H), 7,37 (d, J = 5,7 Hz,

1H), 7,32- 7,28 (m, 1 H), 5,20 (q, J = 6,6 Hz, 1 H), 4,75 (dt, J = 7,7, 4,0 Hz, 1H), 4,40- 4,33 (m, 2 H), 2,61 (dtt, J = 11, 7,0, 3,6 Hz, 1 H), 1,60 (d, J = 6,9 Hz, 3 H), 0,96 (d, J = 7,1 Hz, 3 H), 0,87 (d, J = 6,9 Hz, 3 H); HRMS (B) *m/z* 393.2029 (M + H)+.

Ejemplo 188 segundo producto eluido (11 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,17 (d, J = 5,8 Hz, 1 H), 8,03 (s, 1H), 7,68- 7,62 (m, 3 H), 7,48 - 7,43 (m, 2 H), 7,37 (d, J = 5,8 Hz, 1H), 7,32- 7,27 (m, 1 H), 5,19 (q, J = 7,1 Hz, 1 H), 4,74 (dt, J = 8,5, 3,6 Hz, 1H), 4,38- 4,29 (m, 2 H), 2,37- 2,33 (m, 1 H), 1,60 (d, J = 7,1 Hz, 3 H), 0,79 (d, J = 7,1 Hz, 3 H), 0,73 (s, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 393.2039 (M + H)+.

Ejemplos 189 y 190



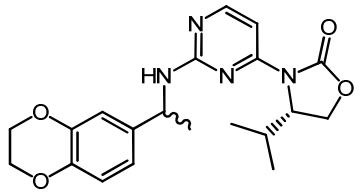
Una solución de (*R*) - 3 - (2- cloropirimidin- 4- il)- 4- feniloxazolidin- 2- ona (97 mg, 0.35 mmol), 1 - (bifenil- 4- il) etanamina (304 mg, 1.30 mmol, 3.7 equiv) y *i*Pr2NEt (0.307 ml, 1.76 mmol, 5.0 equiv) en DMSO (1 ml) se calentó a 110 °C durante 1 ½ h y a 130 ºC durante 20 h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 10 a 50%) proporcionó (*R*) - 3 - (2 - ((*R*) - 1 - (Bifenil- 4- il) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona y (*R*) - 3 - (2 - ((*S*) - 1 - (Bifenil- 4- il) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona.

Ejemplo 189 primer producto eluido (12 mg) $_1$H RMN (400 MHz, CD_3OD) δ 8,10 (d, J = 5,8 Hz, 1H), 7,58- 7,55 (m, 2 H), 7,44- 7,37 (m, 6 H) , 7,33- 7,28 (m, 1 H), 7.24 - 7.14 (m, 6 H), 5,84 (dd, J = 8,6, 3,5 Hz, 1 H), 4,94 (q, J = 6,7 Hz, 1 H), 4,81 (t, J = 8,6 Hz, 1 H), 4,22 (dd, J = 8,8, 3,8 Hz, 1 H), 1,49 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 437.1981 (M + H)+.

Ejemplo 190 segundo producto eluido (11 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,10 (d, J = 5,8 Hz, 1H), 7,60- 7,54 (m, 4 H), 7,44- 7,28 (m, 11 H) , 5,60 (dd, J = 8,6, 4,0 Hz, 1H),

4,77- 4,69 (m, 2 H), 4,19 (dd, J = 8,6, 4,0 Hz, 1 H), 1,25 (d, J = 7,0 Hz, 3 H); HRMS (B) *m/z* 437.1971 (M + H)+.

Ejemplos 191 y 192

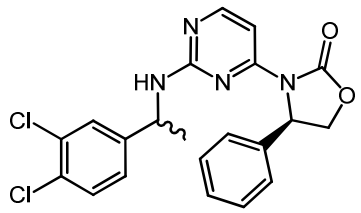


Se separó (4*S*)- 3- (2- (1- (2,3- dihidrobenzo[b][1,4]dioxin- 6- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (Ejemplo 130, 52 mg) en una columna (IA 4.6 x 100 mm) utilizando 40% *i*PrOH en CO_2 para proporcionar (*S*) - 3 - (2 - ((*R*) - 1 - (2,3- dihidrobenzo [b] [1,4] dioxin- 6- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (*S*) - 3 - (2 - ((*S*) - 1 - (2,3- dihidrobenzo [b] [1,4] dioxin- 6- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

Ejemplo 191 primer producto eluido (7 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,10 (d, J = 5,6 Hz, 1H), 7,33- 7,31 (m, 1 H), 6,82- 6,74 (m, 3 H) , 4,88 (q, J = 7,1 Hz, 1H), 4,58- 4,53 (m, 1 H), 4,34- 4,28 (m, 2 H), 4.21- 4.18 (m, 4 H), 2,63 (td, J = 7,1, 3,5 Hz, 1 H), 1,47 (d, J = 7,1 Hz, 3 H), 0,99 (d, J = 7,1 Hz, 3 H), 0,86 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 385.1875 (M + H)+.

Ejemplo 192 segundo producto eluido (19 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,12 (d, J = 5,8 Hz, 1H), 7,33- 7,31 (m, 1 H), 6,78- 6,72 (m, 3 H) , 4,93 (q, J = 6,7 Hz, 1H), 4,68- 4,64 (m, 1 H), 4,36- 4,27 (m, 2 H), 2,08 (br s, 1H), 1,47 (d, J = 7,1 Hz, 3 H), 0,76 (d, J = 7,1 Hz, 3 H), 0,65 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 385.1873 (M + H)+.

Ejemplos 193 y 194



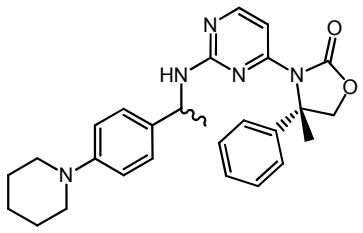
Una solución de (*R*) - 3 - (2- cloropirimidin- 4- il)- 4- feniloxazolidin- 2- ona (83 mg, 0.30 mmol) y 1 - (3,4- diclorofenil) etanamina (260 mg, 1.37 mmol, 4.5 equiv) en DMSO (1.5

ml) se calentó a 110 °C durante 1 ½ h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano 0 a 40%) proporcionó (*R*) - 3 - (2 - ((*R*) - 1 - (3,4- diclorofenil) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona y (*R*) - 3 - (2 - ((*S*) - 1 - (3,4- diclorofenil) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona.

Ejemplo 193 primer producto eluido (13 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,11 (d, J = 5,6 Hz, 1H), 7,44- 7,38 (m, 5 H), 7,35- 7,31 (m, 1 H) , 7.27- 7.25 (m, 2 H), 7,18 (dd, J = 8,3, 2,3 Hz, 1 H), 5,53 (dd, J = 8,8, 3,8 Hz, 1 H), 4,76 (t, J = 8,8 Hz, 1 H), 4,59- 4,53 (m, 1 H), 4,18 (dd, J = 8,8, 4,3 Hz, 1 H), 1,22 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 429.0899 (M + H)+.

Ejemplo 194 segundo producto eluido (26 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,13 (d, J = 5,6 Hz, 1 H), 7,41 (d, J = 6,1 Hz, 1 H), 7.25- 7.18 (m, 5 H), 7.9- 7.6 (m, 2 H), 6,95- 6,93 (m, 1 H), 5,78 (dd, J = 8,6, 3,5 Hz, 1 H), 4,89 (q, J = 6,7 Hz, 1 H), 4,79 (t, J = 8,6 Hz, 1 H), 4,18 (dd, J = 8,8, 3,8 Hz, 1 H), 1,42 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 429.0887 (M + H)+.

Ejemplos 195 y 196

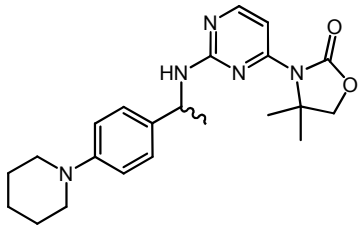


Se separó (4*S*)- 4- metil- 4- fenil- 3- (2 - (1 - (4 - (piperidin- 1- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona (ejemplo 141, 51 mg) en una columna (IA 4.6 x 100 mm) utilizando 45% de MeOH en CO_2 para proporcionar (*S*)- 4- metil- 4- fenil- 3- (2 - ((*S*) - 1 - (4 - (piperidin- 1- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona y (*S*)- 4- metil- 4- fenil- 3- (2 - ((*R*) - 1 - (4 - (piperidin- 1- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona.

Ejemplo 195 producto eluido en primer lugar (21,6 mg) ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,13 (d, J = 5,8 Hz, 1 H), 7,41 (d, J = 5,8 Hz, 1H), 7,36- 7,33 (m, 4 H), 7,32- 7,26 (m, 1 H), 6,88- 6,82 (br m, 4 H), 5,01 (br s, 1 H), 4,30 (s, 2 H), 3.16- 3.13 (m, 4 H), 2,20 (s, 3H), 1,76- 1,57 (br m, 6 H), 1,37 (d, J = 6,7 Hz, 3 H); HRMS (B) *m/z* 458.2558 (M + H)+.

Ejemplo 196 segundo producto eluido (20,6 mg) ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,14 (d, J = 5,8 Hz, 1H), 7,50- 7,27 (m, 6 H), 7,05 (d, J = 8,6 Hz, 2 H), 6,96- 6,92 (br m, 2 H), 5,27 (br s, 1H), 4,22 (s, 2 H), 3.21- 3.13 (m, 4 H), 1,78- 1,76 (br m, 7 H), 1,63- 1,57 (br m, 2 H), 1,07 (d, J = 6,1 Hz, 3 H); HRMS (B) *m/z* 458.2559 (M + H)+.

Ejemplos 197 y 198

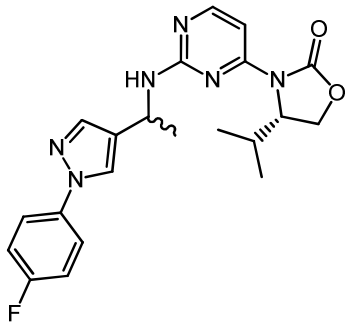


Se separó 4,4- dimetil- 3- (2 - (1 - (4 - (piperidin- 1- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona (ejemplo 183, 70 mg) en un columna (IA 4.6 x 100 mm) utilizando 40% de MeOH en CO_2 para proporcionar (*S*) - 4,4- dimetil- 3- (2 - (1 - (4 - (piperidin- 1- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona y (*R)*- 4,4- dimetil- 3- (2- (1- (4- (piperidin- 1- il)fenil)etilamino)Pirimidin- 4- il) oxazolidin- 2- ona.

Ejemplo 197 primer producto eluido (23.8 mg) ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,17 (br d, J = 5,8 Hz, 1 H), 7.28- 7.23 (m, 3 H), 6,93 (br d, J = 7,7 Hz, 2 H), 5,44 (br s, 1H), 4,97 (br s, 1H), 4,05- 3,99 (m, 2 H), 3.15- 3.12 (m, 4 H), 1,77- 1,70 (m, 8 H), 1,61- 1,54 (m, 5 H), 1,32 (br s, 2 H); HRMS (B) *m/z* 396.2413 (M + H)+.

Ejemplo 198 segundo producto eluido (22,3 mg) ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,17 (br d, J = 5,5 Hz, 1 H), 7.28- 7.23 (m, 3 H), 6,94 (br d, J = 7,5 Hz, 2 H), 5,48 (br s, 1H), 4,97 (br s, 1H), 4,05- 3,99 (m, 2 H), 3.15- 3.12 (m, 4 H), 1,77- 1,70 (m, 8 H), 1,61- 1,54 (m, 5 H), 1,31 (br s, 2 H); HRMS (B) *m/z* 396.2410 (M + H)+.

Ejemplos 199 y 200

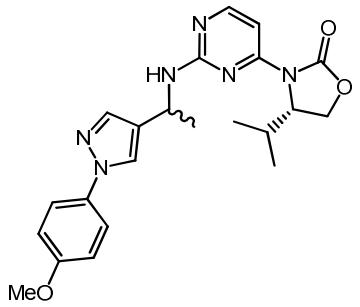


Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (98 mg, 0.41 mmol), 1 - (1 - (4- fluorofenil)- 1H- pirazol- 4- il) etanamina (502 mg, 2.08 mmol, 5.1 equiv) y *i*Pr2NEt (0.637 ml, 3.65 mmol, 9.0 equiv) en DMSO (1.5 ml) se calentó a 110 °C durante 16 h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 20 al 80%) proporcionó (*S*) - 3 - (2 - ((*R*) - 1 - (1 - (4- fluorofenil)- 1H- pirazol- 4- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (*S*) - 3 - (2 - ((*S*) - 1 - (1 - (4- fluorofenil)- 1H- pirazol- 4- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

Ejemplo 199 primer producto eluido (49 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,16 (d, J = 5,8 Hz, 1 H), 8,06 (s, 1H), 7,71- 7,67 (m, 3 H), 7,37 (d, J = 5,9 Hz, 1 H), 7.22- 7.16 (m, 2 H), 5,20 (q, J = 6,6 Hz, 1 H), 4,74 (dt, J = 7,6, 3,8 Hz, 1 H), 4,40- 4,34 (m, 2 H), 2,60 (dtd, J = 14, 7,0, 3,5 Hz, 1 H), 1.59 (d, J = 6,9 Hz, 3 H), 0,96 (d, J = 7,1 Hz, 3 H), 0,87 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 411.1943 (M + H)+.

Ejemplo 200 segundo producto eluido (27 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,17 (d, J = 5,8 Hz, 1 H), 8,00 (s, 1H), 7,69- 7,66 (m, 2 H), 7,61 (s, 1 H), 7,37 (d, J = 5,9 Hz, 1 H), 7.22- 7.16 (m, 2 H), 5,19 (q, J = 6,7 Hz, 1 H), 4,73 (dt, J = 8,1 , 3,5 Hz, 1H), 4,39- 4,30 (m, 2 H), 2,38- 2,31 (m, 1 H), 1,59 (d, J = 6,8 Hz, 3 H), 0,79 (d, J = 7,1 Hz, 3 H), 0,73 (d, J = 7,0 Hz, 3 H); HRMS (B) *m/z* 411.1937 (M + H)+.

Ejemplos 201 y 202

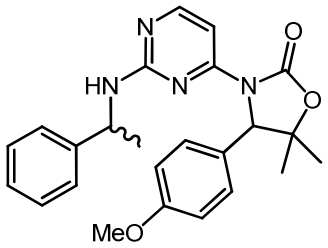


Una solución de (*S*) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (93 mg, 0.38 mmol), 1 - (1 - (4- metoxifenil)- 1H- pirazol- 4- il) etanamina (514 mg, 2.03 mmol, 5.3 equiv) y *i*Pr2NEt (0.605 ml, 3.46 mmol, 9.0 equiv) en DMSO (1.5 ml) se calentó a 110 °C durante 16 h. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano del 10 al 70%) proporcionó (*S*)- 4- isopropil- 3- (2 - ((*R*) - 1 - (1 - (4- metoxifenil)- 1H- pirazol- 4- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona y (*S*)- 4- isopropil- 3- (2 - ((*S*) - 1 - (1 - (4- metoxifenil)- 1H- pirazol- 4- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona.

Ejemplo 201 primer producto eluido (17 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,15 (d, J = 5,8 Hz, 1 H), 7,98 (s, 1 H), 7,63 (s, 1 H), 7,58- 7,54 (m, 2 H), 7,37 (d, J = 5,8 Hz, 1H), 7,03- 6,99 (m, 2 H), 5,19 (q, J = 7,1 Hz, 1 H), 4,75 (dt, J = 7,7 , 4,0 Hz, 1H), 4,40- 4,33 (m, 2 H), 3,83 (s, 3H), 2,61 (dtd, J = 14, 7,1, 3,5 Hz, 1 H), 1,59 (d, J = 7,1 Hz, 3 H), 0,96 (d, J = 7,1 Hz, 3 H), 0,87 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 423.2138 (M + H)+.

Ejemplo 202 segundo producto eluido (18 mg) ^{1}H RMN (400 MHz, CD_3OD) δ 8,16 (d, J = 5,8 Hz, 1 H), 7,91 (s, 1H), 7,58- 7,53 (m, 3 H), 7,37 (d, J = 5,9 Hz, 1H), 7,03- 6,99 (m, 2 H), 5,18 (q, J = 6,7 Hz, 1H), 4,76- 4,72 (m, 1 H), 4,39- 4,30 (m , 2 H), 3,83 (s, 3H), 2,31 (br s, 1H), 1,59 (d, J = 7,1 Hz, 3 H), 0,80 (d, J = 7,1 Hz, 3 H), 0,73 (d, J = 7,1 Hz, 3 H); HRMS (B) *m/z* 423,214 (M + H)+.

Ejemplos 203 y 204

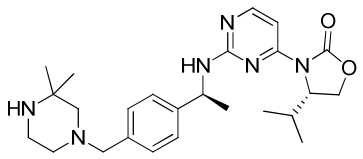


Se separó 4 - (4- metoxifenil) - 5,5- dimetil- 3- (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona (ejemplo 54, 62 mg) en una columna (AD- H de 4.6 x 100 mm) con 30% de MeOH modificado con 0.2% CO_2 en Et_2NH para proporcionar (*S*) - 4 - (4- metoxifenil) - 5,5- dimetil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona y (*R*) - 4 - (4- metoxifenil) - 5,5- dimetil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona.

Ejemplo 203 primer producto eluido (22 mg) ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,12 (br d, J = 5,6 Hz, 1 H), 7,53 (d, J = 5,7 Hz, 1H), 7,37- 7,24 (m , 5 H), 7.8- 7.5 (m, 2 H), 6,92- 6,89 (m, 2 H), 5,47 (br s, 1H), 5,02 (br s, 1H), 4,66 (br s, 1H), 3,83 (s, 3H), 1,50 (s, 3H), 1,28 (br d, J = 6,6 Hz, 3 H), 1,01 (s, 3 H); HRMS (B) *m/z* 419,208 (M + H)+.

Ejemplo 204 segundo producto eluido (22,2 mg) ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,11 (br d, J = 6,1 Hz, 1 H), 7,55 (d, J = 5,8 Hz, 1 H), 7.28- 7.22 (m , 3 H), 7,08 (br s, 2 H), 7,01 (d, J = 8,6 Hz, 2 H), 6,79 (d, J = 8,6 Hz, 2 H), 5,40 (br s, 1H), 5,30 (s, 1 H), 4,83 (br s, 1H), 3,78 (s, 3H), 1,66 (s, 3H), 1,51 (d, J = 6,8 Hz, 3 H), 1,04 (s, 2 H); HRMS (B) *m/z* 419.2083 (M + H)+.

Ejemplo 205

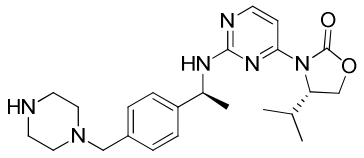


A una solución de 4- (4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzil)- 2,2- dimetilpiperazina- 1- carboxílato de terc- butilo (78 mg, 0.14 mmoles) en DCM (1 ml) se añadió TFA (1 ml, 12 mmol) lentamente a - 78 °C. La reacción se agitó a temperatura ambiente durante 1 h, después se concentró y se diluyó con DCM (10 ml). La solución se agitó con 3 eq. de resina de MP- carbonato (3.28 mmol/g, Biotage) durante 1 h a temperatura ambiente. La resina se separó por filtración y

se lavó (2 x 5 ml) con DCM. El filtrado se concentró y se purificó a través de HPLC para proporcionar (S)- 3- (2- (((S)- 1- (4- ((3,3- dimetilpiperazin- 1- il)metil)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona como un sólido blanco (23 mg, rendimiento del 36%).

^{1}H RMN (400 MHz, MeOD) δ 8,07 (d, J = 5,8 Hz, 1H), 7,30 (d, J = 5,8 Hz, 1H), 7.26- 7.18 (m, 4H), 5,00 (q, J = 6,9 Hz , 1H), 4,62 (br s, 1H), 4,36- 4,16 (m, 2H), 3,36 (s, 2H), 2,81 (br t, J = 5,1 Hz, 2H), 2,30 (br s, 2H), 2,10 (br s, 2H), 1,82 (br s, 1H), 1,45 (d, J = 7,0 Hz, 3H), 1,08 (s, 6H), 0,67 (br s, 3H), 0,52 (br s, 3H); HRMS (B) m/z 453,2969 (M + H)+.

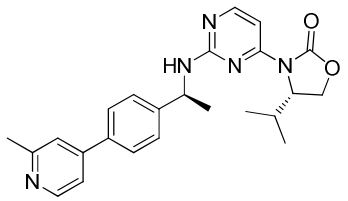
Ejemplo 206



Una mezcla de 4- (4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzil)piperazina- 1- carboxílato de benciclo (190 mg, 0.34 mmol) y Pd- C al 10%- (40 mg, 0.038 mmol) en etanol (3,4 ml) se agitó bajo 1 atmósfera de presión de hidrógeno durante 3 h. La mezcla se filtró y se concentró para proporcionar (S)- 4- isopropil- 3- (2- (((S)- 1- (4- (piperazin- 1- ilmetil)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona como un sólido blanco (97 mg, rendimiento del 67.2%).

^{1}H RMN (400 MHz, MeOD) δ 8,08 (d, J = 5,8 Hz, 1H), 7,30 (d, J = 5,8 Hz, 1H), 7.28- 7.19 (m, 4H), 5,01 (q, J = 7,0 Hz , 1H), 4,63 (br s, 1H), 4,37- 4,14 (m, 2H), 3,44 (s, 2H), 2,78 (t, J = 5,0 Hz, 4H), 2,39 (br s, 4H), 1,89 (br s, 1H), 1,45 (d, J = 7,0 Hz, 3H), 0,68 (br s, 3H), 0,52 (br s, 3H); HRMS (B) m/z 425,2662 (M + H)+.

Ejemplo 207

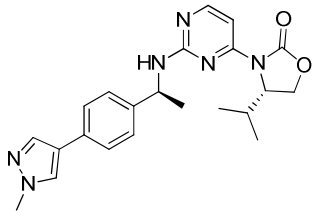


En un vial de microondas de 5 ml de una solución de (S) - 3 - (2 - ((S) - 1 - (4- bromofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (86 mg, 0.21

mmoles), piridin- 4- ilborónico (26 mg, 0.21 mmoles), bicarbonato de sodio (0.21 ml, 0.42 mmol, solución 2 M) en dioxano (1 ml) se burbujeó N_2 durante 3 min y después se añadió $Cl_2Pd(dppf).CH_2Cl_2$ (17 mg, 0.021 mmol). El tubo tapado se calentó a 100 °C durante 16 h. Después de enfriar la mezcla de reacción se diluyó con EtOAc (10 ml) y se lavó con agua (10 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se purificó a través de cromatografía en columna de gel de sílice (EtOAc en heptano 12 a 100%) para proporcionar (S)- 4- isopropil- 3- (2 - (((S) - 1 - (4 - (2- il) fenil) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona como un sólido blanco (27 mg, rendimiento del 30.5%).

^{1}H RMN (400 MHz, MeOD) δ 8,35 (d, J = 5,4 Hz, 1H), 8,08 (d, J = 5,9 Hz, 1H), 7,64-7,60 (m, 2H), 7,49 (br d, J = 1,8 Hz, 1H), 7,43- 7,39 (m, 3H), 7,30 (d, J = 5,8 Hz, 1H), 5,02 (q, J = 6,8 Hz, 1H), 4,55 (br s, 1H), 4.27- 4.18 (m, 2H), 2,52 (s, 3H), 1,65 (br s, 1H), 1,49 (d, J = 7,1 Hz, 3H), 0,55 (br s, 3H), 0,43 (br s, 3H); HRMS (B) m/z 418.2227 (M + H)+.

Ejemplo 208

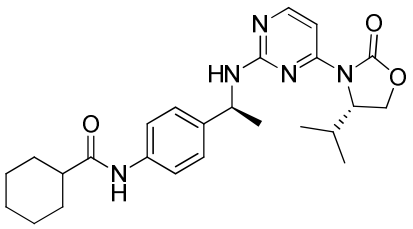


A una solución de 4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il((S)- 1- (4- (1- metil- 1H- pirazol- 4- il)fenil)etil)carbamato de terc- butilo (45 mg, 0.09 mmoles) en DCM (1 ml) se añadió TFA (1 ml, 12 mmol) lentamente a - 78 °C. La reacción se agitó a temperatura ambiente durante 1 h, después se concentró y se diluyó con DCM (10 ml). La solución se lavó con solución saturada de $NaHCO_3$ y salmuera. Después de la separación, la fase acuosa se extrajo con DCM (3 x 10 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron para proporcionar (S)- 4- isopropil- 3- (2- (((S)- 1- (4- (1- metil- 1H- pirazol- 4- il)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona como un sólido blanco (35 mg, rendimiento del 97%).

^{1}H RMN (400 MHz, MeOD) δ 8,09 (d, J = 5,9 Hz, 1H), 7,86 (s, 1H), 7,72 (d, J = 0,8 Hz, 1H), 7,45- 7,41 (m, 2H), 7,30 (d, J = 5,8 Hz, 1H), 7,25 (d, J = 7,9 Hz, 2H), 4,97 (q, J = 7,0

Hz, 1H), 4,58 (br s, 1H), 4.30- 4.21 (m, 2H), 3,86 (s, 3H), 1,66 (br s, 1H), 1,48 (d, J = 7,0 Hz, 3H), 0,60 (br s, 3H), 0,48 (br s, 3H); HRMS (B) m/z 407.2179 (M + H)+.

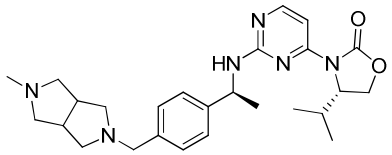
Ejemplo 209



Siguiendo el procedimiento anterior para el Ejemplo 208, N- (4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)fenil)ciclohexanocarboxamida se preparó como un sólido blanco (45 mg, rendimiento del 92%) a partir de (S)- 1- (4- (ciclohexanecarboxamido)fenil)etil(4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il)carbamato de terc- butilo.

^{1}H RMN (400 MHz, MeOD) δ 8,08 (d, J = 5,9 Hz, 1H), 7,47- 7,41 (m, 2H), 7,30 (d, J = 5,8 Hz, 1H), 7.23- 7.16 (m, 2H) , 4,95 (q, J = 7,0 Hz, 1H), 4,60 (br s, 1H), 4,32- 4,19 (m, 2H), 2,30 (tt, J = 11,8, 3,3 Hz, 1H), 1,89- 1,72 (m, 4H), 1,72- 1,63 (m, 1H), 1,54- 1,39 (m, 5H), 1,39- 1,14 (m, 4H), 0,67 (br s, 3H), 0,54 (br s, 3H); HRMS (B) m/z 452.2636 (M + H)+.

Ejemplo 210

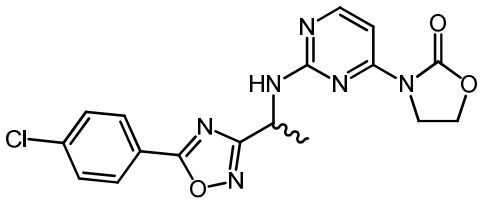


Una solución de 4 - ((S) - 1 - (4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- ilamino) etil) benzaldehído (35 mg, 0,1 mmoles) y 2 - metiloctahidropirrolo[3,4- c]pirrol (14 mg, 0.11 mmol) en MeOH (2 ml) se añadió ácido acético (7.2 mg, 0.12 mmol) y complejo de borano de 5- etil- 2- metilpiridina (14 mg, 0.1 mmoles , sigmaaldrich). La solución se agitó a 50 °C durante 4 h, después se añadieron 5 gotas de agua. La solución se agitó a temperatura ambiente durante otras 2 h, después se diluyó con EtOAc (10 ml) y se lavó con agua (10 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se

concentraron. El material crudo se purificó a través de HPLC para proporcionar (4S)- 4- isopropil- 3- (2- (((1S)- 1- (4- ((5- metilhexahidropirrolo[3,4- c]pirrol- 2(1H)- il)metil)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona como un sólido blanco (10 mg, rendimiento del 21,7%).

^{1}H RMN (400 MHz, MeOD) δ 8,07 (d, J = 5,8 Hz, 1H), 7,29 (d, J = 5,8 Hz, 1H), 7.25- 7.20 (m, 4H), 5,00 (q, J = 7,0 Hz , 1H), 4,63 (br s, 1H), 4.31 - 4.23 (m, 2H), 3,55- 3,48 (m, 2H), 2,68 (dh, J = 13,6, 4,3, 3,7 Hz, 2H), 2,64- 2,48 (m, 4H), 2,36- 2,29 (m, 4H), 2,28 (s, 4H), 1,84 (br s, 1H), 1,45 (d, J = 7,0 Hz, 3H), 0,68 (br s, 3H), 0,52 (br s, 3H); HRMS (B) m/z 465,2975 (M + H)+.

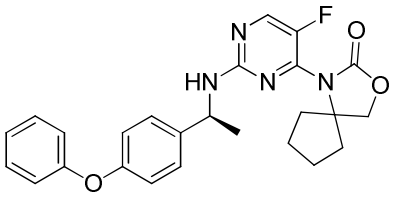
Ejemplo 211



Una solución de 3 - (2- fluoropirimidin- 4- il) oxazolidin- 2- ona (89.1 mg, 0.487 mmol), 1 - (3 - (4- clorofenil) - 1,2,4- oxadiazol- 5- il)etanamina (115.9 mg, 0.518 mmoles, 1.06 equiv), y DIPEA (0.20 ml, 1.1 mmol, 2.4 equiv) en DMSO (1,5 ml) se calentó a 110 °C durante 100 min. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (MeOH en CH_2Cl_2 0 a 5%) proporcionó 3 - (2 - (1 - (3 - (4- clorofenil) - 1,2,4- oxadiazol- 5- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona (18.2 mg, sólido blanco) con un rendimiento del 10.3%.

^{1}H RMN (400 MHz, DMSO- d_6) 8,21 (br s, 1H), 8,00- 7,97 (m, 2 H), 7,65- 7,61 (m, 2 H), 7,30 (br s, 1H), 5,28 (br s, 1 H), 4,44- 4,38 (br m, 2 H), 4.14 - 4.8 (m, 1 H), 3,99 (br s, 0,5 H), 3,75 (br s, 0,5 H), 1,64 (d, J = 7,0 Hz, 3 H); HRMS (B) *m/z* 387.0962 (M + H)+

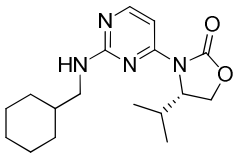
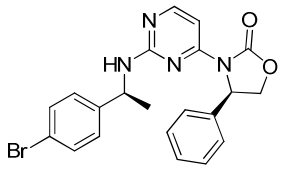
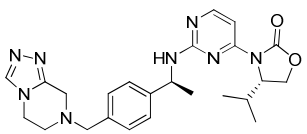
Ejemplo 212

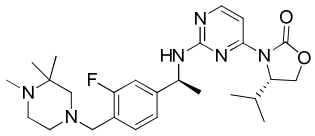
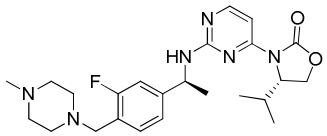
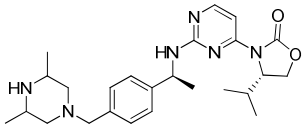
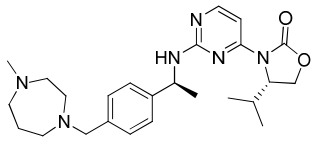
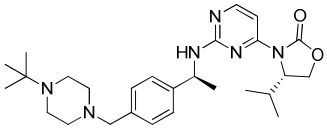
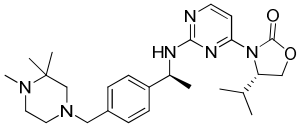
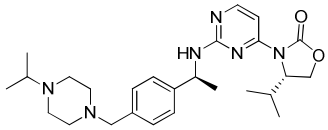
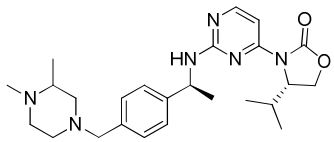
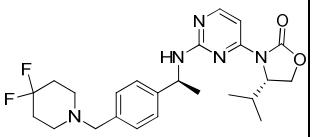
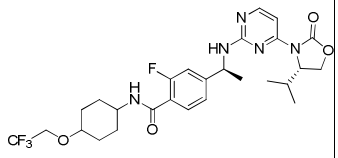
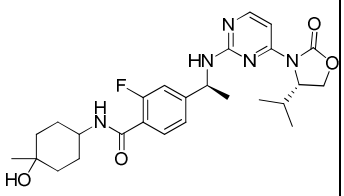
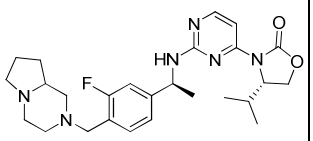
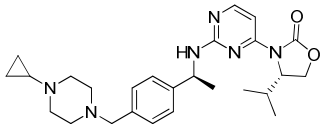
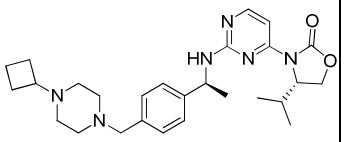
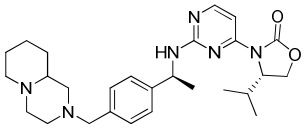
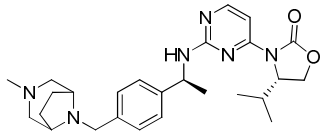
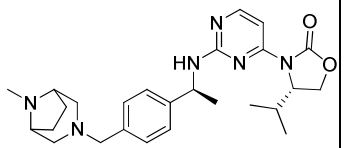
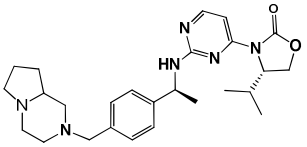


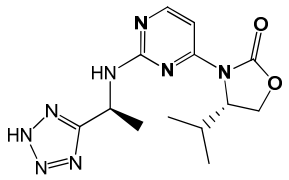
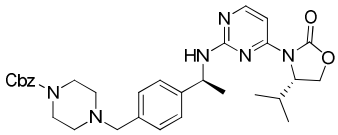
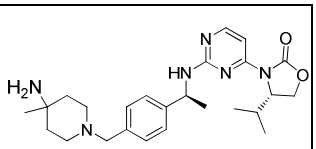
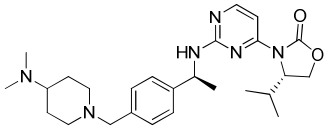
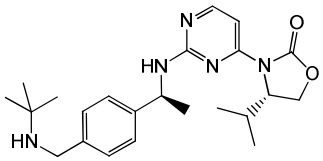
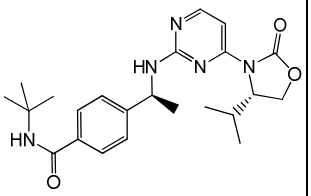
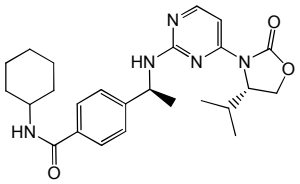
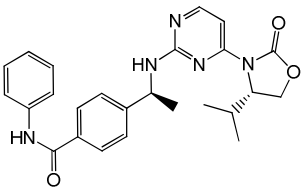
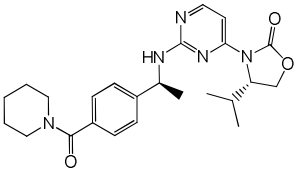
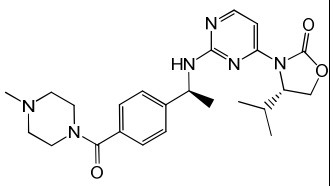
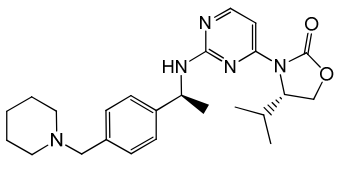
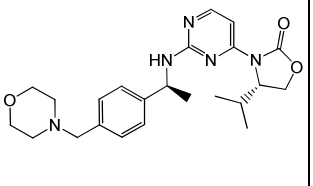
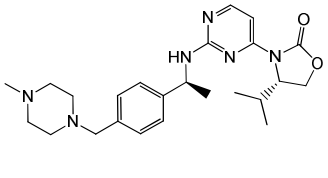
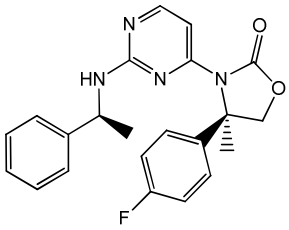
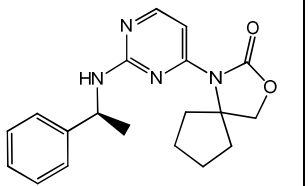
Una solución de (S) - 1 - (4- fenoxifenil) etanamina (281 mg, 1.125mmol), 3 - (2- cloro- 5- fluoropirimidin- 4- il) oxazolidin- 2- ona (103 mg, 0.379mmol) y DIPEA (0.331ml, 1.896mmol) en DMSO se calentó a 110 ºC durante 1 h. LCMS mostró poco producto. Se calentó durante 16 h adicionales. LCMS mostró todavía material de partida. Añadido un adicional de 5 equivalentes de DIPEA y 1 equivalente de KF. Se calentó a 110 º C durante 2 h. LCMS muestro producto. La mezcla de reacción se diluyó con EtOAc (8 ml) y se lavó con agua (30 ml). Después de la separación, la fase acuosa se extrajo con EtOAc (3 x 8 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. Se purificó mediante cromatografía en columna (10% a 50% EtOAc/heptano) para proporcionar (S) - 1 - (5- fluoro- 2- (1 - (4- fenoxifenil) etilamino) pirimidin- 4- il)- 3- oxa- 1- azaespiro [4.4] nonan- 2- ona (62 mg, 0.138mmol). ^{1}H RMN (400 MHz, MeOD) δ 8,25 (d, J = 2,8 Hz, 1H), 7,34 (ddd, J = 8,7, 4,9, 2,3 Hz, 4H), 7.16 - 7.4 (m, 1H), 7,02- 6,90 (m, 4H), 4,96 (q, J = 7,0 Hz, 1H), 4.30- 4.25 (m, 2H), 2,38 (dt, J = 13,1, 8,4 Hz, 1H), 2,02 (br s, 1H), 1,80 (ddd, J = 12,7, 7,3, 4,2 Hz, 1H), 1,71- 1,63 (br m, 2H), 1,61- 1,49 (m, 3H), 1,53 (d, J = 7,0 Hz, 3 H). HRMS (B) (M+H) 449,1984 Calculado (M+H) 449.1989

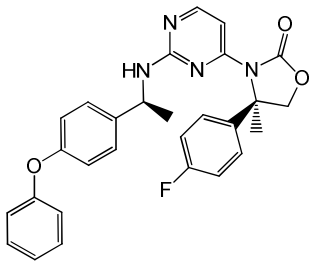
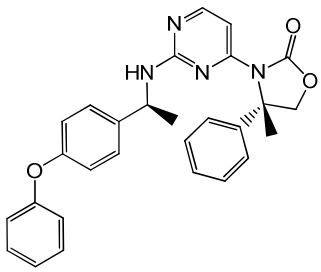
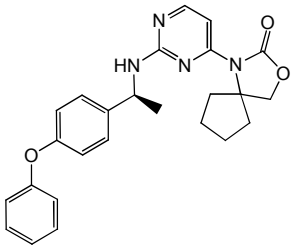
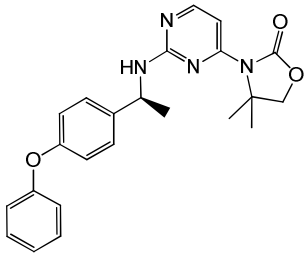
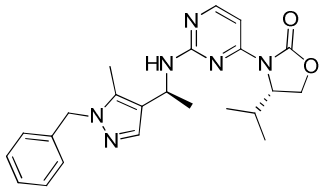
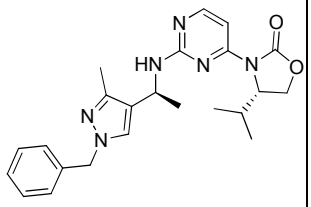
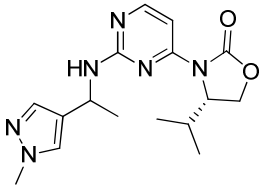
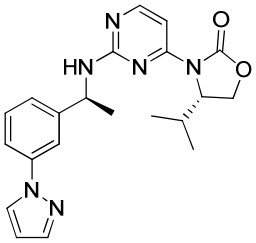
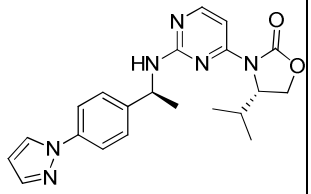
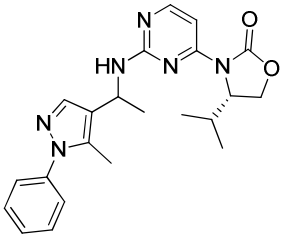
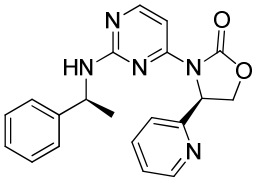
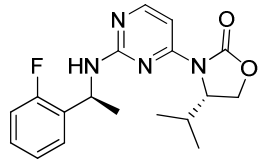
Los compuestos de la Tabla 7 se prepararon usando procedimientos sustancialmente similares a los descritos para la preparación de los Ejemplos 1, 113, 211 y 212.

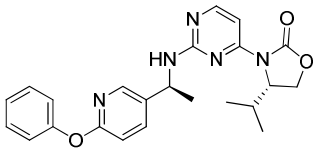
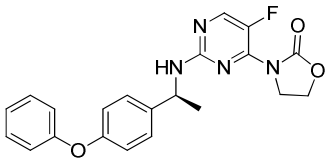
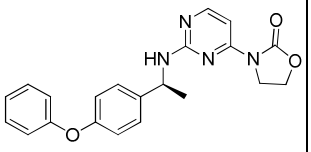
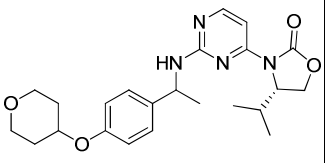
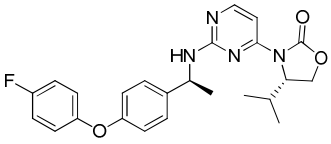
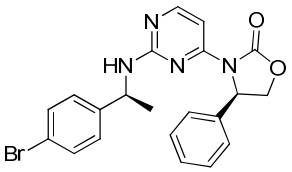
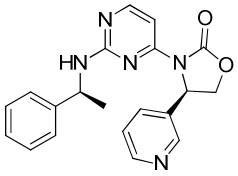
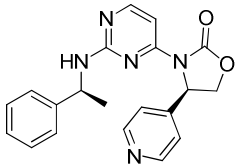
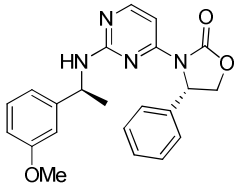
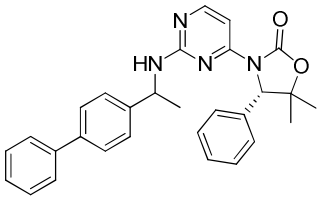
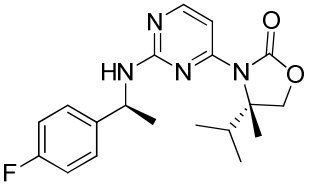
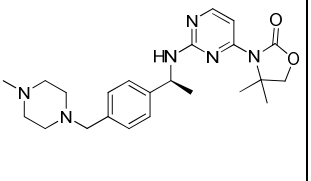
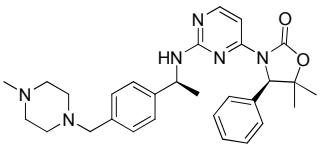
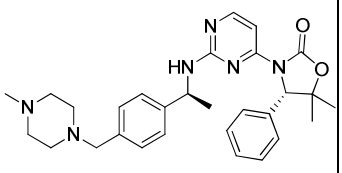
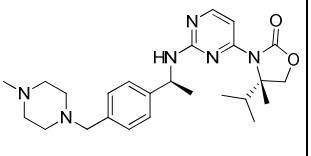
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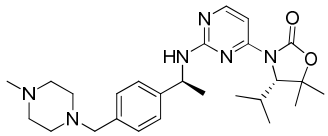
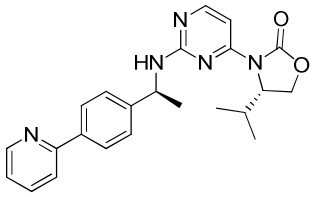
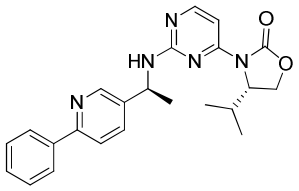
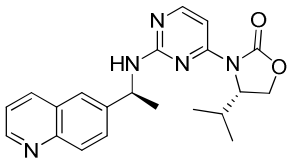
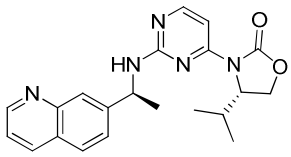
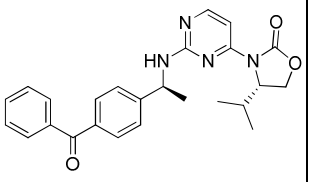
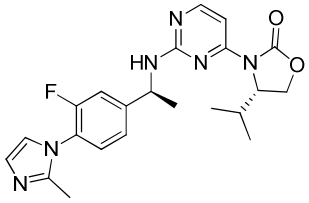
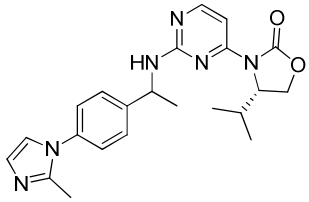
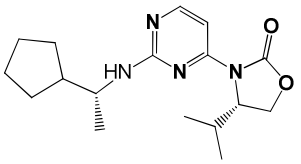
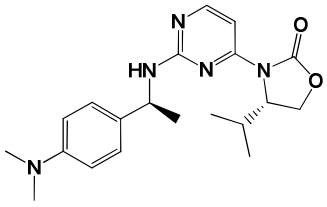
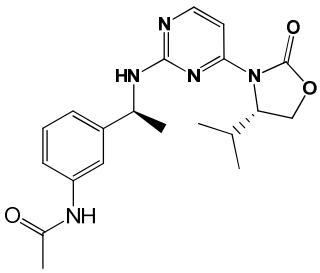
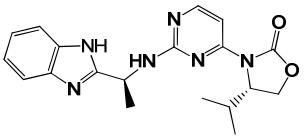
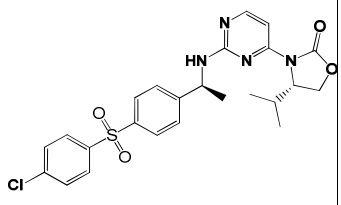
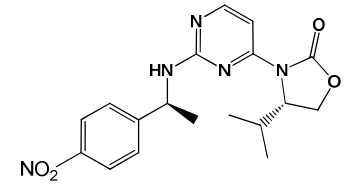
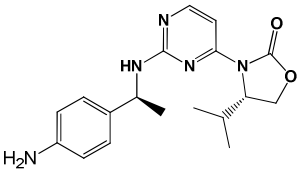
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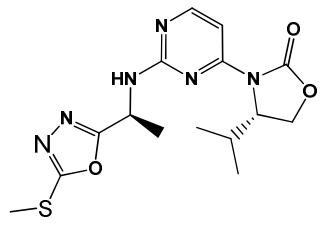
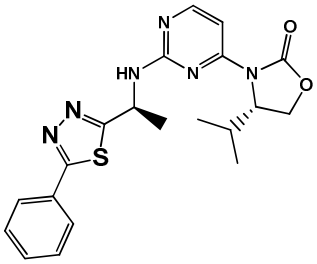
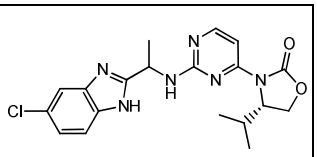
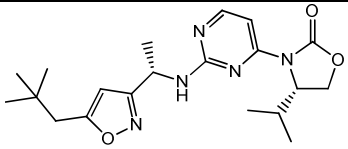
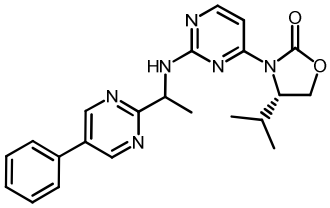
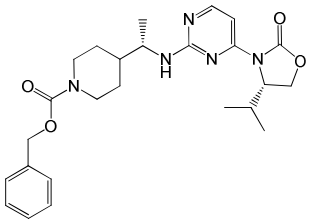
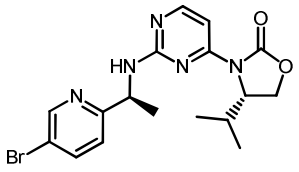
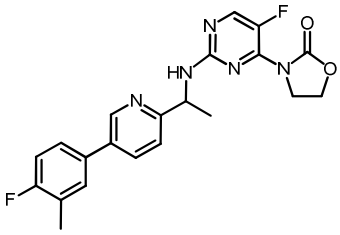
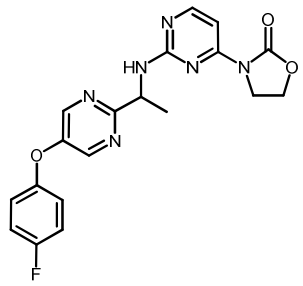
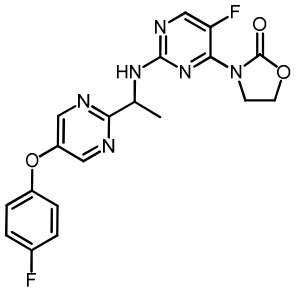
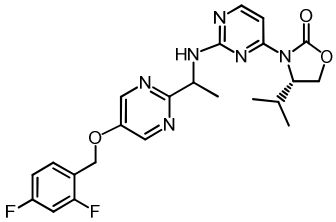
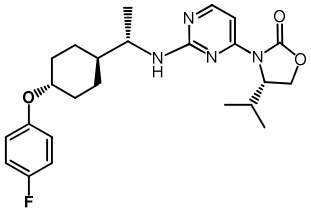
		
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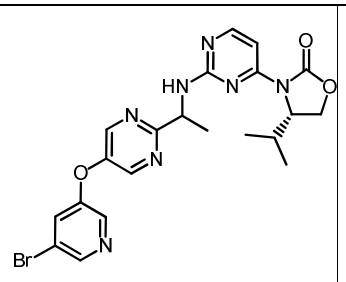
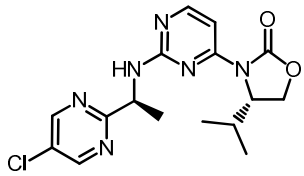
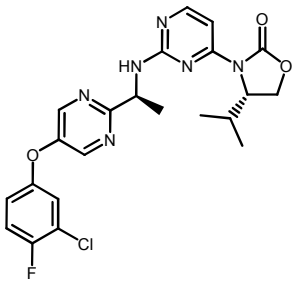
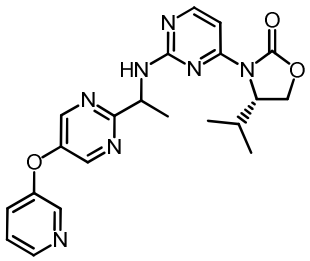
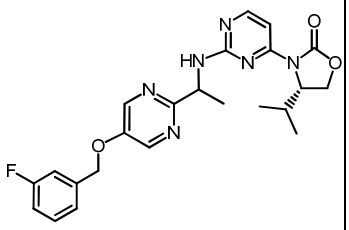
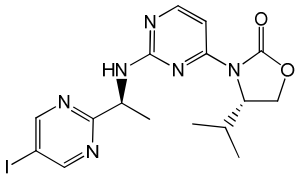
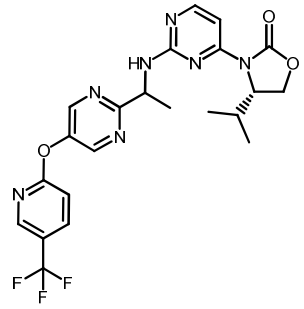
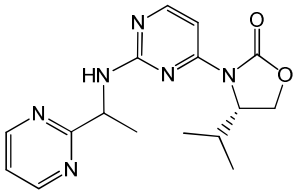
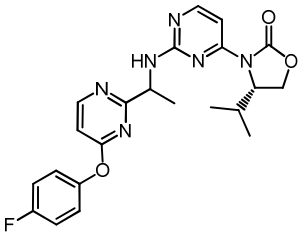
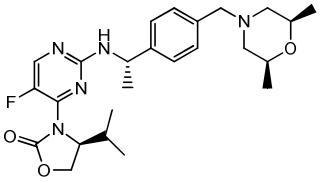
		
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Tabla 8. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada compuesto enumerado en la Tabla 7.

Ejemplo: Nombre	^{1}H RMN **(400 MHz,** CD_3OD**) δ ppm (otros solventes descritos)**	**LCMS**
213: (S) - 3 - (2 - ((ciclohexilmetil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,08 (d, J = 5,8 Hz, 1 H), 7,33 (d, J = 5,8 Hz, 1H), 4,80- 4,76 (m, 1 H), 4,42- 4,37 (m, 2 H), 3,24 (dd, J = 13, 6,3 Hz, 1 H), 3,10 (dt, J = 13, 6,8 Hz, 1H), 2,68- 2,60 (m, 1 H), 1,82- 1,56 (m, 7 H), 1.31 a 1.18 (m, 4 H), 0,98 (d, J = 7,1 Hz, 3 H), 0,87 (d, J = 7,0 Hz, 3 H);	HRMS (B) m/z 319,2132 (M + H)+
214: (R) - 3 - (2 - (((S) - 1 - (4- bromofenil) etil) amino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,46 (d, *J* = 5,8 Hz, 1H), 7,85- 7,73 (m, 5H), 7,73- 7,67 (m, 1H), 7,64 (dd, *J* = 7,1, 1,8 Hz, 2H), 7,58- 7,52 (m, 2H), 5,92 (dd, *J* = 8,6, 4,0 Hz, 1H), 5,13 (t, *J* = 8,7 Hz, 1H), 4,98 (d, *J* = 7,0 Hz, 1H), 4,55 (dd, *J* = 8,7, 4,0 Hz, 1H), 1,58 (d, *J* = 7,0 Hz, 3H);	HRMS (B) *m/z* 439.0762 M +
215: (S)- 3- (2- (((S)- 1- (4- ((5,6- dihidro- [1,2,4]triazolo[4,3- a]pirazin- 7(8H)- il)metil)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,38 (s, 1H), 8,07 (d, J = 5,9 Hz, 1H), 7,30 (d, J = 6,0 Hz, 1H), 7,28 (s, 4H), 5,03 (q, J = 7,0 Hz, 1H), 4,63 (br s, 1H), 4.31- 4.23 (m, 2H), 4,08 (t, J = 5,5 Hz, 2H), 3,78- 3,69 (m, 4H), 2,89 (td, J = 5,4, 2,1 Hz, 2H), 1,80 (br s, 1H), 1,46 (d, J = 7,0 Hz, 3H), 0,68 (br s, 3H), 0,53 (br s, 3H)	HRMS (B) m/z 463,2567 (M + H)+
216: (S)- 3- (2- (((S)- 1- (3- fluoro- 4- ((3,3,4- trimetilpiperazin- 1- il)metil)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,04 (d, J = 5,9 Hz, 1H), 7,36- 7,15 (m, 2H), 7,02 (dd, J = 7,9, 1,8 Hz, 1H), 6,94 (dd, J = 11,0, 1,8 Hz, 1H), 4,95 (q, J = 7,0 Hz, 1H), 4,58 (br s, 1H), 4,32- 4,11 (m, 2H), 3,38 (br s, 2H), 2,46 (br t, J = 4,9 Hz, 2H), 2,32 (br s, 2H), 2,14 (br s, 2 H), 2,10 (s, 3H), 1,73 (br s, 1H), 1,40 (d, J = 7,1 Hz, 3H), 0,95 (s, 3H), 0,95 (s, 3H), 0,63 (br s, 3H), 0,49 (br s, 3H)	HRMS (B) m/z 485,3107 (M + H)+
217: (S)- 3- (2- (((S)- 1- (3- fluoro- 4- ((4- metilpiperazin- 1- il)metil)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,09 (d, J = 6,0 Hz, 1H), 7,41- 7,20 (m, 2H), 7,11 (dd, J = 7,8, 1,7 Hz, 1H), 7,04 (dd, J = 11,0, 1,8 Hz, 1H), 5,01 (q, J = 7,0 Hz, 1H), 4,63 (br s, 1H), 4,36- 4,16 (m, 2H), 3,57 (s, 2H), 2,82 (br s, 4H), 2,60 (br s, 4H) , 2,51 (s, 3H), 1,83 (br s, 1H), 1,45 (d, J = 7,1 Hz, 3H), 0,69 (s, 3H), 0,54 (s, 3H)	HRMS (B) m/z 457,2699 (M + H)+.
218: (4S)- 3- (2- (((1S)- 1- (4- ((3,5- dimetilpiperazin- 1- il)metil)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2-	8,07 (d, J = 5,8 Hz, 1H), 7,30 (d, J = 5,8 Hz, 1H), 7.28- 7.19 (m, 4H), 5,01 (q, J = 7,0 Hz, 1H), 4,63 (br s, 1H), 4,34- 4,18 (m, 2H), 3,46- 3,39 (m, 2H), 2,89- 2,76 (m, 2H), 2,76- 2,67 (m, 2H), 1,82 (br s, 1H), 1,59 (t , J = 10,9 Hz, 2H), 1,45 (d, J = 7,0	HRMS (B) m/z 453,2971 (M + H)+

ona	Hz, 3H), 0,98 (s, 3H), 0,96 (s, 3H), 0,68 (br s, 3H), 0,52 (br s, 3H)	
219: (S)- 4- isopropil- 3- (2- (((S)- 1- (4- ((4- metil- 1,4- diazepan- 1- il)metil)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	8,07 (d, J = 5,8 Hz, 1H), 7,30 (d, J = 5,9 Hz, 1H), 7.28- 7.24 (m, 4H), 5,02 (q, J = 7,0 Hz, 1H), 4,63 (br s, 1H), 4,35- 4,22 (m, 2H), 3,67- 3,59 (m, 2H), 3.9- 3.7 (m, 2H), 2,99 (dd, J = 6,2, 3,5 Hz, 2H), 2,79- 2,77 (m, 2H), 2,72 (t, J = 6,0 Hz, 2H), 2,63 (s, 3H), 1,93- 1,87 (m, 3H), 1,80 (br s, 1H), 1,45 (d, J = 7,0 Hz, 3H) , 0,69 (br s, 3H), 0,54 (br s, 3H)	HRMS (B) m/z 453,2968 (M + H)+
220: (S)- 3- (2- (((S)- 1- (4- ((4- (tert- butil)piperazin- 1- il)metil)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,07 (d, J = 5,9 Hz, 1H), 7,30 (d, J = 5,8 Hz, 1H), 7,24 (q, J = 8,2 Hz, 4H), 5,01 (q, J = 6,9 Hz, 1H), 4,63 (br s, 1H), 4.31- 4.24 (m, 2H), 3,49- 3,42 (m, 2H), 2,60 (br s, 4H), 2,46 (br s, 4H), 1,76 (br s, 1H), 1,45 (d, J = 7,0 Hz, 3H), 1,03 (s, 9H), 0,69 (s, 3H), 0,53 (s, 3H)	HRMS (B) m/z 481,3283 (M + H)+
221: (S)- 4- isopropil- 3- (2- (((S)- 1- (4- ((3,3,4- trimetilpiperazin- 1- il)metil)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	8,08 (d, J = 5,8 Hz, 1H), 7,30 (d, J = 5,8 Hz, 1H), 7.26- 7.18 (m, 4H), 5,01 (q, J = 7,0 Hz, 1H), 4,63 (br s, 1H), 4.31- 4.24 (m, 2H), 3,37 (s, 2H), 2,54 (br t, J = 5,0 Hz, 2H), 2,38 (br s, 2H), 2,17 (s, 3H), 2,14 (br s, 2H), 1,85 (br s, 1H), 1,45 (d, J = 7,0 Hz, 3H), 1,01 (s, 6H), 0,68 (br s, 3H), 0,53 (br s, 3H)	HRMS (B) m/z 467,3127 (M + H)+
222: (S)- 4- isopropil- 3- (2- (((S)- 1- (4- ((4- isopropilpiperazin- 1- il)metil)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	8,07 (d, J = 5,8 Hz, 1H), 7,30 (d, J = 5,8 Hz, 1H), 7,24 (q, J = 8,3 Hz, 4H), 5,01 (q, J = 7,0 Hz, 1H), 4,63 (br s, 1H), 4.31- 4.24 (m, 2H), 3,46 (s, 2H), 2,63- 2,44 (m, 9H), 1,84 (br s, 1H), 1,45 (d, J = 7,1 Hz, 3H) , 1,02 (d, J = 6,5 Hz, 6H), 0,68 (br s, 3H), 0,53 (br s, 3H)	HRMS (B) m/z 467,3120 (M + H)+
223: (4S)- 3- (2- (((1S)- 1- (4- ((3,4- dimetilpiperazin- 1- il)metil)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,07 (d, J = 5,9 Hz, 1H), 7,30 (d, J = 5,8 Hz, 1H), 7,23 (q, J = 8,1 Hz, 4H), 5,01 (q, J = 7,0 Hz, 1H), 4,63 (br s, 1H), 4,35- 4,20 (m, 2H), 3,51- 3,35 (m, 2H), 2,82- 2,61 (m, 3H), 2,36- 2,24 (m, 1H), 2,23 (s, 3H), 2,20 - 2,08 (m, 2H), 1,89- 1,80 (m, 2H), 1,45 (d, J = 7,0 Hz, 3H), 0,99 (d, J = 6,3 Hz, 3H), 0,68 (br s, 3H), 0,52 (br s, 3H)	HRMS (B) m/z 453,2960 (M + H)+
224: (S)- 3- (2- (((S)- 1- (4- ((4,4- difluoropiperidin- 1- il)metil)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,08 (d, J = 5,8 Hz, 1H), 7,31 (d, J = 5,8 Hz, 1H), 7,25 (q, J = 8,2 Hz, 4H), 5,02 (q, J = 7,0 Hz, 1H), 4,63 (br s, 1H), 4,32- 4,24 (m, 2H), 3,51 (s, 2H), 2,52 (br t, J = 5,8 Hz, 4H), 1,98- 1,87 (m, 4H), 1,81 (br s, 1H), 1,46 (d, J = 7,0 Hz, 3H), 0,68 (br s, 3H), 0,52 (br s, 3H)	HRMS (B) m/z 460,2514 (M + H)+
225: 2- fluoro- 4- ((S)- 1- ((4- ((S)- 4- isopropil- 2-	8,09 (d, J = 5,7 Hz, 1H), 7,58 (t, J = 7,7 Hz, 1H), 7,33 (d, J = 5,8 Hz, 1H), 7,20 (dd, J =	HRMS (B) m/z

oxooxazolidin- 3-il)pirimidin- 2-il)amino)etil)- N- (4-(2,2,2-trifluoroetoxi)ciclohexil)benzamida	7,9, 1,6 Hz, 1H), 7,13 (dd, J = 12,1, 1,7 Hz, 1H), 5,03 (q, J = 7,0 Hz, 1H), 4,61 (br s, 1H), 4.31- 4.24 (m, 2H), 3,97- 3,80 (m, 3H), 3,65 (dt, J = 4,7, 2,3 Hz, 1H), 1,90 (dt, J = 12,5, 4,0 Hz, 2H), 1,72- 1,58 (m, 6H), 1,47 (d, J = 7,0 Hz, 3H) , 0,68 (br s, 3H), 0,56 (br s, 3H)	568,2549 (M + H)+
226: 2- fluoro- N- (4-hydroxi- 4-metilciclohexil)- 4- ((S)-1- ((4- ((S)- 4- isopropil-2- oxooxazolidin- 3-il)pirimidin- 2-il)amino)etil)benzamida	8,09 (d, J = 6,0 Hz, 1H), 7,58 (t, J = 7,7 Hz, 1H), 7,33 (d, J = 5,8 Hz, 1H), 7,20 (dd, J = 8,0, 1,6 Hz, 1H), 7,13 (dd, J = 12,0, 1,7 Hz, 1H), 5,03 (q, J = 7,0 Hz, 1H), 4,61 (br s, 1H), 4.31- 4.25 (m, 2H), 3,89 (dt, J = 9,4 , 4,7 Hz, 1H), 1,95- 1,82 (m, 2H), 1,75- 1,49 (m, 7H), 1,47 (d, J = 7,0 Hz, 3H), 1,21 (s, 3H), 0,68 (br s, 3H), 0,56 (br s, 3H)	HRMS (B) m/z 500,2589 (M + H)+
227: (4S)- 3- (2- (((1S)- 1-(3- fluoro- 4-((hexahidropirrolo[1,2-a]pirazin- 2(1H)-il)metil)fenil)etil)amino)pirimidin- 4- il)- 4-isopropiloxazolidin- 2-ona	8,09 (d, J = 5,8 Hz, 1H), 7,32 (d, J = 5,8 Hz, 1H), 7,29 (t, J = 7,7 Hz, 1H), 7,10 (dd, J = 7,9, 1,8 Hz, 1H), 7,03 (dd, J = 11,0, 1,8 Hz, 1H), 5,00 (q, J = 7,0 Hz, 1H), 4,63 (br s, 1H), 4.31- 4.24 (m, 2H), 3,62- 3,53 (m, 2H), 2,98- 2,91 (m, 3H), 2,80- 2,75 (m, 1H), 2,34- 2,18 (m, 2H), 2.18 a 2.1 (m, 2H), 1,90 (t, J = 10,4 Hz, 1H), 1,83- 1,65 (m, 4H), 1,45 (d, J = 7,0 Hz, 3H), 1,36-1,27 (m, 1H), 0,68 (br s, 3H), 0,54 (br s, 3H)	HRMS (B) m/z 483,2878 (M + H)+
228: (S)- 3- (2- ((S)- 1- (4-((4- ciclopropilpiperazin-1-il)metil)fenil)etilamino)pirimidin- 4- il)- 4-isopropiloxazolidin- 2-ona	8,07 (d, J = 5,9 Hz, 1H), 7,30 (d, J = 5,8 Hz, 1H), 7,23 (q, J = 8,0 Hz, 4H), 5,01 (q, J = 7,0 Hz, 1H), 4,62 (br s, 1H), 4,35- 4,19 (m, 2H), 3,45 (s, 2H), 2,62 (br s, 4H), 2,41 (br s, 4H), 1,79 (br s, 1H), 1,65- 1,56 (m, 1H), 1,45 (d, J = 7,0 Hz, 3H), 0,67 (br s, 3H), 0,52 (br s, 3H), 0,45 - 0,38 (m, 2H), 0,38 - 0,29 (m, 2H)	HRMS (B) m/z 465,2975 (M + H)+
229: (S)- 3- (2- ((S)- 1- (4-((4- ciclobutilpiperazin- 1-il)metil)fenil)etilamino)pirimidin- 4- il)- 4-isopropiloxazolidin- 2-ona	8,08 (d, J = 7,2 Hz, 1H), 7,70 (d, J = 7,2 Hz, 1H), 7,47- 7,24 (m, 4H), 5.28 - 5.6 (m, 1H), 4,66 (q, J = 4,8, 4,4 Hz, 1H), 4,34 (d, J = 5,7 Hz, 2H), 3,91 (s, 2H), 3,61 (t, J = 8,3 Hz, 1H), 3,20 (br s, 4H), 3,02 (br s, 4H), 2,32- 2,04 (m, 4H), 1,90- 1,66 (m, 3H), 1,52 (d, J = 7,0 Hz, 3H), 0,71 (d, J = 7,0 Hz, 3H), 0,54 (d, J = 6,7 Hz, 3H)	HRMS (B) m/z 479,3165 (M + H)+
230: (4S)- 3- (2- ((1S)- 1-(4- ((dihidro- 1H-pirido[1,2- a]pirazin-2(6H,7H,8H,9H,9aH)-il)metil)fenil)etilamino)pirimidin- 4- il)- 4-isopropiloxazolidin- 2-ona	8,07 (d, J = 5,8 Hz, 1H), 7,34- 7,19 (m, 5H), 5,01 (q, J = 7,0 Hz, 1H), 4,63 (br s, 1H), 4,33- 4,22 (m, 2H), 3,49- 3,39 (m, 2H), 2,83- 2,71 (m, 2H), 2,66 (dq, J = 11,0, 2,2 Hz, 2H), 2,32- 2,14 (m, 2H), 2,09- 1,94 (m, 2H), 1,82 (t, J = 10,8 Hz, 1H), 1,70 (dt, J = 12,4, 3,5 Hz, 1H), 1,64- 1,50 (m, 2H), 1,48- 1,39 (m, 5H), 1,35- 1,21 (m, 1H),	HRMS (B) m/z 479,3131 (M + H)+

	1,14 (tdd, J = 13,0, 10,8, 3,6 Hz, 1H), 0,68 (br s, 3H), 0,52 (br s, 3H)	
231: (4S)- 4- isopropil- 3- (2- ((1S)- 1- (4- ((3- metil- 3,8- diazabiciclo[3.2.1]octan- 8- il)metil)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	8,07 (d, J = 5,9 Hz, 1H), 7,36- 7,21 (m, 5H), 5,01 (q, J = 7,0 Hz, 1H), 4,62 (br s, 1H), 4,33- 4,21 (m, 2H), 3,45 (s, 2H), 3,07 (qd, J = 4,6, 4,2, 1,9 Hz, 2H), 2,63- 2,50 (m, 2H), 2,25 (ddd, J = 10,7, 4,4, 1,8 Hz, 2H), 2,15 (s, 3H), 2,04- 1,93 (m, 2H), 1,83- 1,72 (m, 3H), 1,45 (d, J = 7,0 Hz, 3H), 0,67 (br s, 3H), 0,51 (br s, 3H)	HRMS (B) m/z 465,2964 (M + H)+
232: (4S)- 4- isopropil- 3- (2- ((1S)- 1- (4- ((8- metil- 3,8- diazabiciclo[3.2.1]octan- 3- il)metil)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	($CDCl_3$) 8,17 (d, J = 5,7 Hz, 1H), 7,42 (d, J = 5,7 Hz, 1H), 7,23 (s, 4H), 5,46 (br s, 1H), 5,01 (br s, 1H), 4,60 (dt, J = 6,9, 3,3 Hz, 1H), 4,28 (t, J = 8,7 Hz, 1H), 4,21 (dd, J = 9,1, 3,1 Hz, 1H), 3,42 (d, J = 1,7 Hz, 2H), 3,10- 2,96 (m, 2H), 2,58- 2,48 (m, 2H), 2,33- 2,18 (m, 5H), 2,06- 1,84 (m, 3H), 1,81 (dd, J = 7,8, 4,4 Hz, 2H), 1,52 (d, J = 6,8 Hz, 3H), 0,71 (br s, 3H), 0,64 (br s, 3H)	HRMS (B) m/z 465,2963 (M + H)+
233: (4S)- 3- (2- ((1S)- 1- (4- ((hexahidropirrolo[1,2- a]pirazin- 2(1H)- il)metil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,12 (d, J = 5,8 Hz, 1H), 7,34 (d, J = 5,8 Hz, 1H), 7,33- 7,24 (m, 4H), 5,05 (q, J = 7,0 Hz, 1H), 4,67 (br s, 1H), 4,38- 4,26 (m, 2H), 3,64- 3,49 (m, 2H), 3,11- 3,00 (m, 2H), 2,96 (br d, J = 11,0 Hz, 1H), 2,83 (br d, J = 11,2 Hz, 1H), 2,45- 2,34 (m, 1H), 2,32- 2,25 (m, 3H), 1,94 (t, J = 10,5 Hz, 1H), 1,88- 1,77 (m, 4H), 1,49 (d, J = 7,0 Hz, 3H), 1,47- 1,35 (m, 1H), 0,72 br (s, 3H), 0,56 (br s, 3H)	HRMS (B) m/z 465,2972 (M + H)+
234: (S) - 3 - (2 - (((S) - 1 - (2H- tetrazol- 5- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona		HRMS (B) m/z 319,1624 (M + H)+, RT = 1,33 min.
235: 4- (4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzil)piperazina- 1- carboxílato de benciclo	8,07 (d, J = 5,8 Hz, 1H), 7,34- 7,18 (m, 10H), 5,05 (s, 2H), 5,01 (q, J = 6,9 Hz, 1H), 4,62 (br s, 1H), 4,32 - 4,18 (m, 2H), 3,49- 3,34 (m, 4H), 3,46 (s, 2H), 2,36 (t, J = 5,1 Hz, 4H), 1,75 (br s, 1H), 1,45 (d, J = 7,0 Hz, 3H), 0,66 (br s, 3H), 0,50 (br s, 3H)	HRMS (B) m/z 559,3026 (M + H)+
236: (S)- 3- (2- ((S)- 1- (4- ((4- amino- 4- metilpiperidin- 1- il)metil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,07 (d, J = 5,8 Hz, 1H), 7,30 (d, J = 5,8 Hz, 1H), 7.27- 7.21 (m, 4H), 5,01 (q, J = 7,0 Hz, 1H), 4,63 (br s, 1H), 4,34- 4,18 (m, 2H), 3,53- 3,40 (m, 2H), 2,59- 2,21 (br m, 4H), 1,78 (br s, 1H), 1,52 (ddt, J = 11,8, 8,7, 5,2 Hz, 4H), 1,45 (d, J = 7,0 Hz, 3H), 1,07 (s, 3H), 0,67 (br s, 3H), 0,51 (br s, 3H)	HRMS (B) m/z 453,2972 (M + H)+
237: (S)- 3- (2- ((S)- 1- (4-	($CDCl_3$) 8,17 (d, J = 5,7 Hz, 1H), 7,42 (d, J	HRMS

((4-(dimetilamino)piperidin-1-il)metil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	= 5,7 Hz, 1H), 7,25 (d, J = 8,2 Hz, 4H), 5,43 (br s, 1H), 5,01 (br s, 1H), 4,60 (dt, J = 8,6, 3,3 Hz, 1H), 4,28 (t, J = 8,7 Hz, 1H), 4,21 (dd, J = 9,1, 3,2 Hz, 1H), 3,44 (s, 2H), 2,89 (dp, J = 11,5, 2,8 Hz, 2H), 2,26 (s, 6H), 2,11 (tt, J = 11,3, 3,6 Hz, 1H), 1,93 (td, J = 11,9, 2,4 Hz, 2H) , 1,90 (br s, 1H), 1,75 (dq, J = 12,0, 2,8 Hz, 2H), 1,60- 1,43 (m, 2H), 1,53 (d, J = 6,8 Hz, 3H), 0,70 (br s, 3H), 0,63 (br s, 3H)	(B) m/z 467,3121 (M + H)+
238: (S)- 3- (2- ((S)- 1- (4- ((tect-butilamino)metil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	($CDCl_3$) δ 8,18 (dd, J = 5,8, 1,3 Hz, 1H), 7,44 (dd, J = 5,7, 1,2 Hz, 1H), 7,37- 7,22 (m, 5H), 5,52 (br s, 1H), 5,15 - 4,95 (m, 1H), 4,70- 4,55 (m, 1H), 4,30 (td, J = 8,8, 2,1 Hz, 1H), 4,23 (dd, J = 9,1, 3,0 Hz, 1H), 3,71 (d, J = 2,0 Hz, 2H), 2,06 (s, 1H), 1,54 (dd, J = 7,1, 1,9 Hz, 3H), 1,18 (sm, 9H), 0,85 - 0,59 (m, 6H);	HRMS (B) m/z 412,2701 (M + H)+
239: N- terc- butil- 4- ((S) - 1 - (4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- ilamino) etil)benzamida	($CDCl_3$) δ 8,16 (dd, J = 5,8, 1,2 Hz, 1H), 7,66 (d, J = 8,3 Hz, 2H), 7,43 (dd, J = 5,8, 0,9 Hz, 1H), 7,35 (d, J = 7,9 Hz, 2H), 5,88 (s, 1H), 5,57 (br s, 1H), 5,04 (br s, 1H), 4,55 (br s, 1H), 4,26 (t, J = 8,7 Hz, 1H), 4,19 (dd, J = 9,2, 3,2 Hz, 1H), 1,53 (d, J = 6,9 Hz, 3H), 1,45 (s, 9H), 0,64 (m, 6H)	HRMS (B) m/z 426,2488 (M + H)+
240: N- ciclohexil- 4- ((S) - 1 - (4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- ilamino)etil)benzamida	(CDCl3) δ 8,17 (d, J = 5,7 Hz, 1H), 7,69 (d, J = 8,1 Hz, 2H), 7,44 (d, J = 5,8 Hz, 1H), 7,36 (d, J = 7,9 Hz, 2H), 5,91 (d, J = 8,3 Hz, 1H), 5,51 (br s, 1H), 5,04 (br s, 1H), 4,53 (br s, 1H), 4,26 (t, J = 8,7 Hz, 1H), 4,19 (dd, J = 9,1, 3,2 Hz, 1H), 4,04- 3,89 (m, 1H), 2,07- 1,95 (m, 2H), 1,74 (dp, J = 11,5, 3,8 Hz, 2H), 1,64 (tt, J = 7,4, 3,7 Hz, 2H), 1,54 (d, J = 6,9 Hz, 3H), 1,42 (qt, J = 12,4, 3,5 Hz, 2H), 1.30- 1.17 (m, 3H), 0,64 (br s, 6H)	HRMS (B) m/z 452,2640 (M + H)+
241: 4 - ((S) - 1 - (4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- ilamino) etil)- N- fenilbenzamida	($CDCl_3$) δ 8,19 (d, J = 5,8 Hz, 1H), 7,83 (d, J = 8,2 Hz, 2H), 7,77 (s, 1H), 7,68- 7,59 (m, 2H), 7,48- 7,41 (m, 3H), 7,37 (dd, J = 8,5, 7,3 Hz, 2H), 7.22- 7.11 (m, 1H), 5,48 (br s, 1H), 5,08 (br s, 1H), 4,56 (br s, 1H), 4,27 (t, J = 8,7 Hz, 1H), 4,20 (dd, J = 9,2, 3,2 Hz, 1H), 1,57 (t, J = 5,6 Hz, 3H), 0,65 (br s, 6H);	HRMS (B) m/z 446,2170 (M + H)+
242: (S)- 4- isopropil- 3- (2- ((S)- 1- (4- (piperidine-1-carbonil)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	($CDCl_3$) δ 8,18 (d, J = 5,7 Hz, 1H), 7,45 (d, J = 5,7 Hz, 1H), 7,33 (s, 4H), 5,45 (br s, 1H), 5,05 (br s, 1H) , 4,59 (dt, J = 7,3, 2,9 Hz, 1H), 4,27 (t, J = 8,7 Hz, 1H), 4,21 (dd, J = 9,1, 3,2 Hz, 1H), 3,51 (d, J = 141,8 Hz, 4H), 1,60 (dd, J = 52,4, 5,9 Hz, 10H), 0,68	HRMS (B) m/z 438,2492 (M + H)+

	(d, J = 25,5 Hz, 6H);	
243: (S)- 4- isopropil- 3- (2- ((S)- 1- (4- (4- metilpiperazina- 1- carbonil)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	($CDCl_3$) δ 8,18 (d, J = 5,7 Hz, 1H), 7,45 (d, J = 5,7 Hz, 1H), 7,35 (s, 4H), 5,42 (br s, 1H), 5,05 (br s, 1H) , 4,58 (br s, 1H), 4,28 (t, J = 8,8 Hz, 1H), 4,21 (dd, J = 9,2, 3,1 Hz, 1H), 3,78 (br s, 2H), 3,44 (br s, 2H) , 2,53- 2,39 (m, 2H), 2,32 (s, 4H), 1,65 (m, 2H), 1,53 (d, J = 6,9 Hz, 3H), 0,82- 0,50 (m, 6H)	HRMS (B) m/z 453,2611 (M + H)+
244: (S)- 4- isopropil- 3- (2- ((S)- 1- (4- (piperidin- 1- ilmetil)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	($CDCl_3$) δ 8,16 (d, J = 5,7 Hz, 1H), 7,42 (d, J = 5,7 Hz, 1H), 7,24 (s, 4H), 5,58 (br s, 1H), 5,15- 4,85 (m, 1H), 4,60 (dt, J = 8,4, 3,4 Hz, 1H), 4,27 (t, J = 8,7 Hz, 1H), 4,20 (dd, J = 9,1, 3,2 Hz, 1H), 3,43 (s, 2H), 2,54 - 2,22 (m, 4H), 1,99 (br s, 1H), 1,61- 1,48 (m, 7H), 1,42 (q, J = 6,6, 6,0 Hz, 2H), 0,86- 0,41 (m, 6H);	HRMS (B) m/z 424,2704 (M + H)+
245: (S)- 4- isopropil- 3- (2 - ((S) - 1 - (4 - (morfolinometil) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) δ 8,18 (d, J = 5,7 Hz, 1H), 7,45 (d, J = 5,7 Hz, 1H), 7,28 (s, 4H), 5,56 (br s, 1H), 5,16- 4,94 (m, 1H), 4,63 (dt, J = 7,6, 3,5 Hz, 1H), 4,30 (t, J = 8,8 Hz, 1H), 4,23 (dd, J = 9,0, 3,1 Hz, 1H), 3,72 (t, J = 4,6 Hz , 4H), 3,49 (s, 2H), 2,45 (t, J = 4,6 Hz, 4H), 2,19- 1,82 (m, 1H), 1,55 (d, J = 6,9 Hz, 3H), 0,90- 0,46 (m, 6H);	HRMS (B) m/z 426,2487 (M + H)+
246: (S)- 4- isopropil- 3- (2- ((S)- 1- (4- ((4- metilpiperazin- 1- il)metil)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	($CDCl_3$) δ 8,17 (d, J = 5,8 Hz, 1H), 7,43 (d, J = 5,8 Hz, 1H), 7,27 (d, J = 6,2 Hz, 4H), 5,52 (br s, 1H), 5,03 (br s, 0H), 4,62 (dt, J = 8,5, 3,4 Hz, 1H), 4,29 (t, J = 8,7 Hz, 1H), 4,22 (dd, J = 9,1, 3,2 Hz, 1H), 3,48 (s, 2H), 2,46 (br s, 9H), 2,30 (s, 3H), 1,54 (d, J = 6,9 Hz, 3H), 0,97- 0,57 (m, 6H);	HRMS (B) m/z 439,2801 (M + H)+
247: (R) - 4 - (4- fluorofenil)- 4- metil- 3- (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) δ 8,18 (d, J = 5,8 Hz, 1 H), 7,41 (d, J = 5,8 Hz, 1H), 7,33- 7,29 (m, 2 H), 7.25 a 7.20 (m, 3 H), 7.15 a 7.6 (m, 4 H), 5,17 (br s, 1H), 4,21 (br s, 1H), 4.20- 4.15 (m, 2 H), 1,61 (s, 3H), 1,21 (d, J = 7,1 Hz, 3 H)	HRMS (B) m/z 393,1726 (M + H)+.
248: (S) - 1 - (2 - (1- feniletilamino) pirimidin- 4- il)- 3- oxa- 1- azaespiro [4.4] nonan- 2- ona	($CDCl_3$) δ 8,19 (d, J = 5,8 Hz, 1H), 7,37- 7,33 (m, 4 H), 7.29- 7.24 (m, 2 H), 5,39 (br s, 1 H), 5.12 a 5.5 (m, 1 H), 4.9- 4.5 (m, 2 H), 2,83- 2,75 (m, 1 H), 2,35 (br s, 1H), 1,95- 1,86 (m, 1 H), 1,71 (br s, 1 H), 1,67- 1,61 (m, 2 H), 1,58 (d, J = 7,0 Hz, 3 H), 1,45 (br s, 2 H)	HRMS (B) m/z 339,1805 (M + H)+
249: (R)- 4- (4- fluorofenil)- 4- metil- 3- (2- ((S)- 1- (4- fenoxifenil)etilamino)pirimidin- 4- il)oxazolidin- 2-	($CDCl_3$) δ 8,18 (d, J = 5,8 Hz, 1 H), 7,42 (d, J = 5,8 Hz, 1H), 7,38- 7,33 (m, 2 H), 7.26- 7.22 (m, 2 H), 07.14 - 07.06 (m, 5 H), 7,00- 6,94 (m, 4 H), 5,21 (br s, 1H), 4.23- 4.17 (m, 3 H), 1,71 (br s, 3 H), 1,20 (d, J =	HRMS (B) m/z 485,1979 (M + H)+

ona	6,8 Hz, 3 H)	
250: (S)- 4- metil- 3- (2 - ((S) - 1 - (4- fenoxifenil) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	($CDCl_3$) δ 8,17 (dd, J = 5,9, 1,1 Hz, 1H), 7,47- 7,23 (m, 8H), 7.16- 7.5 (m, 3H), 7,02- 6,91 (m, 4H), 5,10 (br s, 1H), 4,22 (s, 2H), 1,73 (s, 3H), 1,67- 1,53 (m, 1H), 1,14 (d, J = 7,0 Hz, 3H);	HRMS (B) m/z 467,2065 (M + H)+
251: (S) - 1 - (2 - (1 - (4- fenoxifenil) etilamino) pirimidin- 4- il)- 3- oxa- 1- azaespiro [4.4] nonan- 2- ona	($CDCl_3$) δ 8,19 (d, J = 5,8 Hz, 1H), 7,37- 7,28 (m, 5 H), 7.13 a 7.9 (m, 1 H), 7,01- 6,96 (m, 4 H), 5,47 (br s, 1 H), 5.12- 5.5 (m, 1 H), 4.11 - 4.7 (m, 2 H), 2,84- 2,76 (m, 1 H), 2,42 (br s, 1H), 1,97- 1,88 (m , 1 H), 1,77 (br s, 1H), 1,68- 1,61 (m, 2 H), 1,58 (d, J = 6,9 Hz, 3H), 1,54- 1,46 (m, 2 H)	HRMS (B) m/z 431,2073 (M + H)+
252: (S) - 4,4- dimetil- 3- (2 - (1 - (4- fenoxifenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) δ 8,19 (d, J = 5,8 Hz, 1H), 7,38- 7,26 (m, 5H), 7,11 (tt, J = 7,4, 1,1 Hz, 1H), 7,01- 6,94 (m, 4H), 5,37 (br s, 1H), 5,01 (d, J = 9,1 Hz, 1H), 4,09- 3,93 (m, 2H), 1,71 (s, 3H), 1,57 (d, J = 6,9 Hz, 3H), 1,28 (m, 3H);	MS m/z 405,1 (M + H)+
253: (S)- 3- (2- (((S)- 1- (1- bencil- 5- metil- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,49 (d, J = 5,7 Hz, 1H), 7,84- 7,38 (m, 7H), 5,65 (s, 1,2 H), 5,55 (s, 0,8 H), 5,43 (q, J = 8,9, 6,9 Hz, 1H) , 5,11 (tt, J = 6,1, 3,6 Hz, 1H), 4,79- 4,60 (m, 2H), 2,76 (dtt, J = 22,3, 7,2, 3,5 Hz, 1H), 2,56 (2s, 3H), 1,87 (2d , J = 6,9 Hz, 3H), 1,22 (2d, J = 7,1 Hz, 3H), 1,13 (dd, J = 6,9 Hz, 3H)	HRMS (B) (M+H) 421,2338
254: (S)- 3- (2- (((S)- 1- (1- bencil- 3- metil- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,14 (d, J = 5,8 Hz, 1H), 7,50 (s, 1H), 7,38 (d, J = 5,8 Hz, 1H), 7,36- 7,25 (m, 3H), 7.24- 7.17 (m, 2H), 5,21 (s, 2H), 5,06 (q, J = 6,9 Hz, 1H), 4,76 (dt, J = 7,5, 3,9 Hz, 1H), 4,42- 4,32 (m, 2H), 2,38 (br s, 1H), 2,22 (s, 3H), 1,51 (d, J = 6,8 Hz, 3H), 0,86 (d, J = 7,0 Hz, 3H), 0,75 (d, J = 6,9 Hz, 3H).	HRMS (B) (M+H) 421,2340
255: (4S)- 4- isopropil- 3- (2 - (1 - (1- metil- 1H- pirazol- 4- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	^{1}H RMN (400 MHz, MeOD) δ 8,16 (d, J = 5,8 Hz, 0,5 H), 8,14 (d, J = 5,8 Hz, 0,5 H), 7,54 (s, 0,5 H), 7,48 (s, 0,5 H) , 7,44 (s, 0,5 H), 7,40 (d, J = 2,0 Hz, 0,5 H), 7,38 (d, J = 2,0 Hz, 0,5 H), 7,38 (s, 0,5 H), 5,11 (q, J = 6,9 Hz, 1H), 4,75 (q, J = 9,4, 3,7 Hz, 1H), 4,46- 4,29 (m, 2H), 3,85 (d, J = 5,5 Hz, 3H), 2,62 (ddq, J = 10,4, 7,0, 3,5 Hz, 0,5 H), 2,40 (br s, 0,5 H), 1,53 (d, J = 6,9 Hz, 3H), 0,98 (d, J = 7,1 Hz, 1,5 H), 0,88 (d, J = 7,1 Hz, 1,5 H), 0,86 (d, J = 7,0 Hz, 1,5 H), 0,78 (d, J = 7,0 Hz, 1,5 H). HRMS (B) (M+H) 421,2340 Calculado (M+H) 421,2352	HRMS (B) (M+H) 421,2340
256: (S) - 3 - (2 - ((S) - 1 -	8,20 (d, J = 2,5 Hz, 1H), 8,16 (d, J = 5,8	HRMS

(3 - (1H- pirazol- 1- il) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Hz, 1H), 7,75 (t, J = 2,0 Hz, 1H), 7,72 (d, J = 1,8 Hz, 1H), 7,58 (ddd, J = 8,0, 2,2, 1,0 Hz, 1H), 7,43 (t, J = 7,8 Hz, 1H), 7,37 (d, J = 5,8 Hz, 1H), 7,32 (d, J = 7,6 Hz, 1H), 6,56- 6,49 (m, 1H), 5,13 (q, J = 7,0 Hz, 1H), 4,66 (br s, 1H), 4,39- 4,19 (m, 2H), 1,82 (br s, 1H), 1,58 (d, J = 7,0 Hz, 3H), 0,56 (br s, 6H).	(B) (M+H) 393,2036
257: (S) - 3 - (2 - ((S) - 1 - (4 - (1H- pirazol- 1- il) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,18 (d, J = 2,5 Hz, 1H), 8,16 (d, J = 5,8 Hz, 1H), 7,72 (d, J = 1,8 Hz, 1H), 7,69 (d, J = 1,9 Hz, 1H), 7,67 (d, J = 2,0 Hz, 1H), 7,52- 7,44 (m, 2H), 7,37 (d, J = 5,8 Hz, 1H), 6,56- 6,49 (m, 1H), 5,11 (q, J = 7,1 Hz, 1H), 4,68 (s, 1H), 4,40- 4,24 (m, 2H), 1,86 (s, 1H), 1,57 (d, J = 7,1 Hz, 3H), 0,71 (s, 3H), 0,59 (s, 3H) .	HRMS (B) (M+H) 393,2050
258: (4S)- 4- isopropil- 3- (2- (1- (5- metil- 1- fenil- 1H- pirazol- 4- il)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	8,17 (dd, J = 5,8, 4,6 Hz, 1H), 7,67 (s, 0,5 H), 7,61 (s, 0,5 H), 7,55 (dd, J = 8,5, 6,7 Hz, 2H), 7,52- 7,47 (m, 1H), 7,44 (ddd, J = 8,1, 3,3, 1,4 Hz, 2H), 7,40 (d, J = 5,8 Hz, 1H), 5,17 (dq, J = 10,4, 6,9 Hz, 1H), 4,83- 4,77 (m , 1H), 4,45- 4,34 (m, 2H), 2,66 (td, J = 7,0, 3,5 Hz, 0,5 H), 2,45 (br s, 0,5 H), 2,32 (s, 1,5 H), 2,31 (s, 1,5 H), 1,59 (dd, J = 6,8, 1,7 Hz, 3H), 1,01 (d, J = 7,0 Hz, 1,5 H), 0,94 - 0,85 (m, 3H), 0,81 (d, J = 6,9 Hz, 1,5 H).	HRMS (B) (M+H) 407,2202
259: (R) - 3 - (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) - 4 - (piridin- 2- il) oxazolidin- 2- ona	8,60 (ddd, J = 4,8, 1,7, 0,9 Hz, 1H), 8,10 (d, J = 5,7 Hz, 1H), 7,89 (td, J = 7,7, 1,8 Hz, 1H), 7,46- 7,36 (m, 3H) , 7,33- 7,28 (m, 4H), 7,21 (ddd, J = 8,6, 5,5, 2,2 Hz, 1H), 5,66 (br s, 1H), 4,79 (t, J = 8,9 Hz, 1H), 4,60 (br s , 1H), 4,31 (dd, J = 8,9, 3,8 Hz, 1H), 1,22 (d, J = 6,6 Hz, 3H).	HRMS (B) (M+H) 362,1617
260: (S) - 3 - (2 - ((S) - 1 - (2- fluorofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,51 (d, J = 5,7 Hz, 1H), 7,76- 7,51 (m, 3H), 7,48- 7,37 (m, 2H), 5,71 (q, J = 7,0 Hz, 1H), 5.6 a 5.2 (m, 1H) , 4,75- 4,61 (m, 2H), 2,30 (br s, 1H), 1,89 (d, J = 7,0, 3H), 1,10 (d, J = 7,1 Hz, 3H), 0,95 (d, J = 7,0 Hz, 3H).	HRMS (B) (M+H) 393,2026
261: (S)- 4- isopropil- 3- (2 - ((S) - 1 - (6- fenoxipiridin- 3- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8.25 a 8.5 (m, 2H), 7,83 (dd, J = 8,6, 2,5 Hz, 1H), 7,50- 7,34 (m, 3H), 7.27 a 7.16 (m, 1H), 7.15 - 7.2 (m, 2H), 6,89 (d, J = 8,5 Hz, 1H), 5,10 (q, J = 7,1 Hz, 1H), 4,75- 4,61 (m, 1H), 4,41- 4,29 (m, 2H), 1,94 (br s, 1H), 1,56 (d, J = 7,1 Hz, 3H), 0,78 (br s, 3H), 0,70 (br s, 3H).	HRMS (B) (M+H) 420,2019
262: (S) - 3 - (5- fluoro- 2- (1 - (4- fenoxifenil) etilamino) pirimidin- 4- il)	8,16 (d, J = 3,5 Hz, 1H), 7,45- 7,28 (m, 4H), 7,09 (tt, J = 7,3, 1,1 Hz, 1H), 7,02- 6,89 (m, 4H), 4,99 (q, J = 6,9 Hz, 1H),	HRMS (B) (M+H)

oxazolidin- 2- ona	4,58- 4,48 (m, 2H), 4,18 (ddd, J = 9,7, 8,5, 7,2 Hz, 1H), 3,99 (br s, 1H), 1,52 (d, J = 6,9 Hz, 3H) .	395,1507
263: (S) - 3 - (2 - (1 - (4- fenoxifenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,09 (d, J = 5,8 Hz, 1H), 7,43- 7,29 (m, 5H), 7,09 (tt, J = 7,3, 1,1 Hz, 1H), 7,00- 6,90 (m, 4H), 5,07 (q, J = 7,0 Hz, 1H), 4,53- 4,41 (m, 2H), 4,21 (ddd, J = 10,5, 9,2, 7,0 Hz, 1H), 4,01 (br s, 1H), 1,53 (d, J = 7,0 Hz, 3H) .	HRMS (B) (M+H) 377,1600
264: (4S)- 4- isopropil- 3- (2- ((1- (4- ((tetrahidro- 2H- piran- 4- il)oxi)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	8,12 (dd, J = 8,5, 5,8 Hz, 1H), 7,35 (dd, J = 5,8, 1,0 Hz, 1H), 7,32- 7,19 (m, 2H), 6,95- 6,86 (m, 2H), 4,98 (dq, J = 25,6, 7,2 Hz, 1H), 4,68 (br s, 0,5 H), 4,59- 4,48 (m, 1,5 H), 4,39- 4,25 (m, 2H), 4,01- 3,90 (m, 2H), 3,65- 3,53 (m, 2H), 2,74- 2,61 (m, 0,5 H), 2,08- 1,96 (m, 2H), 1,95 (br s, 0,5 H), 1,78- 1,64 (m, 2H), 1,50 (dd, J = 6,9 , 1,6 Hz, 3H), 1,01 (d, J = 7,0 Hz, 1,5 H), 0,88 (d, J = 6,9 Hz, 1,5 H), 0,75 (br s, 1,5 H), 0,62 (br s, 1,5 H) .	
265: (S) - 3 - (2 - ((S) - 1 - (4 - (4- fluorofenoxi) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,14 (d, J = 5,8 Hz, 1H), 7,37 (d, J = 5,8 Hz, 1H), 7,36- 7,31 (m, 2H), 7.12 - 7.5 (m, 2H), 7,01- 6,94 (m, 2H) , 6,94- 6,89 (m, 2H), 5,06 (q, J = 7,0 Hz, 1H), 4,71 (br s, 1H), 4,41- 4,29 (m, 2H), 1,99 (br s, 1H), 1,52 (d , J = 7,0 Hz, 3H), 0,77 (br s, 3H), 0,67 (br s, 3H).	HRMS (B) (M+H) 437,1981
266: (R) - 3 - (2 - ((S) - 1 - (4- bromofenil) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,46 (d, J = 5,8 Hz, 1H), 7,84- 7,73 (m, 5H), 7,72- 7,67 (m, 1H), 7,64 (dd, J = 7,1, 1,8 Hz, 2H), 7,59- 7,53 (m, 2H), 5,92 (dd, J = 8,6, 4,0 Hz, 1H), 5,13 (t, J = 8,7 Hz, 1H), 4,98 (q, J = 8,4, 7,5 Hz, 1H), 4,55 (dd, J = 8,7 , 4,0 Hz, 1H), 1,58 (d, J = 7,0 Hz, 3H).	HRMS (B) (M+H) 439,0762
267: (R) - 3 - (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) - 4 - (piridin- 3- il) oxazolidin- 2- ona	8,60 (d, J = 2,5 Hz, 1H), 8,55 (dd, J = 4,8, 1,5 Hz, 1H), 8,12 (d, J = 5,8 Hz, 1H), 7,81 (dt, J = 7,8, 2,0 Hz, 1H), 7,54- 7,47 (m, 1H), 7,41 (d, J = 5,8 Hz, 1H), 7,36- 7,25 (m, 4H), 7.25- 7.17 (m, 1H), 5,60 (br s, 1H), 4,80 (t, J = 8,9 Hz, 1H), 4,61 (br s, 1H), 4,27 (dd, J = 9,0, 4,1 Hz, 1H), 1,25 (br d, J = 7,5 Hz, 3H).	HRMS (B) (M+H) 362,1615
268: (R) - 3 - (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) - 4 - (piridin- 4- il) oxazolidin- 2- ona	8,61- 8,60 (m, 2H), 8,14 (d, J = 5,8 Hz, 1H), 7,43 (d, J = 5,8 Hz, 1H), 7,42- 7,37 (m, 2H), 7,32 (t, J = 7,5 Hz , 2H), 7.28- 7.17 (m, 3H), 5,57 (br s, 1H), 4,80 (t, J = 9,0 Hz, 1H), 4,55 (br s, 1H), 4,22 (dd, J = 9,0, 4,1 Hz, 1H), 1,20 (br s, 3H).	HRMS (B) (M+H) 362,1610
269: (S) - 3 - (2 - ((S) - 1 - (3- metoxifenil) etilamino) pirimidin- 4- il)- 4-	8,46 (d, J = 5,7 Hz, 1H), 7,73 (d, J = 5,8 Hz, 1H), 7,64- 7,52 (m, 5H), 7,48 (t, J = 7,8 Hz, 1H), 7.11 - 7.3 (m , 3H), 6,18 (dd, J =	HRMS (B) (M+H)

feniloxazolidin- 2- ona	8,7, 3,7 Hz, 1H), 5.25- 5.13 (m, 2H), 4,60 (dd, J = 8,7, 3,7 Hz, 1H), 4,10 (s, 3H), 1,81 (d, J = 7,0 Hz, 3H).	391,1771
270: (4S) - 3 - (2 - (1 - (bifenil- 4- il) etilamino) pirimidin- 4- il) - 5,5- dimetil- 4- feniloxazolidin- 2- ona	8,50- 8,45 (m, 1H), 7,95 (ddt, J = 7,6, 5,3, 2,3 Hz, 3H), 7,83- 7,64 (m, 8H), 7,63- 7,54 (m, 2H), 7,49 (dd, J = 4,9 , 3,0 Hz, 2H), 5,83 (s, 0,5 H), 5,57 (s, 0,5 H), 5.29- 5.24 (m, 0,5 H), 5,04- 4,99 (m, 0,5 H), 2,02 (s, 1,5 H) , 1,85- 1,84 (m, 3H), 1,62 (d, J = 7,0 Hz, 1,5 H), 1,35 (d, J = 3,3 Hz, 3H).	HRMS (B) (M+H) 465,2284
271: (S) - 3 - (2 - ((S) - 1 - (4- fluorofenil) etilamino) pirimidin- 4- il)- 4- isopropil- 4- metiloxazolidin- 2- ona	8,15 (d, J = 5,8 Hz, 1H), 7,41- 7,29 (m, 2H), 7,25 (d, J = 5,8 Hz, 1H), 7,09- 6,98 (m, 2H), 4,96 (q, J = 7,1 Hz , 1H), 4,29 (d, J = 9,0 Hz, 1H), 3,88 (d, J = 8,9 Hz, 1H), 2,17 (br s, 1H), 1,70 (s, 3H), 1,53 (d, J = 7,0 Hz, 3H), 0,70 (br s, 3H), 0,44 (br s, 3H).	HRMS (B) (M+H) 359,1889
272: (S)- 4,4- dimetil- 3- (2- (1- (4- ((4- metilpiperazin- 1- il)metil)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	8,12 (d, J = 5,8 Hz, 1H), 7,35 - 7.26i (m, 4H), 7,17 (d, J = 5,9 Hz, 1H), 5,02 (q, J = 6,9 Hz, 1H), 4,06 (q, J = 8,4 Hz, 2H), 3,51 (s, 2H), 2,49 (br s, 8H), 2,28 (s, 3H), 1,70 (s, 3H), 1,53 (d, J = 7,0 Hz, 3H), 1,15 (br s, 3H).	HRMS (B) (M+H) 425,2661
273: (R)- 5,5- dimetil- 3- (2- ((S)- 1- (4- ((4- metilpiperazin- 1- il)metil)fenil)etilamino)pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,09 (d, J = 5,8 Hz, 1H), 7,50- 7,39 (m, 3H), 7,36 (tt, J = 7,1, 1,4 Hz, 1H), 7,30 (s, 4H), 7,21 (br s, 2H), 5,22 (br s, 1H), 4,58 (br s, 1H), 3,53 (s, 2H), 2,50 (br s, 8H), 2,28 (s, 3H), 1,52 (s, 3H), 1,19 (d, J = 6,8 Hz, 3H), 0,99 (s, 3H).	HRMS (B) (M+H) 501,2971
274: (S)- 5,5- dimetil- 3- (2- ((S)- 1- (4- ((4- metilpiperazin- 1- il)metil)fenil)etilamino)pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	8,08 (d, J = 5,8 Hz, 1H), 7,45 (d, J = 5,8 Hz, 1H), 7,38- 7,23 (m, 3H), 7,16 (t, J = 7,5 Hz, 4H), 7,00 (br s, 2H), 5,51 (s, 1H), 4,89- 4,83 (m, 1H), 3,49 (d, J = 2,3 Hz, 2H), 2,50 (br s, 8H), 2,29 (s, 3H), 1,67 (s, 3H), 1,44 (d, J = 6,9 Hz, 3H), 1,00 (s, 3H).	HRMS (B) (M+H) 501,2981
275: (S)- 4- isopropil- 4- metil- 3- (2- ((S)- 1- (4- ((4- metilpiperazin- 1- il)metil)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	8,14 (d, J = 5,9 Hz, 1H), 7,29 (s, 4H), 7,24 (d, J = 5,9 Hz, 1H), 4,97 (t, J = 7,0 Hz, 1H), 4,60 (br s, 1H) , 4,29 (d, J = 8,8 Hz, 1H), 3,88 (d, J = 9,0 Hz, 1H), 3,51 (s, 2H), 2,59 (br s, 8H), 2,28 (s, 3H), 1,71 (s , 3H), 1,52 (d, J = 6,9 Hz, 3H), 0,70 (br s, 3H), 0,39 (br s, 3H).	
276: (S)- 4- isopropil- 5,5- dimetil- 3- (2- (((S)- 1- (4- ((4- metilpiperazin- 1- il)metil)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	8,14 (d, J = 5,8 Hz, 1H), 7,39- 7,20 (m, 5H), 5,09 (q, J = 7,0 Hz, 1H), 4,49 (br s, 1H), 3,52 (s, 2H), 2,57 (br s, 8H), 2,32 (s, 3H), 2,03 (br s, 1H), 1,54 (s, 3H), 1,51 (d, J = 7,0 Hz, 3H), 1,42 (s, 3H), 0,75 (br s, 3H), 0,62 (br s, 3H).	HRMS (B) (M+H) 453,2975
277: (S)- 4- isopropil- 3- (2 - ((S) - 1 - (4 - (piridin-	8,60 (ddd, J = 4,9, 1,8, 1,0 Hz, 1H), 8,16 (d, J = 5,8 Hz, 1H), 7,94- 7,86 (m, 3H),	HRMS (B)

2- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	7,84 (dt, J = 7,9, 1,2 Hz, 1H) , 7,51- 7,43 (m, 2H), 7,41- 7,32 (m, 2H), 5,12 (q, J = 7,0 Hz, 1H), 4,67 (br s, 1H), 4,40- 4,18 (m, 2H), 1,83 (br s, 1H), 1,58 (d, J = 7,1 Hz, 3H), 0,68 (br s, 3H), 0,56 (br s, 3H).	(M+H) 404,2089
278: (S)- 4- isopropil- 3- (2 - ((S) - 1 - (6- fenilpiridin- 3- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,60 (d, J = 2,2 Hz, 1H), 8,18 (d, J = 5,8 Hz, 1H), 7,95- 7,89 (m, 2H), 7,87 (dd, J = 8,2, 2,3 Hz, 1H), 7,81 (dd , J = 8,3, 0,8 Hz, 1H), 7,55- 7,42 (m, 3H), 7,40 (d, J = 5,8 Hz, 1H), 5,16 (q, J = 7,1 Hz, 1H), 4,66 (br s, 1H), 4,40- 4,22 (m, 2H), 1,74 (br s, 1H), 1,62 (d, J = 7,0 Hz, 3H), 0,67 (br s, 3H), 0,57 (br s, 3H).	HRMS (B) (M+H) 404,2079
279: (S)- 4- isopropil- 3- (2 - ((S) - 1 - (quinolin- 6- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,81 (dd, J = 4,3, 1,6 Hz, 1H), 8,32 (dt, J = 8,2, 1,1 Hz, 1H), 8,18 (d, J = 5,8 Hz, 1H), 8,01 (d, J = 8,7 Hz, 1H), 7,89- 7,76 (m, 2H), 7,53 (dd, J = 8,3, 4,4 Hz, 1H), 7,37 (d, J = 5,8 Hz, 1H), 5,24 (q, J = 7,1 Hz, 1H), 4,59 (br s, 1H), 4,30 (t, J = 8,7 Hz, 1H), 4,22 (br s, 1H), 1,64 (d, J = 7,1 Hz, 3H), 1,49 (br s, 1H), 0,35 (br s, 6H).	HRMS (B) (M+H) 378,1930
280: (S)- 4- isopropil- 3- (2 - ((S) - 1 - (quinolin- 7- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	8,81 (dd, J = 4,3, 1,7 Hz, 1H), 8,34 (dt, J = 8,4, 1,2 Hz, 1H), 8,13 (d, J = 5,9 Hz, 1H), 8,00 (d, J = 1,6 Hz, 1H), 7,93 (d, J = 8,5 Hz, 1H), 7,68 (dd, J = 8,6, 1,8 Hz, 1H), 7,50 (dd, J = 8,3, 4,4 Hz, 1H), 7,36 (d, J = 5,8 Hz , 1H), 5.23- 5.17 (m, 1H), 4,50 (br d, J = 84,2 Hz, 1H), 4,35- 4,25 (m, 1H), 4,19 (br s, 1H), 2,68 (pd, J = 7,0 , 3,5 Hz, 1H), 1,65 (d, J = 7,0 Hz, 3H), 1,01 (d, J = 7,0 Hz, 3H), 0,86 (d, J = 6,9 Hz, 3H).	HRMS (B) (M+H) 378,1941
281: (S) - 3 - (2 - ((S) - 1 - (4- benzoilfenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,17 (d, J = 5,8 Hz, 1H), 7,81- 7,71 (m, 4H), 7,69- 7,61 (m, 1H), 7,59- 7,49 (m, 4H), 7,39 (d, J = 5,8 Hz, 1H) , 5,15 (q, J = 7,1 Hz, 1H), 4,67 (br s, 1H), 4,41- 4,23 (m, 2H), 1,75 (br s, 1H), 1,58 (d, J = 7,1 Hz, 3H), 0,69 (br s, 3H), 0,61 (br s, 3H).	HRMS (B) (M+H) 431,2072
282: (S)- 3- (2- ((S)- 1- (3- fluoro- 4- (2- metil- 1H- imidazol- 1- il)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	8,18 (d, J = 7,1 Hz, 1H), 7,75 (d, J = 7,3 Hz, 1H), 7,71- 7,62 (m, 3H), 7,58 (dd, J = 10,9, 1,9 Hz, 1H), 7,51 (dd , J = 8,2, 1,8 Hz, 1H), 5,33 (br s, 1H), 4,81- 4,73 (m, 1H), 4,46- 4,36 (m, 2H), 2,54 (s, 3H), 2,03 (br s, 1H), 1,64 (d, J = 7,0 Hz, 3H), 0,84 (br d, J = 7,2 Hz, 3H), 0,70 (br d, J = 7,2 Hz, 3H).	HRMS (B) (M+H) 425,2093
283: (4S)- 4- isopropil- 3- (2- (1- (4- (2- metil- 1H- imidazol- 1- il)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	8,15 (dd, J = 8,9, 5,8 Hz, 1H), 7,60- 7,50 (m, 2H), 7,42- 7,32 (m, 3H), 7,14 (dd, J = 13,3, 1,5 Hz, 1H), 6,96 (dd, J = 3,5, 1,5 Hz, 1H), 5,17 (q, J = 7,1 Hz, 0,5 H), 5,07 (d, J = 7,4 Hz, 0,5 H), 4,71 (br s, 0,5 H), 4,50	HRMS (B) (M +) 406,2217

	(br s, 0,5 H), 4,40- 4,24 (m, 2H), 2,67 (ddq, J = 10,6, 7,0, 3,6 Hz, 0,5 H), 2,323 (s, 1,5 H), 2,321 (s, 1,5 H), 1,95 (br s , 0,5 H), 1,58 (dd, J = 7,0, 2,3 Hz, 3H), 1,02 (d, J = 7,0 Hz, 1,5 H), 0,88 (d, J = 6,9 Hz, 1,5 H), 0,76 (br s, 1,5 H), 0,64 (br s, 1,5 H).	
284: (S) - 3 - (2 - (((R)- 1- ciclopentiletil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona		HRMS (B) m/z 319,2133 (M + H)+, RT = 2,68 min.
285: (S) - 3 - (2 - (((S) - 1 - (4 - (dimetilamino) fenil) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona		HRMS (B) m/z 370,2227 (M + H)+, RT = 2,47 min.
286: N- (3 - ((S) - 1 - ((4 - ((S)- 2- oxooxazolidin- 3- il 4- isopropil- pirimidin- 2- il) amino)) Etilfenil) acetamida		HRMS (B) m/z 384,2032 (M + H)+, RT = 1,97 min
287: (S) - 3 - (2 - (((S) - 1 - (1H- benzo [d] imidazol- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona		HRMS (B) m/z 367,1887 (M + H)+ RT = 2,39 min.
288: (S)- 3- (2- (((S)- 1- (4- ((4- clorofenil)sulfonil)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona		HRMS (B) m/z 501.1343, (M + H)+ RT = 2,68 min.
289: (S)- 4- isopropil- 3- (2 - (((S) - 1 - (4- nitrofenil) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona		HRMS (B) m/z 372.1672, (M + H)+, RT = 2,59 min.
290: (S) - 3 - (2 - (((S) - 1 - (4- aminofenil) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona		HRMS (B) m/z 342.1931, (M + H)+, RT = 2,17 min
291: (S)- 4- isopropil- 3- (2 - ((S) - 1 (- (5 -		HRMS (B) m/z

(metiltio) - 1,3,4-oxadiazol- 2- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona		365.1367, (M + H)+, RT = 1,88 min.
292: (S)- 4- isopropil- 3- (2 - (((S) - 1 - (5- fenil- 1 ,3,4- tiadiazol- 2- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona	($CDCl_3$) δ 8,15 (d, J = 5,9 Hz, 1H), 7,87-7,74 (m, 2H), 7,51 (d, J = 5,9 Hz, 1H), 7,46- 7,28 (m, 3H), 6,39 (b, 1H), 5,43 (s, 1H), 4,58 (dt, J = 8,3, 3,3 Hz, 1H), 4.29-4.12 (m, 2H), 1,94- 1,80 (b, 1H), 1,74 (d, J = 7,0 Hz , 3H), 0,69 (d, J = 6,8 Hz, 3H), 0,60 (d, J = 7,2 Hz, 3H)	HRMS (B) m/z 411,1596 (M + H)+, RT = 2.54min.
293: (S)- 3- {2- [1- (5- Cloro- 1H- benzoimidazol- 2- il)- etilamino]- pirimidin- 4- il}- 4- isopropil- oxazolidin- 2- ona		HRMS (B) m/z 400,1414, RT = 2,04 min.
294: (S)- 3- (2- {(S)- 1- [5- (2,2- Dimetil- propil)- isoxazol- 3- il]- etilamino}- pirimidin- 4- il)- 4- isopropil- oxazolidin- 2- ona	($CDCl_3$) δ 8,22 (d, J = 5,7 Hz, 1,0 H), 7,52 (d, J = 5,8 Hz, 0,95 H), 5,92 (s, 0,96 H), 5,50 (d, J = 7,5 Hz, 0,97 H) , 5,22 (s, 0.83H), 4,72 (d, J = 8,3 Hz, 1,0 H), 4,42-4,20 (m, 2,06 H), 3,51 (s, 0,27 H), 2,61 (s, 2,05 H), 1,62 (d, J = 7,0 Hz, 4,13 H), 0,97 (s, 8,95 H), 0,90 (d, J = 7,0 Hz, 2,56 H), 0,80 (d, J = 7,0 Hz, 2,93 H).	HRMS (B) m/z 387,2271
295: (4S)- 4- isopropil- 3- (2 - (1 - (5- fenilpirimidin- 2- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	(CDCl3) δ 8,93 (d, J = 5,9 Hz, 4H), 8.26-8.17 (m, 2H), 7,64- 7,44 (m, 12H), 6,41 (br s, 1H), 5,31 (br s, 1H), 4,79- 4,65 (m, 2H), 4,41- 4,24 (m, 4H), 2,65 (dddd, J = 27,4, 14,1, 7,1, 3,5 Hz, 1H), 2,20 (br s, 1H), 1,75- 1,64 (m, 4H), 1,07- 0,85 (m, 9H), 0,78 (s, 3H).	HRMS (B) m/z 405,2024 y 405,2025 (M + H)+.
296: éster benciclo del ácido 4- {(S)- 1- [4- ((S)- 4- Isopropil- 2- oxo- oxazolidin- 3- il)- pirimidin- 2- ilamino]- etil}- piperidine- 1- carboxilico		HRMS (B) (M +) = 467.2533 RT:. 2.83 min.
297: (S) - 3 - (2 - ((S) - 1 - (5- bromopiridin- 2- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.		HRMS (B) m/z 406,0870 (M + H)+. RT:. 2,50 min.
298: 3- (5- fluoro- 2- ((1- (5- (4- fluoro- 3- metilfenil)piridin- 2- il)etil)amino)pirimidin- 4-		HRMS (B) m/z 412,1578 (M + H)+.

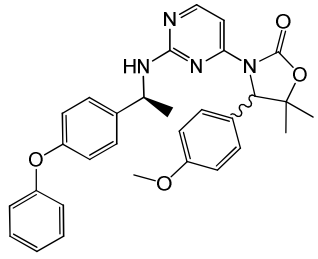
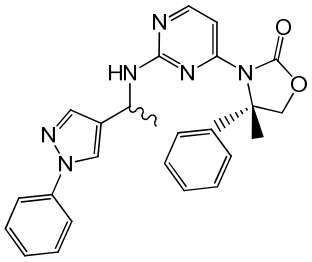
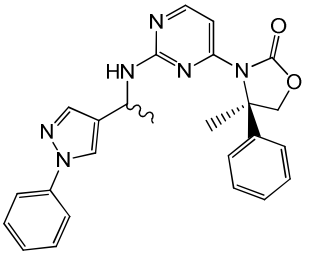
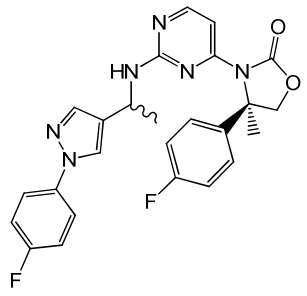
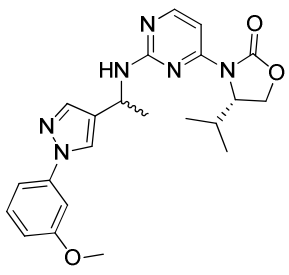
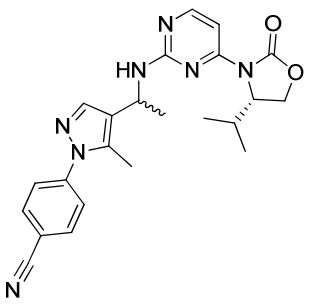
il)oxazolidin- 2- ona		RT:. 2,35 min.
299: 3 - (2 - (1 - (5 - (4- fluorofenoxi) pirimidin- 2- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona.		HRMS (B) m/z 411,1572 (M + H)+. RT:. 2,25 min.
300: 3 - (5- fluoro- 2- (1 - (5 - (4- fluorofenoxi) pirimidin- 2- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona.		HRMS (B) m/z 415,1320 (M + H)+. RT:. 2,26 min.
301: (4S)- 3- (2- (1- (5- (2,4- difluorobencicloxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	($CDCl_3$) δ 8,45 (d, J = 4,6 Hz, 4H), 8,21 (d, J = 5,8 Hz, 2H), 7,53- 7,41 (m, 4H), 6,93 (ddddd, J = 19,9, 9,8, 8,7, 2,6 , 1,2 Hz, 4H), 6,21 (s, 1H), 6,11 (s, 1H), 5,21 (br s, 2H), 5,18 (s, 2H), 5,16 (s, 2H), 4,74 (dt, J = 7,7 , 3,3 Hz, 1H), 4,66 (d, J = 7,4 Hz, 1H), 4,38- 4,24 (m, 4H), 2,65 (ddq, J = 10,5, 7,1, 3,5 Hz, 1H), 2,30 (br s, 1H), 1,65- 1,59 (m, 6H), 1,01 (d, J = 7,0 Hz, 3H), 0,89 (q, J = 7,6, 4,9, 4,4 Hz, 6H), 0,79 (d, J = 6,5 Hz, 3H) .	MS m/z 471,8 (M + H)+.
302: (S)- 3- (2- {(S)- 1- [4- (4- Fluoro- fenoxi)- ciclohexil]- etilamino}- pirimidin- 4- il)- 4- isopropil- oxazolidin- 2- ona		CL- MS m/z 442,53 (M + H)+; RT: 1,77 min..
303: (4S)- 3- (2- (1- (5- (5- bromopiridin- 3- iloxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(CDCl3) δ 8,62- 8,49 (m, 6H), 8,44- 8,36 (m, 2H), 8,22 (dd, J = 5,7, 0,6 Hz, 2H), 7,57- 7,46 (m, 4H), 6,14 (br s, 2H), 5,33 (br s, 2H), 4,76 (dt, J = 8,2, 3,4 Hz, 1H), 4,67 (s, 1H), 4,40- 4,26 (m, 4H), 2,67 (pd, J = 7,0, 3,4 Hz, 1H), 2,32 (br s, 1H), 1,69- 1,61 (m, 6H), 1,02 (d, J = 7,0 Hz, 3H), 0,99 a 0,80 (m, 9H).	HRMS (B) m/z 500,1038 y 500,1034 (M + H)+.
304: (S) - 3 - (2 - ((S) - 1 - (5- cloropirimidin- 2- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.	($CDCl_3$) δ 8,58 (s, 2H), 8,12 (d, J = 5,8 Hz, 1H), 7,40 (d, J = 5,8 Hz, 1H), 5,97 (br s, 1H), 5,17 (br s, 1H) , 4,63 (dt, J = 8,0, 3,2 Hz, 1H), 4.29- 4.15 (m, 2H), 2,10 (br s, 1H), 1,50- 1,46 (m, 3H), 0,88- 0,66 (m, 6H).	CL- MS m/z 363,1 (M + H)+; RT: 1,39 min..
305: (S)- 3- (2- ((S)- 1- (5- (3- cloro- 4- fluorofenoxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin-	($CDCl_3$) δ 8,36 (s, 2H), 8,13 (s, 1H), 7,41 (d, J = 5,4 Hz, 1H), 7,15- 7,00 (m, 2H), 6,85 (ddd, J = 9,0, 3,7, 3,0 Hz, 1H), 6,08 (s, 1H), 5,21 (br s, 1H), 4,66 (dt, J = 8,3, 3,4 Hz, 1H), 4.30- 4.16 (m, 2H), 2,25 (br s,	HRMS (B) m/z 473,1484 (M + H)+.

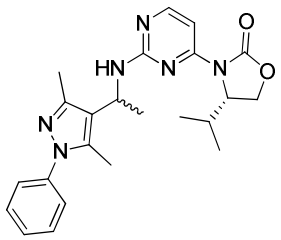
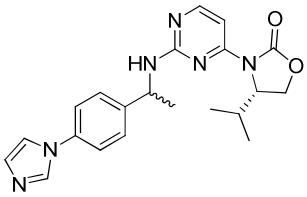
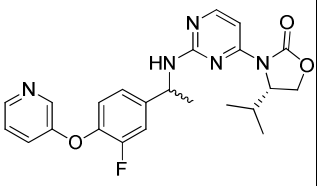
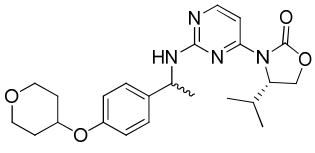
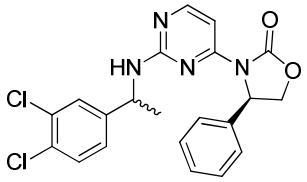
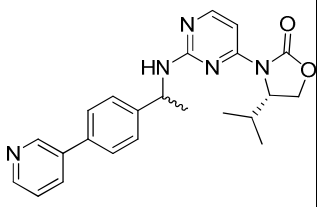
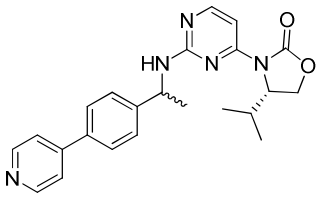
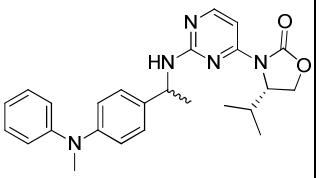
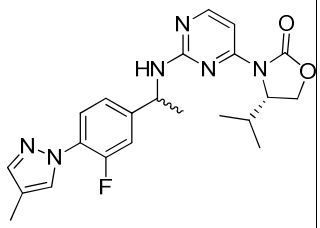
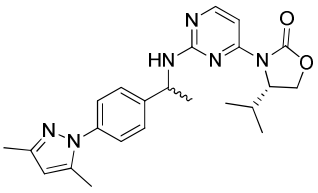
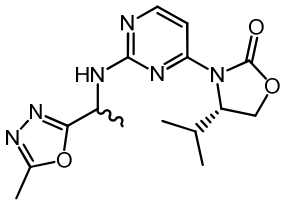
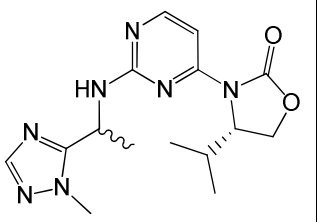
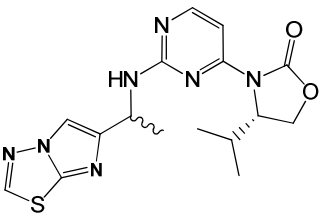
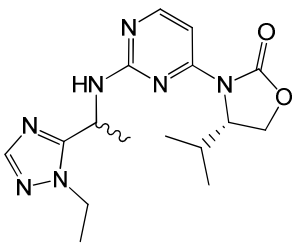
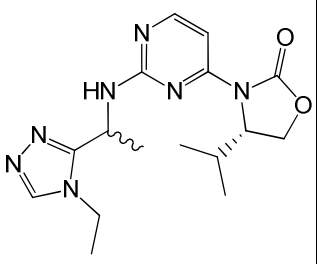
2- ona.	1H) , 1,56- 1,51 (m, 3H), 0,85- 0,78 (m, 3H), 0,77 a 0,70 (m, 3H).	
306: (4S)- 4- isopropil- 3- (2- (1- (5- (piridin- 3- iloxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)oxazolidin- 2- ona		HRMS (B) m/z 422,1938, 422,1944 y RT 1.91min, RT 2.01min (M + H)+.
307: (4S)- 3- (2- (1- (5- (3- fluorobencicloxi)pirimidin - 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	($CDCl_3$) δ 8,43 (d, J = 4,9 Hz, 4H), 8,21 (d, J = 5,7 Hz, 2H), 7,49- 7,34 (m, 4H), 7.26 a 7.2 (m, 6H), 6,20 (br s , 1H), 6,11 (br s, 1H), 5,22 (br s, 2H), 5,16 (s, 2H), 4,74 (dt, J = 7,7, 3,3 Hz, 1H), 4,66 (br s, 1H), 4,38 - 4,23 (m, 4H), 2,66 (heptd, J = 7,0, 3,5 Hz, 1H), 2,26 (br s, 1H), 1,64- 1,58 (m, 6H), 1,00 (d, J = 7,0 Hz, 3H) , 0,94 a 0,85 (m, 6H), 0,78 (br s, 3H).	HRMS (B) m/z 453,2048 y 453,2047 (M + H)+.
308: (S) - 3 - (2 - ((S) - 1 - (5- iodopirimidin- 2- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.		HRMS (B) m/z 454,0614 (M +). RT 2.35min
309: (4S)- 4- isopropil- 3- (2- (1- (5- (5- (trifluorometil)piridin- 2- iloxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)oxazolidin- 2- ona		HRMS (B) m/z 490,1800, 490,1795 y RT 2.17min, RT 2.23min (M + H)+.
310: (4S)- 4- isopropil- 3- (2 - (1 - (pirimidin- 2- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona		HRMS (B) m/z 329,1728, 329,1726 y RT 1.81min, RT 1,93 min (M + H)+.
311: (4S)- 3- (2- (1- (4- (4- fluorofenoxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	($CDCl_3$) δ 8,56 (dd, J = 5,7, 2,3 Hz, 2H), 8,20 (dd, J = 5,7, 4,0 Hz, 2H), 7,46 (dd, J = 5,7, 4,4 Hz, 2H), 7,20- 7,00 (m, 8H), 6,71 (dd, J = 5,7, 2,0 Hz, 2H), 6,03 (br s, 1H), 5,87 (br s, 1H), 5,11 (br s, 2H), 4,72- 4,61 (m, 2H), 4,40- 4,23 (m, 4H), 2,59 (DDP, J = 10,5, 7,1, 3,5 Hz, 1H), 2,21 (br s, 1H),	HRMS (B) m/z 439,1887 y 439,1887 (M + H)+.

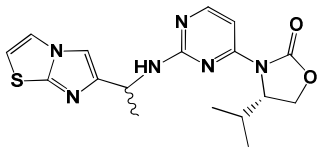
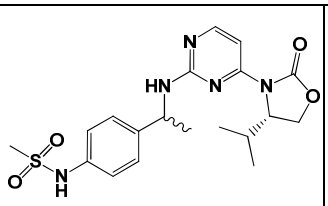
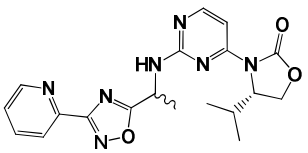
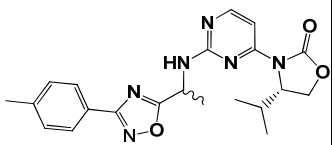
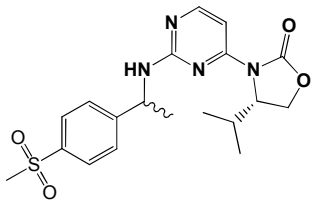
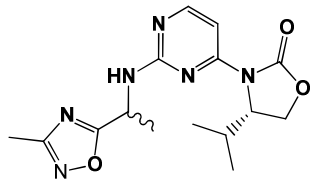
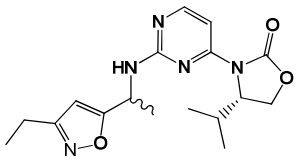
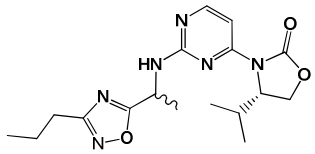
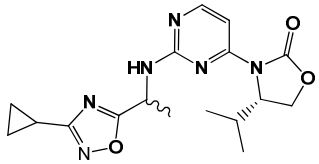
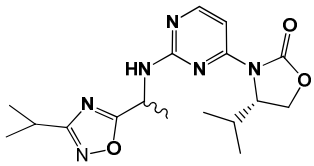
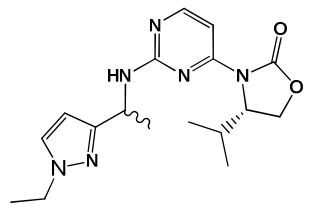
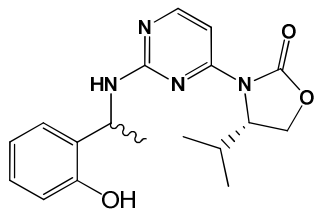
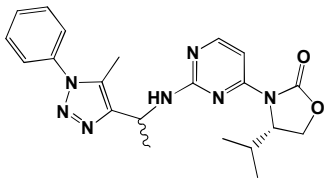
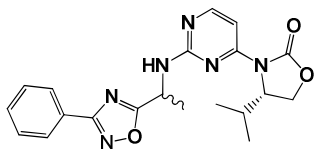
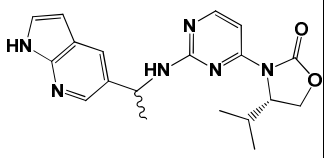
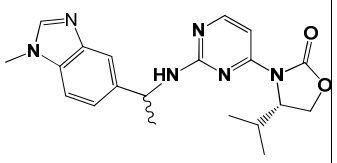
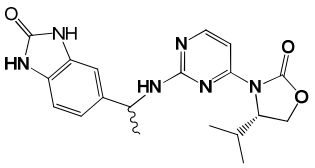
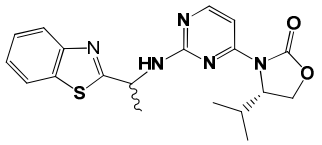
	1,59- 1,55 (m, 6H), 1,00- 0,85 (m, 9H), 0,80 (d, J = 6,3 Hz, 3H).	
312: (S)- 3- (2- ((S)- 1- (4- (((2S,6R)- 2,6- dimetilmorfolino)metil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	^{1}H RMN (400 MHz, CD_3OD) δ ppm 0,63 (br s., 3 H) 0,79 (br s., 3 H) 1,20 (dd, J = 6,26, 2,74 Hz, 6 H) 1,58 (d, J = 7,04 Hz, 3 H) 2,54- 2,82 (m, 2H) 3,73- 3,90 (m, 2 H) 4,32 (d, J = 3,52 Hz, 2 H) 4,39 (d, J = 5,87 Hz, 2 H) 4,68- 4,78 (m, 1 H) 5.15 a 5.31 (m, 1 H) 7,51 (s, 4 H) 7,62- 7,76 (m, 1 H) 8.8 - 8.22 (m, 1 H)	CLMS m/z 454,3 (M + H)+, Rt 0,57 min

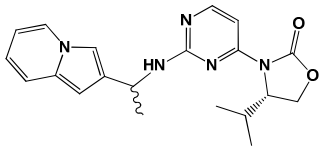
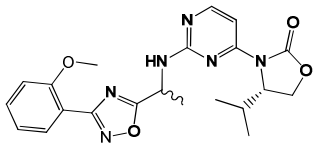
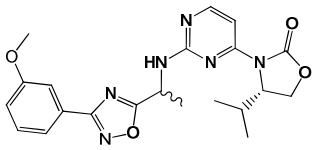
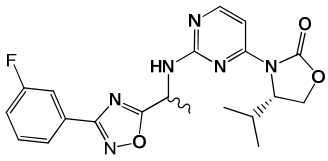
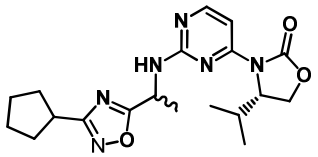
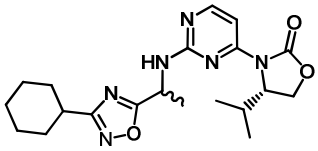
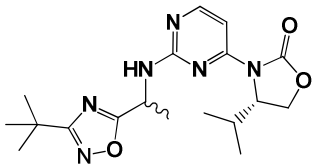
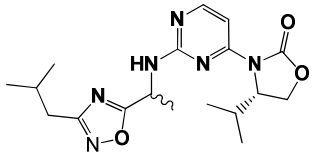
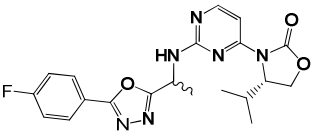
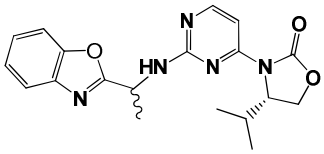
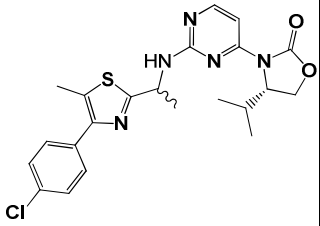
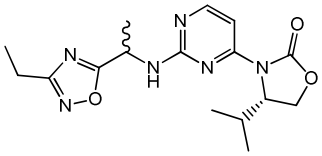
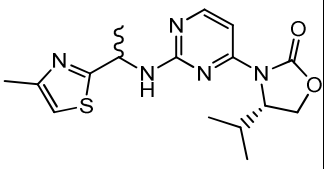
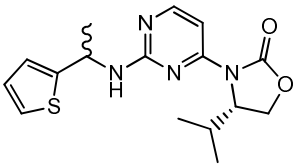
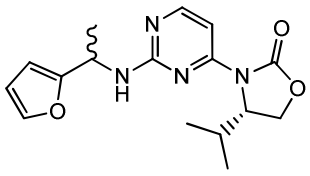
Los compuestos de la Tabla 9 se prepararon usando procedimientos sustancialmente similares a los descritos para la preparación de los Ejemplos 1, 113, y 171 a 212, incluyendo la separación quiral para aislar los dos diastereómeros.

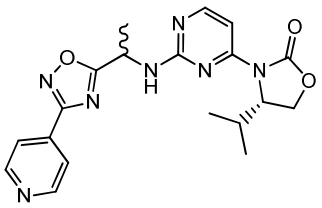
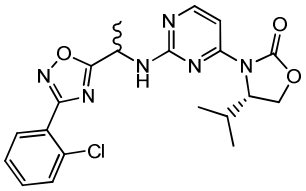
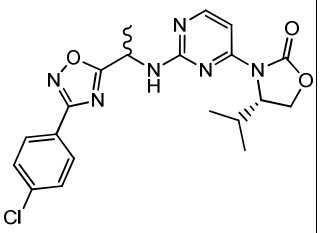
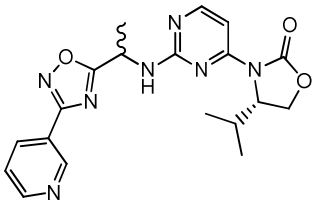
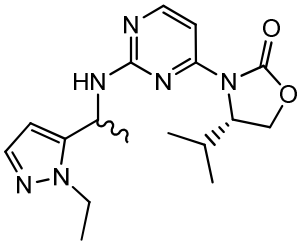
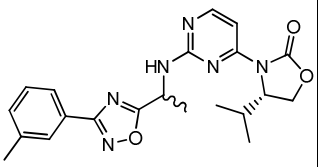
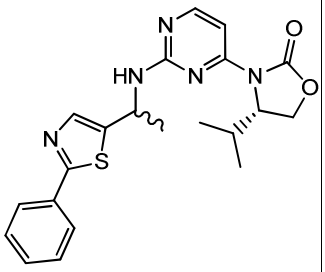
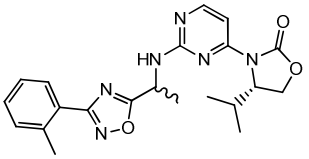
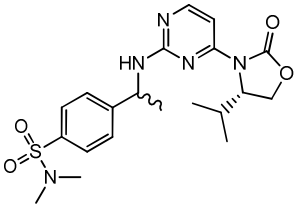
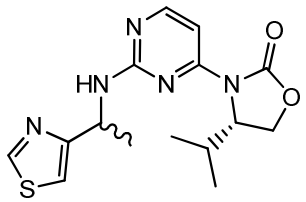
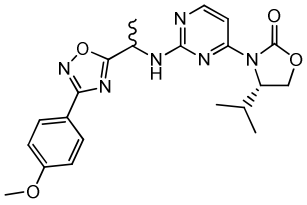
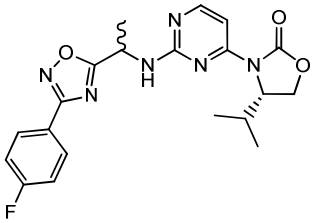
Tabla 9.

313 y 314	315 y 316	317 y 318
		
319 y 320	321 y 322	323 y 324
		
325 y 326	327 y 328	329 y 330

		
331 y 332	333 y 334	335 & 336
		
337 y 338	339 y 340	341 y 342
		
343 y 344	345 y 346	347 y 348
		
349 y 350	351 y 352	353 y 354
		
355 y 356	357 y 358	359 y 360

		
361 y 362	363 y 364	365 y 366
		
367 y 368	369 y 370	371 y 372
		
373 y 374	375 y 376	377 & 378
		
379 y 380	381 y 382	383 y 384
		
385 y 386	387 y 388	389 y 390
		

391 y 392	393 y 394	395 y 396
		
397 y 398	399 y 400	401 y 402
		
403 y 404	405 y 406	407 y 408
		
409 y 410	411 y 412	413 y 414
		
415 y 416	417 y 418	419 y 420
		
421 & 422	423 y 424	425 y 426

		
427	428 y 429	430
		
431 y 432	433 y 434	435 y 436
		
437 y 438	439 y 440	441 y 442
		
443	444 y 445	446 y 447

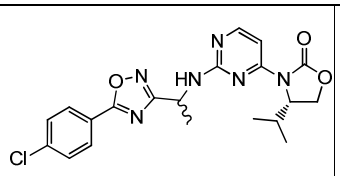
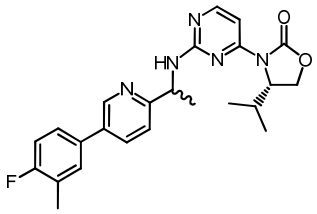
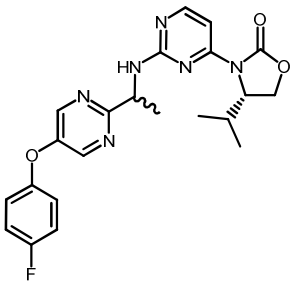
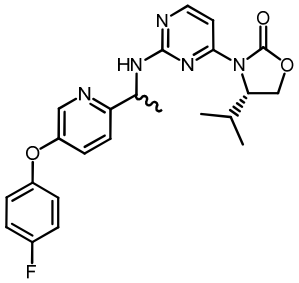
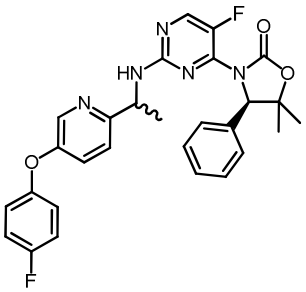
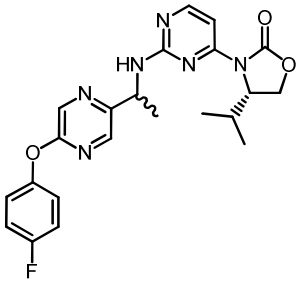
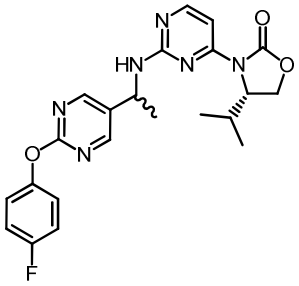
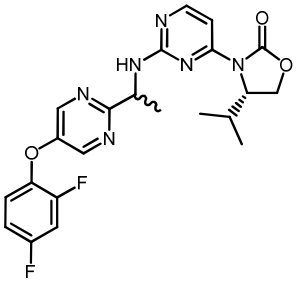
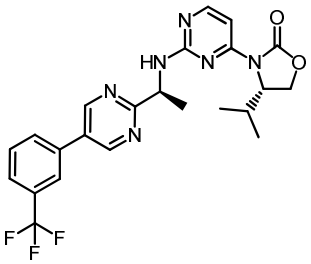
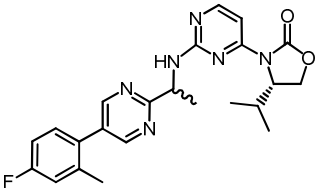
		
448 y 449	450 y 451	452 y 453
		
454 y 455	456	457
		
458		
		

Tabla 10. Nombre químico, desplazamientos químicos de RMN, las condicionas de separación quirales y señal LCMS para cada compuesto enumerado en la Tabla 9.

Ejemplo: Nombre	**Condicionas de separación quiral, identificación de los picos y los datos analíticos**

331 y 314: 4- (4- metoxifenil)- 5,5- dimetil- 3- (2- ((S)- 1- (4- fenoxifenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	La separación quiral se llevó a cabo con la SFC (IA- H, 5µM, 20 x 50 mm) utilizando 28% de MeOH en CO_2 para proporcionar (R)- 4- (4- metoxifenil)- 5,5- dimetil- 3- (2- (((S)- 1- (4- fenoxifenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- (4- metoxifenil)- 5,5- dimetil- 3- (2- (((S)- 1- (4- fenoxifenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona. Primer pico 313: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,03 (dd, J = 5,9, 1,6 Hz, 1H), 7,43 (d, J = 5,7 Hz, 1H), 7.30- 7.22 (m, 2H), 7,20 - 7,14 (m, 2H), 7,06- 7,00 (m, 1H), 6,98 (d, J = 8,2 Hz, 2H), 6,94- 6,86 (m, 4H), 6,83- 6,76 (m, 2H), 5,24 (br s , 1H), 5,01 (s, 1H), 4,57 (br s, 1H), 3,72 (s, 3H), 1,46 (s, 3H), 1.24 - 1.9 (m, 3H), 0,92 (s, 3H); HRMS (B) m/z 511,2326 (M + H)+. Segundo pico 314: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,11 (d, J = 5,7 Hz, 1H), 7,51 (d, J = 5,7 Hz, 1H), 7,38- 7,29 (m, 2H), 7,10 (tt, J = 7,3, 1,2 Hz, 1H), 7,06- 6,90 (m, 6H), 6,89- 6,82 (m, 2H), 6,82- 6,75 (m, 2H), 5,29 (s, 1H), 5,09 (br s, 1H), 4,80 (br s, 1H), 3,72 (s, 3H), 1,63 (s, 3H), 1,48 (d, J = 6,8 Hz, 3H), 1,01 (s, 3H); HRMS (B) m/z 511.2323 (M + H)+.
315 y 316: (S)- 4- metil- 4- fenil- 3- (2 - (1 - (1- fenil- 1H- pirazol- 4- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	La separación quiral se llevó a cabo con SFC (IA, 5µm, 20 x 250 mm) usando iPrOH al 45% con 0.2% CO_2 en Et_2NH para proporcionar (S)- 4- metil- 4- fenil- 3- (2- (((R)- 1- (1- fenil- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- metil- 4- fenil- 3- (2- (((S)- 1- (1- fenil- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona. Primer pico 315: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,19 (d, J = 5,8 Hz, 1H), 7,63- 7,60 (m, 2 H), 7,49- 7,44 (m, 4 H), 7,37- 7,28 (m, 4 H), 7.26 - 7.22 (m, 2 H), 7.12 - 7.8 (m, 1 H), 4,94 (br s, 1H), 4,45 (br s, 1H), 4.31- 4.27 (m, 2 H), 2,19 (s, 3H), 1,44 (d, J = 6,8 Hz, 3 H); HRMS (B) m/z 441,2036 (M + H)+. Segundo pico 316: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,20 (d, J = 5,8 Hz, 1H), 7,67- 7,63 (m, 3 H), 7,53 (s, 1H), 7,49- 7,44 (m, 3 H), 7,40- 7,37 (m, 2 H), 7,33- 7,30 (m, 4 H), 4,99 (br s, 1H), 4,38 (br s, 1H), 4,26 (s, 2 H), 2,00 (s, 3H), 1,07 (br s, 3 H); HRMS (B) m/z 441,2039 (M + H)+.
317 y 318: (R)- 4- metil- 4- fenil- 3- (2 - (1 - (1- fenil- 1H- pirazol- 4- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	La separación quiral se llevó a cabo con l SFC (IA, 5µm, 20 x 250 mm) con iPrOH al 45% modificado con CO_2 al 0.2% en Et_2NH para proporcionar (R)- 4- metil- 4- fenil- 3- (2- (((S)- 1- (1- fenil- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- metil- 4- fenil- 3- (2- (((S)- 1- (1- fenil- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona. Primer pico 317: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,20 (d, J = 5,8 Hz, 1H), 7,68- 7,63 (m, 3 H), 7,53 (s, 1H), 7,49-

	7,44 (m, 3 H), 7,41- 7,37 (m, 2 H), 7,33- 7,30 (m, 4 H), 4,98 (br s, 1H), 4,39 (br s, 1H), 4,26 (s, 2 H), 2,00 (s, 3H), 1,07 (br s, 3 H); HRMS (B) m/z 441,2037 (M + H)+. Segundo pico 318: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,17 (d, J = 5,8 Hz, 1H), 7,63- 7,60 (m, 2 H), 7,49- 7,44 (m, 4 H), 7,36- 7,29 (m, 4 H), 7.26 - 7.22 (m, 2 H), 7.12 a 7.8 (m, 1 H), 5,02 (br s, 1H), 4,45 (br s, 1H), 4.31- 4.26 (m, 2 H), 2,19 (s, 3H), 1,44 (d, J = 6,8 Hz, 3 H); HRMS (B) m/z 441,2039 (M + H)+.
319 y 320: (R)- 4- (4- fluorofenil)- 3- (2- (1- (1- (4- fluorofenil)- 1H- pirazol- 4- il)etilamino)pirimidin- 4- il)- 4- metiloxazolidin- 2- ona	La separación se realizó en una columna de gel de sílice de fase normal con 10 a 50% acetato de etilo/heptano para proporcionar (R)- 4- (4- fluorofenil)- 3- (2- (((R)- 1- (1- (4- fluorofenil)- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)- 4- metiloxazolidin- 2- ona y (R)- 4- (4- fluorofenil)- 3- (2- (((S)- 1- (1- (4- fluorofenil)- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)- 4- metiloxazolidin- 2- ona. Primer pico 319: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,10 (d, J = 5,8 Hz, 1H), 7,53- 7,48 (m, 3 H), 7,44 (s, 1 H), 7,36 (d, J = 5,8 Hz, 1 H), 7.22- 7.17 (m, 2 H), 7.9 a 7.3 (m, 2 H), 7,01- 6,95 (m, 2 H), 4,98 (br s, 1H), 4,33 (br s , 1 H), 4,15 (q, J = 8,6 Hz, 2 H), 1,90 (s, 3H), 1,04 (br s, 3 H); HRMS (B) m/z 477,1827 (M + H)+. Segundo pico 320: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,18 (d, J = 5,8 Hz, 1H), 7,62- 7,56 (m, 2 H), 7,45- 7,39 (m, 3 H), 7.31- 7.26 (m, 2 H), 7.18- 7.12 (m, 2 H), 6,93 (t, J = 8,6 Hz, 2 H), 5,01 (br s, 1 H), 4,50 (br s, 1 H), 4.30 a 4.23 (m, 2 H), 2,17 (s, 3H), 1,45 (d, J = 6,8 Hz, 3 H); HRMS (B) m/z 477,1829 (M + H)+.
321 y 322: (S)- 4- isopropil- 3- (2- (1- (1- (3- metoxifenil)- 1H- pirazol- 4- il)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	La separación se realizó en una columna de gel de sílice de fase normal con 10 a 50% acetato de etilo / heptano para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (1- (3- metoxifenil)- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (1- (3- metoxifenil)- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona. Primer pico 321: ^{1}H RMN (400 MHz, MeOD) δ 8,18 (dd, J = 3,3, 2,5 Hz, 2H), 7,70 (s, 1H), 7,42 (d, J = 5,8 Hz, 1H), 7,38 (t, J = 8,1 Hz, 1H), 7,31 (t, J = 2,3 Hz, 1H), 7,27 (ddd, J = 8,0, 2,1, 0,9 Hz, 1H), 6,89 (ddd, J = 8,1, 2,5, 0,9 Hz, 1H), 5,21 (q, J = 6,8 Hz, 1H), 4,81- 4,73 (m, 1H), 4,44- 4,34 (m, 2H), 3,87 (s, 3H), 2,64 (pd, J = 7,0, 3,5 Hz, 1H), 1,61 (d, J = 6,9 Hz, 3H), 0,99 (d, J = 7,1 Hz, 3H), 0,88 (d, J = 6,9 Hz, 3H). HRMS (B) (M+H) 423,2141 Calc 'd (M+H) 423.2145 Segundo pico 322: ^{1}H RMN (400 MHz, MeOD) δ 8,18 (d, J = 5,8 Hz, 1H), 8,10 (s, 1H), 7,63 (s, 1H), 7,41 (d, J = 5,8 Hz, 1H) , 7,37 (t, J = 8,2 Hz, 1H), 7,28 (t, J = 2,3 Hz, 1H), 7,24 (ddd, J = 8,1, 2,1, 0,9 Hz, 1H), 6,88 (ddd,

	J = 8,3, 2,5 , 0,9 Hz, 1H), 5,19 (q, J = 6,9 Hz, 1H), 4,74 (dt, J = 7,6, 3,5 Hz, 1H), 4,42- 4,28 (m, 2H), 3,86 (s, 3H), 2,31 (br s, 1H), 1,61 (d, J = 6,9 Hz, 3H), 0,79 (br s, 3H), 0,75 - 0,64 (br m, 3H). HRMS (B) (M+H) 423.2139 Calculado (M+H) 423,2145
323 y 324: 4- (4- (1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)- 5- metil- 1H- pirazol- 1- il)benzonitrile	Separación quiral se consiguió por SFC. (Columna: Chiralpak- ID (Semi- Prep 20mm x 250mm) isocrática: 65% de CO2: 35% MeOH (aditivo 5 mM NH4OH) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (1- (3- metoxifenil)- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (1- (3- metoxifenil)- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona. Primer pico 323: ^{1}H RMN (400 MHz, MeOD) δ 8,16 (d, J = 5,8 Hz, 1H), 7,95- 7,88 (m, 2H), 7,75 (s, 1H), 7,73- 7,67 (m, 2H), 7,40 (d, J = 5,8 Hz, 1H), 5,19 (q, J = 6,9 Hz, 1H), 4,79 (td, J = 5,7, 3,5 Hz, 1H), 4,40 (d, J = 5,7 Hz, 2H), 2,65 (pd, J = 7,0, 3,6 Hz, 1H), 2,41 (s, 3H), 1,59 (d, J = 6,8 Hz, 3H), 1,00 (d, J = 7,0 Hz, 3H), 0,89 (d, J = 6,9 Hz, 3H). HRMS (B) (M+H) 432,2138 Calculado (M+H) 432,2148 Segundo pico 324: ^{1}H RMN (400 MHz, MeOD) δ 8,17 (d, J = 5,8 Hz, 1H), 7,97- 7,84 (m, 2H), 7,77- 7,63 (m, 3H), 7,40 (d, J = 5,8 Hz, 1H), 5,16 (q, J = 6,8 Hz, 1H), 4,79 (dt, J = 7,5, 3,8 Hz, 1H), 4,43- 4,33 (m, 2H), 2,41 (s, 4H), 1,59 (d , J = 6,9 Hz, 3H), 0,87 (br d, J = 7,1 Hz, 3H), 0,80 (br d, J = 6,9 Hz, 3H). HRMS (B) (M+H) 432,2137 Calculado (M+H) 432,2148
325 y 326: (S)- 3- (2- (1- (3,5- dimetil- 1- fenil- 1H- pirazol- 4- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna columna AD- H 5 mM 20x250mm 15% de MeOH + DEA) para proporcionar (S)- 3- (2- (((R)- 1- (3,5- dimetil- 1- fenil- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3,5- dimetil- 1- fenil- 1H- pirazol- 4- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona. Primer pico 325: ^{1}H RMN (400 MHz, MeOD) δ 8,16 (d, J = 5,8 Hz, 1H), 7,57- 7,49 (m, 2H), 7,48- 7,42 (m, 1H), 7,42- 7,38 (m, 3H), 5,12 (q, J = 7,0 Hz, 1H), 4,78 (td, J = 5,6, 3,5 Hz, 1H), 4,44- 4,36 (m, 2H), 2,63 (td, J = 7,0, 3,6 Hz, 1H) , 2,34 (s, 3H), 2,32 (s, 3H), 1,59 (d, J = 7,1 Hz, 3H), 1,00 (d, J = 7,0 Hz, 3H), 0,88 (d, J = 7,0 Hz, 3H) . HRMS (B) (M+H) 421,2348 Calculado (M+H) 421,2352 Segundo pico 326: ^{1}H RMN (400 MHz, MeOD) δ 8,18 (d, J = 5,8 Hz, 1H), 7,56- 7,49 (m, 2H), 7,48- 7,41 (m, 1H), 7,40- 7,35 (m, 3H), 5,07 (q, J = 7,1 Hz, 1H), 4,78 (dt, J = 7,8, 3,8 Hz, 1H), 4,44- 4,32 (m, 2H), 2,33 (s, 3H), 2,31 (br s, 1H) 2,29 (s, 3H), 1,59 (d, J = 7,1 Hz, 3H), 0,85 (br d, J = 7,0 Hz, 3H), 0,77 (br d, J = 6,9 Hz,

	3H). HRMS (B) (M+H) 421,2347 Calculado (M+H) 421.2352
327 y 328: (S) - 3 - (2 - (1 - (4 - (1H- imidazol- 1- il) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	La separación se logró mediante HPLC inversa (10-85% de ACN/agua 0.1% modificador de NH_4OH) para proporcionar (S) - 3 - (2 - (((R) - 1 - (4 - (1H- imidazol- 1- il) fenil) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (4- (1H- imidazol- 1- il)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona. Primer pico 327: ^{1}H RMN (400 MHz, MeOD) δ 8,25-8,00 (m, 2H), 7,53 (d, J = 0,7 Hz, 5H), 7,38 (d, J = 5,9 Hz, 1H), 7,15 (s, 1H), 5,04 (q, J = 7,1 Hz, 1H), 4,50 (br s, 1H), 4,40- 4,19 (m, 2H), 2,68 (pd, J = 7,0, 3,6 Hz, 1H), 1,57 (d, J = 7,0 Hz, 3H), 1,02 (d, J = 7,0 Hz, 3H), 0,87 (d, J = 7,0 Hz, 3H). HRMS (B) (M+H) 393,2042 Calculado (M+H) 393,2039 Segundo pico 328: ^{1}H RMN (400 MHz, MeOD) δ 8,16 (d, J = 5,8 Hz, 1H), 8,10 (t, J = 1,2 Hz, 1H), 7,55 (t, J = 1,4 Hz, 1H), 7,52 (s, 4H), 7,38 (d, J = 5,8 Hz, 1H), 7,15 (t, J = 1,2 Hz, 1H), 5,12 (q, J = 7,0 Hz, 1H), 4,67 (br s, 1H), 4,44- 4,23 (m, 2H), 1,84 (br s, 1H), 1,57 (d, J = 7,0 Hz, 3H), 0,71 (br s, 3H), 0,60 (br s, 3H). HRMS (B) (M+H) 393,2026 Calculado (M+H) 393,2039
329 y 330: (S)- 3- (2- (1- (3- fluoro- 4- (piridin- 3- iloxi)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna columna AD- H 5 mM 20x250mm 15% de MeOH + DEA) para proporcionar (S)- 3- (2- (((R)- 1- (3- fluoro- 4- (piridin- 3- iloxi)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- fluoro- 4- (piridin- 3- iloxi)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona. Primer pico 329: ^{1}H RMN (400 MHz, MeOD) δ 8,32-8,23 (m, 2H), 8,15 (d, J = 5,8 Hz, 1H), 7,45- 7,35 (m, 3H), 7,31 (dd, J = 11,8, 2,0 Hz, 1H), 7,26 (dd, J = 8,5, 2,0 Hz, 1H), 7,19 (t, J = 8,2 Hz, 1H), 5,15- 4,95 (m, 1H), 4,51 (s, 1H), 4,41 - 4,26 (m, 2H), 2,68 (pd, J = 7,1, 3,6 Hz, 1H), 1,56 (d, J = 7,0 Hz, 3H), 1,01 (d, J = 7,1 Hz, 3H), 0,88 (d, J = 6,9 Hz, 3H). HRMS (B) (M+H) 438,1935 Calculado (M+H) 438,1941 Segundo pico 330: ^{1}H RMN (400 MHz, MeOD) δ 8,28 (dd, J = 4,7, 1,4 Hz, 1H), 8,26 (d, J = 2,8 Hz, 1H), 8,17 (d, J = 5,8 Hz, 1H) , 7,43- 7,40 (m, 2H), 7,36 (ddd, J = 8,4, 2,9, 1,5 Hz, 1H), 7,30 (dd, J = 11,8, 2,0 Hz, 1H), 7,25 (dd, J = 8,4, 2,0 Hz , 1H), 7,19 (t, J = 8,2 Hz, 1H), 5,10 (q, J = 7,1 Hz, 1H), 4,72 (br s, 1H), 4,43- 4,29 (m, 2H), 1,93 (br s, 1H), 1,55 (d, J = 7,0 Hz, 3H), 0,78 (br s, 3H), 0,69 (br s, 3H). HRMS (B) (M+H) 438,1928 Calculado (M+H) 438,1941
331 y 332: (4S)- 4- isopropil- 3- (2- ((1- (4-	Separación quiral se realizó mediante cromatografía en columna SFC quiral (columna Columna IA- H 5 mM

((tetrahidro- 2H- piran- 4- il)oxi)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	20x250mm 30% MeOH) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (4- ((tetrahidro- 2H- piran- 4- il)oxi)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (4- ((tetrahidro- 2H- piran- 4- il)oxi)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona. Primer pico 331: HRMS (B) (M +) 426,2267, RT = 2.45min Segundo pico 332: HRMS (B) (M +) 426,2267, RT = 2.37min
333 y 334: (R) - 3 - (2 - (1 - (3,4- diclorofenil) etilamino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona	La separación se realizó en una columna de gel de sílice de fase normal con 10 a 40% acetato de etilo / heptano para proporcionar (R) - 3 - (2 - (((S) - 1 - (3,4- diclorofenil) etil) amino) pirimidin- 4- il)- 4- feniloxazolidin- 2- ona y (R) - 3 - (2 - (((R) - 1 - (3,4- diclorofenil) etil) amino) pirimidin- 4- il) - 4 - feniloxazolidin- 2- ona Primer pico 333: ^{1}H RMN (400 MHz, MeOD) δ 8,49 (d, J = 5,7 Hz, 1H), 7,85- 7,74 (m, 5H), 7,74- 7,68 (m, 1H), 7,66- 7,61 (m, 2H), 7,55 (dd, J = 8,3, 2,1 Hz, 1H), 5,90 (dd, J = 8,9, 4,0 Hz, 1H), 5,14 (t, J = 8,7 Hz, 1H), 4,97- 4,89 (m, 1H) , 4,56 (dd, J = 8,8, 4,1 Hz, 1H), 1,60 (d, J = 7,0 Hz, 3H). HRMS (B) (M+H) 429,0899 Calculado (M+H) 429,0885 Segundo pico 334: ^{1}H RMN (400 MHz, MeOD) δ 8,50 (d, J = 5,7 Hz, 1H), 7,79 (d, J = 5,9 Hz, 1H), 7,61 (d, J = 8,4 Hz, 1H), 7,57 (dt, J = 4,6, 2,3 Hz, 3H), 7,45 (dd, J = 6,4, 2,9 Hz, 2H), 7,31 (dd, J = 8,3, 2,2 Hz, 1H), 6,16 (dd, J = 8,6, 3,5 Hz, 1H), 5,26 (q, J = 6,9 Hz, 1H), 5,16 (t, J = 8,6 Hz, 1H), 4,97- 4,88 (m, 1H), 4,56 (dd, J = 8,8, 3,6 Hz, 1H), 1,80 (d, J = 7,0 Hz, 3H). HRMS (B) (M+H) 429,0887 Calculado (M+H) 429,0885
335 y 336: (S)- 4- isopropil- 3- (2 - (1 - (4 - (piridin- 3- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna Columna IA- H 5 mM 20x250mm 40% de MeOH, NH_4OH 10 mM) para proporcionar (S)- 4- isopropil- 3- (2 - (((R) - 1 - (4 - (piridin- 3- il) fenil) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2 - (((S) - 1 - (4 - (piridin- 3- il) fenil) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona. Primer pico 335: ^{1}H RMN (400 MHz, MeOD) δ 8,81 (br s, 1H), 8,52 (br s, 1H), 8,14 (br s, 1H), 8,10 (dt, J = 8,2, 1,7 Hz, 1H) , 7,71- 7,59 (m, 2H) 7,58- 7,46 (m, 3H), 7,37 (d, J = 5,8 Hz, 1H), 5,04 (dd, J = 11,2, 5,3 Hz, 1H), 4,50 (br s, 1H), 4,40- 4,19 (m, 2H), 2,69 (ddd, J = 10,4, 7,0, 3,5 Hz, 1H), 1,58 (d, J = 7,0 Hz, 3H), 1,03 (d, J = 7,0 Hz, 3H), 0,88 (d, J = 7,0 Hz, 3H). HRMS (B) (M+H) 404,2085 Calculado (M+H) 404,2086 Segundo pico 336: ^{1}H RMN (400 MHz, MeOD) δ 8,82 (br s, 1H), 8,55 (br s, 1H), 8,17 (br s, 1H), 8,09 (d, J =

	8,0 Hz, 1H), 7,70 - 7,59 (m, 2H), 7,54 (br s, 1H), 7,51-7,45 (m, 2H), 7,38 (d, J = 5,7 Hz, 1H), 5,11 (q, J = 7,0 Hz, 1H), 4,66 (br s, 1H), 4,36- 4,30 (m, 2H), 1,80 (br s, 1H), 1,58 (d, J = 7,0 Hz, 3H), 0,67 (br s, 3H), 0,56 (br s, 3H). HRMS (B) (M+H) 404,2079 Calculado (M+H) 404,2086
337 y 338: (S)- 4-isopropil- 3- (2 - (1 - (4 - (piridin- 4- il) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	La separación se realizó en una columna de gel de sílice de fase normal con 20 a 100% acetato de etilo/heptano para proporcionar (S)- 4- isopropil- 3- (2 - (((R) - 1 - (4 - (piridin- 4- il) fenil) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2 - (((S) - 1 - (4 - (piridin- 4- il) fenil) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona. Primer pico 337: ^{1}H RMN (400 MHz, MeOD) δ 8,58 (br s, 2H), 8,14 (d, J = 5,9 Hz, 1H), 7,83- 7,66 (m, 4H), 7,60- 7,46 (m, 2H) , 7,37 (d, J = 5,8 Hz, 1H), 5,15- 4,96 (m, 1H), 4,48 (br s, 1H), 4,38- 4,15 (m, 2H), 2,69 (DDP, J = 10,5, 7,0, 3,5 Hz, 1H), 1,58 (d, J = 7,0 Hz, 3H), 1,03 (d, J = 7,0 Hz, 3H), 0,88 (d, J = 6,9 Hz, 3H). HRMS (B) (M+H) 404,2068 Calculado (M+H) 404,2086 Segundo pico 338: ^{1}H RMN (400 MHz, MeOD) δ 8,59 (br s, 2H), 8,17 (br s, 1H), 7,80- 7,68 (m, 4H), 7,56- 7,44 (m, 2H), 7,38 (d , J = 5,8 Hz, 1H), 5,11 (q, J = 7,0 Hz, 1H), 4,65 (br s, 1H), 4,31 (dt, J = 17,1, 9,0 Hz, 2H), 1,76 (br s, 1H) , 1,58 (d, J = 7,1 Hz, 3H), 0,66 (br s, 3H), 0,55 (br s, 3H). HRMS (B) (M+H) 404,1939 Calculado (M+H) 404,2086
339 y 340: (S)- 4-isopropil- 3- (2 - (1 - (4 - (metil (fenil) amino) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	La separación se realizó en una columna de gel de sílice de fase normal con 40 a 100% acetato de etilo / heptano para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (4-(metil(fenil)amino)fenil)etil)amino)pirimidin- 4-il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1-(4- (metil(fenil)amino)fenil)etil)amino)pirimidin- 4-il)oxazolidin- 2- ona. Primer pico 339: 1H RMN (400 MHz, MeOD) δ 8,12 (d, J = 5,8 Hz, 1H), 7,37 (d, J = 5,8 Hz, 1H), 7.31- 7.18 (m, 4H), 7,03- 6,94 (m, 4H), 6,91 (tt, J = 7,4, 1,1 Hz, 1H), 4,99- 4,93 (m, 1H), 4,57 (br s, 1H), 4,42- 4,27 (m, 2H), 3,28 (s, 3H), 2,68 (ddq, J = 10,5, 6,9, 3,4 Hz, 1H), 1,53 (d, J = 6,9 Hz, 3H), 1,01 (d, J = 7,1 Hz, 3H), 0,88 (d, J = 7,0 Hz , 3H). HRMS (B) (M+H) 432,2390 Calculado (M+H) 432,2400 Segundo pico 340: ^{1}H RMN (400 MHz, MeOD) δ 8,15 (d, J = 5,8 Hz, 1H), 7,37 (d, J = 5,8 Hz, 1H), 7.30- 7.18 (m, 4H), 7,02- 6,92 (m, 4H), 6,89 (tt, J = 7,3, 1,1 Hz, 1H), 5,04 (q, J = 7,0 Hz, 1H), 4,77- 4,67 (m, 1H), 4,43-4,26 (m, 2H), 3,27 (s, 3H), 2,11 (br s, 1H), 1,52 (d, J = 7,0 Hz, 3H), 0,79 (br s, 3H), 0,68 (br s, 3H). HRMS (B) (M+H) 432,2386 Calculado (M+H) 432,2400
341 y 342: S)- 3- (2- (1-	Separación quiral se consiguió mediante la columna

(3- fluoro- 4- (4- metil- 1H- pirazol- 1- il)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	SFC quiral (IC 20x250nm 45% IPA en CO_2, flujo 75g/min) para proporcionar (S)- 3- (2- (((R)- 1- (3- fluoro- 4- (4- metil- 1H- pirazol- 1- il)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- fluoro- 4- (4- metil- 1H- pirazol- 1- il)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona. Primer pico 341: ^{1}H RMN (400 MHz, MeOD) δ 8,15 (d, J = 5,8 Hz, 1H), 7,81 (dt, J = 2,9, 0,9 Hz, 1H), 7,66 (t, J = 8,3 Hz, 1H) , 7,56 (s, 1H), 7,40 (d, J = 5,8 Hz, 1H), 7,36- 7,25 (m, 2H), 5,01 (d, J = 7,5 Hz, 1H), 4,46 (br s, 1H), 4,38 - 4,25 (m, 2H), 2,68 (pd, J = 7,0, 3,5 Hz, 1H), 2,17 (d, J = 0,6 Hz, 3H), 1,56 (d, J = 7,0 Hz, 3H), 1,02 (d, J = 7,1 Hz, 3H), 0,87 (d, J = 6,9 Hz, 3H). HRMS (B) (M+H) 425,2089 Calculado (M+H) 425,2101 Segundo pico 342: ^{1}H RMN (400 MHz, MeOD) δ 8,17 (d, J = 5,8 Hz, 1H), 7,80 (d, J = 2,6 Hz, 1H), 7,66 (t, J = 8,3 Hz, 1H), 7,56 (s, 1H), 7,40 (d, J = 5,8 Hz, 1H), 7,35- 7,26 (m, 2H), 5,10 (q, J = 7,0 Hz, 1H), 4,69 (br s, 1H), 4,43- 4,24 (m, 2H) 2,17 (s, 3H), 1,80 (br s, 1H), 1,56 (d, J = 7,1 Hz, 3H), 0,73 (br s, 3H), 0,62 (br s, 3H). HRMS (B) (M+H) 425,2081 Calculado (M+H) 424,2101
343 y 344: (S)- 3- (2- (1- (4- (3,5- dimetil- 1H- pirazol- 1- il)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna Columna IA 20x250mm 25% MeOH, 0,2% DEA) para proporcionar (S)- 3- (2- (((R)- 1- (4- (3,5- dimetil- 1H- pirazol- 1- il)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (4- (3,5- dimetil- 1H- pirazol- 1- il)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona. Primer pico 343: ^{1}H RMN (400 MHz, MeOD) δ 8,14 (d, J = 5,8 Hz, 1H), 7,56- 7,48 (m, 2H), 7,41- 7,34 (m, 3H), 6,06 (s, 1H), 5.7- 5.2 (m, 1H), 4,46 (br s, 1H), 4,39- 4,22 (m, 2H), 2,79- 2,60 (m, 1H), 2,26 (s, 3H), 2,24 (s, 3H), 1,58 (d, J = 7,0 Hz, 3H), 1,02 (d, J = 7,1 Hz, 3H), 0,88 (d, J = 6,9 Hz, 3H). HRMS (B) (M+H) 421,2332 Calculado (M+H) 421,2352 Segundo pico 344: ^{1}H RMN (400 MHz, MeOD) δ 8,15 (d, J = 5,8 Hz, 1H), 7,55- 7,47 (m, 2H), 7,41- 7,33 (m, 3H), 6,06 (s, 1H), 5,17 (q, J = 7,0 Hz, 1H), 4,74 (br s, 1H), 4,45- 4,19 (m, 2H), 2,26 (s, 3H), 2,25 (s, 3H), 2,07 (br s, 1H) , 1,56 (d, J = 7,0 Hz, 3H), 0,80 (br s, 3H), 0,65 (br s, 3H). HRMS (B) (M+H) 421,2335 Calculado (M+H) 421,2352
345 y 346: (S)- 4- isopropil- 3- (2 - ((1 - (5- metil- 1 ,3,4- oxadiazol- 2- il) etil) amino) pirimidin-	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 99 bar, eluyendo con 10% MeOH/CO2) para proporcionar (S)- 4- isopropil- 3- (2-

4- il)- oxazolidin 2- ona	(((R)- 1- (5- metil- 1,3,4- oxadiazol- 2- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (5- metil- 1,3,4- oxadiazol- 2- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona. Primer pico 345: HRMS (B) m/z 333,1668 (M + H)+. Rt = 1,96 min. Segundo pico 346: HRMS (B) m/z 333,1668 (M + H)+. Rt = 1,58 min.
347 y 348: (S)- 4- isopropil- 3- (2- ((1- (1- metil- 1H- 1,2,4- triazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona.	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 99 bar, eluyendo con 10% MeOH/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (1- metil- 1H- 1,2,4- triazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (1- metil- 1H- 1,2,4- triazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona. Primer pico 347: HRMS (B) m/z 332,1831 (M + H)+. Rt = 1,68 min. Segundo pico 348: HRMS (B) m/z 332,1833 (M + H)+. Rt = 1,57 min.
349 y 350: (S)- 3- (2- ((1- (imidazo[2,1- b][1,3,4]tiadiazol- 6- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 99 bar, eluyendo con 10% MeOH/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (imidazo[2,1- b][1,3,4]tiadiazol- 6- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (imidazo[2,1- b][1,3,4]tiadiazol- 6- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona. Primer pico 349: HRMS (B) m/z 374,1384 (M + H)+. Rt = 2,01 min. Segundo pico 350: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,43 (s, 1H), 8,12 (d, J = 5,8 Hz, 1H), 7,60 (s, 1H), 7,38 (d, J = 5,8 Hz, 1H) , 5,13 (s, 1H), 4,60 (dt, J = 8,3, 3,3 Hz, 1H), 4,33- 4,07 (m, 2H), 2,25 (b, 1H), 1,57 (d, J = 6,8 Hz, 3H), 0,84 hasta 0,52 (b, 6H). HRMS (B) m/z 373,1321 (M +), RT = 1,88 min.
351 y 352: (S) - 3 - (2 - (1 (- (1- etil- 1H- 1 ,2,4- triazol- 5- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin - 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 99 bar, eluyendo con 10% MeOH/CO_2) para proporcionar (S)- 3- (2- (((R)- 1- (1- etil- 1H- 1,2,4- triazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (1- etil- 1H- 1,2,4- triazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 351: HRMS (B) m/z 346,1985 (M + H)+. Rt = 1,89 min. Segundo pico 352: HRMS (B) m/z 346,1983 (M + H)+, RT = 1,75 min.
353 y 354: (S) - 3 - (2 - (1	Separación quiral se consiguió mediante cromatografía

(- (4- etil- 4H- 1 ,2,4- triazol- 3- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin - 2- ona	en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 99 bar, eluyendo con 10% MeOH/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (4- etil- 4H- 1,2,4- triazol- 3- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (4- etil- 4H- 1,2,4- triazol- 3- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 353: HRMS (B) m/z 346,1984 (M + H)+. Rt = 1,80 min. Segundo pico 354: HRMS (B) m/z 346,1982 (M + H)+, RT = 1,77 min.
355 y 356: (S) - 3 - (2 - ((1 - (imidazo [2,1- b] tiazol- 6- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 75 ml/min, 120 bar, eluyendo 20- 30% MeOH/CO2) para proporcionar (S) - 3 - (2 - (((R) - 1 - (imidazo [2,1- b] tiazol- 6- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S) - 3 - (2 - (((S) - 1 - (imidazo [2,1- b] tiazol- 6- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 355: HRMS (B) m/z 373,1436 (M + H)+. Rt = 1,92 min. Segundo pico 356: HRMS (B) m/z 373,1439 (M + H)+, RT = 1,84 min.
357 y 358: N- (4- (1- ((4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il)amino)etil)fenil)metano sulfonamida	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 96 bar, eluyendo 25% MeOH/CO2) para proporcionar N- (4- ((R)- 1- ((4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il)amino)etil)fenil)metanosulfonamida y N- (4- ((S)- 1- ((4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il)amino)etil)fenil)metanosulfonamida Primer pico 357: HRMS (B) m/z 420,1689 (M + H)+. Rt = 2,08 min. Segundo pico 358: HRMS (B) m/z 420,1687 (M + H)+, RT = 1,98 min.
359 y 360: (S)- 4- isopropil- 3- (2- ((1- (3- (piridin- 2- il)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	La separación se realizó mediante cromatografía sobre gel de sílice (10 a 40% de EtOAc / heptano) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- (piridin- 2- il)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- (piridin- 2- il)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 359: HRMS (B) m/z 396,1784 (M + H)+. Rt = 2,26 min. Segundo pico 360: HRMS (B) m/z 396,1784 (M + H)+, RT = 2,20 min.
361 y 362: (S)- 4- isopropil- 3- (2- ((1- (3- (p- tolil)- 1,2,4- oxadiazol-	La separación se realizó mediante cromatografía sobre gel de sílice (10 a 40% de EtOAc/heptano) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- (p-

5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	tolil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- (p- tolil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona. Primer pico 361: HRMS (B) m/z 409,1985 (M + H)+. Rt = 2,88 min. Segundo pico 362: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,24 (d, J = 5,8 Hz, 1H), 8,03 (d, J = 5,9 Hz, 2H), 7,59 (d, J = 5,8 Hz, 1H), 7,28 (d, J = 8,0 Hz, 2H), 5,41 (b, 1H), 4,67 (dt, J = 8,2, 3,3 Hz, 1H), 4,36- 4,18 (m, 2H), 2,42 (s, 3 H), 2,29 - 2,13 (m, 1H), 1,78 (d, J = 7,2 Hz, 3H), 0,81 (d, J = 7,1 Hz, 3H), 0,73 (d, J = 7,0 Hz, 3H). HRMS (B) m/z 409,1985 (M + H)+, RT = 2,85 min.
363 y 364: (S)- 4- isopropil- 3- (2 - (4 - - (1 ((metilsulfonil) fenil) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 74 ml/min, 100 bar, eluyendo 25% MeOH/CO2) para proporcionar (S)- 4- isopropil- 3- (2 - (((R) - 1 - (4 - (metilsulfonil) fenil) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2 - (((S) - 1 - (4 - (metilsulfonil) fenil) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona Primer pico 363: HRMS (B) m/z 405,1594 (M + H)+. Rt = 2,26 min. Segundo pico 364: HRMS (B) m/z 405,1595 (M + H)+, RT = 2,14 min.
365 y 366: (S)- 4- isopropil- 3- (2 - ((1 - (3- metil- 1 ,2,4- oxadiazol- 5- il) etil) amino) pirimidin- 4- il)- oxazolidin 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 100 bar, eluyendo 20% IPA/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- metil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- metil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 365: HRMS (B) m/z 333,1679 (M + H)+. Rt = 2,19 min. Segundo pico 366: HRMS (B) m/z 333,1680 (M + H)+, RT = 2,12 min.
367 y 368: (S) - 3 - (2 - ((1 - (3- etilisoxazol- 5- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 79 ml/min, 100 bar, eluyendo 20% IPA/CO2) para proporcionar (S) - 3 - (2 - (((R) - 1 - (3- etilisoxazol- 5- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S) - 3 - (2 - (((S) - 1 - (3- etilisoxazol- 5- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 367: HRMS (B) m/z 346,1886 (M + H)+. Rt = 2,51 min. Segundo pico 368: HRMS (B) m/z 346,1882 (M + H)+, RT = 2,45 min.
369 y 370: (S)- 4-	Separación quiral se consiguió mediante cromatografía

isopropil- 3- (2 - ((1 - (3- propil- 1 ,2,4- oxadiazol- 5- il) etil) amino) pirimidin- 4- il)- oxazolidin 2- ona	en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 75 ml/min, 100 bar, eluyendo 20% IPA/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- propil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- propil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 369: HRMS (B) m/z 361,1989 (M + H)+. Rt = 2,52 min. Segundo pico 370: HRMS (B) m/z 361,1985 (M + H)+, RT = 2.49 min.
371 y 372: (S)- 3- (2- ((1- (3- ciclopropil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 100 bar, eluyendo 15% IPA/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (3- ciclopropil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- ciclopropil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 371: HRMS (B) m/z 359,1830 (M + H)+. Rt = 2,42 min. Segundo pico 372: HRMS (B) m/z 359,1833 (M + H)+, RT = 2,37 min.
373 y 374: (S)- 4- isopropil- 3- (2- ((1- (3- isopropil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 100 bar, eluyendo 20% IPA/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- isopropil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- isopropil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 373: HRMS (B) m/z 361,1990 (M + H)+. RT = 2,58 min. Segundo pico 374: HRMS (B) m/z 361,1987 (M + H)+, RT = 2,54 min.
375 y 376: (S) - 3 - (2 - ((1 - (1- etil- 1H- pirazol- 3- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 78 ml/min, 100 bar, eluyendo 20% IPA/CO2) para proporcionar (S) - 3 - (2 - (((R) - 1 - (1- etil- 1H- pirazol- 3- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S) - 3 - (2 - (((S) - 1 - (1- etil- 1H- pirazol- 3- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 375: HRMS (B) m/z 345,2046 (M + H)+. Rt = 2,31 min. Segundo pico 376: HRMS (B) m/z 345,2050 (M + H)+, RT = 2,26 min.
377 y 378: (S) - 3 - (2 - ((1 - (2- hidroxifenil) etil)	Separación quiral se consiguió mediante cromatografía en columna quiral (DO- H, columna de 4.6x250 mm, 1

amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	ml/min, eluyendo 25% de etanol / heptano) para proporcionar (S) - 3 - (2 - (((R) - 1 - (2- hidroxifenil) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S) - 3 - (2 - (((S) - 1 - (2- hidroxifenil) etil) amino) pirimidin - 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 377: HRMS (B) m/z 343,1767 (M + H)+. Rt = 2,41 min. Segundo pico 378: HRMS (B) m/z 343,1767 (M + H)+, RT = 2,36 min.
379 y 380: (S)- 4- isopropil- 3- (2- ((1- (5- metil- 1- fenil- 1H- 1,2,3- triazol- 4- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 874ml/min, 100 bar, eluyendo 30% IPA/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (5- metil- 1- fenil- 1H- 1,2,3- triazol- 4- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (5- metil- 1- fenil- 1H- 1,2,3- triazol- 4- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 379: HRMS (B) m/z 408,2135 (M + H)+. Rt = 2,37 min. Segundo pico 380: HRMS (B) m/z 408,2140 (M + H)+, RT = 2,31 min.
381 y 382: (S)- 4- isopropil- 3- (2 - ((1 - (3- fenil- 1 ,2,4- oxadiazol- 5- il) etil) amino) pirimidin- 4- il)- oxazolidin 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 74 ml/min, 100 bar, eluyendo 20% - 35% IPA/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- fenil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- fenil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 381: HRMS (B) m/z 395,1792 (M + H)+. Rt = 2,63 min. Segundo pico 382: HRMS (B) m/z 395,1818 (M + H)+, RT = 2.58min.
383 y 384: (S)- 3- (2- (((R)- 1- (1H- pirrolo[2,3- b]piridin- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se realizó mediante cromatografía en columna SFC quiral (IA, columna 20x250 mm, 74 ml/min, 99 bar, eluyendo 45% MeOH con 5 mM NH_4OH / CO2) para proporcionar (S)- 3- (2- (((R)- 1- (1H- pirrolo[2,3- b]piridin- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (1H- pirrolo[2,3- b]piridin- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 383: HRMS (B) m/z 367,1862 (M + H)+. Rt = 2,10 min. Segundo pico 384: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,32 (d, J = 2,2 Hz, 1H), 8,19 (d, J = 5,8 Hz, 1H), 7,94 (d, J = 2,1 Hz, 1H), 7,47 (d, J = 5,8 Hz, 1H), 7,38 (d, J = 3,5 Hz, 1H), 6,46 (d, J = 3,5 Hz, 1H), 5.30- 5.8 (m, 1H), 4,73- 4,51 (m, 1H), 4,28 (t, J = 8,8 Hz, 1H), 4,19 (dd, J = 9,0, 3,1 Hz, 1H), 1,78 (dd, J = 31,8, 17,0 Hz, 1H), 1,66

	(d, J = 6,9 Hz, 3H), 0,56 (s, 6H). HRMS (B) m/z 367,1870 (M + H)+, RT = 2.00min.
385 y 386: (S)- 4- isopropil- 3- (2- ((1- (1- metil- 1H- benzo[d]imidazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 99 bar, eluyendo 20% IPA/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (1- metil- 1H- benzo[d]imidazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (1- metil- 1H- benzo[d]imidazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 385: HRMS (B) m/z 381,2026 (M + H)+. Rt = 2,05 min. Segundo pico 386: HRMS (B) m/z 381,2022 (M + H)+, RT = 1.96min.
387 y 388: (S)- 4- isopropil- 3- (2- ((1- (2- oxo- 2,3- dihidro- 1H- benzo[d]imidazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 100 bar, eluyendo 25% IPA/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (2- oxo- 2,3- dihidro- 1H- benzo[d]imidazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (2- oxo- 2,3- dihidro- 1H- benzo[d]imidazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 387: HRMS (B) m/z 383,1811 (M + H)+. Rt = 1,90 min. Segundo pico 388: HRMS (B) m/z 383,1815 (M + H)+, RT = 1.85min.
389 y 390: (S) - 3 - (2 - ((1 - (benzo [d] tiazol- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se realizó mediante cromatografía quiral en columna SFC (ID, 5 uM, columna de 20x250 mm, 74 ml/min, 100 bar, eluyendo 35% MeOH/CO2) para proporcionar (S) - 3 - (2 - (((R) - 1 - (benzo [D] tiazol- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S) - 3 - (2 - (((S) - 1 - (benzo [d] tiazol- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 389: HRMS (B) m/z 384,1488 (M + H)+. Rt = 2,44 min. Segundo pico 390: HRMS (B) m/z 384,1473 (M + H)+, RT = 2.36min.
391 y 392: (S) - 3 - (2 - ((1 - (indolizin- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se realizó mediante cromatografía en columna SFC quiral (DO, 5 uM, columna de 20x250 mm, 75 ml/min, 120 bar, eluyendo 15- 55% MeOH/CO2) para proporcionar (S) - 3 - (2 - (((R) - 1 - (indolizin- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S) - 3 - (2 - (((S) - 1 - (indolizin- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 391: HRMS (B) m/z 366,1926 (M + H)+. Rt = 2,66 min.

	Segundo pico 392: HRMS (B) m/z 366,1918 (M + H)+, RT = 2.63min.
393 y 394: (S)- 4- isopropil- 3- (2- ((1- (3- (2- metoxifenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 80 ml/min, 100 bar, eluyendo 5- 55% MeOH/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- (2- metoxifenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- (2- metoxifenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 393: HRMS (B) m/z 425,1925 (M + H)+. Rt = 2,57 min. Segundo pico 394: HRMS (B) m/z 425,1916 (M + H)+, RT = 2.52min.
395 y 396: (S)- 4- isopropil- 3- (2- ((1- (3- (3- metoxifenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	Separación quiral se realizó mediante cromatografía en columna SFC quiral (IA, 5 uM, columna de 20x250 mm, 74 ml/min, 100 bar, eluyendo m25% MeOH/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- (3- metoxifenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- (3- metoxifenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 395: HRMS (B) m/z 425,1924 (M + H)+. Rt = 2,60 min. Segundo pico 396: ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,56 (dt, J = 7,7, 1,2 Hz, 1H), 7,49 (dt, J = 3,7, 1,8 Hz, 2H), 7,29 (t, J = 8,0 Hz, 2H), 6,96 (ddd, J = 8,3, 2,7, 0,9 Hz, 1H), 5,34 (b, 1H), 4,58 (dt, J = 8,2, 3,3 Hz, 1H), 4,37- 4,03 (m, 2H), 3,78 (s, 3H), 2,12 (b, 1H), 1,68 (d, J = 7,1 Hz, 3H), 0,73 (d, J = 7,1 Hz, 3H), 0,65 (d, J = 7,0 Hz, 3H). HRMS (B) m/z 425,1924 (M + H)+, RT = 2.54min.
397 y 398: (S)- 3- (2- ((1- (3- (3- fluorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (AD- H, 5 uM, columna de 20x250 mm, 75 ml/min, 100 bar, eluyendo 20% MeOH/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (3- (3- fluorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- (3- fluorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 397: HRMS (B) m/z 413,1729 (M + H)+. Rt = 2,66 min. Segundo pico 398: ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,86 (dt, J = 7,8, 1,2 Hz, 1H), 7,77 (ddd, J = 9,4, 2,7, 1,5 Hz, 2H), 7,60 (d, J = 5,3 Hz, 1H), 7,46 (td, J = 8,0, 5,7 Hz, 1H), 7,22 (tdd, J = 8,4, 2,6, 1,0 Hz, 1H), 5,44 (b, 1H), 4,68 (dt, J = 8,3, 3,3 Hz, 1H), 4,44- 4,11 (m, 2H), 2,18 (d, J = 8,4 Hz, 1H), 1,78 (d, J = 7,1 Hz, 3H), 0,83 (d, J =

	6,9 Hz, 3H) , 0,75 (d, J = 6,9 Hz, 3H). HRMS (B) m/z 413,1732 (M + H)+, RT = 2.61min.
399 y 400: (S)- 3- (2- ((1- (3- ciclopentil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se realizó mediante cromatografía en columna SFC quiral (IA, 5 uM, columna de 20x250 mm, 74 ml/min, 99 bar, eluyendo 15% MeOH/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (3- ciclopentil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- ciclopentil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 399: HRMS (B) m/z 387,2133 (M + H)+. Rt = 2,54 min. Segundo pico 400: HRMS (B) m/z 387,2117 (M + H)+, RT = 2.50min.
401 y 402: (S)- 3- (2- ((1- (3- ciclohexil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se realizó mediante cromatografía en columna SFC quiral (IA, 5 uM, columna de 20x250 mm, 74 ml/min, 99 bar, eluyendo 30% MeOH/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (3- ciclohexil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- ciclohexil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 401: HRMS (B) m/z 401,2277 (M + H)+. Rt = 2,71 min. Segundo pico 402: HRMS (B) m/z 401,2288 (M + H)+, RT = 2.68min.
403 y 404: (S)- 3- (2- ((1- (3- (tert- butil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se realizó mediante cromatografía en columna SFC quiral (IA, 5 uM, columna de 20x250 mm, 74 ml/min, 100 bar, eluyendo 15% MeOH/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (3- (tert- butil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- (tert- butil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 403: HRMS (B) m/z 375,2131 (M + H)+. Rt = 2,47 min. Segundo pico 404: HRMS (B) m/z375.2130 (M + H)+, RT = 2.44min.
405 y 406: (S)- 3- (2- ((1- (3- isobutil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se realizó mediante cromatografía en columna SFC quiral (IA, 5 uM, columna de 20x250 mm, 74 ml/min, 100 bar, eluyendo 15% MeOH/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (3- isobutil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- isobutil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 405: HRMS (B) m/z 375,2120 (M + H)+. Rt = 2,45 min. Segundo pico 406: HRMS (B) m/z 375,2135 (M + H)+, RT = 2.44min.

407 y 408: (S)- 3- (2- ((1- (5- (4- fluorofenil)- 1,3,4- oxadiazol- 2- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se realizó mediante cromatografía en columna SFC quiral (IA, 5 uM, columna de 20x250 mm, 74 ml/min, 99 bar, eluyendo 30% IPA/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (5- (4- fluorofenil)- 1,3,4- oxadiazol- 2- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (5- (4- fluorofenil)- 1,3,4- oxadiazol- 2- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 407: HRMS (B) m/z 413,1713 (M + H)+. Rt = 2,31 min. Segundo pico 408: HRMS (B) m/z 413,1721 (M + H)+, RT = 2.25min.
409 y 410: (S) - 3 - (2 - ((1 - (benzo [d] oxazol- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se realizó mediante cromatografía en columna SFC quiral (IA, 5 uM, columna de 20x250 mm, 74 ml/min, 99 bar, eluyendo 25% MeOH/CO2) para proporcionar (S) - 3 - (2 - (((R) - 1 - (benzo [d] oxazol- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S) - 3 - (2 - (((S) - 1 - (benzo [d] oxazol- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 409: HRMS (B) m/z 368,1729 (M + H)+. Rt = 2,66 min. Segundo pico 410: ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,80- 7,61 (m, 1H), 7,54 (s, 1H), 7,51- 7,42 (m, 2H), 7,40- 7,21 (m, 2H), 6,40 (b , 1H), 5,39 (s, 1H), 4,64 (dt, J = 8,1, 3,2 Hz, 1H), 4,36- 4,17 (m, 2H), 2,11 (b, 1H), 1,77 (d, J = 6,9 Hz, 3H), 0.64 (b, 6H). HRMS (B) m/z 368,1727 (M + H)+, RT = 2.60min.
411 y 412: (S)- 3- (2- ((1- (4- (4- clorofenil)- 5- metiltiazol- 2- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	La separación se realizó mediante cromatografía sobre gel de sílice (10 a 50% de EtOAc / heptano) para proporcionar (S)- 3- (2- (((R)- 1- (4- (4- clorofenil)- 5- metiltiazol- 2- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (4- (4- clorofenil)- 5- metiltiazol- 2- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 411: HRMS (B) m/z 458,1401 (M + H)+. Rt = 3,02 min. Segundo pico 412: HRMS (B) m/z 458,1401 (M + H)+, RT = 2.92min.
413 y 414: (S) - 3 - (2 - ((1 - (3- etil- 1 ,2,4- oxadiazol- 5- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2 - ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna AD- H (80 g / min, 80 bar, 20 x 250 mm), eluyendo 15% MeOH/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (3- etil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- etil- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 413: HRMS (B) m/z 346,1753 RT = 2,13 min. Segundo pico 414: HRMS (B) m/z 346,1753 RT = 2,05

	min.
415 y 416: (S)- 4- isopropil- 3- (2 - (1 (- (4- metiltiazol- 2- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna AD- H (75 ml/min, 120 bar, 20 x 250 mm), eluyendo 10- 25% MeOH/CO2) para proporcionar (S)- 4- isopropil- 3- (2 - (((R) - 1 - (4- metiltiazol- 2- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2 - (((S) - 1 - (4- metiltiazol- 2- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona Primer pico 415: HRMS (B) m/z 347,1416 RT = 2,25 min. Segundo pico 416: HRMS (B) m/z 347,1416 RT = 2,17 min.
417 y 418: (S)- 4- isopropil- 3- (2 - (1 (- (tiofen- 2- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna AD- H (75 ml/min, 120 bar, 20 x 250 mm), eluyendo 10- 25% MeOH/CO2) para proporcionar (S)- 4- isopropil- 3- (2 - (((R) - 1 - (tiofen- 2- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2 - (((S) - 1 - (tiofen- 2- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona Primer pico 417: HRMS (B) m/z 332,1307 RT = 2,54 min. Segundo pico 418: HRMS (B) m/z 332,1307 RT = 2,53 min.
419 y 420: (S) - 3 - (2 - ((1 - (furan- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna AD- H (75 ml/min, 120 bar, 20 x 250 mm), eluyendo 10- 25% MeOH/CO2) para proporcionar (S) - 3 - (2 - (((S) - 1 - (furan- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S) - 3 - (2 - (((R) - 1 - (furano- 2- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 419: HRMS (B) m/z 316,1535 RT = 2,37 min. Segundo pico 420: HRMS (B) m/z 316,1535 RT = 2,39 min.
421 y 422: (S)- 4- isopropil- 3- (2- ((1- (3- (piridin- 4- il)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna IA (75 ml/min, 120 bar, 20 x 250 mm), eluyendo 15- 25% MeOH/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- (piridin- 4- il)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- (piridin- 4- il)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2-

	ona Primer pico 421: HRMS (B) m/z 395,1706 RT = 1,75 min. Segundo pico 422: HRMS (B) m/z 395,1706 RT = 2,25 min.
423 y 424: (S)- 3- (2- ((1- (3- (2- clorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna IA (75 ml/min, 120 bar, 20 x 250 mm), eluyendo 15- 25% MeOH/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (3- (2- clorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- (2- clorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 423: HRMS (B) m/z 428,1364 RT = 3,01 min. Segunda pico 424: HRMS (B) m/z 428,1364 RT = 2,79 min.
425 y 426: (S)- 3- (2- ((1- (3- (4- clorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna IA (75 ml/min, 120 bar, 20 x 250 mm), eluyendo 15- 25% MeOH/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (3- (4- clorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- (4- clorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 425: HRMS (B) m/z 428,1364 RT = 2,65 min. Segundo pico 426: ^{1}H RMN (400 MHz, MeOD) δ 8,22 (d, J = 5,8 Hz, 1,0 H), 8,08- 7,97 (m, 2,07 H), 7,63- 7,40 (m, 3,09 H), 5,41 (q, J = 7,2 Hz, 1,04 H), 4,75- 4,63 (m, 0,97 H), 4,33 (d, J = 6,3 Hz, 2,18 H), 1,76 (d, J = 7,2 Hz, 3,31 H), 1,07- 0,85 (m , 0,95 H), 0,70 (d, J = 38,0 Hz, 5,81 H). HRMS (B) m/z 428,1364
427: (S)- 4- isopropil- 3- (2- ((1- (3- (piridin- 3- il)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna IA (75 ml/min, 120 bar, 20 x 250 mm), eluyendo MeOH/CO2 15- 25%) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- (piridin- 3- il)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- (piridin- 3- il)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Segundo pico de 427: HRMS (B) m/z 395,1706 RT = 2,24 min.
428 y 429: (S) - 3 - (2 - ((1 - (1- etil- 1H- pirazol- 5- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna AD (75 g / min, 120 bar, 20 x 250 mm), eluyendo 25% IPA/0.2% DEA/CO2) para proporcionar (S) - 3 - (2 - (((R) - 1 - (1- etil- 1H- pirazol- 5- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S) - 3 - (2 - (((S) - 1 - (1-

	etil- 1H- pirazol- 5- il) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 428: HRMS (B) m/z 345,2005 (M+H) TR = 2,28 min. Segundo pico 429: HRMS (B) m/z 345,2044 (M+H) TR = 2,21 min.
430: (S)- 4- isopropil- 3- (2- (((S)- 1- (3- (m- tolil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna AD (75 g / min, 120 bar, 20 x 250 mm), eluyendo 25- 35% IPA/0.2% DEA/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- (m- tolil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- (m- tolil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Segundo pico 430: HRMS (B) m/z 345,2044 (M+H) TR = 2,82 min.
431 y 432: (S)- 4- isopropil- 3- (2 - (1 (- (2- feniltiazol- 5- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna AD (75 g / min, 120 bar, 20 x 250 mm), eluyendo 40% IPA/0.2% DEA/CO2) para proporcionar (S)- 4- isopropil- 3- (2 - (((R) - 1 - (2- feniltiazol- 5- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2 - (((S) - 1 - (2- feniltiazol- 5- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona Primer pico 431: HRMS (B) m/z 409,1573 RT = 2,33 min. Segundo pico 432: ^{1}H RMN (400 MHz, MeOD) δ 8,19 (d, J = 5,8 Hz, 1H), 7,92- 7,78 (m, 2H), 7,65 (d, J = 1,1 Hz, 1H), 7,53- 7,27 (m, 4H), 5,43 (q, J = 6,9 Hz, 1H), 4,74 (dt, J = 7,8, 3,7 Hz, 1H), 4,41- 4,20 (m, 2H), 2,16 (s, 1H), 1,69 (d , J = 7,0 Hz, 3H), 1,15 (d, J = 6,1 Hz, 1H), 0,88 a 0,49 (m, 6H). HRMS (B) m/z 409,1573
433 y 434: (S)- 4- isopropil- 3- (2- ((1- (3- (o- tolil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna AD (75 g / min, 120 bar, 20 x 250 mm), eluyendo 25- 40% IPA/0.2% DEA/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- (o- tolil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- (o- tolil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 433: HRMS (B) m/z 409,1 (M+H) TR = 2,25 min. Segundo pico 434: ^{1}H RMN (400 MHz, MeOD) δ 8,20 (d, J = 5,8 Hz, 1H), 7,90 (dd, J = 7,7, 1,4 Hz, 1H), 7,47 (d, J = 5,8 Hz, 1H) , 7,41- 7,25 (m, 3H), 5,40 (q, J = 7,2 Hz, 1H), 4,69 (s, 1H), 4,44- 4,22 (m, 2H), 3,34 (s, 2H), 2,54 (s, 3H), 1,75 (d, J = 7,2 Hz, 3H), 1,15 (d, J = 6,1 Hz, 1H), 0,69 (d, J = 35,0 Hz, 6H). HRMS (B) m/z 409,1 (M+H)
435 y 436: 4- (1- ((4- ((S)-	Separación quiral se consiguió mediante cromatografía

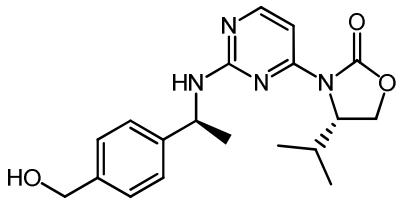
4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il)amino)etil)- N,N- dimetilbenzenosulfonamida	en columna SFC quiral (columna AS- H (80 g / min, 120 bar, 20 x 250 mm), eluyendo 15% IPA/0.2% DEA/CO2) para proporcionar 4- ((R)- 1- ((4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il)amino)etil)- N,N- dimetilbenzenesulfonamida y 4- ((S)- 1- ((4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il)amino)etil)- N,N- dimetilbenzenosulfonamida Primer pico 435: HRMS (B) m/z 433,1784 RT = 2,45 min. Segundo pico 436: HRMS (B) m/z 433,1784 RT = 2,32 min.
437 y 438: (S)- 4- isopropil- 3- (2 - ((1 - (tiazol- 4- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna de IC (75 g / min, 120 bar, 20 x 250 mm), eluyendo 25% IPA/0.2% DEA/CO_2) para proporcionar (S)- 4- isopropil- 3- (2 - (((S) - 1 - (tiazol- 4- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2 - (((R) - 1 - (tiazol- 4- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona Primer pico 437: HRMS (B) m/z 333,1259 RT = 1,88 min. Segundo pico 438: HRMS (B) m/z 333,1259 RT = 1,98 min.
439 y 440: (S)- 4- isopropil- 3- (2- ((1- (3- (4- metoxifenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna AI (70 g / min, 120 bar, 20 x 250 mm), eluyendo 20% IPA/0.2% DEA/CO2) para proporcionar (S)- 4- isopropil- 3- (2- (((R)- 1- (3- (4- metoxifenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- (((S)- 1- (3- (4- metoxifenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona Primer pico 438: HRMS (B) m/z 425,1921 (M+H) TR = 2,49 min. Segundo pico 439: HRMS (B) m/z 425,1923 (M+H) TR = 2,42 min.
441 y 442: (S)- 3- (2- ((1- (3- (4- fluorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se consiguió mediante cromatografía en columna SFC quiral (columna AI (70 g / min, 120 bar, 20 x 250 mm), eluyendo 25% IPA/0.2% DEA/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (3- (4- fluorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (3- (4- fluorofenil)- 1,2,4- oxadiazol- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 441: HRMS (B) m/z 413,1719 (M+H) TR = 2,58 min. Segundo pico 442: HRMS (B) m/z 413,1719 (M+H) TR = 2,52 min.
443: (S)- 3- (2- (((S)- 1-	Separación quiral se consiguió mediante cromatografía

(5- (4- clorofenil)- 1,2,4- oxadiazol- 3- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	en columna SFC quiral (columna ID- H (80 g / min, 120 bar, 20 x 250 mm), eluyendo 30% MeOH/CO2) para proporcionar (S)- 3- (2- (((R)- 1- (5- (4- clorofenil)- 1,2,4- oxadiazol- 3- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- (((S)- 1- (5- (4- clorofenil)- 1,2,4- oxadiazol- 3- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Segundo pico 443: ^{1}H RMN (400 MHz, MeOD) δ 8.25 a 8.3 (m, 6H), 7,71- 7,55 (m, 4H), 7,44 (d, J = 5,7 Hz, 2H), 5,26 (d, J = 5,6 Hz, 2H), 4,71 (d, J = 7,9 Hz, 2H), 4,46- 4,26 (m, 4H), 3,37 (s, 1H), 2,66 (heptd, J = 7,0, 3,3 Hz, 2H), 1,69 (d , J = 7,1 Hz, 6H), 1,17 (d, J = 6,2 Hz, 1H), 1,04 (d, J = 7,1 Hz, 6H), 0,88 (d, J = 6,9 Hz, 6H). HRMS (B) m/z 428,1364 RT = 2,77 min.
444 y 445: (S)- 3- (2- (1- (5- (4- fluoro- 3- metilfenil)piridin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	La separación se realizó mediante cromatografía sobre gel de sílice (10 a 100% de EtOAc/heptano) para proporcionar (S)- 3- (2- ((R)- 1- (5- (4- fluoro- 3- metilfenil)piridin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- ((S)- 1- (5- (4- fluoro- 3- metilfenil)piridin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 444: HRMS (B) m/z 436,2126 (M + H)+, RT = 2.78min Segundo pico 445: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,75 (dd, J = 2,3, 0,9 Hz, 1H), 8,23 (d, J = 5,8 Hz, 1H), 7,78 (dd, J = 8,1, 2,4 Hz, 1H), 7,49 (d, J = 5,7 Hz, 1H), 7,41- 7,27 (m, 3H), 7,12 (dd, J = 9,4, 8,4 Hz, 1H), 5,95 (d, J = 6,5 Hz, 1H), 5,16 (br s, 1H), 4,66 (br s, 1H), 4,34- 4,19 (m, 2H), 2,37 (d, J = 1,9 Hz, 3H), 1,93 (br s, 1H), 1,65- 1,61 (m , 3H), 0,71 (br s, 6H). HRMS (B) m/z 436,2131 (M + H)+.
446 y 447: (S)- 3- (2- (1- (5- (4- fluorofenoxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	Separación quiral se realizó mediante cromatografía en columna SFC quiral (columna Columna IA 20x250mm 30% de IPA, el 70% de CO2) para proporcionar (S)- 3- (2- ((S)- 1- (5- (4- fluorofenoxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- ((R)- 1- (5- (4- fluorofenoxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 446: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,42 (s, 2H), 8,21 (d, J = 5,8 Hz, 1H), 7,49 (d, J = 5,7 Hz, 1H), 7,18- 6,99 (m, 4H), 6,18 (br s, 1H), 5,28 (br s, 1H), 4,75 (dt, J = 8,2, 3,4 Hz, 1H), 4,39- 4,25 (m, 2H), 2,34 (br s, 1H), 1,65 - 1,59 (m, 3H), 0,95 - 0,86 (d, J = 6,9 Hz, 3H), 0,82 (d, J = 6,9 Hz, 3H). HRMS (B) m/z 439,1876 (M + H)+. Segundo pico 447: HRMS (B) m/z 439,1883 (M + H)+, RT = 3.37min
448 y 449: (S) - 3 - (2 - (1 - (5 - (4- fluorofenoxi)	La separación se realizó mediante cromatografía sobre gel de sílice (20 a 100% de EtOAc/heptano) para

piridin- 2- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	proporcionar (S)- 3- (2- ((R)- 1- (5- (4- fluorofenoxi)piridin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- ((S)- 1- (5- (4- fluorofenoxi)piridin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 448: HRMS (B) m/z 438,1922 (M + H)+. RT = 2.62min Segundo pico 449: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,34 (dd, J = 2,7, 0,8 Hz, 1H), 8,21 (d, J = 5,8 Hz, 1H), 7,49 (d, J = 5,8 Hz, 1H) , 7,33- 7,18 (m, 3H), 7,14- 6,95 (m, 3H), 5,95 (d, J = 7,1 Hz, 1H), 5,14 (br s, 1H), 4,68 (d, J = 7,8 Hz, 1H) , 4,36- 4,22 (m, 2H), 1,75 (br s, 1H), 1,61- 1,57 (m, 3H), 0,95 a 0,75 (m, 6H). HRMS (B) m/z 438,1950 (M + H)+.
450 y 451: (R)- 3- (5- fluoro- 2- (1- (5- (4- fluorofenoxi)piridin- 2- il)etilamino)pirimidin- 4- il)- 5,5- dimetil- 4- feniloxazolidin- 2- ona	La separación se realizó mediante cromatografía sobre gel de sílice (10 a 100% de EtOAc/heptano) para proporcionar (R)- 3- (5- fluoro- 2- ((S)- 1- (5- (4- fluorofenoxi)piridin- 2- il)etilamino)pirimidin- 4- il)- 5,5- dimetil- 4- feniloxazolidin- 2- ona y (R)- 3- (5- fluoro- 2- ((R)- 1- (5- (4- fluorofenoxi)piridin- 2- il)etilamino)pirimidin- 4- il)- 5,5- dimetil- 4- feniloxazolidin- 2- ona Primer pico 450: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8.27 a 8.17 (m, 1H), 8,08 (d, J = 2,8 Hz, 1H), 7,31- 6,86 (m, 11H), 5,83 (d, J = 7,2 Hz, 1H), 5,28 (s, 1H), 4,69 (br s, 1H), 1,58 (s, 3H), 1.29- 1.11 (m, 3H), 0,98 (s, 3H). HRMS (B) m/z 518,2005 (M + H)+. Segundo pico 451: HRMS (B) m/z 518,2003 (M + H)+, RT = 3.08min
452 y 453: (S) - 3 - (2 - (1 - (5 - (4- fluorofenoxi) pirazin- 2- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.	La separación se realizó mediante cromatografía sobre gel de sílice (25 a 100% EtOAc/heptano) para proporcionar (S)- 3- (2- ((R)- 1- (5- (4- fluorofenoxi)pirazin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- ((S)- 1- (5- (4- fluorofenoxi)pirazin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona. Primer pico 452: HRMS (B) m/z 439,1877 (M + H)+, RT = 2.66min Segundo pico 453: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,38 (d, J = 1,4 Hz, 1H), 8,20 (d, J = 5,8 Hz, 1H), 8,09 (s, 1H), 7,49 (d, J = 5,8 Hz, 1H), 7,12 (d, J = 6,3 Hz, 4H), 5,71 (s, 1H), 5,20 (br s, 1H), 4,66 (dt, J = 7,7, 2,9 Hz, 1H), 4,36- 4,22 (m, 2H), 2,10 (br s, 1H), 1,61 (d, J = 6,9 Hz, 3H), 0,94- 0,78 (m, 6H). HRMS (B) m/z 439,1882 (M + H)+.
454 y 455: (S)- 3- (2- (1- (2- (4- fluorofenoxi)pirimidin- 5- il)etilamino)pirimidin- 4-	La separación se realizó mediante cromatografía sobre gel de sílice (25 a 100% de EtOAc / heptano) para proporcionar (S)- 3- (2- ((R)- 1- (2- (4- fluorofenoxi)pirimidin- 5- il)etilamino)pirimidin- 4- il)-

il)- 4- isopropiloxazolidin- 2- ona.	4- isopropiloxazolidin- 2- ona y (S)- 3- (2- ((S)- 1- (2- (4- fluorofenoxi)pirimidin- 5- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona. Primer pico 454: HRMS (B) m/z 439,1904 (M + H)+, TR = 3,09 min Segundo pico 455: HRMS (B) m/z 439,1897 (M + H)+, RT = 3,17 min
456: (S)- 3- (2- (1- (5- (2,4- difluorofenoxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.	La separación se realizó en una columna de gel de sílice de fase normal con 20 a 100% acetato de etilo / heptano para proporcionar (S)- 3- (2- ((R)- 1- (5- (2,4- difluorofenoxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- ((S)- 1- (5- (2,4- difluorofenoxi)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona. Segundo pico 456: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,30 (s, 2H), 8,09 (d, J = 5,9 Hz, 1H), 7,42 (d, J = 5,9 Hz, 1H), 7,08 (td, J = 8,9, 5,4 Hz, 1H), 6,98- 6,81 (m, 2H), 5,18 (br s, 1H), 4,64 (dt, J = 7,9, 3,1 Hz, 1H), 4.30- 4.16 (m, 2H), 2,11 (br s, 1H), 1,53- 1,49 (m, 3H), 0,85 - 0,77 (m, 3H), 0,71 (d, J = 6,8 Hz, 3H). HRMS (B) m/z 457,1797 (M + H)+.
457: (S)- 4- isopropil- 3- (2- (1- (5- (3- (trifluorometil)fenil)pirimidin- 2- il)etilamino)pirimidin- 4- il)oxazolidin- 2- ona.	La separación se realizó en una columna de gel de sílice de fase normal con 25 a 100% de gradiente (25% de metanol en acetato de etilo) y heptano para proporcionar (S)- 4- isopropil- 3- (2- ((R)- 1- (5- (3- (trifluorometil)fenil)pirimidin- 2- il)etilamino)pirimidin- 4- il)oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2- ((S)- 1- (5- (3- (trifluorometil)fenil)pirimidin- 2- il)etilamino)pirimidin- 4- il)oxazolidin- 2- ona. Pico 2 457: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,85 (s, 2H), 8,14 (d, J = 5,7 Hz, 1H), 7,77- 7,54 (m, 4H), 7,40 (d, J = 5,7 Hz, 1H), 6,11 (br s, 1H), 5,25 (br s, 1H), 4,67 (dt, J = 7,8, 3,2 Hz, 1H), 4,33- 4,15 (m, 2H), 2,92 2,15 (br s, 1H) , 1,55 (d, J = 8,6 Hz, 3H), 0,85 - 0,76 (m, 3H), 0,70 (br s, 3H). HRMS (B) m/z 473,1897 (M + H)+.
458: (S)- 3- (2- ((S)- 1- (5- (4- fluoro- 2- metilfenil)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	La separación quiral se llevó a cabo con la SFC (IA, 5µm, 20 x 250 mm) utilizando 35% de MeOH en CO2 para proporcionar (S)- 3- (2- ((S)- 1- (5- (4- fluoro- 2- metilfenil)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- ((R)- 1- (5- (4- fluoro- 2- metilfenil)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona Primer pico 458: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,68 (s, 2H), 8,24 (d, J = 5,8 Hz, 1H), 7,49 (d, J = 5,7 Hz, 1H), 7,17 (dd, J = 8,4, 5,8 Hz, 1H), 7,10- 6,98 (m, 2H), 6,28 (br s, 1H), 5,34 (br s, 1H), 4,78 (dt, J = 8,2, 3,3 Hz, 1H), 4,40- 4,25 (m, 2H), 2,30 (s, 3H), 1,79 (br s, 1H), 1,73 (d, J = 7,1 Hz, 3H), 0,95 - 0,75 (m, 6H). HRMS (B) m/z 437,2086 (M + H)+.

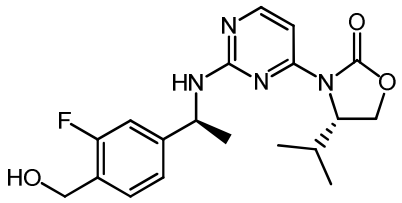
Ejemplo 459



Una solución de clorhidrato de (S) - (4 - (1- aminoetil) fenil)metanol (4.0301 g, 21.47 mmol, comprado en Netchem), (S) - 3 - (2- fluoropirimidin- 4- il)- 4- isopropiloxazolidin - 2- ona (5.3648 g, 23.82 mmol, 1.11 equiv) y DIPEA (38.0 ml, 218 mmol, 10.1 equiv) en DMSO (40 ml) se calentó a 110 °C durante 135 min. La mezcla de reacción se diluyó con EtOAc (200 ml) y se lavó con agua (200 ml). Después de la separación, la fase acuosa se lavó con EtOAc (2 x 150 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (EtOAc/heptano 30 a 100%) proporcionó (S) - 3 - (2 - ((S) - 1 - (4 - (hidroximetil) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin - 2- ona (6,42 g) con un rendimiento del 84%.

^{1}H RMN (400 MHz, CD_3OD) □ 8,13 (d, J = 5,8 Hz, 1H), 7,36- 7,28 (m, 5 H), 5,06 (q, J = 7,0 Hz, 1 H), 4,68 (br s, 1 H), 4,58 (s, 2H), 4,37- 4,29 (m, 2 H), 1,80 (br s, 1H), 1,52 (d, J = 7,1 Hz, 3 H), 0,74 (br s, 3 H), 0,61 (br s, 3 H), MS m/z 355,1 (M - H)

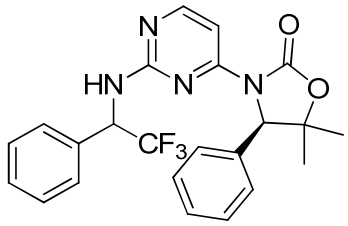
Ejemplo 460



Se preparó S)- 3- (2- ((S)- 1- (3- fluoro- 4- (hydroximetil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona usando un método similar al descrito para la preparación del Ejemplo 459. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,15 (d, J = 5,9 Hz, 1H), 7,51- 7,49 (m, 1 H), 7,37 (t, J = 7,7 Hz, 1 H), 7,11 (d, J = 7,8 Hz, 1 H), 7,01 (d, J = 11, Hz, 1 H), 6,09 (br s, 1H), 5,00 (br s, 1H), 4,73 (s, 2 H), 4,61 - 4,55 (m, 1 H), 4,30 (t, J = 8,7 Hz, 1 H), 4.25-

4.21 (m, 1 H), 3,00 (s, 1 H), 1,89 (br s, 1H), 1,54 (d, J = 7,1 Hz, 3 H), 0,67 (br s, 6 H); MS m/z 375,0 (M+H)

Ejemplo 461

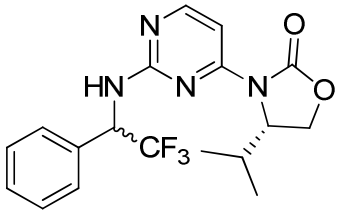


Una solución de (S) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (50 mg, 0.165mmol), 2,2,2- trifluoro- 1- feniletanamina (160mg, 0.913mmol) y p- TsOH (78 mg, 0.412mmol) en 2- BuOH se calentó a 110 °C durante 2.5 h. LCMS mostró material de partida, y tambien producto. Se añadió otro 78 mg de p- TsOH, seguido de 98 mg de 2,2,2- trifluoro- 1- feniletanamina y se calentó a 110 ºC durante 1.5 h. La mayoria de producto tuvo algo de SM.

Después de enfriar la mezcla solidificó. Se añadió acetonitrial y se sonicó. la filtración de sólidos (sal de p- TsOH de 2,2,2- trifluoro- 1- feniletanamina). El agua madre se concentró y se purificó mediante cromatografía en columna (0- 40% de EtOAc/heptano seguido de HPLC (XBridge C18 5 uM 10- 85% ACN/agua durante 12 minutos con 0.01% modificador de NH_4OH) para proporcionar (4R) - 5, 5- dimetil- 4- fenil- 3- (2 - (2,2,2- trifluoro- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona (28 mg, 0.063mmol).

^{1}H RMN (400 MHz, MeOD) δ 8,20 (d, J = 5,8 Hz, 1H), 7,58 (dd, J = 11,4, 5,8 Hz, 1H), 7,51 (br d, J = 6,8 Hz, 1H), 7,40 (dtd, J = 15,9, 9,2, 4,5 Hz, 5H), 7,33- 7,22 (m, 3H), 7,10 (br s, 1H), 5,50 (s, 0,5 H), 5,38 (s, 0,5 H), 5,29 (br s, 1 H), 1,70 (s, 1,5 H), 1,64 (s, 1,5 H), 1,04 (s, 1,5 H), 1,03 (s, 1,5 H). HRMS (B) (M+H) 443.1682 Calculado (M+H) 443.1695

Ejemplo 462 y 463

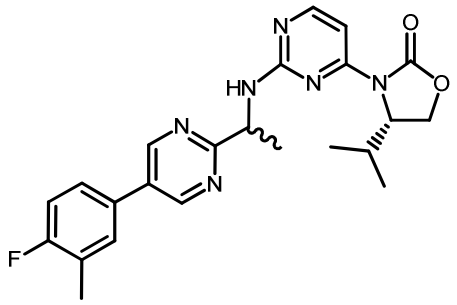


Una solución de (S) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (163 mg, 0,674 mmol), 2,2,2- trifluoro- 1- feniletanamina (624 mg, 3.56 mmol, 5.3 equiv) y monohidrato de ácido p- toluenosulfónico (321 mg, 1,69 mmol, 2.5 equiv) en n- BuOH (3 ml) se calentó a 110 ° C durante 2 h y se trató con monohidrato de ácido p-toluenosulfónico adicional (321 mg , 1.69 mmol, 2.5 equiv), luego se calentó a 110 °C durante 1 ½ h. Después de enfriar, la mezcla de reacción sólido se trató con MeCN, se sonicó y se filtró. El filtrado se concentró y se purificó mediante cromatografía en columna de gel de sílice (EtOAc / heptano del 0 al 30%) para proporcionar (4S)- 4-isopropil- 3- (2 - (2,2,2- trifluoro- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona (65 mg) con un rendimiento del 25%. HRMS (B) m/z 381,1545 (M + H)+. Anal. RP-HPLC tR = 4.31 / / 4.46 min (tasa de flujo 10 ml/min con un gradiente de 5% a 15% acetonitrilo con ácido fórmico al 0.05% en 5,00 minutos y luego acetonitrilo 15% a 95% con 0.05% de ácido fórmico a partir de 5.00 min . a 9,50 min, la fase acuosa modificada con ácido fórmico al 0.1% cromatografía en columna de gel de sílice separa los dos diastereómeros (S)- 4- isopropil- 3- (2 - ((R) - 2,2,2- trifluor- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona y (S)- 4- isopropil- 3- (2 - ((S) - 2,2,2- trifluor- 1-feniletilamino) pirimidin- 4- il) oxazolidin - 2- ona.

Primer pico: ^{1}H RMN (400 MHz, MeOD) δ 8,23 (d, J = 5,8 Hz, 1H), 7,62- 7,53 (m, 2H), 7,50 (d, J = 5,8 Hz, 1H), 7,42 (qt, J = 5,0, 2,2 Hz, 3H), 5,93- 5,86 (m, 1H), 4,80 (dt, J = 7,5, 3,9 Hz, 1H), 4,48- 4,33 (m, 2H), 2,65 (DDP, J = 10,4, 7,0 , 3,4 Hz, 1H), 1,05 (d, J = 7,0 Hz, 3H), 0,89 (d, J = 7,0 Hz, 3H).

Segundo pico: ^{1}H RMN (400 MHz, MeOD) δ 8,23 (d, J = 5,8 Hz, 1H), 7,55 (dd, J = 7,3, 2,1 Hz, 2H), 7,49 (d, J = 5,8 Hz, 1H), 7,45- 7,32 (m, 3H), 5,92- 5,86 (m, 1H), 4,86- 4,82 (m, 1H), 4,44- 4,38 (m, 2H), 2,26 (br s, 1H), 0,94 (d, J = 7,0 Hz, 3H), 0,74 (br s, 3H).

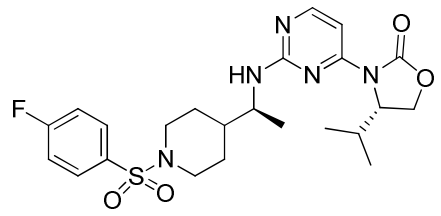
Ejemplo 464



Una solución de (*S*) - 3 - (2- fluoropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (1.055 mg, 4,68 mmol), 1 - (5 - (4- fluoro- 3- metilfenil) pirimidin- 2- il) etanamina (1300 mg, 5,62 mmol, 1,2 equiv) y diisopropiletilamina (908mg, 7.03mmol, 1.5 equiv) en DMSO (20 ml) se calentó a 110 °C durante 1 h. La mezcla de reacción se vertió en agua (60 ml) y se extrajo con EtOAc (2x50 ml). Los orgánicos combinados se lavaron con agua (40mL) salmuera (40mL) se secaron sobre Na_2SO_4 se filtraron y se concentraron directamente a gel sílice. La cromatografía en gel de sílice proporcionó los distereomers mixtos de (S) - 3 - (2 - (1 - (5 - (4- fluoro- 3- metilfenil) pirimidin- 2- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin - 2- ona (560 mg). La separación quiral se llevó a cabo con la SFC (ID, 5µm, 20 x 250 mm) utilizando 35% MeOH en CO2 para proporcionar (S)- 3- (2- ((S)- 1- (5- (4- fluoro- 3- metilfenil)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (S)- 3- (2- ((R)- 1- (5- (4- fluoro- 3- metilfenil)pirimidin- 2- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

Ejemplo 464 primer producto eluido (302 mg) ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,87 (s, 2H), 8,23 (d, J = 5,8 Hz, 1H), 7,49 (d, J = 5,7 Hz, 1H), 7,43 - 7,30 (m, 2H), 7.21- 7.11 (m, 1H), 6,26 (br s, 1H), 5,31 (br s, 1H), 4,75 (dt, J = 7,9, 3,3 Hz, 1H), 4,39- 4,24 (m, 2H), 2,38 (s, 3H), 2,09 (br s, 1H), 1,66- 1,62 (m, 3H), 0,90 (dd, J = 9,8, 6,0 Hz, 3H), 0,78 (br s, 3H). HRMS (B) m/z 437,2093 (M + H)+.

Ejemplo 465



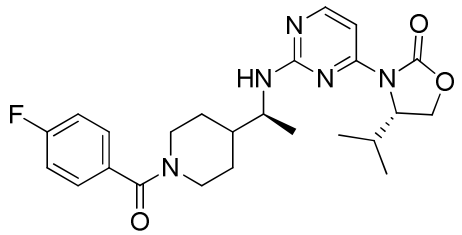
Una solución de (S)- 4- isopropil- 3- (2 - ((S) - 1 - (piperidin- 4- il) etilamino) pirimidin- 4- il) oxazolidin- 2- ona (225 mg, 0.675mmol), cloruro de 4- fluorobenceno- 1- sulfonilo (146 mg, 0.750mmol) y DIPEA (1 ml) en CH_2Cl_2 se agitó a temperatura ambiente durante 2 h.

La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó con agua. La capa acuosa se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se purificó mediante cromatografía en columna para proporcionar (S)- 3- (2- ((S)- 1- (1- (4- fluorofenilsulfonil)piperidin- 4- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (4.5 mg, 0.009mmol).

^{1}H RMN (400 MHz, MeOD) δ 8,45 (d, J = 6,0 Hz, 1H), 8.23- 8.15 (m, 2H), 7,73- 7,63 (m, 3H), 5,13 (dt, J = 7,4, 3,7 Hz, 1H), 4,78- 4,69 (m, 2H), 4,26 (t, J = 6,7 Hz, 1H), 4,17 (dddd, J = 11,8, 6,4, 4,7, 2,3 Hz, 2H), 2,89 (ddq, J = 10,7, 7,1, 3,5 Hz, 1H), 2,69 (tdd, J = 11,6, 8,9, 2,6 Hz, 2H), 2.27- 2.11 (m, 2H), 1,82 (dddt, J = 11,9, 9,0, 5,8, 2,9 Hz, 1H) , 1,77- 1,64 (m, 2H), 1,52 (d, J = 6,8 Hz, 3H), 1,30 (d, J = 7,1 Hz, 3H), 1,21 (d, J = 6,9 Hz, 3H). HRMS (B) (M+H) 492,2069 Calculado (M+H) 492,2081

Los siguientes ejemplos se prepararon usando procedimientos sustancialmente similares a los descritos para el Ejemplo 465:

Ejemplo 466

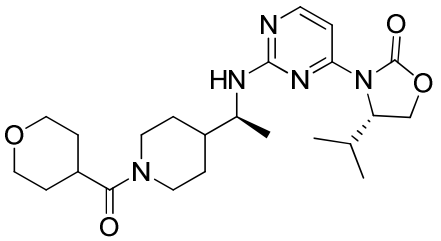


Se purificó mediante cromatografía en columna (20% a 100% de EtOAc/heptano), seguido mediante cromatografía preparativa de fase inversa (columna C18, 10- 85% de ACN/agua 0,1% modificador de NH_4OH durante 12 min.) Para proporcionar (S)- 3- (2- ((S)- 1- (1- (4- fluorobenzoil)piperidin- 4- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (12 mg, 0.026mmol).

^{1}H RMN (400 MHz, MeOD) δ 8,12 (d, J = 5,8 Hz, 1H), 7,51- 7,41 (m, 2H), 7,36 (d, J = 5,8 Hz, 1H), 7.25- 7.15 (m, 2H) , 4,82 (td, J = 5,9, 3,6 Hz, 1H), 4,68 (br s, 1H), 4,41 (d, J

= 5,7 Hz, 2H), 3,98 (t, J = 6,7 Hz, 1H), 3,78 (br s, 1H), 3,12 (br s, 1H), 2,82 (br s, 1H), 2,60 (pd, J = 7,1, 6,5, 3,7 Hz, 1H), 1,92 (br s, 1H), 1,80 (dtd, J = 15,3, 9,4, 7,0, 3,6 Hz, 2H), 1,31 (br s, 2H), 1,22 (d, J = 6,8 Hz, 3H), 0,99 (d, J = 7,1 Hz, 3H), 0,88 (d, J = 6,9 Hz, 3H). HRMS (B) (M+H) 456,2384 Calculado (M+H) 456,2411

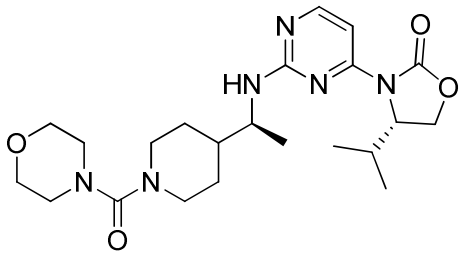
Ejemplo 467



Se purificó mediante cromatografía en columna (MeOH/CH_2Cl_2 al 0 a 20%) para proporcionar (S)- 4- isopropil- 3- (2- ((S)- 1- (1- (tetrahidro- 2H- piran- 4- carbonil)piperidin- 4- il)etilamino)pirimidin- 4- il)oxazolidin- 2- ona (15 mg, 0.034mmol).

^{1}H RMN (400 MHz, MeOD) δ 8,12 (d, J = 5,8 Hz, 1H), 7,36 (d, J = 5,8 Hz, 1H), 4,81 (td, J = 5,6, 3,3 Hz, 1H), 4,59 (br s, 1H), 4,41 (d, J = 5,7 Hz, 2H), 4,13 (br s, 1H), 3,96 (ddd, J = 11,6, 4,3, 2,2 Hz, 3H), 3,51 (tq, J = 11,8, 2,8 Hz, 2H), 3,15- 2,89 (m, 2H), 2,69- 2,48 (m, 2H), 1,99- 1,68 (m, 5H), 1,61 (ddt, J = 10,7, 4,0, 2,3 Hz, 2H), 1,35 - 1,23 (m, 1H), 1,21 (d, J = 6,7 Hz, 3H), 1.19 a 1.9 (m, 1H), 0,98 (dd, J = 7,0, 1,5 Hz, 3H), 0,88 (d, J = 7,0 Hz , 3H). HRMS (B) (M+H) 446,2748 Calculado (M+H) 446,2767

Ejemplo 468

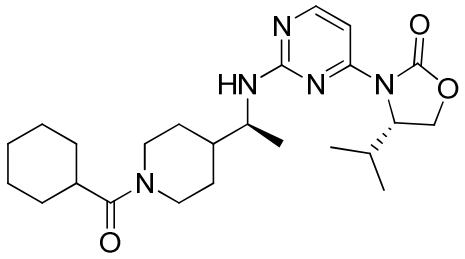


Se purificó mediante cromatografía en columna (50% a 100% de EtOAc / Heptano seguido por 0% a 20% MeOH/CH_2Cl_2) para proporcionar (S)- 4- isopropil- 3- (2- ((S)- 1-

(1- (morfolina- 4- carbonil)piperidin- 4- il)etilamino)pirimidin- 4- il)oxazolidin- 2- ona (21 mg, 0.047mmol).

^{1}H RMN (400 MHz, MeOD) δ 8,11 (d, J = 5,8 Hz, 1H), 7,36 (d, J = 5,8 Hz, 1H), 4,81 (td, J = 5,8, 3,4 Hz, 1H), 4,41 (d , J = 5,7 Hz, 2H), 3,95 (t, J = 6,8 Hz, 1H), 3,84- 3,70 (m, 2H), 3,68- 3,65 (m, 4H), 3.26- 3.23 (m, 4H), 2,80 (tt, J = 12,9, 3,1 Hz, 2H), 2,60 (ddq, J = 10,4, 7,0, 3,5 Hz, 1H), 1,88- 1,73 (m, 2H), 1,67 (ddt, J = 18,5, 10,4, 3,5 Hz, 1H), 1,37- 1,23 (m, 2H), 1,21 (d, J = 6,8 Hz, 3H), 0,99 (d, J = 7,1 Hz, 3H), 0,88 (d, J = 7,0 Hz, 3H). HRMS (B) (M+H) 447,2690 Calculado (M+H) 447,2720

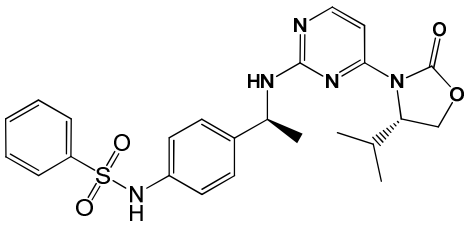
Ejemplo 469



Se purificó mediante cromatografía en columna para proporcionar (S) - 3 - (2 - ((S) - 1 - (1 - (ciclohexanocarbonil) piperidin- 4- il) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona

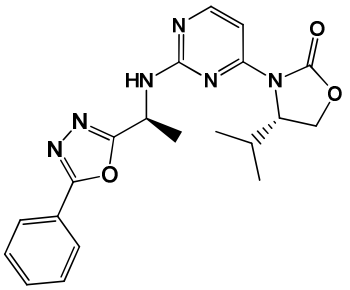
^{1}H RMN (400 MHz, MeOD) δ 8,12 (d, J = 5,7 Hz, 1H), 7,36 (d, J = 5,6 Hz, 1H), 4,80 (dt, J = 5,8, 2,9 Hz, 1H), 4,59 (br s, 1H), 4,40 (d, J = 5,6 Hz, 2H), 4.18 - 4.3 (m, 1H), 3,95 (t, J = 6,8 Hz, 1H), 3,05 (ddd, J = 14,1, 10,1, 6,6 Hz , 1H), 2,58 (td, J = 25,1, 23,5, 13,0 Hz, 3H), 1,97- 1,63 (m, 8H), 1,54- 1,08 (m, 7H), 1,21 (d, J = 6,8 Hz, 3H), 0,98 (d, J = 6,8 Hz, 3H), 0,88 (d, J = 6,9 Hz, 3H). HRMS (B) (M+H) 444,2953 Calculado (M+H) 444,2975

Ejemplos 470



Una solución de (S) - 3 - (2 - (((S) - 1 - (4- aminofenil) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (100 mg, 0,30 mmoles) , cloruro de bencenosulfonilo (65 mg, 0.36 mmol, 1.2 equiv) y piridina (35 mg, 0.45 mmol, 1.5 equiv) en DCM (5 ml) se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se inactivó con MeOH, el disolvente se eliminó para proporcionar el producto crudo, que se purificó mediante cromatografía en columna de gel de sílice (EA: MeOH = 1:0- 9:1), se eliminó el disolvente para proporcionar el producto puro (46.8mg, sólido blanco) con un rendimiento del 31.5%. N- (4- ((S)- 1- ((4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il)amino)etil)fenil)bencenosulfonamida. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,18- 7,90 (m, 2H), 7,74 (d, *J* = 7,8 Hz, 2H), 7,45 (t, *J* = 7,4 Hz, 1H), 7,39- 7,35 (m, 2H), 7,10 (d, *J* = 8,1 Hz, 2H), 6,96 (d, *J* = 8,0 Hz, 2H), 6,41 (s, 1H), 4,99- 4,79 (m, 1H), 4,62- 4,39 (m, 1H), 4,28- 3,99 (m, 2H), 1,91- 1,65 (b, 1H), 1,40 (d, *J* = 7,0 Hz, 3H), 0,53 (b, *J* = 21,1 Hz, 6H). HRMS (B) *m/z* 482.1847 (M + H)+. Rt = 2,60 min.

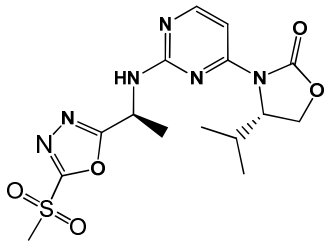
Ejemplos 471



Una solución de (trietoximetil) benceno (360 mg, 1.6 mmol, 5.0 equiv en 5 ml de benceno y 0.5 mL de AcOH glacial.) Se añadió a (S) - 2 - ((4 - ((S)- 4- isopropil - 2- oxooxazolidin- 3- il) pirimidin- 2- il) amino)propanohidrazida (99 mg, 0,30 mmol, 1.0 equiv.), la mezcla de reacción se agitó a reflujo durante 1.5 horas, se eliminó el disolvente para proporcionar el producto crudo . La cromatografía en columna de gel de sílice (acetato de etilo en heptano del 10 al 90%) para producir (S)- 4- isopropil- 3- (2- (((S)- 1-

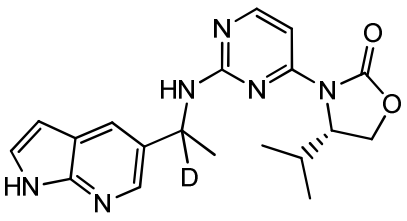
(5- fenil- 1,3,4- oxadiazol- 2- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona (21.2 mg, sólido blanco), con un rendimiento del 15.9%. HRMS (B) m/z 395.1820, $(M+H)^+$, RT = 2,42 min

Ejemplos 472



A una solución de (S)- 4- isopropil- 3- (2 - (((S) - 1 - (5 - (metiltio) - 1,3,4- oxadiazol- 2- il) etil)
amino) pirimidin- 4- il) oxazolidin- 2- ona (102 mg, 0.28 mmol en 1.5 ml de CH_3COOH), se añadió por goteo una solución de $KMnO_4$ (66.4 mg, 0.42 mmol, 1.5 eq en 2.5 ml de agua). La solución se agitó a temperatura ambiente durante 25 min, la mezcla se decoloró con bisulfito de sodio, la solución resultante se extrae con DCM, se lavó con una solución saturada de $NaHCO_3$, se secó sobre Na_2SO_4, el solvente se eliminó para proporcionar el producto crudo deseado como un sólido blanco. (S)- 4- isopropil- 3- (2- (((S)- 1- (5-(metilsulfonil)- 1,3,4- oxadiazol- 2- il)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona (83 mg, sólido blanco) con un rendimiento del 71%. HRMS (B) *m/z* 397.1281 (M + H)+. Rt = 1.80 min.

Ejemplo 473 y 474



1 - (1H- pirrolo [2,3- b] piridin- 5- il)- etanona (75 mg, 0,468 mmol), acetato de amonio (722 mg, 9,36 mmol, 20,0 eq) y cianoborodeuterido de sodio (131 mg, 1.999 mmol , 4.25 eq) se combinaron en propan- 2- ol (5 ml) y se calentó bajo irradiación infrarroja a 130 °C durante 4 min. La reacción se diluyó con EtOAc (15 ml) y agua (15 ml) y se trató con

solución de NaOH 6 M (1 ml) a ~ 10 pH. El producto, 1- deutero- 1- (1H- pirrolo [2,3- b] piridin- 5- il) etanamina, se llevó a la siguiente etapa sin purificación adicional.

Una solución de 3 - (2- fluoropirimidin- 4- il) oxazolidin- 2- ona (99 mg, 0,441 mmoles), 1- deutero- 1- (1H- pirrolo [2,3- b] piridin- 5- il) etanamina (72 mg, 0.441 mmol, 1.0 equiv), y DIEA (0.154 ml, 0.882 mmol, 2.0 equiv) en DMSO (1 ml) se calentó a 130 °C durante 120 min. La mezcla de reacción se diluyó con EtOAc (20 ml) y se lavó con agua (10 ml) y se concentró al vacío. La resolución de (4S)- 3- (2- ((1- deutero- 1- (1H- pirrolo[2,3- b]piridin- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona a través de cromatografía SFC quiral en una columna de AI (75 g / min, 120 bar, 20 x 250 mm), eluyendo 40- 50% MeOH/0.2% DEA/CO2 (v/v) para proporcionar (4S)- 3- (2- (((R)- 1- deutero- 1- (1H- pirrolo[2,3- b]piridin- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona y (4S)- 3- (2- (((S)- 1- deutero- 1- (1H- pirrolo[2,3- b]piridin- 5- il)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona

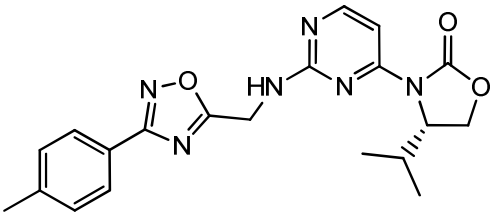
Primer pico 473

^{1}H RMN (400 MHz, $CDCl_3$) δ 10,10 (s, 1H), 8,33 (d, J = 2,2 Hz, 1H), 8,21 (d, J = 5,7 Hz, 1H), 7,92 (d, J = 2,3 Hz, 1H), 7,46 (d, J = 5,7 Hz, 1H), 7,35 (dd, J = 3,5, 2,0 Hz, 1H), 6,47 (dd, J = 3,4, 1,7 Hz, 1H), 5,82 (s, 1H), 1,66 - 1,58 (m, 3H), 4,59 (dt, J = 7,7, 3,2 Hz, 1H), 4,28 (t, J = 8,8 Hz, 1H), 4,19 (dd, J = 9,2, 3,1 Hz, 1H), 3,51 (s, 1H), 1,78 (d, J = 28,5 Hz, 2H), 1.30- 1.15 (m, 1H), 0,57 (s, 6H). CLMS m/z 368,1 (M+H) TR = 2,36 min.

Segundo pico de 474

CLMS m/z 368.1 (M+H) TR = 2.66 min.

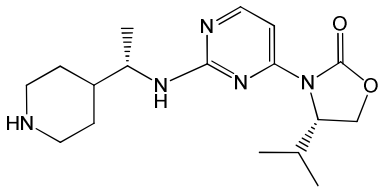
Ejemplo 475



Una solución de 3 - (2- fluoropirimidin- 4- il) oxazolidin- 2- ona (100 mg, 0,444 mmol), (3 - (p- tolil) - 1,2,4- oxadiazol- 5- il) metanamina (84 mg, 0.444 mmol, 1.0 equiv), y TEA (0.186 ml, 1.332 mmol, 3.0 equiv) en butan- 1- ol (2 ml) se calentó a 100 °C durante

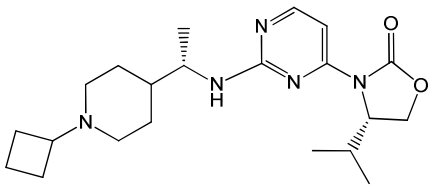
90 min. La adición de propan- 1- ol (1 ml) y se calentó a 150 °C durante 60 min. La mezcla de reacción se concentró al vacío. La cromatografía en columna (sílice, 24 g) eluyendo W/0 - 30% EtOAc/DCM proporcionó (S)- 4- Isopropil- 3- {2- [(3- p- tolil- [1,2,4]oxadiazol- 5- ilmetil)- amino]- pirimidin- 4- il}- oxazolidin- 2- ona (95 mg, espuma blanca) con un rendimiento del 54.2%. HRMS (B) m/z 394.1753 2.38 Min.

Ejemplo 476



A una solución de éster benciclo del ácido 4- {(S)- 1- [4- ((S)- 4- Isopropil- 2- oxo- oxazolidin- 3- il)- pirimidin- 2- ilamino]- etil}- piperidina- 1- carboxilico (22 mg) en metanol (5 ml) se añadió hidróxido de paladio sobre carbono (7 mg, 0.05 mmol). Después, la reacción se agitó a temperatura ambiente durante 16 horas. La reacción se filtró y después se concentró al vacío. Luego el material crudo se purificó usando columna C18 ODB de fase inversa con agua- acetonitrilo, modificador de TFA al 0.1% para proporcionar (S)- 4- isopropil- 3- [2 - ((S)- 1- piperidin- 4- il- etilamino) - pirimidin- 4- il]- oxazolidin- 2- ona (11 mg) con un rendimiento del 70%.
HRMS (B) m/z 333.2165 (M + H)+; RT: 1,09 min..

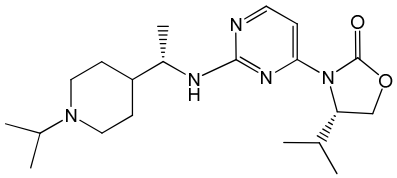
Ejemplo 477



Una solución de (S)- 4- isopropil- 3- [2 - ((S)- 1- piperidin- 4- il- etilamino)- pirimidin- 4- il]- oxazolidin- 2- ona (28 mg, 0.084 mmol) en THF (2 ml) se añadió ciclobutanona (14 mg, 0.20 mmol) y triacetoxiborohidruro de sodio (28 mg, 0.13 mmol). La reacción se agitó a temperatura ambiente durante 18 horas. El disolvente se eliminó entonces al vacío. El material crudo se purificó usando una columna C18 ODB de fase inversa con agua-acetonitrilo, modificador de 0.1% de TFA para proporcionar (S)- 3- {2- [(S)- 1- (1- Ciclobutil- piperidin- 4- il)- etilamino]- pirimidin- 4- il}- 4- isopropil- oxazolidin- 2- ona (20 mg) con un rendimiento del 62%.

HRMS (B) m/z 388,2717 (M + H)+; RT: 2,32 min..

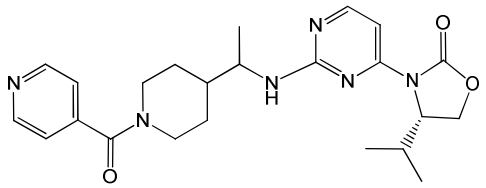
Ejemplo 478



Una solución de (S)- 4- isopropil- 3- [2 - ((S)- 1- piperidin- 4- il- etilamino)- pirimidin- 4- il]- oxazolidin- 2- ona (20 mg, 0.060 mmol) en THF (2 ml) se añadió ciclobutanona (10 mg, 0.17 mmol) y triacetoxiborohidruro de sodio (20 mg, 0.09 mmol). La reacción se agitó a temperatura ambiente durante 18 horas. El disolvente se eliminó entonces al vacío. El material crudo se purificó usando una columna C18 ODB de fase inversa con agua-acetonitrilo, modificador de 0,1% de TFA para proporcionar (S)- 4- Isopropil- 3- {2- [(S)- 1- (1- isopropil- piperidin- 4- il)- etilamino]- pirimidin- 4- il}- oxazolidin- 2- ona (20 mg) con un rendimiento del 62%.

HRMS (B) m/z 376.2705 (M + H)+; RT: 1.24 min..

Ejemplo 479

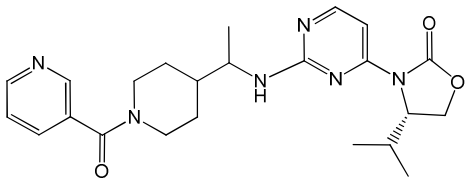


A una solución de S)- 4- isopropil- 3- [2 - ((S)- 1- piperidin- 4- il- etilamino)- pirimidin- 4- il]- oxazolidin- 2- ona (20 mg, 0.48 mmol) en diclorometano (1 ml) y DMF (1 ml) se añadió HATU (23 mg, 0.06 mmol) y DIPEA (0.03 ml, 0.18 mmoles) La reacción se agitó

a temperatura ambiente durante 18 horas. El disolvente se eliminó entonces al vacío. El material crudo se purificó usando una columna C18 ODB de fase inversa con agua-acetonitrilo, modificador de TFA al 0.1% para proporcionar (S)- 4- isopropil- 3- (2- {(S)- 1- [1- (piridina- 4- carbonil)- piperidin- 4- il]- etilamino}- pirimidin- 4- il)- oxazolidin- 2- ona (2 mg) con un rendimiento del 8%.

HRMS (B) m/z 438.2379 (M + H)+; RT: 1.82 min..

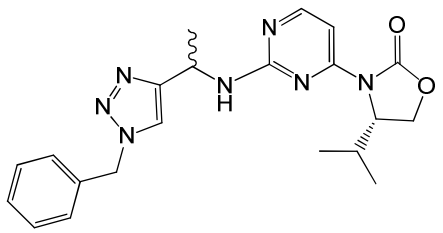
Ejemplo 480



A una solución de S)- 4- isopropil- 3- [2 - ((S)- 1- piperidin- 4- il- etilamino)- pirimidin- 4- il]- oxazolidin- 2- ona (16 mg, 0.48 mmol) en diclorometano (1 ml) y DMF (1 ml) se añadió HATU (20 mg, 0.05 mmol) y DIPEA (0.03 ml, 0.15 mmoles) La reacción se agitó a temperatura ambiente durante 18 horas. El disolvente se eliminó entonces al vacío. El material crudo se purificó usando una columna C18 ODB de fase inversa con agua-acetonitrilo, modificador de TFA al 0.1% para proporcionar (S)- 4- isopropil- 3- (2- {(S)- 1- [1- (piridina- 4- carbonil)- piperidin- 4- il]- etilamino}- pirimidin- 3- il)- oxazolidin- 2- ona (2 mg) con un rendimiento del 8%.

HRMS (B) m/z 438.2379 (M + H)+; RT: 1,83 min..

Ejemplo 481 y 482

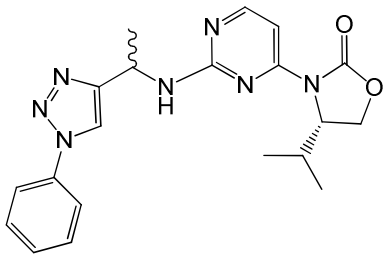


A una solución de (S)- 4- isopropil- 3- [2 - ((S)- 1- metil- prop- 2- inilamino)- pirimidin- 4- il]- oxazolidin- 2- ona (60 mg, 0,22 mmol) y azida de benciclo (30 mg, 0.23 mmol) en agua (0,5 ml) y DMSO (3 ml) se añadió sulfato de cobre pentahidrato (56 mg, 0.23 mmol) y sal sódica del ácido L- ascórbico (45 mg, 0.23 mmoles) . La reacción se agitó durante 48 horas a temperatura ambiente. La mezcla de reacción se diluyó con EtOAc (75 ml) y

se lavó con agua (15 ml) y solución de bicarbonato de sodio 1N (15 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. El material crudo se purificó utilizando una columna C18 de fase inversa con agua- acetonitrilo, TF como un modificador, el cual tembien realizó la separación de los dos productos diastereómericos (S)- 3- {2- [(S)- 1- (1- bencil- 1H- [1,2,3]triazol- 4- il)- etilamino]- pirimidin- 4- il}- 4- isopropil- oxazolidin- 2- ona y (S)- 3- {2- [(R)- 1- (1- bencil- 1H- [1,2,3]triazol- 4- il)- etilamino]- pirimidin- 4- il}- 4- isopropil- oxazolidin- 2- ona

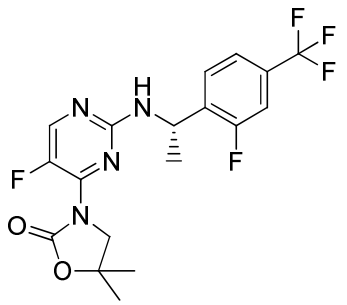
Primer pico 481: HRMS (B) m/z 407.2070 (M + H)+; RT: 2.26 min..
Segundo pico 482: HRMS (B) m/z 407.2070 (M + H)+; RT: 2.32 min..

Ejemplo 483 y 484



A una solución de (S)- 4- isopropil- 3- [2 - ((S)- 1- metil- prop- 2- inilamino)- pirimidin- 4- il]- oxazolidin- 2- ona (82 mg, 0.30 mmol) y azidobenceno (36 mg, 0.30 mmol) en agua (0.5 ml) y DMSO (3 ml) se añadió pentahidrato de sulfato de cobre (75 mg, 0.23 mmol) y la sal de sodio de ácido L- ascórbico (60 mg, 0.23 mmol). La reacción se agitó durante 48 horas a temperatura ambiente. La mezcla de reacción se diluyó con EtOAc (75 ml) y se lavó con agua (15 ml) y solución de bicarbonato de sodio 1N (15 ml). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró. El material crudo se purificó utilizando una columna C18 de fase inversa con agua- acetonitrilo, TFA como un modificador, que también efectúa la separación de los dos productos diastereómericos (S)- 4- isopropil- 3- {2- [(S)- 1- (1- fenil- 1H- [1,2,3]triazol- 4- il)- etilamino]- pirimidin- 4- il}- oxazolidin- 2- ona y (S)- 4- isopropil- 3- {2- [(R)- 1- (1- fenil- 1H- [1,2,3]triazol- 4- il)- etilamino]- pirimidin- 4- il}- oxazolidin- 2- ona
Primer pico 483: HRMS (B) m/z 393.1913 (M + H)+; RT: 2.31 min..
Segundo pico 484: HRMS (B) m/z 393.1913 (M + H)+; RT: 2.40 min..

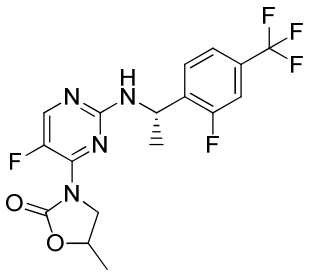
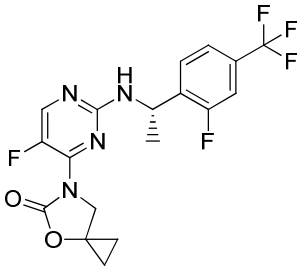
Ejemplo 485

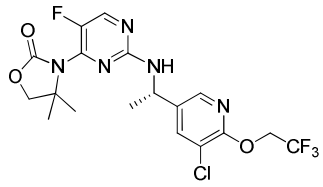
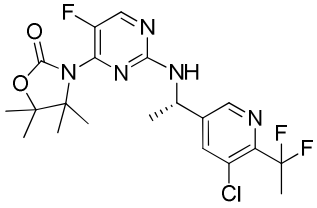
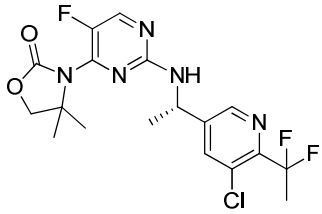
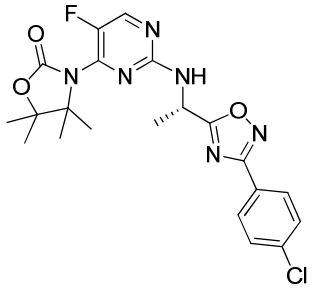
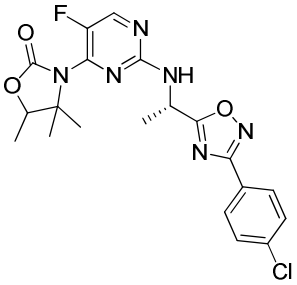
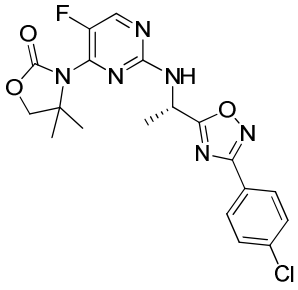
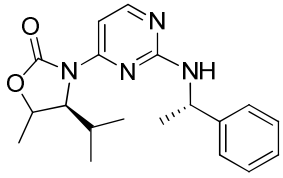
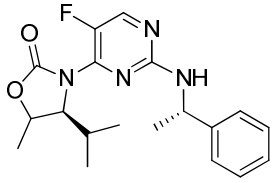
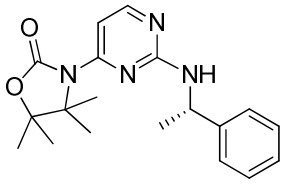
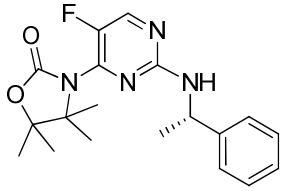
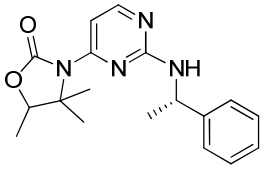


A una solución a temperatura ambiente de 3 - (2- cloro- 5- fluoropirimidin- 4- il) - 5,5- dimetiloxazolidin- 2- ona (30 mg, 0.122 mmol) en DMSO (300 µl) se trató con DIPEA (68 µl, 0.366 mmol) seguido de la adición de (S) - 1 - (2- fluoro- 4- (trifluorometil) fenil) etanamina (41.4 mg, 0.2 mmol). La reacción se selló, se calentó a 95 °C durante ~ 18 horas. La purificación mediante HPLC de fase inversa proporcionó la sal de trifluoroacetato de (S) - 3 - (5- fluoro- 2- (1 - (2- fluoro- 4- (trifluorometil) fenil) etilamino) pirimidin- 4- il) - 5,5 - dimetiloxazolidin- 2- ona. (6.0 mg, sólido blanco). ^{1}H RMN (400 MHz, Metanol- d_4) □□□ ppm 1,44- 1,58 (m, 12 H) 3,50- 3,74 (m, 1 H) 3,88 (d, *J*= 9,8 Hz 1 H) 5,29 (d, *J*= 7,04 Hz, 1 H) 7,38- 7,45 (m, 2 H) 7,6 (t, *J*= 8,22 Hz 1 H) 8,16 (d, *J*= 3,13 Hz, 1 H); HRMS (A) *m/z* 417.1360 (M + H)+, Rt 2,29 min.

Los compuestos de la Tabla 11 se prepararon utilizando métodos similares a los descritos para la preparación del Ejemplo 485**.**

Tabla 11.

486	487	
		
488	489	

		
490	491	492
		
493	494	495
		
496	497	498
		
499	500	501

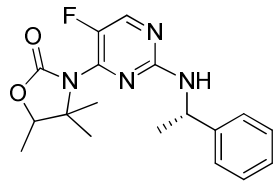
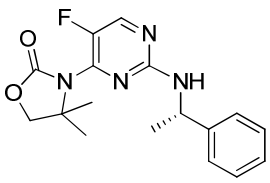
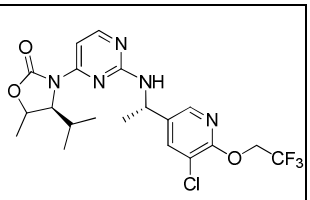
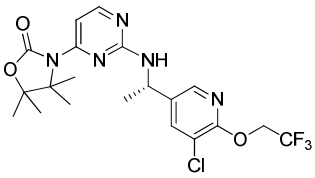
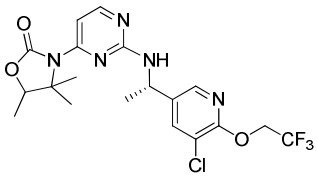
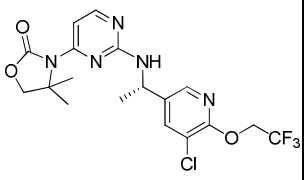
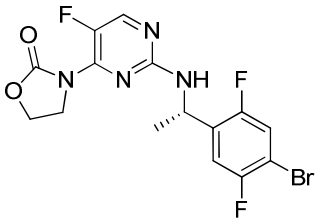
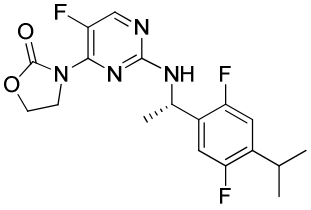
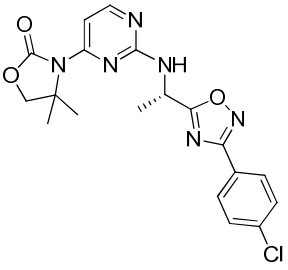
		
502	503	504
		
505	506	507
		

Tabla 12. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada compuesto que aparece en la Tabla 11.

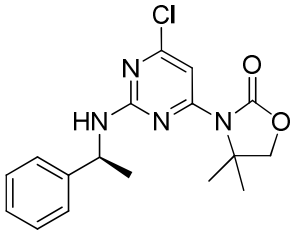
Ejemplo: Nombre	^{1}H RMN (400 MHz) δ ppm	LCMS
486: 3- (5- fluoro- 2- ((S)- 1- (2- fluoro- 4- (trifluorometil)fenil)etilamino)pirimidin- 4- il)- 5- metiloxazolidin- 2- ona	(CD_3OD) 1,41 - (br s., 1 H) 1,58 (m, 8 H) 3,55 3,74- 3,80 (m, 1 H) 4,17 (dd, *J*= 9,59, 7,63 Hz, 1 H) 5,26- 5,33 (m, 1 H) 7,39- 7,45 (m, 2 H) 7,60 (t, *J*= 7,83 Hz, 1 H) 8,15 (d, *J*= 3,52 Hz, 1 H)	HRMS (A) *m/z* 403.1198 (M + H)+, Rt 2,20 min
487: (S)- 6- (5- fluoro- 2- (1- (2- fluoro- 4- (trifluorometil)fenil)etilamino)pirimidin- 4- il)- 4- oxa- 6- azaspiro[2.4]heptan- 5- ona	(CD_3OD) 0,90 (m, 2 H) 1.18 - 1.27 (m, 2 H) 1,53 (d, *J*= 7,04 Hz, 3 H) 4,21 (d, *J*= 9,39 Hz, 1 H) 5,30 (d, *J*= 7,04 Hz, 1 H) 7,38- 7,45 (m, 2 H) 7,60 (t, *J*= 7,83 Hz 1 H) 8,17 (d, *J*= 3,52 Hz, 1 H)	HRMS (A) *m/z* 415.1204 (M + H)+, Rt 2,31 min
488: (S)- 3- (2- (1- (5-	(CD_3OD) 8,22 (d, *J*= 3,13 Hz, 1 H) 8,08 (d,	HRMS

cloro- 6- (2,2,2-trifluoroetoxi)piridin- 3-il)etilamino)- 5-fluoropirimidin- 4- il)- 4,4- dimetiloxazolidin- 2-ona	*J*= 1,96 Hz, 1 H) 7,84 (d, *J*= 1,96 Hz, 1 H) 5.26 a 5.27 (m, 1 H) 4,90 (q, *J*= 8,61 Hz, 3 H) 4.13 a 4.22 (m, 2 H) 1,47-1,59 (m, 9 H)	(A) *m/z* 464.1125 (M + H)+, Rt 2,28 min
489: (S)- 3- (2- (1- (5-cloro- 6- (1,1-difluoroetil)piridin- 3-il)etilamino)- 5-fluoropirimidin- 4- il)- 4,4,5,5-tetrametiloxazolidin- 2-ona	(CD_3OD) 8,51 (d, J = 1,57 Hz, 1 H) 8,23 (d, J = 2,35 Hz, 1 H) 7,93 (d, J = 1,56 Hz, 1 H) 4,99 (q, J = 6,52 Hz, 1 H) 2,02 (t, J = 18,78 Hz, 3 H) 1,57 (d, J = 7,43 Hz, 3 H) 1,34- 1,42 (m, 12 H)	HRMS (A) *m/z* 458.1573 (M + H)+, Rt 2,02 min
490: (S)- 3- (2- (1- (5-cloro- 6- (1,1-difluoroetil)piridin- 3-il)etilamino)- 5-fluoropirimidin- 4- il)- 4,4- dimetiloxazolidin- 2-ona	(CD_3OD) 8,50 (d, J = 1,17 Hz, 1 H) 8,24 (d, J = 2,35 Hz, 1 H) 7,93 (d, J = 1,57 Hz, 1 H) 4,99 (q, J = 6,65 Hz, 1 H) 4,12 - 4,21 (m, 2 H) 2,01 (t, J = 18,78 Hz, 3 H) 1,57 (d, J = 7,04 Hz, 3 H) 1,47 (s, 6 H)	HRMS (A) *m/z* 430.1265 (M + H)+, Rt 2,05 min
491: (S)- 3- (2- (1- (3- (4-clorofenil)- 1,2,4-oxadiazol- 5-il)etilamino)- 5-fluoropirimidin- 4- il)- 4,4,5,5-tetrametiloxazolidin- 2-ona	(CD_3OD) 8,27 (br s., 1 H) 8,00 (d, *J*= 8,61 Hz, 3 H) 7,52 (d, *J*= 8,61 Hz, 4 H) 5,29 (d, *J*= 7,04 Hz, 1 H) 1,73 (s, 3 H) 1,44 (s, 3 H) 1,38 (s, 3 H) 1,28 (s, 3 H)	HRMS (A) *m/z* 461.1512 (M + H)+, Rt 2,37 min
492: 3- (2- ((S)- 1- (3- (4-clorofenil)- 1,2,4-oxadiazol- 5-il)etilamino)- 5-fluoropirimidin- 4- il)- 4,4,5- trimetiloxazolidin- 2- ona (Mezcla 1:1 de diastereómeros)	(CD_3OD) 8,27 (d, *J*= 1,57 Hz, 1 H) 8,00 (d, *J*= 8,61 Hz, 2 H) 7,52 (d, *J*= 8,61 Hz, 2 H) 5,29 (m, 1 H) 4,44 (m, 1 H) 1,73 (d, *J*= 7,43 Hz, 3 H) 1,44 (br s, 3 H) 1.26 - . 1,35 (m, 6 H)	HRMS (A) *m/z* 477.1349 (M + H)+, Rt 2,3 min
493: (S)- 3- (2- (1- (3- (4-clorofenil)- 1,2,4-oxadiazol- 5-il)etilamino)- 5-fluoropirimidin- 4- il)- 4,4- dimetiloxazolidin- 2-ona	(CD_3OD) 8,28 (d, J = 2,35 Hz, 1 H) 8,00 (d, J = 8,61 Hz, 2 H) 7,51 (d, J = 8,61 Hz, 2 H) 5,29 (m, 1 H) 4,11 - 4,24 (m, 2 H) 1,73 (d, J = 7,04 Hz, 3 H) 1,53 (s, 3 H) 1,30 (sa, 3 H)	HRMS (A) *m/z* 433.1201 (M + H)+, Rt 2,21 min
494: (4S)- 4- isopropil- 5-metil- 3- (2 - ((S)- 1-feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona (Mezcla 1:1 de	(CD_3OD) 8,11 (d, *J*= 6,26 Hz, 1 H) 7,71 (d, *J*= 7,43 Hz, 1 H) 7,29- 7,40 (m, 4 H) 7.22 - . 7,28 (m, 1 H) 5,23 (br s, 1 H) 4,82 - (br. s., 1 H) 4,91 (m, 1 H) 4,78 2,01 (br. s., 1 H) 1,59 (d, *J*= 7,04 Hz, 3 H) 1,54	HRMS (A) *m/z* 341.1985 (M + H)+, Rt 1,78

diastereómeros)	(d, *J*= 6,65 Hz, 3 H) 0,76 (br s., 6 H)	min
495: (4S) - 3 - (5- fluoro- 2- ((S)- 1- feniletilamino) pirimidin- 4- il)- 4- isopropil- 5- metiloxazolidin- 2- ona (Mezcla 1:1 de diastereómeros)	(CD_3OD) 7,87 (d, *J*= 3,13 Hz, 1 H) 6,95- 7,02 (m, 2 H) 6,91 (t, *J*= 7,63 Hz, 2 H) 6,75- 6,85 (m, 1 H) 4.52 - 4,61 (m, 2H) 4,00 (br s, 1 H) 1,49 (br s, 1 H) 1,11 (dd, *J*= 9,59, 6,85 Hz, 6 H) 0,38 (d, *J*= 4,30 Hz, 6 H)	HRMS (A) *m/z* 359.1891 (M + H)+, Rt 2,19 min
496: (S) 4,4,5,5- tetrametil- 3- (2 - (1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	(CD_3OD) 8,08 (d, *J*= 6,26 Hz, 1 H) 7,28- 7,40 (m, 5 H) 7.18 - 7.25 (m, 1 H) 5,05 (q, *J*= 7,04 Hz, 1 H) 1,55- 1,62 (m, 6H) 1,37 (s, 3 H) 1,32 (s, 3 H)	HRMS (A) *m/z* 341.1984 (M + H)+, Rt 1,73 min
497: (S) - 3 - (5- fluoro- 2- (1- feniletilamino) pirimidin- 4- il) 4,4,5,5- tetrametiloxazolidin- 2- ona	(CD_3OD) 8,18 (d, *J*= 2,74 Hz, 1 H) 7,30- 7,39 (m, 2 H) 7.23- 7.30 (m, 2 H) 7.12- 7.21 (m, 1 H) 4,90 (q, *J*= 6,91 Hz, 1H) 1,50 (d, *J*= 7,04 Hz, 3 H) 1,42 (s, 3 H) 1,36 (s, 3 H) 1,33 (s, 3 H)	HRMS (A) *m/z* 359.1891 (M + H)+, Rt 2,16 min
498: 4,4,5- trimetil- 3- (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona (Mezcla 1:1 de diastereómeros)	(CD_3OD) 8,09 (d, *J*= 6,65 Hz, 1 H) 7,53 (d, *J*= 7,04 Hz, 1 H) 7,45 (d, *J*= 7,04 Hz, 1 H) 7,30- 7,40 (m, 8 H) 7.20- 7.28 (m, 2 H) 5,09 (t, *J*= 7,04 Hz, 2 H) 4,27- 4,42 (m, 2 H) 1,52- 1,69 (m, 12 H) 1,32 (dd, *J*= 11,15, 6,46 Hz, 6 H) 0,82- 1,20 (m, 6 H)	HRMS (A) *m/z* 327.1826 (M + H)+, Rt 1,66 min
499: 3 - (5- fluoro- 2- ((S)- 1- feniletilamino) pirimidin- 4- il) - 4,4,5- trimetiloxazolidin- 2- ona (Mezcla 1:1 de diastereómeros)	(CD_3OD) 8,18 (d, *J*= 2,74 Hz, 1 H) 7,30- 7,37 (m, 2 H) 7.24 - 7.30 (m, 2 H) 7.11 - 7.21 (m, 1 H) 4,87- 4,97 (m, 1 H) 4,31- 4,46 (m, 1 H) 1,50 (d, *J*= 7,04 Hz, 3 H) 1,41 (d, *J*= 10,96 Hz, 3 H) 1,29 (dd, *J*= 6,46, 3,33 Hz, 3 H) 0,84- 1,16 (br s, 3 H)	HRMS (A) *m/z* 345.1735 (M + H)+, Rt 2,09 min
500: (S) - 3 - (5- fluoro- 2- (1- feniletilamino) pirimidin- 4- il) - 4,4- dimetiloxazolidin- 2- ona	(CD_3OD) 8,19 (d, *J*= 2,35 Hz, 1 H) 7,30- 7,37 (m, 2 H) 7.24 - 7.30 (m, 2 H) 7.13 - 7.21 (m, 1 H) 4,91 (q, *J*= 7,30 Hz, 1H) 4,12 (q, *J*= 8,22 Hz, 2 H) 1.45 - . 1,55 (m, 6 H) 1,08 (br s, 3 H)	HRMS (A) *m/z* 331.1573 (M + H)+, Rt 1,98 min
501: (4S)- 3- (2- ((S)- 1- (5- cloro- 6- (2,2,2- trifluoroetoxi)piridin- 3- il)etilamino)pirimidin- 4- il)- 4- isopropil- 5- metiloxazolidin- 2- ona (Mezcla 1:1 de diastereómeros)	^{1}H RMN (400 MHz, CD_3OD) δ ppm 8,14 (d, *J*= 6,65 Hz, 1 H) 8,10 (d, *J*= 1,96 Hz, 1 H) 7,86 (d, *J*= 2,35 Hz, 1 H) 7,57 (d, *J*= 6,26 Hz, 1 H) 5,17 (d, *J*= 6,65 Hz, 1 H) 4,92 (q, *J*= 8,87 Hz, 1 H) 4,80 - . 4,84 (m, 1H) 2,04 (br s, 2 H) 1,55 (dd, *J*= 15,85, 6,85 Hz, 6 H) 0,79 (sa, 6 H)	HRMS (A) *m/z* 474.1523 (M + H)+, Rt 2,18 min

502: (S)- 3- (2- (1- (5- cloro- 6- (2,2,2- trifluoroetoxi)piridin- 3- il)etilamino)pirimidin- 4- il)- 4,4,5,5- tetrametiloxazolidin- 2- ona	(CD_3OD) 8.7 - 8.16 (m, 1 H) 7,89 (d, *J*= 1,96 Hz, 1 H) 7,32 (d, *J*= 6,26 Hz, 1 H) 5,08 (q, *J*= 6,78 Hz, 1 H) 1,55- 1,65 (m, 8 H) 1,37 (d, *J*= 11,35 Hz, 6 H) 1,20 (d, *J*= 11,35 Hz, 3 H)	HRMS (A) *m/z* 474.1534 (M + H)+, Rt 2,16 min
503: 3- (2- ((S)- 1- (5- cloro- 6- (2,2,2- trifluoroetoxi)piridin- 3- il)etilamino)pirimidin- 4- il)- 4,4,5- trimetiloxazolidin- 2- ona (1:2 mezcla de diastereómeros)	(CD_3OD) 8,47 (d, *J*= 5,87 Hz, 1 H) 8,11 (d, *J*= 2,35 Hz, 3H) 7,99 (d, *J*= 6,26 Hz, 1 H) 7,88 (d, *J*= 1,96 Hz, 3 H) 7,39 (d,*J*= 6,26 Hz, 2 H) 7,32 (d, *J*= 6,65 Hz, 2 H) 5.4 a 5.13 (m, 1 H) 4,87- 4,98 (m, 2 H) 4,45 (d, *J*= 6,65 Hz, 1 H) 4,35 (dd, *J*= 13,69, 6,65 Hz, 2 H) 1,67 (d, *J*= 4,70 Hz, 9 H) 1,59 (d, *J*= 7,04 Hz, 12 H) 1,39 (d, *J*= 6,65 Hz, 3 H) 1,33 (t, *J*= 6,06 Hz, 6 H) 0,99- 1,27 (m, 9 H)	HRMS (A) *m/z* 460.1375 (M + H)+, Rt 2,08, 2,11 min
504: (S)- 3- (2- (1- (5- cloro- 6- (2,2,2- trifluoroetoxi)piridin- 3- il)etilamino)pirimidin- 4- il)- 4,4- dimetiloxazolidin- 2- ona	(CD_3OD) 8.9 - 8.17 (m, 1 H) 7,88 (d, *J*= 2,35 Hz, 1 H) 7,38 (d, *J*= 6,26 Hz, 1 H) 4,91 (q, *J*= 8,61 Hz, 1 H) 4.6 a 4.16 (m, 2 H) 1,71 (m, 5 H) 1,58 (d, *J*= 7,04 Hz, 3 H) 1,28 (br s., 3 H)	HRMS (A) *m/z* 446.1219 (M + H)+, Rt 2,01 min
505: (S) - 3 - (2 - (1 - (2,5- difluoro- 4- isopropilfenil) etilamino)- 5- fluoropirimidin- 4- il) oxazolidin- 2- ona	(CD_3OD) 8,15 (d, *J*= 3,13 Hz, 1 H) 6,92- 7,08 (m, 2 H) 5,21 (q, *J*= 6,78 Hz, 1 H) 4,44- 4,58 (m, 2 H) 4.10- 4.22 (m, 1H) 3,96 (m, 1 H) 3.7 a 3.23 (m, 1 H) 1,48 (d, *J*= 7,04 Hz, 5 H) 1,21 (m, 6 H)	HRMS (A) *m/z* 381.1544 (M + H)+, Rt 2,26 min
506: (S) - 3 - (2 - (1 - (4- bromo- 2 ,5- difluorofenil) etilamino)- 5- fluoropirimidin- 4- il) oxazolidin- 2- ona	(CD_3OD) 8,15 (d, *J*= 3,52 Hz, 1 H) 7,39 (dd, *J*= 9,00, 5,48 Hz, 1H) 7,24 (dd, *J*= 9,19, 6,46 Hz, 1 H) 5,19 (q, *J*= 7,04 Hz, 1 H) 4,44- 4,58 (m, 2 H) 4.09 - . 4,23 (m, 1 H) 3,94 (br s, 1 H) 1,48 (d, *J*= 7,04 Hz, 3 H)	HRMS (A) *m/z* 417,018 (M + H)+, T 2.07 min
507: (S)- 3- (2- (1- (3- (4- clorofenil)- 1,2,4- oxadiazol- 5- il)etilamino)pirimidin- 4- il)- 4,4- dimetiloxazolidin- 2- ona	(CD_3OD) 8,09 (d, *J*= 6,26 Hz, 1 H) 7,91 (d, *J*= 8,61 Hz, 2 H) 7,43 (d, *J*= 8,61 Hz, 3 H) 5,35 (q, *J*= 7,30 Hz, 1 H) 3,97 - 4,09 (m, 2 H) 1,69 (d, *J*= 7,43 Hz, 3 H) 1,62 (s, 3 H) 1,14- 1,45 (m, 3 H)	HRMS (A) *m/z* 415.1287 (M + H)+, Rt 2,14 min

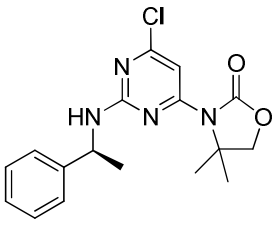
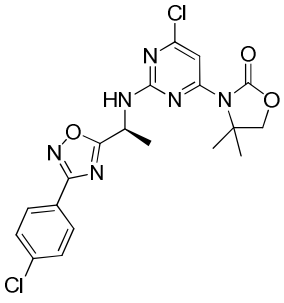
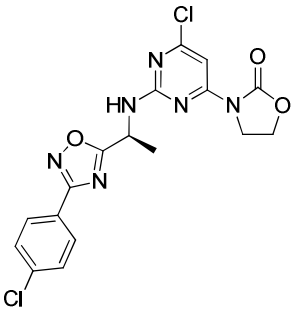
Ejemplo 508

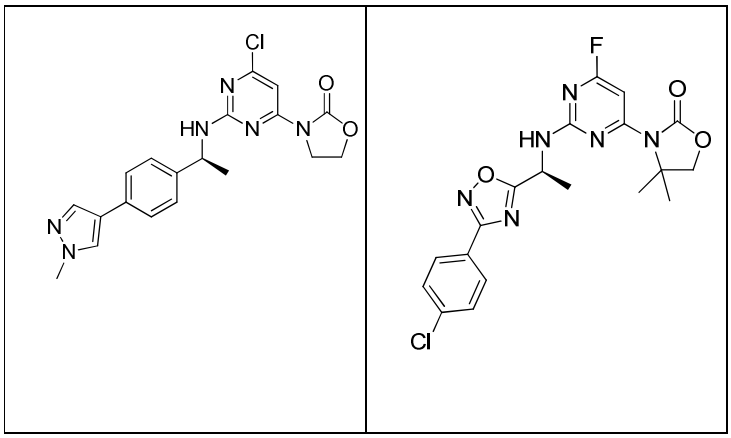


Una solución de 3 - (2,6- dicloropirimidin- 4- il) - 4,4- dimetiloxazolidin- 2- ona (70.0 mg, 0.267 mmoles), (*S*) - (-)- 1- feniletanamina (0.034 ml, 0.267 mmol, 1.0 equiv), y N- etil- N- isopropilpropan- 2- amina (0.070 ml, 0.401 mmol, 1.5 equiv) en DMSO (1.5 ml) se calentó a 85 °C durante 2- 4 h. La purificación mediante HPLC de fase inversa proporcionó la sal de trifluoroacetato de (S) - 3 - (6- cloro- 2- (1- feniletilamino) pirimidin- 4- il) - 4,4- dimetiloxazolidin- 2- ona (20.0 mg, sólido blanco) con un rendimiento del 16%. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,36 (s, 1H), 7,33- 7,31 (m, 4H), 7.26- 7.21 (m, 1H), 5,48 (br m, 1H), 4,02- 3,94 (m, 2H) , 1,65 (s, 3H), 1,55 (d, J = 6,9 Hz, 3H), 1,26 (s, 3H); HRMS (A) *m/z* 347.1274 (M + H)+, Rt 2,32 min.

Los compuestos de la Tabla 13 se prepararon utilizando métodos similares a los descritos para la preparación del Ejemplo 508.

Tabla 13.

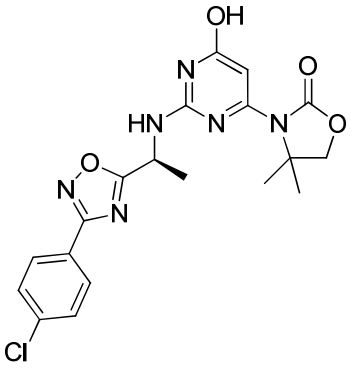
509	510	511
		
512	513	



Cuadro 14. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada compuesto que aparece en la Tabla 13.

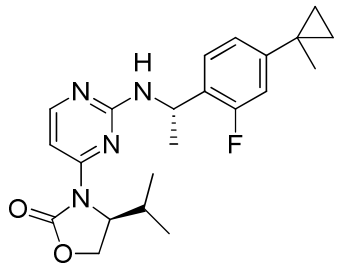
Ejemplo: Nombre	^{1}H RMN **(400 MHz) δ ppm**	**LCMS**
509: (S) - 3 - (6- cloro- 2- (1- feniletilamino) pirimidin- 4- il) - 4,4- dimetiloxazolidin- 2- ona	($CDCl_3$) 7,36 (s, 1H), 7,33- 7,31 (m, 4H), 7.26- 7.21 (m, 1H), 5,48 (br m, 1H), 4,02- 3,94 (m, 2H), 1,65 (s, 3H), 1,55 (d, J = 6,9 Hz, 3H), 1,26 (s, 3H)	HRMS (A) *m/z* 347.1274 (M + H)+, Rt 2,32 min
510: (S)- 3- (6- cloro- 2- (1- (3- (4- clorofenil)- 1,2,4- oxadiazol- 5- il)etilamino)pirimidin- 4- il)- 4,4- dimetiloxazolidin- 2- ona	($CDCl_3$) 8,00 (d, J = 8,4 Hz, 2 H), 7,53 (s, 1H), 7,47 (d, J = 8,4 Hz, 2H), 5,44- 5,29 (br m, 1H), 4.9- 4.2 (m , 2H), 1,78 (d, J = 7,1 Hz, 3H), 1,72 (s, 3H), 1,40 (br s, 3H)	HRMS (A) *m/z* 449.0905 (M + H)+, Rt 2,51 min
511: (S)- 3- (6- cloro- 2- (1- (3- (4- clorofenil)- 1,2,4- oxadiazol- 5- il)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	($CDCl_3$) 8,00 (d, J = 8,7 Hz, 2H), 7,62 (s, 1H), 7,47 (d, J = 8,7 Hz, 2H), 5,32 (br m, 1H), 4,49- 4,43 (m, 2H) , 4.17- 4.14 (m, 1H), 3,95- 3,60 (br m, 1H), 1,77 (d, J = 7,1 Hz, 3H)	HRMS (A) *m/z* 421.0585 (M + H)+, Rt 2,32 min
512: (S)- 3- (6- cloro- 2- (1- (2- fluoro- 4- (1- metil- 1H- pirazol- 4- il)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	($CDCl_3$) 7,76 (s, 1H), 7,60 (s, 1H), 7,50 (s, 1H), 7,34- 7,28 (m, 1H), 7,20 (dd, J = 7,8, 1,6 Hz, 1H), 7.15 - 7.9 (m, 1H), 5,30 (br m, 1H), 4,49- 4,42 (m, 2H), 4.28- 4.23 (m, 1H), 3,97 (s, 3H), 3,92 (br m, 1H), 1,56 (d , J = 6,7 Hz, 3H)	CLMS m/z 417,2 (M + H)+
513: (S)- 3- (2- (1- (3- (4- clorofenil)- 1,2,4- oxadiazol- 5- il)etilamino)- 6- fluoropirimidin- 4- il)- 4,4- dimetiloxazolidin- 2- ona	($CDCl_3$) 7,99 (d, J = 8,4 Hz, 2H), 7,45 (d, J = 8,4 Hz, 2H), 7,11 (s, 1H), 5,38 (br m, 1H), 4.8- 4.3 (m, 2H) , 1,78 (d, J = 7,0 Hz, 3H), 1,73 (s, 3H), 1,38 (br s, 3H)	HRMS (A) *m/z* 433.1201 (M + H)+, Rt 2,42 min

Ejemplo 514:



Una solución de (S)- 3- (2- (1- (3- (4- clorofenil)- 1,2,4- oxadiazol- 5- il)etilamino)- 6- fluoropirimidin- 4- il)- 4,4- dimetiloxazolidin- 2- ona (29.0 mg, 0.053 mmol) y 1 N de ácido clorhídrico acuoso (0.70 ml) en 1,4- dioxano (0.7 ml) se calentó a 100 °C durante 4 h. Después de enfriar a temperatura ambiente, la mezcla de reacción se diluyó con diclorometano (10 ml), se lavó con solución de bicarbonato de sodio acuoso saturado (10 ml), se secó sobre Na_2SO_4, se filtró y se concentró. La purificación mediante HPLC de fase inversa proporcionó la sal de trifluoroacetato de (S)- 3- (2- (1- (3- (4- clorofenil)- 1,2,4- oxadiazol- 5- il)etilamino)- 6- hidroxipirimidin- 4- il)- 4,4- dimetiloxazolidin- 2- ona (16 mg, sólido blanco) con un rendimiento del 55%. ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,00 (d, J = 8,5 Hz, 2H), 7,46 (d, J = 8,5 Hz, 2H), 6,71 (br s, 1H), 5,33 (br m, 1H), 4,02 - 3,99 (m, 2H), 1,83 (d, J = 7,1 Hz, 3H), 1,68 (s, 3H), 1,31 (s, 3H); HRMS (A) *m/z* 431.1245 (M + H)+, Rt 1,80 min.

Ejemplo 515



Paso 1

A un matraz de fondo redondo que contiene (R)- N- ((S) - 1 - (2- fluoro- 4- (1- metilciclopropil) fenil) etil)- 2- metilpropano- 2- sulfinamida (87 mg, 0.29 mmol) se añadió dioxano (2 ml). A esta solución se añadió ácido clorhídrico en dioxano (4.0 M, 0.15 ml, 0,59 mmol) y la solución se dejó en agitación 10 min a temperatura ambiente. Se eliminaron los compuestos volátiles. Se añadió Et_2O (10 ml) y la mezcla de reacción sonicó. Los volátiles se eliminaron de nuevo. Se añadió de nuevo Et_2O (10 ml) y la suspensión sonicó. El material sólido se recogió y se lavó con Et_2O para proporcionar una sal de HCl de (S) - 1 - (2- fluoro- 4- (1- metilciclopropil) fenil)etanamina (42 mg, 0.18 mmol, rendimiento del 63%) como un sólido blanco . LCMS m/z 194.1 (M + H)+, Rt 0.60 min.

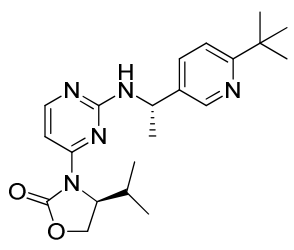
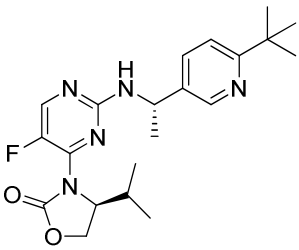
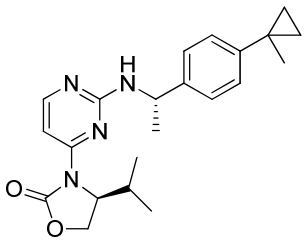
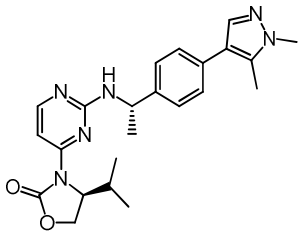
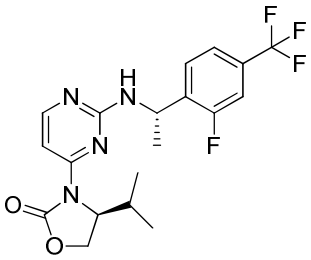
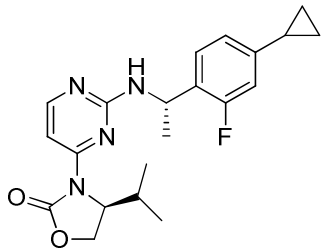
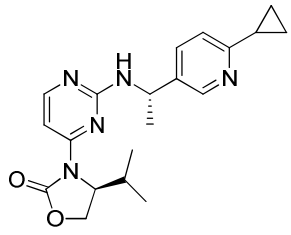
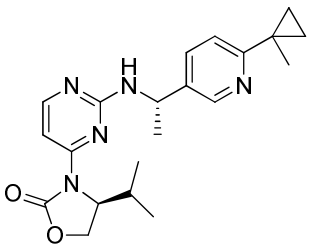
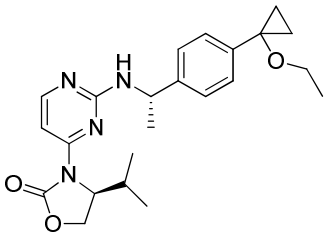
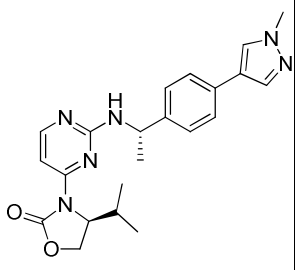
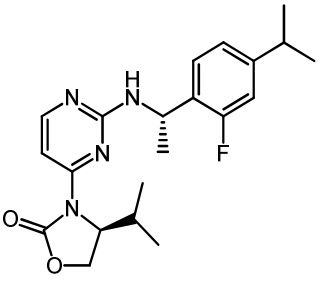
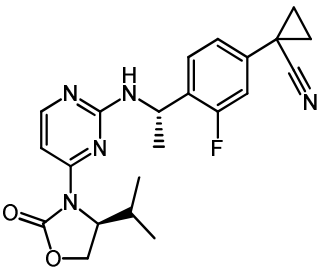
Paso 2

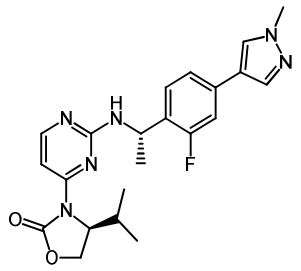
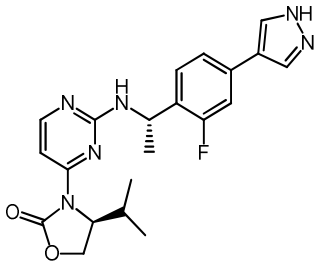
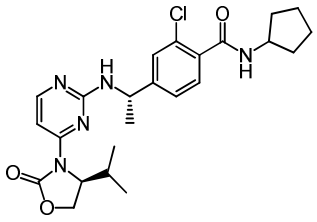
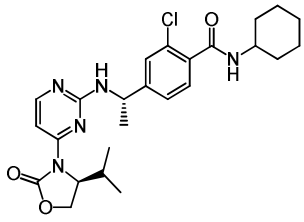
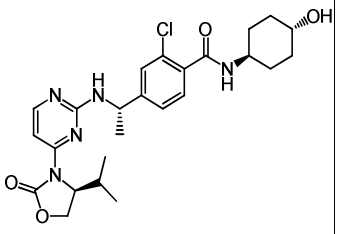
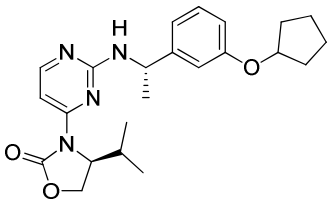
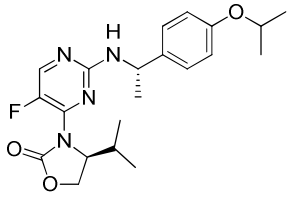
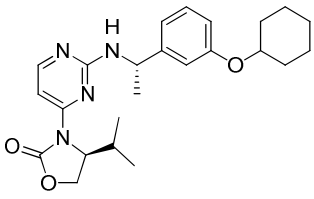
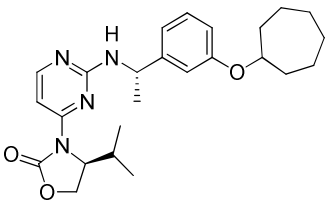
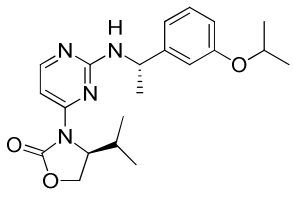
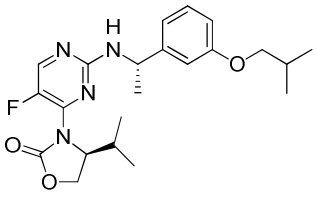
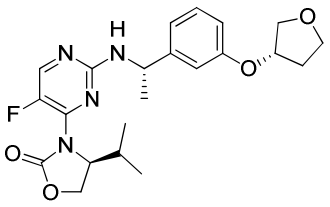
A un vial de microondas con una barra de agitación se añadió (S) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (30 mg, 0.12 mmol) y DMSO (1 ml). A esta mezcla de reacción se añadió (S) - 1 - (2- fluoro- 4- (1- metilciclopropil) fenil) etanamina (51 mg, 0.22 mmol) y DIEA (0.09 ml, 0.50 mmol). El vial se tapó y la mezcla de reacción se calentó en un baño de aceite precalentado a 110 °C durante 18 h. La solución se purificó mediante HPLC de fase inversa. Las fraccionas del producto se combinaron, congelaron y liofilizaron para proporcionar (S) - 3 - (2 - ((S) - 1 - (2- fluoro- 4- (1- metilciclopropil) fenil) etilamino) pirimidin- 4- il) - 4 - isopropiloxazolidin- 2- ona (3.3 mg, 6.3 mmol, rendimiento del 5%) como una sal de TFA. ^{1}H RMN (400 MHz, CD_3OD) δ 0,58 (br s., 3 H) 0,77 (td, *J*= 5,23, 1,76 Hz, 5 H) 0.80 - 0,86 (m, 2 H) 1,38 (s, 3 H) 1,57 (d, *J*= 6,94 Hz, 3 H) 4.34 - . 4,41 (m, 2 H) 4,67 (br s, 1 H) 5,33 (d, *J*= 7,97 Hz, 1 H) 6,95- 7,05 (m, 2 H) 7,22 (t, *J*= 7,97 Hz, 1 H) 7,67 (d, *J*= 6,85 Hz, 1 H) 8,14 (d, *J*= 6,65 Hz, 1 H). LCMS m/z 399,4 (M + H)+, Rt 0,93 min. HRMS (A) *m/z* 399.2202 (M + H)+, Rt 2.23 min.

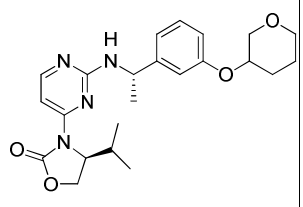
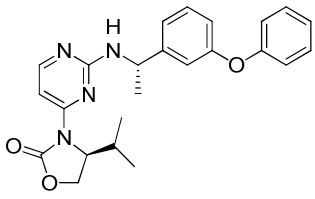
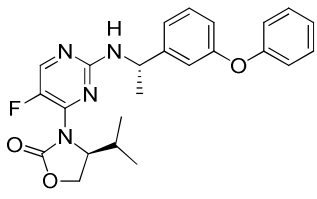
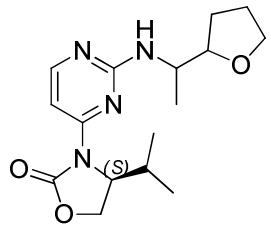
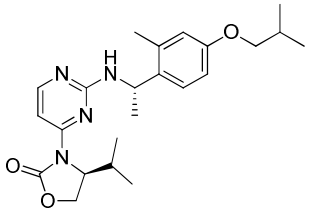
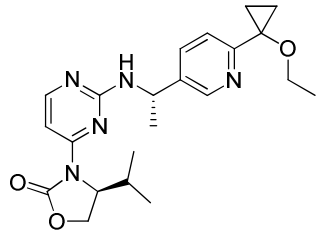
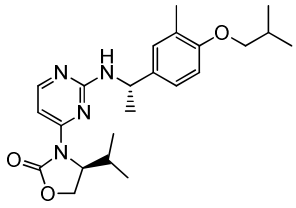
Los compuestos de la Tabla 15 se prepararon utilizando métodos similares a los descritos para la preparación de los Ejemplos 515.

Tabla 15.

516	517	518

		
519	520	521
		
522	523	524
		
525	526	527
		
528	529	530

		
531	532	533
		
534	535	536
		
537	538	539
		
540	541	542

		
543	544	545
		
546		
		

Cuadro 16. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada compuesto que aparece en la Tabla 15.

Tabla 16.

Ejemplo: Nombre	^{1}H RMN **(400 MHz)** δ **ppm**	**LCMS**
516: (S) - 3 - (2 - ((S) - 1 - pirimidin- 4- il (6- terc- butilpiridin- 3- il) etilamino))- 4- isopropiloxazolidin- 2- ona	(DMSO) 0,46 (br s., 3 H) 0,63 (br s., 3 H) 1,35 (s, 9 H) 1,50 (d, *J*= 6,99 Hz, 3 H) 4,34 (d, *J*= 7,92 Hz, 2 H) 4,59 (br s., 1 H) 5,14 (br s., 1 H) 7,32 (d, *J*= 5,92 Hz, 1 H) 7,70 (br s., 1 H) 8,03 (br s., 1 H) 8,24 (br s., 2 H) 8,59 (br s., 1 H)	HRMS (A) *m/z* 384.2410 (M + H)+, Rt 1,34
517: (S)- 3- (2- ((S)- 1- (6- tert- butilpiridin- 3-	(br. s., 6 H) (DMSO) 0,55 1,25 - 1,38 (s, 9 H) 1,47 (d, *J*= 7,04 Hz, 3 H) 4,26 (br s, 1	HRMS (A) *m/z*

il)etilamino)- 5-fluoropirimidin- 4- il)- 4-isopropiloxazolidin- 2-ona	H) 4.45 - ... 4,59 (m, 2 H) 4,98 (br s, 1 H) 7,66 (br s, 1 H) 8,11 (br. s., 2 H) 8,41 (br s., 1 H) 8,60 (br s., 1 H)	402.2314 (M + H)+, Rt 1,45
518: (S)- 4- isopropil- 3-(2 - ((S) - 1 - (4 - (1-ciclopropil metil) fenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona		HRMS (A) *m/z* 381.2295 (M + H)+, Rt 2,10
519: (S)- 3- (2- ((S)- 1- (4-(1,5- dimetil- 1H- pirazol-4-il)fenil)etilamino)pirimidin- 4- il)- 4-isopropiloxazolidin- 2-ona	(DMSO) 0,49 (br s., 3 H) 0,68 (br s., 3 H) 1,48 (d, *J*= 7,04 Hz, 6 H) 2,33 (s, 3 H) 3,76 (s, 3 H) 4,63 (br s, 1 H) 4.75 - .. 4,82 (m, 1 H) 5,03 (br s, 2 H) 7,30 - (br. s., 1 H) 7,37 (m, 4 H) 7,50 (s, 1 H) 8,22 8,36 (br. s., 1 H)	HRMS (A) *m/z* 421.2362 (M + H)+, Rt 1,58
520: (S) - 3 - (2 - ((S) - 1 - (2- fluoro - 4 - (trifluorometil) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO) 0,40 (br s., 3 H) 0,57 (br s., 3 H) 1,40 (br s., 1 H) 1,47 (d, *J*= 7,04 Hz, 3 H) 4.24 - 4,37 (m, 2 H) 4,49 (br s, 1 H) 5,23 (br s, 1 H) 7,30 (d, *J*= 5,82 Hz, 1H) 7,48-7,59 (m, 2 H) 7,65 (d, *J*= 10,56 Hz, 1 H) 8,21 (d, *J*= 18,58 Hz, 2 H)	HRMS (A) *m/z* 413.1602 (M + H)+, Rt 2,16
521: (S) - 3 - (2 - ((S) - 1 - (4- ciclopropil- 2-fluorofenil) etilamino) pirimidin- 4- il)- 4-isopropiloxazolidin- 2-ona	(CD_3OD) 0,61 0,64 - (br. s., 3 H) 0,69 (m, 3 H) 0,77 0,96- 1,04 (m, 2 H) 1,57 (d, *J*= 6,99 Hz, 3 H) 1,88- 1,95 (m, 1 H) 4,39 (d, *J*= 5,97 Hz, 2 H) 4,69 (br s., 1 H) 5,33 (br s., 1 H) 6,82 (dd, *J*= 12,08, 1,71 Hz, 1 H) 6,88 (d, *J*= 7,97 Hz, 1 H) 7,19 (t, *J*= 8,31 Hz, 1 H) 7,70 (d, *J*= 6,90 Hz, 1 H) 8,14 (d, *J*= 7,04 Hz, 1 H)	HRMS (A) *m/z* 385.2042 (M + H)+, Rt 2,06
522: (S) - 3 - (2 - ((S) - 1 - (6- ciclopropilpiridin- 3-il) etilamino) pirimidin- 4-il)- 4- isopropiloxazolidin-2- ona	(CD_3OD) 0,65- 0,83 (m, 6 H) 1.14- 1.20 (m, 2 H) 1,37- 1,43 (m, 2 H) 1,64 (d, *J*= 7,09 Hz, 3 H) 2,26- 2,37 (m, 1 H) 4.36 - . 4,39 (m, 2 H) 4,68 (br s, 1 H) 5,25 (q, *J*= 6,75 Hz, 1 H) 7,57 (d, *J*= 8,51 Hz, 1 H) 7,63 (br s., 1 H) 8,18 (d, *J*= 5,92 Hz, 1 H) 8,33 (d, *J*= 7,24 Hz, 1 H) 8,57 (d, *J*= 2,10 Hz, 1 H)	HRMS (A) *m/z* 368.2097 (M + H)+, Rt 1,12
523: (S)- 4- isopropil- 3-(2- ((S)- 1- (6- (1-metilciclopropil)piridin-3- il)etilamino)pirimidin-4- il)oxazolidin- 2- ona	(CD_3OD) 0,59- 0,84 (m, 6 H) 1.8 - 1.15 (m, 2 H) 1.22 - 1.28 (m, 2 H) 1,56 (s, 3 H) 1,64 (d, *J*= 7,09 Hz, 3 H) 4.35 - . 4,39 (m, 2 H) 4,69 (br s, 1 H) 5.21 - . 5,32 (m, 1 H) 7,62 (br s, 1 H) 7,79 (d, *J*= 8,46 Hz, 1 H) 8,18 (d, *J*= 6,11 Hz, 1 H) 8,33 (d, *J*= 7,14 Hz, 1 H) 8,57 (d, *J*= 2,20 Hz, 1 H)	HRMS (A) *m/z* 382.2247 (M + H)+, Rt 1,30
524: (S)- 3- (2- ((S)- 1- (4-	(CD_3OD) 0,60 0,78 0,92 (br s, 3 H). - 0,98	HRMS

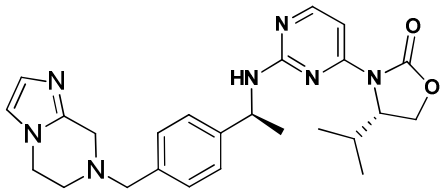
(1- etoxiciclopropil)- 2- fluorofenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(m, 2 H) 1,15 (t, *J*= 7,07 Hz, 3 H) 1.19 a 1.26 (m, 2 H) 1,59 (d, *J*= 6,99 Hz, 3 H) 1,78 (br s., 1 H) 3,43 (q, *J*= 7,09 Hz, 2 H) 4,40 (d, *J*= 5,72 Hz, 2 H) 4,70 (d, *J*= 3,91 Hz, 1 H) 5,38 (br s, 1 H) 7,06 (s, 1 H) 7,07 - . 7,12 (m, 1 H) 7,31 (t, *J*= 7,95 Hz, 1 H) 7,73 (d, *J*= 7,04 Hz, 1 H) 8,15 (d, *J*= 6,90 Hz, 1 H)	(A) *m/z* 429.2310 (M + H)+, Rt 2,08
525: (S)- 4- isopropil- 3- (2- ((S)- 1- (4- (1- metil- 1H- pirazol- 4- il)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	(DMSO) 0,47 (br s., 3 H) 0,69 (br s., 3 H) 1,45 (d, *J*= 6,99 Hz, 3 H) 1,81 (br s., 1 H) 3,84 (s, 3 H) 4,33 (d, *J*= 13,45 Hz, 2 H) 4,62 (br s, 1 H) 4,99 (br s, 1 H) 7.24 - .. 7,33 (m, 3 H) 7,46 (d, *J*= 8,27 Hz, 2 H) 7,79 (d, *J*= 0,73 Hz, 1 H) 8,06 (s, 1 H) 8,18 (br s., 1 H)	HRMS (B) *m/z* 407.2179 (M + H)+, Rt 2.44min
526: (S) - 3 - (2 - ((S) - 1 - (2- fluoro- 4- isopropilfenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(CD_3OD) 0,59 (br s., 3 H) 0,78 (br s., 3 H) 1,23 (dd, *J*= 6,90, 1,03 Hz, 6 H) 1,58 (d, *J*= 6,99 Hz, 3 H) 2,91 (dt, *J*= 13,78, 6,93 Hz, 1 H) 4,39 (d, *J*= 5,97 Hz, 2 H) 4,69 (br s, 1 H) 5,35 (br s, 1 H) 6,97 - .. 7,06 (m, 2 H) 7.20- 7.28 (m, 1 H) 7,73 (d, *J*= 6,99 Hz, 1 H) 8,15 (d, *J*= 6,90 Hz, 1 H)	HRMS (A) *m/z* 387.2207 (M + H)+, Rt 2,20
527: 1 - ((S) - 1 3- fluoro- 4- (- (4 - ((S)- 4- isopropil- 2- oxooxazolidin- 3- il) pirimidin- 2- ilamino) etil) fenil) ciclopropanocarbonitrilo	(br. s., 3 H) (CD_3OD) 0,61 (br. s., 3 H) 0,75 1,40- 1,50 (m, 2 H) 1,57 (d, *J*= 6,94 Hz, 3 H) 1,71- 1,79 (m, 2 H) 4,37 (d, *J*= 6,50 Hz, 2 H) 4,66 (br s., 1 H) 5,34 (d, *J*= 6,55 Hz, 1 H) 7.7 - 7.18 (m, 2 H) 7,36 (t, *J*= 8,19 Hz, 1 H) 7,64 (d, *J*= 6,65 Hz, 1 H) 8,15 (d, *J*= 6,60 Hz, 1 H)	HRMS (A) *m/z* 410.1999 (M + H)+, Rt 1,82
528: (S)- 3- (2- ((S)- 1- (2- fluoro- 4- (1- metil- 1H- pirazol- 4- il)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(CD_3OD) 0,58 (br s., 3 H) 0,78 (br s., 3 H) 1,62 (d, *J*= 7,04 Hz, 3 H) 1,82 (br s., 1 H) 3,92 (s, 3 H) 4,40 (d, *J*= 6,26 Hz, 2 H) 4,70 (br s, 1 H) 5,39 (br s, 1 H) 7.29 - .. 7,39 (m, 3 H) 7,78 (d, *J*= 7,04 Hz, 1 H) 7,82 (s, 1 H) 7,99 (s, 1 H) 8,16 (d, *J*= 7,04 Hz, 1 H)	HRMS (A) *m/z* 425.2112 (M + H)+, Rt 1,64
529: (S)- 3- (2- ((S)- 1- (2- fluoro- 4- (1H- pirazol- 4- il)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(CD_3OD) 0,59 (br s., 3 H) 0,79 (br s., 3 H) 1,63 (d, *J*= 6,94 Hz, 3 H) 1,84 (br s., 1 H) 4,40 (d, *J*= 6,26 Hz, 2 H) 4,71 (br s, 1 H) 5,40 (br s, 1 H) 7.29 - .. 7,36 (m, 1 H) 7,37- 7,43 (m, 2 H) 7,78 (d, *J*= 7,09 Hz, 1 H) 7,99 (s, 2 H) 8,17 (dd, *J*= 6,36, 1,86 Hz, 1 H)	HRMS (A) *m/z* 411.1949 (M + H)+, Rt 1,52
530: 2- cloro- N- ciclopentil- 4- ((S)- 1- (4-	(DMSO) 0,55 (br s., 3 H) 0,78 (br s., 3 H) 1,42 (d, *J*= 7,09 Hz, 3 H) 1,50 (d, *J*= 4,65	HRMS (A) *m/z*

((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida	Hz, 4 H) 1,64 (br s., 2 H) 1,83 (d, *J*= 6,46 Hz, 3 H) 4,14 (dd, *J*= 12,72, 6,60 Hz, 1 H) 4,34 (br s., 2 H) 4,64 (br s., 1 H) 5,03 (br s., 1 H) 7,25 (d, *J*= 5,77 Hz, 1 H) 7,31 (s, 2 H) 7,42 (s, 1 H) 8,19 (br s., 1 H) 8,27 (br s., 1 H)	472.2117 (M + H)+, Rt 1,82
531: 2- cloro- N- ciclohexil- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida	(DMSO) 0,55 (br. s., 3 H) 0,78 1,18- 1,34 (m, 4 H) 1,42 (d, *J*= 7,04 Hz, 3 H) 1,56 (d, *J*= 12,08 Hz, 1 H) 1,69 (d, *J*= 12,86 Hz, 3 H) 1,81 (br s., 3 H) 4,34 (br s., 2 H) 4,63 (br s., 1 H) 5,03 (br s., 1 H) 7,26 (d , *J*= 5,82 Hz, 1 H) 7,31 (s, 2 H) 7,43 (s, 1 H) 8,03 (br s., 1 H) 8,18 (br s., 2 H)	HRMS (A) *m/z* 486.2275 (M + H)+, Rt 1,94
532: 2- cloro- N- ((1r,4S)- 4- hydroxiciclohexil)- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida	(DMSO) 0,54 0,77 1,18 (br s, 3 H). - 1,30 (m, 5 H) 1,36 (s, 1 H) 1,42 (d, *J*= 7,04 Hz, 3 H) 1,81 (d, *J*= 9,19 Hz, 5 H) 3,36 (br s., 1 H) 4,33 (br s., 2 H) 4,63 (br s., 1 H) 5,02 (br s., 1 H) 7,25 (d , *J*= 5,77 Hz, 1 H) 7,30 (s, 2 H) 7,42 (s, 1 H) 8,17 (br s., 2 H)	HRMS (A) *m/z* 502.2226 (M + H)+, Rt 1,40
533: (S) - 3 - (2 - ((S) - 1 - (3 - (ciclopentiloxi) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO) 0,40- 0,73 (m, 6 H) 1,40 (d, *J*= 6,99 Hz, 3 H) 1,47- 1,70 (m, 6 H) 1,83 (dd, *J*= 16,80, 6,72 Hz, 3 H) 4,31 (d,*J*= 8,75 Hz, 2 H) 4,58 (br s., 1 H) 4,71 (br s., 1 H) 4,94 (br s., 1 H) 6,69 (dd, *J*= 7,95, 2,03 Hz, 1 H) 6,81 (d, *J*= 8,31 Hz, 2 H) 7.9- 7.19 (m, 1 H) 7,27 (d, *J*= 6,06 Hz, 1 H) 8,16 (br s., 2 H)	HRMS (A) *m/z* 411.2402 (M + H)+, Rt 2,15 min
534: (S) - 3 - (2 - ((S) - 1 - (3 - (ciclohexiloxi) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO) 0,47 (br. s., 3 H) 0,65 1,14- 1,36 (m, 5 H) 1,40 (d, *J*= 7,04 Hz, 3 H) 1,44- 1,54 (m, 1 H) 1,65 (d, *J*= 9,34 Hz, 2 H) 1,72- 1,91 (m, 3 H) 4.11 - .. 4,39 (m, 3 H) 4,57 (br s, 1 H) 4,94 (br s, 1 H) 6,71 (dd, *J*= 7,85, 1,88 Hz, 1 H) 6,80 (br s., 2 H) 7,14 (t, *J*= 8,07 Hz, 1 H) 7,26 (d, *J*= 6,02 Hz, 1 H) 8,16 (br s., 2 H)	HRMS (A) *m/z* 425.2565 (M + H)+, Rt 2,26 min
535: (S) - 3 - (2 - ((S) - 1 - (3 - (cicloheptiloxi) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO) 0,50 (br s., 3 H) 0,68 (br s., 3 H) 1,43 (d, *J*= 7,04 Hz, 5 H) 1,53 (d, *J*= 2,98 Hz, 4 H) 1,58- 1,71 (m, 4 H) 1,73- 1,97 (m, 3 H) 4,34 (d, *J*= 8,46 Hz, 2 H) 4.38 - .. 4,46 (m, 1 H) 4,60 (br s, 1 H) 4,98 (br s, 1 H) 6,70 (dd, *J*= 8,14, 2,03 Hz, 1 H) 6,76- 6,89 (m, 2 H) 7,18 (t, *J*= 7,87 Hz, 1 H) 7,30 (d, *J*= 6,02 Hz, 1 H) 8,20 (br s., 2 H)	HRMS (A) *m/z* 439.2712 (M + H)+, Rt 2,41 min
536: (S) - 3 - (2 - ((S) - 1 - (3- isopropoxi- fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin-	(DMSO) 0,49 (br. s., 3 H) 0,67 (br. s., 3 H) 1.9 - 1.28 (m, 7 H) 1,32- 1,50 (m, 3 H) 4,23- 4,39 (m, 2 H) 4,52 (dt, *J*= 12,04, 6,08 Hz, 1 H) 4,60 (br s., 1 H) 4,96 (br s., 1 H)	HRMS (A) *m/z* 385.2248 (M + H)+,

2- ona	6,71 (dd, *J*= 8,00, 1,98 Hz, 1 H) 6,82 (br s., 2H) 7,15 (t, *J*= 8,09 Hz, 1 H) 7,30 (d, *J*= 6,02 Hz, 1 H) 8,18 (br s., 1 H) 8,28 (br s., 1 H)	Rt 1,92 min
537: (S) - 3 - (5- fluoro- 2- ((S) - 1 - (3- isobutoxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO) 0,49 (br s., 6 H) 0,92 (d, *J*= 6,7 Hz, 6 H) 1,37 (d, *J*= 7,04 Hz, 3 H) 1,93 (dquin, *J*= 13,25, 6,60, 6,60, 6,60, 6,60 Hz, 1 H) 3,59- 3,70 (m, 2 H) 3.94 - . 4,31 (m, 3 H) 4,45 (br s, 1 H) 6,69 (dd, *J*= 8,17, 1,76 Hz, 1 H) 6,80- 6,89 (m, 2 H) 7,13 (t, *J*= 7,83 Hz, 1H) 7,92 (br s., 1 H) 8,34 (br s., 1 H)	HRMS (A) *m/z* 417,231 (M + H)+, Rt 2,53 min
538: (S)- 3- (5- fluoro- 2- ((S)- 1- (3- ((S)- tetrahidrofuran- 3- iloxi)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO) 1,41 (d, *J*= 7,04 Hz, 6 H) 1,83- 1,93 (m, 1 H) 2.11 - 2.23 (m, 1 H) 3,68- 4,04 (m, 8 H) 4,25 (br s, 1 H) 4,49 (br s.. , 2 H) 4,80 (br s., 1 H) 4,95 (dd, *J*= 6,06, 4,65 Hz, 1 H) 6,72 (dd, *J*= 8,02, 2,10 Hz, 1 H) 6,83- 6,94 (m, 2 H) 7,19 (t, *J*= 7,87 Hz, 1 H) 7,96 (br s., 1 H) 8,38 (br s., 1 H)	HRMS (A) *m/z* 431.2098 (M + H)+, Rt 2,01 min
539: (4S)- 4- isopropil- 3- (2- ((1S)- 1- (3- (tetrahidro- 2H- piran- 3- iloxi)fenil)etilamino)pirimidin- 4- il)oxazolidin- 2- ona	(DMSO) 0,47 (br s., 3 H) 0,66 (br s., 3 H) 1,39 (d, *J*= 6,99 Hz, 3 H) 1,44- 2,00 (m, 5 H) 3,32- 3,50 (m, 2 H) 3,54- 3,88 (m, 3 H) 4.23 - . 4,37 (m, 2 H) 4,61 (br s, 1H) 4,90 (br s., 1H) 6,74 (d, *J*= 8,36 Hz, 1 H) 6,85 (d, *J*= 13,55 Hz, 2 H) 7,15 (t, *J*= 7,87 Hz, 1 H) 7,25 (d, *J*= 5,97 Hz, 1 H) 8,06 (br s., 1 H) 8,16 (br s., 1 H)	HRMS (A) *m/z* 427.2353 (M + H)+, Rt 1,75 min
540: (S)- 4- isopropil- 3- (2 - ((S) - 1 - (3- fenoxifenil) etilamino) pirimidin- 4- il) oxazolidin- 2- ona	(DMSO) 0,50 (br s., 3 H) 0,66 (br s., 3 H) 1,42 (d, *J*= 7,04 Hz, 3 H) 1,75 (br s, 1 H) 4.27 - . 4,37 (m, 2 H) 4,55- 4,62 (m, 1 H) 4,97 - 5,07 (m, 1 H) 6,78 (dd, *J*= 8,02, 1,81 Hz, 1 H) 6,87 (d, *J*= 7,53 Hz, 2 H) 6,96 (br s, 1 H) 7.04 - . 7,14 (m, 2 H) 7,25- 7,37 (m, 4 H) 8,17 (d, *J*= 4,99 Hz, 1 H) 8,36 (br s., 1 H)	HRMS (A) *m/z* 419.2092 (M + H)+, Rt 2,12 min
541: (S) - 3 - (5- fluoro- 2- ((S) - 1 - (3- fenoxifenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO) 0,44 - 0.65 (m, 6 H) 1,37 (d, *J*= 6,99 Hz, 3 H) 4.08 - 4,40 (m, 2 H) 4,45 (br s, 1 H) 4,82 (br s, 1 H) 6,75 (dd, *J*= 8,07, 1,37 Hz, 1 H) 6,86 (d, *J*= 7,48 Hz, 2 H) 6,95 (br s, 1 H) 7.03 - . 7,11 (m, 2 H) 7,28 (dt, *J*= 19,78, 7,86 Hz, 3 H) 7,94 (br s., 1 H) 8,33 (br s., 1 H)	HRMS (A) *m/z* 437.1992 (M + H)+, Rt 2,45 min
542: (S) - 3 - (5- fluoro- 2- ((S) - 1 - (4- isopropoxi- fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(DMSO) 0,56 (br s., 6 H) 1,18 (d, *J*= 2,35 Hz, 3 H) 1,20 (d, *J*= 2,30 Hz, 3 H) 1,36 (d, *J*= 7,04 Hz, 3 H) 4,21 (br s, 1H) 4.36 - .. 4,58 (m, 3 H) 4,75 (br s, 1H) 6,77 (d, *J*= 8,71 Hz, 2 H) 7,18 (d, *J*= 8,56 Hz, 2 H) 7,87 (br s., 1 H) 8,33 (d, *J*= 2,74 Hz, 1 H)	HRMS (A) *m/z* 403.2156 (M + H)+, Rt 2,30 min
543: (4S)- 4- isopropil- 3- (2 - ((1 -	(CD_3OD) 8,00- 8,17 (m, 1H), 7,71 (d, J = 7,04 Hz, 1H), 4,78- 4,85 (m, 1H), 4,41-	HRMS (A) *m/z*

(tetrahidrofurano- 2- il) etil) amino) pirimidin- 4- il) oxazolidin- 2- ona	4,55 (m, 2H), 3,98- 4,14 (m, 1H) , 3,84 - 3,97 (m, 1H), 3,67- 3,82 (m, 1H), 2,55- 2,70 (m, 1H), 1,86- 2,13 (m, 3H), 1,56- 1,82 (m, 1H), 1,24- 1,34 (m, 3H), 1,00- 1,06 (m, 3H), 0,91 (t, J = 6,06 Hz, 3H)	321.1935 (M + H)+, Rt 1,32 min
544: (S) - 3 - (2 - ((S) - 1 - (4- isobutoxi- 3- metilfenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(400 MHz, DMSO) δ ppm 0,54 (br s., 3 H) 0,72 (br s., 3 H) 0,96 (d, J = 6,70 Hz, 6 H) 1,41 (d, J = 6,99 Hz, 3 H) 1,89 (br s, 1 H) 1,99 (dt, J = 13,24, 6,61 Hz, 1 H) 2,11 (s, 3 H) 3,68 (d, J = 6,41 Hz, 2 H) 4.31 - . 4,41 (m , 2 H) 4,62 (dd, J = 6,99, 3,72 Hz, 1 H) 4.94 (quintuplete, J = 6,94 Hz, 1 H) 6,80 (d, J = 8,31 Hz, 1 H) 7,00- 7,13 (m, 2 H) 7,34 (d, J = 6,06 Hz, 1 H) 8,19 (d, J = 4,94 Hz, 1 H) 8,42 (br s., 1 H)	HRMS (A) m/z 413,2561 (M + H)+, Rt 2,34 min
545: (S)- 3- (2- ((S)- 1- (6- (1- etoxiciclopropil)piridin- 3- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	^{1}H RMN (400 MHz, CD_3OD) d 0,65 (br s, 3 H.) 0,75 (br s, 3 H.) 1,23 (t, J = 7,04 Hz, 3 H) 1,28- 1,45 (m, 4 H) 1,64 (d, J = 7,09 Hz, 3 H) 3,55 (q, J = 7,04 Hz, 2 H) 4,36- 4,43 (m, 2 H) 4,70 (br s, 1H.) 5.20 - 5.28 (m, 1 H) 7,66 (d, J = 8,41 Hz, 2 H) 8,04 (br s., 1 H) 8,16 (d, J = 6,41 Hz, 1 H)	HRMS (A) m/z 412,2349 (M + H)+, Rt 1,55 min
546: (S) - 3 - (2 - ((S) - 1 - (4- isobutoxi- 3- metilfenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	^{1}H RMN (400 MHz, DMSO) d ppm 0,54 (br s., 3 H) 0,72 (br s., 3 H) 0,96 (d, J = 6,70 Hz, 6 H) 1,41 (d, J = 6,99 Hz , 3 H) 1.89 (br s, 1H) 1.99 (dt, J = 13.24, 6.61 Hz, 1 H) 2.11 (s, 3 h) 3.68 (d, J 6.41 = Hz, 2H) 4.31 - 4.41 (m, 2 H) 4,62 (dd, J = 6,99, 3,72 Hz, 1 H) 4.94 (quintuplete, J = 6,94 Hz, 1 H) 6,80 (d, J = 8,31 Hz, 1 H) 7,00- 7,13 (m, 2 H) 7,34 (d, J = 6,06 Hz, 1 H) 8,19 (d, J = 4,94 Hz, 1 H) 8,42 (br s., 1 H)	HRMS m/z 413.2561 (M + H)+; Rt- 2.34 min.

Ejemplo 547

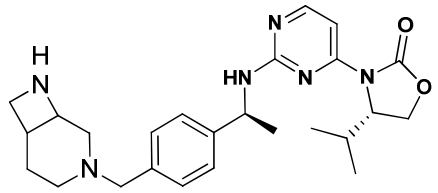


Una solución de (S) - 3 - (2 - ((S) - 1 - (4 - (clorometil) fenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (75 mg, 0.2 mmoles) y 5,6,7,8- tetrahidroimidazo [1,2- a] pirazina (25 mg, 0.2 mmol) en DMSO (2 ml) se calentó a 80 °C durante 16 h. La mezcla de reacción se diluyó con EtOAc (20 ml) y se lavó con agua (20 ml). Después de la

separación, la fase acuosa se lavó con EtOAc (2 x 15 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. La cromatografía en columna de gel de sílice (MeOH en CH_2Cl_2 0 a 10%) proporcionó (S)- 3- (2- ((S)- 1- (4- ((5,6-dihidroimidazo[1,2- a]pirazin- 7(8H)- il)metil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (58 mg, sólido blanco), con un rendimiento del 62.8%. ^{1}H RMN (400 MHz, MeOD) δ 8,12 (d, J = 6,0 Hz, 1H), 7,34 (d, J = 5,9 Hz, 1H), 7,33 (s, 4H), 6,99 (d, J = 1,3 Hz, 1H), 6,89 (d, J = 1,4 Hz, 1H), 5,07 (q, J = 7,0 Hz, 1H), 4,68 (br s, 1H), 4,37- 4,25 (m, 2H), 4,02 (t, J = 5,5 Hz, 2H), 3,72 (s, 2H), 3,63 (s, 2H), 2,90 (td, J = 5,4, 2,6 Hz, 2H), 1,84 (br s, 1H), 1,51 (d, J = 7,0 Hz, 3H), 0,72 (br s, 3H), 0,57 (br s, 3H); HRMS m/z 462.2606 (M + H)+.

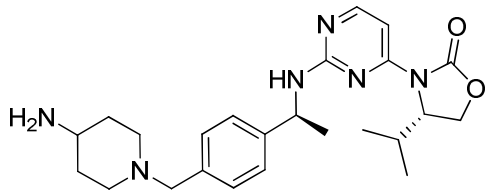
Los siguientes compuestos se prepararon usando métodos similares a los descritos para la preparación de **Ejemplo 205.**

Ejemplo 548



(4S)- 3- (2- ((1S)- 1- (4- (3,8- diazabiciclo[4.2.0]octan- 3- ilmetil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.
^{1}H RMN (400 MHz, MeOD) δ 8.12 - 8.8 (m, 1H), 7,37- 7,22 (m, 5H), 5.10 - 5.1 (m, 1H), 4,66 (br s, 1H), 4,37- 4,23 (m, 2H), 3,92- 3,89 (m, 1H), 3,63- 3,54 (m, 1H), 3,54- 3,47 (m, 1H), 3.24- 3.20 (m, 1H), 3,11- 2,95 (m, 1H), 2,95 - 2,73 (m, 1H), .2.67 - 2.59 (m, 2H), 2,49 (ddd, J = 16,2, 12,8, 5,3 Hz, 1H), 2.20 - 2.8 (m, 1H), 1,99- 1,68 (m, 3H) , 1,50 (d, J = 7,0 Hz, 3H), 0,72 (br s, 1H), 0,56 (br s, 1H); HRMS m/z 451,2810 (M + H)+.

Ejemplo 549

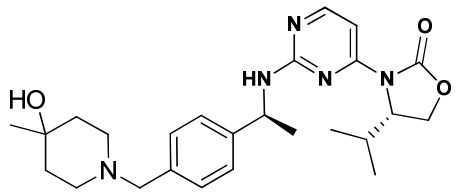


(S)- 3- (2- ((S)- 1- (4- ((4- aminopiperidin- 1- il)metil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

^{1}H RMN (400 MHz, MeOD) d 8,12 (d, J = 5,8 Hz, 1H), 7,34 (d, J = 5,8 Hz, 1H), 7,27 (q, J = 8,2 Hz, 4H), 5,05 (q, J = 7,0 Hz, 1H), 4,67 (s, 1H), 4,38- 4,25 (m, 2H), 3,48 (s, 2H), 2,86 (br d, J = 11,8 Hz, 2H), 2,71 (tt, J = 10,9 , 4,2 Hz, 1H), 2,05 (tt, J = 12,0, 2,5 Hz, 2H), 1,90- 1,75 (m, 3H), 1,54- 1,37 (m, 5H), 0,72 (br s, 4H), 0,55 (br s, 3H); HRMS m/z 439,2805 (M + H)+.

Los siguientes compuestos se prepararon usando métodos similares a los descritos para la preparación de **Ejemplo 210**.

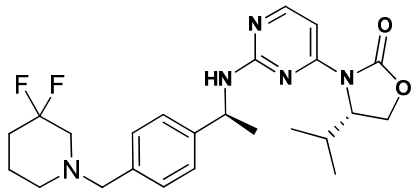
Ejemplo 550



(S)- 3- (2- ((S)- 1- (4- ((4- hydroxi- 4- metilpiperidin- 1- il)metil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

^{1}H RMN (400 MHz, MeOD) δ 8,12 (d, J = 5,7 Hz, 1H), 7,34 (d, J = 5,9 Hz, 1H), 7,27 (t, J = 6,6 Hz, 4H), 5,06 (q, J = 6,8 Hz, 1H), 4,67 (br s, 1H), 4,37- 4,25 (m, 2H), 3,51 (d, J = 3,2 Hz, 2H), 2,52 (br s, 2H), 2,44 (br s, 2H), 1,81 (br s, 1H), 1,59 (br s, 4H), 1,50 (d, J = 7,0 Hz, 3H), 1,19 (s, 3H), 0,72 (br s, 3H), 0,56 (br s, 3H); HRMS m/z 454,2816 (M + H)+.

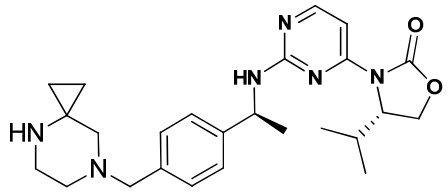
Ejemplo 552



(S)- 3- (2- ((S)- 1- (4- ((3,3- difluoropiperidin- 1- il)metil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

^{1}H RMN (400 MHz, MeOD) δ 8,12 (d, J = 5,8 Hz, 1H), 7,35 (d, J = 5,8 Hz, 1H), 7,28 (q, J = 8,2 Hz, 4H), 5,06 (q, J = 7,0 Hz, 1H), 4,67 (br s, 1H), 4,39- 4,25 (m, 2H), 3,55 (d, J = 2,2 Hz, 2H), 2,56 (t, J = 11,5 Hz, 2H), 2,51 - 2,40 (m, 2H), 1,91- 1,81 (m, 3H), 1,78- 1,70 (m, 2H), 1,50 (d, J = 7,0 Hz, 3H), 0,71 (br s, 3H), 0,56 (br s, 3H); HRMS m/z 460,2537 (M + H)+.

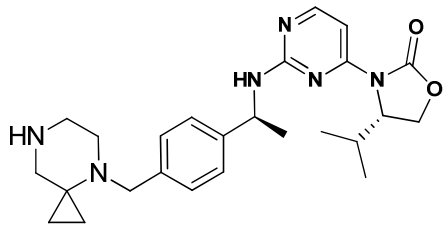
Ejemplo 553



(S)- 3- (2- ((S)- 1- (4- (4,7- diazaspiro[2.5]octan- 7- ilmetil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona

^{1}H RMN (400 MHz, MeOD) δ 8,12 (d, J = 5,8 Hz, 1H), 7,34 (d, J = 5,8 Hz, 1H), 7,32- 7,24 (m, 4H), 5,06 (q, J = 7,0 Hz , 1H), 4,68 (br s, 1H), 4,37- 4,26 (m, 2H), 3,49 (s, 2H), 2,89 (t, J = 5,0 Hz, 2H), 2,47 (br s, 2H), 2,28 (br s, 2H), 1,86 (br s, 1H), 1,49 (d, J = 7,0 Hz, 3H), 0,72 (br s, 3H), 0,64 - 0,49 (m, 5H), 0,45 (t, J = 3,2 Hz, 2H); HRMS m/z 451,2809 (M + H)+.

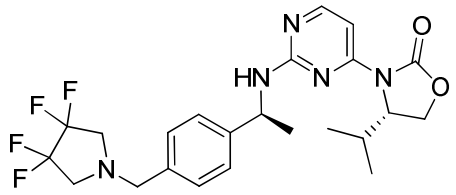
Ejemplo 554



(S)- 3- (2- ((S)- 1- (4- (4,7- diazaspiro[2.5]octan- 4- ilmetil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

^{1}H RMN (400 MHz, MeOD) δ 8,11 (d, J = 5,8 Hz, 1H), 7,33 (d, J = 5,8 Hz, 1H), 7,24 (q, J = 8,3 Hz, 4H), 5,03 (q, J = 7,0 Hz, 1H), 4,67 (br s, 1H), 4,37- 4,25 (m, 2H), 3,85 (s, 2H), 2,85- 2,65 (m, 6H), 1,87 (br s, 1H), 1,48 (d, J = 7,0 Hz, 3H), 0,85 - 0,63 (m, 5H), 0,63- 0,46 (m, 5H); HRMS m/z 451,2810 (M + H)+.

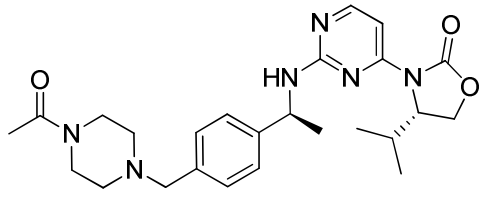
Ejemplo 555



(S)- 4- isopropil- 3- (2 - ((S) - 1 - (4 - (3,3,4,4- tetrafluoropirrolidin- 1- il) metil) fenil) etilamino) pirimidin- 4- il)oxazolidin- 2- ona.

HRMS m/z 482.2161 (M + H)+; RT = 2.78 min.

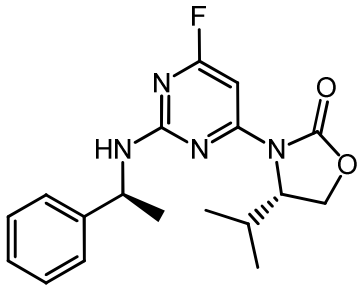
Ejemplo 556



(S)- 3- (2- ((S)- 1- (4- ((4- acetilpiperazin- 1- il)metil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona.

HRMS m/z 467.2752 (M + H)+; RT = 1.92 min.

Ejemplo 557



Se añadió (S) - 4,6- difluoro- N- (1- feniletil)pirimidin- 2- amina (48,8 mg, 0.21 mmol) a NaH (95%, 6.1 mg, 0.25 mmol, 1.2 equiv) en DMF (2 ml) a 0 °C. Después de 5 min, (S)- 4- isopropil- 2- oxazolidinona (27.9 mg, 0,22 mmol, 1.0 equiv). La reacción se agitó durante 10 min a 0 °C y después se calentó a temperatura ambiente. Después de 4 h, la mezcla de reacción se inactivó con agua y se vertió en salmuera diluida (1:1 salmuera saturada: agua) y EtOAc. La fase acuosa se extrajo con EtOAc y las capas orgánicas combinadas se lavaron con salmuera diluida. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró a un aceite de color rosa. La purificación mediante HPLC de fase inversa seguida de liofilización de las fraccionas que contenían el producto proporcionado (S) - 3 - (6- fluoro- 2- (((S)- 1- feniletil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona como un sólido blanco (22.5 mg sal de TFA) con un rendimiento del 31%. ^{1}H RMN (400 MHz, CD_3OD) δ 7,27- 7,39 (m, 4H), 7.17- 7.26 (m, 1H), 6,92 (s, 1H), 5,05 (q, *J*= 7,04 Hz, 1H), 4,63 (br s, 1H), 4,19 - .. 4,41 (m, 2H), 1,77 (br s, 1H), 1,51 (d, *J*= 7,04 Hz, 3H), 0,44- 0,78 (m, 6H); LCMS m/z . 345,1 (M + H)+, Rt 1,00 min; UPLC Rt 5,038 min.

Los compuestos de la Tabla 17 se prepararon utilizando métodos similares a los descritos para la preparación del Ejemplo 557.

Cuadro 17.

558

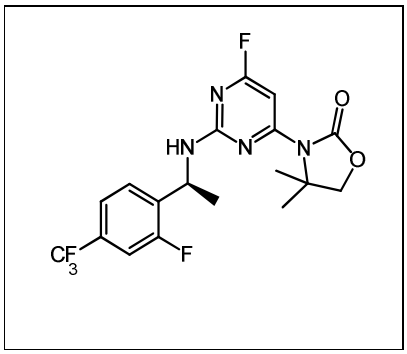
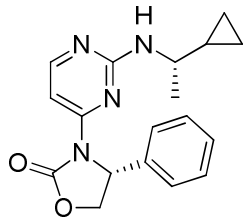


Tabla 18: Nombre químico, desplazamientos químicos RMN y señal LCMS para cada compuesto enumerado en la Tabla **17**.

Ejemplo: Nombre	^{1}H RMN (400 MHz) δ ppm	LCMS
558: (*S*) - 5,5- Dimetil- 4- fenil- 3- (2 - ((*S*)- 1- feniletilamino) pirimidin- 4- il) oxazolidin- 2- ona	(CD_3OD) 8,06 (d, J = 5,8 Hz, 1 H), 7,43 (d, J = 5,8 Hz, 1 H), 7.31- 7.24 (m, 3 H), 7.19- 7.11 (m, 5 H), 7,01 (br s 2 H), 5,48 (s, 1H), 4,86- 4,80 (m, 1 H), 1,65 (s, 3H), 1,43 (d, J = 7,0 Hz, 3 H), 0,98 (s, 3 H)	HRMS (A) *m/z* 389.1987 (M + H)+

Ejemplo 559



Una mezcla de (R) - 3 - (2- cloropirimidin- 4- il)- 4- feniloxazolidin- 2- ona (55.3 mg, 0.20 mmoles), (S)- 1- ciclopropiletilamina (40 µL, 0.26 mmol, 1.3 equiv) y *i*Pr_2NEt (0.20 ml, 1.15 mmol, 5.7 equiv) en NMP (1 ml) se calentó en el microondas a 180 °C durante 20 min. La mezcla de reacción se filtró y se purificó mediante HPLC de fase inversa para proporcionar (R) - 3 - (2 - (((S)- 1- ciclopropiletil) amino) pirimidin- 4- il)- - 4 feniloxazolidin- 2- ona como un sólido de color blanco (8.8 mg) con un rendimiento del 10%. ^{1}H RMN (400 MHz, CD_3OD) δ 7,72 (d, J = 6,26 Hz, 1H), 7,29- 7,43 (m, 6H), 5,76 (dd, J = 4,11, 8,80 Hz, 1H), 4,28 (dd, J = 4,30, 8,61 Hz, 1H), 3.6- 3.19 (m, 1H), 1,39 (dd, J = 3,52, 6,65 Hz, 1H), 0,88 - . 0,97 (m, 1H), 0,83 (br s, 3H), 0,53- 0,62 (m, 1H), 0,50 (dt, J = 4,11, 8,51 Hz, 1H), 0,33 (qd, J = 4,78, 9,54 Hz, 1H), 0,26 (td, J = 4,60, 9,59 Hz, 1H) ; HRMS (A) *m/z* 325.1667 (M + H)+, Rt 1,54 min; UPLC 2,807 min.

Los compuestos de la Tabla 19 se prepararon utilizando métodos similares a los descritos para la preparación del Ejemplo 559.

Tabla 19.

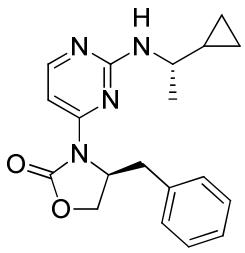
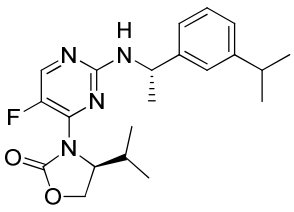
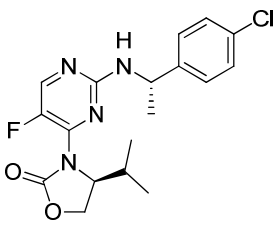
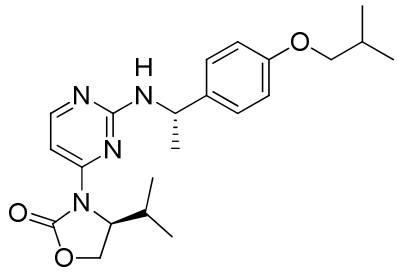
560	561	562
		

Tabla 20. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada compuesto que aparece en la Tabla 19.

Ejemplo: Nombre	^{1}H RMN (400 MHz) δ ppm	LCMS
560: (S)- 4- bencil- 3- (2 - (((S)- 1- ciclopropiletil) amino) pirimidin- 4- il) oxazolidin- 2- ona	(CD_3OD) 8,13 (d, J = 7,04 Hz, 1H), 7,71 (d, J = 7,04 Hz, 1H), 7,22- 7,38 (m, 5H), 5,11 (tt, J = 3,03, 8,12 Hz, 1H), 4,23 - 4,53 (m, 2H), 3,08 (dd, J = 8,41, 13,50 Hz, 1H), 1,42 (D, J = 6,65 Hz, 3H), 1.4- 1.23 (m, 1H), 0,47- 0,73 (m, 2H), 0,17- 0,47 (m, 2H).	HRMS (A) *m/z* 339.1822 (M + H)+, Rt 1,64 min
561: (S) - 3 - (() 5- fluoro- 2- ((S - 1 - (3- isopropilfenil) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona		HRMS (A) *m/z* 387.2203 (M + H)+, Rt 2,52 min
562: (S) - 3 - (2 - (((S) - 1 - (4- clorofenil) etil) amino)- 5- fluoropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona		HRMS (A) *m/z* 379.1341 (M + H)+, Rt 2,30 min

Ejemplo 563



Una mezcla de (S) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (43.2 mg, 0.18 mmoles), (1S) - 1 - [4 - (2- metilpropoxi) fenil] etan- 1- amina (84.0 mg, 0.37 mmol, 2,0 equiv) y *i*Pr$_2$NEt (0.30 ml, 1.72 mmol, 4.7 equiv) en NMP (1 ml) se calentó a 105 °C durante 24 h. La mezcla de reacción se filtró y se purificó mediante HPLC de fase inversa para proporcionar (S) - 3 - (2 - (((S) - 1 - (4- isobutoxifenil) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona como un sólido blanco (5.3 mg, sal de TFA) con un rendimiento del 4%. ^{1}H RMN (400 MHz, CD$_3$OD) δ 7,68 (d, J = 6,65 Hz, 1H), 7,25 (d, J = 8,61 Hz, 2H), 6,90 (d, J = 8,61 Hz, 2H), 4,41 (d, J = 5,87 Hz, 2H), 3,74 (d, J = 6,26 Hz, 2H), 1,96- 2,15 (m, 1H), 1,58 (d, J = 7,04 Hz, 3H), 1,03 (d, J = 6,65 Hz, 6H); HRMS (A) *m/z* 399.2399 (M + H)+, Rt 2,60 min; UPLC 4.223 min.

Los compuestos de la Tabla 21 se prepararon utilizando métodos similares a los descritos para la preparación del Ejemplo 563.

Tabla 21.

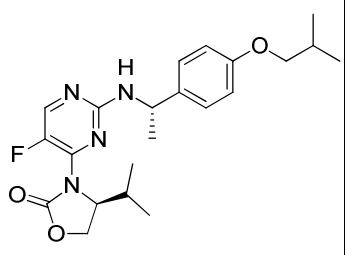
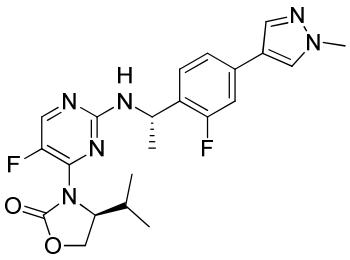
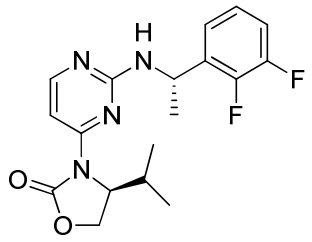
564	565
	

Tabla 22. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada compuesto que aparece en la Tabla 21.

Ejemplo: Nombre	^{1}H RMN (400 MHz) δ ppm	LCMS
564: (S) - 3 - (() 5- fluoro-		HRMS

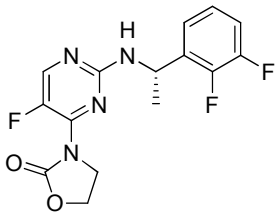
2- ((S - 1 - (4- isobutoxifenil) etil) amino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona		(A) *m/z* 417.2314 (M + H)+, Rt 2,53 min
565: (S)- 3- (5- fluoro- 2- (((S)- 1- (2- fluoro- 4- (1- metil- 1H- pirazol- 4- il)fenil)etil)amino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona		HRMS (A) *m/z* 443.2012 (M + H)+, Rt 1,92 min

Ejemplo 566



A un vial de microondas con una barra de agitación se añadió (S) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (24.96 mg, 0.103 mmol) en DMSO (1.653 µl). A esta mezcla de reacción se añadió (S) - 1 - (2,3- difluorofenil) etanamina (40 mg, 0.207 mmol) y DIEA (144 µl, 0.826 mmol). El vial tapado y se calentó a 110 °C durante el fin de semana. La solución se filtró, después se purificó mediante HPLC de fase inversa. Las fraccionas del producto se combinaron, congelaron y liofilizó para proporcionar ((S) - 3 - (2 - ((S) - 1 - (2,3- difluorofenil) etilamino) pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (10.2 mg, 0.021 mmol, rendimiento del 10,26%) como una sal de TFA. ^{1}H RMN (400 MHz, CD_3OD) δ ppm 0,59 (br s., 3 H) 0,75 (br s., 3 H) 1,59 (d, *J*= 6,99 Hz, 3 H) 1,69 (br s., 1 H) 4,37 (d, *J*= 5,67 Hz, 2 H) 4,66 (br s., 1 H) 5,40 (d, *J*= 7,38 Hz, 1 H) 7.6 - 7.23 (m, 3 H) 7,70 (d, *J*= 6,90 Hz, 1 H) 8,14 (d, *J*= 6,46 Hz, 1 H); LCMS m/z 363,3 (M + H)+, Rt 0,77 min;. HRMS (A) *m/z* 363.1642 (M + H)+, Rt 1,89 min.

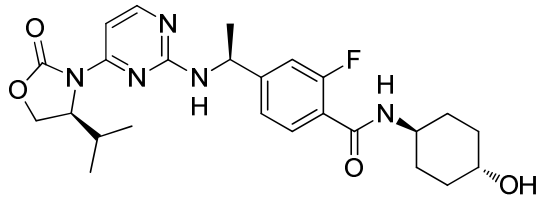
Ejemplo 567



Se preparó (S) - 3 - (2 - (1 - (2,3- difluorofenil) etilamino)- 5- fluoropirimidin- 4- il) oxazolidin- 2- ona usando un método similar al descrito para la preparación del Ejemplo 566 ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1,50 (d, J = 7,04 Hz, 3 H) 3,91 (br s, 1 H). 4.9 - 4.20 (m, 1 H) 4,42- 4,56 (m, 2 H) 5,26 (q, J = 6,68 Hz, 1 H) 6,99- 7,12 (m, 2 H) 7,16 (t, J = 7,48 Hz, 1 H) 8,13 (d, J = 3,37 Hz, 1 H). HRMS (A) m/z 339,1075 (M + H)+, Rt 1,86 min.

Ejemplo 568

2- fluoro- N- (*trans*- 4- hidroxiciclohexil)- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida



Paso 1: Preperation del ácido (S) - 4 - (1 - (terc- butoxicarbonilamino) etil)- 2- fluorobenzoico:

A ácido (S) - 4 - (1- aminoetil)- 2- fluorobenzoico (900 mg, 4,10 mmol) se añadió, DCM (11 ml), base de Hunig (2.147 ml, 12.29 mmol) y Boc- anhídrido (1.998 ml, 8.61 mmoles). Después se añadió NMP (11.00 ml) para ayudar en la solubilidad. La reacción se sometió a ultrasonidos durante 10 minutos y se agitó a temperatura ambiente durante 22 horas, seguido por LCMS. El DCM se concentró principalmente. Luego a la reacción cruda se añadió 120 ml de agua y se basificó con 10 ml de NaOH 5M. La solución acuosa alcalina se extrajo con 2 x 50 ml de (15% acetato de etilo en heptano) solución. A continuación, a la solución acuosa alcalinizada (con el producto) se añadió 150 ml de acetato de etilo con agitación y se acidificó con solución acuosa de HCl 2 M hasta un pH de aproximadamente 3. A continuación, el acetato de etilo se extrajo, se guardo y el agua

ácida se extrajo de nuevo con 100 ml de acetato de etilo. Las capas orgánicas se combinaron y se lavaron con 0,5 M de solución acuosa de HCl 1 x 40 ml, con agua 3 x 40 ml, y se concentraron a masa constante para proporcionar 1104 mg del ácido (S) - (1 - (terc- butoxicarbonilamino) etil)- 2- fluorobenzoico, utilizado como tal. El patrón de LCMS m/z BOC de 269.0 (fragmento M + H- 15) y 228,0 débil (M+H- 56 fragmento) en comparación con 284.0 esperado (M + H)+, Rt 0.72 min.

Paso 2: Preperation de (S) - 1 - (3- fluoro- 4- (*trans*- 4- hidroxiciclohexilcarbamoil) fenil) carbamato de terc- butilo:

A ácido (S) - 4 - (1 (terc- butoxicarbonilamino) etil)- 2- fluorobenzoico (40.8 mg, 0.144 mmol) se añadió NMP (0,5 ml), se *trans*- 4- aminociclohexanol (41.5 mg, 0.360 mmol), base de Hunig (0.101 ml, 0.576 mmol) y HATU (110 mg, 0.288 mmoles) La reacción se agitó a temperatura ambiente durante 6 horas, seguido por LCMS. A la reacción se añadió 0,5 ml de NMP, se filtró, se purificó mediante LC preparativa y se liofilizó para proporcionar 33 mg de (S) - 1 - (3- fluoro- 4- (*trans*- 4- hydroxiciclohexilcarbamoil) fenil) etilcarbamato de terc- butilo como la sal de TFA. LCMS m/z 381.1 (M + H)+, Rt 0.70 min.

Paso 3: Preparacion de 4 - ((S)- 1- aminoetil)- 2- fluoro- N- (*trans*- 4- hidroxiciclohexil) benzamida:

A (S) - 1 - (3- fluoro- 4- (*trans*- 4- hidroxiciclohexilcarbamoil) fenil) etilcarbamato de terc- butilo(33 mg, 0,087 mmol) se añadió, HCl 4 M en dioxano (2 ml, 8.00 mmol) y MeOH (0.2 ml). La reacción se agitó a temperatura ambiente durante 1 hora, seguido por LCMS. El solvente se concentró al residuo para proporcionar 4 - ((S)- 1- aminoetil)- 2- fluoro- N- (*trans*- 4- hidroxiciclohexil)benzamida con un rendimiento cuantitativo (0.087 mmol) como sal de HCl. LCMS m/z 281.1 (M + H)+, Rt 0.33 min.

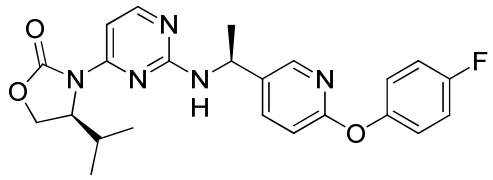
Paso 4: Preperation de 2- fluoro- N- (*trans*- 4- hydroxiciclohexil)- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida:

Se añadió ((S)- 1- aminoetil)- 2- fluoro- N- ((1R, 4S)- 4- hidroxiciclohexil) benzamida (0,024 g, 0.087 mmol) de (S) - 3 - (2- cloropirimidin - 4- il)- 4- isopropiloxazolidin- 2- ona (0.034 g, 0.139 mmol), DMSO (0,6 ml) y base de Hunig (0.053 ml, 0.305 mmol). La reacción se calentó a 100- 105 °C durante 16 horas hasta completarse según LCMS. La reacción se dejó enfriar, se añadió 0.5 ml de DMSO, se filtró, se purificó mediante LC

preparativa y se liofilizó para proporcionar 10.1 mg de 2- fluoro- N- (*trans*- 4- hydroxiciclohexil)- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida como la sal de TFA. LCMS m/z 486,2 (M + H)+, Rt 0,57 min. ^{1}H RMN (400 MHz, CD_3OD) δ ppm 8,13 (d, J = 6,7 Hz, 1H), 7,70 (d, J = 6,7 Hz, 1H), 7,64 (t, J = 7,8 Hz, 1H), 7.13- 7.28 (m, 2H), 5,16 (br s., 1H), 4,67 (br s., 1H), 4,37 (d, J = 5,5 Hz, 2H), 3,82 (br s., 1H), 3,53 (d , J = 3,9 Hz, 1H), 1,97 (dd, J = 5,1, 3,1 Hz, 4H), 1,57 (d, J = 7,0 Hz, 3H), 1,38 (t, J = 8,6 Hz, 4H), 0.50 - 0,88 (m, 6H); HRMS (A) *m/z* 486.2523 (M + H)+.

Ejemplo 569

(S)- 3- (2- ((S)- 1- (6- (4- fluorofenoxi)piridin- 3- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona

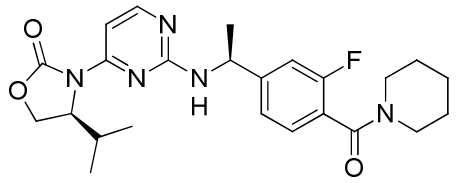


A (S) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (28 mg, 0.116 mmol) se añadió (S) - 1 - (6 - (4- fluorofenoxi) piridin- 3 - il)etanamina (46.7 mg, 0.174 mmol), DMSO (0.6 ml) y base de Hunig (0.071 ml, 0.406 mmol). La reacción se calentó a 105-110 °C durante 24 horas hasta que se completó según LCMS. La reacción se dejó enfriar, se añadió 0.5 ml de DMSO, se filtró, se purifica mediante CL preparativa y se liofilizó para proporcionar 7.1 mg de (S)- 3- (2- ((S)- 1- (6- (4- fluorofenoxi)piridin- 3- il)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona como la sal de TFA. LCMS m/z 438.2 (M + H)+, Rt 0,82 min.

^{1}H RMN (400 MHz, CD_3OD) δ ppm 8,04 (d, J = 6,3 Hz, 1H), 8,01 (d, J = 2,0 Hz, 1H), 7,73 (dd, J = 8,6, 2,3 Hz, 1H), 7,53 (d, J = 6,3 Hz, 1H), 6,94- 7,10 (m, 4H), 6,84 (d, J = 8,6 Hz, 1H), 5,05 (d, J = 7,0 Hz, 1H), 4,61 (d, J = 3,9 Hz, 1H), 4,28 (d, J = 5,5 Hz, 2H), 1,49 (d, J = 7,0 Hz, 3H), 0,51- 0,78 (m, 6H); HRMS (A) *m/z* 438.1946 (M + H)+.

Ejemplo 570

(S)- 3- (2- ((S)- 1- (3- fluoro- 4- (piperidina- 1- carbonil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona

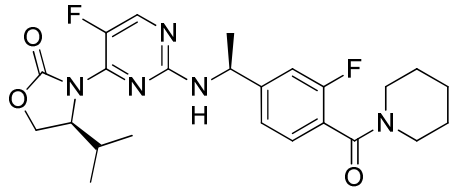


A (S) - (4 - (1- aminoetil)- 2- fluorofenil) (piperidin- 1- il) metanona (0.019 g, 0.076 mmol) se añadió (S) - 3 - (2- cloropirimidin- 4- il) 4- - isopropiloxazolidin- 2- ona (0.028 g, 0.114 mmol), NMP (0.5 ml) y base de Hunig (0.033 ml, 0.190 mmol). La reacción se calentó a 105- 110 °C durante 16 horas hasta que se completó según LCMS. La reacción se dejo enfriar, se añadió 0.5 ml de NMP, se filtró, se purificó mediante CL preparativa y se liofilizó para proporcionar 4,0 mg de (S)- 3- (2- ((S)- 1- (3- fluoro- 4- (piperidina- 1- carbonil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona como sal de TFA. LCMS m/z 456.1 (M + H)+, RT 0.74 min.

^{1}H RMN (400 MHz, CD_3OD) δ ppm 8,13 (d, J = 6,7 Hz, 1H), 7,69 (d, J = 7,0 Hz, 1H), 7,30- 7,38 (m, 1H), 7.23- 7.28 (m, 1H), 7,20 (d, J = 10,6 Hz, 1H), 5,18 (br s, 1H), 4,63 - . 4,74 (m, 1H), 4,33- 4,42 (m, 2H), 3,61- 3,79 (m, 2H), 1,61 - ... 1,76 (m, 5H), 1,57 (d, J = 7,0 Hz, 3H), 1,51 (br s, 2H), 0,77 (br s, 3H), 0,62 (br s, 3H); HRMS (A) *m/z* 456.2416 (M + H)+.

Ejemplo 571

(S)- 3- (5- fluoro- 2- ((S)- 1- (3- fluoro- 4- (piperidina- 1- carbonil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona



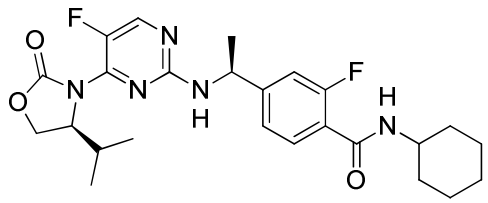
A (S) - (4 - (1- aminoetil)- 2- fluorofenil) (piperidin- 1- il) metanona (0.019 g, 0.076 mmol) se añadió (S) - 3 - (2- cloro- 5- fluoropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (0.030 g, 0.114 mmol), NMP (0.5 ml) y base de Hunig (0.033 ml, 0.190 mmol). La reacción se calentó a 105- 110 °C durante 8 horas hasta que se completo según LCMS. La reacción se dejo enfriar, se añadió 0.5 ml de NMP, se filtró, se purificó mediante CL preparativa y se liofilizó para proporcionar 4,5 mg de (S)- 3- (5- fluoro- 2- ((S)- 1- (3-

fluoro- 4- (piperidine- 1- carbonil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona como sal de TFA. LCMS m/z 474.2 (M + H)+, Rt 0.91 min.

^{1}H RMN (400 MHz, CD_3OD) δ ppm 8,21 (d, J = 2,7 Hz, 1H), 7,22- 7,33 (m, 2H), 7,17 (d, J = 11,0 Hz, 1H), 4,97 (q, J = 7,0 . Hz, 1H), 4,59 (br s, 1H), 4,47 (t, J = 8,8 Hz, 1H), 4,20 - . 4,32 (m, 1H) 3,68 (br s, 2H), 1,57- 1,75 (m, 5H), 1,48 (d, J = 7,0 Hz, 5H), 0,69 (br s, 3H), 0,62 (br s, 3H);.. HRMS (A) *m/z* 474.2330 (M + H)+.

Ejemplo 572

N- ciclohexil- 2- fluoro- 4- ((S)- 1- (5- fluoro- 4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida

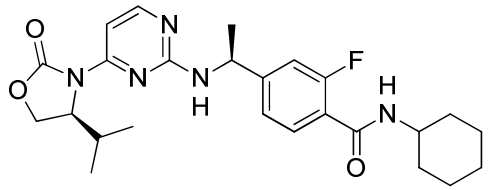


A (S) - 4 - (1- aminoetil)- N- ciclohexil- 2- fluorobenzamida (16 mg, 0,061 mmol) se añadió (S) - 3 - (2- cloro- 5- fluoropirimidin- 4- il) - 4 - isopropiloxazolidin- 2- ona (31.4 mg, 0.121 mmol), NMP (0.5 ml) y base de Hunig (0.032 ml, 0.182 mmol). La reacción se calentó a 125 ºC durante 4 horas hasta que se completó según LCMS. La reacción se dejo enfriar, se añadió 0.5 ml de NMP, se filtró, se purificó mediante CL preparativa y se liofilizó para proporcionar 2.5 mg de N- ciclohexil- 2- fluoro- 4- ((S)- 1- (5- fluoro- 4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida como la sal de TFA. LCMS m/z 488.2 (M + H)+, Rt 0.99 min.

^{1}H RMN (400 MHz, CD_3OD) δ ppm 8,21 (br s., 1H), 7,62 (t, J = 7,8 Hz, 1H), 7,24 (dd, J = 8,0, 1,4 Hz, 1H), 7,16 (d, J = 12,1 Hz, 1H), 4,39- 4,54 (m, 2H), 4,23 (t, J = 7,2 Hz, 1H), 3,83 (t, J = 10.4 Hz, 1H), 1,86- 1,97 (m, 2H), 1,76 (d, J = 12,9 Hz, 2H), 1,64 (d, J = 12,9 Hz, 1H), 1,48 (d, J = 7,0 Hz, 3H), 1,12- 1,42 (m, 6H), 0,61 (br s ., 6H); HRMS (A) *m/z* 488.2484 (M + H)+

Ejemplo 573

N- ciclohexil- 2- fluoro- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida

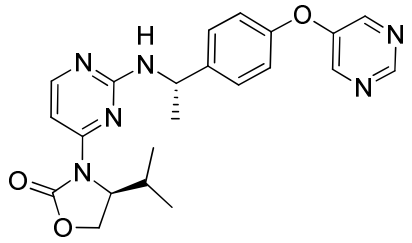


A (S) - 4 - (1- aminoetil)- N- ciclohexil- 2- fluorobenzamida (16 mg, 0.061 mmol) se añadió (S) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2 - ona (29.3 mg, 0.121 mmol), NMP (0.5 ml) y base de Hunig (0.032 ml, 0.182 mmol). La reacción se calentó a 125 ºC durante 4 horas hasta que se completosegún LCMS. La reacción se dejo enfriar, se añadió 0,5 ml de NMP, se filtró, se purifica mediante CL preparativa y se liofilizó para proporcionar 5,6 mg de N- ciclohexil- 2- fluoro- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida como la sal de TFA. LCMS m/z 470.2 (M + H)+, Rt 0,83 min.

^{1}H RMN (400 MHz, CD_3OD) δ ppm 8,12 (br s, 1H.), 7,57- 7,73 (m, 2H), 7.13 - 7.27 (m, 2H), 5,15 (br. s., 1H), 4,66 (br s, 1H), 4,36 (d, J = 5,5 Hz, 2H), 3,76 - . 3,94 (m, 1H), 1,87- 1,99 (m, 2H), 1,77 (d, J = 12,9 Hz, 2H), 1,65 (d, J = 13,7 Hz, 1H), 1,57 (d, J = 7,0 Hz, 3H), 1.12 - . 1,50 (m, 6H), 0,73 (br. s., 3H), 0,62 (br s, 3H); HRMS (A) *m/z* 470.2572 (M + H)+

Ejemplo 574

(S)- 4- isopropil- 3- (2- (((S)- 1- (4- (pirimidin- 5- iloxi)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona

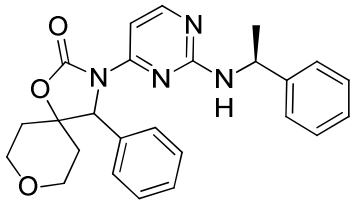


A la solución de (S) - 3 - (S) (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (43 mg, 0.169 mmol) en NMP (0.7 ml) se añadió (S)- 1 - (4 - (pirimidin- 5- iloxi) fenil) etanamina (41 mg, 0.169 mmol) y DIEA (88 µl, 0.507 mmol). La mezcla de reacción marrón se agitó a 110 °C durante 2 días. La mezcla de reacción se diluyó con acetato de etilo y solución acuosa de bicarbonato de sodio. La capa orgánica separada se lavó con

solución de bicarbonato de sodio acuoso saturado, agua y salmuera. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. El residuo se purificó mediante cromatografía en columna de fase inversa [C- 18] para proporcionar (S)- 4- isopropil- 3- (2- (((S)- 1- (4- (pirimidin- 5- iloxi)fenil)etil)amino)pirimidin- 4- il)oxazolidin- 2- ona (7 mg) como su sal de ácido trifluoroacético.
MS m/z 421,3 (M + H)+, Rt 0,68 min.
HRMS (A) *m/z* 421.1996 (M + H)+, Rt 1,54 min.

Ejemplo 575

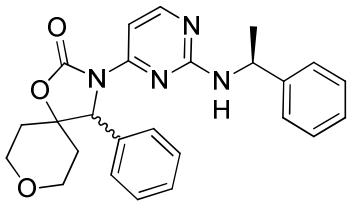
4- fenil- 3- (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) - 1,8- dioxa- 3- azaespiro [4.5] decan- 2- ona



Una mezcla de 3 - (2- cloropirimidin- 4- il)- 4- fenil- 1 ,8- dioxa- 3- azaespiro [4.5] decan- 2- ona cruda (330 mg, 0.954 mmoles), (S) - 1 - feniletanamina (810 mg, 6.68 mmol), base de Hunig (1.17 ml, 6.68 mmol) en DMA (3,5 ml) se calentó en un tubo sellado a 80 °C durante ~ 16 horas. La mezcla se dejó enfriar a temperatura ambiente, se diluyó con DMSO y se purificó mediante HPLC de fase inversa. Las fraccionas seleccionadas se combinaron y liofilizaron, proporcionando 4- fenil- 3- (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) - 1,8- dioxa- 3- azaespiro [4.5] decan- 2- ona como su sal de ácido trifluoroacético como un sólido blanco. LCMS m/z 431.2 (M + H)+, Rt 0.83 min. El sólido se disolvió en solución acuosa de $NaHCO_3$ acetato de etilo/saturada. La capa orgánica separada se lavó con solución acuosa saturada de $NaHCO_3$ (2x), salmuera, se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida proporcionando 4- fenil- 3- (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) - 1,8- dioxa- 3- azaespiro [4.5] decan- 2- ona (120 mg).

Ejemplos 576 y 577

(S)- fenil- 4- 3- (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) - 1,8- dioxa- 3- azaespiro [4.5] decan- 2- ona y (R) - 4- fenil- 3- (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) - 1,8- dioxa- 3- azaespiro [4.5] decan- 2- ona



Mg 120 de 4- fenil- 3- (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) - 1,8- dioxa- 3- azaespiro [4.5] decan- 2- ona fueron disueltos en EtOH (10 ml).

Separación analítica:

Columna: CHIRALPAK AD- H (5 um) 100 x 4,6 mm (Daicel Chemical Industries, LTD.).

Disolvente: n- heptano: alcohol etílico = 70: 30

Tasa de flujo: 1.0 ml/min, detección: UV = 220 nm.

Fracción 1: Tiempo de retención: 5,84 min.

Fracción 2: Tiempo de retención: 10.18 min.

Separación preparativa:

Columna: CHIRALPAK AD- prep (10 um) 2 x 25 cm.

Solvente: n- heptano: alcohol etílico = 70: 30

Tasa de flujo: 20 ml/min; 530 psi; inyección: 4 ml; detección: UV = 210 nm.

Las fraccionas se concentraron bajo presión reducida. El residuo se disolvió en acetonitrilo y se filtró a través de un filtro de jeringa, se diluyó con agua y se liofilizó.

Ejemplo 576: Pico 1: polvo blanco. Rendimiento: 52,0 mg; de = 99% (UV, 220 nm). LCMS m/z 431.3 (M + H)+, Rt 0.81 min.

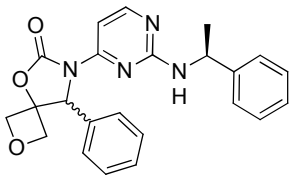
Ejemplo 577: Pico 2: polvo blanco. Rendimiento: 47.8 mg; de = 99% (UV,.220 nm). LCMS m/z 431.3 (M + H)+, Rt 0.81 min.

Ejemplos 578 y 579

(R)- 8- fenil- 7- (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) - 2,5- dioxa- 7- azaespiro [3.4] octan- 6- ona y

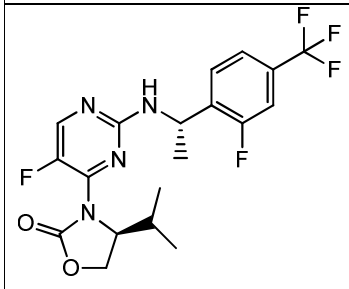
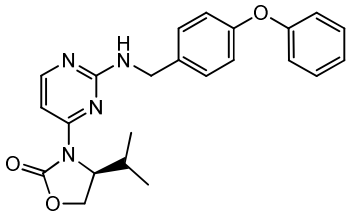
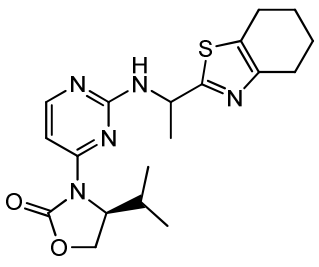
Se preparó (S)- 8- fenil- 7- (2 - ((S)- 1- feniletilamino) pirimidin- 4- il) - 2,5- dioxa- 7- azaespiro [3.4] octan- 6- ona usando métodos similares a los descritos para la preparación del Ejemplo 576 y 577.

Cuadro 23.

Ejemplo No.	Estructura	Columna quiral para la separación / condiciones	Columna quiral para control de calidad / condiciones	Tiempo de retención
578 (pico 1)		Columna AD; 56 mg / 6 ml de EtOH; heptano: EtOH 75:25; 20 ml/min, 400 psi	Columna AD-H; heptano: EtOH 75:25; 1 ml/min	5,4 min
579 (pico 2)			Columna AD-H; heptano: EtOH 75:25; 1 ml/min	8,9 min

Los compuestos de la Tabla 24 se prepararon utilizando métodos similares a los descritos para la preparación del Ejemplo 569

Cuadro 24.

580	581	582
		

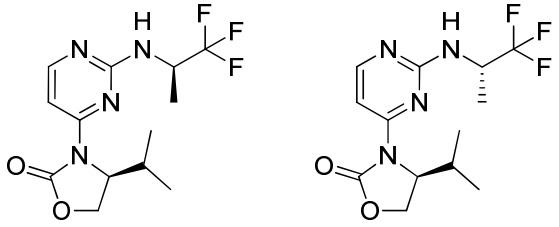
Cuadro 25. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada compuesto que aparece en la Tabla 24.

Ejemplo: Nombre	^{1}H RMN (400 MHz) δ ppm	LCMS
580: (S)- 3- (5- fluoro- 2- ((S)- 1- (2- fluoro- 4- (trifluorometil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(CD_3OD) 0,46- 0,69 (m, 6 H) 0,81- 0,91 (m, 1 H) 1,53 (d, J = 3,00 Hz, 3 H) 4.21- 4.29 (m, 1 H) 4,43- 4,53 (m, 2 H) 5,25 (m, J = 7,00, 7,00, 7,00 Hz, 1 H) 7,43 (m, J = 7,40 Hz, 2 H) 7,52- 7,59 (m, 1 H) 8.21- 8.27 (m, 1 H)	HRMS (A) m/z 431,1516 (M + H)+; Rt 2,40 min-
581: (S)- 4- isopropil- 3- (2 - (4- fenoxibenzilamino) pirimidin- 4- il) oxazolidin- 2- ona	(CD_3OD) 0,63- 1,00 (m, 7 H) 4,37- 4,49 (m, 2 H) 4,58- 4,65 (m, 1 H) 4,66- 4,78 (m, 2 H) 6,95- 7,02 (m, 4 H) 7,10 - 7,16 (m, 1 H) 7,32- 7,40 (m, 4 H) 7,75 (d, J = 7,04 Hz, 1 H) 8,16 (d, J = 6,65 Hz, 1 H)	HRMS (A) m/z 405,1935 (M + H)+; Rt 2,02 min-
582: (4S)- 4- isopropil- 3- (2- (1- (4,5,6,7- tetrahidrobenzo[d]tiazol- 2- il)etilamino)pirimidin- 4- il)oxazolidin- 2- ona		HRMS (A) m/z 388,1814 (M + H)+; Rt- 1.82/1.88 min

Ejemplos 583 y 584

(S)- 4- isopropil- 3- (2 - ((R) - 1,1,1- trifluoropropan- 2- ilamino) pirimidin- 4- il) oxazolidin- 2- ona

(S)- 4- isopropil- 3- (2 - ((S) - 1,1,1- trifluoropropan- 2- ilamino) pirimidin- 4- il) oxazolidin- 2- ona



A una solución de (S) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (40 mg, 0.166 mmol) en 2- butanol se añadió 1,1,1- trifluoropropan- 2- amina (74.9 mg, 0.662 mmoles) y monohidrato de ácido para- toluenosulfónico (74.9 mg, 0.662 mmol). La mezcla se calentó en atmósfera de argón en un vial sellado durante ~ 7 días a 115 °C. Independientemente, a una solución de (S) - 3 - (2- cloropirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona (100 mg, 0.414 mmol) en 2- butanol se añadió 1,1,1-

trifluoropropan- 2- amina (187 mg, 1,655 mmoles) y monohidrato de ácido para-toluenosulfónico (157 mg, 0.828 mmol). La mezcla se calentó en atmósfera de argón en un frasco sellado a 115 °C durante ~ 4 días. Las dos mezclas de reacción se combinaron y se concentraron bajo presión reducida. El residuo se diluyó con DMSO y agua (~ 10 vol.% de DMSO), se filtró a través de un filtro de jeringa y se purificó mediante HPLC de fase inversa. Las fraccionas seleccionadas se recogieron y se liofilizaron proporcionando dos isómeros como sólidos blancos como sus sales de ácido trifluoroacético.

Primer pico 583: Rendimiento: 29.1mg.

^{1}H RMN (400 MHz, CD_3OD) δ ppm 0,90 (d, *J*= 7,04 Hz, 3 H) 0,98- 1,02 (m, 3 H) 1,45 (d, *J*= 7,04 Hz, 3 H) 2,59 (dtd, *J*= 13,89, 6,95, 6,95, 3,52 Hz, 1 H) 4,43- 4,47 (m, 2 H) 4,76- 4,83 (m, 2 H) 7,70 (d, *J*= 5,87 Hz, 1 H) 8,20 (d, *J*= 6,26 Hz, 1 H)

LCMS m/z 319,3 (M + H)+, Rt 0,73 min. HRMS (A) *m/z* 319.1391 (M + H)+, Rt 1,89 min

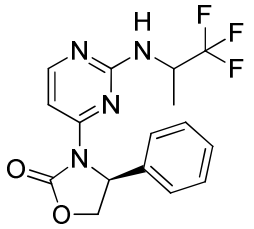
Segundo pico 584: Rendimiento: 38,5 mg.

^{1}H RMN (400 MHz, CD_3OD) δ ppm 0,87 (d, *J*= 7,04 Hz, 3 H) 0,98 (d, *J*= 7,04 Hz, 3 H) 1,45 (d, *J*= 7,04 Hz, 3 H) 2,48- 2,60 (m, 1 H) 4,40- 4,49 (m, 2 H) 4,88- 4,95 (m, 2 H) 7,69 (d, *J*= 5,87 Hz, 1 H) 8,20 (d, *J*= 6,65 Hz, 1 H)

LCMS m/z 319,3 (M + H)+, Rt 0,73 min. HRMS (A) *m/z* 319.1385 (M + H)+, Rt 1,88 min

Ejemplo 585

(4S)- 4- fenil- 3- (2 - (1,1,1- trifluoropropan- 2- ilamino) pirimidin- 4- il) oxazolidin- 2- ona

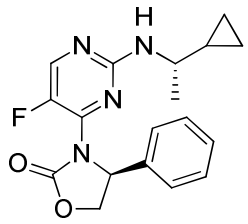


Una mezcla de (S) - 3 - (2- cloropirimidin- 4- il)- 4- feniloxazolidin- 2- ona (40 mg, 0.145 mmol), 1,1,1- trifluoropropan- 2- amina (82 mg, 0,725 mmol), base de Hunig (0,038 ml, 0,218 mmol) en DMSO (0.4 ml) se calentó bajo argón a 115 °C durante ~ 3 días. A continuación, la mezcla se dejó enfriar a temperatura ambiente. La mezcla se diluyó con

DMSO y agua (~ 10 vol.% de DMSO), se filtró a través de un filtro de jeringa y se purificó mediante HPLC de fase inversa. Las fraccionas seleccionadas se recogieron y se liofilizaron proporcionando (4S)- 4- fenil- 3- (2 - (1,1,1- trifluoropropan- 2- ilamino) pirimidin- 4- il) oxazolidin- 2- ona (relación de dos isómeros: 7/3) como un sólido blanco como su sal de ácido trifluoroacético. LCMS m/z 353.2 (M + H)+, Rt 0.78 min. HRMS (A) *m/z* 353.1231 (M + H)+, Rt 1.92/1.96 min.

Ejemplo 586

(S) - 3 - (2 - ((S)- 1- ciclopropiletilamino)- 5- fluoropirimidin- 4- il)- 4- feniloxazolidin- 2- ona



Una mezcla de (S) - 3 - (2- cloro- 5- fluoropirimidin- 4- il)- 4- feniloxazolidin- 2- ona (40 mg, 0,136 mmoles), (S)- 1- ciclopropiletanamina (34,8 mg, 0,409 mmol), base de Hunig (0,119 ml, 0.681 mmol) en DMSO (0,4 ml) se calentó bajo argón a 105- 115 °C durante ~ 18 horas (alternativos: 120- 135 ° C durante ~ 90 min). A continuación, la mezcla se dejó enfriar a temperatura ambiente. La mezcla se diluyó con DMSO y agua (~ 10 vol.% de DMSO), se filtró a través de un filtro de jeringa y se purificó mediante HPLC de fase inversa. Las fraccionas seleccionadas se recogieron y se liofilizaron proporcionando (S) - 3 - (2 - ((S)- 1- ciclopropiletilamino)- 5- fluoropirimidin- 4- il)- 4- feniloxazolidin- 2- ona (26 mg) como un sólido blanco como su sal de ácido trifluoroacético.

^{1}H RMN (400 MHz, CD_3OD) δ ppm - 0,14 - 0,05 (m, 1 H) 0,01 - 0,08 (m, 1 H) 0,23- 0,31 (m, 1 H) 0,36 - 0,44 (m, 1 H) 0,78- 0,86 (m, 1 H) 1,19 (d, J = 6,65 Hz, 3H) 3.5 - 3.14 (m, 1 H) 4,25- 4,32 (m, 1 H) 4,89- 4,90 (m, 1 H) 5,77 (t, J = 8,61 Hz, 1 H) 7,32 - 7,39 (m, 5 H) 8,15 (d, J = 3,52 Hz, 1 H).

LCMS m/z 343,1 (M + H)+, Rt 0,88 min. HRMS (A) *m/z* 343.1577 (M + H)+, Rt 2,09 min

Los compuestos de la Tabla 26 se prepararon utilizando métodos similares a los descritos para la preparación del Ejemplo **586.**

Cuadro 26.

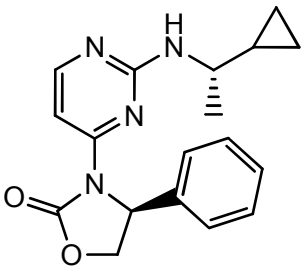
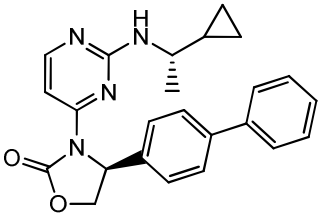
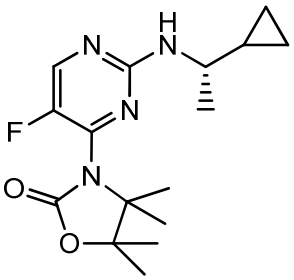
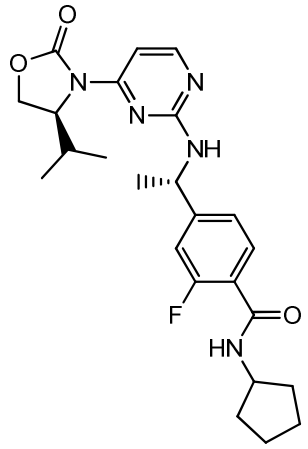
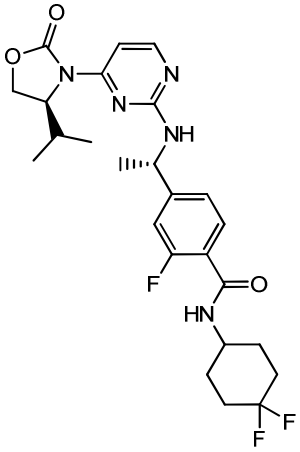
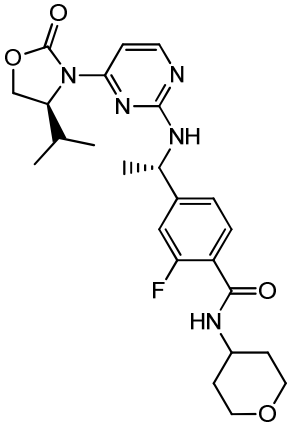
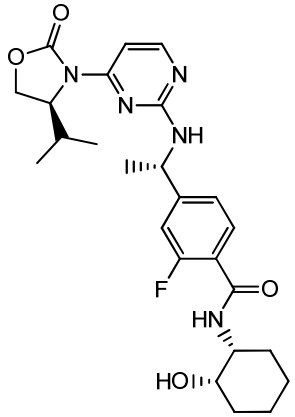
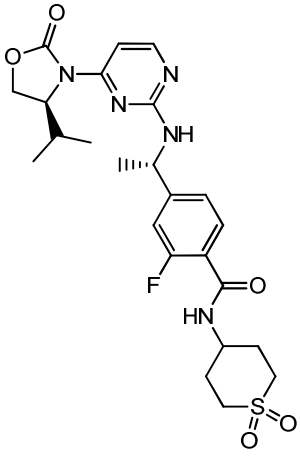
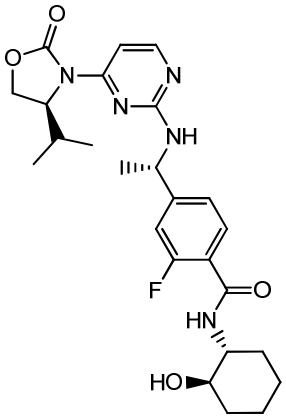
587	588	589
		

Tabla 27. Nombre químico, desplazamientos químicos de RMN y señal LCMS señal para cada compuesto que aparece en la Tabla 26.

Ejemplo: Nombre	^{1}H RMN (400 MHz) δ ppm	LCMS
587: (S) - 3 - (2 - ((S)- 1-ciclopropiletilamino) pirimidin- 4- il)- 4-feniloxazolidin- 2- ona	(CD_3OD) - 0,55 - 0,27 (m, 1 H), - 0,01 (m, J = 9,00, 4,30 Hz, 1 H), 0,12 - 0,32 (m, 1 H) 0,35 a 0,50 (m, 1 H) 0,64 - 0,93 (m, 1 H) 1,28 (d, J = 1,00 Hz, 3 H) 2,77- 3,00 (m, 1 H) 4,26 (dd, J = 1,00 Hz, 1 H) 4,76- 4,95 (m, 1- 2 H; superposición con disolvente) 5,75 (dd, J = 1,00 Hz, 1 H) 7,17- 7,52 (m, 5 H) 7,78 (d, J = 1,00 Hz, 1 H) 8,08 (d, J = 7,04 Hz, 1 H)	MS m/z 325,2 (M + H)+; Rt- 0.77 min. HRMS (A) m/z 325,1664 (M + H)+; Rt 1,53 min-
588: (S) - 4 - (bifenil- 4-il) - 3 - (2 - ((S)- 1-ciclopropiletilamino) pirimidin- 4- il) oxazolidin- 2- ona	(CD_3OD) 0,01 (m, J = 4,30 Hz, 1 H) 0,14-0,26 (m, 1 H) 0,33 - 0,45 (m, 1 H) 0,73 a 0,85 (m, 1 H) 1,28 (d, J = 6,65 Hz , 3 H) 2,91- 3,02 (m, 1 H) 4,32 (dd, J = 9,00, 4,30 Hz, 1 H) 4,89- 4,96 (m, 1 H) 5,81 (dd, J = 9,00, 4,30 Hz, 1 H) 7,34- 7,42 (m, 3 H) 7,45 (t, J = 7,63 Hz, 2 H) 7,59- 7,64 (m, 2 H) 7,67 (m, J = 8,20 Hz, 2 H) 7,79 (d, J = 7,04 Hz , 1 H) 8,10 (d, J = 7,04 Hz, 1 H)	MS m/z 401,3 (M + H)+; Rt- 0.89 min. HRMS (A) m/z 401,1988 (M + H)+; Rt 1,89 min-
589: (S) - 3 - (2 - (1-ciclopropiletilamino)- 5-fluoropirimidin- 4- il) 4,4,5,5-tetrametiloxazolidin- 2-ona	(CD_3OD) 0,17 - 0,24 (m, 1 H) 0,31 (q, J = 9,34, 4,71 Hz, 1 H) 0.41 - 0,55 (m, 2 H) 0,93- 1,04 (m, 1 H) 1,26 (d, J = 6,65 Hz, 3 H) 1,42 (s, 6 H) 1,49 (s, 6 H) 3,34- 3,42 (m, 1 H) 8,17 (d, J = 3,13 Hz, 1 H) MS m/z 323,6 (M+H) +; Rt- 0.89 min. HRMS m/z 323.1891 (M + H)+; Rt 2,10 min-	HRMS (A) *m/z* 464.1125 (M + H)+, Rt 2,28 min

Los compuestos de la Tabla 28 se prepararon utilizando métodos similares a los descritos para la preparación del Ejemplo 568

Cuadro 28.

590	591	592
		
593	594	595
		
596	597	598

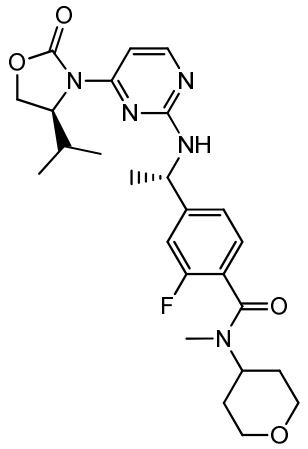
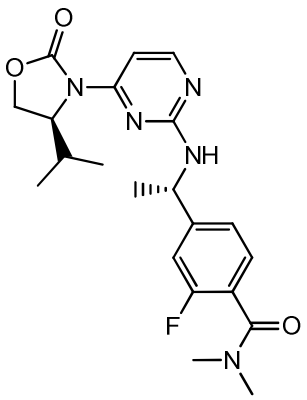
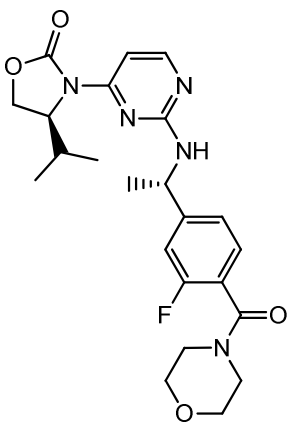
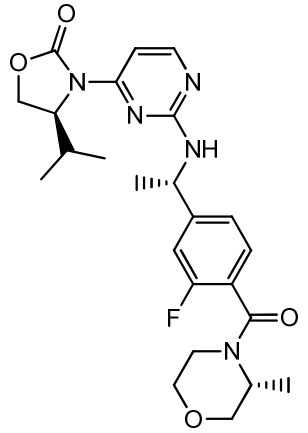
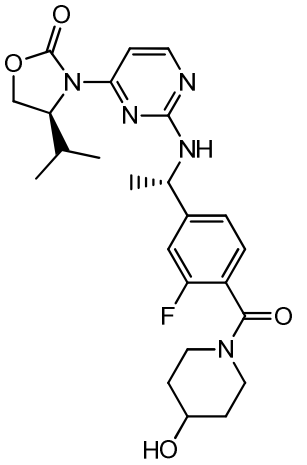
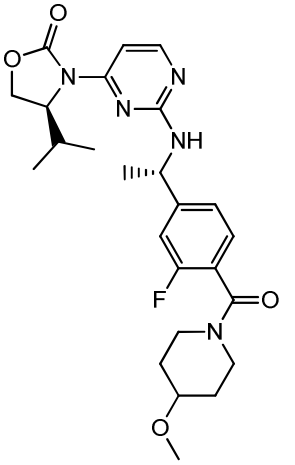
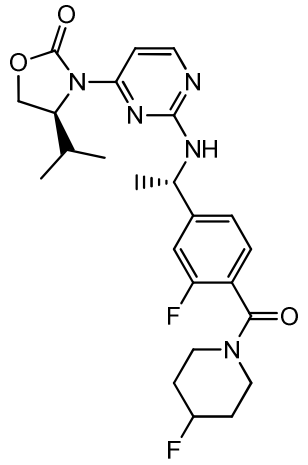
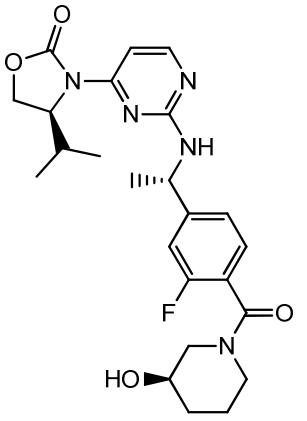
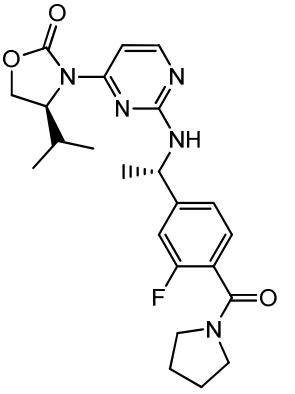
		
599	600	601
		
602	603	604
		

Tabla 29. Nombre químico, desplazamientos químicos de RMN y señal LCMS para cada compuesto que aparece en la Tabla 28.

Ejemplo: Nombre	^{1}H RMN (400 MHz) δ ppm	LCMS
590: N- ciclopentil- 2- fluoro- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida	(CD_3OD) 8,14 (d, J = 6,3 Hz, 1H), 7,72 (d, J = 7,0 Hz, 1H), 7,64 (t, J = 7,6 Hz, 1H), 7.13- 7.31 (m, 2H), 5,17 (br s, 1H), 4,67 (br s, 1H), 4,34 - 4,41 (m, 2H), 4,24- 4,33 (m, 1H), 1,99 (dt, J = 11,7, 5,9 Hz, 2H), 1,73 (d, J = 6,7 Hz, 2H), 1,49- 1,66 (m, 8H), 0,74 (br s, 3H.), 0,61 (br s, 3H.)	HRMS (A) m/z (M + H)+ 456.2422
591: N- (4,4- difluorociclohexil)- 2- fluoro- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida	(CD_3OD) 8,14 (d, J = 6,3 Hz, 1H), 7,70 (d, J = 7,0 Hz, 1H), 7,64 (t, J = 7,8 Hz, 1H), 7,12- 7,32 (m, 2H), 5,16 (br s, 1H), 4,67 (br s, 1H), 4,37 (d, J = 5,9 Hz, 2H), 4,00 (t, J = 10,0 Hz, 1H), 1,82 - 2.13 (m, 6H) , 1,61- 1,77 (m, 2H), 1,57 (d, J = 7,0 Hz, 3H), 0,73 (br. s., 3H), 0,61 (br. s., 3H)	HRMS (A) m/z (M + H)+ 506.2388
592: 2- fluoro- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)- N- (tetrahidro- 2H- piran- 4- il)benzamida	(CD_3OD) 8,13 (d, J = 5,9 Hz, 1H), 7,58- 7,71 (m, 2H), 7,13 - . 7,29 (m, 2H), 5,16 (br. s., 1H), 4,67 (br s, 1H), 4,36 (d, J = 5,5 Hz, 2H), 4.1 a 4.16 (m, 1H), 3,94 (d, J = 11,3 Hz, 2H), 3,50 (td, J = 11,7, 2,0 Hz, 2H), 1,82- 1,94 (m, 2H), 1,59- 1,69 (m, 2H), 1,57 (d, J = 7,0 Hz, 3H), 0,73 (br. s., 3H), 0,61 (br. s., 3H)	HRMS (A) m/z (M + H)+ 472.2366
593: 2- fluoro- N- ((1R,2S)- 2- hidroxiciclohexil)- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- ilamino)etil)benzamida	(CD_3OD) 8,14 (d, J = 6,3 Hz, 1H), 7,83 (t, J = 7,8 Hz, 1H), 7,69 (d, J = 7,0 Hz, 1H), 7,14- 7,36 (m, 2H), 5,15 (. d, J = 6,3 Hz, 1H), 4,65 (br s, 1H), 4,36 (d, J = 5,5 Hz, 2H), 3,96- 4,05 (m, 1H), 3,94 (d, J = 2,3 Hz, 1H), 1,79 (dd, J = 10,4, 4,5 Hz, 1H), 1,69 (d, J = 5,9 Hz, 4H), 1,54- 1,64 (m, 5H), 1,28- 1,48 (m, 2H), 0,70 (br . s., 3H), 0,60 (br s., 3H)	HRMS (A) m/z (M + H)+ 486.2526
594: N- (1,1- dioxidotetrahidro- 2H- tiopiran- 4- il)- 2- fluoro- 4- ((S)- 1- ((4- ((S)- 4- isopropil- 2- oxooxazolidin- 3- il)pirimidin- 2- il)amino)etil)benzamida	(CD_3OD) 8,14 (d, J = 6,3 Hz, 1H), 7,69 (d, J = 7,0 Hz, 1H), 7,64 (t, J = 7,6 Hz, 1H), 7.15- 7.31 (m, 2H), 5,16 (br s, 1H), 4,67 (br s, 1H), 4,36 (d, J = 5,9 Hz, 2H), 4,13 - .. 4,27 (m, 1H), 3,08 (d, J = 13,7 Hz, 2H) , 2,25- 2,36 (m, 2H), 2.7- 2.24 (m, 2H), 1,57 (d, J = 7,0 Hz, 3H), 0,73 (br. s., 3H), 0,61 (br. s., 3H)	HRMS (A) m/z (M + H)+ 520,203
595: 2- fluoro- N- ((1R,2R)- 2- hidroxiciclohexil)- 4- ((S)- 1- (4- ((S)- 4- isopropil- 2-	(CD_3OD) 8,13 (d, J = 6,3 Hz, 1H), 7,63- 7,78 (m, 2H), 7,14 - . 7,30 (m, 2H), 5,15 (br. s., 1H), 4,67 (br s, 1H), 4,36 (d, J = 5,5 Hz, 2H), 3,67- 3,83 (m, 1H), 3,38- 3,51 (m,	HRMS (A) m/z (M + H)+ 486.2521

oxooxazolidin- 3-il)pirimidin- 2-ilamino)etil)benzamida	1H), 2,01 (d, J = 9,0 Hz, 2H), 1,64- 1,81 (m , 3H), 1,57 (d, J = 7,0 Hz, 3H), 1,17 - .. 1,46 (m, 4H), 0,74 (br s, 3H), 0,61 (br s, 3H)	
596: 2- fluoro- 4- ((S)- 1-(4- ((S)- 4- isopropil- 2-oxooxazolidin- 3-il)pirimidin- 2-ilamino)etil)- N- metil- N-(tetrahidro- 2H- piran- 4-il)benzamida	(CD_3OD) 8,14 (d, J = 6,7 Hz, 1H), 7,76 (d, J = 7,4 Hz, 1H), 7,32- 7,42 (m, 1H), 7.17 a 7.31 (m, 2H), 5,22 (br s ., 1H), 4,60- 4,76 (m, 2H), 4,33- 4,44 (m, 2H), 4,02 (dd, J = 11,3, 4,3 Hz, 1H), 3,91 (d, J = 8,6 Hz, 1H), 3,45 - 3,65 (m, 2H), 3.7 a 3.21 (m, 1H), 2,99 (s, 1H), 2,80 (s, 2H), 1,81- 2,05 (m, 3H), 1,52- 1,71 (m, 5H), 0,78 (br s., 3H), 0,63 (br s., 3H)	HRMS (A) m/z (M + H)+ 486.2528
597: 2- fluoro- 4- ((S)- 1-(4- ((S)- 4- isopropil- 2-oxooxazolidin- 3-il)pirimidin- 2-ilamino)etil)- N,N-dimetilbenzamida	(CD_3OD) 8,14 (d, J = 7,0 Hz, 1H), 7,75 (d, J = 7,0 Hz, 1H), 7,32- 7,43 (m, 1H), 7.13-7.31 (m, 2H), 5,20 (br s ., 1H), 4,70 (br s, 1H), 4,33 - .. 4,45 (m, 2H), 3,09 (s, 3H), 2,92 (d, J = 0,8 Hz, 3H), 1,76 (br s, 1H), 1,59 (d, J = 7,0 Hz, 3H), 0,78 (br s., 3H), 0,62 (br s., 3H)	HRMS (A) m/z (M + H)+ 416.2106
598: (S)- 3- (2- ((S)- 1- (3-fluoro- 4- (morfolina- 4-carbonil)fenil)etilamino)pirimidin- 4- il)- 4-isopropiloxazolidin- 2-ona	(CD_3OD) 8,14 (d, J = 6,7 Hz, 1H), 7,73 (d, J = 6,7 Hz, 1H), 7,35- 7,43 (m, 1H), 7,28 (d, J = 7,8 Hz, 1H), 7,22 (d, J = 10,6 Hz, 1H), 5,18 (br s, 1H), 4,69 (br s, 1H), 4,30 - .. 4,42 (m, 2H), 3,73 (d, J = 3,1 Hz, 4H) , 3,59 (t, J = 4,7 Hz, 2H), 1,58 (d, J = 7,0 Hz, 3H), 0,76 (br s., 3H), 0,62 (br s., 3H)	HRMS (A) m/z (M + H)+ 458.2209
599: (S)- 3- (2- ((S)- 1- (3-fluoro- 4- ((R)- 3-metilmorfolina- 4-carbonil)fenil)etilamino)pirimidin- 4- il)- 4-isopropiloxazolidin- 2-ona	(CD_3OD) 8,14 (d, J = 6,7 Hz, 1H), 7,76 (d, J = 7,0 Hz, 1H), 7,36 (d, J = 6,7 Hz, 1H), 7.14- 7.31 (m, 2H), 5,20 (br s, 1H), 4,70 (br s, 1H), 4,65 (br s, 1H), 4,34 - 4,45 (m, 2H), 4,29 (d, J = 13,3 Hz, 1H), 3,96 (d, J = 10,6 Hz, 1H), 3,75 (d, J = 11,3 Hz, 1H), 3,51-3,67 (m, 2H), 3,43- 3,51 (m, 1H), 3.7- 3.19 (m, 1H), 1,76 (br s., 1H), 1,59 (d, J = 7,0 Hz, 3H), 1,36 (d, J = 6,7 Hz, 2H), 1,28 (br s., 1H), 0,77 (br s. , 3H), 0,62 (br s., 3H)	HRMS (A) m/z (M + H)+ 472.2366
600: (S)- 3- (2- ((S)- 1- (3-fluoro- 4- (4-hidroxipiperidina- 1-carbonil)fenil)etilamino)pirimidin- 4- il)- 4-isopropiloxazolidin- 2-ona	(CD_3OD) 8,14 (d, J = 6,7 Hz, 1H), 7,73 (d, J = 7,0 Hz, 1H), 7,31- 7,40 (m, 1H), 7.16-7.29 (m, 2H), 5,18 (br s ., 1H), 4,70 (br s, 1H), 4,31 - . 4,45 (m, 2H), 4,16 (dd, J = 12,9, 5,5 Hz, 1H), 3,87 (br s, 1H), 3,48 (. d, J = 14,1 Hz, 1H), 3,35 (d, J = 3,5 Hz, 1H), 3.5- 3.22 (m, 1H), 1,85- 1,98 (m, 1H), 1,70- 1,83 (m, 2H), 1,58 (d, J = 7,0 Hz, 3H), 1,49- 1,55 (m, 1H), 1,43 (br s, 1H.), 0,76 (br s, 3H.), 0,62 (br s, 3H.)	HRMS (A) m/z (M + H)+ 472.2369
601: (S)- 3- (2- ((S)- 1- (3-fluoro- 4- (4-metoxipiperidina- 1-	(CD_3OD) 8,13 (d, J = 6,7 Hz, 1H), 7,70 (d, J = 6,7 Hz, 1H), 7,31- 7,41 (m, 1H), 7,26 (d, J = 7,8 Hz, 1H), 7,21 (.. d, J = 10,6 Hz,	HRMS (A) m/z (M + H)+

carbonil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	1H), 5,17 (br s, 1H), 4,69 (br s, 1H), 4,33- 4,42 (m, 2H), 3,98 (dd, J = 10,8, 6,5 Hz, 1H), 3,40- 3,60 (m, 3H), 3,34 (s, 3H), 3,18 (d, J = 8,6 Hz, 1H), 1,88 - . 2,03 (m, 1H), 1,79 (br s, 1H), 1,62 (br s., 1H), 1,58 (d, J = 7,0 Hz, 3H), 1,49 (br s., 1H), 0,76 (br s., 3H), 0,62 (br s., 3H)	486.2523
602: (S)- 3- (2- ((S)- 1- (3- fluoro- 4- (4- fluoropiperidine- 1- carbonil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(CD_3OD) 8,14 (d, J = 6,7 Hz, 1H), 7,73 (d, J = 7,0 Hz, 1H), 7,34- 7,44 (m, 1H), 7.16- 7.31 (m, 2H), 5,18 (br s ., 1H), 4,93 (br s, 1H), 4,70 (br s, 1H), 4,29 - .. 4,43 (m, 2H), 3,91 (d, J = 11,3 Hz, 1H), 3,70 (br . s, 1H), 3,40- 3,53 (m, 1H), 1,93- 2,06 (m, 1H), 1,83- 1,93 (m, 2H), 1,77 (dd, J = 10,2, 4,7 Hz, 2H), 1,58 (d , J = 7,0 Hz, 3H), 0,76 (br s., 3H), 0,62 (br s., 3H)	HRMS (A) m/z (M + H)+ 474.2324
603: (S)- 3- (2- ((S)- 1- (3- fluoro- 4- ((R)- 3- hidroxipiperidina- 1- carbonil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(CD_3OD) 8,13 (d, J = 6,7 Hz, 1H), 7,72 (d, J = 7,0 Hz, 1H), 7,36 (t, J = 7,4 Hz, 1H), 7.14 a 7.30 (m, 2H), 5,19 (br s, 1H), 4,70 (br s, 1H), 4,30 - 4,44 (m, 2H), 3,71 (br s, 1H), 3,38- 3,52 (m, 1H), 3.8- 3.19 (m, 1H), 3,02 (br s, 1H), 1,96 (br s, 1H), 1,87 (br s, 1H), 1,66 - .. 1,81 (m, 1H), 1,49- 1,62 (m, 5H), 1,43 (br s., 1H), 0,78 (br s., 3H), 0,63 (br s., 3H)	HRMS (A) m/z (M + H)+ 472.2362
604: (S)- 3- (2- ((S)- 1- (3- fluoro- 4- (pirrolidina- 1- carbonil)fenil)etilamino)pirimidin- 4- il)- 4- isopropiloxazolidin- 2- ona	(CD_3OD) 8,13 (d, J = 6,3 Hz, 1H), 7,71 (d, J = 7,0 Hz, 1H), 7,34- 7,43 (m, 1H), 7.14- 7.30 (m, 2H), 5,18 (br s ., 1H), 4,70 (br s, 1H), 4,28 - . 4,43 (m, 2H), 3,57 (t, J = 6,8 Hz, 2H), 1,93- 2,07 (m, 2H), 1,83- 1,93 (m , 2H), 1,58 (d, J = 7,0 Hz, 3H), 0,77 (br s., 3H), 0,63 (br s., 3H)	HRMS (A) m/z (M + H)+ 442.2263

Datos Biológicos

Ensayo Bioquímico de IDH1Mutante: Detección LC- MS de 2- HG.

La actividad catalítica de IDH1 mutante R132H se monitoreó mediante la detección cuantitativa por medio de cromatografía líquida y espectrometría de masas (LC-MS) de 2HG, un producto de la reacción de reducción alfa- KG dependiente de NADPH.

Más específicamente, las reacciones bioquímicas se realizaron a temperatura ambiente en placas de fondo plano Greiner de 384 pozos (Costar, cat. No. 781201) usando un volumen final de reacción de 30 µL y las siguientes condiciones de buffer de ensayo: 50 mM HEPES pH 7.4, 10 mM MgCl2, 50 mM KCl, 1 mM DTT, 0,02% BSA, 5 uM NADPH y 100 uM alfa- KG.

La mezcla de reacción final contenía DMSO al 3.3% e inhibidores con concentraciones que van desde 0,02 hasta 50 µM. La enzima IDH1 se utilizó a una concentración final de 0.25 nM. Tras 45 minutos de incubación, las mezclas de reacción se apagaron mediante la adición de 10 µL de ácido fórmico al 16% que contiene 800 nM de ^{13}C- 2- HG carbón marcado). Luego la proteína se precipitó mediante la adición de 2,5 volúmenes de acetonitrilo, seguido por la centrifugación (3000 x g, 20 minutos). La concentración de 2- HG en los sobrenadantes resultantes se midió mediante LC- MS (ver más abajo).

Méodo LC- MS. Los sobrenadantes de la mezcla de reacción se sometieron a separación cromatográfica en una columna BiobasicAX (2,1 mm x 20 mm, 5 µm partícula, Thermo Scientific Inc.). Las fases móviles cromatográficas fueron A) biocarbonato de amonio 25 mM y B) acetonitrilo (hidróxido de amonio al 0.1%). La nicotinamida se eluyó a 1 ml/min usando un gradiente B 85- 5% durante 0.9 minutos (sistema Agilent 1200SL LC, automuestreador ThermoFisher LX- 4) y se analizaron mediante monitorización de reacción múltiple (MRM) en un espectrómetro de masas API4000 QTRAP (ABSciex, Framingham , MA) colocado en modo de ionización de electrospray positivo (ESI+). La transición de masas para 2- HG y ^{13}C- 2 HG- 147 fue →129 y 152→134, respectivamente. Las respuestas relativas (2- HG/^{13}C- 2- HG) se midieron a diversas concentraciones de inhibidor y se utilizaron para calcular los valores de IC50 inhibitorios (curvas de regresión de IC50 normalizadas).

Expresión y Purificación de la Proteína R132

IDH1 R132H se clonó en el vector pET47b utilizando los sitios de restricción XmaI/XhoI que produce un sitio His_6 N- terminal dentro de marco escindible con proteasa PreScission. Este plásmido se transformó en células Rosetta™2 (DE3) (Novagen). En matraces de agitación, 8L de células fueron cultivadas en Caldo Terrific (Teknova) (más kanamicina 50µg/mL y cloranfenicol 34µg/mL) a 37 ºC hasta una DO_{600} de 0.8 y la expresión de la proteína fue inducida por la adición de IPTG a una concentración de 0,20 mm. Las células se cultivaron posteriormente durante 18 horas a 18ºC.

Proteína His_6- IDH1 (R132H) sin cortar

MAHHHHHHSAALEVLFQGPGMSKKISGGSVVEMQGDEMTRIIWELIKEKLIFPY
VELDLHSYDLGIENRDATNDQVTKDAAEAIKKHNVGVKCATITPDEKRVEEFKL
KQMWKSPNGTIRNILGGTVFREAIICKNIPRLVSGWVKPIIIGHHAYGDQYRATDF
VVPGPGKVEITYTPSDGTQKVTYLVHNFEEGGGVAMGMYNQDKSIEDFAHSSFQ
MALSKGWPLYLSTKNTILKKYDGRFKDIFQEIYDKQYKSQFEAQKIWYEHRLIDD
MVAQAMKSEGGFIWACKNYDGDVQSDSVAQGYGSLGMMTSVLVCPDGKTVEA
EAAHGTVTRHYRMYQKGQETSTNPIASIFAWTRGLAHRAKLDNNKELAFFANAL
EEVSIETIEAGFMTKDLAACIKGLPNVQRSDYLNTFEFMDKLGENLKIKLAQAKL
(stop) (SEQ ID NO: 1)

Proteína IDH1 (R132H) Prescission Cortada (gpg N- terminal es un artefacto clonador)
*GPG*MSKKISGGSVVEMQGDEMTRIIWELIKEKLIFPYVELDLHSYDLGIENRDAT
NDQVTKDAAEAIKKHNVGVKCATITPDEKRVEEFKLKQMWKSPNGTIRNILGGT
VFREAIICKNIPRLVSGWVKPIIIGHHAYGDQYRATDFVVPGPGKVEITYTPSDGT
QKVTYLVHNFEEGGGVAMGMYNQDKSIEDFAHSSFQMALSKGWPLYLSTKNTI
LKKYDGRFKDIFQEIYDKQYKSQFEAQKIWYEHRLIDDMVAQAMKSEGGFIWAC
KNYDGDVQSDSVAQGYGSLGMMTSVLVCPDGKTVEAEAAHGTVTRHYRMYQ
KGQETSTNPIASIFAWTRGLAHRAKLDNNKELAFFANALEEVSIETIEAGFMTKDL
AACIKGLPNVQRSDYLNTFEFMDKLGENLKIKLAQAKL (stop) (SEQ ID NO: 2)

Purificación

Las células se homogeneizaron en Buffer de Lisis con inhibidores de la proteasa (Tabletas de inhibidor de proteasa libre de EDTA (Roche), 1 tableta por 50 ml de bufer), DNasa, y a 200 mM PMSF y se lisaron en un microfluidizador. Después de la lisis, Triton X- 100 fue añadido al 0.1% y se agitó a 4 ºC durante 30 minutos.

El lisado aclarado se cargó en columnas de crudo HisTrap FF de 2 x 5 mL (GE), se lavó extensivamente con Buffer de Lisis hasta que el A_{280} se estabilizó y se eluyó con Buffer de Elución Ni. Las fracciones eluidas pico se concentraron a 30 ml, se añadió EDTA a 1 mM y se agregó proteasa GST Prescission a 3U/100µg de proteína. La muestra se dializó contra buffer de diálisis 2L I (MWCO 50 kDa) durante 6 horas a 4 °C y luego se dializó contra a 2L de Buffer de Diálisis II durante al menos 6 horas más. Una muestra escindida con GST- PreScission fue agitado con perlas de gutatión agarosa, centrifugada y luego el sobrenadante se cargó a través de una columna HisTrap HP 5 mL y el flujo resultante fue recolectado.

Luego el flujo resultante se diluyó 20mM Tris pH 7.4 helado y 1mM TCEP hasta que la conductividad se redujo a menos de 5 mS/cm (una dilución de aproximadamente tres veces). Esta muestra se hizo fluir luego a través de una columna HiTrap Q y el flujo resultante se concentró hasta 10 ml y se cargó en una columna equilibrada 26/60 Superdex 200 usando SEC Buffer como la fase móvil. Las fracciones pico se recogieron, se concentraron y fueron alicuotadas.

Buffer de Lisis: Tris 50 mM pH = 7.4, NaCl 500 mM, imidazol 20 mM, y TCEP 1 mM

Buffer de elución Ni: Tris 50 mM pH = 7.4, NaCl 150 mM, imidazol 200 mM, y TCEP 1 mM

Buffer de Diálisis: Tris 20 mM pH = 7.4, NaCl 150 mM, TCEP 1 mM, e Imidazol 50 mM

Buffer de Diálisis II: Tris 20 mM pH = 7.4, NaCl 150 mM, y TCEP 1 mM

Buffer SEC: Tris 20 mM pH = 7.4, NaCl 150 mM, y TCEP 1 mM

Los resultados del ensayo bioquímico de IDH1 mutante (MIDH R132H) se dan en la Tabla 30. Algunos de los ejemplos se realizaron en múltiples tiempos de ensayo y por lo tanto los valores de CI50 se expresan como un intervalo de actividad.

Ensayo bioquímico de fluorescencia

El mutante IDH1 (R132H) cataliza la forma reducida de NADP + (NADPH) y α-cetoglutarato (α-KG) para formar fosfato de nicotinamida adenina dinucleótido fosfato (NADP +) y R (-)-2-hidroxiglutarato (2HG). La reacción se puede monitorizar cinéticamente siguiendo la oxidación de NADPH a NADP + que se mide usando fluorescencia, una excitación a 355 nm y una emisión a 530 nm. Las reacciones fueron controladas mediante el equipo Perkin-Elmer Envision, Modelo 2101. Más específicamente, las reacciones bioquímicas se realizaron a temperatura ambiente en placas de fondo plano de 384 pozos Greiner (Cat. No. 781076) usando un volumen final de reacción de 20 µL y las siguientes condiciones de tampón de ensayo: 50 mM de HEPES a un pH de 7,5, 10 mM de $MgCl_2$, 1 mM de DTT, 0,02% de BSA, 0,02% de

Tween-20, 10 μM NADPH y 100 μM α-KG. La mezcla de reacción final contenía 2,5% de DMSO y los compuestos de ensayo con concentraciones que van desde 0,0000008 hasta 25 μM. Se utilizó la enzima IDH1 (R132H) a una concentración final de 10 nM. El ajuste para las determinaciones de CI50 de la curva de dosis-respuesta se realizó en el módulo de Helios del paquete de software DAVID. Se utilizó el modelo logístico de 4 parámetros: y = min + ((max - min) / 1 + (x / CI50) ^{pendiente}).

Tabla 30. Resultados de LC-MS y ensayos bioquímicos de fluorescencia.

Número de Ejemplo	**Ensayo Bioquímico LC-MS IC_{50} (μM)**	**Ensayo Bioquímico de Fluorescencia IC50 (μM)**
1	0.084 – 0.236	
2	>50	
3	0.086 – 0.575	0.091-0.501
4	4.612	
5	0.410-0.600	
6	12.175	
7	2.527	
8	13.011	
9	6.444	
10	0.355-0.419	
11	0.770 – 4.552	
12	1.990 – 2.391	9.55
13	18.344 – 29.100	
14	2.333 – 2.814	
15	5.383	
16	>50	
17	7.625	
18	>50	
19	>50	
20	>50	
21	4.169	

22	19.671	
23	0.502 –0.591	
24	3.564	
25	18.182 – >50	
26	>50	
27	2.486 – 2.730	
28	4.427 – 4.625	
29	4.630 – 11.566	
30	1.072	
31	1.721	
32	9.797	
33	3.483	
34	7.588	
35	0.222 – 0.273	
36	17.576	
37	4.595	
38	>50	
39	8.806	
40	20.34	
41	0.291 – 0.581	
42	0.584	
43	7.686	
44	0.125	
45	>50	
46	0.234	
47	7.481	
48	2.090 – 2.601	1.91
49	2.803	
50	0.076 – 0.100	
51	19.457	
52	23.847	
53	3.852	
54	0.141	

55	3.494	
56	9.502	
57	1.393-3.153	7.58
58	>50	
59	0.575	
60	0.052	0.094
61	12.729	
62	0.117 – 0.178	
63	0.085 – 0.124	
64	6.79	
65	0.25	
66	0.073	
67	5.342	
68	6.302	
69	0.127 – 0.390	
70	0.195 – 0.230	
71	20.503	
72	37.361	
73	0.316	
74	2.569	
75	1.338	4.27
76	8.008	
77	11.26	
78	28.611	
79	0.09	
80	0.679	
81	0.103	
82	0.163 – 0.217	
83	0.238 – 0.462	
84	0.075	
85	1.061	17.9
86	9.767	
87	0.126	0.245

88	0.148 – 0.344	
89	0.203	0.308
90	0.272	0.275
91	2.875	
92	0.211 – 0.544	0.598
93	0.405 – 0.905	
94	4.487	
95	0.655	0.571
96	>50	
97	0.195	0.166
98	0.628	
99	0.184	
100	0.169	
101	2.382	
102	0.401	
103	3.184	
104	0.207	
105	0.352	0.352
106	1.918	
107	3.445	
108	>50	
109	0.542	0.939
110	0.188	0.284
111	0.125	
112	7.768	
113	1.925	
114	0.697	1.14
115	0.092	0.126
116	2.038	
117	0.163 – 0.217	
118	1.302 – 2.152	
119	0.117	0.149
120	0.258-0.847	

121	0.081-0.448	
122	0.157-0.379	
123	0.112	0.162
124	0.081 – 0.298	0.791
125	1.012	
126	0.118	
127	0.158	0.215
128	0.565	
129	0.467	
130	0.549 – 0.615	
131	14.319	
132	31.016	
133	7.115	
134	3.102	
135	11.6	
136	6.455	
137	3.14	
138	1.061	
139	1.252	2.5
140	0.089	0.114-0.181
141	0.095	
142	0.390 – 0.512	
143	>50	
144	>50	
145	6.807	
146	11.362	
147	6.445	
148	3.544	
149	0.647	
150	0.53	0.538
151	1.363	
152	0.385	0.598
153	0.759	0.582

154	0.049	0.091
155	0.04	
156	0.232	0.248
157	>50	
158	0.873	1.41
159	0.287	
160	6.078	
161	6.502	
162	0.009-0.035	0.020-0.043
163	0.149	
164	0.067	0.0339
165	0.183	0.143
166	0.637	1.56
167	0.254	
168	0.102	
169	0.195	
170	1.083	
171	6.161	
172	0.245 – 0.274	
173	2.908	
174	0.056 – 0.118	0.283
175	8.156	
176	0.125	0.138
177	4.333	
178	0.097	0.0687
179	5.973	
180	0.194	
181	10.232	
182	0.309-0.370	
183	36.818	
184	0.696	
185	6.066	
186	0.04	

187	3.899	
188	0.089	0.17
189	0.117	
190	2.134	
191	6.969	
192	0.221	0.294
193	0.097	
194	4.333	
195	5.748	
196	0.083	
197	15.05	
198	0.173	0.179
199	2.435	
200	0.08	0.0665
201	0.927	
202	0.025	0.0541
203	1.856	
204	0.062	0.0955
205	0.199	0.219
206	1.458	0.81
207	0.069	0.0169
208	0.085	0.108-0.183
209	0.088	0.0881
210	0.576	0.343
211		0.439
212	0.132	0.024
213	2.913	
214	0.298	0.791
215	0.390	0.419
216	0.031	0.0206
217	0.177 - 0.206	0.079-0.146
218	1.373	0.625
219	0.613	

220	0.529	0.247
221	0.098	0.0476
222	0.505	0.296
223	0.293	0.14
224	<0.022	0.0166
225	0.026	0.0173
226	0.114	0.0832
227	0.065	0.0339
228	0.067	0.0463
229	0.113	0.0662
230	0.072	0.0415
231	0.327	0.242
232	0.251	0.755
233	0.147	0.0684
234	> 50	> 25
235	0.039	0.0141
236	0.372	0.338
237	0.877	0.219
238		9.8
239	0.038	0.073
240	0.030	0.0506
241	0.155	0.213
242	0.048	0.242
243	0.260 - 0.914	1.21-1.6
244	0.863	0.774
245	0.184	0.103
246	0.497 - 0.589	0.236-0.316
247	1.373	1.79
248	0.687	0.842
249	0.585	0.616
250	0.031	0.0468
251	0.064	0.0878
252	0.033	0.0608

253		0.559
254	0.656	1.12
255	10.369	
256	0.197	
257	0.242 - 0.282	0.221-0.27
258	0.378	
259	2.569	
260	0.186	
261	0.040	0.0639
262	0.058	0.0991
263		0.679
264	0.108	
265	<0.022	0.0232
266	0.152	
267	3.308	
268	20.567	
269	0.467	
270	0.463	
271	0.100	0.108
272	1.717	2.28
273	0.202	0.143
274	0.104	0.0524
275	0.261	0.273
276	0.298	0.175
277	0.094	0.0899
278	0.241	0.29
279	0.312	
280	7.823	
281	<0.022	
282	0.180	
283	0.538	0.635
284	2.023	1.38
285	0.390	0.375

286	1.807	2.54
287	34.794	> 25
288	0.053	0.269
289	0.316	0.19
290	2.222	0.414-0.975
291		4.64
292	0.049	0.0645
293	2.696	
294	0.095	0.648
295	0.342	0.252
296	0.085	
297		0.848
298	0.188	1.04
299	4.052	10.4
300	1.639	1.84
301		0.0887
302	0.131	
303		0.326
304	2.107	
305	0.065	0.0413
306	4.043	12.5
307		0.225
308	0.259	0.703
309	0.868	1.66
310	36.281	> 25
311	4.139	
312	0.051	0.024
313	0.073	0.0799
314	1.311	1.59
315	5.916	
316	0.131	
317	0.050	
318	5.007	

319	0.705	
320	2.410	
321	1.214	
322	0.026	0.0666
323		17.1
324		0.483
325	15.718	18.5-21.4
326	0.115	0.268-0.369
327		19.2
328	0.329 - 1.144	0.558-0.843
329	2.164	5.62
330	0.026	0.0545
331	6.083	7.65
332	0.052 - 0.072	0.0693
333	0.128	0.335
334	0.646	
335		6.53
336		0.236
337		7.22
338	0.148	0.145
339	3.101	4.4
340	<0.022	0.0276
341		2.13
342	0.029	0.0278
343		4.08
344		0.265
345	> 50	
346	32.256	
347	> 50	
348	> 50	
349	4.010	24.2
350	0.583	0.731
351	> 50	

352	> 50	
353	> 50	
354	> 50	
355	33.589	> 25
356	1.642	4.53
357	13.229	
358	0.864	1.53
359	> 50	> 25
360	3.035	4.37-11.9
361	0.781	0.736
362	0.063	0.0621
363	14.441	23.3
364	0.964	1.06
365	> 50	> 25
366	2.602	20.2-21.7
367	20.809	> 25
368	0.706	0.862
369	> 50	> 25
370	6.649	3.01
371	25.036	> 25
372		4.19
373	39.696	> 25
374	1.617	1.89-2.42
375	> 50	> 25
376	2.321	3.27-4.33
377		>25
378		4.19
379		> 25
380		0.839
381		20
382	0.203	0.349
383		5.16
384	0.068	0.107

385		22.5
386		4.74
387		20.6
388		4.37
389		1.83
390	0.140	0.213
391		2.35-5.33
392	0.694	0.355-0.697
393		12.1
394	0.268	0.34
395		9.36
396	0.189	0.224
397		7.14
398	0.094 - 0.123	0.189
399		> 25
400		0.648
401		19
402	0.362	0.39
403		> 25
404		0.964
405		21.1
406		1.82
407		6.39
408	0.237	0.349
409		1.35
410	0.340 - 0.440	0.098-0.521
411	2.907	
412	0.190	
413	21.616	
414	6.026 - 7.675	5.47-8.32
415	26.674	
416	1.592	
417	20.287	

418	0.808	
419	2.833	
420	> 50	
421	27.999	> 25
422	2.136	3.81
423	7.595	14.8
424	0.162	0.491-0.747
425	0.909	2.45
426	<0.022 - 0.038	0.019-0.058
427	1.229	2.09
428	> 50	> 25
429	6.407	9.78
430	0.133	0.0908
431	0.568	0.811
432	0.040	0.0448
433	6.675	5.31
434	0.153	2.19-3.96
435		> 25
436	0.291	0.364-0.373
437		2.69-3.18
438		> 25
439		6.155
440	0.125	0.105-0.122
441	4.229	1.63-10.6
442	0.136	0.225
443	0.063 - 0.077	0.0414
444	0.040	0.0266
445	2.526	2.46
446	0.079 - 0.081	0.039
447	3.876	
448	0.034	0.0373
449		5.43
450	0.062	0.0518

451	0.207	0.386
452	0.063 - 0.065	0.134
453	11.400	14.5
454	0.401	0.601
455	6.218	> 25
456	0.082	0.041
457	<0.022	0.013
458	0.069	0.0588
459	0.991	1.16
460		
461	2.275	
462	1.924	2.87
463	> 50	
464	<0.022	0.020-0.055
465		0.164
466	0.665	0.821
467		9.82
468		3.03-11.8
469	0.077	0.185-0.198
470	0.075	0.172
471	0.925	0.78
472		14.8
473		0.0986
474		7.1
475	0.341	0.355
476	> 50	
477	> 50	
478	> 50	
479	> 50	
480	> 50	
481	0.780	2.52
482	>50	>25
483	0.096	0.202

484	5.160	21.3
485		2.12
486		0.873
487		1
488	0.311	0.437
489		4.15
490		2.61
491		0.821
492		0.249
493	0.067	0.139
494	1.649	0.595
495	0.712	0.734
496	0.751	0.723
497		1.13
498		5.27
499		2.39
500		1.45
501		0.494
502		0.305
503	0.546	0.96
504	0.268	0.243
505		0.275
506		0.46
507		0.0773
508	0.553	0.484
509	0.553	0.484
510		0.0294
511	0.062	
512	0.450	0.38
513		0.0336
514		
515		0.0287
516	0.082	0.0592

517		1.58
518		0.0785
519	0.123	0.363
520	0.080	0.053-0.321
521		0.23
522		0.745
523		0.165
524	0.026	0.0211
525	0.085	0.108-0.183
526	0.088	0.0427
527		0.0851
528	0.077	0.0613
529	0.117	0.0622
530	<0.022	0.00835
531		0.00812
532		0.0727
533	0.307	0.227
534	0.188	0.331
535		0.183
536		0.104
537	0.400	0.257
538	0.416	0.268
539		2.66
540	0.878	0.573
541	0.266	0.0899
542	0.090	0.0877
543		> 25
544	0.075	0.0477
545		0.0943
546	0.059	0.0423
547	0.158	0.146
548	0.184	
549	1.840	

550	0.791	0.276
552	<0.022	0.0199
553	0.521	0.41
554	0.075	0.217
555	<0.022	
556	<0.072	
557	0.246	0.237
558		0.283
559		17.6
560		25
561		0.552
562		0.364
563		0.04
564		0.0501
565		0.309
566	0.135	0.13
567		5.41
568	0.086 - 0.141	0.067-0.161
569		0.0575
570		0.0446
571		0.0742
572		0.0781
573		0.00786
574	0.204	0.324
575		1.91
576		2.37
577		1.65
578		1.07
579	0.911	0.591
580	0.153	0.193
581	0.260	0.432
582		0.204
583		> 25

584		10.6
585		6.7
586	2.797	1.02
587		1.95
588	0.764	0.85
589		2.92
590	<0.022	0.006-0.009
591	<0.022	0.018
592	0.138	0.077
593	0.077	0.036
594	0.257	0.178
595	0.121	0.053
596	0.161	0.154
597	0.457	0.741
598	0.519	0.715
599	0.155	0.265
600	0.488	0.729
601	0.042	0.042
602	0.049	0.034
603	0.244	0.336
604	0.112	0.161

Ensayo celular de IDH

El ensayo celular de IDH consta de dos ensayos de comparación lado a lado: 1) ensayo de detección del oncometabolito 2HG utilizando LC-MS (Ver detalles del ensayo bioquímico mutante IDH1 para detección de LC-MS) y 2) ensayo de proliferación celular para supervisar la desviación de la matanza de las células y para normalizar el cambio del nivel de 2HG. Se realizó un tamizaje de células IDH1 con la línea de células HCT-116 (que expresan el nivel endógeno de IDH1mut R132H, disponible en Horizon Discoveries X-Man isogenic human cell lines, catalog # HD104-013). Las células se cultivaron en DMEM (LONZA Cat # 12-540F) con 10% de suero fetal bovino (Gibco Cat # 10099) y aminoácidos no esenciales 1X (NEAA LONZA cat # 13-114E). Panel de ensayos se llevó

a cabo periódicamente para probar la actividad del compuesto en líneas celulares con diferentes mutaciones endógenas - HT1080 (IDH1mut R132C, EMEM + 10% de FBS), SNU-1079 (IDH1mut R132C, RPMI + 10% de FBS + 1% de piruvato de sodio), y SW1353 (IDH2mut R172S, RPMI + 10% de FBS + 1% de piruvato de sodio).

El procedimiento de ensayo es el siguiente:

Día 1: las células fueron sembradas en placas de 384 pozos (Corning Cat # 3707) por triplicado tanto para el ensayo de proliferación celular y de 2HG, y se incubaron a 37 ºC, 95% HR, 5% de CO_2 durante la noche.

Día 2: Los compuestos se diluyeron en serie 1:3 (10 puntos dilución de soluciones 10 mM en DMSO) y se transfieren a las placas de ensayo celular a través de distribuidor acústico, con una concentración final que va desde 30 um a 1,5 nM. Las placas se devolvieron a la incubadora después del tratamiento y se incubaron durante 48 horas.

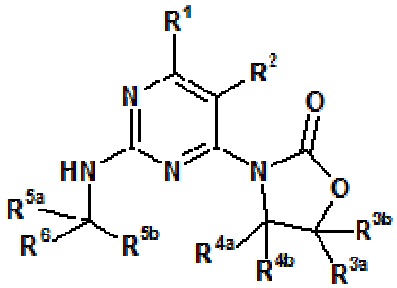
Día 4 Ensayo de proliferación: se añadió CTG (cell titer-glo, Promega part # G755B) a las placas de ensayo y se leyó la señal de luminiscencia en el lector de placas.

Día 4 ensayo 2HG: La preparación de la muestra consistió en la extracción de aspiración de todos los medios de cultivo de las placas de ensayo, la adición de 70 ul de metanol al 90% en agua, la incubación hielo seco durante 15 minutos, centrifugar a 2.000 rpm durante 30 minutos para asegurar que todas las partículas se han asentado, y la transferencia de 30 ul del sobrenadante en placas de listas LC-MS. El análisis por CL-EM se da a continuación.

Ciertos compuestos de la invención se han evaluado en el Ensayo celular de IDH.

REIVINDICACIONES:

1. Un compuesto de la Fórmula (I)



(I)

en donde:

R^1 y R^2 son cada uno independientemente hidrógeno, deuterio, halo, hidroxilo, NH_2, arilo, heteroarilo, o alquilo C_{1-4} opcionalmente sustituido,

en donde dicho alquilp C_{1-4} es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, y NH_2;

R^{3a} es hidrógeno, deuterio, alquilo C_{1-6}, fenilo, o bencilo y

R^{3b} es hidrógeno, deuterio, o C_{1-6} alquilo; o

R^{3a} y R^{3b} se unen juntos formando un anillo cicloalquilo de 3-7 miembros opcionalmente sustituido o un anillo heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dichos anillos cicloalquilo y heterocíclico son cada uno opcionalmente sustituidos por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3};

R^{4a} es hidrógeno, alquilo C_{1-6}, fenilo opcionalmente sustituido, bencilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o metileno-dibenceno,

en donde dicho fenilo, bencilo, y anillos de heteroarilo son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-4}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6} cicloalquilo C_{3-6}, fenilo, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, fenoxilo, $-COOR^b$, $-SO_2R^b$, $-NHC(O)R^b$, y $-NR^bR^b$ y

R^{4b} es hidrógeno, deuterio, o alquilo C_{1-3}; o

R^{4a} y R^{4b} se unen juntos formando un anillo cicloalquilo de 3-7 miembros opcionalmente sustituido o un anillo heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dichos anillos cicloalquilo y heterocíclico son opcionalmente sustituidos por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3},

proporciono que solo uno de R^{3a} y R^{3b} y R^{4a} y R^{4b} se unen juntos formando un anillo;

R^{5a} es hidrógeno o deuterio;

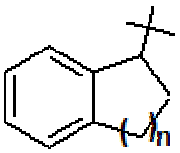
R^{5b} es hidrógeno, deuterio, metilo, etilo, CD_3, CF_3, CH_2F, o CHF_2 y

R^6 es opcionalmente sustituido alquilo C_{1-6}, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heterocíclico opcionalmente sustituido, o cicloalquilo C_{3-10} opcionalmente sustituido,

en donde dicho alquilo C_{1-6} es opcionalmente sustituido por un sustituyente seleccionado a partir del grupo que consta de hidroxilo, alcoxilo C_{1-3} y $–OR^a$,

en donde dicho arilo, heteroarilo, heterocíclico y cicloalquilo C_{3-10} son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo; hidroxilo; ciano; nitro; alcoxilo C_{1-4}; haloalquilo C_{1-3}; haloalcoxilo C_{1-3}; alquilo C_{1-6}; cicloalquilo C_{3-6} opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: hidroxilo, ciano, alquilo C_{1-3}, alcoxilo C_{1-3}, y haloalquilo C_{1-3}; fenilo opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6} , heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, fenoxilo, $-COOR^b$, $-SO_2R^b$, $-NHC(O)R^b$, y NR^bR^b; heteroarilo de 5-6 miembros opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, alquilo C_{1-3}, alcoxilo C_{1-3}; heterocíclico de 5-6 miembros opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente

seleccionado a partir del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3}; -CH_2R^a; -OR^a; -$C(O)R^a$; -NR^aR^b; -$COOR^a$; –SO_2R^a; –SO_2R^b; -$NHC(O)R^a$; -$NHC(O)R^b$; □$C(O)NR^aR^b$; -$C(O)NHR^b$; y -$SO_2NR^bR^b$; o

R^{5b} y R^6 se unen juntos formando un grupo cicloalquilo C_{3-7} opcionalmente sustituido o un grupo opcionalmente sustituido de la Fórmula (a):  (a),

en donde n es 1, 2, o 3 y

dicho cicloalquilo C_{3-7} y grupo de la Fórmula (a) son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquiloC_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, benciloxilo, -$COOR^b$, □SO_2R^b, -$NHC(O)R^b$, y -NR^bR^b;

cada R^a es independientemente fenilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heterocíclico opcionalmente sustituido, o cicloalquilo C_{3-7} opcionalmente sustituido,

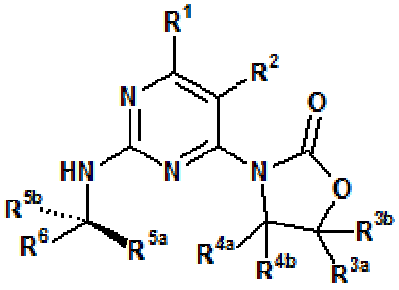
en donde dicho fenil y heteroaril son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, y alquilo C_{1-3},

en donde dicho heterocíclico es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de halo, hidroxilo, oxo, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-4}, cicloalquilo C_{3-5}, -$C(O)R^b$, y –NR^bR^b, y

en donde dicho cicloalquilo C_{3-7} es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de halo, hidroxilo, oxo, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, y alquilo C_{1-3}; y

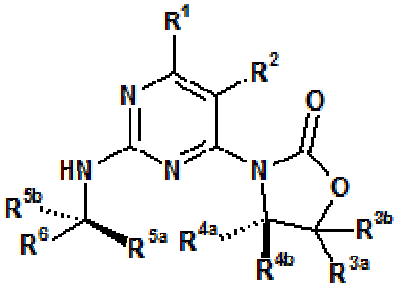
cada R^b es independientemente hidrógeno o alquilo C_{1-6}; o una sal farmacéuticamente aceptable del mismo.

2. El compuesto según la reivindicación 1 de la Fórmula (III)



(III); o una sal farmacéuticamente aceptable del mismo.

3. El compuesto según la reivindicación 2 de la Fórmula (IV)



(IV); o una sal farmacéuticamente aceptable del mismo.

4. El compuesto según la reivindicación 3 en donde R^{3a} y R^{3b} son ambos hidrógeno; o una sal farmacéuticamente aceptable del mismo.

5. El compuesto según la reivindicación 4 en donde R^{5a} es hidrógeno y R^{5b} es hidrógeno, metilo, etilo, o CF_3; o una sal farmacéuticamente aceptable del mismo.

6. El compuesto según la reivindicación 5 en donde R^{5b} es metilo; o una sal farmacéuticamente aceptable del mismo.

7. El compuesto según la reivindicación 6 en donde R^1 es hidrógeno, fluoro o cloro y R^2 es hidrógeno, flúor, cloro, o metilo; o una sal farmacéuticamente aceptable del mismo.

8. El compuesto según la reivindicación 7 en donde R^1 y R^2 son ambos hidrógeno; o una sal farmacéuticamente aceptable del mismo.

9. El compuesto según la reivindicación 8 en donde R^{4a} es hidrógeno, alquilo C_{1-6}, fenilo opcionalmente sustituido, bencilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o metileno-dibenceno,

en donde dicho fenilo, bencilo, y anillos de heteroarilo son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6} , heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, fenoxilo, □$COOR^b$, -SO_2R^b,- $NHC(O)R^b$, y- NR^bR^b y R^{4b} es hidrógeno o alquilo C_{1-3}; o una sal farmacéuticamente aceptable del mismo.

10. El compuesto según la reivindicación 9 en donde R^{4b} es hidrógeno o metilo; o una sal farmacéuticamente aceptable del mismo.

11. El compuesto según la reivindicación 10 en donde R^{4b} es hidrógeno; o una sal farmacéuticamente aceptable del mismo.

12. El compuesto según la reivindicación 11 en donde R^{4a} es hidrógeno, metilo, etilo, isopropilo, fenilo, 4-fluorofenilo, 4-metoxifenilo, bifenilo, bencilo, o piridinilo; o una sal farmacéuticamente aceptable del mismo.

13. El compuesto según la reivindicación 12 en donde R^{4a} es isopropilo; o una sal farmacéuticamente aceptable del mismo.

14. El compuesto según cualquiera de las reivindicaciones 1-13 en donde R^6 es metilo, cicloalquilo C_{5-10}, fenilo opcionalmente sustituido, piridinilo opcionalmente sustituido, pirimidinilo opcionalmente sustituido, piridazinilo opcionalmente sustituido, pirazinilo opcionalmente sustituido, triazolilo opcionalmente sustituido, pirazolilo opcionalmente sustituido, tiazolilo opcionalmente sustituido, 1,3,4-oxadiazolilo

opcionalmente sustituido, 1,2,4-oxadiazolilo opcionalmente sustituido, isoxazolilo opcionalmente sustituido, tienilo, oxazolilo, quinolinilo, bencimidazolilo opcionalmente sustituido, benztiazolilo, benzoxazolilo, tetrazolo[1,5-a]piridinilo, imidazo[2,1-b][1,3,4]tiadiazolilo, piperidinilo opcionalmente sustituido, piperazinilo opcionalmente sustituido, tetrahidrofuranilo, tetrahidropiranil, opcionalmente sustituido tetrahidro-tiopiran1,1-dióxido, 1H-pirrolo[2,3-b]piridinilo, 2,3-dihidro-benzo[1,4]dioxinilo, 5,6,7,8-tetrahidro-[1,2,4]trazolo[4,3-a]pirazinilo, 4,5,6,7-tetrahidro-benzotiazolilo, indolizinilo, ciclopropilo, ciclopentilo, o ciclohexilo, en donde dicho fenilo, piridinilo, pirimidinilo, piridazinilo, pirazinilo, triazolilo, pirazolil, tiazolilo, 1,3,4-oxadiazolilo, 1,2,4-oxadiazolilo, isoxazolilo, bencimidazolilo, piperidinilo, piperazinilo, y tetrahidro-tiopiran1,1-dióxido son cada uno opcionalmente sustituido por uno o dos sustituyentes como se define en la Fórmula (I).

15. El compuesto según la reivindicación 14 en donde R^6 es opcionalmente sustituido por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo; hidroxilo; nitro; alcoxilo C_{1-4}; haloalquilo C_{1-3}; haloalcoxilo C_{1-3}; alquilo C_{1-6}; cicloalquilo C_{3-6} opcionalmente sustituido por un sustituyente seleccionado a partir del grupo que consta de: ciano, alquilo C_{1-3}, y alcoxilo C_{1-3}; fenilo opcionalmente sustituido por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: flúor, cloro, metilo, ciano, y metoxilo; y heteroarilo de 5-6 miembros opcionalmente sustituido por uno o dos grupos de metilo; o una sal farmacéuticamente aceptable del mismo.

16. El compuesto según la reivindicación 15 en donde R^6 es 1,3,4-oxadiazolilo opcionalmente sustituido o 1,2,4-oxadiazolilo opcionalmente sustituido; o una sal farmacéuticamente aceptable del mismo.

17. El compuesto según la reivindicación 14 en donde R^6 es sustituido por un grupo $-CH_2R^a$, $-C(O)R^a$, $-NHC(O)R^a$, $-NHC(O)R^b$, $-C(O)NHR^a$, $C(O)NHR^b$, $-OR^a$, $-NR^aR^b$, $-SO_2NR^bR^b$, $-SO_2R^a$, o $-SO_2R^b$; o una sal farmacéuticamente aceptable del mismo.

18. El compuesto según la reivindicación 17 en donde R^a es

(a) fenilo opcionalmente sustituido por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de flúor, cloro y bromo;

(b) heteroarilo de 5-6 miembros opcionalmente sustituido;

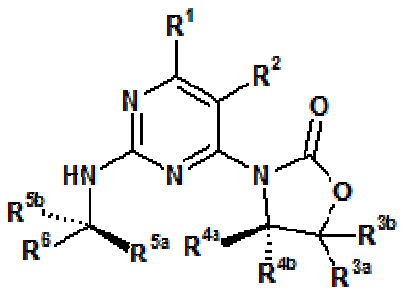
(c) cicloalquilo C_{5-7} opcionalmente sustituido por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de flúor, hidroxilo, metilo, y haloalcoxilo C_{1-3}; o

(d) un grupo heterocíclico seleccionado a partir del grupo que consta de: piperidinilo, piperazinil, morfolinilo, tetrahidropiranil, tetrahidro-tiopiran1,1-dióxido, 1,4-diazepanil, 4,7-diaza-spiro[2.5]octanil, 3,8-diaza-biciclo[3.2.1]octanil, 3,8-diaza-biciclo[4.2.0]octanil, octahidro-pirrolo[1,2-a]pirazinilo, octahidro-pirido[1,2-a]pirazinilo, octahidro-pirrolo[3,4-c]pirrolilo, y 5,6,7,8-tetrahidro-imidazo[1,2-a]pirazinilo cada uno de los cuales es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: hidroxilo, flúor, amino, dimetilamino, haloalcoxilo C_{1-3}, alquilo C_{1-3}, y cicloalquilo C_{3-5}; o una sal farmacéuticamente aceptable del mismo.

19. El compuesto según la reivindicación 18 en donde R^6 es fenilo opcionalmente sustituido; o una sal farmacéuticamente aceptable del mismo.

20. El compuesto según la reivindicación 19 en donde el fenilo es sustituido por un grupo $–CH_2R^a$, $-C(O)R^a$, o $-C(O)NHR^a$ en la posición para; o una sal farmacéuticamente aceptable del mismo.

21. El compuesto según la reivindicación 2 de la Fórmula (V)



(V);

en donde R^{4a} es fenilo y R^{4b} es hidrógeno; o una sal farmacéticamente aceptable del mismo

22. El compuesto según la reivindicación 1 seleccionado a partir del grupo que consta de:

(S)-4-isopropi-3-(2-(((S)-1-(4-(2-il)fenil)etil)amino)pirimidin-4-il)oxazolidin-2-ona;

N-(4-((S)-1-(4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)fenil)ciclohexanocarboxamida;

(S)-3-(2-(((S)-1-(3-fluoro-4-((4-metilpiperazin-1-il)metil)fenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-4-isopropil-3-(2-(((S)-1-(4-((3,3,4-trimetilpiperazin-1-il)metil)fenil)etil)amino)pirimidin-4-il)oxazolidin-2-ona;

2-fluoro-N-(4-hidroxi-4-metilciclohexil)-4-((S)-1-((4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-il)amino)etil)benzamida;

(S)-3-(2-((S)-1-(4-((4-amino-4-metilpiperidin-1-il)metil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(2-((S)-1-(4-((4-(dimetilamino)piperidin-1-il)metil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-4-isopropil-3-(2-((S)-1-(4-((4-metilpiperazin-1-il)metil)fenil)etilamino)pirimidin-4-il)oxazolidin-2-ona;

(S)-4-isopropil-4-metil-3-(2-((S)-1-(4-((4-metilpiperazin-1-il)metil)fenil)etilamino)pirimidin-4-il)oxazolidin-2-ona;

(S)-4-isopropil-3-(2-((S)-1-(6-fenilpiridin-3-il)etilamino)pirimidin-4-il)oxazolidin-2-ona;

(S)-3-(2-((S)-1-(4-benzoilfenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-4-isopropil-3-(2-(((S)-1-(5-fenil-1,3,4-tiadiazol-2-il)etil) amino) pirimidin-4-il)oxazolidin-2-ona;

(4S)-4-isopropil-3-(2-(1-(5-fenilpirimidin-2-il)etilamino)pirimidin-4-il)oxazolidin-2-ona;

3-(5-fluoro-2-((1-(5-(4-fluoro-3-metilfenil)piridin-2-il)etil)amino)pirimidin-4-il)oxazolidin-2-ona;

(S)-4-isopropil-3-(2-(((S)-1-(1-(3-metoxifenil)-1H-pirazol-4-il)etil)amino)pirimidin-4-il)oxazolidin-2-ona;

(S)-3-(2-(((S)-1-(5-(4-fluorofenil)-1,3,4-oxadiazol-2-il)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(2-(((S)-1-(3-(4-clorofenil)-1,2,4-oxadiazol-5-il)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-4-isopropil-3-(2-(((S)-1-(3-(m-tolil)-1,2,4-oxadiazol-5-il)etil)amino)pirimidin-4-il)oxazolidin-2-ona;
(S)-3-(2-(((S)-1-(3-(4-fluorofenil)-1,2,4-oxadiazol-5-il)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(5-(4-fluoro-2-metilfenil)pirimidin-2-il)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-4-Isopropil-3-{2-[(3-p-tolil-[1,2,4]oxadiazol-5-ilmetil)-amino]-pirimidin-4-il}-oxazolidin-2-ona;
(S)-4-isopropil-3-(2-((S)-1-(4-(1-metil-1H-pirazol-4-il)fenil)etilamino)pirimidin-4-il)oxazolidin-2-ona;
(S)-3-(2-((S)-1-(2-fluoro-4-isopropilfenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(4-isobutoxi-3-metilfenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-(((S)-1-(4-isobutoxifenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(5-fluoro-2-(((S)-1-(4-isobutoxifenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
2-fluoro-N-(*trans*-4-hidroxiciclohexil)-4-((S)-1-(4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)benzamida;
(S)-3-(5-fluoro-2-((S)-1-(3-fluoro-4-(piperidina-1-carbonil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
N-ciclohexil-2-fluoro-4-((S)-1-(5-fluoro-4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)benzamida;
N-ciclohexil-2-fluoro-4-((S)-1-(4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)benzamida; y
(S)-3-(5-fluoro-2-((S)-1-(2-fluoro-4-(trifluorometil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona; o una sal farmacéuticamente aceptable del mismo.

23. El compuesto según la reivindicación 1 seleccionado a partir del grupo que consta de:
(S)-3-(2-(((S)-1-(3-fluoro-4-((3,3,4-trimetilpiperazin-1-il)metil)fenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-(((S)-1-(4-((4,4-difluoropiperidin-1-il)metil)fenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(5-fluoro-2-(1-(4-fenoxifenil)etilamino)pirimidin-4-il)oxazolidin-2-ona;
(S)-3-(2-((S)-1-(4-(4-fluorofenoxi)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(4-(((2S,6R)-2,6-dimetilmorfolino)metil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-(((S)-1-(3-(4-clorofenil)-1,2,4-oxadiazol-5-il)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-(((S)-1-(5-(4-clorofenil)-1,2,4-oxadiazol-3-il)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(5-(4-fluoro-3-metilfenil)piridin-2-il)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(5-(4-fluorofenoxi)pirimidin-2-il)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(5-(4-fluorofenoxi)pirazin-2-il)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-4-isopropil-3-(2-((S)-1-(5-(3-(trifluorometil)fenil)pirimidin-2-il)etilamino)pirimidin-4-il)oxazolidin-2-ona; y
(S)-3-(2-((S)-1-(5-(4-fluoro-3-metilfenil)pirimidin-2-il)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona; o una sal farmacéuticamente aceptable del mismo.

24. El compuesto según la reivindicación 1 seleccionado del grupo que consta de:
(S)-3-(2-(1-(3-(4-clorofenil)-1,2,4-oxadiazol-5-il)etilamino)-5-fluoropirimidin-4-il)-4,4-dimetiloxazolidin-2-ona;
(S)-3-(6-cloro-2-(1-(3-(4-clorofenil)-1,2,4-oxadiazol-5-il)etilamino)pirimidin-4-il)oxazolidin-2-ona;
(S)-3-(2-((S)-1-(2-fluoro-4-(1-metilciclopropil) fenil) etilamino) pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(2-fluoro -4-(trifluorometil) fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
2-cloro-N-ciclopentil-4-((S)-1-(4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)benzamida;
(S)-3-(2-((S)-1-(4-((3,3-difluoropiperidin-1-il)metil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;

(S)-3-(2-((S)-1-(4-(4,7-diazaspiro[2.5]octan-4-ilmetil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-((S)-1-(4-((4-acetilpiperazin-1-il)metil)fenil)etilamino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(2-(((S)-1-(4-isobutoxifenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona;
(S)-3-(5-fluoro-2-(((S)-1-(4-isobutoxifenil)etil)amino)pirimidin-4-il)-4-isopropiloxazolidin-2-ona; y
2-fluoro-N-(trans-4-hidroxiciclohexil)-4-((S)-1-(4-((S)-4-isopropil-2-oxooxazolidin-3-il)pirimidin-2-ilamino)etil)benzamida; o una sal farmacéuticamente aceptable del mismo.

25. El compuesto según la reivindicación 1 en donde

cada R^1 y R^2 es independientemente hidrógeno, deuterio, halo, hidroxilo, NH_2, arilo, heteroarilo, o alquilo C_{1-4} opcionalmente sustituido,

en donde dicho alquilo C_{1-4} es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, y NH_2;

R^{3a} es hidrógeno, deuterio, alquilo C_{1-6}, fenilo, o bencilo y

R^{3b} es hidrógeno, deuterio, o alquilo C_{1-6}; o

R^{3a} y R^{3b} se unen juntos formando un anillo cicloalquilo de 3-7 miembros opcionalmente sustituido o un anillo heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dichos anillos cicloalquilo y heterocíclico son cada uno opcionalmente sustituido por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3};

R^{4a} es hidrógeno, alquilo C_{1-6}, fenilo opcionalmente sustituido, bencilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o metileno-dibenceno,

en donde dicho fenilo, bencilo, y anillos de heteroarilo son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3},

haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, fenoxilo, $COOR^b$, SO_2R^b, $NHC(O)R^b$, y NR^bR^b y

R^{4b} es hidrógeno, deuterio, o alquilo C_{1-3}; o

R^{4a} y R^{4b} se unen juntos formando un anillo cicloalquilo de 3-7 miembros opcionalmente sustituido o un anillo heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dichos anillos cicloalquilo y heterocíclico son opcionalmente sustituidos por uno o dos sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3},

siempre que solo uno entre R^{3a} y R^{3b} y R^{4a} y R^{4b} se unan juntos formando un anillo;

R^{5a} es hidrógeno o deuterio;

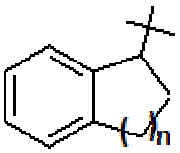
R^{5b} es hidrógeno, deuterio, metilo, etilo, CD_3, CF_3, CH_2F, o CHF_2 y

R^6 es alquilo C_{1-6} opcionalmente sustituido, arilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heterocíclico opcionalmente sustituido, o cicloalquilo C_{5-10} opcionalmente sustituido,

en donde dicho alquilo C_{1-6} es opcionalmente sustituido por un sustituyente seleccionado a partir del grupo que consta de hidroxilo, alcoxilo C_{1-3} y $–OR^a$;

en donde dicho arilo, heteroarilo, heterocíclico y cicloalquilo C_{5-10} son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo; hidroxilo; ciano; nitro; alcoxilo C_{1-3}; haloalquilo C_{1-3}; haloalcoxilo C_{1-3}; alquilo C_{1-6}; cicloalquilo C_{3-6}; fenilo opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, fenoxilo, $COOR^b$, SO_2R^b, $NHC(O)R^b$, y NR^bR^b; heteroarilo de 5-6 miembros; heterocíclico de 5-6 miembros opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir

del grupo que consta de: halo, hidroxilo, oxo, NH_2, y alquilo C_{1-3}; $-CH_2R^a$; $-OR^a$; $-C(O)R^a$; $-NR^aR^b$; $-COOR^a$; $–SO_2R^a$; $NHC(O)R^a$; y $-SO_2NR^bR^b$; o

R^{5b} y R^6 se unen juntos formando un grupo cicloalquilo C_{3-7} opcionalmente sustituido o un grupo opcionalmente sustituido de la Fórmula (a):  (a),

en donde n es 1, 2, o 3 y

dicho cicloalquilo C_{3-7} y grupo de la Fórmula (a) son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de: halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, alquilo C_{1-6}, cicloalquilo C_{3-6}, heteroarilo de 5-6 miembros, heterocíclico de 5-6 miembros, benciloxilo, $COOR^b$, SO_2R^b, $NHC(O)R^b$, y NR^bR^b;

cada R^a es independientemente fenilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o heterocíclico de 4-7 miembros opcionalmente sustituido,

en donde dicho fenilo y heteroarilo son opcionalmente sustituidos por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de halo, hidroxilo, ciano, nitro, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, y alquilo C_{1-3},

en donde dicho heterocíclico de 4-7 miembros es opcionalmente sustituido por uno a tres sustituyentes cada uno independientemente seleccionado a partir del grupo que consta de halo, hidroxilo, oxo, alcoxilo C_{1-3}, haloalquilo C_{1-3}, haloalcoxilo C_{1-3}, y alquilo C_{1-3}; y

cada R^b es independientemente hidrógeno o alquilo C_{1-6}; o una sal farmaceuticamente aceptable del mismo.

26. El compuesto según la reivindicación 25 en donde

R^1 es hidrógeno, flúor, cloro, o metilo;

R^2 es hidrógeno;

R^{3a} es hidrógeno, metilo, o fenilo;

R^{3b} es hidrógeno o metilo;

R^{4a} es hidrógeno, C_{1-4} alquilo, fenilo opcionalmente sustituido, bencilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o metileno-dibenceno;

R^{4b} es hidrógeno o metilo;

R^{5a} es H; y

R^{5b} es hidrógeno, metilo, etilo, o CF_3; o una sal farmacéuticamente aceptable del mismo.

27. El compuesto según la reivindicación 26 en donde R^6 es isopropilo, arilo opcionalmente sustituido, pirazolilo opcionalmente sustituido, piridinilo opcionalmente sustituido, 2,3-dihidrobenzofuranil, 2,3-dihidrobenzo[b][1,4]dioxinilo, o cicloalquilo C_{5-10} opcionalmente sustituido; o una sal farmacéuticamente aceptable del mismo.

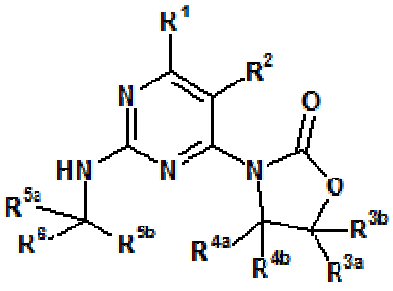
28. Una composición farmacéutica que comprende un compuesto según la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y un vehículo o excipiente farmacéuticamente aceptable.

29. Un método para el tratamiento de una enfermedad o trastorno asociado con una proteína IDH mutante que tiene una actividad neomorfica que comprende la administración de una cantidad terapéuticamente eficaz de un compuesto según la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, a un sujeto en necesidad del mismo.

30. Un método para el tratamiento de una enfermedad o trastorno asociado con una proteína IDH mutante que tiene una actividad neomorfica que comprende la administración de una cantidad terapéuticamente eficaz de un compuesto según la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y otro agente terapéutico a un sujeto en necesidad del mismo.

RESUMEN

La invención se refiere a un compuesto de la fórmula (I)



(I)

ó una sal farmacéuticamente aceptable del mismo, en donde R^1-R^6 son como se definen en la presente. La invención también se refiere a composiciones que contienen un compuesto de la fórmula (I) y al uso de tales compuestos en la inhibición de proteínas IDH mutantes que tienen una actividad neomórfica. La invención se refiere además al uso de un compuesto de la Fórmula (I) en el tratamiento de enfermedades o trastornos asociados con tales proteínas IDH mutantes incluyendo pero sin limitar a, trastornos de proliferación celular, como el cáncer.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

MADDEN, Laura
Novartis Pharma AG
Patent Department
CH-4002 Basel
SUISSE

Date of mailing *(day/month/year)*
03 December 2012 (03.12.2012)

Applicant's or agent's file reference
54800-WO-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/IB2012/055133

International filing date *(day/month/year)*
26 September 2012 (26.09.2012)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

LEI, Huangshu
No. 565, Tushan Rd., Nan'an District
Chongqing 400061
China

State of Nationality: CA
State of Residence: CN
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

LEI, Huangshu
No. 565, Tushan Rd., Nan'an District
Chongqing 400061
China

State of Nationality: US
State of Residence: CN
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

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
Martinez Sandrine
e-mail ro.ib@wipo.int
Telephone No. +4122 338 9741

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 54800-WO-PCT	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/IB2012/055133	International filing date *(day/month/year)* 26/09/2012	(Earliest) Priority Date *(day/month/year)* 27/09/2011
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 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [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. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/055133

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 C07D413/14 C07D417/14 C07D471/04 C07D487/04
C07D498/10 C07D513/04 A61K31/506 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/080937 A1 (BASF SE [DE]; NAVE BARBARA [DE]; HARMSEN SVEN [DE]; MUELLER BERND [DE]) 10 July 2008 (2008-07-10) page 44; claims 1-4, 12, 14; table B	1-30
A	WO 01/60816 A1 (AMGEN INC [US]) 23 August 2001 (2001-08-23) page 3, line 29; example 5; compound 25	1-30
A	WO 2010/090290 A1 (NIPPON SHINYAKU CO LTD [JP]; FUJIHARA HIDETAKA [JP]; ASAKI TETSUO [JP]) 12 August 2010 (2010-08-12) use against cancer mentioned in some claims; page 204; example 67	1-30

☐ 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
12 December 2012	19/12/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Stroeter, Thomas

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/055133

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008080937 A1	10-07-2008	AR 064571 A1	08-04-2009
		CL 38472007 A1	18-04-2008
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		CN 102307869 A	04-01-2012
		EP 2394999 A1	14-12-2011
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		US 2011288065 A1	24-11-2011
		WO 2010090290 A1	12-08-2010