SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-001857- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 12-001857- -00000-0000

Fecha: 2012-01-05 16:55:32 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1164

Industria y C
SUPERINTEN

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** _____

54. **TÍTULO** COMPUESTOS PARA LA REDUCCION DE PRODUCCION DE β-AMILOIDE

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** BRISTOL-MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS

74. **APODERADO** ALVARO CORREA ORDOÑEZ

22. **BOGOTÁ, D. C.,** ENERO 04, 2012

(FORMA P-10)

115198-Imprenta Nacional de Colombia-2011

PETITOR

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

Fecha: 2012-01-05 16:55:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Follos: 1164

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOI
PCT
ENTRADA EN FASI

(1) **SOLICITUD DE :**

[X] Patente de Invención [ ] Patente de Modelo de Utilidad
[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE** (71)	Nombre: **BRISTOL-MYERS SQUIBB COMPANY** Dirección: Route 206 and Province Line Road Princeton, New Jersey 08543-4000, U.S.A. Nacionalidad o Domicilio: Estados Unidos de América Lugar de Constitución: Estados Unidos de América Teléfono: Fax: E-Mail	**IDENTIFICACION** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual Número
(3) **REPRESENTANTE O APODERADO**	Nombre: ALVARO CORREA ORDOÑEZ Dirección: Avenida 82 No. 10-62 Piso 6 Teléfono: 6341500 Fax: 3762211 E-Mail: office.bogota@bakermckenzie.com	**IDENTIFICACION** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual Número 79.143.366 Usaquén TP 20281
(4) **INVENTOR (ES)** (72)	Nombre: BOY, Kenneth M.; GUERNON, Jason M.; MACOR, John E.; OLSON, Richard E.; SHI, Jianliang; THOMPSON, III, Lorin A.; WU, Yong-Jin; XU, Li; ZHANG, Yunhui; ZUEV, Dmitry S. Dirección: Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US); Bristol-Myers Squibb Company 5 Research Parkway Wallingford, CT 06492 (US) Nacionalidad o Domicilio: Estados unidos de América(Respectivamente)	

(5) **PCT (85)**

Solicitud Internacional No.	PCT/US2010/043487	Fecha	28-07-2010
Publicación Internacional No.	WO2011/014535	Fecha	03-02-2011

(6) **Título (54)** COMPUESTOS PARA LA REDUCCION DE PRODUCCION DE β-AMILOIDE

(7) **Clasificación Internacional (51)** A61K 31/517; A61K 31/519; A61K 31/5377; C07D 239/70; C07D 401/12; C07D 401/14; C07D 403/12; C07D 403/14; C07D 407/12, C07D 413/14; C07D 417/12; C07D 471/04 ; C07D 491/052 ; C07D 491/08; C07D 491/113

(8) **Prioridad** SI [X] NO [ ]

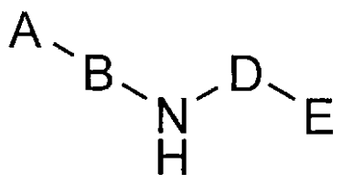
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	31-07-2009	61/167,989
US	14-04-2010	61/324,201

(9) **Comprobante de pago No.** 11-0079886 – 11-111602 – 11-111652 – 11-111722 – 11-125724 – 11-111603 – 11-111651 – 11-111676 **Fecha** 18-08-11 – 16-11-11 – 26-12-11

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [X] Documento de cesión del inventor al solicitante o a su causante
- [X] Declaraciones
- [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: Extractos

(11) **FIGURA CARATERISTICA**



(I),

(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página


RECIBO DE PAGO

2011/013 3

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0079886

Bogotá D.C., Agosto 18 de 2011 - 16:59:22

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	411692035	17/08/2011	82.279.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	9.000.00	9.000.00
				$9.000.00

SON: **NUEVE MIL PESOS MONEDA CORRIENTE***

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

Fecha: 2012-01-05 16:55:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1164

2011/018 4

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 111602

Bogotá D.C., Noviembre 16 de 2011 - 17:33:43

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325105933	16/11/2011	113.696.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	10.000.00	10.000.00
				$10.000.00

SON: **DIEZ MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

Fecha: 2012-01-05 16:55:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1164

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 111652

Bogotá D.C., Noviembre 16 de 2011 - 17:33:43

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325105933	16/11/2011	113.695.000.00

*** Conceptos Pagados ***

CANT	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-08 PRORROGA DE TERMINOS	1608 N.CREACION PRORROGA DE TERMINOS O PLAZO ADICIONAL	86.000.00	86.000.00
				$86.000.00

SON: **OCHENTA Y SEIS MIL PESOS MONEDA CORRIENTE***

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

Fecha: 2012-01-05 16:55:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1164

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 111722

Bogotá D.C., Noviembre 16 de 2011 - 17:33:43

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325105933	16/11/2011	113.695.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD DE INVENSION	485.000.00	485.000.00
				$485.000.00

SON: **CUATROCIENTOS OCHENTA Y CINCO MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000
Fecha: 2012-01-05 16:55:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1164

7

2011/020

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 125724

Bogotá D.C., Diciembre 26 de 2011 - 16:52:26

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325065753	26/12/2011	73.455.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	21 CERTIFICACIONES	14.000.00	14.000.00
				$14.000.00

SON: **CATORCE MIL PESOS MONEDA CORRIENTE*

Responsable: _____
- -

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000
Fecha: 2012-01-05 16:55:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1164

2011/018 8

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 111603

Bogotá D.C., Noviembre 16 de 2011 - 17:33:43

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325105933	16/11/2011	113.695.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	10.000.00	10.000.00
				$10.000.00

SON: **DIEZ MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000
Fecha: 2012-01-05 16:55:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1164

2011/018 9

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 111651

Bogotá D.C., Noviembre 16 de 2011 - 17:33:43

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325105933	16/11/2011	113.685.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-08 PRORROGA DE TERMINOS	1608 N.CREACION PRORROGA DE TERMINOS O PLAZO ADICIONAL	86.000.00	86.000.00
				$86.000.00

SON: **OCHENTA Y SEIS MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-*****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000
Fecha: 2012-01-05 16:55:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1164

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
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Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 111676

Bogotá D.C., Noviembre 16 de 2011 - 17:33:43

RECIBIDO DE : BAKER & MCKENZIE NI 900.034.906

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	325105933	16/11/2011	113.695.000.00

*** Conceptos Pagados ***

CANT	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	83 INVOCACION DE UNA PRIORIDAD EN SIGNOS DISTINTIVOS	160.000.00	160.000.00
				$160.000.00

SON: **CIENTO SESENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000
Fecha: 2012-01-05 16:55:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII I Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1164


EXTRACTOS

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional: A61K 31/517; A61K 31/519; A61K 31/5377; C07D 239/70; C07D 401/12; C07D 401/14; C07D 403/12; C07D 403/14; C07D 407/12, C07D 413/14; C07D 417/12; C07D 471/04 ; C07D 491/052 ; C07D 491/08; C07D 491/113

(71)Solicitante(s): **BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es): BOY, Kenneth M.; GUERNON, Jason M.; MACOR, John E.; OLSON, Richard E.; SHI, Jianliang; THOMPSON, III, Lorin A.; WU, Yong-Jin; XU, Li; ZHANG, Yunhui; ZUEV, Dmitry S.

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/230,202	31-07-2009	US
	61/324,201	14-04-2010	US

(85) Fecha inicio fase nacional: 29-02-2012

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 28-07-2010
No. de solicitud: PCT/US2010/043487

(87) Publicación internacional
Fecha: 03-02-2011
N° publicación: WO2011/014535

(54) Titulo: COMPUESTOS PARA LA REDUCCION DE PRODUCCION DE β-AMILOIDE

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMATICO

SUPERINTENDENCIA PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional: A61K 31/517; A61K 31/519; A61K 31/5377; C07D 239/70; C07D 401/12; C07D 401/14; C07D 403/12; C07D 403/14; C07D 407/12, C07D 413/14; C07D 417/12; C07D 471/04 ; C07D 491/052 ; C07D 491/08; C07D 491/113

(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es): BOY, Kenneth M.; GUERNON, Jason M.; MACOR, John E.; OLSON, Richard E.; SHI, Jianliang; THOMPSON, III, Lorin A.; WU, Yong-Jin; XU, Li; ZHANG, Yunhui; ZUEV, Dmitry S.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

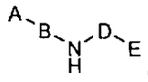
(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/230,202	31-07-2009	US
	61/324,201	14-04-2010	US

(85) Fecha límite inicio fase nacional: 29-02-2012
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud 28-07-2010
No. de solicitud: PCT/US2010/043487

(87) Publicación internacional:
Fecha: 03-02-2011
No. Publicación: WO2011/014535

(54) Titulo: COMPUESTOS PARA LA REDUCCION DE PRODUCCION DE β-AMILOIDE

(57) Resumen: La presente revelación proporciona una serie de compuestos de fórmula (I)



(I),

que modulan producción de péptido β-amiloide (β-AP) y son útiles en el tratamiento de Enfermedad de Alzheimer y de otras afecciones afectadas por la producción de péptido β-amiloide (β-AP).

CONTINUA AL RESPALDO ...

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad

(31) *No.*	32) *Fecha*	(33) *País*
61/230,202	31-07-2009	US
61/324,201	14-04-2010	US

(51) Int Cl: A61K 31/517; A61K 31/519; A61K 31/5377; C07D 239/70; C07D 401/12; C07D 401/14; C07D 403/12; C07D 403/14; C07D 407/12, C07D 413/14; C07D 417/12; C07D 471/04 ; C07D 491/052 ; C07D 491/08; C07D 491/113

(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

(72)Inventor(es): BOY, Kenneth M.; GUERNON, Jason M.; MACOR, John E.; OLSON, Richard E.; SHI, Jianliang; THOMPSON, III, Lorin A.; WU, Yong-Jin; XU, Li; ZHANG, Yunhui; ZUEV, Dmitry S.

(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

(85) Fecha limite inicio fase nacional: 29-02-2012

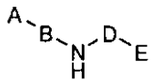
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 28-07-2010
No. de solicitud PCT/US2010/043487

(87) Publicación internacional
Fecha: 03-02-2011
N° publicación: WO2011/014535

(54) Titulo: COMPUESTOS PARA LA REDUCCION DE PRODUCCION DE β-AMILOIDE

RESUMEN:

La presente revelación proporciona una serie de compuestos de fórmula (I)



(I),

que modulan producción de péptido β-amiloide (β-AP) y son útiles en el tratamiento de Enfermedad de Alzheimer y de otras afecciones afectadas por la producción de péptido β-amiloide (β-AP).

COPIA SOLICITUD
INTERNACIONAL

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 February 2011 (03.02.2011)

PCT

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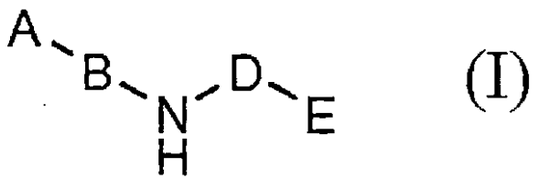
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(54) Title: COMPOUNDS FOR THE REDUCTION OF β-AMYLOID PRODUCTION



(I)

(57) Abstract: The present disclosure provides a series of compounds of the formula (I) which modulate β-amyloid peptide (β-AP) production and are useful in the treatment of Alzheimer's Disease and other conditions affected by β-amyloid peptide (β-AP) production.

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COMPOUNDS FOR THE REDUCTION OF β-AMYLOID PRODUCTION

FIELD OF THE INVENTION

The present disclosure relates to methods of treating Alzheimer's Disease (AD) and other conditions related to β-amyloid production using compounds which are inhibitors of β-amyloid peptide (Aβ) production. The disclosure further relates to pharmaceutical compositions comprising these compounds.

BACKGROUND OF THE INVENTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease which begins with memory loss and progresses to include severe cognitive impairment, altered behavior, and decreased motor function (Grundman, M. *et al., Arch Neurol.* (2004) 61: 59-66; Walsh, D.M. *et al., Neuron* (2004) 44: 181-193). It is the most common form of dementia and represents the third leading cause of death after cardiovascular disorders and cancer. The cost of AD is enormous and includes the suffering of the patients and families and the lost productivity of patients and caregivers. No treatment that effectively prevents AD or reverses the clinical symptoms and underlying pathophysiology is currently available.

A definitive diagnosis of AD for a demented patient requires a histopathological evaluation of the number and localization of neuritic plaques and neurofibrillary tangles upon autopsy (Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. *Neurobiol Aging* (1997) 18: S1-2). Similar alterations are observed in patients with Trisomy 21 (Down syndrome). Plaques primarily consist of β-amyloid (Aβ) peptides that are formed by a stepwise proteolytic cleavage of the amyloid precursor protein (APP) by β-site APP-cleaving enzyme (BACE), to generate the N-terminus, and γ-secretase, to generate the C-terminus (Selkoe, D.J., *Physiol Rev.* (2001) 81: 741-766). γ-Secretase is a transmembrane protein complex that includes Nicastrin, Aph-1, PEN-2, and either Presenilin-1 (PS-1) or Presenilin-2 (PS-2) (Wolfe, M.S. *et al., Science* (2004) 305: 1119-1123). PS-1 and PS-2 are believed to contain the catalytic sites of γ-secretase.

Aβ40 is the most abundant form of Aβ synthesized (80-90%), while Aβ42 is most closely linked with AD pathogenesis. In particular, mutations in the APP, PS-1, and PS-2 genes that lead to rare, familial forms of AD implicate Aβ42 aggregates as the primary

toxic species (Selkoe, D.J., *Physiol Rev.*, (2001) 81: 741-766). Current evidence suggests that oligomeric, protofibrillar and intracellular Aβ42 play a significant role in the disease process (Cleary, J.P. *et al., Nat Neurosci.* (2005) 8: 79-84). Inhibitors of the enzymes that form Aβ42, such as γ-secretase, represent potential disease-modifying therapeutics for the treatment of AD.

Evidence suggests that a reduction in brain Aβ levels by inhibition of γ-secretase may prevent the onset and progression of AD (Selkoe, D. *Physiol. Rev.* (2001) 81: 741-766; Wolfe, M., *J. Med. Chem.* (2001) 44: 2039-2060). There are emerging data for the role of Aβ in other diseases, including mild cognitive impairment (MCI), Down syndrome, cerebral amyloid angiopathy (CAA), dementia with Lewy bodies (DLB), amyotrophic lateral sclerosis (ALS-D), inclusion body myositis (IBM), and age-related macular degeneration. Advantageously, compounds that inhibit γ-secretase and reduce production of Aβ could be used to treat these or other Aβ-dependent diseases.

Excess production and/or reduced clearance of Aβ causes CAA (Thal, D. *et al., J. Neuropath. Exp. Neuro.* (2002) 61: 282-293). In these patients, vascular amyloid deposits cause degeneration of vessel walls and aneurysms that may be responsible for 10-15% of hemorrhagic strokes in elderly patients. As in AD, mutations in the gene encoding Aβ lead to an early onset form of CAA, referred to as cerebral hemorrhage with amyloidosis of the Dutch type, and mice expressing this mutant protein develop CAA that is similar to patients. Compounds that reduce Aβ levels could reduce or prevent CAA.

DLB manifests with visual hallucinations, delusions, and parkinsonism. Interestingly, familial AD mutations that cause Aβ deposits can also cause Lewy bodies and DLB symptoms (Yokota, O. *et al., Acta Neuropathol (Berl)* (2002) 104: 637-648). Further, sporadic DLB patients have Aβ deposits similar to those in AD (Deramecourt, V. *et al., J Neuropathol Exp Neurol* (2006) 65: 278-288). Based on this data, Aβ likely drives Lewy body pathology in DLB and, therefore, compounds that reduce Aβ levels could reduce or prevent DLB.

Approximately 25% of ALS patients have significant dementia or aphasia (Hamilton, R.L. *et al., Acta Neuropathol (Berl)* (2004) 107: 515-522). The majority (~60%) of these patients, designated ALS-D, contain ubiquitin-positive inclusions comprised primarily of the TDP-43 protein (Neumann, M. *et al., Science* (2006) 314: 130-133). About 30% of the ALS-D patients have amyloid plaques consistent with Aβ

causing their dementia (Hamilton, R.L. *et al., Acta Neuropathol (Berl)* (2004) 107: 515-522). These patients should be identifiable with amyloid imaging agents and potentially could be treated by compounds that reduce Aβ levels.

IBM is a rare, age-related degenerative disease of skeletal muscle. The appearance of Aβ deposits in IBM muscle and the recapitulation of several aspects of the disease by directing APP overexpression to muscle in transgenic mice support the role of Aβ in IBM (reviewed in Murphy, M.P. *et al., Neurology* (2006) 66: S65-68). Compounds that reduce Aβ levels could reduce or prevent IBM.

In age-related macular degeneration, Aβ was identified as one of several components of drusen, extracellular deposits beneath the retinal pigment epithelium (RPE) (Anderson, D.H. *et al., Exp Eye Res* (2004) 78: 243-256). A recent study has shown potential links between Aβ and macular degeneration in mice (Yoshida, T. *et al., J Clin Invest* (2005) 115: 2793-2800). Increases in Aβ deposition and supranuclear cataracts have been found in AD patients (Goldstein, L.E. *et al., Lancet* (2003) 361: 1258-1265). Compounds that reduce Aβ levels could reduce or prevent age-related macular degeneration.

Compounds which inhibit gamma secretase may also be useful in treating conditions associated with loss of myelination, for example multiple sclerosis (Watkins, T.A., *et al.*, Neuron (2008) 60: 555-569).

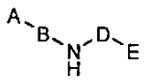
A recent study by Georgetown University Medical Center researchers suggests that gamma-secretase inhibitors may prevent long-term damage from traumatic brain injury (Loane, D. J., *et al., Nature Medicine* (2009): 1-3).

A logical approach to reducing Aβ levels is to block the action of the secretases. A complementary approach is to selectively reduce production of Aβ1-42 by the action of certain compounds that serve to direct the γ-secretase-mediated cleavage of APP to instead produce shorter forms of Aβ. These shorter forms appear to aggregate less easily and solutions of the shorter forms of Aβ are less neurotoxic than solutions of Aβ1-42 (See Barten, Donna M.; Meredith, Jere E., Jr.; Zaczek, Robert; Houston, John G.; Albright, Charles F. *Drugs in R&D* (2006), 7(2), 87-97). Thus, compounds that selectively reduce Aβ1-42 production and their pharmaceutical compositions are beneficial agents that will prevent damage from overproduction of Aβ and are useful in treating Alzheimer's disease, Down syndrome, CAA, and inclusion body myositis, DLB, and

other disorders where Aβ is overproduced.

SUMMARY OF THE INVENTION

In its first aspect the present disclosure provides a compound of formula (I)



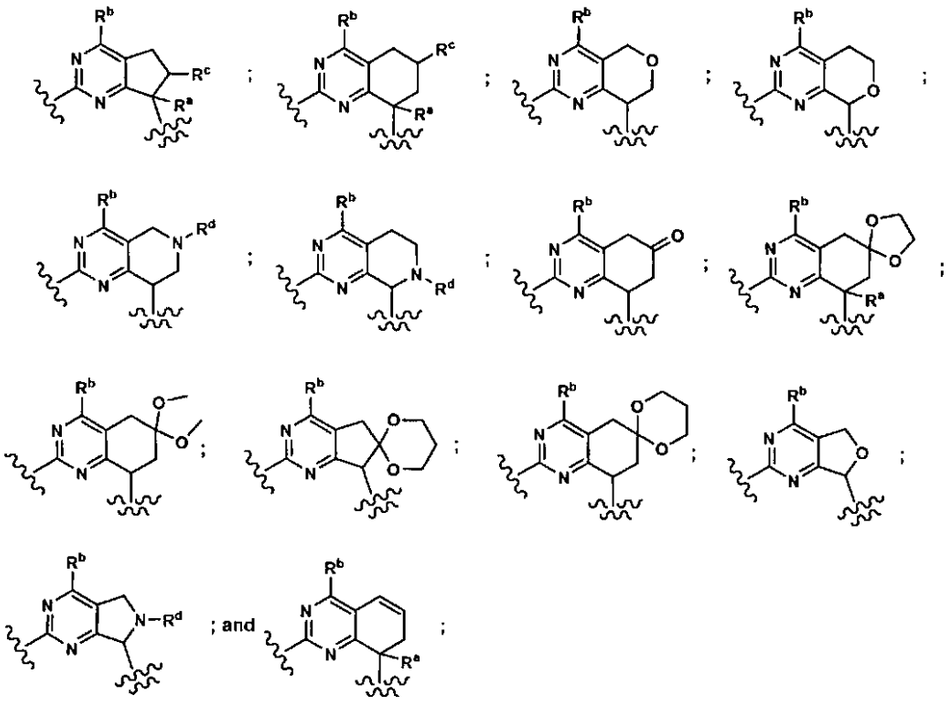
(I),

or a pharmaceutically acceptable salt thereof, wherein

A is a five- or six-membered heteroaromatic ring containing from one to three heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said heteroaromatic ring is optionally substituted with one or two groups selected from halo, halo$C_{1\text{-}6}$alkyl, hydroxy, amino, $C_{1\text{-}6}$alkoxy, and $C_{1\text{-}6}$alkyl;

B is selected from phenyl and pyridinyl, wherein the phenyl and pyridinyl are optionally substituted with one or two substituents independently selected from $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$alkyl, $C_{1\text{-}3}$alkylamino-$C_{1\text{-}6}$alkoxy, cyano, $C_{1\text{-}3}$dialkylamino-$C_{1\text{-}6}$alkoxy, halo, halo$C_{1\text{-}6}$alkoxy, halo$C_{1\text{-}6}$alkyl, hydroxy, methylamino, and amino;

D is selected from



"  " denotes the point of attachment to the nitrogen atom of the parent molecule;

"  " denotes the point of attachment to the 'E' moiety;

R^a is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, and hydroxy;

R^b is $-NR^xR^y$, wherein R^x and R^y are independently selected from hydrogen, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, (C_{3-7}cycloalkyl)C_{1-4}alkyl, hydroxyC_{1-4}alkyl, and trideuteromethyl, wherein the alkyl part of the (C_{3-7}cycloalkyl)C_{1-4}alkyl can be optionally substituted with a C_{1-4}alkoxy group; or, R^x and R^y, together with the nitrogen atom to which they are attached, form a four- to seven-membered monocyclic or bicyclic ring optionally containing one double bond and optionally containing one additional heteroatom selected from O, NR^z, and S; wherein R^z is selected from hydrogen, C_{1-6}alkyl, and C_{1-4}alkoxycarbonyl; and wherein the ring is optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkyl, halo, haloC_{1-4}alkyl, hydroxy, $-NR^fR^g$, oxo, spirocyclic dioxolanyl; wherein R^f and R^g are independently selected from hydrogen, C_{1-4}alkoxycarbonyl, and C_{1-6}alkyl;

R^c is selected from hydrogen, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfonylamido, amino, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{3-7}cycloalkylamino, hydroxy, and C_{1-4}alkoxy;

R^d is selected from hydrogen, C_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkylcarbonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{3-7}cycloalkylsulfonyl, C_{3-7}cycloalkylcarbonyl, C_{1-6}dialkylaminoC_{1-4}alkylcarbonyl, and haloC_{1-4}alkyl, wherein the alkyl part of the alkoxycarbonyl, the alkylcarbonyl, and the alkylsulfonyl are optionally substituted with one substituent selected from C_{1-4}dialkylamino, and C_{1-4}alkoxy; and

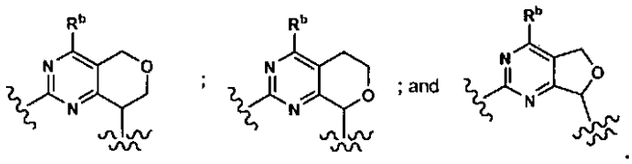
E is selected from C_{1-6}alkyl, C_{4-6}cycloalkyl, (C_{4-7}cycloalkyl)C_{1-4}alkyl, benzyl, phenyl, and a five- to six-membered heteroaromatic ring containing one or two nitrogen atoms, wherein the phenyl, the phenyl part of the benzyl, and the heteroaromatic ring are each optionally substituted with one, two, or three substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo, halo C_{1-6}alkoxy, and haloC_{1-6}alkyl.

The present invention is directed to these, as well as other important ends,

hereinafter described.

DETAILED DESCRIPTION OF THE EMBODIMENTS

In a first embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, as set forth above wherein A is a five-membered heteroaromatic ring containing from one to three nitrogen atoms; and wherein said heteroaromatic ring is optionally substituted with one group selected from halo and C_{1-6}alkyl. In a second embodiment, B is selected from phenyl and pyridinyl, wherein the phenyl and pyridinyl are optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy and halo. In a third embodiment, E is phenyl optionally substituted with one, two, or three substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl. In a fourth embodiment, D is selected from



In a fifth embodiment, R^b is $-NR^xR^y$, wherein R^x and R^y are independently selected from hydrogen, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, hydroxyC_{1-4}alkyl, and trideuteromethyl, wherein the alkyl part of the (C_{3-7}cycloalkyl)C_{1-4}alkyl can be optionally substituted with a C_{1-4}alkoxy group.

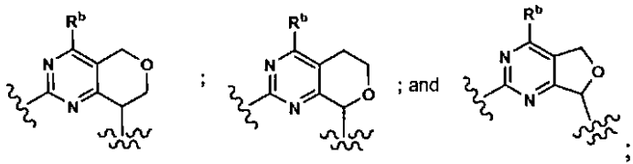
In a sixth embodiment of the first aspect, the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein:

A is a five-membered heteroaromatic ring containing from one to three nitrogen atoms; wherein said heteroaromatic ring is optionally substituted with one group selected from halo and C_{1-6}alkyl;

B is selected from phenyl and pyridinyl, wherein the phenyl and pyridinyl are optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy and halo;

E is phenyl optionally substituted with one, two, or three substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl;

D is selected from



; and

R^b is $-NR^xR^y$, wherein R^x and R^y, together with the nitrogen atom to which they are attached, form a four- to seven-membered monocyclic or bicyclic ring optionally containing one additional heteroatom selected from O and NR^z; wherein R^z is selected from C_{1-6}alkyl, and C_{1-4}alkoxycarbonyl; and wherein the ring is optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkyl, halo, haloC_{1-4}alkyl, hydroxy, $-NR^fR^g$, oxo, and spirocycle dioxolanyl; wherein R^f and R^g are independently selected from hydrogen, C_{1-4}alkoxycarbonyl, and C_{1-6}alkyl.

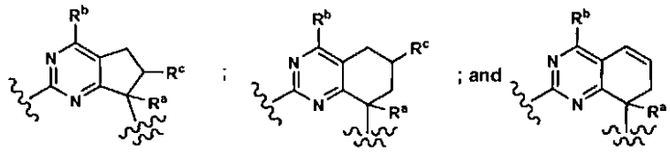
In a seventh embodiment of the first aspect, the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein:

A is a five-membered heteroaromatic ring containing from one to three nitrogen atoms; wherein said heteroaromatic ring is optionally substituted with one group selected from halo and C_{1-6}alkyl;

B is selected from phenyl and pyridinyl, wherein the phenyl and pyridinyl are optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy and halo;

E is phenyl optionally substituted with one, two, or three substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl; and

D is selected from



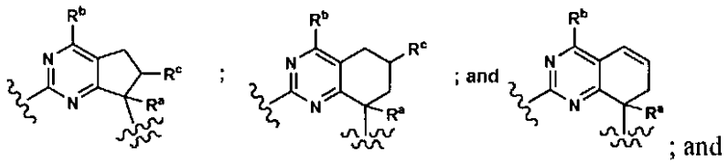
In an eighth embodiment of the first aspect, the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein:

A is a five-membered heteroaromatic ring containing from one to three nitrogen atoms; wherein said heteroaromatic ring is optionally substituted with one group selected from halo and C_{1-6}alkyl;

B is selected from phenyl and pyridinyl, wherein the phenyl and pyridinyl are optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy and halo;

E is phenyl optionally substituted with one, two, or three substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl;

D is selected from



; and

R^b is $-NR^xR^y$, wherein R^x and R^y are independently selected from hydrogen, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, hydroxyC_{1-4}alkyl, and trideuteromethyl, wherein the alkyl part of the (C_{3-7}cycloalkyl)C_{1-4}alkyl can be optionally substituted with a C_{1-4}alkoxy group.

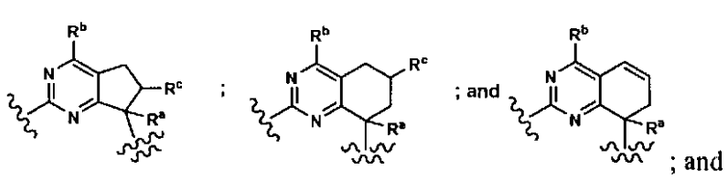
In a ninth embodiment of the first aspect, the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein:

A is a five-membered heteroaromatic ring containing from one to three nitrogen atoms; wherein said heteroaromatic ring is optionally substituted with one group selected from halo and C_{1-6}alkyl;

B is selected from phenyl and pyridinyl, wherein the phenyl and pyridinyl are optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy and halo;

E is phenyl optionally substituted with one, two, or three substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl;

D is selected from



; and

R^b is $-NR^xR^y$, wherein R^x and R^y, together with the nitrogen atom to which they are attached, form a four- to seven-membered monocyclic or bicyclic ring optionally containing one additional heteroatom selected from O and NR^z; wherein R^z is selected

from C_{1-6}alkyl, and C_{1-4}alkoxycarbonyl; and wherein the ring is optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkyl, halo, haloC_{1-4}alkyl, hydroxy, -NR^fR^g, oxo, and spirocycle dioxolanyl; wherein R^f and R^g are independently selected from hydrogen, C_{1-4}alkoxycarbonyl, and C_{1-6}alkyl.

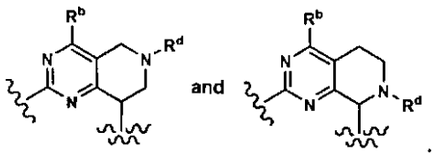
In a tenth embodiment of the first aspect, the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein:

A is a five-membered heteroaromatic ring containing from one to three nitrogen atoms; wherein said heteroaromatic ring is optionally substituted with one group selected from halo and C_{1-6}alkyl;

B is selected from phenyl and pyridinyl, wherein the phenyl and pyridinyl are optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy and halo;

E is phenyl optionally substituted with one, two, or three substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl; and

D is selected from



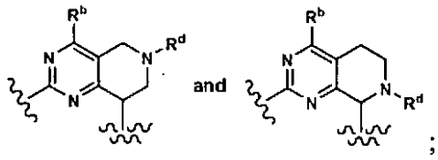
In an eleventh embodiment of the first aspect, the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein:

A is a five-membered heteroaromatic ring containing from one to three nitrogen atoms; wherein said heteroaromatic ring is optionally substituted with one group selected from halo and C_{1-6}alkyl;

B is selected from phenyl and pyridinyl, wherein the phenyl and pyridinyl are optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy and halo;

E is phenyl optionally substituted with one, two, or three substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl;

D is selected from



; and

R^b is $-NR^xR^y$, wherein R^x and R^y are independently selected from hydrogen, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, hydroxyC_{1-4}alkyl, and trideuteromethyl, wherein the alkyl part of the (C_{3-7}cycloalkyl)C_{1-4}alkyl can be optionally substituted with a C_{1-4}alkoxy group.

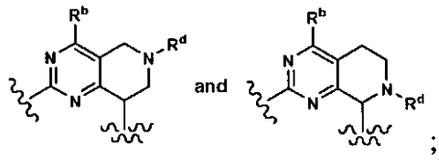
In a twelfth embodiment of the first aspect, the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein:

A is a five-membered heteroaromatic ring containing from one to three nitrogen atoms; wherein said heteroaromatic ring is optionally substituted with one group selected from halo and C_{1-6}alkyl;

B is selected from phenyl and pyridinyl, wherein the phenyl and pyridinyl are optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy and halo;

E is phenyl optionally substituted with one, two, or three substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl;

D is selected from



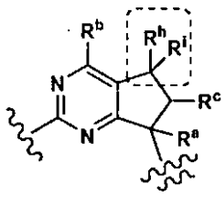
; and

R^b is $-NR^xR^y$, wherein R^x and R^y, together with the nitrogen atom to which they are attached, form a four- to seven-membered monocyclic or bicyclic ring optionally containing one additional heteroatom selected from O and NR^z; wherein R^z is selected from C_{1-6}alkyl, and C_{1-4}alkoxycarbonyl; and wherein the ring is optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkyl, halo, haloC_{1-4}alkyl, hydroxy, $-NR^fR^g$, oxo, and spirocycle dioxolanyl; wherein R^f and R^g are independently selected from hydrogen, C_{1-4}alkoxycarbonyl, and C_{1-6}alkyl.

In a thirteenth embodiment of the first aspect, the definition of A is expanded to also include acyl, acetyl, nitrile, CF_3, bromo, and CH_2CN; and the heteroaromatic ring

may be additionally substituted with $CHCF_2$ and/or CN.

In a fourteenth embodiment of the first aspect, B may also include pyrimidinyl.

In a fifteenth embodiment of the first aspect, R^h as part of D may also include SO_2C_{1-6}alkyl, acetyl, and phenyl optionally substituted with 1-3C_{1-6}alkyl; and further wherein the ring as part of R^z can also include spirocyclic tetrahydrofuranyl. In addition, D may also include  , wherein Rh, Ri =H, OH, or taken together to form C=O, C=N-OH, or C=N-OC_{1-6}alkyl.

In a second aspect, the present disclosure provides a pharmaceutical composition for the treatment of disorders responsive to the reduction of β-amyloid peptide production comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier or diluent.

In a third aspect, the present disclosure provides a method for the treatment of disorders responsive to the reduction of β-amyloid peptide production in a mammal in need thereof, which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof. In a first embodiment of the first aspect said disorder is selected from Alzheimer's Disease (AD), Down Syndrome, mild cognitive impairment (MCI), cerebral amyloid angiopathy (CAA), dementia with Lewy bodies (DLB), amyotrophic lateral sclerosis (ALS-D), inclusion body myositis (IBM), age-related macular degeneration, and cancer. In a second embodiment of the third aspect, said disorder is selected from Alzheimer's Disease and Down Syndrome. In a third embodiment of the third aspect, said disorder is Alzheimer's Disease.

Other aspects of the present disclosure may include suitable combinations of embodiments disclosed herein.

Yet other aspects and embodiments may be found in the description provided herein.

The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order accommodate a substituent at any given location.

It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule.

All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

In some instances, the number of carbon atoms in any particular group is denoted before the recitation of the group. For example, the term "haloC_{1-6}alkoxy" denotes a haloalkoxy group containing one to six carbon atoms and the term "C_{1-4}alkoxyC_{1-2}alkyl" denotes an alkoxy group containing one to four alkoxy groups attached to the parent molecular moiety through an alkyl group of one or two carbon atoms. Where these designations exist they supersede all other definitions contained herein.

As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to ten carbon atoms.

The term "alkylamino," as used herein, refers to -NHR^x, wherein R^x is an alkyl group.

The term "alkylaminoalkoxy," as used herein, refers to an alkylamino group attached to the parent molecular moiety through an alkoxy group.

The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "alkylsulfonylamido," as used herein refers to $-C(O)NHS(O)_2R^x$ wherein R^x is an alkyl group.

The term "amino," as used herein, refers to $-NH_2$.

The term "carbonyl," as used herein, refers to -C(O)-.

The term "cyano," as used herein, refers to -CN.

The term "cycloalkyl," as used herein, refers to a saturated monocyclic hydrocarbon ring system having three to fourteen carbon atoms and zero heteroatoms.

The term "(cycloalkyl)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyl groups.

The term "cycloalkylamino," as used herein, refers to $-NHR^x$ wherein Rx is a cycloalkyl group.

The term "cycloalkylcarbonyl," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "cycloalkylsulfonyl," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "dialkylamino," as used herein, refers to $-NR^xR^y$, wherein R^x and R^y are each alkyl groups.

The term "dialkylaminoalkoxy," as used herein, refers to a dialkylamino group attached to the parent molecular moiety through an alkoxy group.

The term "dialkylaminoalkyl," as used herein, refers to an alkyl group substituted with one, two, or three dialkylamino groups.

The term "dialkylaminoalkylcarbonyl," as used herein, refers to a dialkylaminoalkyl group attached to the parent molecular moiety through a carbonyl group.

The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, and I.

The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkyl," as used herein, refers to an alkyl group substituted with one, two, three, or four halogen atoms.

The term "hydroxy," as used herein, refers to -OH.

The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three hydroxy groups.

The term "methylamino," as used herein, refers to $-NHCH_3$.

The term "oxo," as used herein, refers to =O.

The term "sulfonyl," as used herein, refers to $-SO_2-$.

It should be understood that the disclosure encompasses all stereochemical forms, or mixtures thereof, which possess the ability to reduce β-amyloid peptide production.

Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

The present disclosure is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds may have a variety of potential uses, for example as standards and reagents in determining biological activity. In the case of stable isotopes, such compounds may have the potential to favorably modify biological, pharmacological, or pharmacokinetic properties.

Certain compounds of the present disclosure may exist in zwitterionic form and the present disclosure includes each zwitterionic form of these compounds and mixtures thereof.

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk

ratio, and are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the disclosure further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s),

diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients.

The dosage of the compounds of Formula I to achieve a therapeutic effect will depend not only on such factors as the age, weight and sex of the patient and mode of administration, but also on the degree of β-AP reduction desired and the potency of the particular compound being utilized for the particular disorder of disease concerned. It is also contemplated that the treatment and dosage of the particular compound may be administered in unit dosage form and that the unit dosage form would be adjusted accordingly by one skilled in the art to reflect the relative level of activity. The decision as to the particular dosage to be employed (and the number of times to be administered per day) is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect.

A suitable dose of a compound of Formula I or pharmaceutical composition thereof for a mammal, including man, suffering from, or likely to suffer from any condition related to β-AP production as described herein, generally the daily dose will be from about 0.05 mg/kg to about 10 mg/kg and preferably, about 0.1 to 2 mg/kg when administered parenterally. For oral administration, the dose may be in the range from about 0.1 to about 75 mg/kg and preferably from 0.1 to 10 mg/kg body weight. The active ingredient will preferably be administered in equal doses from one to four times a day. However, usually a small dosage is administered, and the dosage is gradually increased until the optimal dosage for the host under treatment is determined. In accordance with good clinical practice, it is preferred to administer the instant compounds at a concentration level that will produce an effective anti-amyloid effect without causing any harmful or untoward side effects. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances including the condition to be treated, the choice of compound of be administered, the chosen route of administration, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture

is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation 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 formula (I), and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phopholipids, such as cholesterol, stearylamine, or phophatidylcholines.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the

compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl residues. Furthermore, the compounds 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, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles, and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a course powder which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for

administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and soutes 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 formulations 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.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The present disclosure will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

The compounds of the present application can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred

methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The compounds may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

The starting materials useful to synthesize the compounds of the present disclosure are known to those skilled in the art and can be readily manufactured or are commercially available.

The following methods set forth below are provided for illustrative purposes and are not intended to limit the scope of the claims. It will be recognized that it may be necessary to prepare such a compound in which a functional group is protected using a conventional protecting group then to remove the protecting group to provide a compound of the present disclosure. The details concerning the use of protecting groups in accordance with the present disclosure are known to those skilled in the art.

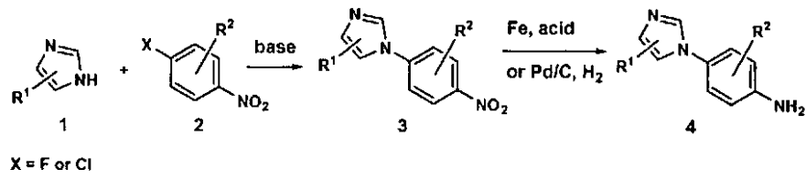
The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows:

Chemical abbreviations used in the specification and Examples are defined as follows: "dba" for dibenzylideneacetone; "*t*-Bu" for tert-butyl; "DCM" for dichloromethane; "LDA" for lithium diisopropylamide; "Ph" for phenyl; "TFA" for trifluoracetic acid; "Et" for ethyl; "DMF" for N,N-dimethylformamide; "OAc" for acetate; "h" for hours, "min" for minutes; and "THF" for tetrahydrofuran.

Examples of methods useful for the production of compounds of this disclosure are illustrated in *Schemes 1-24*. *Schemes 1-3* outline different routes for the synthesis of

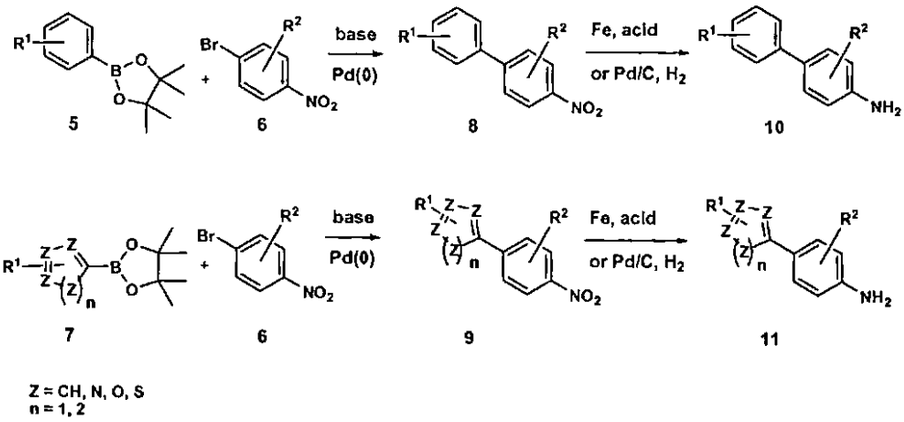
substituted aniline fragments used in the preparation of the title compounds. As illustrated in *Scheme 1*, a variety of substituted heterocycles 1, including but not limited to 1*H*-imidazole, 4-methyl-1*H*-imidazole, 4-chloro-1*H*-imidazole, 4-(difluoromethyl)-1*H*-imidazole can be added to substituted chloro- or fluoronitroarenes 2, including but not limited to 2-chloro-4-nitroanisole, under basic conditions to provide heteroaryl substituted nitroarenes 3. Reduction of the compounds 3 using reagents including iron in acidic medium or catalytic hydrogenation, employing catalysts such as palladium on carbon or other catalysts known to one skilled in the art, affords substituted anilines 4. While *Scheme 1* illustrates the preparation of 4-(1*H*-imidazol-1-yl)anilines 4, it should be recognized to one skilled in the art that this method is widely applicable to the synthesis of other 4-heteroarylanilines, including but not limited to variously substituted 4-(1*H*-1,2,4-triazol-1-yl)anilines and 4-(1*H*-1,2,3-triazol-1-yl)anilines. In addition, substituted nitropyridines can be used in place of the nitroarenes of formula 2 to ultimately provide amino-substituted pyridines.

Scheme 1

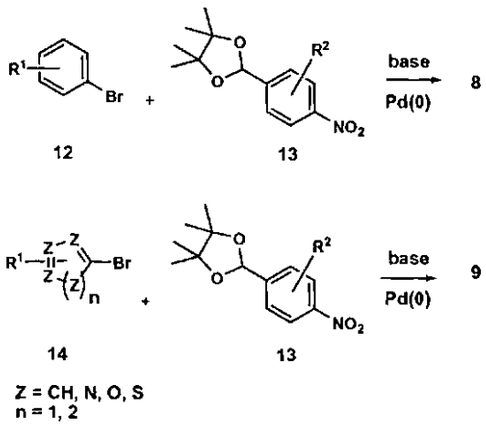


Additional procedures for creating substituted anilines rely on the palladium-catalyzed coupling of aryl halides or heteroaryl halides to boronic acids (the Suzuki coupling reaction). As shown in *Scheme 2*, biaryl anilines 10 and 11, and their nitro precursors 8 and 9, can be created by the coupling of an aryl or heteroaryl boronic esters 5 and 7, respectively, to substituted aryl halides 6, including 1-bromo-2-methoxy-4-nitrobenzene. Alternatively, the coupling partners can be reversed as is shown in *Scheme 3*, where coupling of an aryl halide 12 or heteroaryl halide 14 to the boronic ester of the nitro arene 13 creates the substituted nitro arenes 8 and 9, respectively.

Scheme 2



Scheme 3

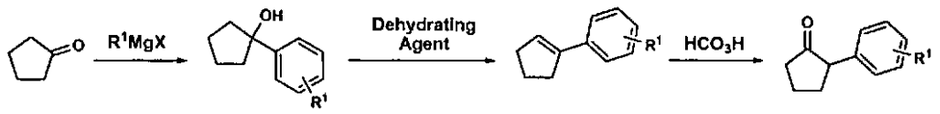


These general reaction schemes are intended as illustrations of a general reaction process that is highly tolerant of a variety of functional groups, and these processes are not limited by the specific structures shown in *Schemes 2* and *3*. Those skilled in the art will also recognize that similar processes including the Stille coupling of aryl or heteroaryl halides and aryl or heteroaryl stannanes are also excellent processes to prepare the necessary anilines or their nitro precursors.

The following schemes outline different routes for the synthesis of 2,4-dichloro-7-aryl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidines used in the preparation of the title compounds. As illustrated on *Scheme 4*, cyclopentanone 15 can react with a variety of arylmagnesium halides to produce tertiary alcohols 16. In the presence of dehydrating agents, such as mineral acids or thionyl chloride, these tertiary alcohols can undergo

elimination of water to yield olefins 17. Upon treatment with peroxidizing agents, such as performic acid, olefins 17 can be transformed to 2-arylcyclopentanones 18. Abu Thaher, B.; Koch, P.; Del Amo, V.; Knochel, P.; Laufer, S. *Synthesis* 2008, *2*, 225-228.

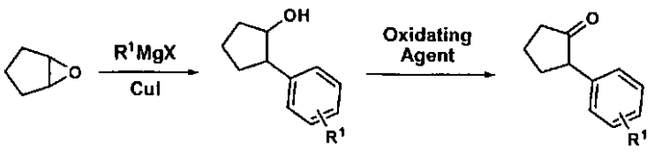
Scheme 4



15 16 17 18

Alternatively, as indicated in *Scheme 5*, 2-arylcyclopentanones 18 can be prepared by treatment of cyclopenteneoxide 19 with various arylmagnesium halides, in the presence of copper salts, such as copper iodide, followed by oxidation of resulting alcohols 20. The said oxidation can be carried out by a number of oxidation agents known to those skilled in the arts, with superior results achieved by the use of Dess-Martin periodinane. Dess, D. B.; Martin, J.C. *J. Org. Chem.* 1983, 48, 4155-4156.

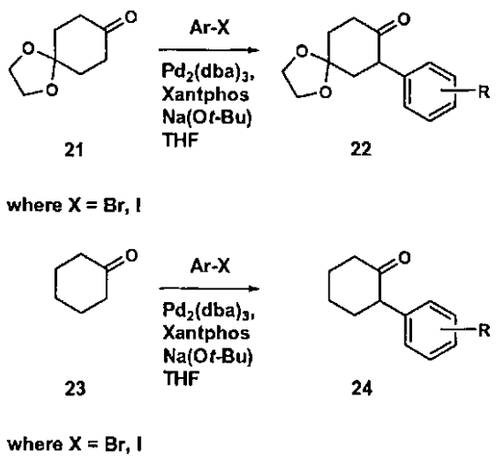
Scheme 5



19 20 18

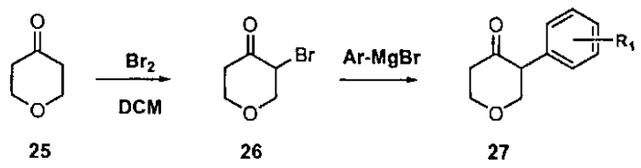
Additional ketones useful in the preparation of compounds of claim 1 can be prepared using the method described in O. Dirat et al, *Tetrahedron Letters*, 2006,*47*, 1295. This method, described in *Scheme 6*, relies on alpha-arylation (Fox et al, *Journal of the American Chemical Society*, 2000, *122*, 1360) of available ketones 21 that incorporate acetals or ketals at the 4-position. The corresponding ketone starting materials 21 are available commercially or can easily be prepared by those skilled in the art, and a variety of acetals can be used, including the shown ethylene glycol ketal or ketals of other alcohols including 1,3-propanediol, methanol, ethanol, and others. This chemistry works equally well to produce unsubstituted alpha-aryl ketones 24.

Scheme 6



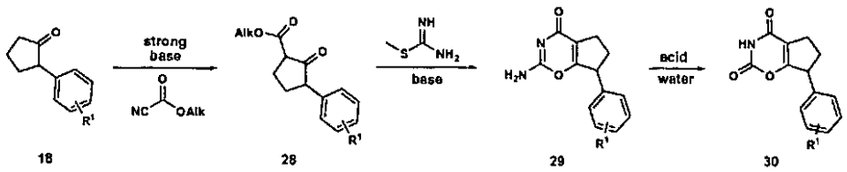
Additional alpha-aryl ketones can be prepared using the chemistry shown in *Scheme 7*, where tetrahydro-4H-pyran-4-one is brominated, typically using bromine in dichloromethane or pyrrolidine hydrotribromide as a brominating agent. The resulting alpha-bromo ketone can then be reacted with a Grignard reagent, and after migration of the aryl group the desired alpha-aryl ketone 27 is obtained.

Scheme 7



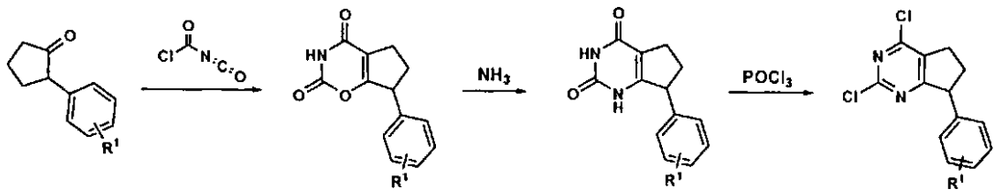
As indicated in *Scheme 8*, 2-arylcyclopentanones 18 can be deprotonated with a strong base, such as LDA and treated with alkylcyanoformate to give ketoesters 28, which upon reaction with 2-methyl-2-thiopseudourea provide 2-amino-7-aryl-6,7-dihydrocyclopenta[*e*][1,3]oxazin-4(5*H*)-ones 29. The latter compounds undergo acid-catalyzed hydrolysis to form 7-aryl-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-diones 30. Larsen, J. S.; Christensen, L.; Ludvig, G.; Jørgensen, P. T.; Pedersen, E. B.; Nielsen, C. *J. Chem. Soc., Perkin Trans. 1* 2000, *3035-3038.*

Scheme 8



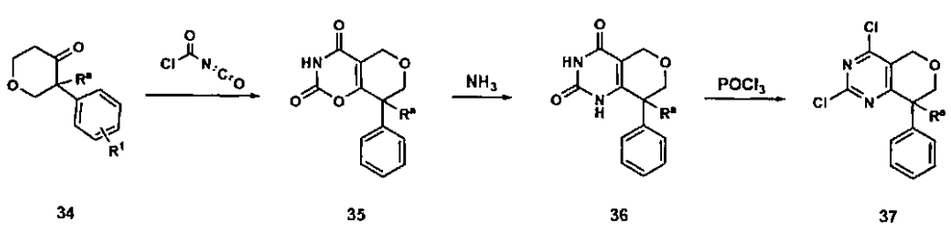
Alternatively, 7-aryl-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-diones 31 are available by reaction of 2-arylcyclopentanones 18 with *N*-(chlorocarbonyl)isocyanate (*Scheme 9*). Subsequent treatment of 7-aryl-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-diones 31 with ammonia in water, followed by chlorination with phosphorus oxychloride affords 2,4-dichloro-7-aryl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidines 33.

Scheme 9

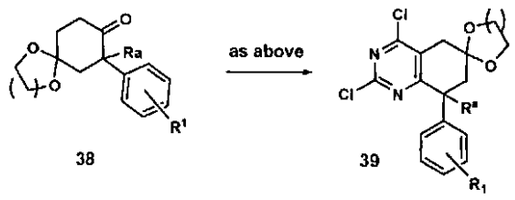


In a similar manner to the synthesis described in *Scheme 9*, additional ketones can be reacted with *N*-(chlorocarbonyl)isocyanate to provide additional oxazine diones 35 that can be reacted with ammonia to provide the pyrimidine diones 36 (*Scheme 10*). Chlorination then provides the intermediate dichlorides 37. In a similar way, this chemistry can be performed using the ketal-protected ketones produced in *Scheme 6* to prepare the corresponding fused dichloropyrimidines (*Scheme 11*).

Scheme 10

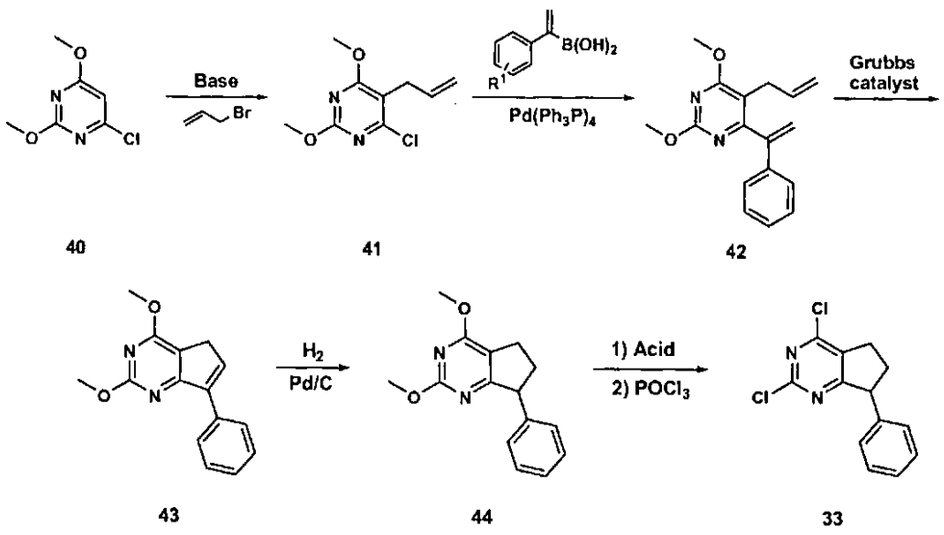


Scheme 11



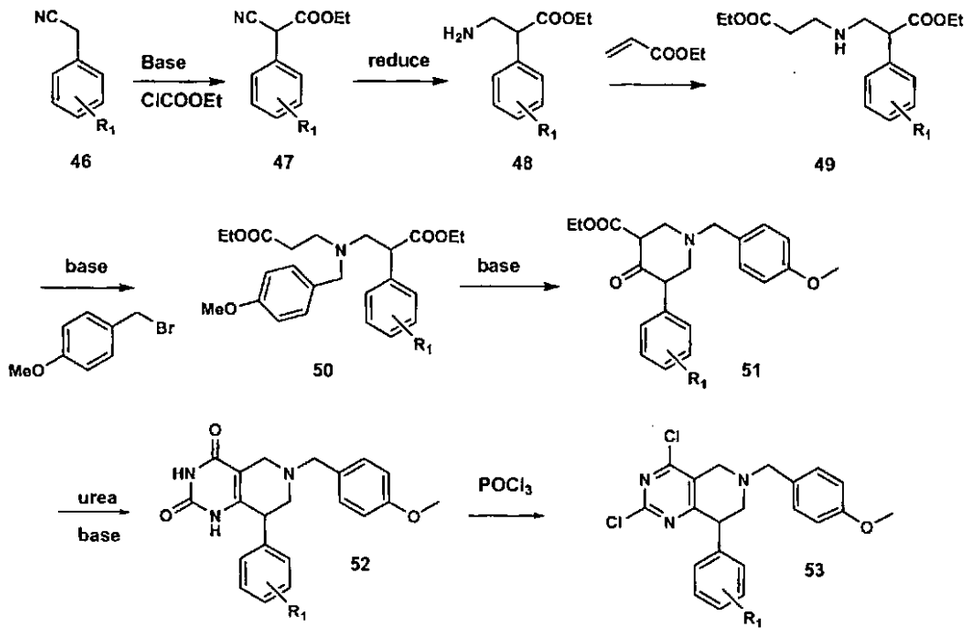
Synthesis of 2,4-dichloro-7-aryl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidines 33 could also be performed according to the pathway described on *Scheme 12*. 4-Chloro-2,6-dimethoxypyrimidine 40 could be deprotonated with a strong base, such as *n*-butyllithium or 2,2,6,6-tetramethylpiperidine, and quenched with allyl bromide to give 5-allyl-4-chloro-2,6-dimethoxypyrimidine 41. Nencka, R.; Votruba, I.; Hřebabecký, H.; Jansa, P.; Tloušťová, E.; Horská, K.; Masojídková, M.; Holý, A. *J. Med. Chem.* 2007, *50*, 6016-6023. The latter compound can react with α-styrylborinic acids in the presence of a palladium catalyst, such as tetrakis(triphenylphosphine)palladium, to provide compounds of formula 42 which can undergo ring closure olefin metathesis under Grubbs conditions to form 2,4-dimethoxy-7-aryl-5*H*-cyclopenta[*d*]pyrimidines 43. Grubbs, R. H. *Handbook of Metathesis*, 2003, First Edition, Wiley-VCH. The double bond in compounds 43 can be reduced to give 2,4-dimethoxy-7-aryl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidines 44, which upon acid-catalyzed hydrolysis, followed by chlorination with phosphorus oxychloride afford intermediates 33.

Scheme 12



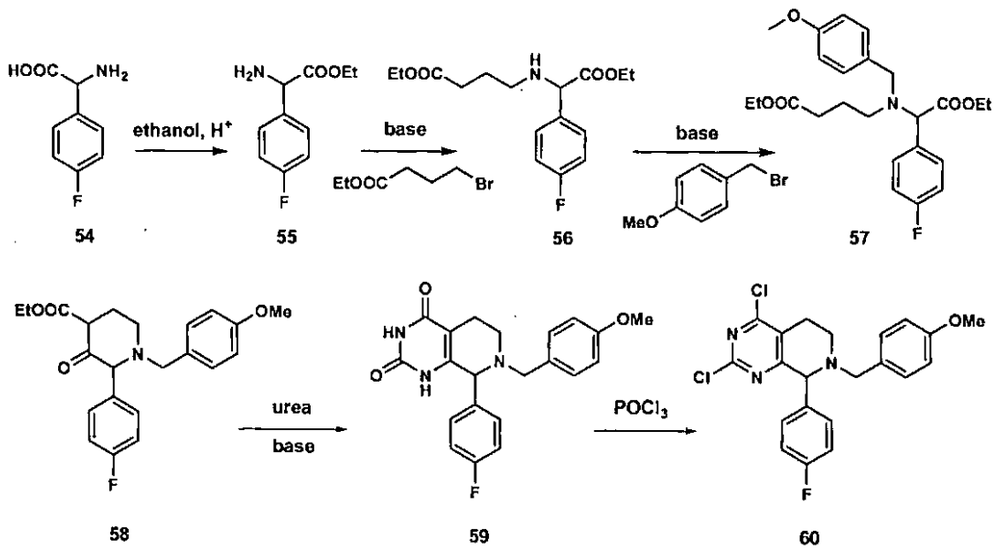
Additional members of the class of compounds of claim 1 can be prepared as is shown in *Scheme 13*. Carboxylation of benzonitriles followed by simple reduction using metal catalysis (Palladium on carbon or similar methods) provides the substituted beta-amino ester 48. Condensation with an acrylic ester provides intermediate 49, which can be alkylated on nitrogen to either directly provide access to R^d substituents, or using the chemistry shown can be protected with a p-methoxybenzyl group for later deprotection and introduction of R^d. The intermediate 50 is then cyclized in the presence of base (usually KO*t*-Bu) to provide the beta-keto ester 51. Condensation of the beta-keto ester 51 with urea under basic conditions provides the pyrimidine dione intermediate 52, which can then be chlorinated under standard conditions to provide the dichloride 53. This dichloride can be converted into compounds of claim 1 in the usual way (vide infra).

Scheme 13



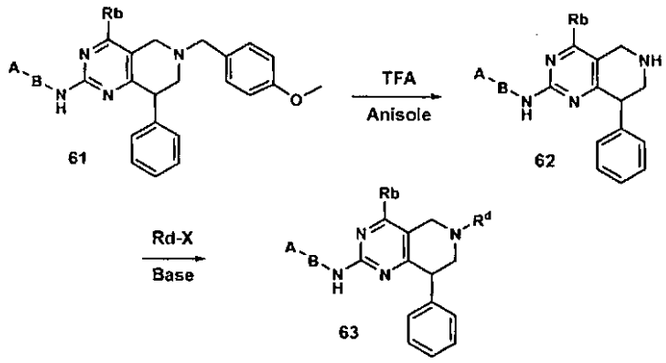
Additional members of the class of compounds of claim 1 can be prepared as is shown in *Scheme 14*. Esterification of an amino acid followed by alkylation with ethyl 4-bromobutyrate provides intermediate 56, which can be alkylated on nitrogen to either directly provide access to R^d substituents, or using the chemistry shown can be protected with a p-methoxybenzyl group for later deprotection and introduction of R^d. The intermediate 57 is then cyclized in the presence of base (usually KO*t*-Bu) to provide the beta-keto ester 58. Condensation of the beta-keto ester 58 with urea under basic conditions provides the pyrimidine dione intermediate 59, which can then be chlorinated under standard conditions to provide the dichloride 60. This dichloride can be converted into compounds of claim 1 in the usual way (vide infra).

Scheme 14

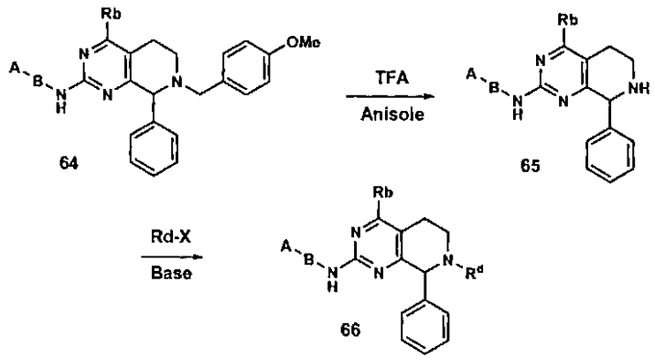


As shown in *Scheme 15*, the dimethoxybenzyl group used to protect the nitrogen atom on compounds of structure 61 can be deprotected, for instance by the action of a strong acid (TFA in the presence of anisole as a cation scavenger) to provide the free amine, which can then be further derivatized, for instance by acylation, sulfonylation, or alkylation in the usual ways to prepare additional compounds of claim 1. Similarly, amine the positional isomer 64 as shown in *Scheme 16* participates in identical chemistry to access an additional class of compounds of claim 1.

Scheme 15

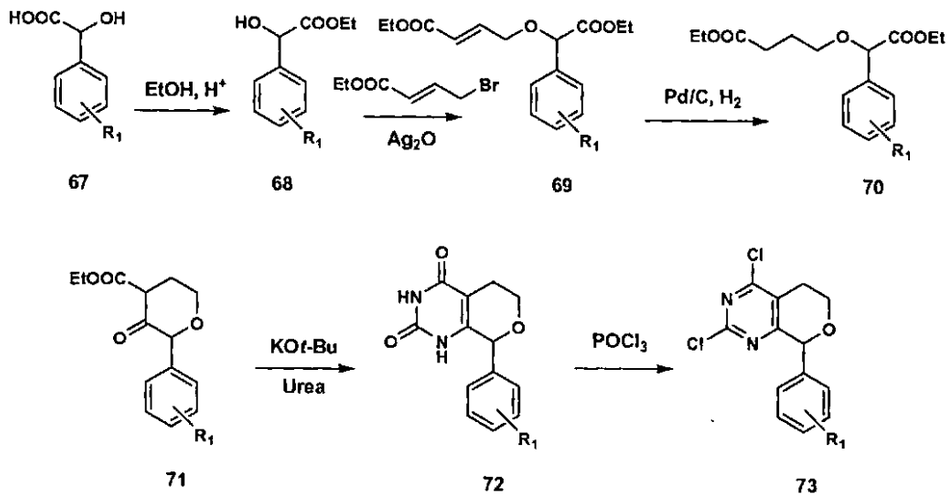


Scheme 16



Further analogs can be prepared by the chemistry detailed in *Scheme 17.* Formation of the ester from commercial hydroxyacids 67 under Fisher conditions is followed by alkylation of the alcohol under silver(I) oxide catalysis. Reduction of the olefin and cyclization gives the beta-keto ester 71. Formation of the pyrimidine dione with KO*t*-Bu and urea followed by chlorination with $POCl_3$ gives the dichloride 73, which is carried forward to compounds of claim 1 as described in *Scheme 22.*

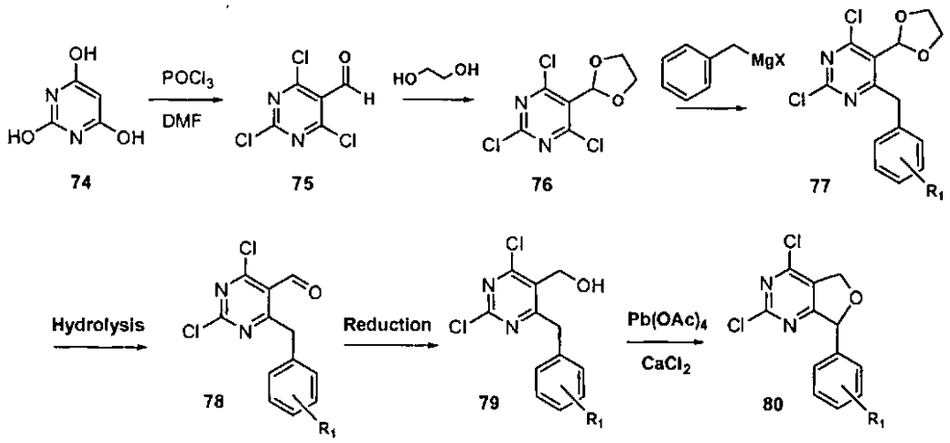
Scheme 17



Additional analogs can be prepared using the chemistry shown in *Scheme 18.* Reaction of pyrimidine-2,4,6-triol with $POCl_3$ in DMF provides the chlorinated aldehyde 75. Protection of the aldehyde is followed by reaction with a Grignard reagent to produce the dichloride reagent 77. After hydrolytic deprotection and reduction of the aldehyde to

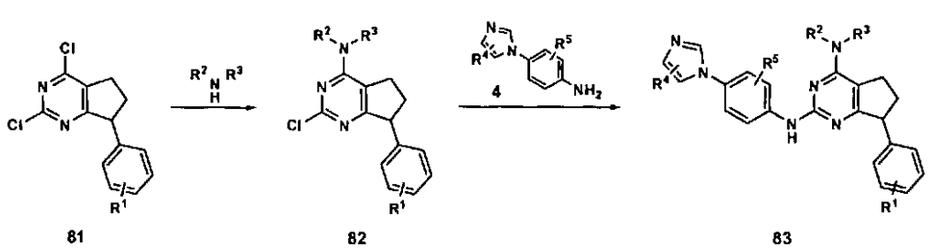
the alcohol, the tetrahydrofuran ring can be closed by the action of lead tetraacetate to provide the substituted dichloride 80 which can then be used according to the methods described below to prepare further compounds of claim 1.

Scheme 18



2,4-Dichloro-7-aryl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidines 81 selectively react with primary and secondary amines to give 2-amino derivatives 82, which under heating can be coupled with anilines 4 to form title compounds 83. (*Scheme 19*). The said coupling can be performed either under acidic conditions (for example, using acetic acid), or under basic conditions, (for example, using sodium hydride). Alternatively, the coupling can be completed under metal catalysis, with conditions known in the literature, for instance the use of palladium Xantphos catalyst in the presence of a strong base (NaO*t*-Bu) or Na_2CO_3 in an aqueous cosolvent mixture (typically THF/water or dioxane/water).

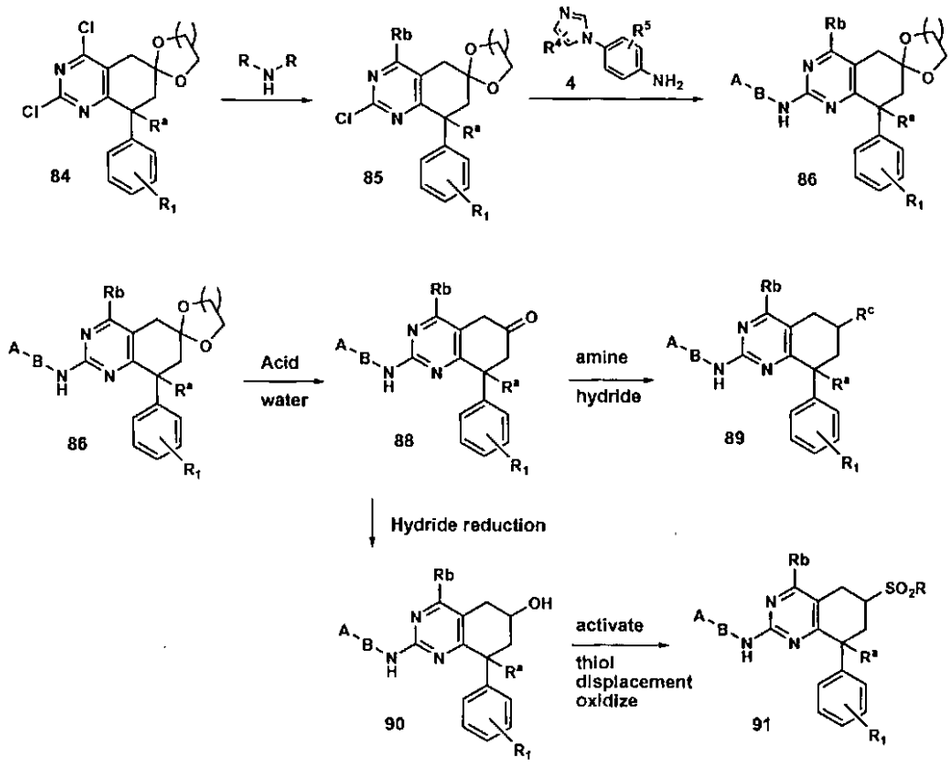
Scheme 19



Additional compounds of claim 1 can be prepared by condensation of the appropriate ketal-containing dichlorides with animes and anilines in the manner already

described to prepare intermediates 86 (*Scheme 20).* Deprotection of the ketal, for instance with aqueous acid produces the ketone 88 which is a very useful intermediate for the production of further compounds. The ketone can be directly condensed with amines under reductive conditions (reductive alkylation) to prepare substituted amine compounds 89. Alternatively, the ketone can be reduced with hydride reagents such as $NaBH_4$ or $LiAlH_4$ to provide the alcohol. The alcohol 90 can be activated, for instance as the methanesulfonate, and then displaced with nucleophiles including thiols, azide or other nucleophiles. Oxidation of the thiol prepares the sulfoxide and the sulfone. Reduction of the azide produces a facile entry into the amine, which can also be further alkylated to produce additional compounds of claim 1.

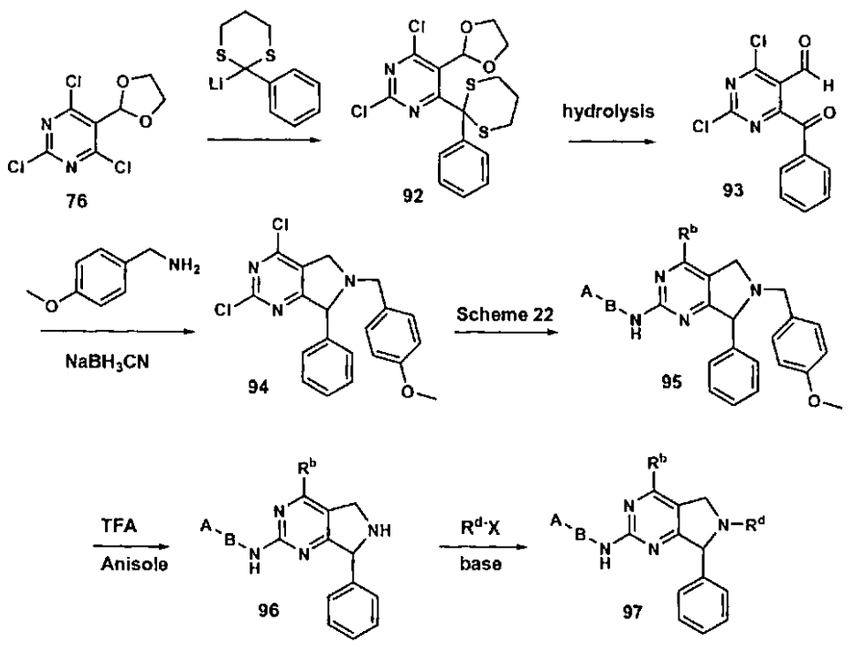
Scheme 20



An additional method for the preparation of analogs of claim 1 is described in *Scheme 21.* Again starting with the aldehyde 76, addition of lithiated phenyldithiane provides intermediate 92. Deprotection of the protecting groups provides the keto aldehyde 93, which can be closed to the substituted pyrrolidine 94 by sequential reductive

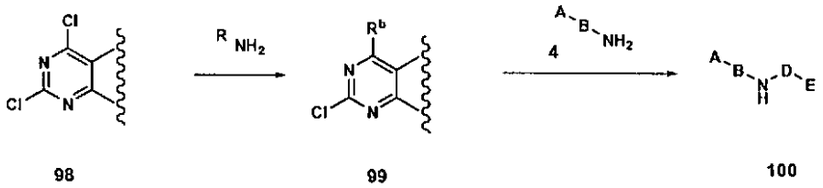
alkylation. The amine can either directly introduce a desired R^d substituent, or as is described in the scheme an amine that introduces a protecting group (including 4-methoxybenzyl) can be used. According to the methods herein, the dichloride thus obtained can be transformed into compounds of claim 1. Additional analogs can then be prepared by deprotection of the 4-methoxybenzyl group using methods known to those in the art, such as TFA with Anisole as a cation scavenger, followed by additional alkylation, acylation, or sulfonylation using known methods.

Scheme 21



In a general way, the additional pyrimidine dichlorides prepared using the methods described above, or other methods known in the art can be transformed into additional analogs of claim 1 as demonstrated in Scheme 22. Pyrimidine dichlorides are reacted with amines to provide the chlorides 99 which correspond to the structures D-E as described in claim 1, where the bond that attaches the structure D-E to the ABNH fragment is activated as a displaceable chloride group. The title compounds of claim 1 are then prepared by condensing the chlorides 99 with the anilines $ABNH_2$ according to the methods previously described (*Scheme 19*).

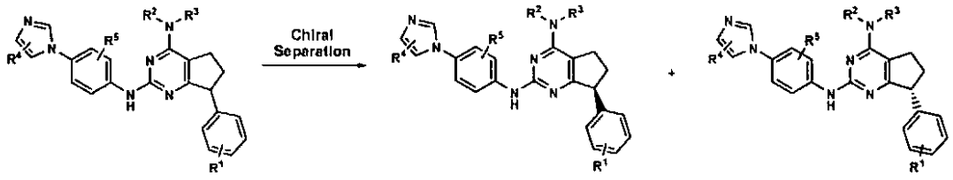
Scheme 22



98 99 100

The racemic title compounds can be separated by chiral methods known to a reasonable person skilled in the arts, to provide individual enantiomers (*Scheme 23*). This is demonstrated below in the cyclopenta[*d*]pyrimidine series, but equally applies to the other racemic compounds described herein.

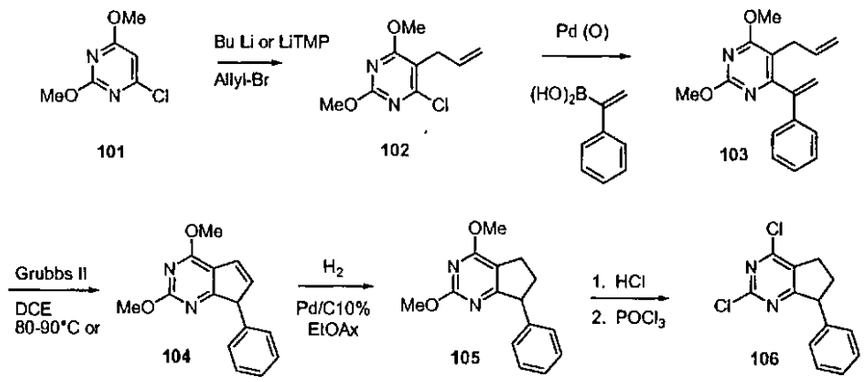
Scheme 23



101 102 103

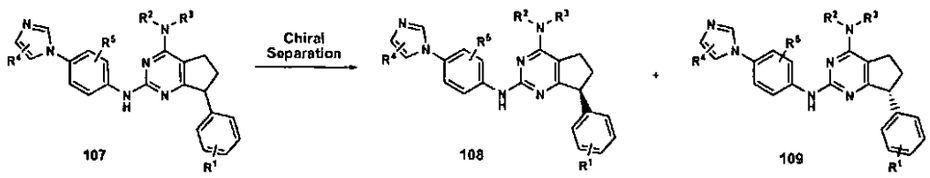
An additional method for producing compounds of claim 1 is demonstrated in *Scheme 23*. Commercial 4-chloro-2,6-dimethoxypyrimidine 101 can be deprotonated using either butyllithium or lithium tetramethylpiperidide followed by allylation to produce the protected pyrimidine 102. Suzuki coupling of phenyl vinyl boronic acid under palladium catalysis provides the diene 103 which can be efficiently cyclized by ring-closing metathesis using standard conditions with Grubbs' II catalyst. The olefin can then be reduced to provide intermediate 105. Deprotection and chlorination under standard conditions provides an additional route to make dichlorides 106 which can be converted to compounds of claim 1 using the chemistry shown in *Scheme 22*.

Scheme 23



The racemic title compounds can be separated by chiral methods known to a reasonable person skilled in the arts, to provide individual enantiomers (*Scheme 24*). This is demonstrated below in the cyclopenta[*d*]pyrimidine series, but equally applies to the other racemic compounds described herein.

Scheme 24



"HPLC" is an abbreviation used herein for high pressure liquid chromatography. "LC-MS" refers to high pressure liquid chromatography carried out according to the definition for HPLC with a mass spectrometry detector. HPLC solvent conditions: When described as performed under "standard conditions", samples were dissolved in methanol (1 mg/mL) and run using a gradient program with a solvent flow rate of 1.0 mL/min. Reverse phase preparatory HPLC: When described as performed under "standard conditions", samples (approx. 20 mg) were dissolved in methanol (10 mg/mL) and purified on a 30mm X 100 mm Waters-Atlantis S5 column using a 10 minute gradient elution from 0 % to 100 % buffer B in buffer A (buffer A = 10% CH_3OH/90% water/0.1% TFA and buffer B = 90% MeOH/10% water /0.1% TFA).at 40 mL/minute.

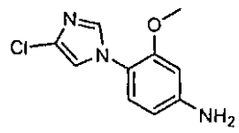
Proton NMR spectra were obtained on a Bruker 400 or 500 spectrometer. Data were referred to the lock solvent.

The examples provided are intended to assist in a further understanding of the present disclosure. Particular materials employed, species and conditions are intended to further illustrate the specific embodiments of the invention and not limit the reasonable scope thereof.

SYNTHESIS OF INTERMEDIATES

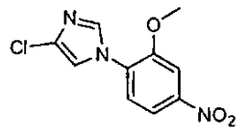
Preparation A

4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline



Intermediate A(1)

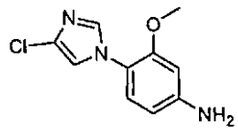
4-chloro-1-(2-methoxy-4-nitrophenyl)-1H-imidazole



A mixture of 4-chloro-1H-imidazole (5.0 g, 48.8 mmol), 1-chloro-2-methoxy-4-nitrobenzene (9.15 g, 48.8 mmol), and potassium hydroxide flakes (2.74 g, 48.8 mmol) in anhydrous DMSO (50 mL) was heated at 80 °C for 20 h. The reaction mixture was allowed to cool to rt and was poured into 800 mL of water with vigorous stirring. The resulting yellow-orange precipitate was collected by vacuum filtration using a coarse sintered glass funnel. The crude wet solid was transferred to a 1 L Erlenmeyer flask. Absolute ethanol (250 mL) was added to the flask and the resulting suspension was heated until all of the solids dissolved. The clear solution was cooled to rt and the desired product slowly crystallized. After 2 h, the crystalline solid was collected by vacuum filtration and rinsed with 100 mL of fresh ethanol. The solid was dried under high vacuum to afford 4-chloro-1-(2-methoxy-4-nitrophenyl)-1H-imidazole (5.2 g, 42 % yield) as an off-white crystalline solid. LC–MS $(M+H)^+ = 254.0$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.94 - 8.01 (m, 2 H) 7.76 (d, *J*=1.53 Hz, 1 H) 7.45 (d, *J*=8.55 Hz, 1 H) 7.21 (d, *J*=1.53 Hz, 1 H) 4.02 (s, 3 H).

Preparation A

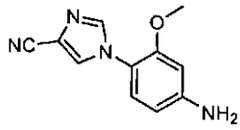
4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline



Iron powder–325 mesh (4.6 g, 82 mmol) was added to a 500 mL round bottom flask charged with a mixture of 4-chloro-1-(2-methoxy-4-nitrophenyl)-1H-imidazole (5.2 g, 20.5mmol), absolute ethanol (100 mL), and glacial acetic acid (50 mL). A water-cooled reflux condenser was attached to the flask and the heterogeneous mixture was heated to 100 °C with vigorous stirring for 30 min. The reaction mixture allowed to cool to rt and was added to a chilled and stirred solution of 3 M NaOH (291 mL). The resulting mixture was poured into a separatory funnel and extracted with EtOAc (3 x 250 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (4.57 g, 97 % yield) as a solid. LC–MS $(M+H)^+$ 224.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.47 (d, *J*=1.22 Hz, 1 H) 7.00 (d, *J*=8.24 Hz, 1 H) 6.99 (d, *J*=1.53 Hz, 1 H) 6.32 (d, *J*=2.44 Hz, 1 H) 6.29 (dd, *J*=8.24, 2.44 Hz, 1 H) 3.88 (br. s., 2 H) 3.78 (s, 3 H).

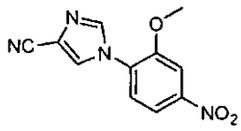
Preparation AA

4-(4-cyano-1H-imidazol-1-yl)-3-methoxyaniline



Intermediate AA(1)

4-cyano-1-(2-methoxy-4-nitrophenyl)-1H-imidazole

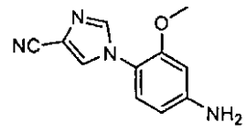


To a solution of 1H-Imidazole-4-carbonitrile (300 mg, 3.22 mmol) and 4-Fluoro-3-methoxynitrobenzene (552 mg, 3.22 mmol) in DMF (Volume: 6446 µl) was added K2CO3 (891 mg, 6.45 mmol). The resulting mixture was brought to 120 °C and stirred overnight. The reaction mixture was diluted with EtOAc (20 mL), washed with water (2

x 10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give 1-(2-methoxy-4-nitrophenyl)-1H-imidazole-4-carbonitrile (698 mg, 2.86 mmol, 89 % yield). LC–MS $(M+H)^+ = 245.0$. 1H NMR (500 MHz, *MeOD*) δ ppm 8.30 - 8.34 (1 H), 8.19 - 8.23 (1 H), 8.09 - 8.12 (1 H), 8.00 - 8.05 (1 H), 7.71 - 7.79 (1 H), 4.02 - 4.10 (3 H).

Preparation AA

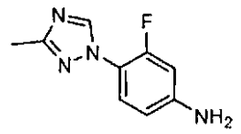
4-(4-cyano-1H-imidazol-1-yl)-3-methoxyaniline



To a solution of 1-(2-methoxy-4-nitrophenyl)-1H-imidazole-4-carbonitrile (689 mg, 2.82 mmol) in EtOH (Ratio: 2, Volume: 15 mL) was added Acetic Acid (Ratio: 1.000, Volume: 7.50 mL) and Iron (630 mg, 11.29 mmol). The resulting mixture was brought to 100 °C and stirred for 2 h. The reaction was then diluted with water and brought to pH 8 by the addition of 1 N aqueous sodium hydroxide. This mixture was extracted with EtOAc (3 x 5 mL). The combined extracts were washed with water (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. LC–MS $(M+H)^+ = 215.0$.

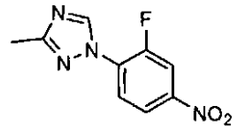
Preparation B

3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline



Intermediate B(1)

1-(2-fluoro-4-nitrophenyl)-3-methyl-1H-1,2,4-triazole

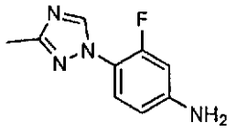


A mixture of 3-methyl-1H-1,2,4-triazole (15.0 g, 181 mmol), 1,2-difluoro-4-nitrobenzene (28.7 g, 181 mmol), and sodium bicarbonate (15.2 g, 181 mmol) in DMSO

(100 mL) was heated at 80 °C for 48 h. The reaction mixture was allowed to cool to rt and was poured into water (800 mL). The aqueous mixture was extracted with EtOAc (3 x 200 mL). The combined organic extracts were sequentially washed with water (500 mL) and brine solution (100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude reaction mixture was purified using silica gel chromatography (30-80% EtOAc/hexane, linear gradient) to afford two regioisomeric products. Pure fractions of the less polar regioisomer were combined and concentrated to afford 1-(2-fluoro-4-nitrophenyl)-3-methyl-1H-1,2,4-triazole (7.2 g, 30.8 mmol, 17 % yield) as an off-white solid. Pure fractions of the more polar regioisomer were combined and concentrated to afford 1-(2-fluoro-4-nitrophenyl)-5-methyl-1H-1,2,4-triazole (6.23 g, 28.0 mmol, 15 % yield) as an off-white solid. Data for 1-(2-fluoro-4-nitrophenyl)-3-methyl-1H-1,2,4-triazole: LC–MS $(M+H)^+ = 223.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.73 (d, *J*=2.7 Hz,1 H), 8.15 - 8.26 (m, 3 H), 2.53 (s, 3 H).

Preparation B

3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline

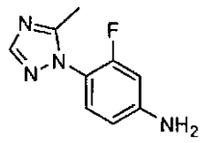


10% Palladium on carbon (2.50 g, 23.5 mmol) was added under an atmosphere of nitrogen to a chilled (ice-water bath) solution of 1-(2-fluoro-4-nitrophenyl)-5-methyl-1H-1,2,4-triazole (15.0 g, 67.5 mmol, from preparation A, step1) dissolved in methanol (400 mL). The flask was repeatedly evacuated and flushed with hydrogen gas (double balloon). The resulting mixture was allowed to warm to rt and left to stir for 72 h under the hydrogen atmosphere. The vessel was subsequently purged with nitrogen gas. The reaction vessel and it contents were chilled (ice-water bath) and an additional portion of 10% Palladium on carbon (2.50 g, 23.5 mmol) was added. The flask was repeatedly evacuated and flushed with hydrogen gas (double balloon). The resulting mixture was allowed to warm to rt and left to stir for 6 h under the hydrogen atmosphere. The vessel was subsequently purged with nitrogen gas. The crude reaction mixture was filtered through a short plug of diatomaceous earth (Celite®). The reaction vessel and the Celite® were rinsed with fresh methanol. The combined filtrates were concentrated in vacuo.

The residue was dried under high vacuum overnight to afford 3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline (12.1 g, 63.0 mmol, 93 % yield) as a blackish/grey solid . LC–MS $(M+H)^+$ 193.2. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.31 (d, *J*=2.4 Hz, 1 H), 7.47 (t, *J*=8.7 Hz, 1 H), 6.47 - 6.58 (m, 2 H), 3.97 (br. s., 2 H), 2.48 (s, 3 H).

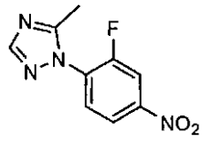
Preparation C

3-Fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline



Intermediate C(1)

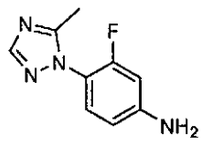
1-(2-fluoro-4-nitrophenyl)-5-methyl-1H-1,2,4-triazole



A mixture of 3-methyl-1H-1,2,4-triazole (15.0 g, 181 mmol), 1,2-difluoro-4-nitrobenzene (28.7 g, 181 mmol), and sodium bicarbonate (15.2 g, 181 mmol) in DMSO (100 mL) was heated at 80 °C for 48 h. The reaction mixture was allowed to cool to rt and was poured into water (800 mL). The aqueous mixture was extracted with EtOAc (3 x 200 mL). The combined organic extracts were sequentially washed with water (500 mL) and brine solution (100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude reaction mixture was purified using silica gel chromatography (30-80% EtOAc/hexane, linear gradient) to afford two regioisomeric products. Pure fractions of the less polar regioisomer were combined and concentrated to afford 1-(2-fluoro-4-nitrophenyl)-3-methyl-1H-1,2,4-triazole (7.2 g, 30.8 mmol, 17 % yield) as an off-white solid. Pure fractions of the more polar regioisomer were combined and concentrated to afford 1-(2-fluoro-4-nitrophenyl)-5-methyl-1H-1,2,4-triazole (6.23 g, 28.0 mmol, 15 % yield) as an off-white solid. Data for 1-(2-fluoro-4-nitrophenyl)-5-methyl-1H-1,2,4-triazole: LC–MS $(M+H)^+ = 223.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.18 - 8.24 (m, 2 H) 8.04 (s, 1 H) 7.69 - 7.78 (m, 1 H) 2.47-2.53 (m, 3 H).

Preparation C

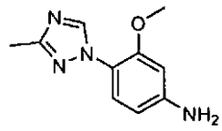
3-Fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline



10% Palladium on carbon (1.5 g, 14.1 mmol) was added under an atmosphere of nitrogen to a chilled (ice-water bath) solution of 1-(2-fluoro-4-nitrophenyl)-5-methyl-1H-1,2,4-triazole (3.7 g, 17 mmol) dissolved in methanol (200 mL). The flask was repeatedly evacuated and flushed with hydrogen gas (double balloon). The resulting mixture was allowed to warm to rt and left to stir for 18 h under the hydrogen atmosphere. The vessel was subsequently purged with nitrogen gas. The crude reaction mixture was filtered through a short plug of diatomaceous earth (Celite®). The reaction vessel and Celite® were rinsed with fresh methanol. The combined filtrates were concentrated in vacuo. The residue was dried under high vacuum to afford 3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline (3.14 g, 91 % yield) as a blackish/grey solid . LC–MS $(M+H)^+$ 193.1. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.91 (s, 1 H) 7.14 (t, *J*=8.55 Hz, 1 H) 6.43 - 6.53 (m, 2 H) 4.04 (br. s., 2 H) 2.36 (s, 3 H).

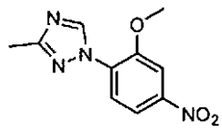
Preparation D

3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline



Intermediate D(1)

1-(2-methoxy-4-nitrophenyl)-3-methyl-1H-1,2,4-triazole

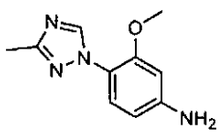


A mixture of 3-methyl-1H-1,2,4-triazole (5.0 g, 60.2 mmol), 1-chloro-2-methoxy-4-nitrobenzene (11.3 g, 60.2 mmol), and KOH flakes (3.4 g, 48.1 mmol) in anhydrous DMSO (50 mL) was heated at 80 °C for 6 h. The reaction mixture was allowed to cool to rt and was poured into 800 mL of water with vigorous stirring. The aqueous mixture was

extracted with EtOAc (3 x 200 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified using silica gel chromatography (0-2% MeOH/chloroform, linear gradient) to afford 1-(2-methoxy-4-nitrophenyl)-3-methyl-1H-1,2,4-triazole (3.7 g, 26 % yield). LC–MS $(M+H)^+$ = 235.2.

Preparation D

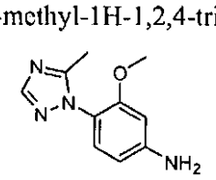
3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline



10% Palladium on carbon (1.2 g) was added under an atmosphere of nitrogen to a chilled (ice-water bath) solution of 1-(2-methoxy-4-nitrophenyl)-3-methyl-1H-1,2,4-triazole (3.7 g, 12.7 mmol) dissolved in methanol (250 mL). The flask was repeated evacuated and flushed with hydrogen gas (double balloon). The resulting mixture was allowed to warm to rt and left to stir for 18 h under the hydrogen atmosphere. Purged with nitrogen gas. Filtered the crude reaction mixture through a short diatomaceous earth (Celite®) plug. Rinsed reaction vessel and plug with methanol. Concentrated filtrate in vacuo. Dried residue on high vacuum overnight to afford 3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline (2.44 g, 94 % yield) as a reddish solid. LC–MS $(M+H)^+$ 205.2. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.35 (s, 1 H) 7.36 (d, *J*=8.55 Hz, 1 H) 6.29 - 6.34 (m, 2 H) 3.80 (s, 3 H) 2.46 (s, 3 H).

Preparation DD

3-methoxy-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline

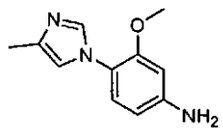


Intermediate C(1) was reacted with NaOMe in DMF to afford 1-(2-methoxy-4-nitrophenyl)-5-methyl-1H-1,2,4-triazole, which was reduced with Fe and ammonium chloride to afford the title compound. LC–MS $(M+H)^+$ 205.1. 1H NMR (500 MHz,

CHLOROFORM-d) δ ppm 7.90 (1 H, s), 7.05 (1 H, d, *J*=7.93 Hz), 6.27 - 6.34 (2 H, m), 3.91 (2 H, br. s.), 3.73 (3 H, s), 2.29 (3 H, s).

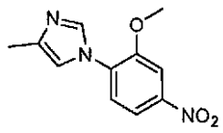
Preparation E

3-methoxy-4-(4-methyl-1H-imidazol-1-yl)aniline



Intermediate E(1)

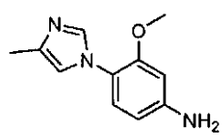
1-(2-methoxy-4-nitrophenyl)-4-methyl-1H-imidazole



A mixture of 4-methyl-1H-imidazole (18.0 g, 53.5 mmol), 1-chloro-2-methoxy-4-nitrobenzene (10.0 g, 53.5 mmol), and potassium hydroxide (4.5 g, 80.3 mmol) in DMSO (50 mL) was heated at 110 °C for 24 h. The reaction mixture was allowed to cool to rt and was poured into 1000 mL of water. The aqueous mixture was extracted with dichloromethane (3 x 250 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude reaction mixture was purified using silica gel chromatography (330 g silica cartridge, 0-2% MeOH/chloroform, linear gradient over 72 min, flow 25 mL/min) to afford 1-(2-methoxy-4-nitrophenyl)-4-methyl-1H-imidazole (2.56 g, 20 % yield) as a yellow/orange solid. LC–MS $(M+H)^+ = 234.1$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.97 - 8.00 (m, 1 H) 7.93 - 7.97 (m, 2 H) 7.45 (d, *J*=8.85 Hz, 1 H) 7.02 (s, 1 H) 4.02 (s, 3 H) 2.35 (s, 3 H).

Preparation E

3-methoxy-4-(4-methyl-1H-imidazol-1-yl)aniline

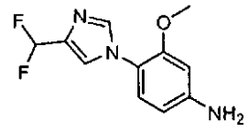


10% Palladium on carbon (250 mg) was added under an atmosphere of nitrogen to a chilled (ice-water bath) solution of 1-(2-methoxy-4-nitrophenyl)-4-methyl-1H-imidazole (2.56 g, 11.0 mmol) dissolved in methanol (150 mL). The flask was repeated

evacuated and flushed with hydrogen gas (double balloon). The resulting mixture was allowed to warm to rt and left to stir for 18 h under the hydrogen atmosphere. Purged with nitrogen gas. Filtered the crude reaction mixture through a short diatomaceous earth (Celite®) plug. Rinsed reaction vessel and plug with methanol. Concentrated filtrate in vacuo. Dried residue on high vacuum overnight to afford 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)aniline (2.25 g, 100 % yield) as a blackish/grey waxy solid . LC–MS $(M+H)^+$ 204.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.69 (s, 1 H) 7.01 (d, *J*=8.55 Hz, 1 H) 6.82 (s, 1 H) 6.33 (d, *J*=2.14 Hz, 1 H) 6.30 (d, *J*=8.55 Hz, 1 H) 3.78 (s, 3 H) 2.33 (s, 3 H).

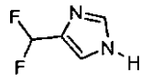
Preparation EE

3-methoxy-4-(4-difluoromethyl-1H-imidazol-1-yl)aniline



Intermediate EE(1)

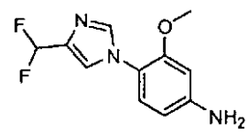
4-(difluoromethyl)-1H-imidazole



A solution of 1-trityl-1H-imidazole-4-carbaldehyde in dichloromethane at 0 oC was added deoxyfluor and stirred for 3 days. The product was then treated with 1:5 AcOH/HCl at ambient temperature overnight to afford 4-(difluoromethyl)-1H-imidazole.

Preparation EE

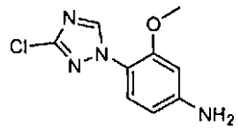
3-methoxy-4-(4-difluoromethyl-1H-imidazol-1-yl)aniline



Intermediate EE(1) was reacted as described for Preparation E to afford the desired Preparation EE. LC–MS $(M+H)^+$ 240.2. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.42 (s, 1 H) 7.93 (s, 1 H), 7.48 (d, J = 8.4 Hz, 1 H) 7.19-6.88 (m, 3 H) 3.81 (s, 3 H).

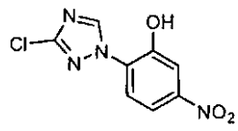
Preparation F

4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyaniline



Intermediate F(1)

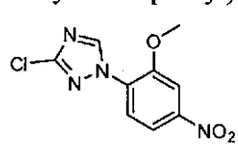
2-(3-chloro-1H-1,2,4-triazol-1-yl)-5-nitrophenol



A mixture of 3-chloro-1H-1,2,4-triazole (2.76 g, 26.7 mmol), 1-chloro-2-methoxy-4-nitrobenzene (5.0 g, 26.7 mmol), potassium hydroxide flakes (1.496 g, 26.7 mmol), and DMSO (25 mL) was heated in a sealed reaction vessel 100 °C for 24 h. The reaction was allowed to cool to rt and additional portions of 3-chloro-1H-1,2,4-triazole (1.38 g, 0.5 equiv) and potassium hydroxide (0.75 g, 0.5 equiv) were added. The reaction vessel was resealed and heated to 110 °C for an additional 24 h. The resulting mixture was allowed to cool to rt and was poured into 500 mL of water. The aqueous mixture was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified using silica gel chromatography (0-5% MeOH/chloroform, linear gradient over 144 min, flow 25 mL/min) to afford 2-(3-chloro-1H-1,2,4-triazol-1-yl)-5-nitrophenol (0.924 g, 3.84 mmol, 14.4 % yield). LC–MS $(M+H)^+ = 241.0$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.97 (br. s., 1 H) 9.24 (s, 1 H) 7.90 - 7.95 (m, 1 H) 7.89 (d, *J*=2.44 Hz, 1 H) 7.84 (dd, *J*=8.85, 2.44 Hz, 1 H).

Intermediate F(2)

3-chloro-1-(2-methoxy-4-nitrophenyl)-1H-1,2,4-triazole

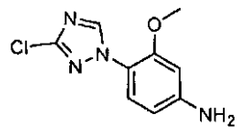


Iodomethane (0.860 mL, 13.82 mmol) was added to a mixture of 2-(3-chloro-1H-1,2,4-triazol-1-yl)-5-nitrophenol (1.33 g, 5.53 mmol), potassium hydroxide (0.388 g, 6.91

mmol), and DMSO (25 mL). The mixture was left to stir at rt for 24 h. The reaction mixture was poured into water (250 mL) and extracted with EtOAc (3x100 mL). The combined extracts were washed with water, washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified using silica gel column chromatography (0-1% MeOH/chloroform, linear gradient over 72 min, flow 25 mL/min). The pure fractions were combined and concentrated to afford 3-chloro-1-(2-methoxy-4-nitrophenyl)-1H-1,2,4-triazole (0.924 g, 3.63 mmol, 65.6 % yield) as a light yellow solid. LC–MS $(M+H)^+ = 255.0$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.35 (s, 1 H) 7.36 (d, *J*=8.55 Hz, 1 H) 6.29 - 6.34 (m, 2 H) 3.80 (s, 3 H) 2.46 (s, 3 H).

Preparation F

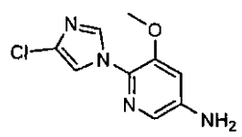
4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyaniline



Water (8 mL) and dioxane (8 mL) were added to a mixture of 3-chloro-1-(2-methoxy-4-nitrophenyl)-1H-1,2,4-triazole (0.900 g, 3.53 mmol) and sodium sulfide (1.379 g, 17.67 mmol) in a 20 mL vial. The vial was capped and heated at 70-80 °C for 24 hours. The mixture was cooled to rt, poured into water (300 mL) and extracted with EtOAc (2x150 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo to afford 4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyaniline (577 mg, 73%) as a brown solid. LC–MS $(M+H)^+$ 225.1.

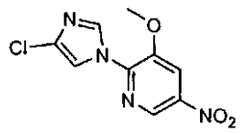
Preparation FF

6-(4-chloro-1H-imidazol-1-yl)-5-methoxypyridin-3-amine



Intermediate FF(1)

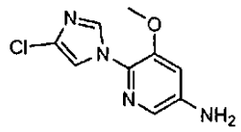
2-(4-chloro-1H-imidazol-1-yl)-3-methoxy-5-nitropyridine



A mixture of 4-chloro-1H-imidazole (2.72 g, 26.5 mmol), 2-chloro-3-methoxy-5-nitropyridine (5.0 g, 26.5 mmol), and KOH flakes 1.488 g, 26.5 mmol) in anhydrous DMSO (25 mL) was heated at 80 °C for 5 h. The reaction mixture was allowed to cool to rt and was poured into 1.0 L of water with vigorous stirring. The mixture was stirred at rt for 16 h. The precipitate was collected by vacuum filtration using a coarse sintered glass funnel. The solid was dried under high vacuum for 24 h to provide 2-(4-chloro-1H-imidazol-1-yl)-3-methoxy-5-nitropyridine (5.22 g, 20.50 mmol, 77 % yield) as a light brown solid. LC–MS $(M+H)^+ = 255.0$. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.94 (d, J=2.44 Hz, 1 H) 8.51 (d, J=1.83 Hz, 1 H) 8.42 (d, J=2.44 Hz, 1 H) 8.02 (d, J=1.83 Hz, 1 H) 4.12 (s, 3 H).

Preparation FF

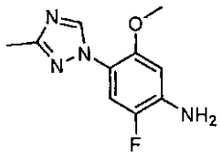
6-(4-chloro-1H-imidazol-1-yl)-5-methoxypyridin-3-amine



Iron powder–325 mesh (2.19 g, 39.3 mmol) was added to a flask charged with a mixture of 2-(4-chloro-1H-imidazol-1-yl)-3-methoxy-5-nitropyridine (5.0 g, 19.64 mmol), absolute ethanol (50 mL), and glacial acetic acid (20 mL). A water-cooled reflux condenser was attached to the flask and the heterogeneous mixture was heated to 100 °C with vigorous stirring for 30 min. The reaction mixture was allowed to cool to rt and was neutralized upon addition to a chilled and vigorously stirred solution of 5 M NaOH. The resulting mixture was poured into a separatory funnel and extracted with EtOAc. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford 6-(4-chloro-1H-imidazol-1-yl)-5-methoxypyridin-3-amine (3.12 g, 71 % yield). LC–MS $(M+H)^+$ 225.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.06 (d, J=1.83 Hz, 1 H) 7.53 (dd, J=13.28, 1.98 Hz, 2 H) 6.70 (d, J=2.44 Hz, 1 H) 3.90 (s, 3 H) 3.86 (br. s., 2 H).

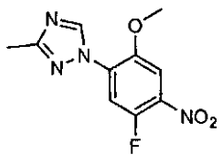
Preparation FFF

2-fluoro-5-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline



Intermediate FFF(1)

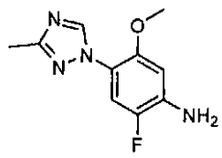
1-(5-fluoro-2-methoxy-4-nitrophenyl)-3-methyl-1H-1,2,4-triazole



A mixture of 3-methyl-1H-1,2,4-triazole (2.20 g, 26.4 mmol), 1,5-difluoro-2-methoxy-4-nitrobenzene (5.00 g, 26.4 mmol), and potassium carbonate (3.65 g, 26.4 mmol) in anhydrous DMSO (50 mL) was heated at 80 °C for 24 h. The reaction mixture was allowed to cool to rt and was poured into 500 mL of water/10 mL brine solution. The aqueous mixture was extracted with EtOAc (2 x 250 mL). The combined organic extracts were washed with water (500 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude reaction mixture was purified using silica gel column chromatography (50% EtOAc/hexane) to afford 1-(5-fluoro-2-methoxy-4-nitrophenyl)-3-methyl-1H-1,2,4-triazole (1.24 g, 18 % yield). LC–MS $(M+H)^+ = 253.2$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.95 (s, 1 H) 8.00 (d, *J*=11.60 Hz, 1 H) 7.80 (d, *J*=6.10 Hz, 1 H) 4.09 (s, 3 H) 2.50 (s, 3 H).

Preparation FFF

2-fluoro-5-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline

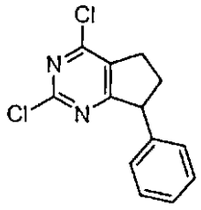


10% Palladium on carbon (0.523 g, 4.92 mmol) was added under an atmosphere of nitrogen to a chilled (ice-water bath) solution of 1-(5-fluoro-2-methoxy-4-nitrophenyl)-

3-methyl-1H-1,2,4-triazole (1.24 g, 4.92 mmol) dissolved in methanol (100 mL). The flask was repeatedly evacuated and flushed with hydrogen gas (double balloon). The resulting mixture was allowed to warm to rt and left to stir for 18 h under the hydrogen atmosphere. The vessel was subsequently purged with nitrogen gas. The crude reaction mixture was filtered through a short diatomaceous earth (Celite®) plug. The reaction vessel and plug were rinsed with fresh methanol. The combined filtrates were concentrated in vacuo. The residue was dried on high vacuum overnight to afford 2-fluoro-5-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline (1.05 g, 96 % yield) as a gray solid. LC–MS $(M+H)^+$ 223.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.46 (s, 1 H) 7.39 (d, *J*=11.29 Hz, 1 H) 6.44 (d, *J*=7.63 Hz, 1 H) 3.89 (br. s., 2 H) 3.83 (s, 3 H) 2.47 (s, 3 H).

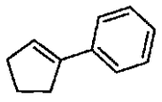
Preparation G

2,4-Dichloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



Intermediate G(1)

Cyclopentenylbenzene

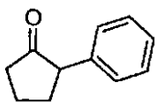


To a solution of 3.0 M solution of phenylmagnesium bromide in ether (49.7 mL, 149 mmol) was added THF (300 mL). To this solution cooled to 0°C cyclopentanone (13.23 mL, 149 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, then - at reflux for 2 h. Ice (20 g) was added, followed by 6N HCl, until the precipitate dissolved. The product was extracted with ether. The combined etherial layers were washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give cyclopentenylbenzene (21.49 g, 149 mmol, 100 % yield) as colorless oil. LC–MS $(M+H)^+$ = 145.1. ^{1}H NMR (500 MHz,

$CDCl_3$) δ ppm 7.48 (2H, d, *J*=7.3 Hz), 7.35 (2H, t, *J*=7.8 Hz), 7.22 - 7.27 (1H, m), 6.22 (1H, t, *J*=2.1 Hz), 2.70 - 2.80 (2H, m), 2.52 - 2.64 (2H, m), 2.01 - 2.12 (2H, m).

Intermediate G(2)

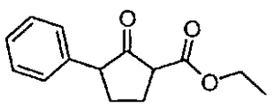
2-Phenylcyclopentanone



A mixture of 30% hydrogen peroxide (23 mL, 149 mmol) and 85% formic acid (100 mL, 2619 mmol) was heated at 40°C. for 15 minutes. The mixture was carefully added to cyclopentenylbenzene (21.49 g, 149 mmol) and the resulting two-phase system was vigorously stirred at room temperature for 4 h. An exothermic reaction was observed in the beginning. In the end of the stirring the solution became homogeneous. The reaction mixture was carefully quenched with saturated aqueous solution of sodium bicarbonate. The product was extracted with ether. The combined etherial layers were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the product was purified by column chromatography on silica gel to give 2-phenylcyclopentanone (19.995 g, 125 mmol, 84 % yield) as brown oil. LC–MS $(M+H)^+$ = 161.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.38 (1H, t, *J*=7.3 Hz), 7.30 - 7.35 (2H, m), 7.19 (2H, d, *J*=7.3 Hz), 3.28 - 3.37 (1H, m), 2.71 (1H, td, *J*=4.6, 2.7 Hz), 2.58 - 2.63 (1H, m), 2.43 - 2.55 (1H, m), 2.29 (1H, ddd, *J*=19.0, 10.5, 9.0 Hz), 2.07 - 2.21 (1H, m), 1.88 - 1.99 (1H, m).

Intermediate G(3)

Ethyl 2-oxo-3-phenylcyclopentanecarboxylate

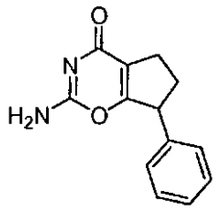


To a solution of diisopropylamine (6.62 mL, 46.8 mmol) in THF (200 mL) at -78 °C was added a 1.6 M solution of *n*-butyllithium in hexanes (29.3 mL, 46.8 mmol). The solution was stirred for 30 min at -78 °C and treated with a solution of 2-phenylcyclopentanone (5 g, 31.2 mmol) in 50 mL of dry THF. After stirring for 30 min at -78 °C, ethyl carbonocyanidate (3.36 mL, 34.3 mmol) was added to the reaction mixture. The resulting solution was warmed to 25 °C with stirring over 3 h. The reaction

mixture was quenched with 10 mL of water, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuum, and purified by column chromatography on silica gel to afford ethyl 2-oxo-3-phenylcyclopentanecarboxylate (5.3 g, 22.82 mmol, 73 % yield) as colorless oil. LC–MS $(M+K)^+ = 273.2$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 - 7.39 (2H, m), 7.25 - 7.31 (1H, m), 7.19 - 7.25 (2H, m), 4.18 - 4.32 (2H, m), 3.29 - 3.55 (2H, m), 1.87 - 2.62 (4H, m), 1.28 - 1.39 (3H, m).

Intermediate G(4)

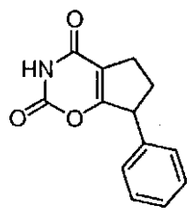
2-Amino-7-phenyl-6,7-dihydrocyclopenta[*e*][1,3]oxazin-4(5*H*)-one



2-Methyl-2-thiopseudourea sulfate (1.336 g, 9.61 mmol) was dissolved in water (10 mL) and KOH (1.128 g, 20.10 mmol) was added. Under stirring, ethyl 2-oxo-3-phenylcyclopentanecarboxylate (2.03 g, 8.74 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered, washed with water and ether, and dried over anhydrous sodium sulfate to afford 2-amino-7-phenyl-6,7-dihydrocyclopenta[*e*][1,3]oxazin-4(5*H*)-one (1.22 g, 5.35 mmol, 61.2 % yield) as white solid. LC–MS $(M+H)^+ = 229.1$. ^{1}H NMR (500 MHz, dimethylsulfoxide-*d6*) δ ppm 7.57 - 7.85 (2H, m), 7.08 - 7.47 (5H, m), 4.25 - 4.38 (1H, m), 1.72 - 2.73 (3H, m), 1.09 - 1.31 (1H, m).

Intermediate G(5)

7-Phenyl-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione



2-Amino-7-phenyl-6,7-dihydrocyclopenta[*e*][1,3]oxazin-4(5*H*)-one (900 mg, 3.94 mmol) was dissolved in a 3M aqueous hydrogen chloride solution (32 mL, 96 mmol)

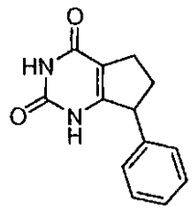
under stirring. The mixture was heated at reflux for 1 h. The reaction mixture was cooled and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, concentrated in vacuum and purified by column chromatography on silica gel to afford 7-phenyl-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (350 mg, 1.527 mmol, 38.7 % yield). LC–MS $(M+H)^+$ = 230.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.34 (1H, br s), 7.35 (2H, t, *J*=7.3 Hz), 7.27 - 7.32 (1H, m), 7.18 (2H, d, *J*=7.3 Hz), 4.20 (1H, t, *J*=7.6 Hz), 2.82 - 2.91 (1H, m), 2.61 - 2.79 (2H, m), 2.11 - 2.21 (1H, m).

or

A solution of 2-phenylcyclopentanone (19.995 g, 125 mmol) and N-(chlorocarbonyl)isocyanate (23.70 g, 225 mmol) was stirred at 58°C for 1 h and at 130°C for 45 min. The resulting tarrified reaction mixture was dissolved in ethyl acetate and neutralized with saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and filtered. The product was purified by column chromatography on silica gel to give 7-phenyl-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (3.751 g, 16.36 mmol, 13 % yield) as brownish solid. LC–MS $(M+H)^+$ = 230.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.34 (1H, br s), 7.35 (2H, t, *J*=7.3 Hz), 7.27 - 7.32 (1H, m), 7.18 (2H, d, *J*=7.3 Hz), 4.20 (1H, t, *J*=7.6 Hz), 2.82 - 2.91 (1H, m), 2.61 - 2.79 (2H, m), 2.11 - 2.21 (1H, m).

Intermediate G(6)

7-Phenyl-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione

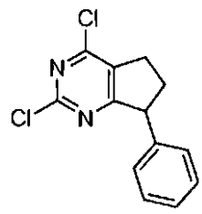


A solution of 7-phenyl-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (3.751 g, 16.36 mmol) in concentrated ammonia in water (80 mL, 16.36 mmol) was heated in a 350 mL high-pressure flask for 5 h. The solvent was removed in vacuum to give 7-phenyl-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (3.73 g, 16.34 mmol, 100 % yield) as brown solid. LC–MS $(M+H)^+$ = 229.1. ^{1}H NMR (500 MHz, dimethylsulfoxide-*d6*) δ ppm 7.34 (2H, t, *J*=7.5 Hz), 7.26 (1H, t, *J*=7.3 Hz), 7.18 (2H, d,

J=7.3 Hz), 5.39 (1H, br s), 4.14 (1H, d, *J*=7.3 Hz), 2.43 - 2.68 (2H, m), 1.80 - 1.88 (2H, m).

Preparation G

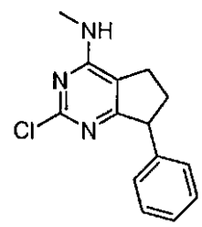
2,4-Dichloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



A solution of 7-phenyl-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (1.241 g, 5.44 mmol) in phosphoryl trichloride (14.93 mL, 163 mmol) was heated in microwave at 110 °C for 1 h. Once ice melted, the product was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2,4-dichloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (3.132 g, 72%) as light brown solid. LC–MS $(M+H)^+ = 265.0$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.31 - 7.37 (2H, m), 7.27 (1H, d, *J*=7.0 Hz), 7.15 (2H, d, *J*=7.9 Hz), 4.44 (1H, t, *J*=8.2 Hz), 3.09 - 3.18 (1H, m), 2.97 - 3.06 (1H, m), 2.73 (1H, ddd, *J*=9.0, 4.7, 4.6 Hz), 2.26 (1H, ddd, *J*=8.5, 7.0, 6.7 Hz).

Preparation Ga

2-chloro-N-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine

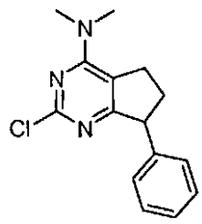


To a solution of 2,4-dichloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation G) (395 mg, 1.49 mmol) in THF (3700 µL), 2 M $MeNH_2$ in THF (3700 µL, 7.45 mmol) was added. The reaction was allowed to stir at rt. When the reaction was complete, removed solvent and applied residue to silica gel. Eluted with EtOAc/Hex to afford the desired 2-chloro-N-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-

4-amine (80.8 mg, 0.220 mmol, 69.1 % yield). LC–MS $(M+H)^+ = 260.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.07 (3H, dd, *J*=8.5, 5.5 Hz), 6.96 (2H, t, *J*=8.7 Hz), 4.72 (1H, br s), 4.23 (1H, t, *J*=7.2 Hz), 3.09 (3H, d, *J*=4.9 Hz), 2.67 - 2.77 (1H, m), 2.58 - 2.67 (2H, m), 2.01 - 2.11 (1H, m).

Preparation Gb

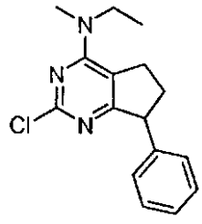
2-Chloro-*N*,*N*-dimethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



A solution of 2,4-dichloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (200 mg, 0.754 mmol) and excess dimethylamine (3.77 mL, 7.54 mmol) in MeOH (2 mL) was stirred at rt for 1 h. The solvent was removed in vacuum to afford 2-chloro-*N*,*N*-dimethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (207 mg, 0.756 mmol, 100 % yield). LC–MS $(M+H)^+ = 274.2$.

Preparation Gc

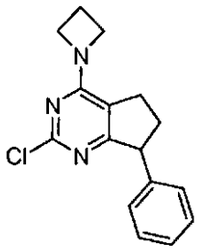
2-Chloro-*N*-ethyl-*N*-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



A solution of 2,4-dichloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (150 mg, 0.566 mmol) and excess *N*-methylethanamine (0.486 mL, 5.66 mmol) in MeOH (2 mL) was stirred at rt for 1 h. The solvent was removed in vacuum to afford 2-chloro-*N*-ethyl-*N*-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (163 mg, 0.566 mmol, 100 % yield). LC–MS $(M+H)^+ = 288.2$.

Preparation Gd

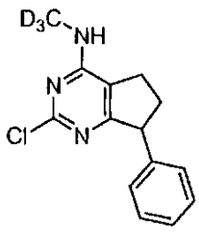
4-(Azetidin-1-yl)-2-chloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



A solution of 2,4-dichloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (150 mg, 0.566 mmol) and excess azetidine (162 mg, 2.83 mmol) in methanol (1 mL) was stirred at rt for 30 min. The solvent was removed in vacuum to afford 4-(azetidin-1-yl)-2-chloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (162 mg, 0.567 mmol, 100 % yield). LC–MS $(M+H)^+ = 286.3$.

Preparation Ge

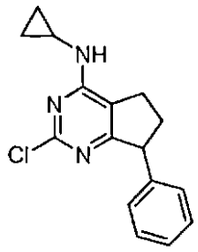
2-Chloro-*N*-trideuteromethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (350 mg, 1.236 mmol) and trideuteromethylamine hydrochloride (174 mg, 2.472 mmol) in methanol (3 mL) was added DIPEA (0.432 mL, 2.472 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2-chloro-*N*-trideuteromethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine as brown oil. LC-MS $(M+H)^+ = 281.2$.

Preparation Gf

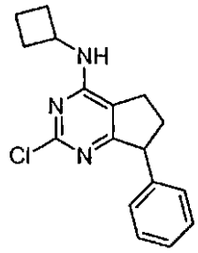
2-chloro-N-cyclopropyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine



To a solution of 2,4-dichloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine (170 mg, 0.641 mmol) in NMP (2 mL) was added cyclopropanamine (110 mg, 1.924 mmol) dropwise. The mixture was stirred at RT for 3 hours. 8 mL of water was added to precipitate out the product. The solid was filtered out and air-dried to give a crude 2-chloro-N-cyclopropyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (175 mg, 0.612 mmol, 96 % yield), which was used for the next step without any purification. LC-MS $(M+H)^+ = 286.1$

Preparation Gg

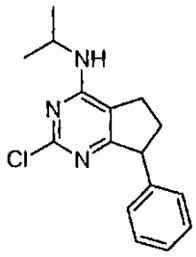
2-chloro-N-cyclobutyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine



To a solution of 2,4-dichloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine (160 mg, 0.60 mmol) in NMP (2 mL) was added cyclobutanamine (129 mg, 1.81 mmol) dropwise. The mixture was stirred at RT for 3 hrs. 8 mL of water was added to precipitate out the product. The solid was filtered out and air-dried to give a crude 2-chloro-N-cyclobutyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (177 mg, 0.57 mmol, 94 % yield), which was used for the next step without any purification. LC-MS $(M+H)^+ = 300.1$

Preparation Gh

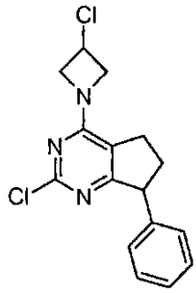
2-chloro-7-phenyl-N-isopropyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine



To a solution of 2,4-dichloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine (172 mg, 0.65 mmol) in NMP (2 mL) was added propan-2-amine (115 mg, 1.95 mmol) dropwise. The mixture was stirred at RT for 3 hrs. 8 mL of water was added to precipitate out the product. The solid was filtered out, air-dried, and purified via Biotage (12g, hexanes-70%EtOAc) to give 2-chloro-N-isopropyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (154 mg, 0.535 mmol, 82 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.30 (2 H, t, *J*=7.5 Hz), 7.20 - 7.25 (1 H, m), 7.15 (1 H, d, *J*=1.5 Hz), 7.13 (1 H, s), 4.53 (1 H, d, *J*=7.3 Hz), 4.37 - 4.45 (1 H, m), 4.23 - 4.28 (1 H, m), 2.58 - 2.78 (3 H, m), 2.10 - 2.17 (1 H, m), 1.27 - 1.29 (6 H, m).

Preparation Gi

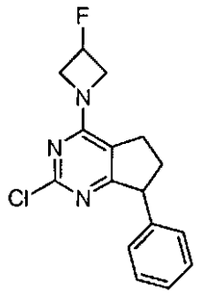
2-chloro-4-(3-chloroazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine



The mixture of 3-chloroazetidine, HCl (217 mg, 1.697 mmol), 2,4-dichloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine (150 mg, 0.566 mmol) and DIEA (0.395 mL, 2.263 mmol) in N-Methyl-2-pyrrolidinone (2.0 mL) was stirred at RT for 3 h. Water (8 ml) was added to the reaction mixture. The product precipitated out which was filtered, rinsed with water and air dried. LC–MS $(M+H)^+$ = 320.0. ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.21 - 7.39 (m, 3 H) 7.14 (d, *J*=7.02 Hz, 2 H) 4.65 - 4.84 (m, 3 H) 4.34 - 4.48 (m, 2 H) 4.23 (dd, *J*=9.16, 6.41 Hz, 1 H) 3.00 (dd, *J*=8.85, 5.80 Hz, 1 H) 2.83 - 2.93 (m, 1 H) 2.54 - 2.72 (m, 1 H) 2.02 - 2.20 (m, 1 H).

Preparation Gj

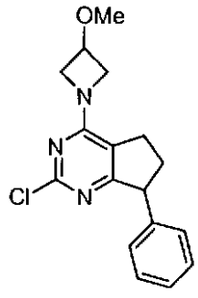
2-chloro-4-(3-fluoroazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine



3-fluoroazetidine was reacted with Preparation G in the manner of Preparation Gi to afford the title compound. LC–MS $(M+H)^+ = 304.1$. ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.19 - 7.37 (m, 3 H) 7.15 (d, *J*=7.32 Hz, 2 H) 5.39 – 5.52 (m, 1 H) 4.59 (dddd, *J*=14.88, 10.15, 5.19, 4.88 Hz, 2 H) 4.30 - 4.50 (m, 2 H) 4.23 (dd, *J*=9.00, 6.26 Hz, 1 H) 2.96 - 3.07 (m, 1 H) 2.84 - 2.96 (m, 1 H) 2.56 - 2.70 (m, 1 H) 2.05 - 2.21 (m, 1 H).

Preparation Gk

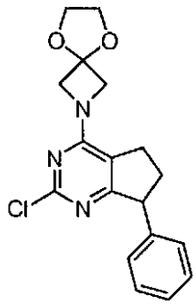
2-chloro-4-(3-methoxyazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine



3-methoxyazetidine was reacted with Preparation G in the manner of Preparation Gi to afford the title compound. LC–MS $(M+H)^+ = 316.1$.

Preparation Gl

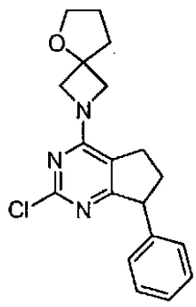
2-(2-chloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-5,8-dioxa-2-azaspiro[3.4]octane



Azetidin-3-one was reacted with Preparation G in the manner of Preparation Gi to afford 1-(2-chloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)azetidin-3-one. LC–MS $(M+H)^+ = 300.0$ A mixture of ethylene glycol (119 μL, 2.135 mmol), 1-(2-chloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)azetidin-3-one (320 mg, 1.068 mmol) and 4-methylbenzenesulfonic acid, H2O (20.31 mg, 0.107 mmol) in Benzene (2965 μL) was heated at reflux for 24 h in a Dean-stark apparatus. The resulting mixture was concentrated and purified by Prep-HPLC to afford the title compound. LC–MS $(M+H)^+ = 344.0$. ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.21 - 7.40 (m, 3 H) 7.15 (d, *J*=7.63 Hz, 2 H) 4.35 - 4.53 (m, 4 H) 4.23 (dd, *J*=9.00, 6.26 Hz, 1 H) 4.03 (s, 4 H) 2.96 - 3.09 (m, 1 H) 2.80 - 2.96 (m, 1 H) 2.51 - 2.70 (m, 1 H) 2.03 - 2.16 (m, 1 H).

Preparation Gm

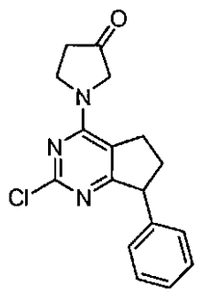
2-(2-chloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-5-oxa-2-azaspiro[3.4]octane



5-oxa-2-azaspiro[3.4]octane was reacted with Preparation G in the manner of Preparation Gi to afford the title compound. LC–MS $(M+H)^+ = 342.1$.

Preparation Gn

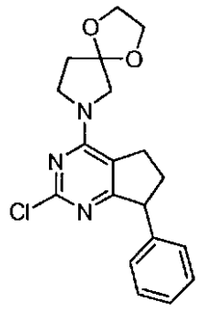
1-(2-chloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)pyrrolidin-3-one



Pyrrolidin-3-one was reacted with Preparation G in the manner of Preparation Gi to afford the title compound. LC–MS $(M+H)^+ = 314.1$.

Preparation Go

7-(2-chloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-1,4-dioxa-7-azaspiro[4.4]nonane

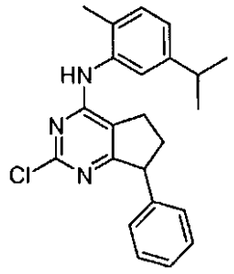


The mixture of ethylene glycol (46.9 µL, 0.841 mmol), 1-(2-chloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)pyrrolidin-3-one (Intermediate Gn) (132 mg, 0.421 mmol) and 4-methylbenzenesulfonic acid, H2O (8.00 mg, 0.042 mmol) in Benzene (1169 µL) was heated at reflux for 24 h in a Dean-stark apparatus. The resulting mixture was concentrated and purified by Prep-HPLC (Column: PHENOMENEX LUNA C18 30 x100 mm, Solvent A = 10 mM Ammonium Acetate in 95 : 5 H2O / ACN, Solvent B = 10 mM Ammonium Acetate in 5 : 95 H2O / ACN,. Flow rate: 40 ml / min, 30-100, 20 min) to get 7-(2-chloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-1,4-dioxa-7-azaspiro[4.4]nonane (24 mg, 0.067 mmol, 15.94 % yield). LC–MS $(M+H)^+ = 358.1$. 1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.31 (2 H, t, *J*=7.63 Hz), 7.20 - 7.25 (1 H, m), 7.15 (2 H, d, *J*=7.63 Hz), 4.21 (1 H, dd, *J*=9.16, 6.10 Hz), 4.01 - 4.06 (4 H, m), 3.89 - 3.97 (2 H, m), 3.77 - 3.84 (2 H, m), 3.26

(1 H, ddd, *J*=15.03, 8.62, 5.95 Hz), 3.13 (1 H, ddd, *J*=14.95, 8.85, 5.80 Hz), 2.53 - 2.63 (1 H, m), 2.17 (2 H, t, *J*=7.17 Hz), 2.03 - 2.12 (1 H, m).

Preparation Gp

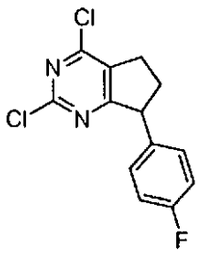
2-chloro-N-(5-isopropyl-2-methylphenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine



To a solution of 2,4-dichloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine (500 mg, 1.886 mmol) inNMP (Volume: 7543 µl) was added 5-isopropyl-2-methylaniline (281 mg, 1.886 mmol) and DIPEA (329 µl, 1.886 mmol). The resulting mixture was brought to 120 °C and stirred for 2 h. The mixture was then diluted with EtOAc(25 mL), washed with water(2 x 10 mL), brine(10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (Silica, Thomson 40g, 0 - 35% EtOAc/Hexanes) gave 2-chloro-N-(5-isopropyl-2-methylphenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (81421-078-01) (220 mg, 0.582 mmol, 30.9 % yield). LC–MS $(M+H)^+$ = 378.1. 1H NMR (500 MHz, *MeOD*) δ ppm 7.30 - 7.41 (3 H, m), 7.19 - 7.26 (3 H, m), 7.16 (2 H, d, *J*=7.93 Hz), 7.11 (1 H, d, *J*=7.63 Hz), 4.27 (1 H, t, *J*=7.63 Hz), 2.91 (1 H, ddd, *J*=13.89, 6.87, 6.71 Hz), 2.77 - 2.86 (1 H, m), 2.61 - 2.76 (2 H, m), 2.24 (3 H, s), 2.03 - 2.13 (1 H, m), 1.27 (5 H, dd, *J*=7.02, 1.53 Hz).

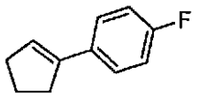
Preparation H

2,4-Dichloro-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



Intermediate H(1)

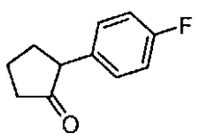
1-Cyclopentenyl-4-fluorobenzene



To a 0.5M solution of 4-fluorophenylmagnesium bromide (298 mL, 149 mmol) in THF at 0°C was carefully added cyclopentanone (13.23 mL, 149 mmol). Upon the end of the addition, the reaction mixture was heated at reflux for 2 h. Ice (10 g) and 6N aqueous hydrochloric acid were added. The reaction mixture was extracted with ether. The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogen sulfite, a saturated aqueous solution of sodium bicarbonate and water. The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 1-cyclopentenyl-4-fluorobenzene (24.155 g, 149 mmol, 100 % yield) as colorless oil. LC-MS $(M+H)^+$ = 163.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.35 - 7.42 (2H, m), 6.95 - 7.02 (2H, m), 6.06 - 6.13 (1H, m), 2.63 - 2.71 (2H, m), 2.47 - 2.56 (2H, m), 1.96 - 2.06 (2H, m).

Intermediate H(2)

2-(4-Fluorophenyl)cyclopentanone

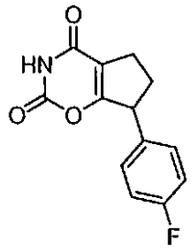


A mixture of 80% formic acid (100 mL, 2618 mmol) and 30% hydrogen peroxide (23 mL, 149 mmol) was warmed at 40°C for 10 min. The resulting solution was carefully added to 1-cyclopentenyl-4-fluorobenzene (24.155 g, 149 mmol) under stirring. The two-phase system was initially stirred at room temperature. After a certain period of time, a spontaneous exothermic reaction took place, and the temperature rose to about 50°C. The

reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by careful addition of a saturated sodium bicarbonate solution. Ether was added and the content of the separatory funnel was vigorously shaken. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2-(4-fluorophenyl)cyclopentanone (18.557 g, 104 mmol, 69.9 % yield) as colorless oil. LC-MS $(M+H)^+ = 177.2$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.12 - 7.18 (2H, m), 6.98 - 7.04 (2H, m), 3.29 (1H, dd, *J*=11.6, 8.5 Hz), 2.42 - 2.54 (2H, m), 2.27 (1H, ddd, *J*=19.1, 10.5, 8.9 Hz), 2.12 - 2.20 (1H, m), 2.01 - 2.12 (1H, m), 1.87 - 1.99 (1H, m, *J*=11.7, 11.7, 8.2, 6.3 Hz).

Intermediate H(3)

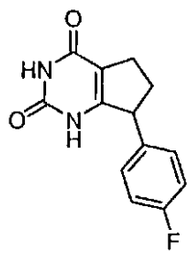
7-(4-Fluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione



A mixture of 2-(4-fluorophenyl)cyclopentanone (18.557 g, 104 mmol) and carbonisocyanatidic chloride (19.77 g, 187 mmol) was heated at 58°C for 1 h and at 130°C for 2 h. Upon cooling to room temperature, the tarrified reaction mixture was dissolved in ethyl acetate and washed with saturated aqueous solution of sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 7-(4-fluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (13.527 g, 54.7 mmol, 52.5 % yield) as brown solid. LC-MS $(M+H)^+ = 248.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.80 (1H, br s), 7.31 - 7.39 (2H, m), 7.16 - 7.22 (2H, m), 4.30 - 4.38 (1H, m), 2.63 - 2.73 (1H, m), 2.53 - 2.63 (2H, m), 1.84 - 1.95 (1H, m).

Intermediate H(4)

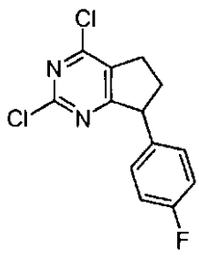
7-(4-Fluorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione



A solution of 7-(4-fluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (13.527 g, 54.7 mmol) in concentrated ammonium hydroxide (150 mL, 3852 mmol) was heated at 100°C in a high-pressure (350 mL) vessel overnight. The reaction mixture was cooled to 0°C and filtered. The precipitate was consecutively washed with water and dried, first - by passing air through the filter, and then - in pump vacuum to give 7-(4-fluorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (4.670 g, 18.97 mmol, 34.7 % yield). LC-MS $(M+H)^+ = 247.3$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.70 - 11.81 (2H, br s), 7.31 - 7.39 (2H, m), 7.16 - 7.22 (2H, m), 4.30 - 4.38 (1H, m), 2.63 - 2.73 (1H, m), 2.53 - 2.63 (2H, m), 1.84 - 1.95 (1H, m).

Preparation H

2,4-Dichloro-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine

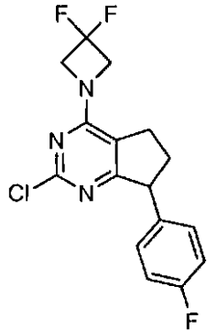


A solution of 7-(4-fluorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (1 g, 4.06 mmol) in phosphorus oxychloride (11.81 mL, 127 mmol) and *N*,*N*-dimethylaniline (3.94 mL, 31.1 mmol) was stirred at 110 °C overnight. The reaction mixture was carefully poured into ice. Once the ice melted, the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (700.0 mg, 2.472 mmol, 60.9 %

yield) as dark burgundy solid. LC-MS $(M+H)^+ = 283.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.09 - 7.15 (2H, m), 7.03 (2H, t, *J*=8.5 Hz), 4.42 (1H, t, *J*=8.4 Hz), 3.10 (1H, dd, *J*=9.2, 4.6 Hz), 3.01 (1H, d, *J*=8.2 Hz), 2.73 (1H, d, *J*=8.9 Hz), 2.15 - 2.27 (1H, m).

Preparation Ha

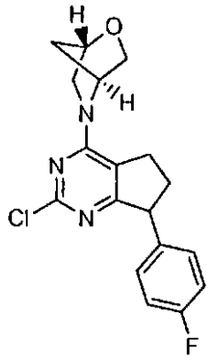
2-chloro-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine



To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (521 mg, 1.840 mmol) in MeOH (18.400 mL) was added DIPEA (0.803 mL, 4.60 mmol), then 3,3-difluoroazetidine, HCl (358 mg, 2.76 mmol). The reaction was allowed to stir at RT for 2 h and was then concentrated *in vacuo*. Purification by flash chromatography (silica, ethyl acetate/hexanes) gave 2-chloro-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (528 mg, 1.554 mmol, 84 % yield) as a clear, colorless oil which crystallized on standing. LC-MS $(M+H)^+ = 340.0$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.05 - 7.13 (2 H, m), 6.94 - 7.02 (2 H, m), 4.60 (4 H, td, *J*=11.75, 4.27 Hz), 4.18 - 4.30 (1 H, m), 2.93 - 3.06 (1 H, m), 2.80 - 2.95 (1 H, m), 2.56 - 2.70 (1 H, m), 1.96 - 2.18 (1 H, m).

Preparation Hb

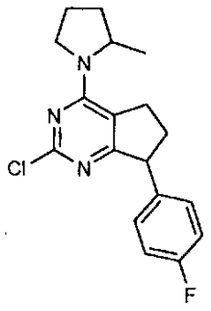
(1S,4S)-5-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-2-oxa-5-azabicyclo[2.2.1]heptane



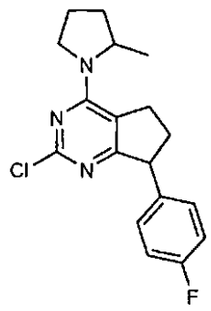
To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (200 mg, 0.706 mmol) in MeOH (7064 µL) was added (1S,4S)-2-Oxa-5-azabicyclo[2.2.1]heptane monohydrochloride (115 mg, 0.848 mmol) and DIPEA (271 µL, 1.554 mmol). The resulting mixture was stirred at RT overnight. The reaction mixture was then concentrated *in vacuo*. The resulting oil was purified by flash chromatography (Silica, EtOAc/Hexanes) to give (1S,4S)-5-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-2-oxa-5-azabicyclo[2.2.1]heptane (148 mg, 0.428 mmol, 60.6 % yield). LC-MS $(M+H)^+$ = 346.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.12 - 7.21 (2 H, m), 7.00 - 7.08 (2 H, m), 5.11 - 5.21 (1 H, m), 4.69 - 4.74 (1 H, m), 4.15 - 4.26 (1 H, m), 3.88 - 3.94 (2 H, m), 3.68 - 3.86 (2 H, m), 3.11 - 3.21 (1 H, m), 2.56 - 2.69 (1 H, m), 1.92 - 2.11 (2 H, m), 1.24 - 1.42 (2 H, m).

Preparations Hc1 and Hc2

2-chloro-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine



Hc1
Diastereomer 1
Racemic

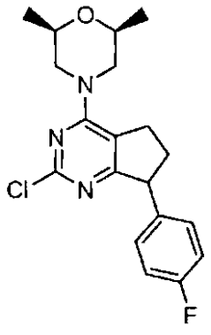


Hc2
Diastereomer 2
Racemic

To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation *H*) (200 mg, 0.706 mmol) in MeOH (7064 μL) was added 2-Methylpyrrolidine (82 μL, 0.848 mmol). The resulting mixture was stirred at RT for 2 days. The reaction mixture was then concentrated *in vacuo*. The resulting oil was purified by flash chromatography (Silica, EtOAc/Hexanes) to give two racemic pairs of diasteriomers 2-chloro-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine. (*Hc1*, Diastereomer 1, racemic, first to elute) (79.5 mg, 0.240 mmol, 33.9 % yield). LC-MS $(M+H)^+$ = 332.1; ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.16 (2 H, d, *J*=5.49 Hz), 7.04 (2 H, s), 4.42 - 4.54 (1 H, m), 4.09 - 4.22 (1 H, m), 3.86 - 4.00 (1 H, m), 3.71 - 3.82 (1 H, m), 3.24 - 3.31 (1 H, m), 3.10 - 3.22 (1 H, m), 2.54 - 2.65 (1 H, m), 2.05 - 2.16 (2 H, m), 1.94 - 2.05 (2 H, m), 1.69 - 1.80 (1 H, m), 1.27 (3 H, d, *J*=6.10 Hz). (*Hc2*, Diastereomer 2, racemic, second to elute) (89.5 mg, 0.270 mmol, 38 % yield). LC-MS $(M+H)^+$ = 332.1; ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.14 (2 H, d, *J*=5.49 Hz), 6.99 - 7.08 (2 H, m), 4.42 - 4.54 (1 H, m), 4.13 - 4.22 (1 H, m), 3.86 - 4.00 (1 H, m), 3.71 - 3.83 (1 H, m), 3.25 - 3.32 (1 H, m), 3.14 - 3.25 (1 H, m), 2.52 - 2.67 (1 H, m), 2.05 - 2.19 (2 H, m), 1.94 - 2.05 (2 H, m), 1.68 - 1.78 (1 H, m), 1.19 - 1.32 (3 H, m). The relative stereochemistry for *Hc1* and *Hc2* was not determined.

Preparation Hd

(2S,6R)-4-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-2,6-dimethylmorpholine

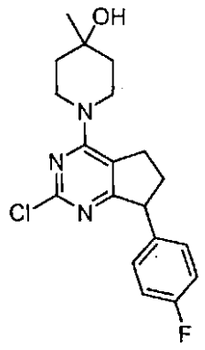


To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (200 mg, 0.706 mmol) in MeOH (7064 μL) was added cis-2,6-Dimethylmorpholine (105 μL, 0.848 mmol). The resulting mixture was stirred at RT overnight. An additional 2 equ. of cis-2,6-Dimethylmorpholine was

then added and the mixture was again stirred overnight at RT. The reaction mixture was then concentrated *in vacuo*. The resulting oil was purified by flash chromatography (Silica, EtOAc/Hexanes) to give (2S,6R)-4-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-2,6-dimethylmorpholine (223 mg, 0.616 mmol, 87 % yield). LC-MS $(M+H)^+$ = 332.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.11 - 7.24 (2 H, m), 6.99 - 7.09 (2 H, m), 4.39 - 4.51 (2 H, m), 4.20 (1 H, s), 3.70 (2 H, td, *J*=4.12, 2.44 Hz), 3.14 - 3.25 (1 H, m), 3.03 - 3.13 (1 H, m), 2.69 - 2.80 (2 H, m), 2.54 - 2.68 (1 H, m), 1.95 - 2.13 (1 H, m), 1.23 (6 H, d, *J*=6.10 Hz).

Preparation He

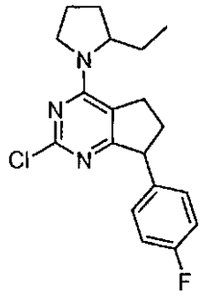
1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-4-methylpiperidin-4-ol



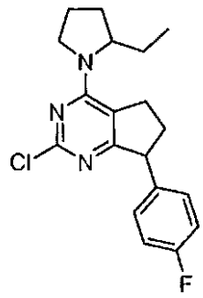
To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (400 mg, 1.413 mmol) in MeOH (14.100 mL) was added 4-methylpiperidin-4-ol (163 mg, 1.413 mmol). The resulting mixture was stirred at RT overnight. The reaction mixture was then concentrated *in vacuo*. Purification by flash chromatography (Silica, EtOAc/Hexanes) gave 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-4-methylpiperidin-4-ol (374 mg, 1.034 mmol, 73.2 % yield). LC-MS $(M+H)^+$ = 362.0. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.12 - 7.21 (2 H, m), 7.04 (2 H, t, *J*=8.85 Hz), 4.11 - 4.30 (3 H, m), 3.48 - 3.63 (2 H, m), 3.14 - 3.23 (1 H, m), 3.00 - 3.12 (1 H, m), 2.54 - 2.66 (1 H, m), 1.94 - 2.09 (1 H, m), 1.68 (4 H, t, *J*=4.12 Hz), 1.28 (3 H, s).

Preparations Hf1 and Hf2

2-chloro-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine



Hf1
Diastereomer 1
Racemic

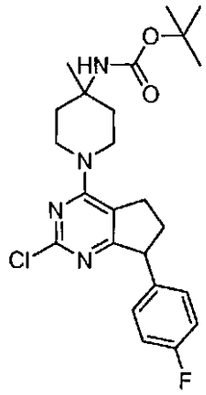


Hf2
Diastereomer 2
Racemic

2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (200 mg, 0.706 mmol) and 2-ethylpyrrolidine (84 mg, 0.848 mmol) were combined and purified as per *Preparation Hd* to give two pairs of racemic diasteriomers 2-chloro-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine. (*Hf1*, Diastereomer 1, racemic, first to elute) (77 mg, 0.223 mmol, 32% yield) LC-MS $(M+H)^+ = 346$. (*Hf2*, Diastereomer 2, racemic, second to elute) (80 mg, 0.232 mmol, 33% yield); LC-MS $(M+H)^+ = 346.2$. The relative stereochemistry for *Hf1* and *Hf2* was not determined.

Preparation Hg

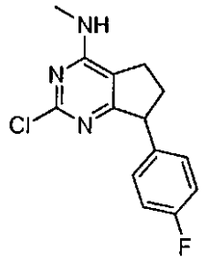
tert-butyl 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-4-methylpiperidin-4-ylcarbamate



To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (400 mg, 1.413 mmol) in MeOH (14.100 mL) was added tert-butyl 4-methylpiperidin-4-ylcarbamate (303 mg, 1.413 mmol). The resulting mixture was stirred at RT for 7 days. At that time, the reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (Silica, EtOAc/Hexanes) gave tert-butyl 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-4-methylpiperidin-4-ylcarbamate (159 mg, 0.345 mmol, 24.41 % yield) as a yellow foam. LC-MS $(M+H)^+ = 461.2$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.12 - 7.22 (2 H, m), 6.98 - 7.09 (2 H, m), 4.19 (3 H, d, *J*=2.14 Hz), 3.38 - 3.56 (2 H, m), 3.13 - 3.25 (1 H, m), 3.02 - 3.13 (1 H, m), 2.53 - 2.67 (1 H, m), 2.11 - 2.24 (2 H, m), 1.96 - 2.08 (1 H, m), 1.53 - 1.65 (2 H, m), 1.47 (9 H, s), 1.37 (3 H, s).

Preparation Hh

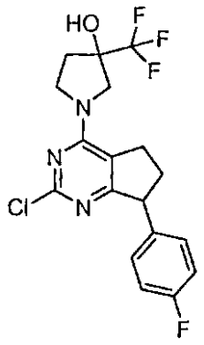
2-chloro-7-(4-fluorophenyl)-N-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine



2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (500 mg, 1.766 mmol) and methanamine hydrochloride (179 mg, 2.65 mmol) were combined and purified as per *Preparation Ha* to give 2-chloro-7-(4-fluorophenyl)-N-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (344 mg, 1.239 mmol, 70.1 % yield). LC-MS $(M+H)^+ = 278.0$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.03 - 7.12 (2 H, m), 6.91 - 7.03 (2 H, m), 4.53 - 4.79 (1 H, m), 4.19 - 4.29 (1 H, m), 3.09 (3 H, d, *J*=4.88 Hz), 2.56 - 2.80 (3 H, m), 2.00 - 2.15 (1 H, m).

Preparation Hi

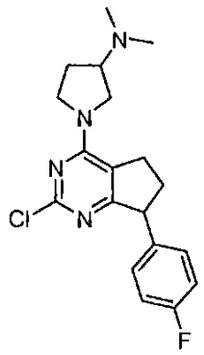
1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol



2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (286 mg, 1.010 mmol) and 3-(trifluoromethyl)pyrrolidin-3-ol (157 mg, 1.010 mmol) were combined and purified as per *Preparation Hb* to give 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol (62% yield). LC-MS $(M+H)^+ = 402.0$.

Preparation Hj

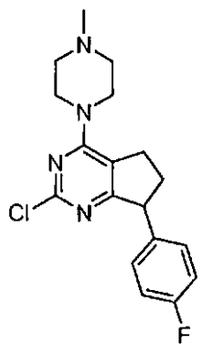
1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine



2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (100 mg, 0.353 mmol) and N,N-dimethylpyrrolidin-3-amine (44.3 μL, 0.353 mmol) were combined and purified as per *Preparation Hb* to give 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine (109 mg, 86% yield). LC-MS $(M+H)^+ = 361.2$.

Preparation Hk

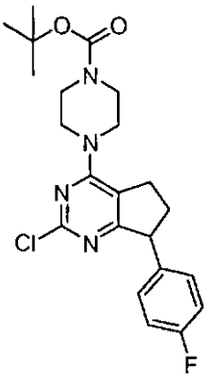
2-chloro-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine



2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (100 mg, 0.353 mmol) and 1-methylpiperazine (39.2 µL, 0.353 mmol) were combined and purified as per *Preparation Hb* to give 2-chloro-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine(109 mg, 0.314 mmol, 89 % yield). LC-MS $(M+H)^+ = 347.2$.

Preparation Hl

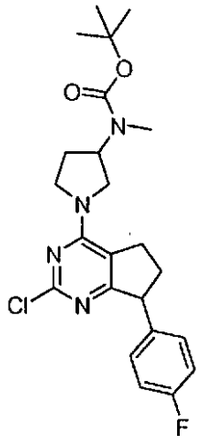
tert-butyl 4-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazine-1-carboxylate



2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (100 mg, 0.353 mmol) and tert-Butyl 1-piperazinecarboxylate (65.8 mg, 0.353 mmol) were combined and purified as per *Preparation Hb* to give tert-butyl 4-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazine-1-carboxylate (116.9 mg, 76% yield). LC-MS $(M+H)^+ = 433.3$.

Preparation Hm

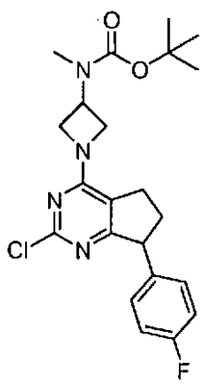
tert-butyl 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)pyrrolidin-3-yl(methyl)carbamate



2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (100 mg, 0.353 mmol) and 3-(N-tert-Butoxycarbonyl-N-methylamino)pyrrolidine (69.4 µL, 0.353 mmol) were combined and purified as per *Preparation Hb* to give tert-butyl 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)pyrrolidin-3-yl(methyl)carbamate (148 mg, 94% yield). LC-MS $(M+H)^+ = 447.2$.

Preparation Hn

tert-butyl 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)azetidin-3-yl(methyl)carbamate

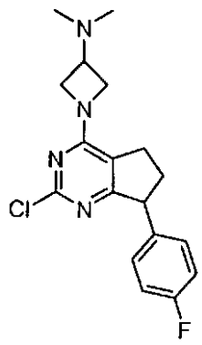


2,4-Dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (100 mg, 0.353 mmol) and carbamic acid, 3-azetidinylmethyl-, 1,1-

dimethylethyl ester (82 mg, 0.441 mmol) were combined and purified as per *Preparation Hb* to give tert-butyl 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)azetidin-3-yl(methyl)carbamate (147 mg, 96% yield). LC-MS $(M+H)^+ = 377.1$.

Preparation Ho

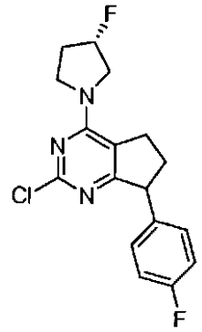
1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine



2,4-Dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation H*) (100 mg, 0.353 mmol) and N,N-dimethylazetidin-3-amine, 2 HCl (122 mg, 0.706 mmol) were combined and purified as per *Preparation Hb* to give 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine (quantitative). LC-MS $(M+H)^+ = 347.2$.

Preparation Hp1 and Hp2

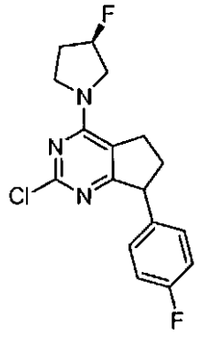
2-chloro-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H cyclopenta[d]pyrimidine



To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation H) (135 mg, 0.477 mmol) in MeOH (4768 μL) was added DIPEA (208 μL, 1.192 mmol), then (S)-3-fluoropyrrolidine (46.7 mg, 0.524 mmol). The reaction was allowed to stir at ambient temperature for 2 h. The solvent was removed and the residue applied to Silica gel and eluted with an EtOAc/Hex gradient to afford two diasteriomers (Hp1 and Hp2). Hp1: LC–MS $(M+H)^+$ = 336.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.06 - 7.13 (2 H, m), 6.93 - 7.00 (2 H, m), 5.32 (1 H, td, *J*=52.57, 3.17 Hz), 4.17 (1 H, dd, *J*=9.16, 5.49 Hz), 4.06 - 4.14 (1 H, m), 3.98 - 4.06 (1 H, m), 3.76 - 3.90 (2 H, m), 3.25 (1 H, ddd, *J*=15.11, 8.55, 6.26 Hz), 3.08 - 3.16 (1 H, m), 2.51 - 2.60 (1 H, m, *J*=13.20, 9.12, 9.12, 6.41 Hz), 2.32 - 2.42 (1 H, m), 2.00 - 2.17 (2 H, m). Hp2: LC–MS $(M+H)^+$ = 336.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.06 - 7.14 (2 H, m), 6.94 - 7.02 (2 H, m), 5.25 - 5.40 (1 H, m), 3.99 - 4.24 (3 H, m), 3.75 - 3.92 (2 H, m), 3.19 - 3.28 (1 H, m), 3.10 - 3.19 (1 H, m), 2.57 (1 H, dddd, *J*=13.24, 8.74, 8.55, 4.58 Hz), 2.31 - 2.43 (1 H, m), 1.94 - 2.17 (2 H, m)

Preparation Hq

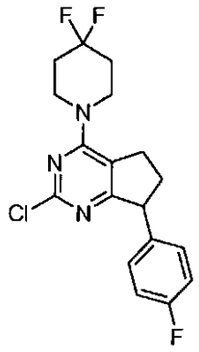
2-chloro-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H cyclopenta[d]pyrimidine



2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation H) was reacted as described in Preparation Hp1 and Hp2 with (R)-3-fluoropyrrolidine. The solvent was removed and the residue applied to Silica gel and eluted with an EtOAc/Hex gradient to afford the combined two diasteriomers (Hq). Ha1: LC–MS $(M+H)^+$ = 336.0.

Preparation Hr

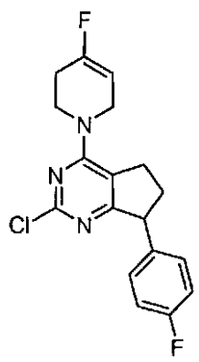
2-chloro-4-(4,4-difluoropiperidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine



To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation H) (90 mg, 0.318 mmol) in MeOH (3179 μL), 4,4-difluoropiperidine (115 mg, 0.95 mmol) was added. The reaction was allowed to stir at rt. When the reaction was complete, removed solvent and applied residue to Silica gel. Eluted with EtOAc/Hex to afford the desired 2-chloro-4-(4,4-difluoropiperidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (80.8 mg, 0.220 mmol, 69.1 % yield). LC–MS $(M+H)^+ = 368.0$.

Preparation Hs

2-chloro-4-(4-fluoro-5,6-dihydropyridin-1(2H)-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine

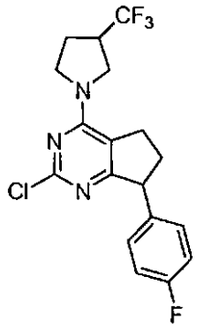


2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation H) was reacted as described in Preparation Hc with 4-fluoro-1,2,3,6-

tetrahydropyridine to afford 2-chloro-4-(4-fluoro-5,6-dihydropyridin-1(2H)-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation Hs).

Preparation Ht

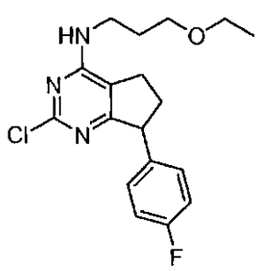
2-chloro-7-(4-fluorophenyl)-4-(3-(trifluoromethyl)pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine



2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation H) was reacted as described in *Preparation Hr* with 3-trifluoromethylpyrrolidine to afford 2-chloro-7-(4-fluorophenyl)-4-(3-(trifluoromethyl)pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation Ht) as a mixture of 4 diasteriomers. LC–MS $(M+H)^+ = 386.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.05 - 7.11 (2 H, m), 6.96 (2 H, t, *J*=8.70 Hz), 4.14 - 4.20 (1 H, m), 3.89 - 4.02 (2 H, m), 3.75 - 3.86 (2 H, m), 3.17 - 3.28 (1 H, m), 3.06 - 3.16 (1 H, m), 2.99 (1 H, dq, *J*=15.95, 8.01 Hz), 2.50 - 2.61 (1 H, m), 2.13 - 2.30 (2 H, m), 1.95 - 2.06 (1 H, m)

Preparation Hu

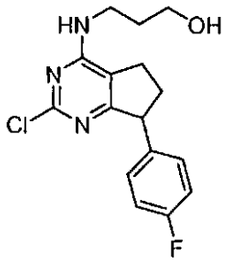
2-chloro-N-(3-ethoxypropyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine



2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation H) was reacted as described in Preparation Hr with 3-ethoxypropan-1-amine to afford 2-chloro-N-(3-ethoxypropyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (Preparation Hu).LC–MS $(M+H)^+ = 350.1$.

Preparation Hv

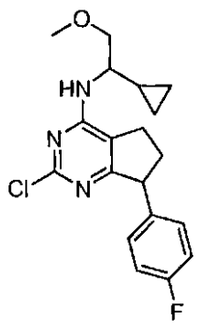
3-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-ylamino)propan-1-ol



2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation H) was reacted as described in Preparation Hr with 3-hydroxypropan-1-amine to afford 3-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-ylamino)propan-1-ol (Preparation Hv). LC–MS $(M+H)^+ = 322.1$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.08 (2 H, dd, J=8.55, 5.49 Hz), 6.97 (2 H, t, J=8.70 Hz), 5.18 (1 H, br. s.), 4.22 - 4.27 (1 H, m), 3.66 - 3.75 (4 H, m), 3.18 (1 H, br. s.), 2.60 - 2.77 (3 H, m), 2.02 - 2.12 (1 H, m), 1.78 - 1.86 (2 H, m)

Preparation Hw

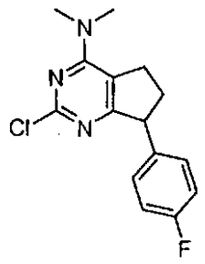
2-chloro-N-(1-cyclopropyl-2-methoxyethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine



2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation H) was reacted as described in Preparation Hr with 1-cyclopropyl-2-methoxyethanamine to afford 2-chloro-N-(1-cyclopropyl-2-methoxyethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (Preparation Hw) as a mixture of 4 diasteriomers. LC–MS $(M+H)^+ = 362.1$.

Preparation Hx

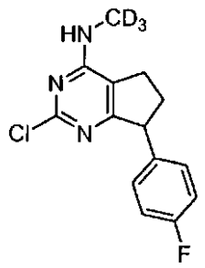
2-Chloro-7-(4-fluorophenyl)-*N*,*N*-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



A solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (260 mg, 0.918 mmol) and excess dimethylamine (4.59 mL, 9.18 mmol) in methanol (2 mL) was stirred at rt for 30 min. The solvent was removed in vacuum to afford crude 2-chloro-7-(4-fluorophenyl)-*N*,*N*-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (268 mg, 0.919 mmol, 100 % yield). LC–MS $(M+H)^+ = 292.3$.

Preparation Hy

2-Chloro-7-(4-fluorophenyl)-*N*-trideuteromethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine

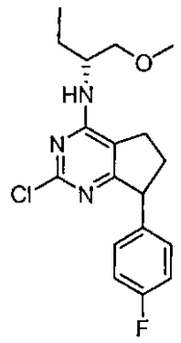


To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (350 mg, 1.236 mmol) and trideuteromethylamine hydrochloride

(174 mg, 2.472 mmol) in methanol (3 mL) was added DIPEA (0.432 mL, 2.472 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (350 mg, 1.236 mmol) as brown oil. LC-MS $(M+H)^+ = 281.2$.

Preparation Hz

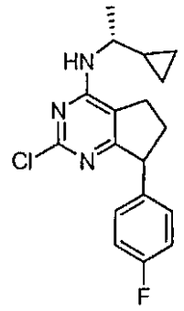
2-chloro-7-(4-fluorophenyl)-N-((R)-1-methoxybutan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine



To a mixture of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation H) (100 mg, 0.353 mmol) in THF (1766 µL) was added (R)-1-methoxybutan-2-amine, HCl (197 mg, 1.413 mmol) and DIEA (493 µL, 2.83 mmol). The mixture was heated at 60 °C for 3 days. The crude product was purified by Prep-HPLC to get 2-chloro-7-(4-fluorophenyl)-N-((R)-1-methoxybutan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (Preparation Hz) (78 mg, 0.223 mmol, 63.1 % yield). LC–MS $(M+H)^+ = 350.4$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.12 (dd, J=8.24, 5.49 Hz, 2 H) 6.87 - 7.05 (m, 2 H) 4.86 (d, J=7.63 Hz, 1 H) 4.35 (d, J=3.05 Hz, 1 H) 4.18 - 4.30 (m, 1 H) 3.47 - 3.60 (m, 2 H) 3.40 (d, J=6.71 Hz, 3 H) 2.62 - 2.82 (m, 3 H) 2.03 - 2.15 (m, 1 H) 1.58 - 1.78 (m, 2 H) 0.89 - 1.07 (m, 3 H).

Preparation Haa

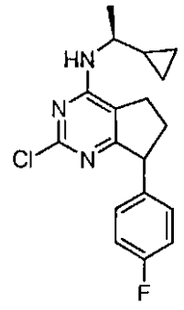
2-chloro-N-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine



To a solution of 2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation H) (100 mg, 0.353 mmol) in THF (1766 μL) was added (R)-1-cyclopropylethanamine, HCl (172 mg, 1.413 mmol) and DIEA (493 μL, 2.83 mmol). The mixture was stirred at 60 °C for 5 days. The crude product was purified by Prep-HPLC get 2-chloro-N-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (Preparation Haa) (74 mg, 0.223 mmol, 63.1 % yield). LC–MS $(M+H)^+ = 332.3$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.06 - 7.18 (m, 2 H) 7.00 (td, J=8.70, 1.53 Hz, 2 H) 4.65 (d, J=5.80 Hz, 1 H) 4.26 (t, J=7.17 Hz, 1 H) 3.63 - 3.79 (m, 1 H) 2.62 - 2.82 (m, 3 H) 2.04 - 2.16 (m, 1 H) 1.26 - 1.40 (m, 3 H) 0.94 (qd, J=8.24, 3.36 Hz, 1 H) 0.42 - 0.62 (m, 3 H) 0.24 - 0.40 (m, 1 H).

Preparation Hab

2-chloro-N-((S)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine

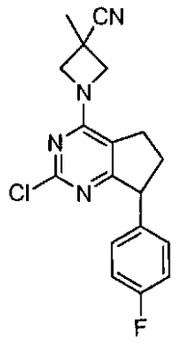


2,4-dichloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation H) was reacted as described in Preparation Haa with (S)-1-cyclopropylethanamine, HCl to give 2-chloro-N-((S)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (Preparation Hab).LC–MS $(M+H)^+ = 332.3$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.07 - 7.21 (m, 2 H) 6.93 -

7.07 (m, 2 H) 4.65 (d, J=5.80 Hz, 1 H) 4.26 (t, J=7.32 Hz, 1 H) 3.61 - 3.79 (m, 1 H) 2.62 - 2.82 (m, 3 H) 2.05 - 2.16 (m, 1 H) 1.25 - 1.39 (m, 3 H) 0.84 - 1.00 (m, 1 H) 0.42 - 0.62 (m, 3 H) 0.29 - 0.40 (m, 1 H).

Preparation Hac

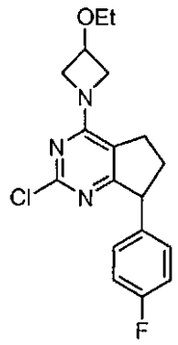
1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-methylazetidine-3-carbonitrile



3-cyano-3-methylazetidine was reacted with Preparation H in the manner of Preparation Gi to afford the title compound. LC–MS $(M+H)^+ = 343.0$ ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 6.96 - 7.13 (m, 5 H) 4.73 (d, *J*=6.71 Hz, 1 H) 4.35 (d, *J*=7.32 Hz, 2 H) 4.33 (br. s., 1 H) 4.27 (dd, *J*=9.00, 2.90 Hz, 1 H) 2.99 - 3.09 (m, 1 H) 2.85 - 2.99 (m, 1 H) 2.64 - 2.78 (m, 1 H) 2.11 (dd, *J*=13.89, 7.48 Hz, 1 H) 1.76 - 1.91 (m, 3 H).

Preparation Had

2-chloro-4-(3-ethoxyazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine

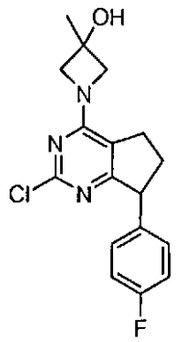


3-ethoxyazetidine was reacted with Preparation H in the manner of Preparation Gi to afford the title compound. LC–MS $(M+H)^+ = 348.0$ ^{1}H NMR (500 MHz,

CHLOROFORM-*d*) δ ppm 7.03 - 7.12 (m, 2 H) 6.91 - 7.01 (m, 2 H) 4.51 (br. s., 2 H) 4.36 - 4.48 (m, 1 H) 4.13 - 4.32 (m, 3 H) 3.50 (qd, *J*=6.97, 3.20 Hz, 2 H) 2.97 - 3.10 (m, 1 H) 2.82 - 2.96 (m, 1 H) 2.51 - 2.70 (m, 1 H) 1.93 - 2.11 (m, 1 H) 1.16 - 1.35 (m, 3 H).

Preparation Hae

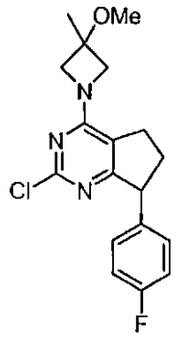
1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-methylazetidin-3-ol



3-methylazetidin-3-ol was reacted with Preparation H in the manner of Preparation Gi to afford the title compound. LC–MS $(M+H)^+ = 334.0$ ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.04 - 7.13 (m, 2 H) 7.00 (t, *J*=8.55 Hz, 2 H) 4.41 (d, *J*=6.71 Hz, 2 H) 4.39 (br. s., 3 H) 3.05 - 3.17 (m, 1 H) 2.90 - 3.04 (m, 1 H) 2.73 (ddd, *J*=9.08, 4.88, 4.65 Hz, 1 H) 2.03 - 2.19 (m, 1 H) 1.65 (s, 3 H).

Preparation Haf

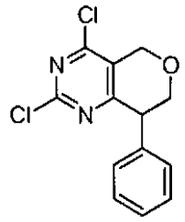
2-chloro-7-(4-fluorophenyl)-4-(3-methoxy-3-methylazetidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine



3-methoxy-3-methylazetidine was reacted with Preparation H in the manner of Preparation Gi to afford the title compound. LC–MS $(M+H)^+ = 348$.

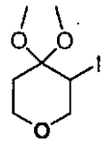
Preparation I

2,4-dichloro-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



Intermediate I(1)

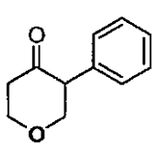
3-iodo-4,4-dimethoxytetrahydro-2H-pyran



To a mixture of tetrahydro-4H-pyran-4-one (18.52 mL, 200 mmol) and trimethyl orthoformate (100 mL, 914 mmol) at 0°C was added Iodine (49.2 mL, 200 mmol) slowly over 10 min. When the addition was complete, the reaction mixture was allowed to stir at 0°C for 30 min. and was then allowed to come to RT and stir until TLC indicated all starting material had been consumed (approx. 1 h). The reaction was then cooled to 0°C and quenched by the slow addition of sat. aqu. sodium thiosulfate (300 mL). The resulting mixture was extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Silica, EtOAc/Hexanes) gave 3-iodo-4,4-dimethoxytetrahydro-2H-pyran (43.95 g, 162 mmol, 81 % yield) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 4.25 (1 H, q, *J*=2.44 Hz), 3.93 - 4.01 (1 H, m), 3.84 - 3.93 (2 H, m), 3.57 (1 H, td, *J*=11.75, 2.44 Hz), 3.19 - 3.30 (6 H, m), 2.34 (1 H, ddd, *J*=14.34, 12.21, 4.88 Hz), 1.80 (1 H, dq, *J*=14.34, 2.44 Hz).

Intermediate I(2)

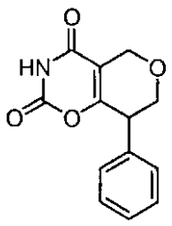
3-phenyldihydro-2H-pyran-4(3H)-one



To a stirred mixture of phenylboronic acid (16.81 g, 138 mmol), trans-2-Aminocyclohexanol hydrochloride (1.393 g, 9.19 mmol), and Nickel(II) chloride hexahydrate (1.092 g, 4.59 mmol) in THF (92 mL) at 0°C was added Sodium bis(trimethylsilyl)amide (1.0 M in THF) (184 mL, 184 mmol) dropwise over 10 min. When the addition was complete, the reaction mixture was sparged with N_2 for 15 min. To the reaction mixture at 0°C was then added 2-Propanol (375 mL)(previously sparged with N_2). The resulting mixture was allowed to come to RT at which time 3-iodo-4,4-dimethoxytetrahydro-2H-pyran (Intermediate I(1)) (25 g, 92 mmol) was added dropwise over 5 min. The reaction mixture was then brought to 60°C and stirred overnight. The reaction mixture was then cooled to 0°C and quenched by the careful addition of aqu. 1 N HCl until acidic. The resulting mixture was extracted with EtOAc (3 x 150 mL). The combined organic extracts were washed with Brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Silica, EtOAc/Hexanes) gave 3-phenyldihydro-2H-pyran-4(3H)-one (8.37 g, 47.5 mmol, 51.7 % yield) as a slightly orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 - 7.39 (2 H, m), 7.26 - 7.31 (1 H, m), 7.21 - 7.26 (2 H, m), 4.17 - 4.31 (2 H, m), 3.91 - 4.05 (2 H, m), 3.78 (1 H, dd, *J*=8.55, 6.10 Hz), 2.61 - 2.74 (1 H, m), 2.51 - 2.61 (1 H, m).

Intermediate I(3)

8-phenyl-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione

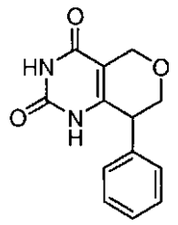


A mixture of 3-phenyldihydro-2H-pyran-4(3H)-one (Intermediate I(2)) (3 g, 17.02 mmol) and carbonisocyanatidic chloride (10.48 g, 29.8 mmol) in a sealed tube was heated to 58°C and stirred for 1 h. The mixture was then brought to 130°C and stirred for an additional 2 h. The reaction turned black during this time. After cooling to RT, the tar was taken up in EtOAc (100 mL). The resulting solution was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Silica, EtOAc/Hexanes)

gave 8-phenyl-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione (2.58 g, 10.52 mmol, 61.8 % yield) as a brown solid. LC-MS $(M+H)^+ = 246.0$. ^1H NMR (500 MHz, *MeOD*) δ ppm 7.34 - 7.41 (4 H, m), 7.29 - 7.34 (1 H, m), 4.42 - 4.63 (2 H, m), 4.08 - 4.15 (1 H, m), 3.94 (1 H, dd, *J*=11.44, 4.12 Hz), 3.85 (1 H, ddd, *J*=4.20, 2.44, 2.21 Hz).

Intermediate I(4)

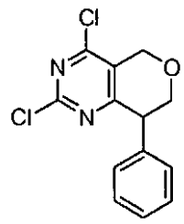
8-phenyl-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione



A solution of 8-phenyl-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione (Intermediate I(3)) (2.58 g, 10.52 mmol) in ammonium hydroxide (28.7 mL, 736 mmol) was heated to 80 °C in a sealed tube and stirred overnight. The reaction mixture was then concentrated to dryness giving 8-phenyl-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione. The crude material was carried on as-is. LC-MS $(M+H)^+ = 245.2$.

Preparation I

2,4-dichloro-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine

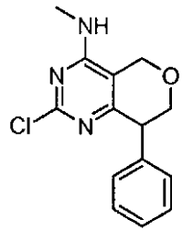


A mixture of 8-phenyl-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione (Intermediate I(4)) (2569 mg, 10.52 mmol) and POCl3 (29.400 mL, 315 mmol) was heated to 100 °C under microwave irradiation in a sealed tube for 1h. The resulting mixture was poured over ice. When all the ice was melted, the mixture was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Silica, EtOAc/Hexanes) gave 2,4-dichloro-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (194 mg, 0.690 mmol, 6.56 % yield). LC-MS $(M+H)^+ = 281.1$.

^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.30 - 7.37 (2 H, m), 7.25 - 7.30 (1 H, m), 7.18 - 7.25 (2 H, m), 4.90 - 5.00 (1 H, m), 4.75 - 4.84 (1 H, m), 4.16 - 4.26 (2 H, m), 4.02 - 4.15 (1 H, m).

Preparation Ia

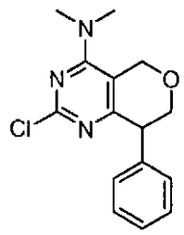
2-chloro-N-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



To a solution of 2,4-dichloro-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation I) (194 mg, 0.690 mmol) in MeOH (6901 µL) was added methanamine hydrochloride (69.9 mg, 1.035 mmol) and N,N-Diisopropylethylamine (301 µL, 1.725 mmol). The resulting mixture was stirred at RT for 2 h. The reaction mixture was then concentrated *in vacuo*. Purification by flash chromatography (Silica, EtOAc/Hexanes) gave 2-chloro-N-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (126 mg, 0.457 mmol, 66.2 % yield). LC-MS $(M+H)^+ = 276.0$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.28 (2 H, t, *J*=7.32 Hz), 7.20 - 7.25 (1 H, m), 7.14 - 7.20 (2 H, m), 4.47 - 4.62 (2 H, m), 4.47 (1 H, s), 4.00 - 4.11 (2 H, m), 3.95 (1 H, d, *J*=3.36 Hz), 3.08 (3 H, d, *J*=4.88 Hz).

Preparation Ib

2-Chloro-*N*,*N*-dimethyl-8-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidin-4-amine

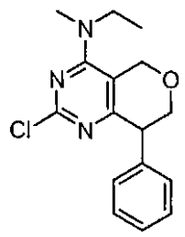


A solution of 2,4-dichloro-8-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidine (135 mg, 0.480 mmol) and excess dimethylamine (216 mg, 4.80 mmol) in MeOH (2 mL) was stirred at rt for 1.5 h. The solvent was removed in vacuum to afford 2-chloro-*N*,*N*-

dimethyl-8-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidin-4-amine (139 mg, 0.480 mmol, 100 % yield). LC–MS $(M+H)^+ = 290.3$.

Preparation Ic

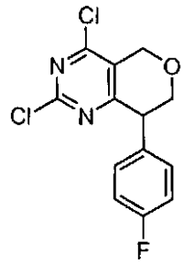
2-Chloro-*N*-ethyl-*N*-methyl-8-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidin-4-amine



A solution of 2,4-dichloro-8-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidine (135 mg, 0.480 mmol) and excess *N*-methylethanamine (284 mg, 4.80 mmol) in MeOH (2 mL) was stirred at rt for 1 h. The solvent was removed in vacuum to afford 2-chloro-*N*-ethyl-*N*-methyl-8-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidin-4-amine (146 mg, 0.481 mmol, 100 % yield). LC–MS $(M+H)^+ = 304.2$.

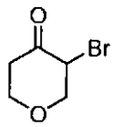
Preparation J:

2,4-dichloro-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



Intermediate J(1):

3-bromodihydro-2H-pyran-4(3H)-one

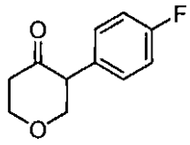


To a cooled solution of dihydro-2H-pyran-4(3H)-one (10.0 g, 99.8 mmol) in THF was added a solution of pyrrolidone hydrotribromide (49.54 g, 99.8 mmol) in THF over a period of 10 min. at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for 2 h. The solvent was removed under reduced pressure and the

residue was diluted with ethyl acetate (300 mL). The organic solution was washed with aqueous saturated $NaHCO_3$ (100 mL), water (100 mL x 2), brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 3-bromodihydro-2H-pyran-4(3H)-one (12.0 g, 67%) as oily liquid. The crude compound was taken to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 4.89-4.87 (1H, m) 4.28-4.27 (1H, m) 4.25-4.4.24 (1H, m) 3.85-3.74 (2H, m) 2.71-2.66 (2H, m).

Intermediate J(2):

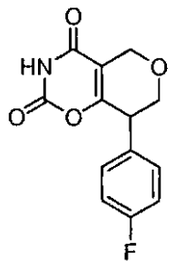
3-(4-fluorophenyl)dihydro-2H-pyran-4(3H)-one



To a solution of Intermediate J(1) (12.0 g, 66.9 mmol) in benzene was added 2 M solution of 4-fluorophenyl magnesium bromide in ether (13.34 g, 33.48 mL, 66.9 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 40 min. The reaction mixture was quenched with aqueous 1.5 N HCl (80 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 x 2). The combined organic layer was washed with water (100 mL x 2), brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give crude compound as oily liquid. The crude compound was dissolved in benzene and was added a solution of 4-fluorophenyl magnesium bromide in ether (9.7 g, 24.5 mL, 49.0 mmol) at 0 °C. The reaction mixture was heated at reflux for 30 min. The reaction mixture was quenched with aqueous 1.5 N HCl (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 x 2). The combined organic layer was washed with water (100 mL x 2), brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give crude compound. The crude compound was purified by column chromatography (Silica gel, 230- 400 mesh) using 5% ethyl acetate in pet-ether as mobile phase to give 3-(4-fluorophenyl)dihydro-2H-pyran-4(3H)-one (3.0 g, 36%) as oily liquid. LC–MS $(M+H)^+$ = 195.2. ^{1}H NMR (400 MHz, chlorofom-*d*): δ ppm 7.7.21-7.18 (2H, m), 7.06-7.01 (2H, m), 4.28-4.21 (2H, m), 3.99-3.91 (2H, m), 3.79-3.76 (1H, m) 2.72-2.67 (1H, m) 2.64-2.55 (1H, m).

Intermediate J(3)

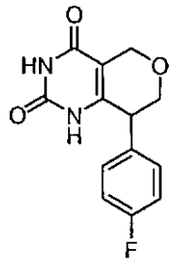
8-(4-fluorophenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione



A solution of Intermediate J(2) (1.5 g, 7.72 mmol) and N-chlorocarbonyl isocyanate (0.97 g, 9.2 mmol) was heated at 58 °C under nitrogen atmosphere for 1 h. Then, the reaction temperature was increased to 130 °C and maintained for 2 h. The reaction mass was diluted with ethyl acetate (50 mL). The resulting organic solution was washed with saturated $NaHCO_3$ (25 mL), brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give 8-(4-fluorophenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione (0.8 g, 38%) as brown solid. LC–MS $(M-H)^+ = 262.0$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 11.97 (1H, s), 7.43-7.39 (2H, m), 7.21-7.16 (2H, m), 4.48-4.32 (2H, m), 4.05 (2H, m), 3.77 (1H, m).

Intermediate J(4)

8-(4-fluorophenyl)-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione

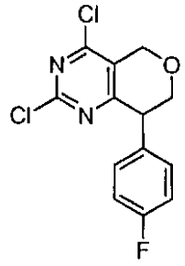


A solution of Intermediate J(3) (0.8 g, 3.0 mmol) in aqueous ammonia (50 mL) was heated at reflux for 18 h. The excess ammonia was removed under reduced pressure and the aqueous solution was extracted with ethyl acetate (25 mL x 4). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 8-(4-fluorophenyl)-7,8-dihydro-1H-

pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione (0.4 g, 50%). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 263.4. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 11.16 (1H, s), 10.79 (1H, s), 7.33-7.29 (2H, m), 7.19-7.15 (2H, m), 4.43 (1H, m), 4.25 (1H, m), 3.90 (1H, m), 3.75-3.68 (2H, m).

Preparation J

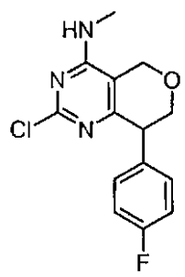
2,4-dichloro-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



A solution of Intermediate J(4) (0.7 g, 2.6 mmol) and catalytic amount of DMF in $POCl_3$ (20 vol.) was heated at reflux for 18 h. The excess of $POCl_3$ was evaporated under reduced pressure. The residue was poured in to crushed ice and stirred for 15 min. The aqueous solution was extracted with ethyl acetate (20 mL x 2). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (50 mL x 2), brine solution (25 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give 2,4-dichloro-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (0.79 g) as crude compound. The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 299.0.

Preparation Ja

2-chloro-8-(4-fluorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine

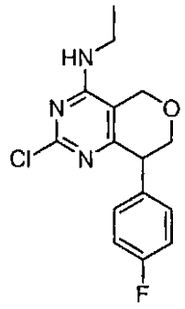


To a solution of Preparation J (0.7 g, 2.3 mmol) in methanol was added Cs_2CO_3 (1.49 g, 4.6 mmol) followed by addition of methylamine hydrochloride (0.78 g, 11.7

mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue diluted with ethyl acetate (25 mL), washed with water (25 mL), brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give 2-chloro-8-(4-fluorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (0.34 g, 49%) as off-white solid. LC–MS $(M+H)^+ = 294.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 7.22-7.19 (2H, m), 7.13-7.07 (2H, m), 4.91 (1H, m), 4.75 (1H, m), 4.12-4.08 (2H, m), 3.74 (1H, m), 3.05 (6H, s).

Preparation Jb

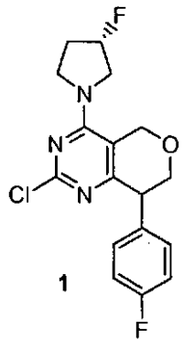
2-chloro-N-ethyl-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine

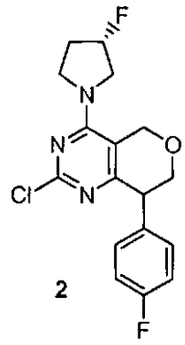


To a solution of Preparation J (0.350 g, 1.17 mmol) in methanol was added diisopropylethylamine (0.30 g, 2.2 mmol) followed by ethylamine hydrochloride (0.113 g, 1.17 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue diluted with ethyl acetate (25 mL), washed with water (25 mL), brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 50-55% ethyl acetate in pet-ether as mobile phase to give 2-chloro-N-ethyl-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (0.16 g, 60%) as off-white solid. LC–MS $(M+H)^+ = 308.2$.

Preparation Jc1 and Jc2

2-chloro-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine

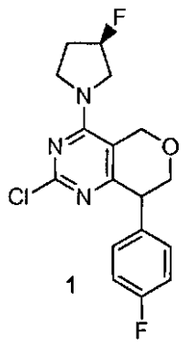


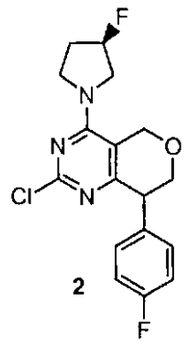


To a solution of Preparation J (0.70 g, 2.34 mmol) in methanol was added diisopropylethylamine (0.60 g, 4.6 mmol) followed by (R)-3-fluoropyrrolidine (0.58 g, 4.6 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by prep-HPLC (40% ethanol in hexane) to give 2-chloro-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (0.90 g, 11% Isomer 1, 0.110 g, 13% Isomer 2) as off-white solid. LC–MS $(M+H)^+ = 352.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.24 (2H, m), 7.13 (2H, m), 5.40 (1H, m), 4.12 (1H, d, $J = 14.8$ Hz), 4.88 (1H, d, $J = 14.8$ Hz), 4.14-4.09 (2H, m), 3.91-3.81 (3H, m), 3.75-3.66 (2H, m), 2.51-2.18 (2H, m).

Preparation Jd 1 and Jd2

2-chloro-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine





To a solution of Preparation J (0.70 g, 2.34 mmol) in methanol was added diisopropylethylamine (0.60 g, 4.6 mmol) followed by (S)-3-fluoropyrrolidine (0.58 g, 4.6 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by

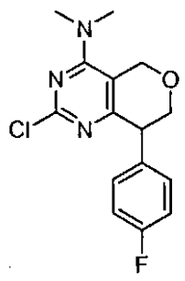
prep-HPLC (40% ethanol in hexane) to give 2-chloro-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (0.100 g, 12% Isomer 1, 0.110 g, 13% Isomer 2) as off-white solid. LC–MS $(M+H)^+ = 352.2$.

Jd1: ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.24 (2H, m), 7.13 (2H, m), 5.40 (1H, m), 4.12 (1H, d, $J = 14.4$ Hz), 4.88 (1H, d, $J = 14.4$ Hz), 4.11 (2H, m), 3.94-3.89 (3H, m), 3.72-3.58 (2H, m), 2.20-2.01 (2H, m).

Jd2: ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.21 (2H, m), 7.13 (2H, m), 5.39 (1H, m), 5.02 (2H, m), 4.02-3.97 (2H, m), 3.91-3.84 (4H, m), 3.73 (1H, m), 2.23-2.01 (2H, m).

Preparation Je

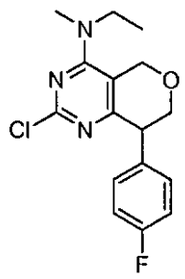
2-chloro-8-(4-fluorophenyl)-N,N-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



To a solution of Preparation J (0.7 g, 2.3 mmol) in methanol was added Cs_2CO_3 (1.49 g, 4.6 mmol) followed by addition of dimethylamine hydrochloride (0.95 g, 11.7 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue diluted with ethyl acetate (50 mL), washed with water (25 mL), brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 40% ethyl acetate in pet-ether as mobile phase to give 2-chloro-8-(4-fluorophenyl)-N,N-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (0.35 g, 49%) as off-white solid. LC–MS $(M+H)^+ = 308.2$. This compound was taken to the next step without further purification.

Preparation Jf

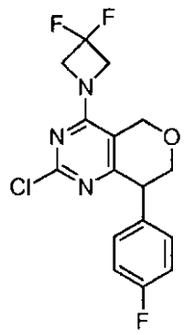
2-chloro-N-ethyl-8-(4-fluorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



To a solution of Preparation J (0.7 g, 2.3 mmol) in methanol was added Cs_2CO_3 (1.49 g, 4.6 mmol) followed by addition of ethylmethylamine hydrochloride (1.1 g, 11.7 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue diluted with ethyl acetate (25 mL), washed with water (25 mL), brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give 2-chloro-N-ethyl-8-(4-fluorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (0.39 g, 52%) as off-white solid. LC–MS $(M+H)^+ = 322.2$. This compound was taken to the next step without further purification.

Preparation Jg

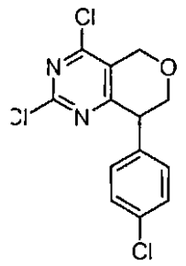
2-chloro-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



To a solution of Preparation J (0.7 g, 2.3 mmol) in methanol was added Cs_2CO_3 (1.49 g, 4.6 mmol) followed by addition of 3,3-difluoroazetidine hydrochloride (0.60 g, 4.6 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue diluted with ethyl acetate (25 mL), washed with water (25 mL), brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give 2-chloro-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (0.42 g, 50%) as off-white solid. LC–MS $(M+H)^+ = 355.2$. This compound was taken to the next step without further purification.

Preparation K

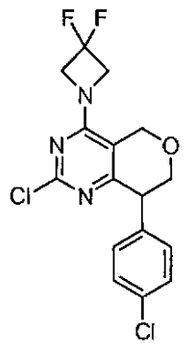
2,4-dichloro-8-(4-chlorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



The title compound was prepared in the analogous fashion to Preparation J, as a pale yellow solid. LC–MS $(M+H)^+ = 315.0$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 (2H, dd, $J = 2.0, 6.4$ Hz), 7.17 (2H, dd, $J = 2.0, 6.4$ Hz), 4.91 (1H, d, $J = 16.4$ Hz), 4.76 (1H, d, $J = 16.0$ Hz), 4.18 - 4.09 (3H, m).

Preparation Ka

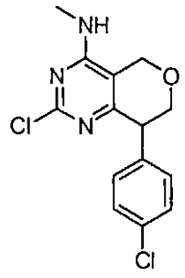
2-chloro-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



2,4-dichloro-8-(4-chlorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (*Preparation K*) (500 mg, 1.584 mmol) and 3,3-Difluoroazetidine hydrochloride (308 mg, 2.377 mmol) were combined and purified as per *Preparation Ha* to give 2-chloro-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (400 mg, 1.075 mmol, 67.8 % yield) as a white solid. LC-MS $(M+H)^+ = 372.0$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.22 - 7.34 (2 H, m), 7.12 (2 H, d, *J*=8.24 Hz), 4.63 - 4.85 (2 H, m), 4.46 - 4.64 (3 H, m), 4.04 - 4.17 (1 H, m), 3.91 - 4.04 (2 H, m).

Preparation Kb

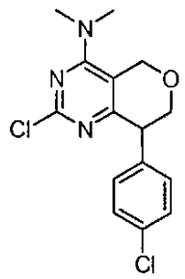
2-chloro-8-(4-chlorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



2,4-dichloro-8-(4-chlorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (*Preparation K*) (500 mg, 1.584 mmol) and methanamine hydrochloride (160 mg, 2.377 mmol) were combined and purified as per *Preparation Ha* to give 2-chloro-8-(4-chlorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (150 mg, 0.484 mmol, 30.5 % yield). LC-MS $(M+H)^+ = 310.0$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.22 - 7.31 (2 H, m), 7.13 (2 H, d, *J*=8.55 Hz), 4.46 - 4.64 (1 H, m), 4.43 (1 H, br. s.), 3.97 - 4.14 (1 H, m), 3.91 (1 H, d, *J*=3.36 Hz), 3.09 (3 H, d, *J*=4.88 Hz).

Preparation Kc

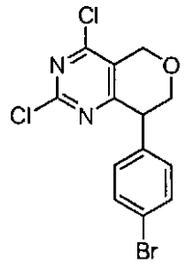
2-chloro-8-(4-chlorophenyl)-N,N-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



2,4-dichloro-8-(4-chlorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (*Preparation K*) (500 mg, 1.584 mmol) and Dimethylamine (2.0 M in THF) (1.188 mL, 2.377 mmol) were combined an purified as per *Preparation Ha* to give 2-chloro-8-(4-chlorophenyl)-N,N-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (400 mg, 1.234 mmol, 78 % yield) as a white solid. LC-MS $(M+H)^+ = 324.0$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.20 - 7.31 (2 H, m), 7.04 - 7.15 (2 H, m), 4.70 - 4.89 (2 H, m), 4.17 (1 H, dd, *J*=11.60, 5.49 Hz), 4.05 (1 H, t, *J*=5.49 Hz), 3.87 (1 H, dd, *J*=11.60, 5.49 Hz), 3.05 - 3.19 (6 H, m).

Preparation L

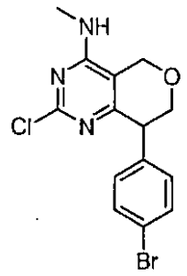
2,4-dichloro-8-(4-bromophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



The title compound was prepared in the analogous fashion to Preparation J, as a pale yellow solid. LC–MS $(M+H)^+ = 359.0$. ^1H NMR (400 MHz, CD_3OD) δ ppm 7.52 (2H, d, $J = 8.4$ Hz), 7.22 (2H, d, $J = 8.4$ Hz), 4.87 (1H, d, $J = 16.0$ Hz), 4.30 (1H, t, $J =$ 4.6 Hz), 4.14 (1H, dd, $J = 4.6$, 11.4 Hz), 3.95 (1H, dd, $J = 4.8$, 11.6 Hz).

Preparation La

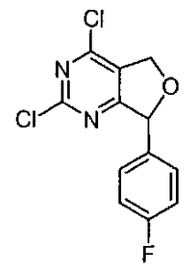
8-(4-bromophenyl)-2-chloro-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



8-(4-bromophenyl)-2,4-dichloro-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (*Preparation L*) (500 mg, 1.389 mmol) and methanamine hydrochloride (141 mg, 2.083 mmol) were combined and purified as per *Preparation Ha* to give 8-(4-bromophenyl)-2-chloro-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (210 mg, 0.592 mmol, 42.6 % yield). LC-MS $(M+H)^+$ = 356.0. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.46 (2 H, d, *J*=8.24 Hz), 7.13 (2 H, d, *J*=8.55 Hz), 4.43 - 4.71 (2 H, m), 4.09 (1 H, dd, *J*=11.44, 4.12 Hz), 3.92 - 4.03 (1 H, m), 3.86 (1 H, d, *J*=3.05 Hz), 3.00 (3 H, s).

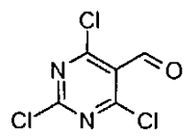
Preparation M

2,4-dichloro-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine



Intermediate M(1)

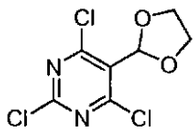
ethyl 2-hydroxy-2-phenylacetate



A solution of pyrimidine-2,4,6-triol (10.0 g, 78.2 mmol), DMF (12 mL) in $POCl_3$ (10 vol.) was heated at reflux for 15 h. The excess of $POCl_3$ was evaporated under reduced pressure. The residue was poured in to crushed ice. The precipitated solid was filtered and washed with water to give 2,4,6-trichloropyrimidine-5-carbaldehyde (8.0 g, 47%) as yellow solid. This compound was taken to the next step without further purification.

Intermediate M(2)

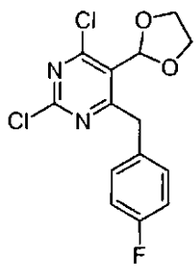
2,4,6-trichloro-5-(1,3-dioxolan-2-yl)pyrimidine



To a solution of Intermediate M(1) (5.0 g, 23.6 mmol) in dry benzene was added ethylene glycol (4.0 mL, 64.5 mmol) followed by *p*-toluenesulfonic acid (0.15 g, 0.87 mmol) at room temperature. The reaction mixture was heated at reflux for 20 h. The reaction mixture was filtered and washed with warm benzene. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in pet-ether as mobile phase to give (4.5 g, 75%) as off-white solid. LC–MS $(M+H)^+ = 256.0$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.6 (1H, s), 7.99 (1H, s), 7.98 (1H, s), 7.76-7.41 (3H, m), 7.23-7.13 (4H, m), 5.87 (1H, s), 5.33 (1H, dd, $J = 27$, 8 Hz), 5.17 (1H, dd, $J = 27$, 8), 4.67 (4H, m), 3.72 (3H, s).

Intermediate M(3)

2,4-dichloro-5-(1,3-dioxolan-2-yl)-6-(4-fluorobenzyl)pyrimidine

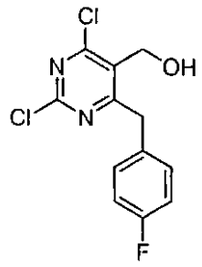


To a solution of Intermediate M(2) (4.0 g, 15.6 mmol) in dry diethyl ether was added 4-fluorobenzyl magnesium bromide (75.2 mL, 18.8 mmol, 0.25 M solution in THF) at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for 4 h. The reaction mixture was quenched with aqueous saturated ammonium chloride. The organic layer was separated and the aqueous layer was extracted with diethyl ether (50 mL x 2). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated to get crude compound. The crude compound was purified by combiflash using 1.4% ethyl acetate in pet ether as mobile phase to give 2,4-dichloro-5-

(1,3-dioxolan-2-yl)-6-(4-fluorobenzyl)pyrimidine (2.2 g, 43.1%) as off-white solid. LC–MS $(M-H)^+ = 327.0$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 7.26 (2H, m), 7.10 (2H, m), 6.19 (1H, s), 4.25 (2H, s), 4.19 (2H, m), 4.02 (2H, m).

Intermediate M(4)

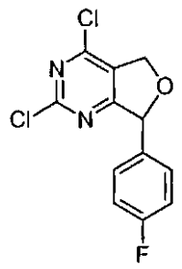
(2,4-dichloro-6-(4-fluorobenzyl)pyrimidin-5-yl)methanol



To a solution of Intermediate M(3) (2.0 g, 6.07 mmol) in THF was added aqueous 6 N HCl over a period of 5 min. at room temperature. The reaction mixture was heated at reflux for 1 h. The reaction volume was reduced to half and the solution was extracted with diethyl ether (50 mL x 2). The combined organic layer was washed with water (50 mL), brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound (1.2 g). The crude compound was dissolved in methanol and cooled to 0 °C. Sodium borohydride (0.234 g) was added to the reaction mixture. The resulting solution was allowed to come to room temperature and stirred for 1 h. The reaction mixture was quenched with aqueous saturated ammonium chloride, and then solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate (50 mL). The organic solution was washed with water (25 mL), brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 20% ethyl acetate in pet ether as mobile phase to give (2,4-dichloro-6-(4-fluorobenzyl)pyrimidin-5-yl)methanol (1.0 g, 58%) as oily liquid. LC–MS $(M+H)^+ = 488.1$. ^1H NMR (300 MHz, $CDCl_3$): δ ppm 7.25 (2H, m), 7.01 (2H, m), 4.82 (2H, m), 4.27 (2H, s).

Preparation M

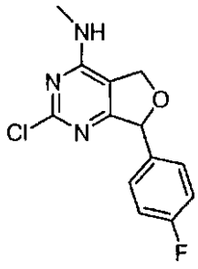
2,4-dichloro-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine



To a solution of Intermediate M(4) (1.0 g, 3.48 mmol) in dry benzene (100 mL) was added Cs_2CO_3 (0.4 g, 3.48 mmol) followed by lead tetra acetate (0.3 g, 3.48 mmol) at room temperature (the color of the reaction mixture was changed from colorless to brown). The reaction mass was heated at reflux for 18 h using Dean Stark apparatus. The reaction mixture was filtered through celite bed and washed with diethyl ether. The filtrate was evaporated under reduced pressure and the residue was diluted with diethyl ether. The organic solution was washed with water (25 mL x 2), aqueous saturated $NaHCO_3$, brine solution (10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by Combiflash using 0.9% ethyl acetate in pet-ether as mobile phase to give 2,4-dichloro-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine (0.250 mg, 30%) as oily liquid. LC–MS $(M+H)^+ = 485.0$. ^1H NMR (400 MHz, methanol-*d4*): δ ppm 7.48-7.44 (2H, m), 7.16-7.12 (2H, m), 6.15 (1H, s), 5.40 (1H, dd, $J = 13.6$ Hz), 5.27 (1H, dd, $J = 13.6$).

Preparation Ma

2-chloro-7-(4-fluorophenyl)-N-methyl-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine

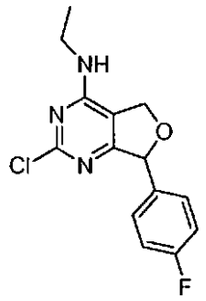


2,4-dichloro-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation M) (250 mg, 0.877 mmol) and methanamine hydrochloride (89 mg, 1.315 mmol) were combined and purified as per Preparation Ia to give 2-chloro-7-(4-fluorophenyl)-N-methyl-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine (149 mg, 0.533 mmol, 60.8 % yield).

LC-MS $(M+H)^+ = 280.0$. ^1H NMR (500 MHz, *MeOD*) δ ppm 7.31 - 7.44 (2 H, m), 7.05 - 7.17 (2 H, m), 5.80 - 5.95 (1 H, m), 4.94 - 5.21 (2 H, m), 2.93 - 3.07 (3 H, m).

Preparation Mb

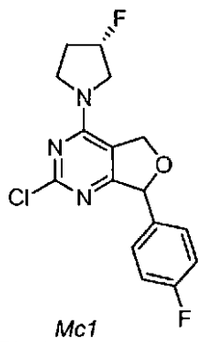
2-chloro-N-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine



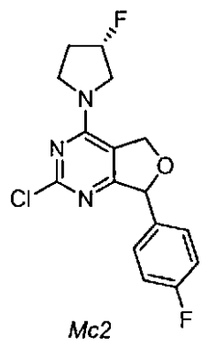
2,4-dichloro-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation M) (125 mg, 0.438 mmol) and ethylamine hydrochloride (53.6 mg, 0.658 mmol) were combined and purified as per Preparation Ha to give 2-chloro-N-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine (38.17 mg, 0.130 mmol, 29.6 % yield). LC-MS $(M+H)^+ = 294.0$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.24 - 7.38 (2 H, m), 6.92 - 7.08 (2 H, m), 5.73 - 5.98 (1 H, m), 4.83 - 5.21 (2 H, m), 3.36 - 3.63 (2 H, m), 1.13 - 1.28 (3 H, m).

Preparations Mc1 and Mc2

2-chloro-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidine



Mc1
Diastereomer 1
Racemic



Mc2
Diastereomer 2
Racemic

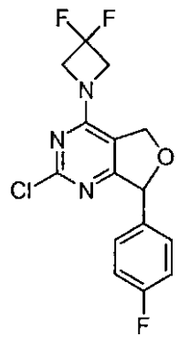
2,4-dichloro-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation M) (125 mg, 0.438 mmol) and (S)-3-fluoropyrrolidine, HCl (83 mg, 0.658 mmol) were

combined and purified as per Preparation Ha to give 2-chloro-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidine (*Mc1*, Diastereomer 1, first to elute) (49 mg, 0.145 mmol, 33.1 % yield). LC-MS $(M+H)^+$ = 338.0.

(*Mc2*, Diastereomer 2, second to elute) (40 mg, 0.118 mmol, 27.0 % yield). LC-MS $(M+H)^+$ = 338.0. The relative stereochemistry of *Mc1* and *Mc2* was not determined.

Preparation Md

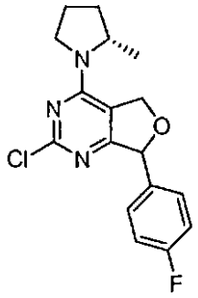
2-chloro-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine



To a solution of Preparation M (0.05 g, 0.176 mmol) in methanol was added diisopropylethylamine (0.045 g, 0.30 mmol) followed by addition of 3,3-difluoroazitidine hydrochloride (0.03 g, 0.193 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 6% ethyl acetate in pet-ether as mobile phase to give 2-chloro-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine (0.035 g, 46%) as white solid. LC–MS $(M+H)^+$ = 342.2.

Preparation Me

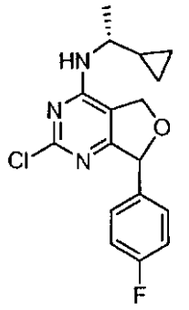
2-chloro-7-(4-fluorophenyl)-4-((S)-2-methylpyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d] pyrimidine



2,4-dichloro-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation M) was reacted as described in Preparation Hp1 and Hp2 with (S)-2-methylpyrrolidine *p*-toluenesulfonate salt to afford 2-chloro-7-(4-fluorophenyl)-4-((S)-2-methylpyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d] pyrimidine (Preparation Me) as a mixture of 2 diasteriomers.*LC*–MS $(M+H)^+ = 334.1$.

Preparation Mf

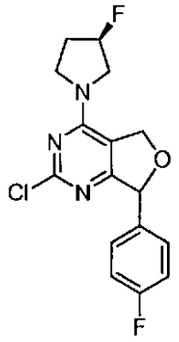
2-chloro-N-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine



To a solution of 2,4-dichloro-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation M) (150 mg, 0.526 mmol) in THF (2631 µL) was added (R)-1-cyclopropylethanamine, HCl (128 mg, 1.052 mmol) and DIEA (368 µL, 2.105 mmol). The mixture was heated at 40 °C for 2 h and stirred at RT overnight. The mixture was concentrated and purified by column chromatography on silica gel to give 2-chloro-N-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine (Preparation Mf) (25 mg, 0.075 mmol, 14.24 % yield) as a mixture of 2 diasteriomers. LC–MS $(M+H)^+ = 334.1$.

Preparation Mg

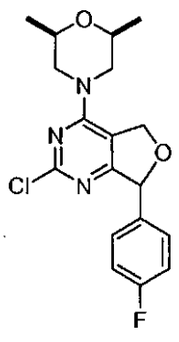
2-chloro-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidine



2,4-dichloro-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation M) was reacted as described in Preparation Xa with (R)-3-fluoropyrrolidine, HCl to give 2-chloro-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation Mg). LC–MS $(M+H)^+ = 338.1$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.33 - 7.47 (m, 2 H) 7.00 - 7.14 (m, 2 H) 5.83 - 5.97 (m, 1 H) 5.54 (dd, J=11.33, 3.53 Hz, 1 H) 5.36 - 5.49 (m, 2 H) 3.88 - 4.00 (m, 1 H) 3.65 - 3.88 (m, 3 H) 2.30 - 2.52 (m, 1 H) 2.02 - 2.20 (m, 1 H).

Preparation Mh

2-chloro-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine

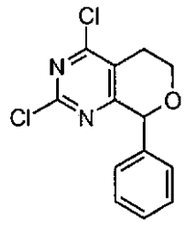


2,4-dichloro-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation M) was reacted as described in Preparation Xa with (2R,6S)-2,6-dimethylmorpholine to give 2-chloro-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation Mh). LC–MS $(M+H)^+ = 364.2$. ^{1}H NMR

(500 MHz, $CDCl_3$) δ ppm 7.39 (dd, J=8.70, 5.34 Hz, 2 H) 7.07 (t, J=8.70 Hz, 2 H) 5.90 (br. s., 1 H) 5.34 - 5.42 (m, 1 H) 5.24 - 5.34 (m, 1 H) 4.14 (q, J=7.02 Hz, 2 H) 3.67 (ddd, J=10.38, 6.41, 2.44 Hz, 4 H), 1.20 (m, 6H).

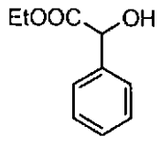
Preparation N

2,4-dichloro-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine



Intermediate N(1)

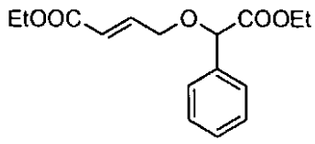
ethyl 2-hydroxy-2-phenylacetate



To a cooled solution of ethyl 2-hydroxy-2-phenylacetate (25.0 g, 164.3 mmol) in ethanol was added con. H_2SO_4 (15 mL) over a period of 10 min. The reaction mixture was heated at reflux for 5 h. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate (250 mL). The organic solution was washed with aqueous saturated $NaHCO_3$ (200 mL x 2), water (100 mL x 2), brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give ethyl 2-hydroxy-2-phenylacetate (24.5 g, 83%) as crude compound (oily liquid). The crude compound was taken to the next step without further purification. LC–MS $(M+H_2O)^+$ = 198.2. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 7.41-7.28 (5H, m), 6.04 (1H, d, *J*= 4.0 Hz), 5.11 (1H, d, *J*= 4.0 Hz), 4.13 (2H, m), 1.13 (3H, t, *J* = 7.2 Hz).

Intermediate N(2)

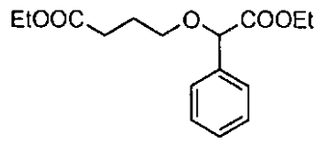
ethyl 4-(2-ethoxy-2-oxo-1-phenylethoxy)but-2-enoate



To a solution of Intermediate N(1) (20.0 g, 110.9 mmol) in hexane was added silver oxide (66.75 g, 288.5 mmol) followed by magnesium sulphate (2.66 g, 220 mmol) at room temperature. The reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to 0 °C and was added silver oxide (71.8 g, 310.9 mmol) followed by ethyl-4-bromochrotonate (32.0 g, 166 mmol). The resulting solution was stirred at room temperature for 3 days. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure to give ethyl 4-(2-ethoxy-2-oxo-1-phenylethoxy)but-2-enoate (20.0 g, 62.5%) as oily liquid. LC–MS $(M+H_2O)^+ = 310.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.42-7.35 (5H, m), 6.90 (1H, m), 6.05 (1H, m), 5.09 (1H, s), 4.26 (2H, m), 4.16 (4H, m), 1.21 (3H, t, *J*= 7.2 Hz), 1.13 (3H, t, *J* = 7.2 Hz).

Intermediate N(3)

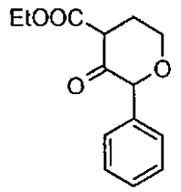
ethyl 4-(2-ethoxy-2-oxo-1-phenylethoxy)butanoate



To a solution of Intermediate N(2) (20.0 g, 68.41 mmol) in ethanol was added palladium on carbon (10%, w/w) at room temperature. The reaction mixture was hydrogenated under balloon pressure of hydrogen for 30 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethanol. The solvent was removed under reduced pressure and the residue was purified by column chromatography (Silica gel, 60-120 mesh) using 5% ethyl acetate in petroleum-ether as mobile phase to give ethyl 4-(2-ethoxy-2-oxo-1-phenylethoxy)butanoate (12.0 g, 59.5%) as oily liquid. LC–MS $(M+H)^+ = 295.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.41-7.27 (5H, m), 4.96 (1H, s), 4.07 (4H, m), 3.62 (1H, m), 3.49 (1H, m), 2.36 (2H, m), 1.79 (2H, m), 1.15 (6H, m).

Intermediate N(4)

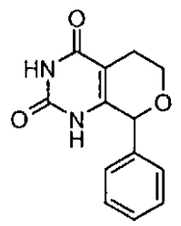
ethyl 3-oxo-2-phenyltetrahydro-2H-pyran-4-carboxylate



To a cooled solution of Intermediate N(3) (12.0 g, 40.76 mmol) in THF was added *t*-BuOK (9.13 g, 81.3 mmol) at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for 1 h. The reaction mixture was quenched with water and evaporated the solvent under reduced pressure. The residue was diluted with ethyl acetate (200 mL). The organic layer was washed with water (100 mL x 2), brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give ethyl 3-oxo-2-phenyltetrahydro-2H-pyran-4-carboxylate (6.0 g, 59.4%) as oily liquid. LC–MS $(M+H)^+$ = 249.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 11.81 (1H, s), 7.36 (5H, m), 5.20 (1H, s), 4.23 (2H, q, *J* = 7.2.0 Hz), 3.71 (1H, m), 3.67 (1H, m), 2.36 (1H, m), 2.32 (1H, m), 1.29 (3H, t, *J* = 7.2 Hz).

Intermediate N(5)

8-phenyl-5,6-dihydro-1H-pyrano[3,4-d]pyrimidine-2,4(3H,8H)-dione

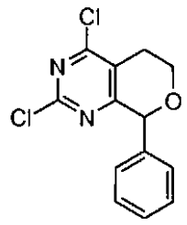


To a solution of Intermediate N(4) (6.0 g, 24.16 mmol) in ethanol was added *t*-BuOK (6.76 g, 60.41 mmol) followed by urea (3.62 g, 60.41 mmol) at room temperature. The reaction mass was heated at reflux for 18 h. The reaction mixture was quenched with water and evaporated the solvent under reduced pressure. The residue was diluted with ethyl acetate (100 mL). The organic layer was washed with water (100 mL x 2), brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure

to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using ethyl acetate as mobile phase to give 8-phenyl-5,6-dihydro-1H-pyrano[3,4-d]pyrimidine-2,4(3H,8H)-dione (3.0 g, 50.8%) as pale yellow solid. LC–MS $(M-H)^+ = 243.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 11.10 (1H, s), 10.57 (1H, s), 7.42-7.39 (3H, m), 7.32 (2H, m), 5.32 (1H, s), 3.71-3.56 (2H, m), 2.38-2.27 (2H, m).

Preparation N

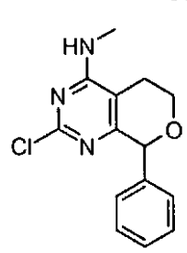
2,4-dichloro-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine



A solution of Intermediate N(5) (2.0 g, 8.18 mmol) and catalytic amount of DMF in $POCl_3$ (10 vol.) was heated at reflux for 18 h. The excess of $POCl_3$ was evaporated under reduced pressure. The residue was poured in to crushed ice and stirred for 15 min. The aqueous solution was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (50 mL x 2), brine solution (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give 2,4-dichloro-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine (2.0 g, crude) as brown solid. LC–MS $(M+H)^+ = 281.0$.

Preparation Na

2-chloro-N-methyl-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-4-amine

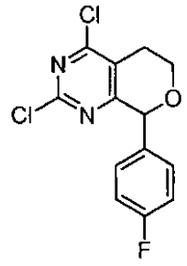


To a solution of Preparation N (2.1 g, crude) in acetonitrile was added diisopropylethylamine (1.83 g, 14.2 mmol) followed by addition of methylamine

hydrochloride (0.96 g, 14.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 40% ethyl acetate in pet-ether as mobile phase to give 2-chloro-N-methyl-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-4-amine (0.7 g, 35.7%) as off-white solid. LC–MS $(M+H)^+$ = 276.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.49 (1H, m), 7.36-7.31 (3H, m), 7.25-7.23 (2H, m), 5.45 (1H, s), 4.0 (1H, m), 3.79 (1H, m), 2.87 (3H, d, *J* = 4.4 Hz), 2.55 (1H, m), 2.44 (1H, m).

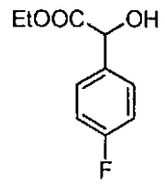
Preparation O

2,4-dichloro-8-(4-fluorophenyl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine



Intermediate O(1)

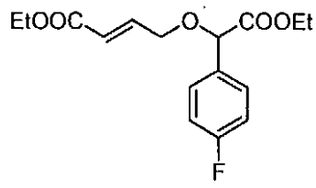
ethyl 2-(4-fluorophenyl)-2-hydroxyacetate



To a cooled solution of 2-(4-fluorophenyl)-2-hydroxyacetic acid (5.0 g, 29.4 mmol) in ethanol was added con. H_2SO_4 (10 mL) over a period of 10 min. The reaction mixture was heated at reflux for 5 h. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate (25 mL). The organic solution was washed with aqueous saturated $NaHCO_3$ (25 mL x 2), water (20 mL), brine solution (10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give ethyl 2-(4-fluorophenyl)-2-hydroxyacetate (5.0 g, 90%) as crude compound (oily liquid). The crude compound was taken to the next step without further purification. LC–MS $(M+H_2O)^+$ = 216. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.43-7.46 (2H, m), 7.17-7.20 (2H, m), 6.11-6.13 (1H, m), 5.14 (1H, d, *J* = 5.20 Hz), 3.35-4.13 (2H, m), 1.12-1.15 (3H, m).

Intermediate O(2)

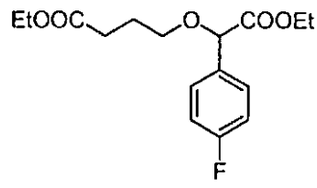
ethyl 4-(2-ethoxy-1-(4-fluorophenyl)-2-oxoethoxy)but-2-enoate



To a solution of Intermediate O(1) (3.0 g, 15.1 mmol) in hexane was added silver oxide (9.1 g, 39.3 mmol) followed by magnesium sulphate (1.8 g, 3.0 mmol) at room temperature. The reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to 0 °C and was added silver oxide (9.7 g, 39.9 mmol) followed by ethyl-4-bromochrotonate (4.3 g, 22.7 mmol). The resulting solution was stirred at room temperature for 3 days. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure to give ethyl 4-(2-ethoxy-1-(4-fluorophenyl)-2-oxoethoxy)but-2-enoate (3.0 g, 90%) as oily liquid. LC–MS $(M+H_2O)^+$= 328.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.42-7.45 (2H, m), 7.04-7.26 (2H, m), 6.95 (1H, m), 6.12 (1H, m), 4.89 (1H, s), 4.13-4.28 (6H, m), 1.30 (3H, t, J = 7.20 Hz), 1.26 (3H, J = 6.8 Hz).

Intermediate O(3)

ethyl 4-(2-ethoxy-1-(4-fluorophenyl)-2-oxoethoxy)butanoate

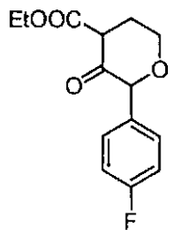


To a solution of Intermediate O(2) (3.0 g, 9.6 mmol) in ethanol was added palladium on carbon (10%, w/w) at room temperature. The reaction mixture was hydrogenated under balloon pressure of hydrogen for 30 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethanol. The solvent was removed under reduced pressure and the residue was purified by column chromatography (Silica gel, 60-120 mesh) using 5% ethyl acetate in pet-ether as mobile phase to give ethyl 4-(2-ethoxy-1-(4-fluorophenyl)-2-oxoethoxy)butanoate

(3.0 g, 63%) as oily liquid. LC–MS $(M+H)^+ = 313.2$ ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.29-7.46 (2H, m), 7.05-7.09 (2H, m), 4.84 (1H, s), 4.10-4.23 (4H, m), 3.59-3.63 (1H, m), 3.42-3.53 (1H, m), 2.47 (2H, t, J = 7.6 Hz), 1.99 (2H, t, J = 7.6 Hz), 1.22-1.32 (6H, m).

Intermediate O(4)

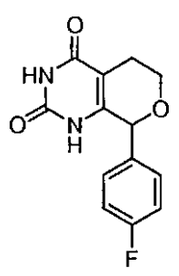
ethyl 2-(4-fluorophenyl)-3-oxotetrahydro-2H-pyran-4-carboxylate



To a cooled solution of Intermediate O(3) (3.0 g, 9.6 mmol) in THF was added *t*-BuOK (2.1 g, 19.0 mmol) at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for 1 h. The reaction mixture was quenched with water and evaporated the solvent under reduced pressure. The residue was diluted with ethyl acetate (200 mL). The organic layer was washed with water (100 mL x 2), brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 50% ethyl acetate in petroleum-ether as mobile phase to give ethyl 2-(4-fluorophenyl)-3-oxotetrahydro-2H-pyran-4-carboxylate (1.0 g, 55%) as oily liquid. LC–MS $(M+H)^+ = 267.1$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 11.81 (1H, s), 7.22-7.42 (2H, m), 7.12-7.20 (2H, m), 5.23 (1H, s), 4.22 (2H, q, J = 7.2 Hz), 3.87-3.88 (1H, m), 3.69-3.84 (1H, m), 2.34-2.35 (1H, m), 2.30-2.33 (1H, m), 1.27 (3H, t, J = 7.2 Hz).

Intermediate O(5)

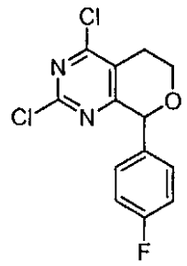
8-(4-fluorophenyl)-5,6-dihydro-1H-pyrano[3,4-d]pyrimidine-2,4(3H,8H)-dione



To a solution of Intermediate O(4) (0.30 g, 1.12 mmol) in ethanol was added *t*-BuOK (0.253 g, 2.2 mmol) followed by urea (0.135 g, 2.2 mmol) at room temperature. The reaction mass was heated at reflux for 18 h. The reaction mixture was quenched with water and evaporated the solvent under reduced pressure. The residue was diluted with ethyl acetate (100 mL). The organic layer was washed with water (100 mL x 2), brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using ethyl acetate as mobile phase to give 8-(4-fluorophenyl)-5,6-dihydro-1H-pyrano[3,4-d]pyrimidine-2,4(3H,8H)-dione (0.150 g, 40%) as pale yellow solid. LC–MS $(M-H)^+ = 263.1$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 11.14 (1H, s), 10.57 (1H, s), 7.35-7.36 (2H, m), 7.22 (2H, m), 5.34 (1H, s), 3.66-3.71 (1H, m), 3.58-3.64 (1H, m), 2.33 (2H, m).

Preparation O

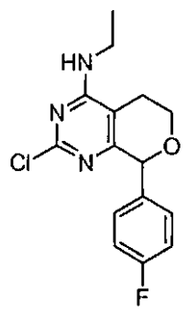
2,4-dichloro-8-(4-fluorophenyl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine



A solution of Intermediate O(5) (0.30 g, 1.1 mmol) and catalytic amount of DMF in $POCl_3$ (10 vol.) was heated at reflux for 18 h. The excess of $POCl_3$ was evaporated under reduced pressure. The residue was poured in to crushed ice and stirred for 15 min. The aqueous solution was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (50 mL x 2), brine solution (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give 2,4-dichloro-8-(4-fluorophenyl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine (0.20 g, crude) as brown liquid. LC–MS $(M+H)^+ = 299.0$.

Preparation Oa

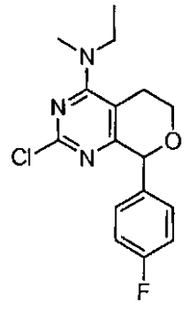
2-chloro-N-ethyl-8-(4-fluorophenyl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-4-amine



To a solution of Preparation O (0.35 g, 1.1 mmol) in methanol was added diisopropylethylamine (0.30 g, 2.2 mmol) followed by addition of ethylamine hydrochloride (0.113 g, 1.1 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 35% ethyl acetate in pet-ether as mobile phase to give 2-chloro-N-ethyl-8-(4-fluorophenyl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-4-amine (0.15 g, crude) as off-white solid. LC–MS $(M+H)^+$ = 308.2.0.

Preparation Ob

2-chloro-N-ethyl-8-(4-fluorophenyl)-N-methyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-4-amine

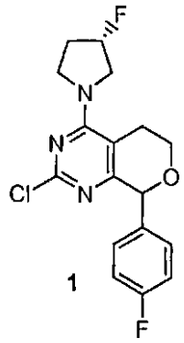


To a solution of Preparation O (0.20 g, 0.61 mmol) in methanol was added diisopropylethylamine (0.172 g, 1.3 mmol) followed by addition of ethylmethylamine hydrochloride (0.47 g, 0.81 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 40% ethyl acetate in pet-ether as mobile phase to give 2-chloro-N-ethyl-8-(4-fluorophenyl)-N-methyl-6,8-

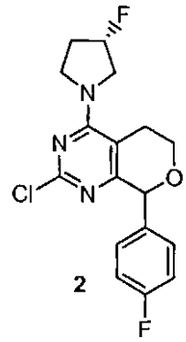
dihydro-5H-pyrano[3,4-d]pyrimidin-4-amine (0.020 g crude) as off-white solid. LC–MS $(M+H)^+ = 322.2$.

Preparation Oc1 and Oc2

2-chloro-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine



1



2

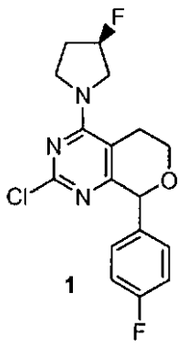
To a solution of Preparation O (0.60 g, 2.1 mmol) in methanol was added diisopropylethylamine (0.516 g, 4.6 mmol) followed by addition of (R)-3-fluoropyrrolidine (0.301 g, 2.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by pep-HPLC to give 2-chloro-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine (0.110 g, 40% Isomer 1, 0.109 g, 40% Isomer 2) as off-white solid. LC–MS $(M+H)^+ = 352.0$.

Oc1: ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.36-7.36 (2H, m), 7.16 (2H, m), 5.50 (2H, d, $J = 8.40$ Hz), 5.35 (1H, s), 3.58-3.98 (7H, m), 3.24-3.34 (1H, m), 2.78 (1H, m), 2.04-2.28 (2H, m).

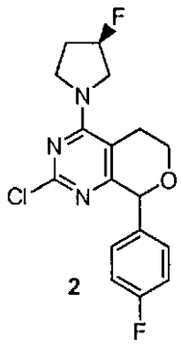
Oc2: ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.19-7.33 (2H, m), 7.15-7.20 (2H, m), 5.34 (1H, m), 5.40 (1H, m), 3.91-4.10 (2H, m), 3.75-3.90 (2H, m), 3.69-3.75 (2H, m), 3.05 (2H, t, $J = 5.20$ Hz), 2.01 (2H, d, $J = 8.0$ Hz).

Preparation Od1 and Od2

2-chloro-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine



1



2

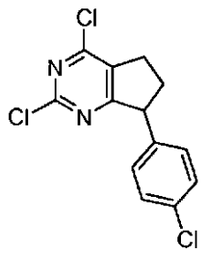
To a solution of Preparation O (0.60 g, 2.1 mmol) in methanol was added diisopropylethylamine (0.516 g, 4.6 mmol) followed by addition of (S)-3-fluoropyrrolidine (0.301 g, 2.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by pep-HPLC to give 2-chloro-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine (0.102 g, 39% Isomer 1, 0.111 g, 40% Isomer 2) as off-white solid. LC–MS $(M+H)^+ = 352.0$.

Od1: ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.36-7.36 (2H, m), 7.16 (2H, m), 5.50 (2H, d, $J = 8.4$ Hz), 5.35 (1H, s), 3.58-3.98 (7H, m), 3.24-3.34 (1H, m), 2.78 (1H, d, $J = 8.4$ Hz), 2.04-2.28 (2H, m).

Od2: ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.19-7.33 (2H, m), 7.15-7.20 (2H, m), 5.34 (1H, m), 5.40 ((1H, m), 3.91-4.10 (2H, m), 3.75-3.90 (2H, m), 3.69-3.75 (m, 2H), 3.05 (2H, t, $J = 5.20$ Hz), 2.01 (2H, d, $J = 8.0$ Hz).

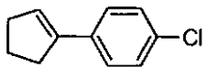
Preparation P

2,4-Dichloro-7-(4-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



Intermediate P(1)

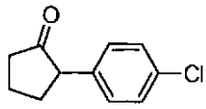
1-Chloro-4-cyclopentenylbenzene



To a 1 M solution of 4-chlorophenyl)magnesium bromide (149 mL, 149 mmol) was added cyclopentanone (13.23 mL, 149 mmol). The solution turned warm upon the addition. The reaction mixture was stirred at reflux for 2 h. The reaction mixture was cooled to room temperature and quenched with 10 g of ice. 6N hydrochloric acid solution was added until the precipitate dissolved completely. Ether was added. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with saturated aqueous solution of sodium hydrogen sulfite, saturated aqueous solution of sodium bicarbonate and water. The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 1-chloro-4-cyclopentenylbenzene (20.0 g, 112 mmol, 75 % yield) as a colorless oil. LC–MS $(M+H)^+$ = 179.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.27 - 7.39 (4H, m), 6.19 (1H, s), 2.66 - 2.74 (2H, m), 2.52 - 2.61 (2H, m), 2.01 - 2.12 (2H, m).

Intermediate P(2)

2-(4-Chlorophenyl)cyclopentanone

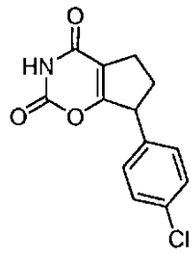


A mixture of formic acid (60 mL, 84 mmol) and hydrogen peroxide (15 mL, 84 mmol) was warmed at 40°C for 10 min. The resulting solution was carefully added to 1-chloro-4-cyclopentenylbenzene (15 g, 84 mmol) under stirring. The two-phase system was initially stirred at room temperature. After a certain period of time, a spontaneous exothermic reaction took place, and the temperature rose to about 50°C. The reaction mixture was stirred at room temperature for 1 h. The LC/MS analysis of the reaction mixture shows the disappearance of the starting material and the formation of the product. The reaction mixture was quenched by careful addition of a saturated sodium bicarbonate solution. Ether was added and the reaction mixture was vigorously shaken. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on

silica gel to give 2-(4-chlorophenyl)cyclopentanone (5.7 g, 29.3 mmol, 34.9 % yield) as a colorless oil. LC–MS $(M+H)^+$ = 195.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.21 - 7.37 (2H, m), 7.11 (2H, d, *J*=8.5 Hz), 3.25 (1H, dd, *J*=11.6, 8.5 Hz), 2.44 (2H, d, *J*=6.1 Hz), 2.15 - 2.31 (1H, m), 1.96 - 2.15 (3H, m), 1.78 - 1.95 (1H, m).

Intermediate P(3)

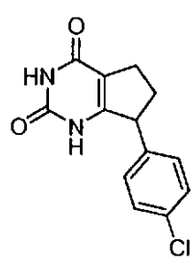
7-(4-Chlorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione



A solution of 2-(4-chlorophenyl)cyclopentanone (7.80 g, 40.1 mmol) and carbonisocyanatidic chloride (7.61 g, 72.1 mmol) was stirred at 58 °C in a high-pressure vessel for 1 h. The temperature was raised to 130 °C and the reaction mixture was stirred for an additional 2 h. After cooling to rt, the reaction mixture solidified. The solid residue was dissolved in ethyl acetate and washed with saturated aqueous solution of sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The solvent was removed in vacuum and the oily residue was purified by column chromatography on silica gel to provide 7-(4-chlorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (5.4 g, 20.48 mmol, 51.1 % yield). LC–MS $(M+H)^+$ = 264.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.32 (2H, d, *J*=8.5 Hz), 7.12 (2H, d, *J*=8.5 Hz), 4.15 - 4.25 (1H, m), 2.56 - 2.93 (4H, m).

Intermediate P(4)

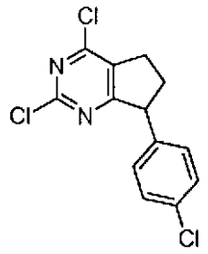
7-(4-Chlorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione



A solution of 7-(4-chlorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (5.4 g, 20.48 mmol) in concentrated ammonium hydroxide (59.8 mL, 1536 mmol) was stirred at 100 °C in a high-pressure vessel for 6 h. The formation of white precipitate was observed during the heating. The solvent was removed in vacuum to provide 7-(4-chlorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (4.9 g, 18.65 mmol, 91 % yield) as a off-white solid. LC–MS $(M+H)^+ = 263.2$. ^1H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.37 (2H, d, *J*=8.2 Hz), 7.19 (1H, d, *J*=8.5 Hz), 4.16 (1H, d, *J*=5.2 Hz), 3.79 (1H, br s), 3.17 (1H, s), 2.51 (2H, d, *J*=1.8 Hz), 1.75 - 1.85 (1H, m).

Preparation P

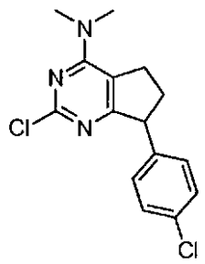
2,4-Dichloro-7-(4-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



A mixture of 7-(4-chlorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (4.7 g, 17.89 mmol), $POCl_3$ (53.4 mL, 573 mmol) and *N*,*N*-dimethylaniline (18.26 mL, 143 mmol) was heated at 110 °C overnight. The reaction mixture was poured into a beaker with ice. The inside walls of the reaction vessel was washed with DCM. As soon as the ice completely melted, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to provide 2,4-dichloro-7-(4-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (1.2 g, 4.01 mmol, 22.39 % yield). LC–MS $(M+H)^+ = 299.0$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.41 - 7.99 (2H, m), 7.09 (2H, d, *J*=8.5 Hz), 4.41 (1H, t, *J*=8.4 Hz), 2.94 - 3.18 (2H, m), 2.73 (1H, dt, *J*=8.9, 4.5 Hz), 2.15 - 2.33 (1H, m).

Preparation Pa

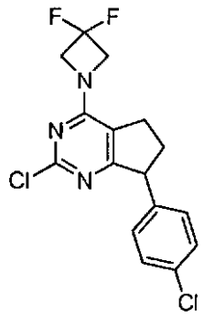
2-Chloro-7-(4-chlorophenyl)-*N*,*N*-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



A solution of 2,4-dichloro-7-(4-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (200 mg, 0.668 mmol) and excess dimethylamine (3.34 mL, 6.68 mmol) in MeOH (4 mL) was stirred at rt for 30 min. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to afford 2-chloro-7-(4-chlorophenyl)-*N*,*N*-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (98 mg, 0.318 mmol, 47.6 % yield). LC–MS $(M+H)^+$ = 308.1.

Preparation Pb

2-Chloro-7-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine

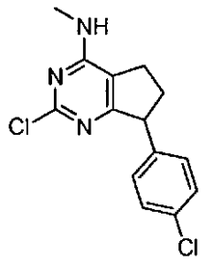


A solution of 2,4-dichloro-7-(4-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (325 mg, 1.085 mmol), *N*-ethyl-*N*-isopropylpropan-2-amine (0.945 mL, 5.42 mmol) and 3,3-difluoroazetidine, HCl salt (281 mg, 2.170 mmol) in MeOH (5 mL) was stirred at rt for 1 h. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to afford 2-chloro-7-

(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (70 mg, 0.197 mmol, 18.12 % yield). LC–MS $(M+H)^+ = 356.1$.

Preparation Pc

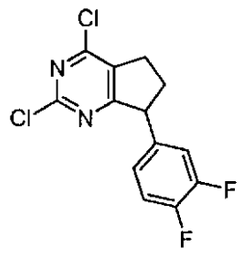
2-Chloro-7-(4-chlorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



A solution of 2,4-dichloro-7-(4-chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (300 mg, 1.001 mmol), methanamine, HCl salt (135 mg, 2.003 mmol) and DIPEA (0.700 mL, 4.01 mmol) in MeOH (6 mL) was stirred at rt for 30 min. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to afford 2-chloro-7-(4-chlorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (101 mg, 0.343 mmol, 34.3 % yield). LC–MS $(M+H)^+ = 294.2$.

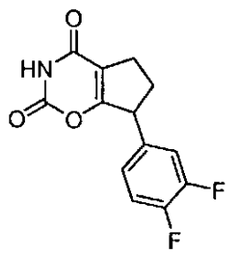
Preparation Q

2,4-Dichloro-7-(3,4-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



Intermediate Q(1)

7-(3,4-Difluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione

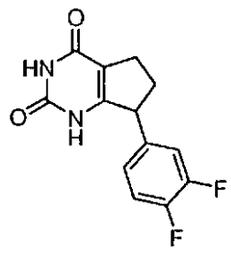


A solution of 2-(3,4-difluorophenyl)cyclopentanone, (prepared in the manner of Intermediate P(1) and P(2)) (1.5 g, 7.65 mmol) and carbonisocyanatidic chloride (1.129 g, 10.70 mmol) was stirred at 58 °C in a high-pressure vessel for 1 h. The temperature was raised to 130 °C and the reaction mixture was stirred for an additional 2 h. After cooling to rt, the reaction mixture solidified. The solid residue was dissolved in ethyl acetate and washed with saturated aqueous solution of sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The solvent was removed in vacuum and the oily residue was purified by column chromatography on silica gel to provide 7-(3,4-difluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (1.05 g, 3.96 mmol, 51.8 % yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.16 (1H, br s), 7.15 (1H, dt, *J*=10.0, 8.3 Hz), 6.97 - 7.05 (1H, m), 6.88 - 6.95 (1H, m), 2.80 - 2.90 (1H, m), 2.61 - 2.78 (2H, m), 0.78 - 0.86 (2H, m).

Intermediate Q(2)

7-(3,4-Difluorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione

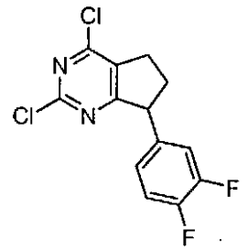


A solution of 7-(3,4-difluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (1.05 g, 3.96 mmol) in concentrated ammonium hydroxide (0.154 mL, 3.96 mmol) was stirred at 100 °C in a high-pressure vessel (75 mL) for 6 h. The formation of white precipitate was observed during the heating. The solvent was removed in vacuum to provide 7-(3,4-difluorophenyl)-6,7-dihydro-1*H*-

cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (1.046 g, 3.96 mmol, 100 % yield) as a off-white solid. LC–MS $(M+H)^+ = 265.2$.

Preparation Q

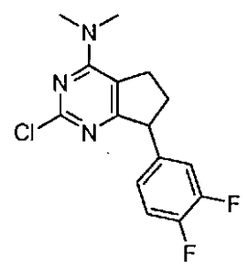
2,4-Dichloro-7-(3,4-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



A mixture of 7-(3,4-difluorophenyl)-6,7-dihydro-*1H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (500 mg, 1.892 mmol), $POCl_3$ (5644 µL, 60.6 mmol) and *N*,*N*-dimethylaniline (1931 µL, 15.14 mmol) was heated at 120 °C overnight. The reaction mixture was poured into a beaker with ice. The inside walls of the reaction vessel was washed with DCM. As soon as the ice completely melted, the content of the beaker was placed into a separatory funnel. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to provide 2,4-dichloro-7-(3,4-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (446 mg, 1.481 mmol, 78 % yield). LC–MS $(M+H)^+ = 301.1$.

Preparation Qa

2-Chloro-7-(3,4-difluorophenyl)-*N*,*N*-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine

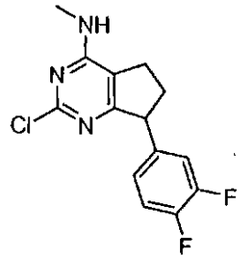


A solution of 2,4-dichloro-7-(3,4-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (446 mg, 1.481 mmol) and excess dimethylamine (2.222 mL,

4.44 mmol) in MeOH (6 mL) was stirred at rt for 30 min. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to afford 2-chloro-7-(3,4-difluorophenyl)-*N*,*N*-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (146 mg, 0.471 mmol, 31.8 % yield). LC–MS $(M+H)^+$ = 310.2.

Preparation Qb

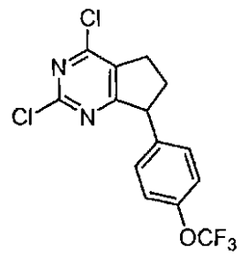
2-Chloro-7-(3,4-difluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



A solution of 2,4-dichloro-7-(3,4-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (421 mg, 1.398 mmol), methanamine, HCl (283 mg, 4.19 mmol) and DIPEA (1.465 mL, 8.39 mmol) in methanol (10 mL) was stirred at rt for 1 h. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to afford 2-chloro-7-(3,4-difluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (154 mg, 0.521 mmol, 37.2 % yield). LC–MS $(M+H)^+$ = 296.2.

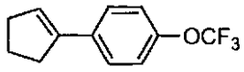
Preparation R

2,4-dichloro-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine



Intermediate R(1)

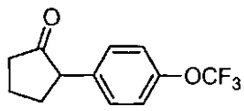
1-cyclopentenyl-4-(trifluoromethoxy)benzene



(4-(trifluoromethoxy)phenyl)magnesium bromide was reacted in the manner of Intermediate P(1) to give 1-cyclopentenyl-4-(trifluoromethoxy)benzene.

Intermediate R(2)

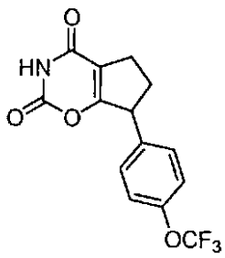
2-(4-(trifluoromethoxy)phenyl)cyclopentanone



1-cyclopentenyl-4-(trifluoromethoxy)benzene was reacted in the manner of Intermediate P(2) to give 2-(4-(trifluoromethoxy)phenyl)cyclopentanone.

Intermediate R(3)

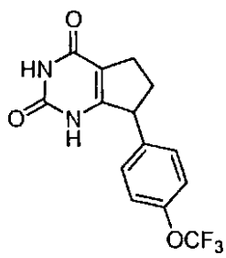
7-(4-(trifluoromethoxy)phenyl)-6,7-dihydrocyclopenta[e][1,3]oxazine-2,4(3H,5H)-dione



2-(4-(trifluoromethoxy)phenyl)cyclopentanone was reacted in the manner of Intermediate P(3) to provide 7-(4-(trifluoromethoxy)phenyl)-6,7-dihydrocyclopenta[e][1,3]oxazine-2,4(3H,5H)-dione.

Intermediate R(4)

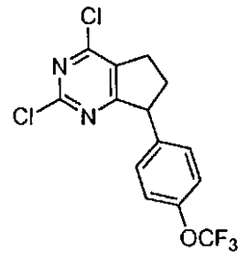
7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-1H-cyclopenta[d]pyrimidine-2,4(3H,5H)-dione



7-(4-(trifluoromethoxy)phenyl)-6,7-dihydrocyclopenta[c][1,3]oxazine-2,4(3H,5H)-dione was reacted in the manner of Intermediate P(4) to provide 7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-1H-cyclopenta[d]pyrimidine-2,4(3H,5H)-dione.

Preparation R

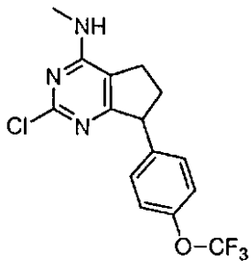
2,4-dichloro-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine



7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-1H-cyclopenta[d]pyrimidine-2,4(3H,5H)-dione was reacted in the manner of Preparation P to provide 2,4-dichloro-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine as a pink solid. LC–MS $(M+H)^+ = 349.2$. ^{1}H NMR (500 MHz, *CD3OD*) δ ppm 7.31 (2H, dd, *J*=2.0, 7.7 Hz), 7.25 (2H, d, *J*=7.4 Hz), 4.56 (1H, t, *J*=8.8 Hz), 3.15 (1H, ddd, *J* = 3.8, 9.1, 16.9 Hz), 3.09-3.00 (1H, m), 2.81-2.72 (1H, m), 2.27-2.22 (1H,m).

Preparation Ra

2-Chloro-*N*-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine

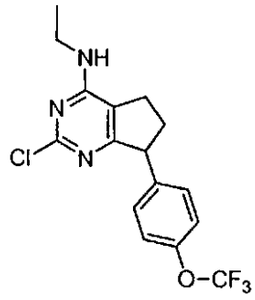


A solution of 2,4-dichloro-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (200 mg, 0.573 mmol), and methanamine (0.286 mL, 0.573 mmol) in MeOH (5 mL) was stirred at rt for 1 h. The solvent was removed in vacuum to afford crude 2-chloro-*N*-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-

cyclopenta[*d*]pyrimidin-4-amine (220 mg, 0.640 mmol, 112 % yield). LC–MS $(M+H)^+$ = 343.9.

Preparation Rb

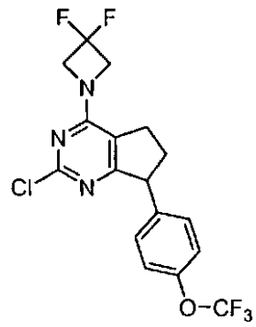
2-Chloro-*N*-ethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



A solution of 2,4-dichloro-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (200 mg, 0.573 mmol), and ethanamine (0.286 mL, 0.573 mmol) in MeOH (2 mL) was stirred at rt for 1 h. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to afford 2-chloro-*N*-ethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (190 mg, 0.531 mmol, 93 % yield). LC–MS $(M+H)^+$ = 358.2.

Preparation Rc

2-Chloro-4-(3,3-difluoroazetidin-1-yl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine

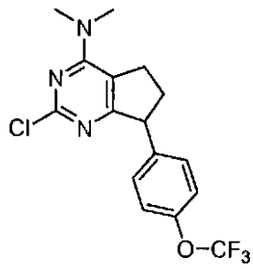


A solution of 2,4-dichloro-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (250 mg, 0.716 mmol), 3,3-difluoroazetidine, HCl salt (186 mg, 1.432 mmol) and DIPEA (0.500 mL, 2.86 mmol) in MeOH (3 mL) was stirred at rt for

1.5 h. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to afford 2-chloro-4-(3,3-difluoroazetidin-1-yl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (244 mg, 0.601 mmol, 84 % yield). LC–MS $(M+H)^+ = 406.0$.

Preparation Rd

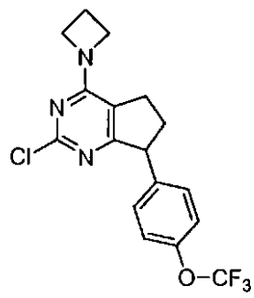
2-Chloro-*N*,*N*-dimethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



A solution of 2,4-dichloro-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (250 mg, 0.716 mmol) and dimethylamine (0.716 mL, 1.432 mmol) in MeOH (2 mL) was stirred at rt for 1 h. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to afford 2-chloro-*N*,*N*-dimethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (250 mg, 0.699 mmol, 98 % yield). LC–MS $(M+H)^+ = 358.0$.

Preparation Re

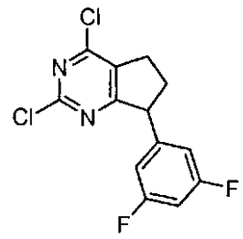
4-(Azetidin-1-yl)-2-chloro-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



A solution of 2,4-dichloro-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (250 mg, 0.716 mmol) and azetidine (82 mg, 1.432 mmol) in MeOH (3 mL) was stirred at rt for 1 h. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to afford 4-(azetidin-1-yl)-2-chloro-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (238 mg, 0.644 mmol, 90 % yield). LC–MS $(M+H)^+ = 371.2$.

Preparation S

2,4-Dichloro-7-(3,5-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



Intermediate S(1)

(1S,2R)-2-(3,5-Difluorophenyl)cyclopentanol



A flask was charged with (3,5-difluorophenyl)magnesium bromide (149 mL, 149 mmol) and copper (I) iodide (1.901 g, 9.98 mmol). To this reaction mixture, 6-oxabicyclo[3.1.0]hexane (12.53 g, 149 mmol) dissolved in THF (25 mL) was added dropwise. The reaction mixture warmed upon the addition of the epoxide. The reaction was stirred at rt for 2 h at rt. The reaction mixture was quenched by the addition of a solution of ammonium chloride. Ether was added and the organic layer was collected, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel to afford (1S,2R)-2-(3,5-difluorophenyl)cyclopentanol (26.5 g, 134 mmol, 90 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.72 (2H, dd, *J*=8.7, 2.0 Hz), 6.50 - 6.63 (1H, m), 2.97 (1H, br s), 2.78 (1H, d, *J*=10.1 Hz), 1.96 - 2.15 (2H, m), 1.66 - 1.85 (2H, m), 1.53 - 1.65 (2H, m).

Intermediate S(2)

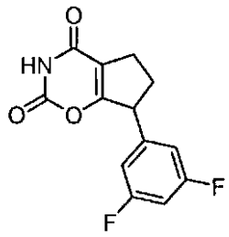
2-(3,5-Difluorophenyl)cyclopentanone



To a solution of (1S,2R)-2-(3,5-difluorophenyl)cyclopentanol (6 g, 30.3 mmol) in CH_2Cl_2 (150 mL) was added Dess-Martin periodinane (15.41 g, 36.3 mmol). The reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with dichloromethane and quenched with the addition of 1 N NaOH. The organic layer was collected, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel to afford 2-(3,5-difluorophenyl)cyclopentanone (4.765 g, 24.29 mmol, 80 % yield). LC–MS $(M+H)^+ = 197.0$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.70 (2H, d, *J*=6.7 Hz), 6.52 - 6.67 (1H, m), 3.17 - 3.33 (1H, m), 2.33 - 2.56 (2H, m), 2.06 - 2.26 (2H, m), 2.01 (1H, dd, *J*=11.7, 6.3 Hz), 1.89 (1H, br s).

Intermediate S(3)

7-(3,5-difluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione

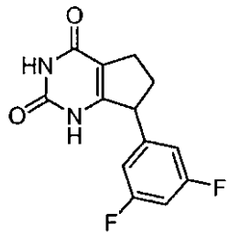


A mixture of 2-(3,5-difluorophenyl)cyclopentanone (4.765 g, 24.29 mmol) and carbonisocyanatidic chloride (4.61 g, 43.7 mmol) was heated at 58°C for 1 h and at 130 °C for 2 h. Upon cooling to room temperature, the reaction mixture was dissolved in ethyl acetate and washed with saturated aqueous solution of sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 7-(3,5-difluorophenyl)-6,7-

dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (700 mg, 2.64 mmol, 10.87 % yield). LC–MS $(M+H)^+ = 266.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.79 (1H, br s), 6.68 - 6.86 (3H, m), 4.22 (1H, br s), 2.87 (1H, dt, *J*=7.0, 4.4 Hz), 2.63 - 2.82 (2H, m), 2.15 (1H, br s).

Intermediate S(4)

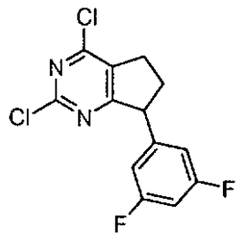
7-(3,5-Difluorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione



A solution of 7-(3,5-difluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (700 mg, 2.64 mmol) in concentrated ammonium hydroxide (50 mL, 1284 mmol) was heated at 100°C in a high-pressure (350 mL) vessel overnight. The reaction mixture was cooled and concentrated in vacuum to give crude 7-(3,5-difluorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (740 mg, 2.80 mmol, 106 % yield). LC–MS $(M+H)^+ = 265.0$.

Preparation S

2,4-Dichloro-7-(3,5-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine

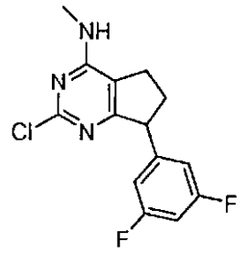


A solution of 7-(3,5-difluorophenyl)-6,7-dihydro-1*H*-cyclopenta[d]pyrimidine-2,4(3*H*,5*H*)-dione (740 mg, 2.80 mmol) in phosphoryl trichloride (7.691 mL, 84 mmol) was heated in microwave at 110 °C for 1 h. The reaction mixture was poured into ice. Once ice melted, the product was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel

to give 2,4-dichloro-7-(3,5-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (200 mg, 0.664 mmol, 23.72 % yield). LC–MS $(M+H)^+$ = 301.0.

Preparation Sa

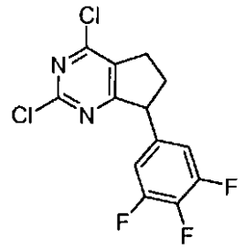
2-Chloro-7-(3,5-difluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



A solution of 2,4-dichloro-7-(3,5-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (200 mg, 0.664 mmol) and methanamine (0.664 mL, 1.328 mmol) in MeOH (3 mL) was stirred at rt for 1 h. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to give 2-chloro-7-(3,5-difluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (60 mg, 0.203 mmol, 30.5 % yield). LC–MS $(M+H)^+$ = 296.1.

Preparation T

2,4-Dichloro-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



Intermediate T(1)

(1S,2R)-2-(3,4,5-Trifluorophenyl)cyclopentanol



To a suspension of magnesium (2.88 g, 118 mmol) in THF (110 mL) was slowly added 5-bromo-1,2,3-trifluorobenzene (25 g, 118 mmol). After the addition, the reaction mixture was heated at reflux for 2 h. To this reaction mixture, copper (I) iodide (1.506 g, 7.91 mmol) and 6-oxabicyclo[3.1.0]hexane (9.93 g, 118 mmol) dissolved in THF (20 mL) were added dropwise. The reaction mixture warmed upon the addition of the epoxide. The reaction was stirred at rt for 2 h at rt. The reaction mixture was quenched by the addition of a solution of ammonium chloride. Ether was added and the organic layer was collected, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel to give (1S,2R)-2-(3,4,5-trifluorophenyl)cyclopentanol (20.2 g, 93 mmol, 79 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.79 - 7.02 (2H, m), 4.10 - 4.21 (1H, m), 2.75 - 2.91 (1H, m), 2.08 - 2.24 (2H, m), 1.75 - 1.93 (2H, m), 1.50 - 1.75 (2H, m).

Intermediate T(2)

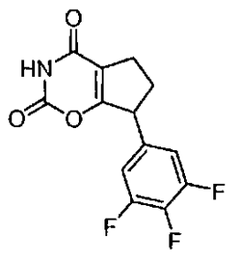
2-(3,4,5-Trifluorophenyl)cyclopentanone



To a solution of (1S,2R)-2-(3,4,5-trifluorophenyl)cyclopentanol (1 g, 4.63 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (2.354 g, 5.55 mmol). The reaction mixture was stirred at rt for 1 h. The reaction was diluted with dichloromethane and quenched with the addition of 1 N NaOH. The organic layer was collected, dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel to afford 2-(3,4,5-trifluorophenyl)cyclopentanone (310 mg, 1.447 mmol, 31.3 % yield). LC–MS $(M+H)^+$ = 215.1.

Intermediate T(3)

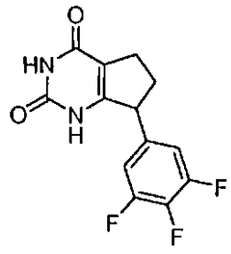
7-(3,4,5-Trifluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione



A mixture of 2-(3,4,5-trifluorophenyl)cyclopentanone (2 g, 9.34 mmol) and carbonisocyanatidic chloride (1.773 g, 16.81 mmol) was heated at 58°C for 1 h and at 130 °C for 2 h. Upon cooling to room temperature, the reaction mixture was dissolved in ethyl acetate and washed with saturated aqueous solution of sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 7-(3,4,5-trifluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (1.227 g, 4.33 mmol, 46.4 % yield). LC–MS $(M+H)^+ = 284.0$.

Intermediate T(4)

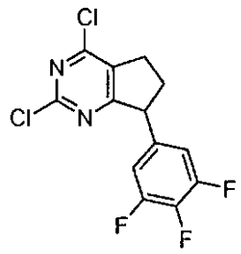
7-(3,4,5-Trifluorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione



A solution of 7-(3,4,5-trifluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (1.23 g, 4.34 mmol) in concentrated ammonium hydroxide (75 mL, 1926 mmol) was heated at 100°C in a high-pressure (350 mL) vessel overnight. The reaction mixture was cooled and concentrated in vacuum to give crude 7-(3,4,5-trifluorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (1.3 g, 4.61 mmol, 106 % yield). LC–MS $(M+H)^+ = 283.0$.

Preparation T

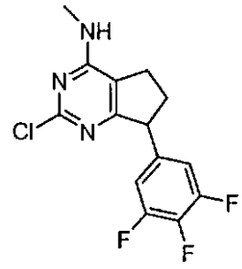
2,4-Dichloro-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



A solution of 7-(3,4,5-trifluorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (1.3 g, 4.61 mmol) in phosphoryl trichloride (5 mL, 54.6 mmol) was heated in microwave at 110 °C for 1 h. The reaction was repeated with an additional 800 mg of the starting material. The reaction mixtures was poured into ice and combined. Once ice melted, the product was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2,4-dichloro-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (498 mg, 1.561 mmol, 33.9 % yield). LC–MS $(M+H)^+ = 318.9$.

Preparation Ta

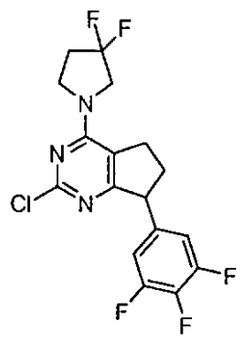
2-Chloro-*N*-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



A solution of 2,4-dichloro-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (498 mg, 1.561 mmol) and methanamine (1.561 mL, 3.12 mmol) in MeOH (10 mL) was stirred at rt for 1 h. Incomplete reaction was observed. Additional portions of methanamine (1.561 mL, 3.12 mmol) were added to the reaction mixture until the reaction was complete. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2-chloro-7-(3,5-difluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (60 mg, 0.203 mmol, 30.5 % yield). LC–MS $(M+H)^+ = 314.0$.

Preparation Tb

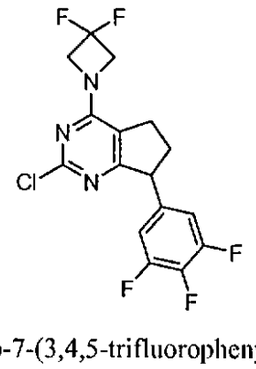
2-Chloro-4-(3,3-difluoropyrrolidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



A solution of 2,4-dichloro-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (100 mg, 0.313 mmol), DIPEA (0.066 mL, 0.376 mmol) and 3,3-difluoropyrrolidine, HCl salt (45.0 mg, 0.313 mmol) were stirred at rt for 1 h. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2-chloro-4-(3,3-difluoropyrrolidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (105 mg, 0.269 mmol, 86 % yield). LC–MS $(M+H)^+ = 390.0$.

Preparation Tc

2-Chloro-4-(3,3-difluoroazetidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine

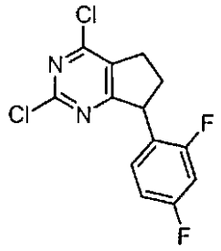


A solution of 2,4-dichloro-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (100 mg, 0.313 mmol), DIPEA (0.109 mL, 0.627 mmol) and 3,3-difluoroazetidine, HCl salt (44.7 mg, 0.345 mmol) were stirred at rt for 1 h. The solvent was removed in vacuum and the residue was purified by column chromatography

on silica gel to give 2-chloro-4-(3,3-difluoroazetidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (105 mg, 0.279 mmol, 89 % yield). LC–MS $(M+H)^+ = 376.0$.

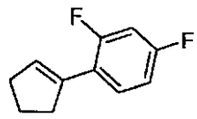
Preparation U

2,4-Dichloro-7-(2,4-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



Intermediate U(1)

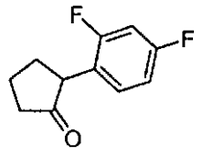
1-Cyclopentenyl-2,4-difluorobenzene



To a 0.497M solution of (2,4-difluorophenyl)magnesium bromide (32.4 g, 149 mmol) in THF at 0°C was carefully added cyclopentanone (13.23 mL, 149 mmol). Upon the end of the addition, the reaction mixture was heated at reflux for 2 h. Ice (10 g) and 6N aqueous hydrochloric acid were added. The reaction mixture was extracted with ether. The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogen sulfite, a saturated aqueous solution of sodium bicarbonate and water. The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 1-cyclopentenyl-2,4-difluorobenzene (7.064 g, 39.2 mmol, 26.3 % yield) as colorless oil. LC-MS $(M+H)^+ = 181.0$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.22 - 7.31 (1H, m), 6.75 - 6.85 (2H, m), 6.26 - 6.31 (1H, m), 2.68 - 2.74 (2H, m), 2.51 - 2.58 (2H, m), 1.93 - 2.02 (2H, m).

Intermediate U(2)

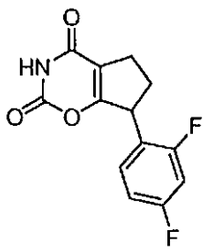
2-(2,4-Difluorophenyl)cyclopentanone



A mixture of 90% formic acid (26.4 mL, 689 mmol) and 30% hydrogen peroxide (6.0 mL, 39.2 mmol) was warmed at 40°C for 10 min. The resulting solution was carefully added to 1-cyclopentenyl-2,4-difluorobenzene (7.064 g, 39.2 mmol) under stirring. The two-phase system was initially stirred at room temperature. After a certain period of time, a spontaneous exothermic reaction took place, and the temperature rose to about 50°C. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by careful addition of a saturated sodium bicarbonate solution. Ether was added and the content of the separatory funnel was vigorously shaken. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2-(2,4-difluorophenyl)cyclopentanone (3.503 g, 17.85 mmol, 45.5 % yield) as colorless oil. LC-MS $(M+H)^+$ = 195.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.08 (1H, td, *J*=8.4, 6.4 Hz), 6.76 - 6.86 (2H, m), 3.42 (1H, dd, *J*=12.2, 8.9 Hz), 2.42 - 2.53 (2H, m), 2.28 - 2.39 (1H, m), 2.13 - 2.23 (1H, m), 1.86 - 2.10 (2H, m).

Intermediate U(3)

7-(2,4-Difluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione

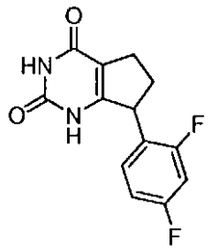


A mixture of 2-(2,4-difluorophenyl)cyclopentanone (1.014 g, 5.17 mmol) and 50% wt. carbonisocyanatidic chloride solution in toluene (1.963 g, 9.30 mmol) was heated at 58 °C for 1 h and at 120°C for 3 h. The reaction mixture was dissolved in ethyl acetate and washed with an aqueous solution of sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined

organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 7-(2,4-difluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (499.3 mg, 1.883 mmol, 36.4 % yield) as brown solid. LC-MS $(M+H)^+ = 266.2$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 8.19 - 8.64 (1H, m), 7.10 (1H, td, *J*=8.5, 6.3 Hz), 6.78 - 6.92 (2H, m), 4.36 - 4.49 (1H, m), 2.79 - 2.92 (1H, m), 2.59 - 2.78 (2H, m), 2.08 (1H, ddd, *J*=9.3, 6.9, 6.7 Hz).

Intermediate U(4)

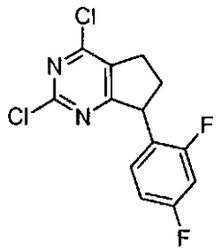
7-(2,4-Difluorophenyl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione



A mixture of 2-(2,4-difluorophenyl)cyclopentanone (1.014 g, 5.17 mmol) and 50% wt. carbonisocyanatidic chloride solution in toluene (1.963 g, 9.30 mmol) was heated at 58 °C for 1 h and at 120°C for 3 h. The reaction mixture was dissolved in ethyl acetate and washed with an aqueous solution of sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 7-(2,4-difluorophenyl)-6,7-dihydrocyclopenta[*e*][1,3]oxazine-2,4(3*H*,5*H*)-dione (499.3 mg, 1.883 mmol, 36.4 % yield) as brown solid. LC-MS $(M+H)^+ = 265.1$.

Preparation U

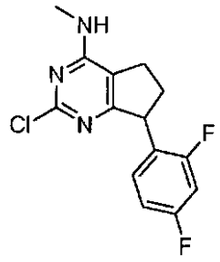
2,4-Dichloro-7-(2,4-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine



A solution of 7-phenyl-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (248.5 mg, 0.940 mmol) in phosphoryl trichloride (10 mL) was heated in microwave at 130 °C for 2 h. The reaction mixture was poured in a beaker with ice. Once ice melted, the product was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2,4-dichloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (267.9 mg, 95%) as light brown solid. LC-MS $(M+H)^+ = 301.1$.

Preparation Ua

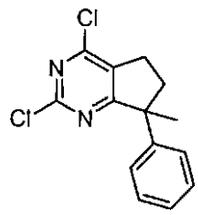
2-Chloro-7-(2,4-difluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine



To a solution of 2,4-dichloro-7-(2,4-difluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (267.9 mg, 0.890 mmol) in methanol (5 mL) was added a 2M solution of methylamine in methanol (0.890 mL, 1.779 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuum and the residue was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2-chloro-7-(2,4-difluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (184.6 mg, 0.624 mmol, 70.2 % yield) as brown solid. LC-MS $(M+H)^+ = 296.1$.

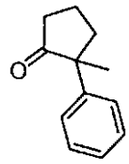
Preparation V

2,4-dichloro-7-methyl-7-phenyl-6,7-dihydro-5H- cyclopenta[d]pyrimidine



Intermediate V(1)

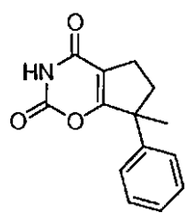
2-methyl-2-phenylcyclopentanone



To a slurry of 60% NaH (125 mg, 3.12 mmol) in DME (3571 μL) at 0 °C was added 2-phenylcyclopentanone (500 mg, 3.12 mmol). After stirring for 1h, MeI (898 μL, 14.36 mmol) was added, and the solution heated to reflux for 2h. The reaction was poured onto ice and extracted 3 times into Et2O. The organic extracts were washed with brine, dried over MgSO4, filtered and concentrated in vacuo. Applied to Silica gel and eluted with an EtOAc/Hex gradient to afford 2-methyl-2-phenylcyclopentanone (401.7 mg, 2.305 mmol, 73.9 % yield).LC–MS $(M+H)^+$ = 175.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.29 - 7.37 (4 H, m), 7.20 - 7.24 (1 H, m), 2.54 (1 H, dt, *J*=12.51, 6.26 Hz), 2.34 (2 H, t, *J*=7.63 Hz), 1.82 - 2.05 (3 H, m), 1.38 (3 H, s).

Intermediate V(2)

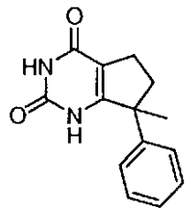
7-methyl-7-phenyl-6,7-dihydrocyclopenta[e][1,3]oxazine-2,4(3H,5H)-dione



Combined 2-methyl-2-phenylcyclopentanone (Intermediate V(1) (705.5 mg, 4.05 mmol) and carbonisocyanatidic chloride (1700 mg, 8.06 mmol), flushed with N2, and sealed in a sealed tube. Heated at 58 °C for 1 h, then 130 °C for 1.75 h. Let cool to rt. Carefully opened the tube (HCl), and dissolved the residue in EtOAc. Partitioned with NaHCO3 (aq), and extracted 3 times into EtOAc. Washed combined organic layers with brine, dried over MgSO4, filtered, and concentrated *in vacuo*. Loaded the residue onto Silica gel and eluted with an EtOAc/Hexane gradient to afford 7-methyl-7-phenyl-6,7-dihydrocyclopenta[e][1,3]oxazine-2,4(3H,5H)-dione (43% yield)LC–MS $(M+H)^+$ = 244.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.12 (1 H, br. s.), 7.32 - 7.38 (2 H, m), 7.26 - 7.30 (3 H, m), 2.69 - 2.75 (2 H, m), 2.43 - 2.52 (1 H, m), 2.21 - 2.29 (1 H, m), 1.68 (3 H, s).

Intermediate V(3)

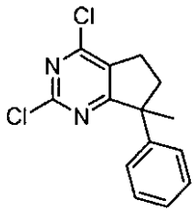
7-methyl-7-phenyl-6,7-dihydro-1H-cyclopenta[d]pyrimidine-2,4(3H,5H)-dione



To solid 7-methyl-7-phenyl-6,7-dihydrocyclopenta[e][1,3]oxazine-2,4(3H,5H)-dione (420 mg, 1.727 mmol) was added concentrated Ammonium Hydroxide (4706 µL, 121 mmol) in a sealed tube. The tube was heated for 4h at 80 °C. Cooled to rt. Removed the solvent under a stream of N2. Loaded the residue onto Silica gel and eluted with an EtOAc/Hexane gradient to afford 7-methyl-7-phenyl-6,7-dihydro-1H-cyclopenta[d]pyrimidine-2,4(3H,5H)-dione (293 mg, 1.209 mmol, 70.0 % yield). LC–MS $(M+H)^+$ = 243.1.

Preparation V

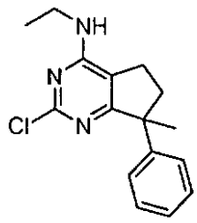
2,4-dichloro-7-methyl-7-phenyl-6,7-dihydro-5H- cyclopenta[d]pyrimidine



Dissolved 7-methyl-7-phenyl-6,7-dihydro-1H-cyclopenta[d]pyrimidine-2,4(3H,5H)-dione (48.2 mg, 0.199 mmol) in POCl3 (742 µL, 7.96 mmol) and placed in a microwave vial. Heated the reaction for 1h at 120 °C in the microwave. Cooled to rt, and poured into ice. As soon as the ice melted, extracted 3 times into EtOAc. Dried over MgSO4, filtered, and concentrated in vacuo. A quick EtOAc/Hex SG column provided 2,4-dichloro-7-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine (43.1 mg, 0.154 mmol, 78 % yield).LC–MS $(M+H)^+$ = 279.1.

Preparation Va

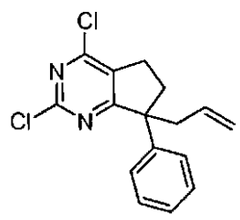
2-chloro-N-ethyl-7-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine



To a solution of 2,4-dichloro-7-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation V) (43.1 mg, 0.154 mmol) in THF (772 µL) at rt was added a solution of 2M Ethylamine (386 µL, 0.772 mmol) diluted with 390 uL MeOH (overall reaction is .1M in 1:1 THF/MeOH). Let stir at rt. Removed the solvent and subjected the residue to a Silica gel column with an EtOAc/Hex gradient to afford 2-chloro-N-ethyl-7-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (38.0 mg, 0.132 mmol, 86 % yield).

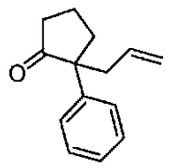
Preparation W

2,4-dichloro-7-allyl-7-phenyl-6,7-dihydro-5H- cyclopenta[d]pyrimidine



Intermediate W(1)

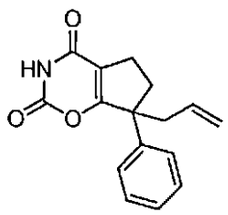
2-allyl-2-phenylcyclopentanone



The procedure of Intermediate V(1) was utilized with allyl bromide to obtain 2-allyl-2-phenylcyclopentanone.

Intermediate W(2)

7-allyl-7-phenyl-6,7-dihydrocyclopenta[e][1,3]oxazine-2,4(3H,5H)-dione

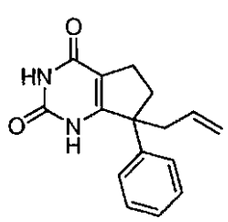


The method of Intermediate V(2) was utilized to obtain 7-allyl-7-phenyl-6,7-dihydrocyclopenta[e][1,3]oxazine-2,4(3H,5H)-dione.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.06 (1 H, br. s.), 7.23 - 7.43 (5 H, m), 5.59 - 5.72 (1 H, m, *J*=17.09, 9.99, 7.21, 7.21 Hz), 5.08 - 5.23 (2 H, m), 2.73 - 2.87 (2 H, m), 2.63 - 2.71 (2 H, m), 2.38 - 2.49 (2 H, m)

Intermediate W(3)

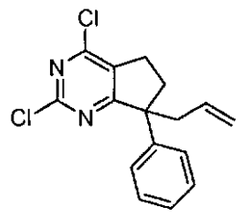
7-allyl-7-phenyl-6,7-dihydro-1H-cyclopenta[d]pyrimidine-2,4(3H,5H)-dione



The method of Intermediate V(3) was utilized to obtain 7-allyl-7-phenyl-6,7-dihydro-1H-cyclopenta[d]pyrimidine-2,4(3H,5H)-dione. LC–MS $(M+H)^+ = 269.1$.

Preparation W

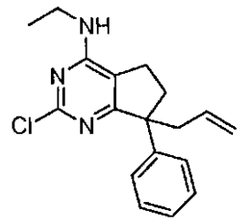
2,4-dichloro-7-allyl-7-phenyl-6,7-dihydro-5H- cyclopenta[d]pyrimidine



The method of Preparation V was used to obtain 2,4-dichloro-7-allyl-7-phenyl-6,7-dihydro-5H- cyclopenta[d]pyrimidine.LC–MS $(M+H)^+ = 305.0$.

Preparation Wa

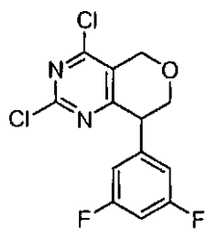
2-chloro-N-ethyl-7-allyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine



Utilizing the procedure for Preparation Va, 2-chloro-N-ethyl-7-allyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine was obtained. LC–MS $(M+H)^+ = 314.1$.

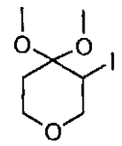
Preparation X

2,4-dichloro-8-(3,5-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



Intermediate X(1)

3-iodo-4,4-dimethoxytetrahydro-2H-pyran

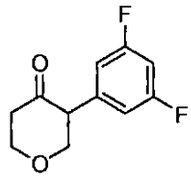


The mixture of trimethoxymethane (82 mL, 745 mmol) and dihydro-2H-pyran-4(3H)-one (14.92 g, 149 mmol) was cooled to 4 °C. Added diiodine (37.8 g, 149 mmol) in lots and keep the temperature between 4 °C and 5 °C. The reaction mixture was stirred at 4 °C for 10 min. Cooling bath was removed, stirred at 28 °C for 10 min. The mixture was cooled to 10 °C and stirred for 10 min, and then stirred at RT for 1 h.

The reaction mixture was diluted with CH_2Cl_2 and cooled in ice water. Slowly quenched with saturated $Na_2S_2O_3$ solution. The mixed layers were separated. The aqueous layer was extracted with CH2Cl2. The combined organic layer was washed with brine, dried over Na2SO4 and concentrated. The crude product was purified by column chromatography on silica gel to give 3-iodo-4,4-dimethoxytetrahydro-2H-pyran (33.05 g, 121 mmol, 82 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 4.24 (1 H, t, J=2.29 Hz), 3.93 - 4.02 (1 H, m), 3.83 - 3.92 (2 H, m), 3.55 (1 H, d, J=2.44 Hz), 3.24 (3 H, s), 3.20 (3 H, s), 2.33 (1 H, dd, J=4.88, 2.14 Hz), 1.79 (1 H, dd, J=14.34, 2.44 Hz)

Intermediate X(2)

3-(3,5-difluorophenyl)dihydro-2H-pyran-4(3H)-one

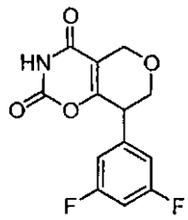


To a mixture of (1R,2R)-2-aminocyclohexanol hydrochloride (0.418 g, 2.76 mmol), nickel(II) chloride hexahydrate (0.328 g, 1.378 mmol) and 3,5-difluorophenylboronic acid (6.53 g, 41.3 mmol) was added NaHMDS in THF (55.1 mL, 55.1 mmol) at 10 °C dropwise under N_2. After addition, the mixture was stirred at 10 °C for 20 min. 2-Propanol (113 mL) (previously bubbled by N2) was added at 0 °C and then the mixture was stirred at RT for 10 min. 3-iodo-4, 4-dimethoxytetrahydro-2H-pyran (Preparation X1) (7.5 g, 27.6 mmol). in THF was added dropwise and the mixture was heated at 60 °C overnight. The reaction mixture was cooled in ice bath, added 1.0 HCl until acidic and stirred for 10 min. Concentrated in vacuum. Extracted with EtOAc and

the organic layer was washed with brine and concentrated. The residue was purified by column chromatography on silica gel to give 3-(3,5-difluorophenyl)dihydro-2H-pyran-4(3H)-one (1.6 g, 7.54 mmol, 27.4 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.78 (dd, J=8.24, 2.14 Hz, 2 H) 6.62 - 6.75 (m, 1 H) 4.21 (dd, J=11.44, 5.65 Hz, 2 H) 3.85 - 4.01 (m, 2 H) 3.76 (dd, J=8.55, 6.10 Hz, 1 H) 2.60 - 2.75 (m, 1 H) 2.48 - 2.60 (m, 1 H)

Intermediate X(3)

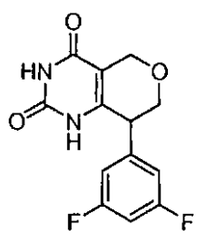
8-(3,5-difluorophenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione



The mixture of 3-(3, 5-difluorophenyl) dihydro-2H-pyran-4(3H)-one (Preparation X2) (800 mg, 3.77 mmol) and carbonisocyanatidic chloride (557 mg, 5.28 mmol) was heated in a sealed bottle at 55 °C for 1 h and then at 130 °C for 2 h. The mixture was cooled to RT. Partition between EtOAc and saturated $NaHCO_3$ solution. Extracted with EtOAc(x 3 times). The combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel to give 8-(3,5-difluorophenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione (230 mg, 0.818 mmol, 21.69 % yield). LC–MS $(M+H)^+$ = 282.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.94 (br, s., 1 H) 6.85 - 7.01 (m, 2 H) 6.81 (tt, J=8.81, 2.17 Hz, 1 H) 4.70 (d, J=15.56 Hz, 1 H) 4.49 (dd, J=15.56, 2.14 Hz, 1 H) 4.03 - 4.12 (m, 2 H) 3.68 (br. s., 1 H)

Intermediate X(4)

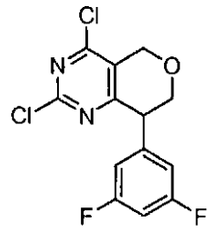
8-(3,5-difluorophenyl)-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione



The mixture of 8-(3,5-difluorophenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione (Preparation X3)(230 mg, 0.818 mmol) and ammonium hydroxide (2229 µL, 57.3 mmol) in a sealed bottle was heated at 80 °C for 4 h. Blowed by N2 overnight to get 8-(3,5-difluorophenyl)-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione (191 mg, 0.682 mmol, 83 % yield) which was used as is.
LC–MS $(M+H)^+$ = 281.1.

Preparation X

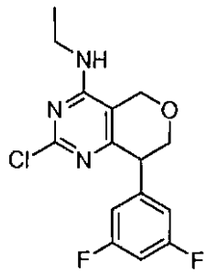
2,4-dichloro-8-(3,5-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



The mixture of 8-(3,5-difluorophenyl)-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione (Intermediate X(4)) (191 mg, 0.682 mmol) and $POCl_3$ (1906 µL, 20.45 mmol) in a microwave vial was heated by microwave at 100 °C for 2.5 h. The mixture was poured on ice, as long as ice was melted, extracted with EtOAc (x3 times), washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel to give 2,4-dichloro-8-(3,5-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (117 mg, 0.369 mmol, 54.1 % yield).
LC–MS $(M+H)^+$ = 317.1. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.66 - 6.91 (m, 3 H) 4.87 - 5.01 (m, 1 H) 4.70 - 4.83 (m, 1 H) 4.13 - 4.27 (m, 2 H) 4.10 (t, J=4.03 Hz, 1 H)

Preparation Xa

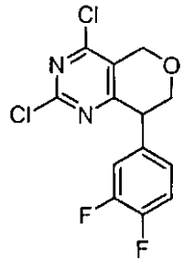
2-chloro-8-(3,5-difluorophenyl)-N-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



The mixture of ethanamine (406 μL, 0.812 mmol), 2,4-dichloro-8-(3,5-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation X)(117 mg, 0.369 mmol) and DIEA (161 μL, 0.922 mmol) in THF (1845 μL) was stirred at RT for 2 h. The mixture was concentrated and purified by column chromatography on silica gel to give 2-chloro-8-(3, 5-difluorophenyl)-N-ethyl-7, 8-dihydro-5H-pyrano [4, 3-d] pyrimidin-4-amine (104 mg, 0.319 mmol, 87 % yield). LC–MS $(M+H)^+ = 326.1$.

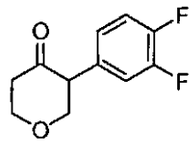
Preparation Y

2,4-dichloro-8-(3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



Intermediate Y(2)

3-(3,4-difluorophenyl)dihydro-2H-pyran-4(3H)-one

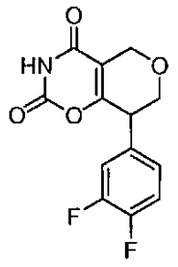


3,4-difluorophenylboronic acid was reacted as described in Intermediate X(2) with 3-iodo-4,4-dimethoxytetrahydro-2H-pyran (Intermediate X(1)) to give 3-(3,4-difluorophenyl)dihydro-2H-pyran-4(3H)-one (Intermediate Y(2)).

^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.03 - 7.22 (m, 2 H) 6.95 (ddd, J=6.33, 4.20, 1.98 Hz, 1 H) 4.17 - 4.32 (m, 2 H) 3.96 (ddd, J=11.52, 9.84, 3.97 Hz, 1 H) 3.91 (dd, J=11.44, 9.00 Hz, 1 H) 3.77 (dd, J=8.85, 5.80 Hz, 1 H) 2.63 - 2.76 (m, 1 H) 2.49 - 2.62 (m, 1 H).

Intermediate Y(3)

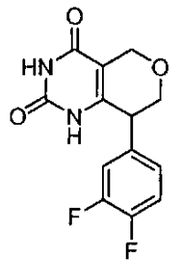
8-(3,4-difluorophenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione



3-(3,4-difluorophenyl)dihydro-2H-pyran-4(3H)-one (Intermediate Y(2)) was reacted as described in Intermediate X(3) with carbonisocyanatidic chloride to give 8-(3,4-difluorophenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione (Intermediate Y(3)). LC–MS $(M+H)^+ = 282.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.08 - 7.20 (m, 3 H) 4.67 (d, J=15.26 Hz, 1 H) 4.46 (dd, J=15.56, 2.14 Hz, 1 H) 3.98 - 4.10 (m, 2 H) 3.67 (br. s., 1H).

Intermediate Y(4)

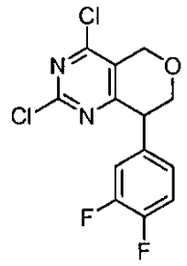
8-(3,4-difluorophenyl)-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione



8-(3,4-difluorophenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione (Intermediate Y(3)) was reacted as described in Intermediate X(4) with ammonium hydroxide to give 8-(3,4-difluorophenyl)-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione (Intermediate Y(4)). LC–MS $(M-H)^+ = 279.1$.

Preparation Y

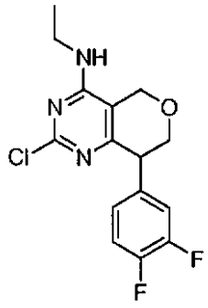
2,4-dichloro-8-(3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



2,4-dichloro-8-(3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Intermediate Y(4)) was reacted as described in Preparation X with $POCl_3$ to give 2,4-dichloro-8-(3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation Y). LC–MS $(M+H)^+ = 317.1$.

Preparation Ya

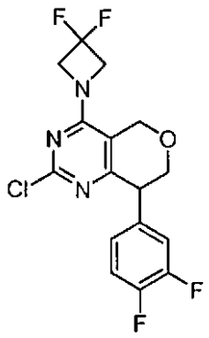
2-chloro-8-(3,4-difluorophenyl)-N-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



2,4-dichloro-8-(3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation Y) was reacted as described in Preparation Xa with ethanamine to give 2-chloro-8-(3,4-difluorophenyl)-N-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Ya). LC–MS $(M+H)^+ = 326.1$.

Preparation Yb

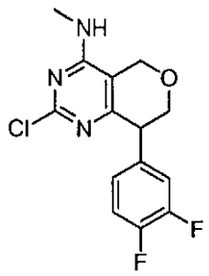
2-chloro-4-(3,3-difluoroazetidin-1-yl)-8-(3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



2,4-dichloro-8-(3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation Y) was reacted as described in Preparation Xa with 3,3-difluoroazetidine, HCl to give 2-chloro-4-(3,3-difluoroazetidin-1-yl)-8-(3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation Yb). LC–MS $(M+H)^+ = 374.1$.

Preparation Yc

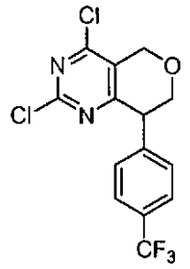
2-chloro-8-(3,4-difluorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



2,4-dichloro-8-(3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation Y) was reacted as described in Preparation Xa with methanamine to give 2-chloro-8-(3,4-difluorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Yc). LC–MS $(M+H)^+ = 312.3$.

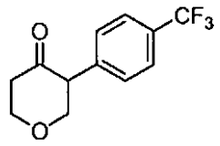
Preparation Z

2,4-dichloro-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



Intermediate Z(2)

3-(4-(trifluoromethyl)phenyl)dihydro-2H-pyran-4(3H)-one

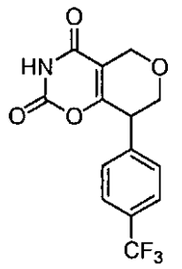


4-(trifluoromethyl)phenylboronic acid was reacted as described in Intermediate X(2) with 3-iodo-4,4-dimethoxytetrahydro-2H-pyran (Intermediate X(1)) to give 3-(4-(trifluoromethyl)phenyl)dihydro-2H-pyran-4(3H)-one (Intermediate Z(2)).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.61 (m, J=8.24 Hz, 2 H) 7.37 (m, J=7.93 Hz, 2 H) 4.26 (dd, J=11.44, 5.95 Hz, 2 H) 3.93 - 4.05 (m, 2 H) 3.82 - 3.93 (m, 1 H) 2.64 - 2.81 (m, 1 H) 2.49 - 2.64 (m, 1 H)

Intermediate Z(3)

8-(4-(trifluoromethyl)phenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione

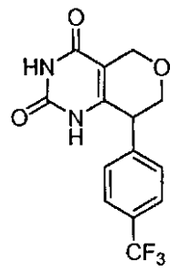


3-(4-(trifluoromethyl)phenyl)dihydro-2H-pyran-4(3H)-one (Intermediate Z(2)) was reacted as described in Intermediate X(3) with carbonisocyanatidic chloride to give 8-(4-(trifluoromethyl)phenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione (Intermediate Z(3)).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.47 (br. s., 1 H) 7.58 - 7.75 (m, 2 H) 7.42 - 7.55 (m, 2 H) 4.68 (d, J=15.56 Hz, 1 H) 4.42 - 4.57 (m, 1 H) 4.03 - 4.22 (m, 2 H) 3.79 (br. s., 1 H)

Intermediate Z(4)

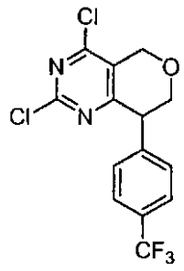
8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione



8-(4-(trifluoromethyl)phenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione (Intermediate Z(3)) was reacted as described in Intermediate X(4) with ammonium hydroxide to give 8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione (Intermediate Z(4)). LC–MS $(M-H)^+ = 313.1$.

Preparation Z

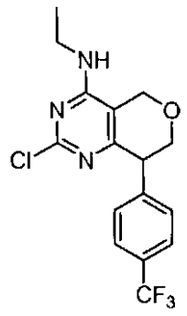
2,4-dichloro-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione (Intermediate Z(4)) was reacted as described in Preparation X with $POCl_3$ to give 2,4-dichloro-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation Z). LC–MS $(M+H)^+ = 349.1$.

Preparation Za

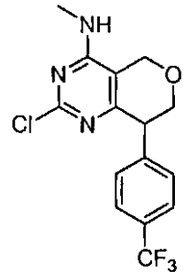
2-chloro-N-ethyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



2,4-dichloro-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation Z) was reacted as described in Preparation Xa with ethanamine to give 2-chloro-N-ethyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Za). LC–MS $(M+H)^+ = 358.1$.

Preparation Zb

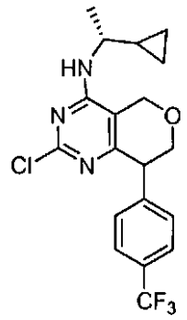
2-chloro-N-methyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



2,4-dichloro-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation Z) was reacted as described in Preparation Xa with methanamine to give 2-chloro-N-methyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Zb). LC–MS $(M+H)^+ = 344.1$.

Preparation Zc

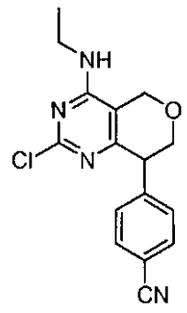
2-chloro-N-((R)-1-cyclopropylethyl)-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine



2,4-dichloro-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation Z) was reacted as described in Preparation Xa with (R)-1-cyclopropylethanamine, HCl to give 2-chloro-N-((R)-1-cyclopropylethyl)-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Zc). LC–MS $(M+H)^+ = 398.2$.

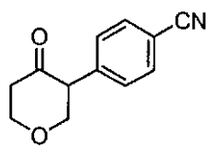
Preparation AAa

4-(2-chloro-4-(ethylamino)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile



Intermediate AA(2)

4-(4-oxotetrahydro-2H-pyran-3-yl)benzonitrile

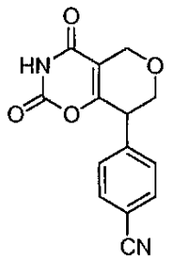


4-cyanophenylboronic acid was reacted as described in Intermediate X(2) with 3-iodo-4,4-dimethoxytetrahydro-2H-pyran (Intermediate X(1)) to give 4-(4-oxotetrahydro-2H-pyran-3-yl)benzonitrile (Intermediate AA(2)). LC–MS $(M+H)^+ = 202.1$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.66 (d, J=8.24 Hz, 2 H) 7.38 (d, J=8.55 Hz, 2 H) 4.23 - 4.31

(m, 2 H) 3.94 - 4.02 (m, 2 H) 3.85 - 3.92 (m, 1 H) 2.55 - 2.65 (m, 1 H) 2.52 (t, J=5.80 Hz, 1 H).

Intermediate AA(3)

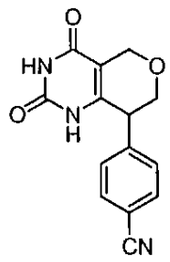
4-(2,4-dioxo-2,3,4,5,7,8-hexahydropyrano[3,4-e][1,3]oxazin-8-yl)benzonitrile



4-(4-oxotetrahydro-2H-pyran-3-yl)benzonitrile (Intermediate AA(2)) was reacted as described in Intermediate X(3) with carbonisocyanatidic chloride to give 4-(2,4-dioxo-2,3,4,5,7,8-hexahydropyrano[3,4-e][1,3]oxazin-8-yl)benzonitrile (Intermediate AA(3)). LC–MS $(M+H)^+ = 271.1$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.57 - 7.78 (m, 2 H) 7.41 - 7.51 (m, 2 H) 4.61 - 4.75 (m, 1 H) 4.50 (dd, J=15.49, 2.14 Hz, 1 H) 4.04 - 4.20 (m, 2 H) 3.78 (br. s., 1 H).

Intermediate AA(4)

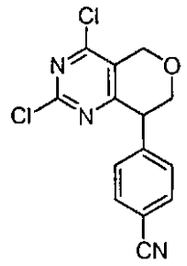
4-(2,4-dioxo-2,3,4,5,7,8-hexahydro-1H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile



4-(2,4-dioxo-2,3,4,5,7,8-hexahydropyrano[3,4-e][1,3]oxazin-8-yl)benzonitrile (Intermediate AA(3)) was reacted as described in Intermediate X(4) with ammonium hydroxide to give 4-(2,4-dioxo-2,3,4,5,7,8-hexahydro-1H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile (Intermediate AA(4)). LC–MS $(M-H)^+ = 270.2$.

Preparation AA

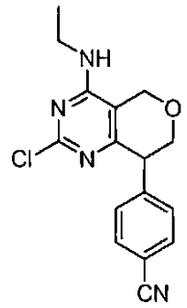
4-(2,4-dichloro-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile



4-(2,4-dioxo-2,3,4,5,7,8-hexahydro-1H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile (Intermediate AA(4)) was reacted as described in Preparation X with $POCl_3$ to give 4-(2,4-dichloro-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile (Preparation AA). LC–MS $(M+H)^+ = 306.1$.

Preparation AAa

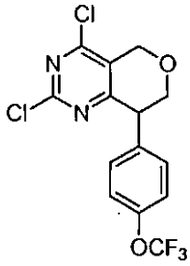
4-(2-chloro-4-(ethylamino)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile



4-(2,4-dichloro-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile (Preparation AA) was reacted as described in Preparation Xa with ethanamine to give 4-(2-chloro-4-(ethylamino)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile (Preparation AAa). LC–MS $(M+H)^+ = 315.1$.

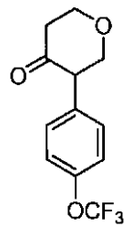
Preparation AB

2,4-dichloro-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



Intermediate AB(2)

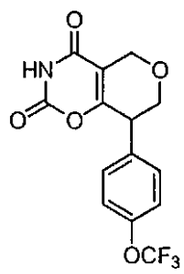
3-(4-(trifluoromethoxy)phenyl)dihydro-2H-pyran-4(3H)-one



The procedure of Intermediate X(2) was utilized with 4-(trifluoromethoxy)phenylboronic acid to obtain 3-(4-(trifluoromethoxy)phenyl)dihydro-2H-pyran-4(3H)-one. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 (2 H, d, *J*=7.05 Hz), 7.19 - 7.25 (2 H, m), 4.23 - 4.32 (2 H, m), 3.91 - 4.04 (2 H, m), 3.84 (1 H, dd, *J*=8.81, 6.30 Hz), 2.66 - 2.77 (1 H, m), 2.56 - 2.63 (1 H, m)

Intermediate AB(3)

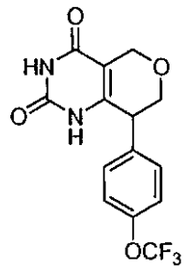
8-(4-(trifluoromethoxy)phenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione



The procedure of Intermediate X(3) was utilized to obtain 8-(4-(trifluoromethoxy)phenyl)-7,8-dihydropyrano[3,4-e][1,3]oxazine-2,4(3H,5H)-dione. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 11.98 (1 H, s), 7.52 (2 H, d, *J*=8.55 Hz), 7.37 (2 H, d, *J*=7.93 Hz), 4.45 - 4.51 (1 H, m), 4.36 (1 H, dd, *J*=14.95, 2.14 Hz), 4.00 - 4.08 (2 H, m), 3.82 (1 H, dd, *J*=10.68, 3.36 Hz).

Intermediate AB(4)

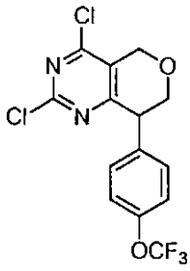
8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione



The procedure of Intermediate X(4) was utilized to obtain 8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-1H-pyrano[4,3-d]pyrimidine-2,4(3H,5H)-dione. LC–MS $(M+H)^+ = 329.0$.

Preparation AB

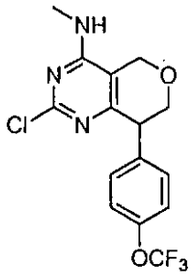
2,4-dichloro-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



The procedure of Preparation X was utilized to obtain 2,4-dichloro-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine.LC–MS $(M+H)^+ = 365.0$.

Preparation ABa

2-chloro-N-methyl-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine

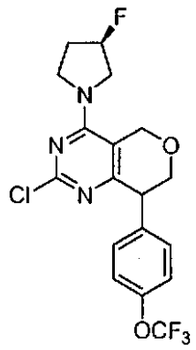


To a solution of 2,4-dichloro-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation AB) (80.7 mg, 0.221 mmol) in MeOH (2210 μL)

was added methylamine (1000 μL, 2.0 mmol) (2M in THF). The reaction was allowed to stir overnight. Removed the solvent and applied to silica gel, eluting with an EtOAc/Hex gradient to afford 2-chloro-N-methyl-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (69.8 mg, 0.194 mmol, 88 % yield).LC–MS $(M+H)^+$ = 360.0.

Preparation ABb

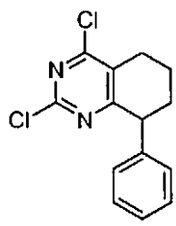
2-chloro-4-((R)-3-fluoropyrrolidin-1-yl)-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine



To a solution of 2,4-dichloro-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation AB) (56.4 mg, 0.154 mmol) in MeOH (1545 μL) was added DIPEA (67.4 μL, 0.386 mmol), then solid (R)-3-fluoropyrrolidine, HCl (21.34 mg, 0.170 mmol). The reaction was allowed to stir at rt. Removed the solvent and applied to silica gel. Eluted with a EtOAc/Hex gradient to afford the diasteriomeric mixture 2-chloro-4-((R)-3-fluoropyrrolidin-1-yl)-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (57.6 mg, 0.138 mmol, 89 % yield).LC–MS $(M+H)^+ = 418.1$.

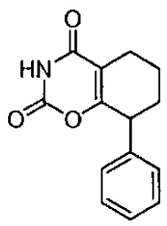
Preparation AC

2,4-Dichloro-8-phenyl-5,6,7,8-tetrahydroquinazoline



Intermediate AC(1)

8-Phenyl-5,6,7,8-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-2,4(3*H*)-dione



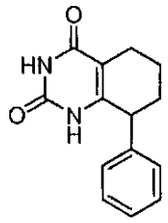
A solution of 2-phenylcyclohexanone (1.500 g, 8.61 mmol) and carbonisocyanatidic chloride (0.966 mL, 12 mmol) was stirred at 58 °C in a high-pressure vessel (75 mL) for 1 h. The temperature was raised to 130°C and the reaction mixture was stirred for 2 h. After cooling to room temperature, the reaction mixture solidified. The solid residue was dissolved in ethyl acetate and washed with saturated aqueous solution of sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The solvent was removed in vacuum and the oily residue was purified by column chromatography on silica gel to provide 8-phenyl-5,6,7,8-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-2,4(3*H*)-dione (415.0 mg, 1.689 mmol, 19.62 % yield) as white solid and 4*a*-phenyl-4*a*,5,6,7-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-2,4(3*H*)-dione (746.4 mg, 3.04 mmol, 35.3 % yield) as white solid.

8-phenyl-5,6,7,8-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-2,4(3*H*)-dione. LC-MS $(M+H)^+$ = 244.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.61 (1H, br s), 7.22 - 7.38 (3H, m), 7.09 - 7.19 (2H, m), 3.81 (1H, t, *J*=4.9 Hz), 2.39 - 2.63 (2H, m), 2.15 (1H, dddd, *J*=13.2, 9.8, 6.3, 3.1 Hz), 1.84 - 1.96 (1H, m), 1.52 - 1.84 (2H, m).

4*a*-phenyl-4*a*,5,6,7-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-2,4(3*H*)-dione. LC–MS $(M+H)^+$ = 244.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.66 (1H, br s), 7.40 - 7.46 (2H, m), 7.29 - 7.39 (3H, m), 5.99 - 6.06 (1H, m), 2.37 (1H, ddd, *J*=14.0, 3.4, 3.1 Hz), 2.10 - 2.29 (3H, m), 1.54 - 1.64 (1H, m), 1.21 - 1.36 (1H, m).

Intermediate AC(2)

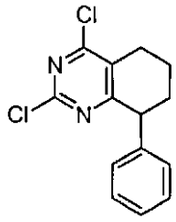
8-Phenyl-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione



A solution of 8-phenyl-5,6,7,8-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-2,4(3*H*)-dione (415.0 mg, 1.706 mmol) in concentrated ammonium hydroxide (35 mL, 899 mmol) was stirred at 100 °C in a high-pressure vessel (75 mL) for 6 h. The formation of white precipitate was observed during the heating. The LC/MS analysis of the filtrate shows the presence of the product with the desired mass (M+H) = 243.20. The solvent was removed in vacuum to provide 8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione (435 mg, 1.706 mmol, 100 % yield) as off-white solid. LC-MS $(M+H)^+$ = 243.2. ^{1}H NMR (500 MHz, DMSO - d_6) δ ppm 10.2 (2H, br. s.), 7.34 (2H, t, *J*=7.5 Hz), 7.26 (1H, t, *J*=7.3 Hz), 7.14 (2H, d, *J*=7.3 Hz), 3.80 (1H, br. s.), 2.32 - 2.43 (1H, m), 2.15 (1H, ddd, *J*=16.9, 10.5, 6.1 Hz), 1.93 - 2.04 (1H, m), 1.67 - 1.75 (1H, m), 1.56 (1H, ddd, *J*=7.8, 5.2, 2.6 Hz), 1.36 (1H, dt, *J*=13.1, 2.7 Hz).

Preparation AC

2,4-Dichloro-8-phenyl-5,6,7,8-tetrahydroquinazoline

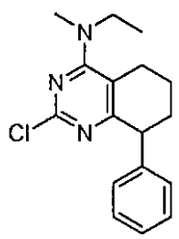


A mixture of 8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione (233.1 mg, 0.962 mmol), phosphorus oxychloride (2798 µL, 30.0 mmol) and *N*,*N*-dimethylaniline (933 µL, 7.36 mmol) was heated at 110 °C in a capped vial overnight. The reaction mixture was poured into a beaker with ice and the inside of the reaction vessel was washed with dichloromethane. As soon as the ice completely melted, the content of the beaker was placed into a separatory funnel. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel

to provide 2,4-dichloro-8-phenyl-5,6,7,8-tetrahydroquinazoline (320.3 mg, 83%) as yellow oil. LC-MS $(M+H)^+ = 279.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.28 (2H, t, *J*=7.5 Hz), 7.19 - 7.24 (1H, m), 6.95 (2H, d, *J*=7.3 Hz), 4.23 (1H, t, *J*=5.6 Hz), 2.82 - 2.92 (1H, m), 2.72 - 2.82 (1H, m), 2.10 - 2.22 (1H, m), 1.97 - 2.06 (1H, m), 1.76 - 1.93 (2H, m).

Preparation ACa

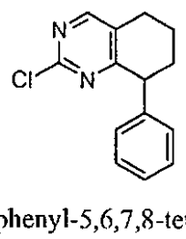
2-Chloro-*N*-ethyl-*N*-methyl-8-phenyl-5,6,7,8-tetrahydroquinazolin-4-amine



To a solution of 2,4-dichloro-8-phenyl-5,6,7,8-tetrahydroquinazoline (53.9 mg, 0.193 mmol) in methanol (1 mL) was added *N*-methylethanamine (0.033 mL, 0.386 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2-chloro-*N*-ethyl-*N*-methyl-8-phenyl-5,6,7,8-tetrahydroquinazolin-4-amine (42.9 mg, 0.141 mmol, 72.9 % yield) as colorless oil. LC-MS $(M+H)^+ = 302.2$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.25 (2H, t, *J*=7.5 Hz), 7.13 - 7.20 (1H, m), 7.01 (2H, d, *J*=7.3 Hz), 4.06 - 4.14 (1H, m), 3.42 - 3.53 (2H, m), 3.05 (3H, s), 2.56 - 2.74 (2H, m), 2.17 - 2.27 (1H, m), 1.76 - 1.89 (2H, m), 1.52 - 1.64 (1H, m), 1.24 (3H, t, *J*=7.2 Hz).

Preparation ACb

2-Chloro-8-phenyl-5,6,7,8-tetrahydroquinazoline

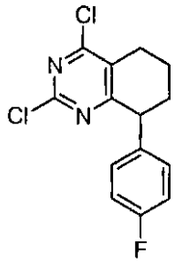


A mixture of 2,4-dichloro-8-phenyl-5,6,7,8-tetrahydroquinazoline (51.9 mg, 0.186 mmol), ammonium chloride (13.0 mg, 0.243 mmol) and zinc (130 mg, 1.988 mmol) in acetone (0.75 mL) and water (0.75 mL) was heated at 90 °C with stirring for 2 h. The

reaction mixture was filtered through a short plug of diatomaceous earth (Celite®). The solvent was removed in vacuum, and the residue was partitioned between dichloromethane and water. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2-chloro-8-phenyl-5,6,7,8-tetrahydroquinazoline (24.1 mg, 0.097 mmol, 52.4 % yield) as white solid. LC-MS $(M+H)^+$ = 245.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.39 (1H, s), 7.27 (2H, t, *J*=7.6 Hz), 7.16 - 7.23 (1H, m), 6.95 (2H, d, *J*=7.3 Hz), 4.21 (1H, t, *J*=6.0 Hz), 2.72 - 2.91 (2H, m), 2.14 - 2.26 (1H, m), 1.95 - 2.06 (1H, m), 1.81 - 1.93 (1H, m), 1.71 - 1.81 (1H, m).

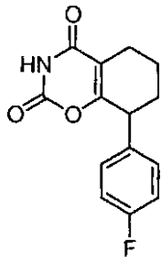
Preparation AD

2,4-dichloro-8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline



Intermediate AD(1)

8-Phenyl-5,6,7,8-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-2,4(3*H*)-dione

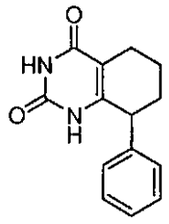


2-(4-fluorophenyl)cyclohexanone and carbonisocyanatidic chloride (0.966 mL, 12 mmol) was reacted as in Intermediate AC(1) to provide 8-(4-fluorophenyl)-5,6,7,8-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-2,4(3*H*)-dione (415.0 mg, 1.689 mmol, 19.62 % yield) as white solid and 4*a*-(4-fluorophenyl)-4*a*,5,6,7-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-2,4(3*H*)-dione (746.4 mg, 3.04 mmol, 35.3 % yield) as white solid.

8-(4-fluorophenyl)-5,6,7,8-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-2,4(3*H*)-dione. LC-MS $(M+H)^+ = 262.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 9.61 (1H, br s), 7.10 (2H, dd, *J* = 5.0,8.5 Hz), 6.98 (2H, app t, *J* = 8.5 Hz), 3.77 (1H, t, *J*= 4.9 Hz), 2.38 - 2.53 (2H, m), 2.16-2.07 (1H, m), 1.87 - 1.62 (3H, m).

Intermediate AD(2)

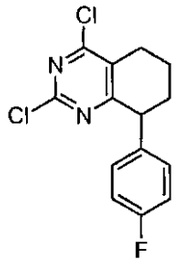
8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione



A solution of 8-(4-fluorophenyl)-5,6,7,8-tetrahydro-2*H*-benzo[*e*][1,3]oxazine-2,4(3*H*)-dione was reacted in the manner of Intermediate AC(2) to provide 8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione. LC-MS $(M+H)^+ = 261.2$.

Preparation AD

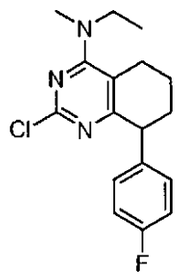
2,4-dichloro-8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline



A mixture of 8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione was reacted in the manner of Preparation AC to provide 2,4-dichloro-8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline, which was not characterized at this step.

Preparation ADa

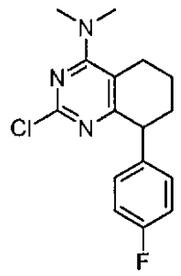
2-Chloro-*N*-ethyl-8-(4-fluorophenyl)-*N*-methyl-5,6,7,8-tetrahydroquinazolin-4-amine



A solution of 2,4-dichloro-8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline (115 mg, 0.387 mmol) and excess *N*-methylethanamine (0.332 mL, 3.87 mmol) in MeOH (2 mL) was stirred at room temperature for 30 min. The solvent was removed in vacuum to afford 2-chloro-*N*-ethyl-8-(4-fluorophenyl)-*N*-methyl-5,6,7,8-tetrahydroquinazolin-4-amine (124 mg, 0.388 mmol, 100 % yield). LC–MS $(M+H)^+ = 320.2$.

Preparation ADb

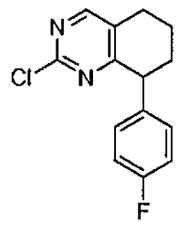
2-Chloro-8-(4-fluorophenyl)-*N*,*N*-dimethyl-5,6,7,8-tetrahydroquinazolin-4-amine



A solution of 2,4-dichloro-8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline (115 mg, 0.387 mmol) and excess dimethylamine (1.935 mL, 3.87 mmol) in MeOH (1 mL) was stirred at room temperature for 1 h. The solvent was removed in vacuum to afford 2-chloro-8-(4-fluorophenyl)-*N*,*N*-dimethyl-5,6,7,8-tetrahydroquinazolin-4-amine (118 mg, 0.386 mmol, 100 % yield). LC–MS $(M+H)^+ = 306.2$.

Preparation ADc

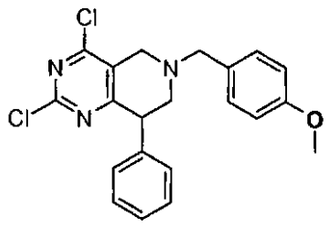
2-Chloro-8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline



A mixture of 2,4-dichloro-8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline (115 mg, 0.387 mmol), Ammonium chloride(26.9 mg, 0.503 mmol) and zinc (266 mg, 4.06 mmol) in acetone (1 mL) and water (1.000 mL) was heated at 90 °C with stirring for 2 h. The reaction mixture was filtered through a short plug of celite. The solvent was removed in vacuum, and the residue was partitioned between dichloromethane and water. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give 2-chloro-8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline (20 mg, 0.076 mmol, 19.67 % yield) as a white solid. LC–MS $(M+H)^+ = 263.2$.

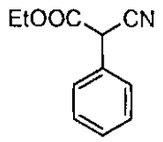
Preparation AE

2,4-dichloro-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



Intermediate AE(1)

Ethyl 2-cyano-2-phenylacetate

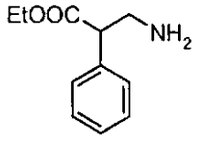


To a solution of sodium hydride (24.5 g, 1.02 mol) in THF was added benzyl cyanide (50.0 g, 0.426 mol) at -10 °C. The reaction mixture was stirred for 15 min at the same temperature. Diethyl carbonate (60.5 g, 0.512 mol) was added to the reaction mixture and the reaction mixture was allowed to come to room temperature and heated to 40 °C. (Caution: Reaction will start suddenly and exothermic). The heating path was removed immediately once the reaction was started and the reaction mixture was cooled under ice/acetone. The solution was allowed to come to room temperature and stirred for 1 h. The reaction mass was cooled to 0 °C and quenched with aqueous saturated

ammonium chloride and extracted with ethyl acetate (250 mL x 3). The combined organic layer was washed with water (200 mL), brine solution (200 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give ethyl 2-cyano-2-phenylacetate as crude compound as crude compound (71.0 g). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+ = 190.1$. ^1H NMR (400 MHz, DMSO-*d6*) δ ppm 7.45 (5H, m), 5.65 (1H, s), 4.18 (2H, m), 1.18 (3H, t, J = 7.2 Hz).

Intermediate AE(2)

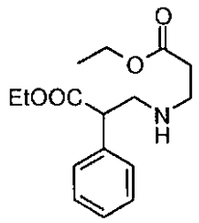
ethyl 3-amino-2-phenylpropanoate



To a solution of Intermediate AE(1) (25.0 g, 0.132 mol) in methanol was added palladium on carbon (10%, w/w) followed by trifluoroacetic acid (2.0 vol., 50 mL) at room temperature. The reaction mixture was hydrogenated under 5 kg of hydrogen pressure for 3 h. The reaction mixture was filtered through celite bed and washed with methanol. The filtrate was evaporated under reduced pressure and the residue was neutralized with aqueous saturated bicarbonate solution. The aqueous solution was extracted with ethyl acetate (200 mL x 4). The combined organic layer was washed with brine solution (200 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 10% methanol in dichloromethane as mobile phase to give ethyl 3-amino-2-phenylpropanoate (17.0 g, 67%) as oily liquid. LC–MS $(M+H)^+ = 194.0$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 7.42-7.2 (7H, m), 4.11 (2H, m), 4.09 (1H, m), 3.44 (1H, m), 3.09 (1H, m), 1.15 (3H, t, J = 5.6 Hz).

Intermediate AE(3)

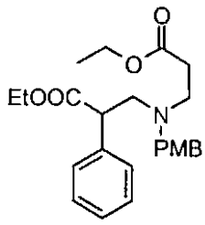
ethyl 3-(3-ethoxy-3-oxopropylamino)-2-phenylpropanoate



To a solution of Intermediate AE(2) (10.0 g, 51.7 mmol) in ethanol was added ethyl acrylate (4.1 g, 40.9 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 18 h. The solvent was evaporated under reduced pressure and the crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give ethyl 3-(3-ethoxy-3-oxopropylamino)-2-phenylpropanoate (12.1 g, 80%) as yellowish oily liquid. LC–MS $(M+H)^+ = 294.1$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.29 (5H, m), 4.11 (4H, m), 3.76 (1H, m), 3.26 (1H, m), 2.90 (3H, m), 2.44 (2H, m), 1.20 (6H, m).

Intermediate AE(4)

ethyl 3-((3-ethoxy-3-oxopropyl)(4-methoxybenzyl)amino)-2-phenylpropanoate

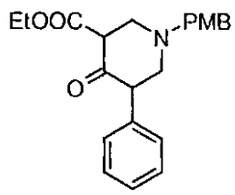


To a solution Intermediate AE(3) (15.0 g, 51.1 mmol) in acetone was added K_2CO_3 (8.4 g, 61.4 mmol) followed by *p*-methoxybenzyl bromide (15.4 g, 76.7 mmol) at room temperature. The reaction mixture was heated at reflux for 3 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous layer was extracted with ethyl acetate (100 x 3). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 30% ethyl acetate in pet-ether as mobile phase to give ethyl 3-((3-ethoxy-3-oxopropyl)(4-methoxybenzyl)amino)-2-phenylpropanoate (12.1 g, 60%) as oily liquid. LC–MS $(M+H)^+ = 414.2$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.27 (5H, m), 7.13, (2H, m), 6.82 (2H, m), 4.11 (4H, m), 4.08 (3H,

s), 4.06 (1H, m), 3.81 (1H, d, J = 4.0 Hz), 3.79 (1H, d, J = 4.0 Hz), 3.25 (1H, m), 2.73 (3H, m), 2.43 (2H, m), 1.24 (6H, m).

Intermediate AE(5)

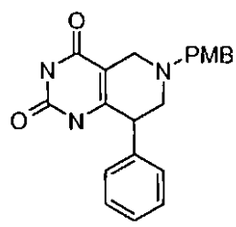
ethyl 1-(4-methoxybenzyl)-4-oxo-5-phenylpiperidine-3-carboxylate



To a cooled solution of Intermediate AE(4) (12.0 g, 29.0 mmol) in THF was added *t*-BuOK (6.5 g, 58.0 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mass was quenched with water then evaporated the solvent under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (100 mL x 2). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 25% ethyl acetate in pet-ether as mobile phase to give ethyl 1-(4-methoxybenzyl)-4-oxo-5-phenylpiperidine-3-carboxylate (7.1 g, 67%) as oily liquid. LC–MS $(M+H)^+$ = 368.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.26 (4H, m), 7.15 (2H, m), 6.88 (2H, m), 4.15 (2H, m), 4.09 (3H, s), 3.82 (2H, m), 3.66 (2H, m), 2.80 (3H, m), 2.40 (1H, m), 1.24 (3H, m).

Intermediate AE(6)

6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione

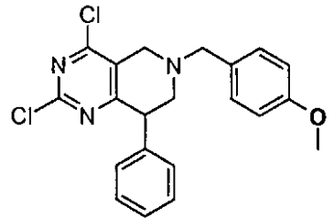


To a cooled solution of Intermediate AE(5) (7.0 g, 19.0 mmol) in ethanol was added *t*-BuOK (5.3 g, 47.6 mmol) followed by urea (2.8 g, 47.6 mmol). The reaction

mixture was heated at reflux for 24 h. The reaction mass was quenched with water and evaporated the solvent under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with brine solution (100 mL), dried over Na2SO4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 10% pet-ether in ethyl acetate as mobile phase to give 6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione (4.0 g, 57%) as pale yellow solid. LC–MS $(M+H)^+ = 364.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 11.05 (1H, s), 10.60 (1H, s), 7.30 (5H, m), 6.99 (2H, m), 6.77 (2H, m), 3.72 (2H, m), 3.57 (3H, s), 3.44 (1H, m), 3.34 (1H, m), 2.90 (1H, m), 2.51 (2H, m).

Preparation AE

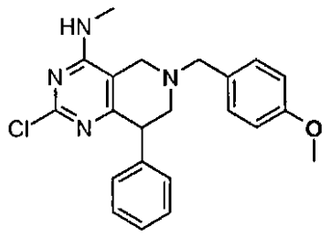
2,4-dichloro-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



A solution of Intermediate AE(6) (2.0 g, 5.5 mmol) and catalytic amount of DMF in $POCl_3$ (20 vol.) was heated at reflux for 10 h. The excess of $POCl_3$ was evaporated under reduced pressure. The residue was poured in to crushed ice and stirred for 15 min. The aqueous solution was extracted with ethyl acetate (75 mL x 3). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (50 mL x 2), brine solution (100 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give 2,4-dichloro-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.5 g, 69%) as brown solid. LC–MS $(M+H)^+ = 400.0$. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.30 (3H, m), 7.26 (4H, m), 6.81 (2H, m), 4.20 (1H, m), 3.79 (2H, m), 3.72 (3H, s), 3.68 (2H, m), 3.57 (1H, m), 3.02 (1H, m), 2.98 (1H, m).

Preparation AEa

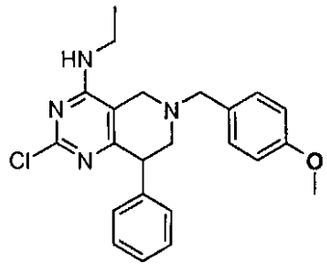
2-chloro-6-(4-methoxybenzyl)-N-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine



To a solution of Preparation AE (1.1 g, 2.7 mmol) in acetonitrile was added diisopropylethylamine (1.0 g, 8.3 mmol) followed by addition of methylamine hydrochloride (0.28 g, 4.1 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 30% ethyl acetate in pet-ether as mobile phase to give 2-chloro-6-(4-methoxybenzyl)-N-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine (0.8 g, 74%) as off-white solid. LC–MS $(M+H)^+ = 395.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 7.29 (4H, m), 7.16 (4H, m), 6.80 (2H, m), 3.93 (1H, m), 3.73 (3H, s), 3.66 (2H, m), 3.57 (1H, m), 3.46 (1H, m), 3.23 (1H, m), 2.67 (3H, d, $J = 4.0$ Hz), 2.51 (1H, m).

Preparation AEb

2-chloro-N-ethyl-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine

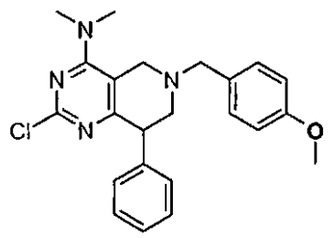


To a solution of Preparation AE (1.6 g, 4.0 mmol) in acetonitrile was added diisopropylethylamine (1.5 g, 12.0 mmol) followed by addition of ethylamine hydrochloride (0.52 g, 6.0 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 30% ethyl acetate in pet-ether as mobile phase to give 2-chloro-N-ethyl-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine (0.9 g, 56%) as off-white solid.

LC–MS $(M-H)^+ = 407.0$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 7.31-7.12 (7H, m), 6.83-6.79 (2H, m), 4.47 (1H, *bs*), 4.06 (1H, m), 3.83 (3H, s), 3.66 (2H, m), 3.58 (2H, m), 3.44 (1H, m), 3.20 (1H, m), 3.08 (1H, m), 2.88 (1H, m), 1.25 (3H, d, $J = 7.2$ Hz).

Preparation AEc

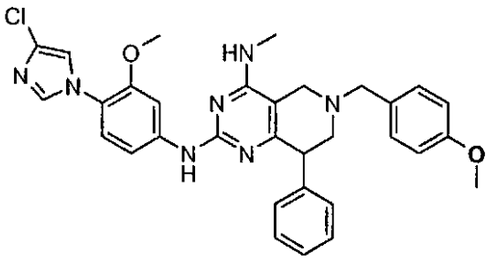
2-chloro-N,N-dimethyl-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine



Using the procedure of Preparation AEb, utilized dimethylamine to produce 2-chloro-*N,N*-dimethyl-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine.

Preparation AEd

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



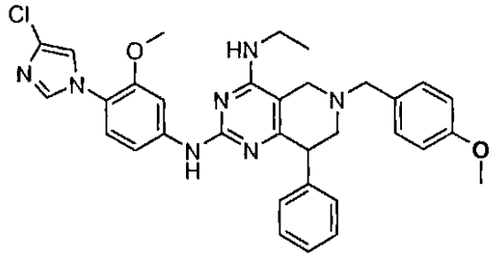
A solution of Preparation A (0.229 g, 1.02 mmol), Preparation AEa (0.45 g, 1.14 mmol), Na_2CO_3 (0.24 g, 2.28 mmol) and xantphos (0.659 g, 1.14 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.59 g, 0.57 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (100 mL x 2). The combined organic layer was washed with brine solution

hoja en
blanco

(100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 5% ethyl acetate in dichloromethane as mobile phase to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.28 g, 43%) as off-white solid. LC–MS $(M+H)^+ = 582.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.06 (1H, s), 8.05 (1H, s), 7.71 (1H, s), 7.4 (1H, s), 7.39-7.06 (11H, m), 6.79 (2H, m), 6.73 (1H, m), 3.93 (1H, m), 3.71 (3H, s), 3.62 (2H, m), 3.55 (3H, s), 3.46 (1H, m), 3.26 (1H, m), 2.92 (3H, d, $J = 4.4$ Hz).

Preparation AEe

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

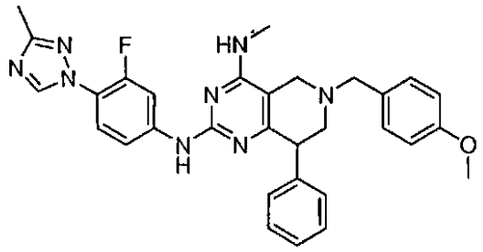


A solution of Preparation A (0.442 g, 1.98 mmol), Preparation AEb (0.9 g, 2.2 mmol), Na_2CO_3 (0.467 g, 4.4 mmol) and xantphos (1.27 g, 2.2 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (1.1 g, 1.1 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 5% ethyl acetate in dichloromethane as mobile phase to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.71 g, 54%) as off-white solid. LC–MS $(M+H)^+ = 596.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.03 (1H, s), 7.98 (1H, s), 7.71 (1H, s), 7.40 (1H, s), 7.27-7.10 (9H, m), 6.81-6.78 (2H, m), 6.72 (1H,

m), 3.91 (1H, m), 3.71 (3H, s), 3.65 (2H, m), 3.56 (3H, s), 3.51-3.49 (3H, m), 3.28 (1H, m), 2.87 (1H, m), 2.65 (1H, m), 1.18 (3H, t, J = 7.2 Hz).

Preparation AEf

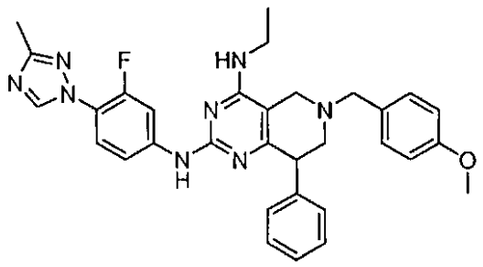
N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(4-methoxybenzyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



A solution of Preparation B (0.175 g, 0.913 mmol), Preparation AEa (0.40 g, 1.01 mmol), Na_2CO_3 (0.20 g, 2.02 mmol) and xantphos (0.585 g, 1.01 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.525 g, 0.50 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (100 mL x 2). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 5% ethyl acetate in dichloromethane as mobile phase to give N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(4-methoxybenzyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.24 g, 42%) as off-white solid. LC–MS $(M+H)^+$ = 551.1.

Preparation AEg

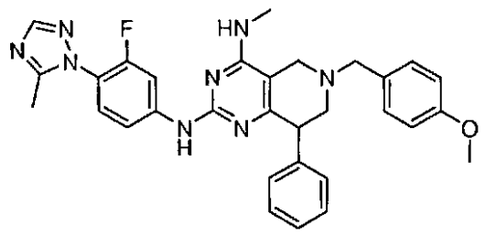
N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



A solution of Preparation B (0.423 g, 2.20 mmol), Preparation AEb (1.0 g, 2.44 mmol), Na_2CO_3 (0.520 g, 4.89 mmol) and xantphos (1.41 g, 2.44 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (1.26 g, 1.22 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 5% ethyl acetate in dichloromethane as mobile phase to give N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.70 g, 53%) as off-white solid. LC–MS $(M+H)^+$ = 565.2.

Preparation AEh

N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(4-methoxybenzyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

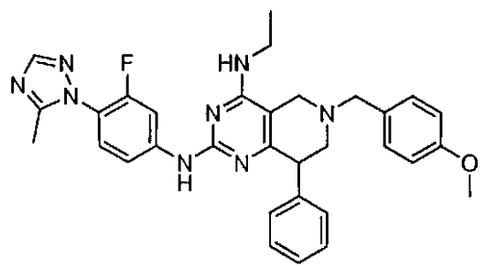


A solution of Preparation C (0.175 g, 0.913 mmol), Preparation AEa (0.40 g, 1.01 mmol), Na_2CO_3 (0.20 g, 2.02 mmol) and xantphos (0.586 g, 1.01 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.525 g, 0.50 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h.

The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (100 mL x 2). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 5% ethyl acetate in dichloromethane as mobile phase to give N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(4-methoxybenzyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.27 g, 51%) as off-white solid. LC–MS $(M+H)^+$ = 565.2.

Preparation AEi

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

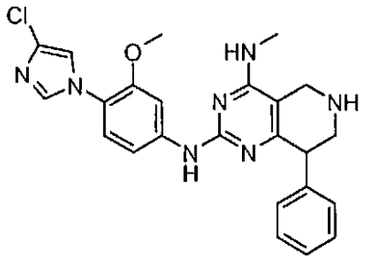


A solution of Preparation C (0.423 g, 2.20 mmol), Preparation AEb (1.0 g, 2.44 mmol), Na_2CO_3 (0.520 g, 4.89 mmol) and xantphos (1.41 g, 2.44 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (1.26 g, 1.22 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (100 mL x 3). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 5% ethyl acetate in dichloromethane as mobile phase to give N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-

(4-methoxybenzyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.72 g, 54%) as off-white solid. LC–MS $(M+H)^+ = 565.4$.

Preparation AEj

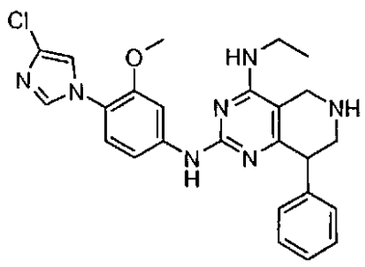
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AEd (0.28 g, 0.48 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (25 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine as crude compound (0.195 g). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+ = 462.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.03 (1H, s), 8.06 (1H, s), 7.71 (1H, s), 7.39 (1H, s), 7.27-7.24 (2H, m), 7.18-7.05 (5H, m), 6.68 (1H, m), 5.76 (1H, s), 3.81 (1H, m), 3.69-3.63 (2H, m), 3.57 (3H, s), 3.22 (1H, m), 2.95 (3H, d, $J = 4.0$ Hz), 2.84 (1H, m).

Preparation AEk

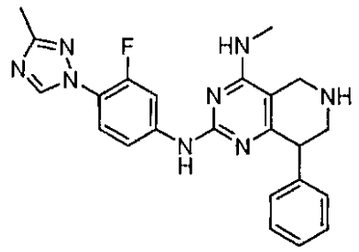
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AEe (0.25 g, 0.42 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (50 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine as crude compound (0.19 g). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+ = 476.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.00 (1H, s), 7.99 (1H, s), 7.71 (1H, s), 7.40 (1H, s), 7.28-7.24 (2H, m), 7.19-7.09 (6H, m), 5.76 (1H, m), 3.70 (1H, m), 3.58 (2H, m), 3.51 (3H, s), 3.48 (2H, m), 3.25 (1H, m), 2.80 (1H, m), 1.20 (3H, t, $J = 7.2$ Hz).

Preparation AEl

N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

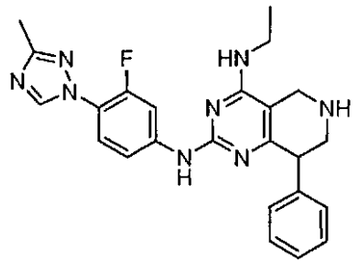


To a solution of Preparation AEf (0.24 g, 0.436 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (25 mL

x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine as crude compound (0.190 g). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 431.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.13 (1H, s), 8.66 (1H, s), 8.00 (1H, m), 7.43-7.36 (2H, m), 7.29-7.26 (3H, m), 7.25-7.17 (3H, m), 6.75 (1H, m), 5.78 (1H, m), 3.83 (1H, m), 3.65 (2H, m), 3.33 (1H, m), 2.94 (3H, d, J = 4.4 Hz), 2.33 (3H, s).

Preparation AEm

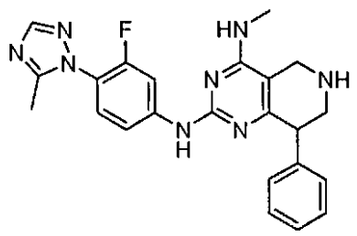
N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AEg (0.490 g, 0.868 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (50 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine as crude compound (0.220 g). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 445.2.

Preparation AEn

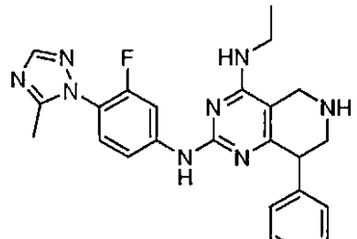
N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AEh (0.27 g, 0.490 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (25 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine as crude compound (0.210 g). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 551.2.

Preparation AEo

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

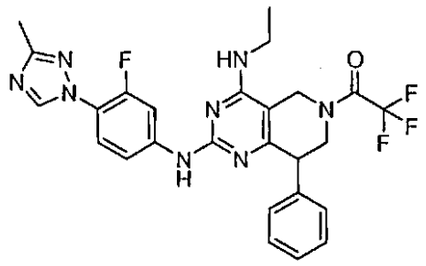


To a solution of Preparation AEi (0.75 g, 1.32 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (50 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N4-ethyl-N2-(3-

fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine as crude compound (0.60 g). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+ = 445.2$.

Preparation AEp

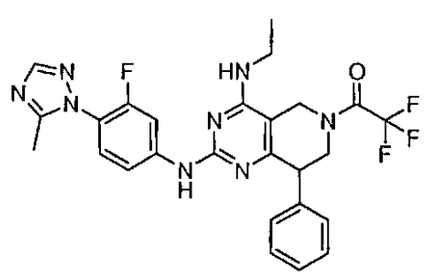
1-(4-(ethylamino)-2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2,2,2-trifluoroethanone



To a solution of Preparation AEm (0.20 g, 0.449 mmol) in dichloromethane was added triethylamine (0.068 g, 0.67 mmol) followed by trifluoroacetic anhydride (0.14 g, 0.67 mmol) and catalytic amount of DMAP at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for 18 h. The reaction mixture was diluted with dichloromethane, washed with aqueous saturated $NaHCO_3$ (25 mL), brine solution (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 1-(4-(ethylamino)-2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2,2,2-trifluoroethanone as crude compound (0.18 g, 74%). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+ = 541.2$.

Preparation AEq

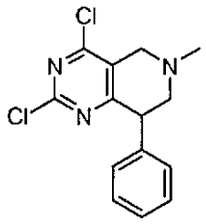
1-(4-(ethylamino)-2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2,2,2-trifluoroethanone



To a solution of Preparation AEo (0.21 g, 0.47 mmol) in dichloromethane was added triethylamine (0.071 g, 0.70 mmol) followed by trifluoroacetic anhydride (0.15 g, 0.70 mmol) and catalytic amount of DMAP at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for 18 h. The reaction mixture was diluted with dichloromethane, washed with aqueous saturated $NaHCO_3$ (25 mL), brine solution (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 1-(4-(ethylamino)-2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2,2,2-trifluoroethanone as crude compound (0.185 g, 73%). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+ = 541.2$.

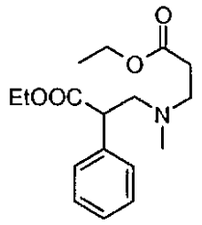
Preparation AF

2,4-dichloro-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



Intermediate AF(1)

ethyl 3-((3-ethoxy-3-oxopropyl)(methyl)amino)-2-(4-fluorophenyl)propanoate

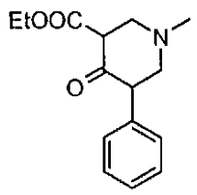


To a solution of Intermediate AE(3) (4.0 g, 13.65 mmol) in acetone was added K_2CO_3 (3.7 g, 27.3 mmol) followed by methyl iodide (2.3 g, 16.3 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous layer was extracted with ethyl acetate (25 x 3). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced

pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 40% ethyl acetate in pet-ether as mobile phase to give ethyl 3-((3-ethoxy-3-oxopropyl)(methyl)amino)-2-phenylpropanoate (0.9 g, 22%) as oily liquid. LC–MS $(M+H)^+$ = 308.0. ^{1}H NMR (400 MHz, DMSO-*d*): δ ppm 7.33-7.26 (5H, m), 4.07-4.01 (4H, m), 3.83 (1H, m), 3.07 (1H, m), 2.69-2.52 (2H, m), 2.47-2.41 (3H, m), 2.21 (3H, s), 1.19-0.10 (6H, m).

Intermediate AF(2)

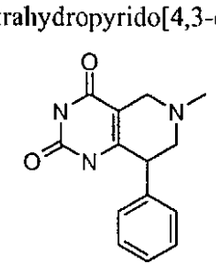
ethyl 1-methyl-4-oxo-5-phenylpiperidine-3-carboxylate



To a cooled solution of Intermediate AF(1) (0.9 g, 2.93 mmol) in THF was added *t*-BuOK (0.65 g, 5.86 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mass was quenched with water then evaporated the solvent under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (25 mL x 2). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in pet-ether as mobile phase to give ethyl 1-methyl-4-oxo-5-phenylpiperidine-3-carboxylate (7.1 g, 67%) as oily liquid. LC–MS $(M+H)^+$ = 262.2.

Intermediate AF(3)

6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione

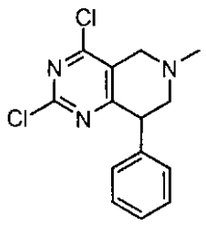


To a cooled solution of Intermediate AF(2) (4.5 g, 17.2 mmol) in ethanol was added *t*-BuOK (4.8 g, 43.1 mmol) followed by urea (2.58 g, 43.1 mmol). The reaction

mixture was heated at reflux for 24 h. The reaction mass was quenched with water and evaporated the solvent under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine solution (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 10% methanol in dichloromethane as mobile phase to give 6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione (2.5 g, 56%) as pale yellow solid. LC–MS $(M+H)^+ = 258.2$ ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 11.04 (1H, s), 10.56 (1H, s), 7.33-7.23 (5H, m), 3.73 (1H, m), 4.75 (1H, m), 2.83 (1H, m), 2.78 (1H, m), 2.68 (1H, m), 2.22 (3H, s).

Preparation AF

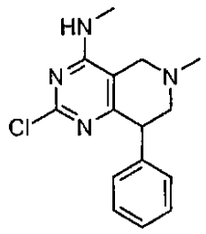
2,4-dichloro-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



A solution of Intermediate AF(3) (4.0 g, 15.56 mmol) and catalytic amount of DMF in $POCl_3$ (20 vol.) was heated at reflux for 10 h. The excess of $POCl_3$ was evaporated under reduced pressure. The residue was poured in to crushed ice and stirred for 15 min. The aqueous solution was extracted with ethyl acetate (75 mL x 3). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (50 mL x 2), brine solution (75 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give 2,4-dichloro-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (1.2 g, 27%) as brown solid. LC–MS $(M+H)^+ = 294.0$.

Preparation AFa

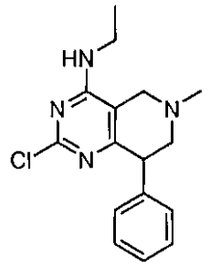
2-chloro-N,6-dimethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine



To a solution of Preparation AF (1.0 g, 3.4 mmol) in acetonitrile was added diisopropylethylamine (1.3 g, 10.2 mmol) followed by addition of methylamine hydrochloride (0.34 g, 5.1 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 10% methanol in dichloromethane as mobile phase to give 2-chloro-N,6-dimethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine (0.9 g, 91%) as off-white solid. LC–MS $(M+H)^+ = 289.2$.

Preparation AFb

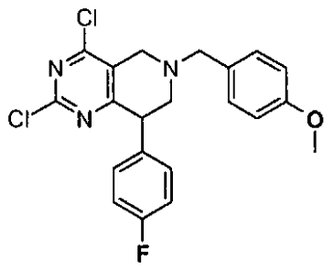
2-chloro-N-ethyl-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine



To a solution of Preparation AF (0.4 g, 1.36 mmol) in acetonitrile was added diisopropylethylamine (0.52 g, 4.0 mmol) followed by addition of ethylamine hydrochloride (0.16 g, 2.0 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give 2-chloro-N-ethyl-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine (0.4 g, 97%) as off-white solid. LC–MS $(M-H)^+ = 303.2$.

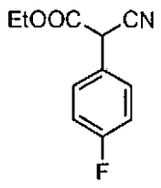
Preparation AG

2,4-dichloro-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



Intermediate AG(1)

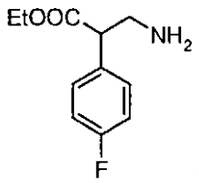
ethyl 2-cyano-2-(4-fluorophenyl)acetate



To a solution of sodium hydride (4.2 g, 177.7 mmol) in THF was added 4-fluoro phenyl acetonitrile (10 g, 74.0 mmol) at -10 °C. The reaction mixture was stirred for 15 min at the same temperature. Diethyl carbonate (10.5 g, 88.0 mmol) was added to the reaction mixture and the reaction mixture was allowed to come to room temperature and heated to 40 °C. (Caution: Reaction will start suddenly and exothermic). The heating path was removed immediately once the reaction was started and the reaction mixture was cooled under ice/acetone. The solution was allowed to come to room temperature and stirred for 1 h. The reaction mass was cooled to 0 °C and quenched with aqueous saturated ammonium chloride and extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with water (50 mL), brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give ethyl 2-cyano-2-(4-fluorophenyl)acetate as crude compound as crude compound (10 g). The crude compound was taken to the next step without further purification. LC–MS $(M-H)^+$ = 206.2. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.44 (2H, m), 7.11 (2H, m), 4.69 (1H, s), 4.27-4.22 (2H, q, J = 7.2 Hz).1.26 (3H, m)

Intermediate AG(2)

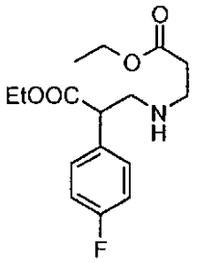
ethyl 3-amino-2-(4-fluorophenyl)propanoate



To a solution of Intermediate AG(1) (10.0 g, 40.0 mmol) in acetic acid was added palladium on carbon (10%, w/w) followed by H_2SO_4 (0.5 vol., 5 mL) at room temperature. The reaction mixture was hydrogenated under 5 kg of hydrogen pressure for 18 h. The reaction mixture was filtered through celite bed and washed with methanol. The filtrate was evaporated under reduced pressure and the residue was neutralized with aqueous saturated bicarbonate solution. The aqueous solution was extracted with ethyl acetate (100 mL x 4). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 10% methanol in dichloromethane as mobile phase to give ethyl 3-amino-2-(4-fluorophenyl)propanoate (6.0 g, 59%) as oily liquid. LC–MS $(M+H)^+$ = 212.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.26-7.22 (2H, m), 7.04-6.98 (2H, m), 4.15 (2H, m), 3.66 (1H, m), 3.28 (1H, m), 2.99 (1H, m).1.20 (3H, m).

Intermediate AG(3)

ethyl 3-(3-ethoxy-3-oxopropylamino)-2-(4-fluorophenyl)propanoate

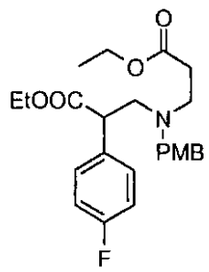


To a solution of Intermediate AG(2) (3.0 g, 14.0 mmol) in ethanol was added ethyl acrylate (1.7 g, 17.0 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 18 h. The solvent was evaporated under reduced pressure and the crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give ethyl 3-(3-ethoxy-3-

oxopropylamino)-2-(4-fluorophenyl)propanoate (2.5 g, 60%) as yellowish oily liquid. LC–MS $(M+H)^+ = 313.2$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.27-7.21 (2H, m), 7.03-6.97 (2H, m), 4.13 (4H, m), 3.77 (1H, m), 3.23(1H, m), 2.89 (3H, m), 2.48 (2H, m). 1.22 (6H, m).

Intermediate AG(4)

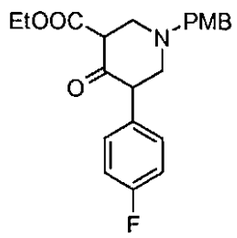
ethyl 3-((3-ethoxy-3-oxopropyl)(4-methoxybenzyl)amino)-2-(4-fluorophenyl)propanoate



To a solution of Intermediate AG(3) (2.0 g, 6.42 mmol) in acetone was added K_2CO_3 (1.39 g, 9.6 mmol) followed by *p*-methoxybenzyl bromide (1.68 g, 8.35 mmol) at room temperature. The reaction mixture was heated at reflux for 3 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous layer was extracted with ethyl acetate (25 x 2). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 30% ethyl acetate in pet-ether as mobile phase to give ethyl 3-((3-ethoxy-3-oxopropyl)(4-methoxybenzyl)amino)-2-(4-fluorophenyl)propanoate (1.6 g, 60%) as oily liquid. LC–MS $(M+H)^+ = 432.2$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.22 (2H, m), 7.09, (2H, m), 6.95 (2H, m), 6.78 (2H, m) 4.14 (4H, m), 3.80 (3H, s), 3.77 (2H, m), 3.53 (2H, m), 3.16 (1H, m), 2.79 (2H, m), 2.43 (2H, m), 1.24 (6H, m).

Intermediate AG(5)

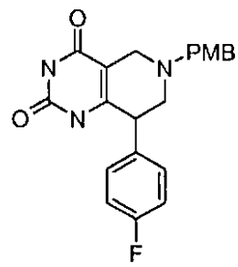
ethyl 5-(4-fluorophenyl)-1-(4-methoxybenzyl)-4-oxopiperidine-3-carboxylate



To a cooled solution of Intermediate AG(4) (1.6 g, 3.71 mmol) in THF was added *t*-BuOK (0.62 g, 5.56 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mass was quenched with water then evaporated the solvent under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (25 mL x 2). The combined organic layer was washed with brine solution (30 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 25% ethyl acetate in pet-ether as mobile phase to give ethyl 5-(4-fluorophenyl)-1-(4-methoxybenzyl)-4-oxopiperidine-3-carboxylate (1.0 g, 70%) as oily liquid. LC–MS $(M+H)^+ = 386.2$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 12.0 (1H, s) 7.26 (4H, m), 7.15 (2H, m), 6.88 (2H, m), 4.15 (2H, m), 3.80 (3H, s), 3.77 (2H, m), 3.57 (2H, m), 2.80 (1H, m), 2.40 (1H, m), 1.24 (3H, m).

Intermediate AG(6)

8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione

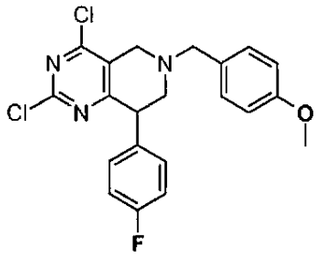


To a cooled solution of Intermediate AG(5) (1.0 g, 2.59 mmol) in ethanol was added *t*-BuOK (0.436 g 3.89 mmol) followed by urea (0.233 g, 3.89 mmol). The reaction mixture was heated at reflux for 24 h. The reaction mass was quenched with water and evaporated the solvent under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (25 mL x 2). The combined organic layer was washed with brine solution (30 mL), dried over Na_2SO_4 and evaporated under reduced pressure to get

crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 10% pet-ether in ethyl acetate as mobile phase to give 8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione (0.6 g, 63%) as pale yellow solid. LC–MS $(M+H)^+ = 382.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 11.06 (1H, s), 10.60 (1H, s), 7.35 (2H, m), 7.29 (2H, m), 7.05 (2H, m), 6.77 (2H, m), 4.05 (1H m), 3.75 (3H, s), 3.53 (1H, m), 3.44 (2H, m), 2.88 (1H, m), 2.65 (2H, m).

Preparation AG

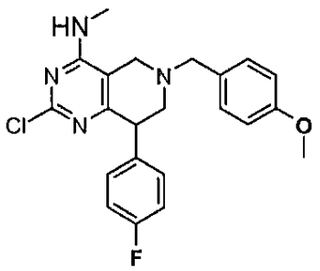
2,4-dichloro-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



A solution of Intermediate AG(6) (0.6 g, 1.57 mmol) and catalytic amount of DMF in $POCl_3$ (20 vol.) was heated at reflux for 10 h. The excess of $POCl_3$ was evaporated under reduced pressure. The residue was poured in to crushed ice and stirred for 15 min. The aqueous solution was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (10 mL x 2), brine solution (10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 2,4-dichloro-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.35 g,) as brown solid. LC–MS $(M+H)^+ = 418.3$.

Preparation AGa

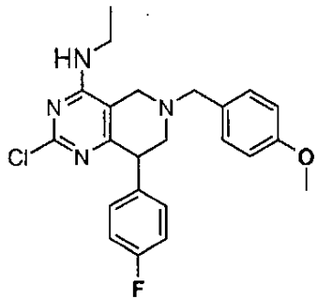
2-chloro-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-N-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine



To a solution of Preparation AG (1.0 g, 2.39 mmol) in methanol was added diisopropylethylamine (0.62 g, 4.79 mmol) followed by methylamine hydrochloride (0.192 g, 2.87 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 35% ethyl acetate in pet-ether as mobile phase to give 2-chloro-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-N-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine (0.408 g, 41%) as off-white solid. LC–MS $(M+H)^+ = 413.0$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.32 (1H, m), 7.24-7.20 (2H, m), 7.14-7.06 (4H, m), 6.82 (2H, m), 3.96 (1H, m), 3.72 (3H, s), 3.67 (1H, m), 3.59 (1H, m), 3.50 (1H, m), 3.20 (1H, m), 2.82 (3H, d, $J = 4.0$ Hz), 2.80 (1H, m), 2.51(1H, m).

Preparation AGb

2-chloro-N-ethyl-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine

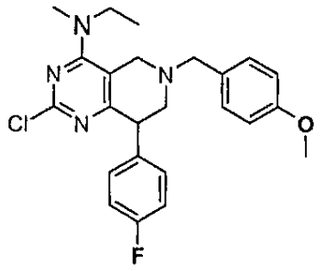


To a solution of Preparation AG (1.0 g, 2.39 mmol) in methanol was added diisopropylethylamine (0.61 g, 4.79 mmol) followed by ethylamine hydrochloride (0.23 g, 2.86 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue

was purified by column chromatography (60-120 mesh) using 30-35% ethyl acetate in pet-ether as mobile phase to give 2-chloro-N-ethyl-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine (0.54 g, 54%) as off-white solid. LC–MS $(M+H)^+ = 427.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.32 (1H, m), 7.30-7.19 (2H, m), 7.13-7.05 (4H, m), 6.80 (2H, m), 3.93 (1H, m), 3.71 (3H, s), 3.68-3.48 (5H, m), 3.22 (1H, m), 2.80 (1H, m), 2.68 (1H, m), 1.15 (3H, m).

Preparation AGc

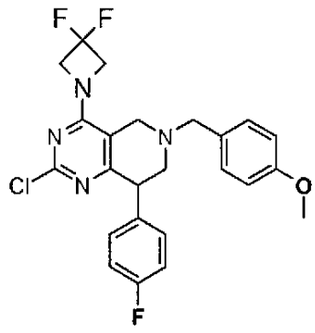
2-chloro-N-ethyl-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-N-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine



To a solution of Preparation AG (1.2 g, 2.87 mmol) in methanol was added diisopropylethylamine (0.74 g, 5.75 mmol) followed by ethylmethylamine (0.20 g, 3.44 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 30-35% ethyl acetate in petroleum-ether as mobile phase to give 2-chloro-N-ethyl-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-N-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine (0.50 g, 41%) as off-white solid. LC–MS $(M+H)^+ = 441.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.23-7.16 (4H, m), 7.11-7.07 (2H, m), 6.84 (2H, m), 4.10 (1H, m), 3.73 (3H, s), 3.65-3.56 (3H, m), 3.51-3.40 (3H, m), 3.04 (1H, m), 2.99 (3H, s), 2.58 (1H, m), 1.11 (3H, t, $J = 7.0$ Hz).

Preparation AGd

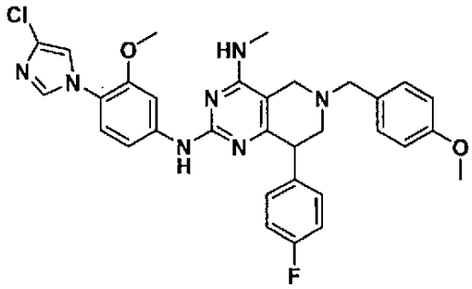
2-chloro-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



To a solution of Preparation AG (0.75 g, 1.79 mmol) in methanol was added diisopropylethylamine (0.58 g, 4.49 mmol) followed by 3,3-difluoroazetidine (0.25 g, 1.97 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 30% ethyl acetate in pet-ether as mobile phase to give 2-chloro-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.4 g, 48%) as off-white solid. LC–MS $(M+H)^+ = 475.2$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.25-7.10 (4H, m), 6.97-6.82 (2H, m), 6.80 (2H, m), 4.52 (4H, m), 4.07 (1H, m), 3.80 (3H, s), 3.59 (3H, m), 3.36 (1H, m), 2.93 (1H, m), 2.80 (1H, m).

Preparation AGe

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

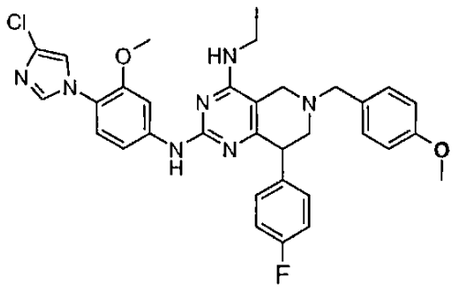


A solution of Preparation A (0.215 g, 0.966 mmol), Preparation AGa (0.40 g, 0.966 mmol), Na_2CO_3 (0.205 g, 1.93 mmol) and xantphos (0.558 g, 0.966 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.50 g, 0.48 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The

reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 5% ethyl acetate in dichloromethane as mobile phase to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.20 g, 35%) as off-white solid. LC–MS $(M+H)^+$ = 600.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.09 (1H, s), 8.05 (1H, s), 7.72 (1H, s), 7.41 (1H, s), 7.26-7.22 (2H, m), 7.14-7.05 (7H, m), 6.82-6.75 (2H, m), 3.93 (1H, m), 3.76 (4H, m), 3.74 (2H, m), 3.72 (1H, m), 3.70 (3H, s), 2.92 (3H, d, *J* = 4.0 Hz), 2.90 (1H, m), 2.70 (1H, m).

Preparation AGf

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

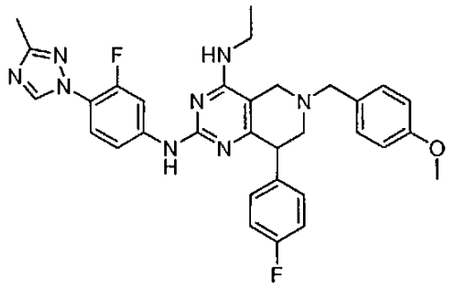


A solution of Preparation A (0.283 g, 1.26 mmol), Preparation AGb (0.54 g, 1.26 mmol), Na_2CO_3 (0.26 g, 2.53 mmol) and xantphos (0.73 g, 1.26 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.65 g, 0.63 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced

pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 7% ethyl acetate in dichloromethane as mobile phase to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.22 g, 29%) as off-white solid. LC–MS $(M+H)^+$ = 614.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.05 (1H, s), 7.97 (1H, s), 7.72 (1H, s), 7.41 (1H, s), 7.39-7.29 (3H, m), 7.25-7.09 (6H, m), 6.81-6.75 (2H, m), 6.72 (1H, m), 3.93 (1H, m), 3.71 (3H, s), 3.67 (1H, m), 3.57 (3H, s), 3.52 (1H, m), 3.49 (2H, m), 3.24 (1H, m) 2.83 (1H, m), 2.65 (1H, m), 1.16 (3H, t, *J* = 7.2 Hz).

Preparation AGg

N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

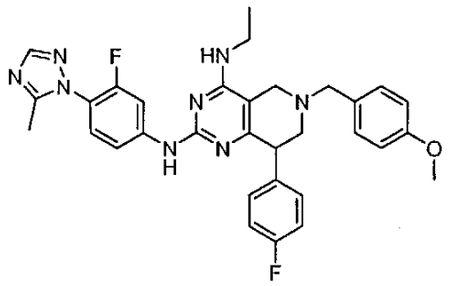


A solution of Preparation B (0.275 g, 1.43 mmol), Preparation AGb (0.68 g, 1.59 mmol), Na_2CO_3 (0.33 g, 3.19 mmol) and xantphos (0.92 g, 1.59 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.82 g, 0.79 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in dichloromethane as mobile phase to give N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-

(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.6 g, 65%) as off-white solid. LC–MS $(M+H)^+$ = 583.2.

Preparation AGh

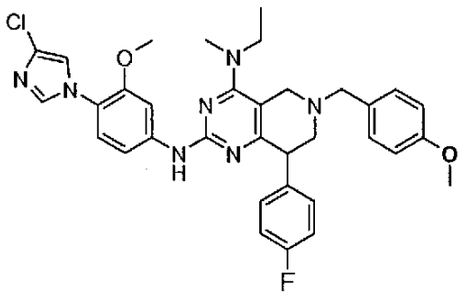
N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



A solution of Preparation C (0.20 g, 1.05 mmol), Preparation AGb (0.50 g, 1.17 mmol), Na_2CO_3 (0.24 g, 2.34 mmol) and xantphos (0.67 g, 1.17 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.60 g, 0.58 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 2). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 10% ethyl acetate in dichloromethane as mobile phase to give N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.51 g, 73%) as off-white solid. LC–MS $(M+H)^+$ = 583.2.

Preparation AGi

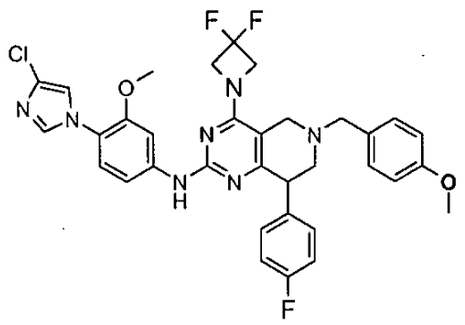
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



A solution of Preparation A (0.25 g, 1.13 mmol), Preparation AGc (0.50 g, 1.13 mmol), Na_2CO_3 (0.24 g, 2.28 mmol) and xantphos (0.65 g, 1.14 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.60 g, 0.560 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 5-10% ethyl acetate in dichloromethane as mobile phase to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.45 g, 63%) as off-white solid. LC–MS $(M+H)^+ = 628.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.15 (1H, s), 7.86 (1H, s), 7.73 (1H, s), 7.42 (1H, s), 7.24-7.21 (4H, m), 7.18-7.07 (4H, m), 6.86 (2H, m), 4.11 (1H, m), 3.70 (3H, s), 3.65 (2H, m), 3.56 (3H, s), 3.47 (2H, m), 3.40 (2H, m), 3.07 (1H, m), 2.98 (3H, s), 2.51 (1H, m), 1.24 (3H, t, $J = 7.2$ Hz).

Preparation AGj

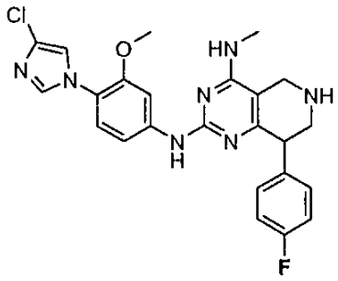
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine



A solution of Preparation A (0.20 g, 0.92 mmol), Preparation AGd (0.40 g, 0.84 mmol), Na_2CO_3 (0.18 g, 1.77 mmol) and xantphos (0.48 g, 0.84 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.43 g, 0.420 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 5% ethyl acetate in dichloromethane as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-6-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine (0.25 g, 49%) as off-white solid. LC–MS $(M+H)^+ = 663.0$.

Preparation AGk

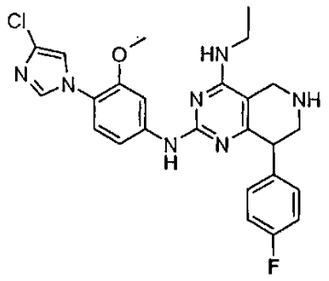
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AGe (0.20 g, 0.330 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (25 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.08 g, 51%) as crude compound. The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 480.2. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.36 (1H, s), 7.86 (1H, s), 7.75 (1H, s), 7.43 (1H, s), 7.32-7.28 (3H, m), 7.23-7.11 (4H, m), 4.30 (1H, m), 4.02 (1H, m), 3.98 (1H, m), 3.71 (1H, m), 3.56 (3H, s), 3.38 (1H, m), 2.98 (3H, d, J = 4.0 Hz).

Preparation AGl (BBRC-7610)

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

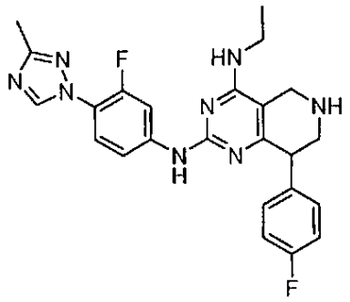


To a solution of Preparation AGf (0.22 g, 0.35 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (25 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine as crude compound (0.16 g, 93%). The

crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 494.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.01 (1H, s), 7.98 (1H, s), 7.72 (1H, s), 7.41 (1H, s), 7.21-7.17 (2H, m), 7.13-7.05 (4H, m), 6.67 (1H, m), 3.82 (1H, m), 3.66 (2H, m), 3.56 (3H, s), 3.50 (2H, m), 3.20 (1H, m), 2.85 (1H, m), 1.20 (3H, t, *J* = 7.2 Hz).

Preparation AGm

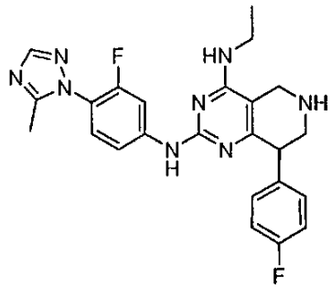
N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AGg (0.40 g, 0.68 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (20 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.30 g, 94%) as crude compound. The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 463.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.29 (1H, s), 8.68 (1H, s), 8.03 (1H, m), 7.44-7.37 (2H, m), 7.25-7.21 (2H, m), 7.12-7.07 (2H, m), 6.76 (1H, m), 3.83 (1H, m), 3.68-3.60 (2H, m), 3.55-3.46 (2H, m), 3.22 (1H, m), 2.91 (1H, m), 2.34 (3H, s), 1.20 (3H, t, *J* = 7.2 Hz).

Preparation AGn

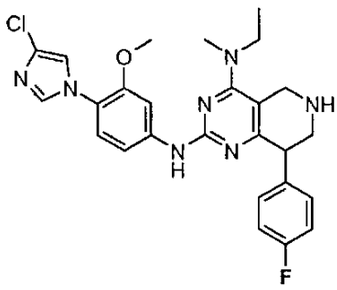
N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AGh (0.51 g, 0.87 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (25 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.31 g, 78%) as crude compound. The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 463.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.29 (1H, s), 8.68 (1H, s), 8.02 (1H, m), 7.42 (2H, m), 7.23 (2H, m), 7.28-7.10 (2H, m), 6.75 (1H, m), 3.80 (1H, m), 3.67-3.60 (2H, m), 3.55-3.48 (2H, m), 3.22 (1H, m), 2.89 (1H, m), 2.34 (3H, s), 1.24 (3H, t, J = 7.0 Hz).

Preparation AGo(BBRC-4363)

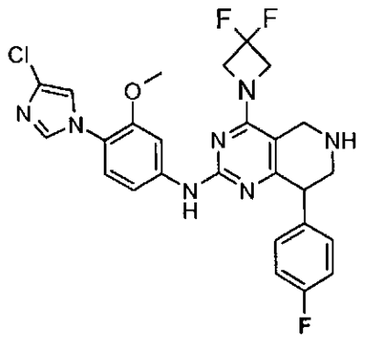
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AGi (0.10 g, 0.15 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (10 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.03 g) as crude compound. The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 508.2. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 7.78 (1H, s), 7.77 (1H, s), 7.37 (1H, s), 7.20-7.16 (3H, m), 7.12-7.06 (4H, m), 4.04 (2H, m), 3.80 (1H, m), 3.50 (3H, s), 3.42-3.32 (3H, m), 3.15 (3H, s), 2.81 (1H, m), 1.17 (3H, t, J = 7.2 Hz).

Preparation AGp (BBRC-4364)

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine

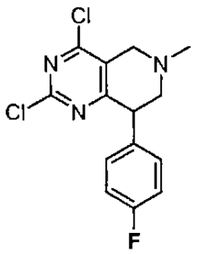


To a solution of Preparation AGj (0.20 g, 0.30 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (10 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-

5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine (0.12 g, 70%) as crude compound. The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 542.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.31 (1H, s), 7.87 (1H, s), 7.73 (1H, s), 7.41 (1H, s), 7.22 (2H, m), 7.15-7.07 (4H, m), 4.74-4.59 (4H, m), 3.97 (1H, m), 3.87 (1H, m), 3.76 (1H, m), 3.51 (3H, s), 3.27 (1H, m), 2.83 (1H, m).

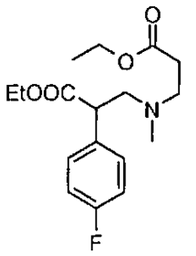
Preparation AH

2,4-dichloro-8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



Intermediate AH(1)

ethyl 3-((3-ethoxy-3-oxopropyl)(4-methoxybenzyl)amino)-2-(4-fluorophenyl)propanoate

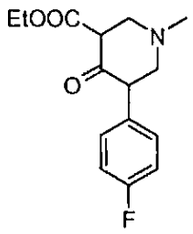


To a solution of Intermediate AG(3) (12.0 g, 38.5 mmol) in acetone was added K_2CO_3 (6.38 g, 46.3 mmol) followed by methyl iodide (6.5 g, 46.3 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous layer was extracted with ethyl acetate (50 x 3). The combined organic layer was washed with brine solution (75 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 20% ethyl acetate in pet-ether as mobile phase to give ethyl 3-((3-ethoxy-3-oxopropyl)(methyl)amino)-2-phenylpropanoate (6.0 g, 50%) as oily liquid. LC–MS $(M+H)^+$ = 326.2. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.01 (2H, m),

6.98, (2H, m), 4.16-4.07 (4H, m), 3.77 (1H, m), 3.13 (1H, t, *J* = 2.4 Hz), 2.75-2.51 (5H, m), 2.17 (3H, s), 1.26-1.19 (6H, m).

Intermediate AH(2)

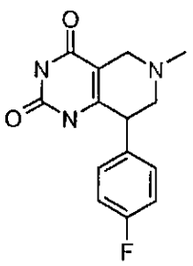
ethyl 5-(4-fluorophenyl)-1-methyl-4-oxopiperidine-3-carboxylate



To a cooled solution of Intermediate AH(1) (6.0 g, 18.4 mmol) in THF was added *t*-BuOK (4.1 g, 36.9 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mass was quenched with water then evaporated the solvent under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (25 mL x 4). The combined organic layer was washed with brine solution (30 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 20% ethyl acetate in pet-ether as mobile phase to give ethyl 5-(4-fluorophenyl)-1-methyl-4-oxopiperidine-3-carboxylate (3.0 g, 51%) as oily liquid. LC–MS $(M+H)^+ = 278.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 7.35 (1H, m), 7.15 (1H, m), 7.12 (1H, m), 6.98 (1H, m), 4.01 (2H, m), 3.88 (1H, m), 2.60 (1H, m), 2.38 (2H, m), 2.19 (3H, s), 1.19-1.08 (3H, m).

Intermediate AH(3)

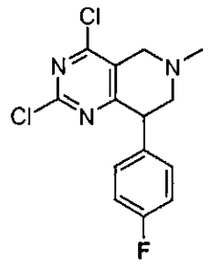
8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione



To a cooled solution of Intermediate AH(2) (3.0 g, 10.75 mmol) in ethanol was added *t*-BuOK (3.0 g 26.8 mmol) followed by urea (1.6 g, 26.8 mmol). The reaction mixture was heated at reflux for 36 h. The reaction mass was quenched with water and evaporated the solvent under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (30 mL), dried over Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 100% ethyl acetate as mobile phase to give 8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione (1.5 g, 51%) as pale yellow solid. LC–MS $(M+H)^+ = 276.0$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 11.08 (1H, s), 10.59 (1H, s), 7.31 (2H, m), 7.13 (2H, m), 3.74 (1H, m), 3.17 (1H, m), 2.80-2.59 (2H, m), 2.23 (3H, s).

Preparation AH

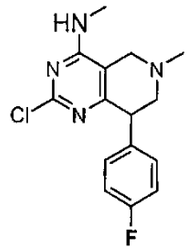
2,4-dichloro-8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine



A solution of Intermediate AH(3) (1.5 g, 5.45 mmol) and catalytic amount of DMF in $POCl_3$ (20 vol.) was heated at reflux for 10 h. The excess of $POCl_3$ was evaporated under reduced pressure. The residue was poured in to crushed ice and stirred for 15 min. The aqueous solution was extracted with ethyl acetate (20 mL x 2). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (10 mL x 2), brine solution (10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 2,4-dichloro-8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (0.7 g, 56%) as brown solid. LC–MS $(M+H)^+ = 312.2$.

Preparation AHa

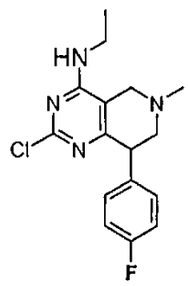
2-chloro-8-(4-fluorophenyl)-N,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine



To a solution of Preparation AH (0.4 g, 1.28 mmol) in methanol was added diisopropylethylamine (0.33 g, 2.57 mmol) followed by methylamine hydrochloride (0.16 g, 2.57 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give 2-chloro-8-(4-fluorophenyl)-N,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine (0.20 g, 51.2%) as off-white solid. LC–MS $(M+H)^+ = 307.2$.

Preparation AHb

2-chloro-N-ethyl-8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine

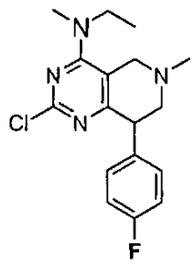


To a solution of Preparation AH (0.7 g, 2.25 mmol) in methanol was added diisopropylethylamine (0.58 g, 4.50 mmol) followed by ethylamine hydrochloride (0.4 g, 4.50 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 30-35% ethyl acetate in pet-ether as mobile phase to give 2-chloro-N-ethyl-8-(4-fluorophenyl)-6-methyl-5,6,7,8-

tetrahydropyrido[4,3-d]pyrimidin-4-amine (0.21 g, 29%) as off-white solid. LC–MS $(M+H)^+ = 321.2$.

Preparation AHc

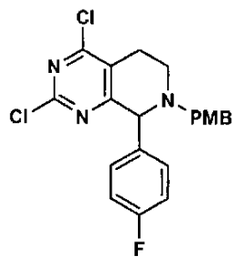
2-chloro-N-ethyl-8-(4-fluorophenyl)-N,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine



To a solution of Preparation AH (0.35 g, 1.1 mmol) in methanol was added diisopropylethylamine (0.29 g, 2.2 mmol) followed by ethylmethylamine (0.67 g, 1.35 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 35% ethyl acetate in pet-ether as mobile phase to give 2-chloro-N-ethyl-8-(4-fluorophenyl)-N,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine (0.22 g, 58%) as off-white solid. LC–MS $(M+H)^+ = 333.9$.

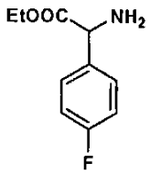
Preparation AI

2,4-dichloro-8-(4-fluorophenyl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine



Intermediate AI(1)

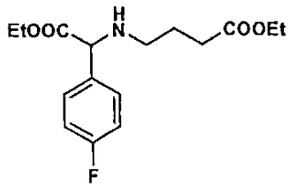
ethyl 2-amino-2-(4-fluorophenyl)acetate



To a cooled solution of 2-amino-2-(4-fluorophenyl)acetic acid (1.0 g, 6.17 mmol) in ethanol was added con. H_2SO_4 (1 mL) over a period of 1 min. The reaction mixture was heated at reflux for 5 h. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate (20 mL). The organic solution was washed with aqueous saturated $NaHCO_3$ (15 mL x 2), water (20 mL), brine solution (10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give ethyl 2-amino-2-(4-fluorophenyl)acetate (0.75 g, 65%) as crude compound (oily liquid). The crude compound was taken to the next step without further purification. LC–MS $(M+H_2O)^+$ = 198.0. ^1H NMR (400 MHz, DMSO-d6): δ 7.44-7.40 (2H, m), 7.18-7.13 (2H, m), 4.51 (1H, s), 4.12-4.01 (2H, m), 2.26 (2H, s), 1.12 (3H, t, J = 8.0 Hz).

Intermediate AI(2)

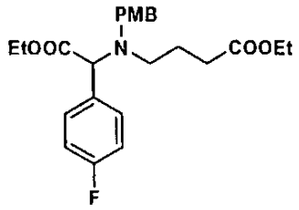
ethyl 4-(2-ethoxy-1-(4-fluorophenyl)-2-oxoethylamino)butanoate



To a solution of Intermediate AI(1) (4.2 g, 21.3 mmol) in DMF was added cesium carbonate (8.3 g, 2.25 mmol) followed ethyl 4-bromobutyroate (4.98 g, 2.55 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 18 h. The solvent was evaporated under reduced pressure and the crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 25% ethyl acetate in pet-ether as mobile phase to give ethyl 4-(2-ethoxy-1-(4-fluorophenyl)-2-oxoethylamino)butanoate (2.0 g, 30%) as yellowish oily liquid. LC–MS $(M+H)^+$ = 312.2. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.33 (2H, m), 7.06 (2H, m), 4.31 (1H, m), 4.18 (4H, m), 2.63 (1H, m), 2.49 (1H, m), 2.35 (2H, m), 1.81 (1H, m), 1.24 (6H, m).

Intermediate AI(3)

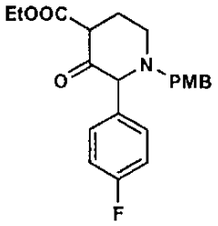
ethyl 4-((2-ethoxy-1-(4-fluorophenyl)-2-oxoethyl)(4-methoxybenzyl)amino)butanoate



To a solution Intermediate AI(2) (15.0 g, 48.23 mmol) in acetone was added K_2CO_3 (7.9 g, 57.8 mmol) followed by 4-methoxybenzyl bromide (14.5 g, 72.3 mmol) at 0 °C. The reaction mixture was heated at 70 °C for 18 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous layer was extracted with ethyl acetate (100 x 2). The combined organic layer was washed with brine solution (75 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 30% ethyl acetate in pet-ether as mobile phase to give ethyl 4-((2-ethoxy-1-(4-fluorophenyl)-2-oxoethyl)(4-methoxybenzyl)amino)butanoate (12.0 g, 60%) as oily liquid. LC–MS $(M+H)^+$ 432.2. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.30 (2H, m), 7.22 (2H, m), 7.01 (2H, m), 6.99 (2H, m), 4.52 (1H, s), 4.22 (2H, m), 4.04 (2H, m), 3.79 (5H, m), 3.61 (1H, m), 2.71 (1H, m), 2.57 (1H, m), 2.20 (1H, m), 2.07 (1H, m), 1.70 (2H, m), 1.28 (3H, m, J = 7.2 Hz), 1.20 (3H, m, J = 7.2 Hz).

Intermediate AI(4)

ethyl 2-(4-fluorophenyl)-1-(4-methoxybenzyl)-3-oxopiperidine-4-carboxylate

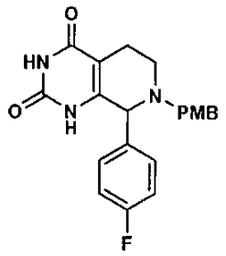


To a cooled solution of Intermediate AI(3) (12.0 g, 27.7 mmol) in THF was added *t*-BuOK (6.2 g, 55.5 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mass was quenched with water then evaporated the solvent under reduced

pressure. The residue was diluted with water and extracted with ethyl acetate (50 mL x 4). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 20% ethyl acetate in pet-ether as mobile phase to give ethyl 2-(4-fluorophenyl)-1-(4-methoxybenzyl)-3-oxopiperidine-4-carboxylate (7.0 g, 67%) as oily liquid. LC–MS $(M+H)^+ = 386.2$. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.02 (1H, s), 7.43 (2H, m), 7.15 (2H, m), 7.04 (2H, m), 6.84 (2H, m), 4.23 (2H, q, $J = 7.2$ Hz), 4.05 (1H, s), 3.79 (3H, s), 3.65 (1H, d, $J = 13.6$ Hz), 3.22 (1H, d, $J = 13.6$ Hz), 2.92 (1H, m), 2.35 (3H, m), 1.32 (3H, t, $J = 7.2$ Hz).

Intermediate AI(5)

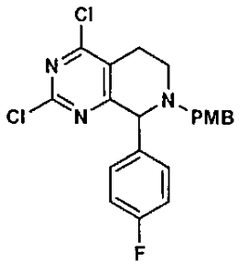
8-(4-fluorophenyl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione



To a cooled solution of Intermediate AI(4) (7.0 g, 18.1 mmol) in ethanol was added *t*-BuOK (5.0 g 45.4 mmol) followed by urea (2.7 g, 45.4 mmol). The reaction mixture was heated at reflux for 18 h. The reaction mass was quenched with water and evaporated the solvent under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine solution (75 mL), dried over Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 50% pet-ether in ethyl acetate as mobile phase to give 8-(4-fluorophenyl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4(1H,3H)-dione (3.0 g, 45%) as pale yellow solid. LC–MS $(M+H)^+ = 382.0$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 11.08 (1H, s), 10.44 (1H, s), 7.26-7.17 (6H, m), 6.92 (2H, m), 4.36 (1H, s), 3.75 (3H, s), 3.73 (1H, d, $J = 13.2$ Hz) 3.58 (1H, d, $J = 13.2$ Hz), 2.63 (2H, m), 2.51 (1H, m), 2.35 (1H, m).

Preparation AI

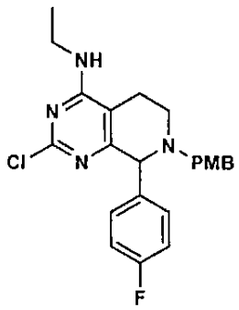
2,4-dichloro-8-(4-fluorophenyl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine



A solution of Intermediate AI(5) (2.0 g, 5.24 mmol) and catalytic amount of DMF in $POCl_3$ (30 vol.) was heated at 85 °C for 18 h. The excess of $POCl_3$ was evaporated under reduced pressure. The residue was poured in to crushed ice and stirred for 15 min. The aqueous solution was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with aqueous saturated $NaHCO_3$ (10 mL x 4), brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 2,4-dichloro-8-(4-fluorophenyl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine (1.4 g, crude) as brown solid. LC–MS $(M+H)^+ = 418.0$.

Preparation AIa

2-chloro-N-ethyl-8-(4-fluorophenyl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine

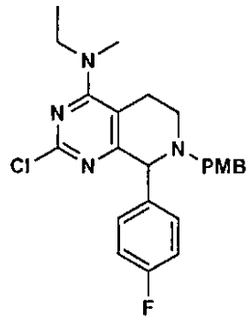


To a solution of Preparation AI (0.7 g, 1.67 mmol) in methanol was added diisopropylethylamine (0.43 g, 3.35 mmol) followed by ethylamine hydrochloride (0.27 g, 3.35 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue

was purified by column chromatography (60-120 mesh) using 35% ethyl acetate in pet-ether as mobile phase to givechloro-N-ethyl-8-(4-fluorophenyl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine (0.36 g, 50%) as off-white solid. LC–MS $(M+H)^+$ = 427.2. ^{1}H NMR: (400 MHz, DMSO-*d6*): δ ppm 7.38 (2H, m), 7.30 (2H, m), 7.20-7.13 (4H, m), 6.88 (2H, m), 4.45 (1H, s), 3.73 (3H, s), 3.45 (1H, m), 3.40-3.34 (3H, m), 2.88 (1H, m), 2.42 (2H, m), 1.16 (3H, t, J = 7.2 Hz).

Preparation AIb

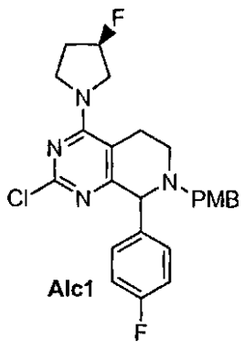
2-chloro-N-ethyl-8-(4-fluorophenyl)-7-(4-methoxybenzyl)-N-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine



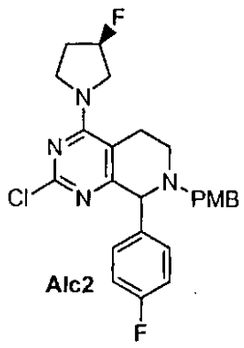
To a solution of Preparation AI (0.7 g, 1.67 mmol) in methanol was added diisopropylethylamine (0.43 g, 3.3 mmol) followed by ethylmethylamine.HCl (0.19 g, 3.35 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (60-120 mesh) using 20% ethyl acetate in pet-ether as mobile phase to give 2-chloro-N-ethyl-8-(4-fluorophenyl)-7-(4-methoxybenzyl)-N-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine (0.40 g, 54%) as off-white solid. LC–MS $(M+H)^+$ = 441.2. ^{1}H NMR: (400 MHz, DMSO-d6) δ ppm 7.49 (2H, m), 7.19-7.14 (4H, m), 6.87 (2H, m), 4.42 (1H, s), 3.73 (3H, s), 3.55 (2H, m), 3.42 (1H, m), 3.21 (1H, m), 3.04 (3H, s), 2.95 (2H, m), 2.56 (1H, m), 2.25 (1H, m), 1.16 (3H, t , J = 7.2 Hz).

Preparation AIc1 and AIc2

2-chloro-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine



AIc1



AIc2

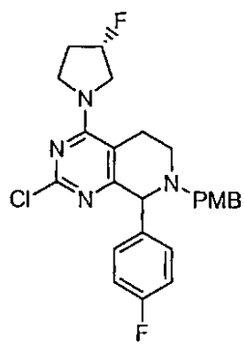
To a solution of Preparation AI (0.70 g, 1.6 mmol) in methanol was added diisopropylethylamine (0.40 g, 3.35 mmol) followed by (S)-3-fluoropyrrolidine (0.25 g, 2.14 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by pep-HPLC to give 2-chloro-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine (0.150 g, 37% & 190 mg, 43%).

AIc1: LC–MS $(M+H)^+ = 471.1$. ^1H NMR (400 MHz, chlorofom-*d*): δ ppm 7.48 (2H, m), 7.15 (2H, m), 7.01 (2H, m), 6.83 (2H, m), 5.30 (1H, m), 4.43 (1H, s), 3.97-3.90 (4H, m), 3.88-3.72 (4H, m), 3.65 (1H, m), 3.17 (1H, m), 3.02 (2H, m), 2.33 (2H, m), 1.95 (1H, m).

AIc2: LC–MS $(M+H)^+ = 471.1$. ^1H NMR (400 MHz, chlorofom-*d*): δ ppm 7.28 (2H, m), 7.18 (2H, m), 6.99 (2H, m), 6.84 (2H, m), 5.30 (1H, m), 4.58 (1H, s), 4.20-4.11 (2H, m), 3.97-3.80 (6H, m), 3.69 (1H, m), 3.35 (1H, m), 2.88 (2H, m), 2.35 (1H, m), 2.17 (1H, m), 2.05 (1H, m).

Preparation AId

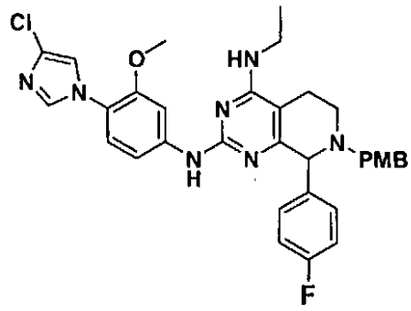
2-chloro-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine



To a solution of Preparation AI (0.70 g, 1.6 mmol) in methanol was added diisopropylethylamine (0.43 g, 3.35 mmol) followed by (R)-3-fluoropyrrolidine (0.25 g, 2.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was purified by prep-HPLC to give 2-chloro-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine (0.150 g, 37% & 190 mg, 43%). LC–MS $(M+H)^+$ = 471.2.

Preparation AIe

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine

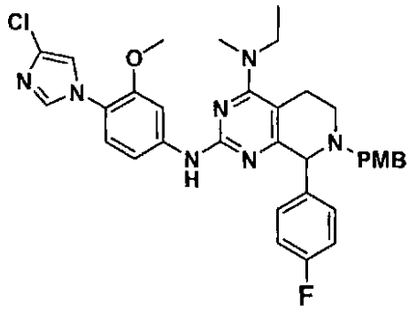


A solution of Preparation A (0.36 g, 0.845 mmol), Preparation AIa (0.189 g, 0.845 mmol), Na_2CO_3 (0.179 g, 1.69 mmol) and xantphos (0.488 g, 0.845 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.870 g, 0.845 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 20% ethyl acetate in pet-ether as mobile phase to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine (0.30 g, 58%) as off-white solid. LC–MS $(M+H)^+$ = 614.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 8.96 (1H, s), 7.79 (1H, s), 7.74 (1H, s), 7.43 (1H, s), 7.33 (2H, m),

7.20 (6H, m), 6.89 (2H, m), 6.80 (1H, m), 4.44 (1H, s), 3.74 (3H, s), 3.66 (3H, s), 3.50 (4, m), 2.90 (1H, m), 2.33 (3H, m), 1.24 (3H, t, J = 7.2 Hz).

Preparation AIf

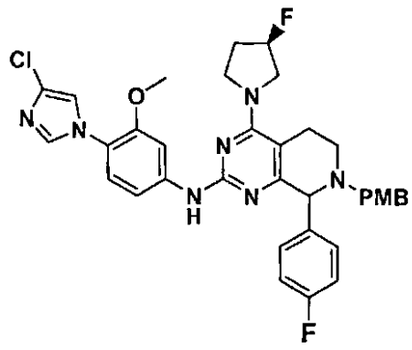
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7-(4-methoxybenzyl)-N4-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine



A solution of Preparation A (0.20 g, 0.90 mmol), Preparation AIb (0.41 g, 0.90 mmol), Na_2CO_3 (0.192 g, 1.80 mmol) and xantphos (0.525 g, 0.90 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.470 g, 0.45 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (50 mL x 3). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 30% ethyl acetate in pet-ether as mobile phase to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7-(4-methoxybenzyl)-N4-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine (0.34 g, 59%) as off-white solid. This compound was taken to the next step without further analysis. LC–MS $(M+H)^+$ = 628.2.

Preparation AIg

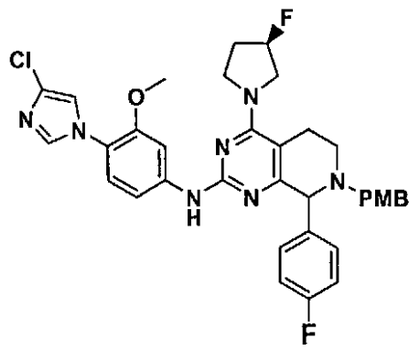
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine



A solution of Preparation A (0.070 g, 0.319 mmol), Preparation AIc1 (0.150 g, 0.319 mmol), Na_2CO_3 (0.067 g, 0.63 mmol) and xantphos (0.184 g, 0.319 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.165 g, 0.159 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine (0.1 g, 48%) as off-white solid. LC–MS $(M+H)^+ = 658.2$.

Preparation AIh

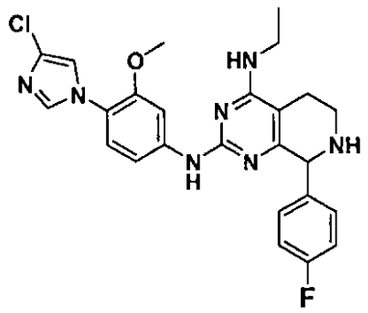
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine



A solution of Preparation A (0.09 g, 0.404 mmol), Preparation AIc2 (0.190 g, 0.404 mmol), Na_2CO_3 (0.085 g, 0.80 mmol) and xantphos (0.230 g, 0.404 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.209 g, 0.202 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine (0.120 g, 48%) as off-white solid. LC–MS $(M+H)^+ = 538.2$.

Preparation AIk

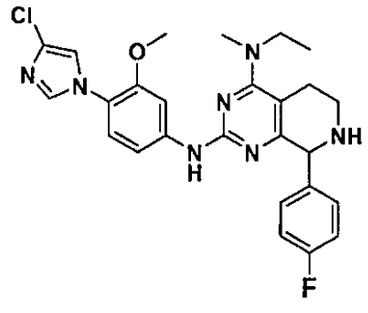
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine



To a solution of Preparation Ale (0.30 g, 0.489 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (25 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine as crude compound (0.20 g). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 494.2.

Preparation AII (Example 1)

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine

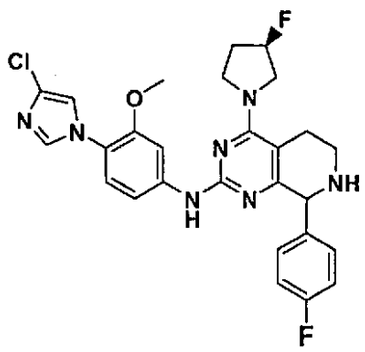


To a solution of Preparation AIf (0.340 g, 0.541 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (10 mL

x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine as crude compound (0.20 g). The crude compound was taken to the next step without further purification. LC–MS $(M+H)^+$ = 508.2. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.05 (1H, s), 7.78 (1H, s), 7.74 (1H, s), 7.43 (1H, s), 7.32 (2H, m), 7.21-7.0 (5H, m), 4.85 (1H, s), 3.59 (3H, s), 3.49 (2H, m), 3.05 (3H, s), 2.68 (2H, m), 2.51 (2H, m), 1.22 (3H, t, J = 7.2 Hz).

Preparation AIm

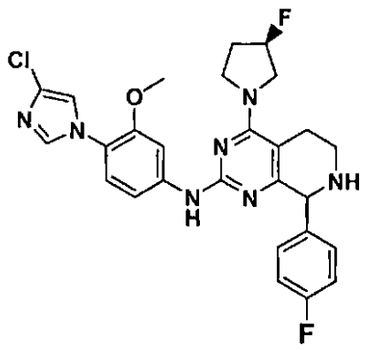
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine



To a solution of Intermediate AIg (0.120 g, 0.182 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (10 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine (0.040 g, 50%). LC–MS $(M+H)^+$ = 538.2.

Preparation AIn

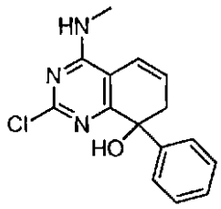
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine



To a solution of Preparation AIh (0.120 g, 0.182 mmol) in toluene was added trifluoromethanesulfonic acid (3.0 vol.) at room temperature. The reaction mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was washed with dichloromethane (10 mL x 2), basified by using aqueous saturated $NaHCO_3$ and extracted with ethyl acetate (20 mL x 2). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine (0.045 g, 51%). LC–MS $(M+H)^+$ = 538.2.

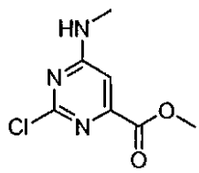
Preparation AJ

2-chloro-4-(methylamino)-8-phenyl-7,8-dihydroquinazolin-8-ol



Intermediate AJ(1)

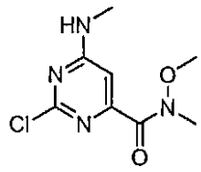
methyl 2-chloro-6-(methylamino)pyrimidine-4-carboxylate



To a mixture of methyl 2,6-dichloropyrimidine-4-carboxylate (2 g), methylamine hydrochloride (0.72 g) in CH_2Cl_2 (48 mL) at 0 °C was added Hunig's base (3.7 mL) dropwise, and the reaction mixture was stirred at ice bath for 1 h and then rt for 1 h. The solvent was removed in vacuo, and the white residue was purified directly by Biotage eluting with 40-600% EtOAc/Hexanes (1000 mL) followed by 90% CH2Cl2/10% MeOH (4 L) to give the title compound as a white solid (1.8 g). . These fractions were combined and evaporated in vacuo. During the solvent removal, some white solid was formed. Several filtrations gave the title compound as a white solid (1.8 g, very white solid).). LC–MS $(M+H)^+ = 202.00$

Intermediate AJ(2)

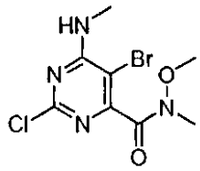
2-chloro-N-methoxy-N-methyl-6-(methylamino)pyrimidine-4-carboxamide



To a suspension of methyl 2-chloro-6-(methylamino)pyrimidine-4-carboxylate (1.95 g) and N,O-dimethylhydroxylamine hydrochloride (1.887 g, 19.34 mmol) in THF at -20 °C was added isopropylmagnesium chloride (23.60 mL, 47.2 mmol) dropwise through a dropping funnel over a period of 30 min, and the reaction mixture was stirred at -10 °C for 40 min. The reaction was worked up with sat. NH_4Cl and EtOAc, and the crude product was purified by Biotage eluting with 40-90% EtOAc/Hexanes to give the title compound as a colorless oil (786 mg). LC–MS $(M+H)^+ = 231.01$.

Intermediate AJ(3)

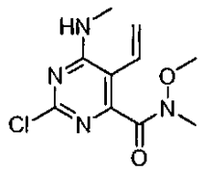
5-bromo-2-chloro-N-methoxy-N-methyl-6-(methylamino)pyrimidine-4-carboxamide



To a solution of 2-chloro-N-methoxy-N-methyl-6-(methylamino)pyrimidine-4-carboxamide (959 mg) in MeCN (21 mL) was added NBS (814 mg), and the reaction mixture was heated at 60 °C for 8 h. The solvent was removed, and the residue was purified by Biotage eluting with 50%-70 EtOAc/Hexanes (1.2 L) to give the title compound as a white solid (1.1g). LC–MS $(M+H)^+ = 310.95$.

Intermediate AJ(4)

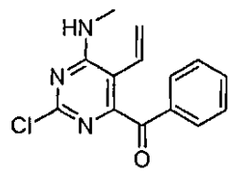
2-chloro-N-methoxy-N-methyl-6-(methylamino)-5-vinylpyrimidine-4-carboxamide



A solution of 5-bromo-2-chloro-N-methoxy-N-methyl-6-(methylamino)pyrimidine-4-carboxamide (100 mg), tributyl(vinyl)stannane (113 mg), tetrakis (23 mg) in toluene (1.6 mL) was heated at 95 °C for 12 h, and the solvent was removed. The residue was purified by preparative TLC eluting with 50% EtOAc/Hexanes to give the title compound as a colorless oil (23 mg). LC–MS $(M+H)^+ = 257.06$.

Intermediate AJ(5)

(2-chloro-6-(methylamino)-5-vinylpyrimidin-4-yl)(phenyl)methanone

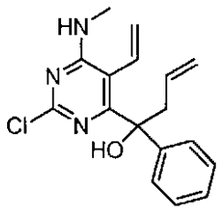


To a solution of 2-chloro-N-methoxy-N-methyl-6-(methylamino)-5-vinylpyrimidine-4-carboxamide (136 mg) in THF (1.8 mL) at 0 °C was added phenylmagnesium bromide (1 M solution in THF, 1.3 mL)) dropwise, and the reaction mixture was stirred at 0 °C for 30 min. The reaction was worked up with EtOAc/sat.

NH_4Cl, and the crude product was purified by preparative TLC eluting with 40% EtOAc/Hexanes to give the title compound as a colorless oil (87 mg). LC–MS $(M+H)^+$ = 274.03.

Intermediate AJ(6)

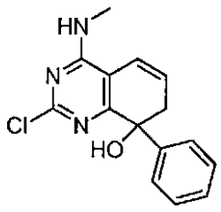
1-(2-chloro-6-(methylamino)-5-vinylpyrimidin-4-yl)-1-phenylbut-3-en-1-ol



To a solution of (2-chloro-6-(methylamino)-5-vinylpyrimidin-4-yl)(phenyl)methanone (142 mg) in THF (2.6 mL) at rt was added allylmagnesium bromide (1.0 M solution in THF, 1.1 mL) dropwise, and the reaction mixture was stirred at rt for 30 min. The reaction was worked up with EtOAc/sat. NH_4Cl, and the crude product was purified by prep. TLC eluting with 30% EtOAc/Hexanes to give the title compound as a colorless oil (133 mg). LC–MS $(M-H_2O+H)^+$ = 298.18.

Preparation AJ

2-chloro-4-(methylamino)-8-phenyl-7,8-dihydroquinazolin-8-ol

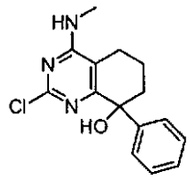


To a solution of 1-(2-chloro-6-(methylamino)-5-vinylpyrimidin-4-yl)-1-phenylbut-3-en-1-ol (60 mg) in benzene (5 mL) was added Grubbs I (16 mg), and the reaction mixture was heated at 85 °C for 1 h. The solvent was removed, and the residue was purified by preparative TLC eluting with 40% EtOAc/Hexanes to give the title compound as a colorless oil (50 mg). ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.4 (5H, m), 6.25 (1H, m), 6.07 (1H, m), 5.14 (1H, br. S), 4.52 (1H, s), 3.10 (3H, d< J = 5.0 Hz), 2.99 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) 164.32, 159.38, 158.85, 144.15, 128.24, 128.02,

127.83, 125.51, 117.54, 108.14, 60.51, 38.50, and 28.57. HRMS calcd. for $C_{15}H_{15}ClN_3O$ (M+H) 288.0904; found: 288.0899.

Preparation AK

2-chloro-4-(methylamino)-8-phenyl-5,6,7,8-tetrahydroquinazolin-8-ol

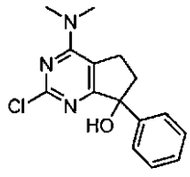


To a solution of 2-chloro-4-(methylamino)-8-phenyl-7,8-dihydroquinazolin-8-ol (20 mg) in EtOAc (5 mL) was added 5% Pd/C (6 mg), and the resulting suspension was stirred under a hydrogen balloon for 1 h. The reaction mixture was filtered through a pad of Celite to give the title compound as a colorless oil (20 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.3 (5H, m), 4.9 (1H, br. S), 4.02 (1H, s), 3.14 (3H, br. S), 1.5-2.5 (6H, m) ^{13}C NMR (125 MHz, $CDCl_3$) 164.82, 162.72, 158.56, 146.54, 128.02, 127.37, 126.72, 110.92, 74.81, 37.58, 28.61, 21.89, 17.47. HRMS calcd. for $C_{15}H_{17}ClN_3O$ (M+H) 290.1060; found: 290.1052.

Preparation AL

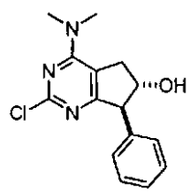
2-chloro-4-(dimethylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-7-ol



2-chloro-4-(dimethylamino)-7-phenyl-7H-cyclopenta[d]pyrimidin-7-ol was prepared from methyl 2,6-dichloropyrimidine-4-carboxylate using the same transformations as shown in Preparation AJ/AK with the following differences: Intermediate AL(1): dimethylamine was used instead of methylamine hydrochloride, and 1.1 equiv of Hünig's base was used; Intermediate AL(6): vinylmagnesium bromide was used instead of allylmagnesium bromide. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.3 (5H, m), 3.28 (6H, s), 1.5-3.4 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) 174.66, 161.76, 159.58, 144.61, 128.49, 127.58, 125.35, 113.92, 82.86, 41.07, 39.00, 28.59. HRMS calcd. for $C_{15}H_{17}ClN_3O$ (M+H) 290.1060; found: 290.1050.

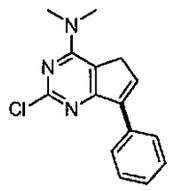
Preparation AM

(6S,7S)-2-chloro-4-(dimethylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-ol



Intermediate AM(1)

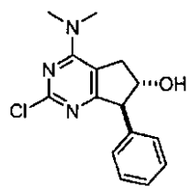
2-chloro-N,N-dimethyl-7-phenyl-5H-cyclopenta[d]pyrimidin-4-amine



To a solution of 2-chloro-4-(dimethylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-7-ol (85 mg) in i-PrOH (5 mL) was added HCl in ether (1M solution), and the reaction mixture was heated at 80 °C from 3 h. The solution was cloudy and turned to clear yellow solution by the end of the reaction. The solvents were removed, and the reaction mixture was worked up with EtOAc and saturated $NaHCO_3$ to give the title compound as a brownish solid (50 mg). LC–MS $(M-H_2O+H)^+ = 272.07$.

Preparation AM

(6S,7S)-2-chloro-4-(dimethylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-ol

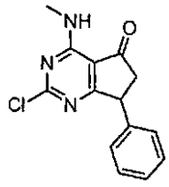


To a solution of 2-chloro-N,N-dimethyl-7-phenyl-5H-cyclopenta[d]pyrimidin-4-amine (113 mg) in THF (2 mL) at rt was added borane dimethyl sulfide complex in THF (2.0 M solution, 0.41 mL), and the reaction mixture was stirred at rt for 5 h. Water (0.50 mL) was added carefully , followed by 30% H_2O_2 (0.50 mL) and 1 N NaOH (1 mL). 5

mL EtOAc was added, and the rxn mixture was stirred at rt for 12 h. The crude product was purified by prep. TLC eluting with 50% EtOAc/Hexanes to give the title compound as a yellowish solid (44 mg). LC–MS $(M-H_2O+H)^+ = 290.05$.

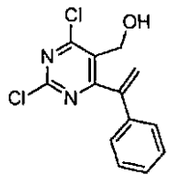
Preparation AN

2-chloro-4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-5-one



Intermediate AN(1)

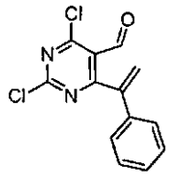
2,4-dichloro-6-(1-phenylvinyl)pyrimidin-5-yl)methanol



A mixture of 2,4,6-trichloropyrimidin-5-yl)methanol (1.1 g), 1-phenylvinylboronic acid (0.8 g), Tetrakis (0.3 g), sodium carbonate (1.64 g) in toluene (14 mL) and water (3 mL) was heated at 100 °C for 12 h. Water was added followed by ethyl acetate, the aqueous layer was extracted with ethyl acetate (x3), and the combined organic layers were dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated, and the residue was purified Biotage eluting with 10-40% EtOAc/Hexanes to give the title compound as a white solid (325 mg). LC–MS $(M+H)^+ = 281.02$. ^{1}H NMR (500 MHz, chloroform-*d*) δ ppm 7.5 (5H, m), 6.01 (1H, s), 5.67 (1H, s), 4.62 (2H, s).

Intermediate AN(2)

2,4-dichloro-6-(1-phenylvinyl)pyrimidine-5-carbaldehyde

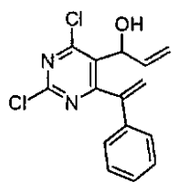


To a solution of 2,4-dichloro-6-(1-phenylvinyl)pyrimidin-5-yl)methanol (327 mg)

in CH_2Cl_2 was added PCC (600 mg) and 4A MS (600 mg), and the rxn mixture was stirred at rt for 30 min. The solution turned to dark brown from orange a few min after addition of PCC. The reaction mixture was filtered through a pad of silica gel eluting with CH_2Cl_2 to give the title compound as a s a brownish solid (209 mg) and used directly for the next step.

Intermediate AN(3)

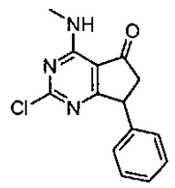
1-(2,4-dichloro-6-(1-phenylvinyl)pyrimidin-5-yl)prop-2-en-1-ol



To a solution of 2,4-dichloro-6-(1-phenylvinyl)pyrimidine-5-carbaldehyde (200 mg) in THF (3.6 mL) at -78C was added vinylmagnesium bromide (0.79 mL, 1M solution in THF) dropwise, and the reaction mixture was stirred at -78 °C for 20 min. Saturated NH_4Cl was added followed by ethyl acetate, the aqueous layer was extracted with ethyl acetate (x3), and the combined organic layers were dried over anhydrous sodium sulfate and then filtered. The filtrate was concentrated *in vacuo* to give the title compound (156 mg) as a colorless oil. The crude product was used directly for the next step.

Preparation AN

2-chloro-4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-5-one

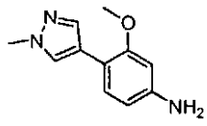


To a solution of 1-(2,4-dichloro-6-(1-phenylvinyl)pyrimidin-5-yl)prop-2-en-1-ol (20 mg) in CH_2Cl_2 (6.5 mL) was added Grubbs II catalyst (6 mg), and the reaction mixture was heated under reflux for 30 min . The solvent was removed, and the residue was dissolved in EtOAc (4 mL), and 10% Pd/C (5 mg) was added. The reaction mixture was stirred under a hydrogen balloon for 35 min. Hydrogen balloon was removed, and then Hunig's base(23 μL) was added followed by methylamine (36 μL, 2 M solution in methanol) . The reaction mixture was stirred at room temperature for 10 min, and the

solvents were removed. The residue was purified by preparative TLC eluting with 35% EtOAc/Hexanes to give the title compound as a yellow solid (6.6 mg, 37% yield). ^{1}H NMR (500 MHz, chloroform-*d*) δ ppm 7.1-7.4 (5H, m), 4.45 (1H, dd, J = 3.0, 8.0 Hz), 3.24 (1H, dd, J = 8.0, 19.5 Hz), 3.20 (3H, s), 3.19 (3H, s), 2.71 (1H, dd, J = 3.0, 19.5 Hz). ^{13}C NMR (125 MHz, chloroform-*d*) δ 203.12, 186.69, 166.52, 159.93, 139.88 129.16 (2C), 127.73 (2C), 127.59, 110.98, 46.50, 45.48, and 27.53. HRMS calcd. for $C_{14}H_{13}ClN_3O$ (M+H) 274.0742; found: 274.0741.

Preparation AO

3-methoxy-4-(1-methyl-1H-pyrazol-4-yl)aniline

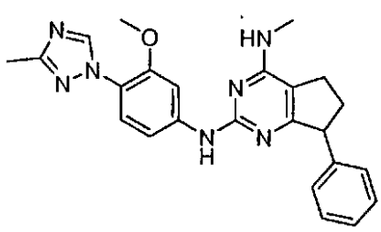


A DMF solution of diethyl 1-methyl-1H-pyrazol-4-ylboronate, 4-bromo-3-methoxy nitrobenzene together with Pd(dppf) and K2CO3 were heated at reflux overnight. The product obtained was reduced with Fe in MeOH/ammonium chloride to provide the title compound. LC–MS $(M+H)^+ = 204.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 7.84 (1H, s), 7.66 (1H, s), 7.19 (1H, J = 8.2 Hz, d), 6.29 (1H, s), 6.18 (1H, J = 2.0, 8.2 Hz, dd), 5.31 (2H, br s), 3.80 (3H, s), 3.75 (3H, s).

EXAMPLES

Example 1

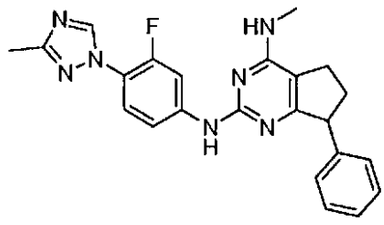
N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



The method of Example 74 was used to combine Preparation Ga and 3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline (Preparation D) to afford N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (Example 1).LC–MS $(M+H)^+ = 428.2$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.95 (1 H, br. s.), 7.72 (1 H, d, *J*=2.14 Hz), 7.65 (1 H, d, *J*=8.55 Hz), 7.37 - 7.42 (2 H, m), 7.30 - 7.34 (1 H, m), 7.26 (2 H, d, *J*=7.02 Hz), 7.22 (1 H, dd, *J*=8.85, 2.14 Hz), 4.42 - 4.48 (1 H, m), 3.93 (3 H, s), 3.16 (3 H, s), 2.88 - 2.96 (1 H, m), 2.72 - 2.83 (2 H, m), 2.46 (3 H, s), 2.12 - 2.21 (1 H, m).

Example 2

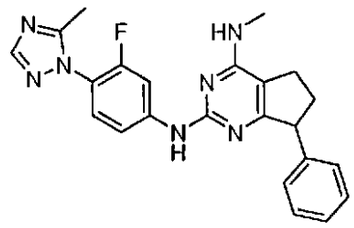
N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



The method of Example 74 was used to combine Preparation Ga and 3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline (Preparation B) to afford N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (Example 2).LC–MS $(M+H)^+ = 416.2$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.77 (1 H, br. s.), 7.95 (1 H, dd, *J*=13.43, 2.14 Hz), 7.77 (1 H, t, *J*=8.70 Hz), 7.48 (1 H, dd, *J*=8.85, 1.53 Hz), 7.40 (2 H, t, *J*=7.48 Hz), 7.33 (1 H, t, *J*=7.48 Hz), 7.28 (2 H, d, *J*=7.02 Hz), 4.49 (1 H, dd, *J*=7.63, 4.58 Hz), 3.18 (3 H, s), 2.88 - 2.98 (1 H, m), 2.77 - 2.86 (2 H, m), 2.46 (3 H, s), 2.14 - 2.24 (1 H, m).

Example 3

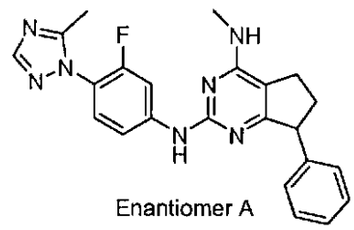
N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



The method of Example 74 was used to combine Preparation Ga and 3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline (Preparation C) to afford N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (Example 3).LC–MS $(M+H)^+ = 416.2$. ^1H NMR (500 MHz, *MeOD*) δ ppm 8.11 (1 H, s), 7.99 (1 H, dd, *J*=12.51, 1.83 Hz), 7.51 - 7.60 (2 H, m), 7.41 (2 H, t, *J*=7.48 Hz), 7.31 - 7.36 (1 H, m), 7.28 (2 H, d, *J*=7.02 Hz), 4.47 - 4.54 (1 H, m), 2.90 - 3.00 (1 H, m), 2.76 - 2.87 (2 H, m), 2.42 (3 H, s), 2.15 - 2.26 (1 H, m).

Example 3A

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

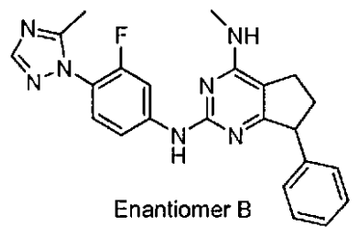


Enantiomer A

Example 3 was separated by multiple chiral prep HPLC injections (OJ-H 30 x 250mm, 10μM, 30% EtOH/Heptane/0.1%DEA) to give N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (first to elute, enantiomer A) as a slightly yellow, opaque glass. LC-MS $(M+H)^+ = 416.2$. ^1H NMR (500 MHz, *MeOD*) δ ppm 8.15 (1 H, dd, *J*=13.73, 2.14 Hz), 8.03 (1 H, s), 7.36 - 7.42 (1 H, m), 7.28 - 7.36 (3 H, m), 7.16 - 7.26 (3 H, m), 4.21 (1 H, t, *J*=7.78 Hz), 3.07 - 3.13 (3 H, m), 2.78 - 2.88 (1 H, m), 2.59 - 2.76 (2 H, m), 2.35 - 2.41 (3 H, m), 1.99 - 2.13 (1 H, m).

Example 3B

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

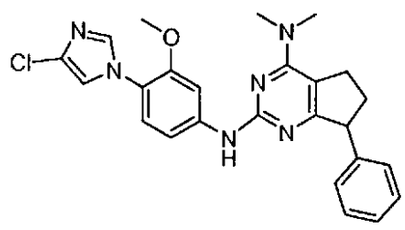


Enantiomer B

Enantiomer B of N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine was prepared as per *Example 3A* except that it was the second to elute off of the chiral HPLC column as a slightly yellow, opaque glass. LC-MS $(M+H)^+ = 416.2$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.17 (1 H, dd, *J*=13.89, 2.29 Hz), 8.02 (1 H, s), 7.28 - 7.46 (4 H, m), 7.16 - 7.27 (3 H, m), 4.19 (1 H, t, *J*=7.78 Hz), 3.05 - 3.16 (3 H, m), 2.78 - 2.89 (1 H, m), 2.57 - 2.78 (2 H, m), 2.33 - 2.48 (3 H, m), 1.99 - 2.17 (1 H, m).

Example 4

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



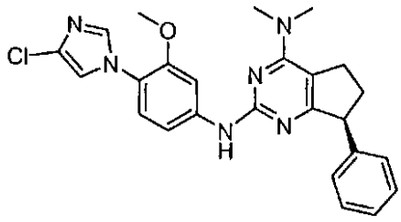
2-Chloro-*N*,*N*-dimethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (200 mg, 0.731 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (163 mg, 0.731 mmol) in THF (1 mL) and acetic acid (1.000 mL). The reaction mixture was stirred overnight at 75°C. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (180.7 mg, 0.308 mmol, 42.2 % yield). LC–MS $(M+H)^+ = 461.2$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.12 (1H, s), 7.98 - 8.17 (2H, m), 7.09 - 7.56 (6H, m), 7.01 - 7.09 (1H, m), 4.31 - 4.52 (2H, m), 3.97 (1H, s), 3.81 - 3.89 (2H, m), 3.45 - 3.55 (2H, m), 3.32 - 3.43 (3H, m), 3.16 - 3.29 (2H, m), 2.81 - 3.03 (1H, m), 2.56 - 2.75 (2H, m), 2.07 - 2.32 (2H, m).

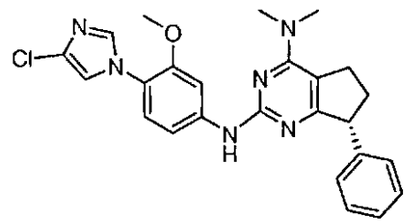
Example 4A & 4B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

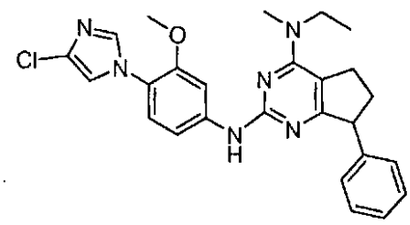




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (*Example 4*) was purified using chiral SFC to afford peak A (*Example 4A*) and peak B (*Example 4B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 35 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 22 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 5.1 min, t_R (peak B) 18.1 min. The absolute stereochemistry of individual enantiomers (*Examples 4A and 4B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 4*).

Example 5

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



2-Chloro-*N*-ethyl-*N*-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (160 mg, 0.556 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (124 mg, 0.556 mmol) in THF (1.5 mL) and acetic acid (1.5 mL). The reaction mixture was stirred overnight at 80°C. The crude reaction mixture was purified

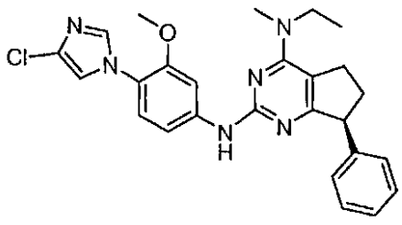
by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (85.3 mg, 0.171 mmol, 30.7 % yield). LC–MS $(M+H)^+ = 475.2$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.49 - 7.61 (1 H, m), 7.38 (1 H, br. s.), 7.23 - 7.34 (6 H, m), 7.13 (1 H, d, *J*=8.5 Hz), 7.05 (1 H, s), 4.35 (1 H, dd, *J*=9.3, 4.1 Hz), 3.69 - 3.82 (4 H, m), 3.47 (2 H, br. s.), 3.27 - 3.38 (4 H, m), 3.11 - 3.23 (1 H, m), 2.56 - 2.72 (1 H, m), 2.24 (1 H, ddd, *J*=9.0, 4.4, 4.3 Hz), 1.31 (3 H, t, *J*=7.2 Hz).

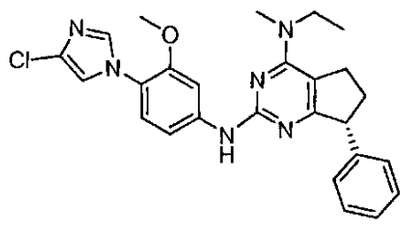
Example 5A & 5B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

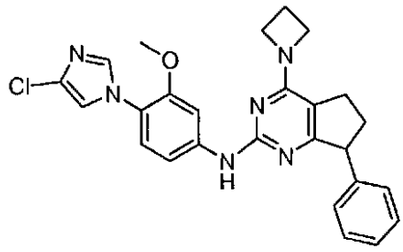




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (*Example 5*) was purified using chiral SFC to afford peak A (*Example 5A*) and peak B (*Example 5B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 35 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 22 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 4.5 min, t_R (peak B) 16.7 min. The absolute stereochemistry of individual enantiomers (*Examples 5A and 5B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 5*).

Example 6

4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



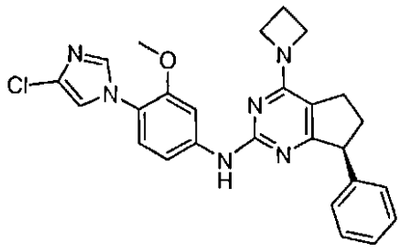
4-(Azetidin-1-yl)-2-chloro-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (162 mg, 0.567 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (127 mg, 0.567 mmol) in acetic acid (1.000 mL) and THF (1 mL). The reaction mixture was heated at 80°C overnight. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford 4-(azetidin-1-yl)-*N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine, TFA salt (39.2 mg, 0.066 mmol, 11.66 % yield). LC–MS $(M+H)^+$ = 473.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.44 (1H, s), 7.94 (1H, d, *J*=1.5 Hz), 7.52 (1H, d, *J*=2.1 Hz), 7.27 - 7.44 (4H, m), 6.96 - 7.23 (3H, m), 4.64 (3H, br s), 4.38 (2H, d, *J*=7.6 Hz), 3.83 (2H, s), 3.29 - 3.52 (1H, m), 3.11 (1H, d, *J*=7.9 Hz), 2.98 (1H, s), 2.62 - 2.76 (1H, m), 2.57 (2H, s), 2.14 - 2.38 (2H, m).

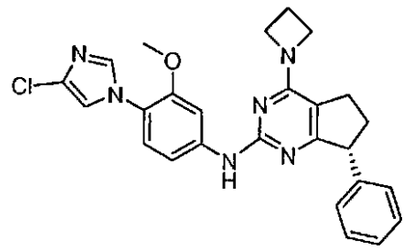
Example 6A & 6B

(S)-4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

and

(R)-4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



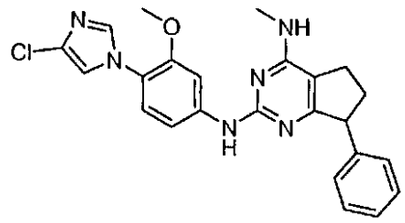


A racemic mixture of 4-(azetidin-1-yl)-*N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine (*Example 6*) was purified using chiral SFC to afford peak A (*Example 6A*) and peak B (*Example 6B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 35 % methanol (0.1%

diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 30 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in 50:50 methanol/chloroform (multiple stacked injections), t_R (peak A) = 5.9 min, t_R (peak B) 24.6 min. The absolute stereochemistry of individual enantiomers (*Examples 6A and 6B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 6*).

Example 7

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



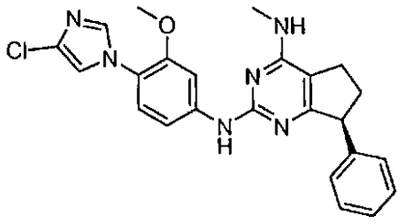
A solution of 2-chloro-*N*-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (833 mg, 3.21 mmol) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (717.9 mg, 3.21 μmol) in THF (5.6 mL) and acetic acid (5.6 mL) was heated at 85 °C in a 350 mL high-pressure vessel overnight. The solvent was removed in vacuum and the residue was dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate solution. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, which was contaminated with 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline. The material was triturated with methanol, cooled in the freezer and filtered. The residue was washed with freezing cold methanol and dried to give pure N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (673.5 mg, 47%) as light brown solid. LC–MS $(M+H)^+$ = 446.9. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.99 (1H, d, *J*=1.8 Hz), 7.48 (1H, s), 7.27 - 7.33 (2H, m), 7.16 - 7.24 (3H, m), 6.96 - 7.07 (3H, m), 6.71 (1H, dd, *J*=8.4, 1.7 Hz), 4.50 (1H, br s), 4.20 (1H, s), 3.48 (3H, s), 3.11 (3H, d, *J*=4.9 Hz), 2.59 - 2.79 (3H, m), 2.01 - 2.13 (1H, m).

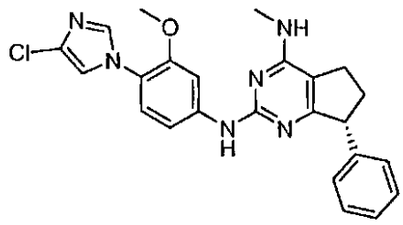
Examples 7A and 7B

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

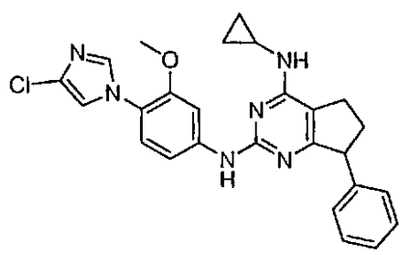




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (92 mg, 0.206 mmol from *Example 7*) was purified using chiral supercritical fluid chromatography (SFC) to afford 28.4 mg of peak A (*Example 7A*) and 27.4 mg of peak B (*Example 7B*). SFC Method: Chiralpak OJ-H (30 x 250 mm, 5 μM), 40 % methanol (0.1% diethylamine) in CO_2, 35 °C, flow rate 70 mL/min for 16 min, absorbance 268 nm, injection 1mL of 15 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 5.0 min, t_R (peak B) 12.3 min. The absolute stereochemistry of individual enantiomers (*Examples 7A and 7B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 7*).

Example 8

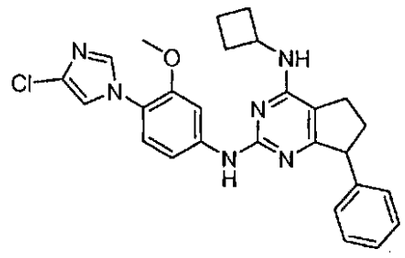
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-cyclopropyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



To a mixture of 2-chloro-N-cyclopropyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (175 mg, 0.612 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (151 mg, 0.674 mmol) in NMP (2 mL) was added Conc. H2SO4 (0.046 mL, 0.857 mmol). The mixture was stirred at 97°C for 20 hours. After cooled down to room temperature, 100 mL of EtOAc was added, washed with saturated NaHCO3/water and water, dried over Na2SO4, and finally removed. The residue was purified via Biotage (12g, hexanes-80%EtOAc) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-cyclopropyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (200 mg, 0.423 mmol, 69.1 % yield).LC-MS $(M+H)^+ = 473.10$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.81 (1 H, d, *J*=1.8 Hz), 7.51 (1 H, d, *J*=1.5 Hz), 7.44 (1 H, s), 7.27 - 7.35 (2 H, m), 7.19 - 7.25 (3 H, m), 6.99 - 7.06 (2 H, m), 6.95 (1 H, d, *J*=8.2 Hz), 4.89 (1 H, br. s.), 4.20 (1 H, t, *J*=8.2 Hz), 3.45 (3 H, s), 2.92 (1 H, td, *J*=6.7, 3.1 Hz), 2.76 - 2.86 (1 H, m), 2.59 - 2.75 (2 H, m), 2.07 - 2.14 (1 H, m), 0.85 - 0.91 (2 H, m), 0.63 - 0.70 (2 H, m).

Example 9

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-cyclobutyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

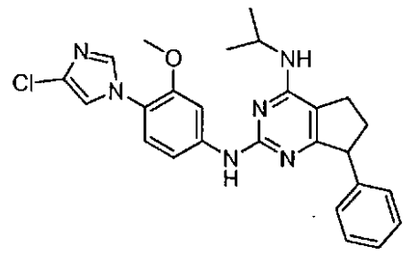


To a mixture of 2-chloro-N-cyclobutyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (165 mg, 0.55 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (135 mg, 0.605 mmol) in NMP (2 mL) was added Conc. H2SO4 (0.041 mL, 0.771 mmol). The mixture was stirred at 97°C for 20 hours. After cooled down to room temperature, 100 mL of EtOAc was added, washed with saturated NaHCO3/water and water, dried over Na2SO4, and finally removed. The residue was purified via Biotage (12g, hexanes-80%EtOAc) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-cyclobutyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (202 mg, 0.394 mmol, 71.6 % yield).LC-MS $(M+H)^+ = 487.14$. ^1H NMR

(500 MHz, $CDCl_3$) δ ppm 7.92 (1 H, d, *J*=1.8 Hz), 7.51 (1 H, d, *J*=1.2 Hz), 7.28 - 7.33 (2 H, m), 7.18 - 7.24 (3 H, m), 7.13 (1 H, s), 7.03 (1 H, d, *J*=8.5 Hz), 7.01 (1 H, d, *J*=1.2 Hz), 6.74 (1 H, dd, *J*=8.5, 2.1 Hz), 4.64 - 4.80 (2 H, m), 4.17 - 4.23 (1 H, m), 3.49 (3 H, s), 2.72 - 2.81 (1 H, m), 2.61 - 2.71 (2 H, m), 2.43 - 2.53 (2 H, m), 2.09 (1 H, td, *J*=8.0, 2.3 Hz), 1.92 - 2.04 (2 H, m), 1.70 - 1.88 (2 H, m).

Example 10

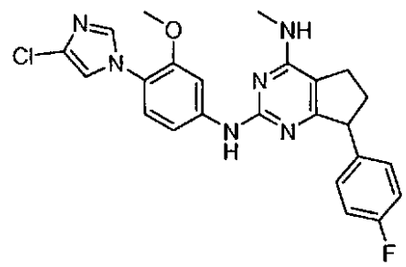
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-isopropyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



To a solution of 2-chloro-N-isopropyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (154 mg, 0.535 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (114 mg, 0.508 mmol) in DMF (2.5 mL) was added Conc. H2SO4 (0.040 mL, 0.749 mmol). The mixture was stirred at 94 °C for 20 hrs. After cooled down to room temperature, 100 mL of EtOAc was added, washed with saturated NaHCO3/H2O, dried over Na2SO4, and removed. The residue was purified via Biotage (12g, hexanes-100%EtOAC) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-isopropyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (120 mg, 0.253 mmol, 47.2 % yield).LC-MS $(M+H)^+$ = 475.2. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 7.92 (1 H, d, *J*=2.1 Hz), 7.51 (1 H, d, *J*=1.5 Hz), 7.31 (2 H, d, *J*=7.3 Hz), 7.22 - 7.25 (2 H, m), 7.22 (1 H, s), 7.08 (1 H, s), 7.04 (1 H, d, *J*=8.5 Hz), 7.01 (1 H, d, *J*=1.5 Hz), 6.74 (1 H, dd, *J*=8.4, 2.3 Hz), 4.38 - 4.46 (1 H, m), 4.33 (1 H, d, *J*=7.9 Hz), 4.18 - 4.24 (1 H, m), 3.49 (3 H, s), 2.72 - 2.80 (1 H, m), 2.61 - 2.71 (2 H, m), 2.07 - 2.14 (1 H, m), 1.33 (6 H, t, *J*=6.6 Hz).

Example 11

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



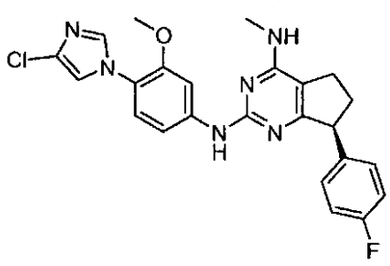
A solution of 2-chloro-7-(4-fluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (307.5 mg, 1.107 mmol) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (248 mg, 1.107 mmol) in THF (3 mL) and acetic acid (3.00 mL) was heated at 80 °C overnight. The solvent was removed in vacuum and the residue was triturated with methanol, cooled in the freezer and filtered. The precipitate was thoroughly washed with methanol and dried to give N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (207.9 mg, 0.447 mmol, 40.4 % yield) as off-white solid. LC-MS $(M+H)^+$ = 465.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.18 (1H, s), 8.15 (1H, d, *J*=1.8 Hz), 7.73 (1H, d, *J*=1.5 Hz), 7.41 (1H, d, *J*=1.5 Hz), 7.18 - 7.26 (2H, m), 7.07 - 7.18 (2H, m), 6.88 - 7.00 (1H, m), 4.12 - 4.20 (1H, m), 4.04 - 4.12 (1H, br s), 3.60 (3H, s), 3.17 (1H, s), 2.96 (3H, d, *J*=4.6 Hz), 2.71 - 2.81 (1H, m), 2.52 - 2.66 (2H, m), 1.83 - 1.96 (1H, m).

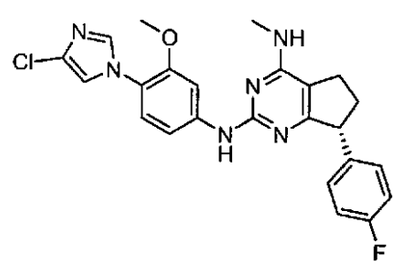
Examples 11A and 11B

(S)- N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)- N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



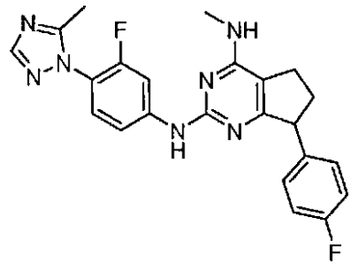


A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-trideuteromethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (150

mg, 0.206 mmol from *Example 11*) was purified using chiral supercritical fluid chromatography (SFC) to afford 74.6 mg of peak A (*Example 11A*) and 71.7 mg of peak B (*Example 11B*). SFC Method: Chiralpak OJ-H (30 x 250 mm, 5 μM), 35 % methanol (0.1% diethylamine) in CO_2, 35 °C, flow rate 70 mL/min for 12 min, absorbance 268 nm, injection 0.75mL of 15 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 4.0 min, t_R (peak B) 8.6 min. The absolute stereochemistry of individual enantiomers (*Examples 11A and 11B*) was not determined. LC-MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 11*).

Example 12

N^2-(3-Fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

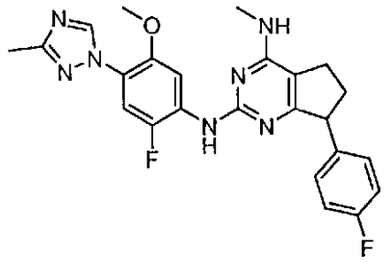


To a solution of 2-chloro-7-(4-fluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (105.0 mg, 0.378 mmol) and 3-fluoro-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)aniline (72.7 mg, 0.378 mmol) in THF (2 mL) was added 60% suspension of sodium hydride in mineral oil (30.2 mg, 0.756 mmol). The reaction mixture was stirred at 80°C for 40 minutes. The reaction mixture was further stirred at 80°C for 4 h. The reaction mixture was quenched with an aqueous solution of ammonium chloride and extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by a reversed phase preparative HPLC system to give N^2-(3-fluoro-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, 2 TFA (45.6 mg, 0.069 mmol, 18.25 % yield) as brown oil. LC-MS $(M+H)^+$ = 434.0. ^{1}H NMR (500 MHz, methanol-*d4*) δ ppm 8.86 (1H, s), 7.88 (1H, t, *J*=8.4 Hz), 7.21 - 7.31 (3H, m), 7.19 (1H, d, *J*=8.9 Hz), 7.07 (2H, t, *J*=8.7 Hz), 4.27 (1H, t, *J*=8.5 Hz), 3.73 (3H, s), 3.33 (3H, s), 2.52 (1H, dd,

J=8.2, 4.0 Hz), 2.49 (3H, s), 2.38 (1H, d, *J*=7.6 Hz), 2.30 (1H, d, *J*=3.7 Hz), 1.95 - 2.07 (1H, m).

Example 13

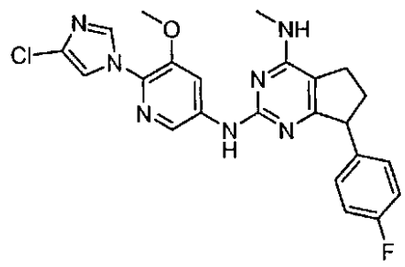
N^2-(2-Fluoro-5-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



To a solution of 2-chloro-7-(4-fluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (105.0 mg, 0.378 mmol) and 2-fluoro-5-methoxy-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)aniline (84 mg, 0.378 mmol) in THF (2 mL) was added 60% suspension of sodium hydride in mineral oil (9.07 mg, 0.378 mmol). The reaction mixture was stirred at 80°C for 40 minutes. The reaction mixture was further stirred at 80°C for 4 h. The reaction mixture was quenched with an aqueous solution of ammonium chloride and extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by a reversed phase preparative HPLC system to give N^2-(2-fluoro-5-methoxy-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, 2 TFA (20.2 mg, 0.027 mmol, 7.19 % yield) as brown oil. LC-MS $(M+H)^+$ = 464.0. ^{1}H NMR (500 MHz, methanol-*d4*) δ ppm 9.06 (1H, s), 7.74 (1H, d, *J*=10.4 Hz), 7.19 - 7.28 (3H, m), 7.07 (2H, t, *J*=8.5 Hz), 4.24 (1H, s), 4.00 (3H, s), 3.76 (3H, s), 2.48 (3H, s), 2.40 - 2.54 (1H, m), 2.26 - 2.38 (2H, m), 1.89 - 2.02 (1H, m).

Example 14

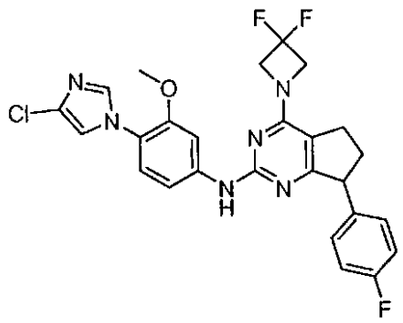
N^2-(6-(4-Chloro-1H-imidazol-1-yl)-5-methoxypyridin-3-yl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



To a solution of 2-chloro-7-(4-fluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (165.3 mg, 0.595 mmol) and 6-(4-chloro-1*H*-imidazol-1-yl)-5-methoxypyridin-3-amine (134 mg, 0.595 mmol) in THF (3.5 mL) was added 60% suspension of sodium hydride in mineral oil (28.6 mg, 1.190 mmol). The reaction mixture was heated at 80°C in a capped vial for 6 h. The reaction was carefully quenched with aqueous ammonium chloride solution and the product was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by a reversed-phase preparative HPLC method to provide N^2-(6-(4-chloro-1*H*-imidazol-1-yl)-5-methoxypyridin-3-yl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, 2 TFA (26.2 mg, 0.029 mmol, 4.88 % yield) as brown oil. LC-MS $(M+H)^+ = 466.0$. ^{1}H NMR (500 MHz, methanol-*d4*) δ ppm 8.43 (1H, s), 7.96 (1H, s), 7.87 (1H, s), 7.55 (1H, br. s.), 7.19 - 7.32 (2H, m), 7.07 (2H, t, *J*=8.7 Hz), 4.20 - 4.29 (1H, m), 4.06 (3H, s), 3.75 (3H, s), 2.42 - 2.55 (1H, m), 2.21 - 2.39 (2H, m), 1.90 - 2.05 (1H, m).

Example 15

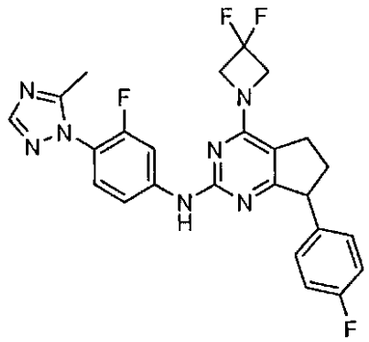
N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



A solution of 2-chloro-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (42.6 mg, 0.125 mmol) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (28.0 mg, 0.125 mmol) in THF (1 mL) and acetic acid (1.000 mL) was heated at 80°C overnight. The heating was continued at 120°C overnight. Upon cooling, the reaction mixture was purified by column chromatography on silica gel to give *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine, TFA (11.8 mg, 0.018 mmol, 14.54 % yield) as brown oil. LC-MS $(M+H)^+$ = 527.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.75 (1H, s), 8.02 (1H, s), 7.40 (1H, dd, *J*=8.5, 2.1 Hz), 7.32 (1H, d, *J*=2.1 Hz), 7.16 - 7.23 (3H, m), 7.12 (1H, s), 7.02 (2H, t, *J*=8.7 Hz), 4.42 (1H, dd, *J*=9.5, 4.9 Hz), 4.80 (4H, s), 3.85 (3H, s), 3.11 (1H, s), 2.98 (1H, s), 2.67 - 2.79 (1H, m), 2.26 (1H, d).

Example 16

4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

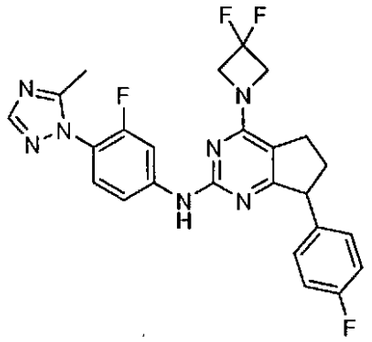


To a solution of 2-chloro-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation Ha*) (170 mg, 0.500 mmol) in THF (1498 µL) was added 3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline (*Preparation C*) (125 mg, 0.650 mmol) and Acetic Acid (1498 µL). The resulting mixture was heated to 100 °C and stirred overnight. The reaction mixture was then concentrated *in vacuo* and purified by prep HPLC (C18, 30 X 150mm, MeOH/H_2O/TFA) to give 4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (racemate) (101.49 mg, 33.27 % yield) as a beige solid. LC-MS $(M+H)^+$ = 496.1. ^{1}H NMR (500 MHz,

MeOD) δ ppm 8.06 - 8.11 (1 H, m), 7.86 (1 H, dd, *J*=12.51, 2.14 Hz), 7.47 - 7.57 (2 H, m), 7.28 - 7.35 (2 H, m), 7.11 - 7.19 (2 H, m), 4.93 (4 H, t, *J*=11.90 Hz), 4.47 (1 H, t, *J*=7.93 Hz), 3.11 - 3.18 (1 H, m), 2.99 - 3.08 (1 H, m), 2.71 - 2.81 (1 H, m, *J*=13.31, 8.91, 8.91, 4.27 Hz), 2.42 (3 H, s), 2.08 - 2.19 (1 H, m, *J*=13.24, 9.04, 6.71, 6.71 Hz).

Example 16A

4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

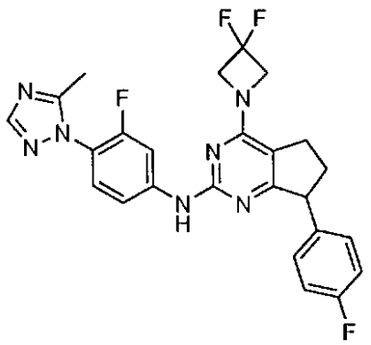


Enantiomer A of *Example 16*

4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 16*) was separated by multiple injections on chiral SFC (Chiracel OJ-H 30 x 250mm, 5μM, 30% MeOH (0.1% DEA)/CO_2 to give 4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (first to elute, enantiomer A) as an off-white solid. LC-MS $(M+H)^+$ = 496.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.87 - 8.08 (2 H, m), 7.35 - 7.44 (1 H, m), 7.31 (1 H, t, *J*=8.70 Hz), 7.24 (2 H, dd, *J*=8.55, 5.49 Hz), 7.04 (2 H, t, *J*=8.70 Hz), 4.64 (4 H, t, *J*=12.05 Hz), 4.19 (1 H, t, *J*=8.24 Hz), 2.98 - 3.08 (1 H, m), 2.86 - 2.98 (1 H, m), 2.55 - 2.68 (1 H, m, *J*=12.86, 8.60, 8.60, 4.12 Hz), 2.37 (3 H, s), 1.97 - 2.12 (1 H, m). The absolute stereochemistry of *Example 16A* was not determined.

Example 16B

4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

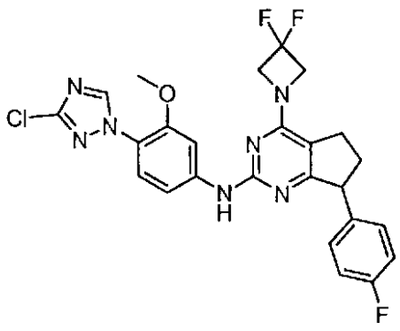


Enantiomer B of *Example 16*

4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 16*) was separated by multiple injections on chiral SFC (Chiracel OJ-H 30 x 250mm, 5μM, 30% MeOH (0.1% DEA)/CO_2 to give 4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (second to elute, enantiomer B) as an off-white solid. LC-MS $(M+H)^+$ = 496.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.96 - 8.09 (2 H, m), 7.39 (1 H, dd, *J*=9.00, 1.98 Hz), 7.32 (1 H, t, *J*=8.55 Hz), 7.20 - 7.28 (2 H, m), 6.99 - 7.11 (2 H, m), 4.65 (4 H, t, *J*=12.21 Hz), 4.20 (1 H, t, *J*=8.24 Hz), 2.99 - 3.09 (1 H, m), 2.88 - 2.99 (1 H, m), 2.56 - 2.71 (1 H, m), 2.31 - 2.46 (3 H, m), 1.98 - 2.15 (1 H, m). The absolute stereochemistry of *Example 16B* was not determined.

Example 17

N-(4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

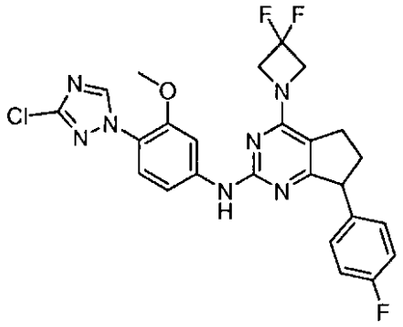


To a solution of 2-chloro-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation Ha*) (170 mg, 0.500 mmol) and 4-(3-

chloro-1H-1,2,4-triazol-1-yl)-3-methoxyaniline (*Preparation F*) (146 mg, 0.650 mmol) in THF (1498 µL) was added Acetic Acid (1498 µL). The resulting mixture was heated to 100 °C and stirred overnight. The reaction mixture was then concentrated *in vacuo*. MeOH was added to the residue which resulted in a suspension. This was filtered to give a solid which was taken up in hot MeOH and filtered. The filtrate was then concentrated *in vacuo* to give N-(4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (racemate) (130 mg, 49.22 % yield) as a yellow solid. LC-MS $(M+H)^+ = 528.1$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.81 (1 H, s), 7.65 (1 H, d, *J*=8.55 Hz), 7.59 (1 H, s), 7.29 - 7.36 (2 H, m), 7.11 - 7.21 (3 H, m), 4.87 - 4.88 (4 H, m), 4.47 (1 H, s), 3.91 (3 H, s), 3.11 - 3.19 (1 H, m), 2.99 - 3.08 (1 H, m), 2.77 (1 H, dddd, *J*=13.47, 8.96, 4.43, 4.27 Hz), 2.13 (1 H, dq, *J*=8.89, 6.70 Hz).

Example 17A

N-(4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



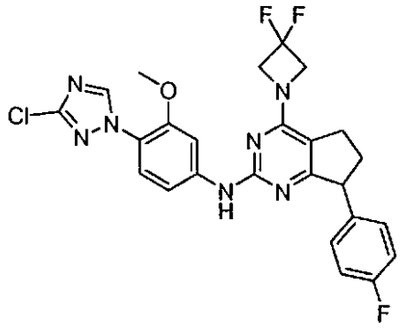
Enantiomer A of *Example 17*

N-(4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 17*) was separated by multiple injections on chiral SFC (Chiracel AD-H 30 x 250mm, 5µM, 45% MeOH (0.1% DEA)/CO_2 to give 4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (first to elute, enantiomer A) as a yellow film. LC-MS $(M+H)^+ = 528.1$. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ ppm 8.82 (1 H, d, *J*=1.53 Hz), 8.06 (1 H, s), 7.35 (1 H, d, *J*=8.85 Hz), 7.21 - 7.31 (2 H, m), 7.07 - 7.21 (3 H, m), 4.70 (4 H, t, *J*=12.36 Hz), 4.20 (1 H, t, *J*=8.24 Hz), 3.63 (3 H, br. s.), 3.01 (1 H, br. s.), 2.80 - 2.95 (1

H, m), 2.53 - 2.63 (1 H, m), 1.93 (1 H, d, *J*=8.24 Hz). The absolute stereochemistry of *Example 17A* was not determined.

Example 17B

N-(4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

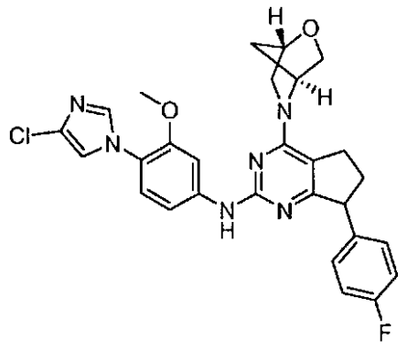


Enantiomer B of *Example 17*

N-(4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 17*) was separated by multiple injections on chiral SFC (Chiracel AD-H 30 x 250mm, 5μM, 45% MeOH (0.1% DEA)/CO_2 to give 4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (second to elute, enantiomer B) as a yellow film. LC-MS $(M+H)^+$ = 528.1. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 8.76 - 8.92 (1 H, m), 8.06 (1 H, br. s.), 7.30 - 7.45 (1 H, m), 7.25 (2 H, d, *J*=5.49 Hz), 7.05 - 7.19 (3 H, m), 4.57 - 4.80 (4 H, m), 4.20 (1 H, br. s.), 3.63 (3 H, br. s.), 3.00 (1 H, br. s.), 2.82 - 2.94 (1 H, m), 2.53 - 2.61 (1 H, m), 1.91 (1 H, br. s.). The absolute stereochemistry of *Example 17B* was not determined.

Example 18

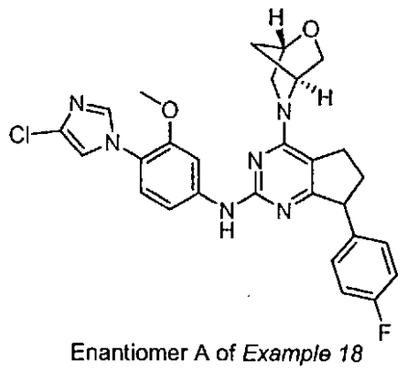
4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



(1S,4S)-5-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-2-oxa-5-azabicyclo[2.2.1]heptane (*Preparation Hb*) (148 mg, 0.428 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (124 mg, 0.556 mmol) were combined and purified as per *Example 16* to give 4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (diastereomer mixture) (106 mg, 0.164 mmol, 38.3 % yield) as a brown solid. LC-MS $(M+H)^+ = 533.1$. ^{1}H NMR (500 MHz, *DMSO-d_6*) δ ppm 7.81 (1 H, s), 7.67 (1 H, br. s.), 7.49 (1 H, s), 7.32 (3 H, d, *J*=7.93 Hz), 7.19 (2 H, t, *J*=8.70 Hz), 7.14 (1 H, d, *J*=2.14 Hz), 5.17 (1 H, br. s.), 4.74 (1 H, s), 4.34 (1 H, br. s.), 3.58 - 3.95 (7 H, m), 2.89 - 3.39 (2 H, m), 2.55 (1 H, s), 1.97 (3 H, br. s.).

Example 18A

4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



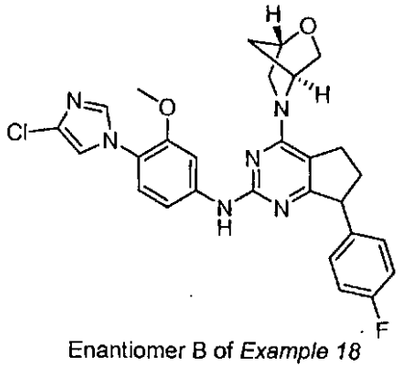
Enantiomer A of *Example 18*

4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-

amine (*Example 18*) was separated by multiple chiral SFC injections (OD-H 30 x 250mm, 5 μM, 30% MeOH (0.1% DEA)/CO_2) to give 4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (first to elute, enantiomer A) as a beige residue. LC-MS $(M+H)^+$ = 532.9. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.82 (1 H, br. s.), 7.67 (1 H, s), 7.18 - 7.30 (3 H, m), 7.11 - 7.18 (1 H, m), 6.96 - 7.09 (3 H, m), 5.14 (1 H, br. s.), 4.72 (1 H, br. s.), 4.18 (1 H, t, *J*=8.55 Hz), 3.94 - 4.01 (1 H, m), 3.92 (1 H, d, *J*=6.41 Hz), 3.78 - 3.86 (1 H, m), 3.69 - 3.78 (1 H, m), 3.57 (3 H, s), 3.01 - 3.15 (2 H, m), 2.51 - 2.69 (1 H, m), 1.84 - 2.11 (3 H, m). The absolute stereochemistry of *Example 18A* was not determined.

Example 18B

4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



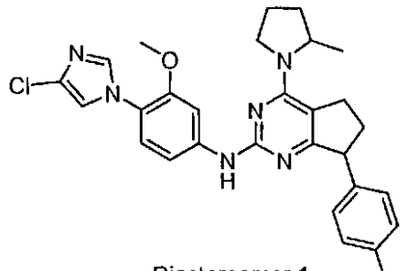
Enantiomer B of *Example 18*

4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 18*) was separated by multiple chiral SFC injections (OD-H 30 x 250mm, 5 μM, 30% MeOH (0.1% DEA)/CO_2) to give 4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (second to elute, enantiomer B) as a beige residue. LC-MS $(M+H)^+$ = 532.9. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.20 - 7.31 (3 H, m), 7.17 (1 H, d, *J*=8.55 Hz), 7.05 (3 H, t, *J*=8.09 Hz), 5.17 (1 H, br. s.), 4.72 (1 H, s), 4.14 (1 H, t, *J*=8.09 Hz), 3.94 - 4.02 (1 H, m), 3.89 - 3.94 (1 H, m), 3.70 - 3.85 (2 H, m), 3.50 - 3.68 (3 H, m), 3.20 - 3.31 (1 H, m), 2.96 (1 H, ddd, *J*=14.65,

7.78, 7.48 Hz), 2.48 - 2.66 (1 H, m, *J*=13.08, 8.72, 8.72, 4.27 Hz), 1.89 - 2.11 (3 H, m). The absolute stereochemistry of *Example 18B* was not determined.

Example 19

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

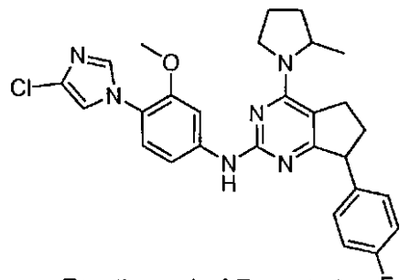


Diastereomer 1
Racemic

2-chloro-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidinen (*Preparation Hc1*) (159 mg, 0.479 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (139 mg, 0.623 mmol) were combined and purified as per *Example 16* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (racemate, diastereomer 1) (84.37 mg, 0.133 mmol, 27.8 % yield) as a brown solid. LC-MS $(M+H)^+ = 519.1$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.80 (1 H, s), 7.41 (1 H, d, *J*=8.55 Hz), 7.30 - 7.37 (4 H, m), 7.21 - 7.32 (1 H, m), 7.17 (2 H, t, *J*=8.55 Hz), 4.68 (1 H, br. s.), 4.44 (1 H, br. s.), 3.94 - 4.23 (2 H, m), 3.88 (3 H, s), 3.37 (3 H, s), 3.18 (1 H, s), 2.72 (1 H, br. s.), 2.11 (4 H, br. s.), 1.83 (1 H, br. s.). The relative stereochemistry of *Example 19* was not determined.

Example 19A

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

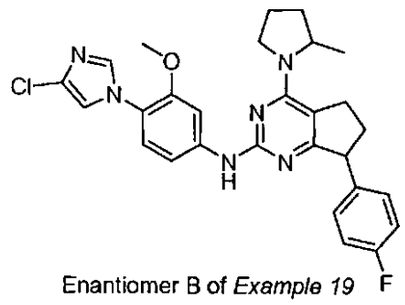


Enantiomer A of *Example 19*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 19*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 45% MeOH (0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (first to elute, enantiomer A, diastereomer 1) as a brown wax. LC-MS $(M+H)^+$ = 519.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.76 (1 H, s), 7.66 (1 H, d, *J*=1.53 Hz), 7.16 - 7.27 (3 H, m), 7.07 - 7.16 (2 H, m), 7.02 (2 H, t, *J*=8.85 Hz), 4.54 (1 H, t, *J*=5.65 Hz), 4.07 (1 H, t, *J*=8.24 Hz), 3.91 (1 H, dt, *J*=10.45, 4.08 Hz), 3.68 - 3.79 (1 H, m), 3.54 - 3.68 (3 H, m), 3.15 - 3.28 (1 H, m), 2.96 - 3.13 (1 H, m), 2.45 - 2.58 (1 H, m), 2.02 - 2.18 (2 H, m), 1.95 - 2.02 (1 H, m), 1.85 - 1.95 (1 H, m), 1.67 - 1.81 (1 H, m), 1.27 (3 H, d, *J*=6.10 Hz). The absolute stereochemistry of *Example 19A* was not determined.

Example 19B

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



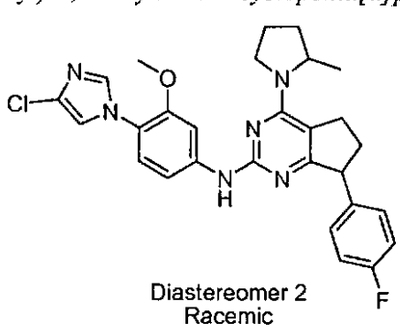
Enantiomer B of *Example 19*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 19*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 45% MeOH

(0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (second to elute, enantiomer B, diastereomer 1) as a brown wax. LC-MS $(M+H)^+$ = 519.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.76 (1 H, d, *J*=1.53 Hz), 7.65 (1 H, d, *J*=1.22 Hz), 7.15 - 7.23 (3 H, m), 7.06 - 7.14 (2 H, m), 6.96 - 7.05 (2 H, m), 4.48 - 4.57 (1 H, m), 4.05 (1 H, t, *J*=8.39 Hz), 3.85 - 3.94 (1 H, m), 3.66 - 3.76 (1 H, m), 3.60 (3 H, s), 3.16 - 3.26 (1 H, m), 2.95 - 3.08 (1 H, m), 2.44 - 2.55 (1 H, m, *J*=12.78, 8.56, 8.56, 3.97 Hz), 2.01 - 2.14 (2 H, m), 1.94 - 2.01 (1 H, m), 1.85 - 1.94 (1 H, m), 1.68 - 1.77 (1 H, m), 1.26 (3 H, d, *J*=6.10 Hz). The absolute stereochemistry of *Example 19B* was not determined.

Example 20

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

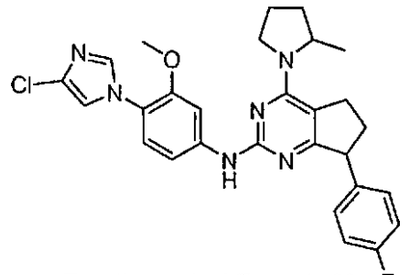


Diastereomer 2
Racemic

2-chloro-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidinen (*Preparation Hc2*) (179 mg, 0.539 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (157 mg, 0.701 mmol) were combined and purified as per *Example 16* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (racemate, diastereomer 2) (99.55 mg, 0.157 mmol, 29.2 % yield) as a brown solid. LC-MS $(M+H)^+$ = 519.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.80 (1 H, d, *J*=1.53 Hz), 7.41 - 7.60 (1 H, m), 7.40 (1 H, s), 7.30 - 7.37 (3 H, m), 7.21 - 7.29 (1 H, m), 7.16 (2 H, t, *J*=8.70 Hz), 4.68 (1 H, br. s.), 4.45 (1 H, d, *J*=7.93 Hz), 4.17 (1 H, br. s.), 4.00 (1 H, br. s.), 3.88 (3 H, s), 3.34 - 3.48 (2 H, m), 3.17 - 3.30 (1 H, m), 2.73 (1 H, br. s.), 2.11 (4 H, br. s.), 1.81 (1 H, br. s.), 1.35 (3 H, d, *J*=6.41 Hz). The relative stereochemistry of *Example 20* was not determined.

Example 20A

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

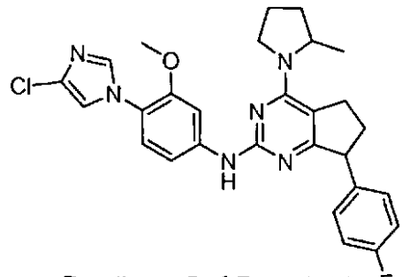


Enantiomer A of *Example 20*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 20*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 45% MeOH (0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (first to elute, enantiomer A, diastereomer 2) as a brown wax. LC-MS $(M+H)^+$ = 519.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.75 (1 H, d, *J*=1.83 Hz), 7.65 (1 H, d, *J*=1.53 Hz), 7.14 - 7.22 (3 H, m), 7.05 - 7.14 (2 H, m), 6.96 - 7.05 (2 H, m), 4.55 (1 H, td, *J*=6.41, 2.44 Hz), 4.10 (1 H, t, *J*=8.39 Hz), 3.86 - 3.95 (1 H, m), 3.73 (1 H, dt, *J*=10.15, 7.74 Hz), 3.59 (3 H, s), 3.16 - 3.25 (1 H, m), 3.06 - 3.16 (1 H, m), 2.52 (1 H, dddd, *J*=12.70, 8.70, 8.51, 3.97 Hz), 2.02 - 2.16 (2 H, m), 1.82 - 2.02 (2 H, m), 1.65 - 1.78 (1 H, m), 1.27 (3 H, d, *J*=6.10 Hz). The absolute stereochemistry of *Example 20A* was not determined.

Example 20B

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

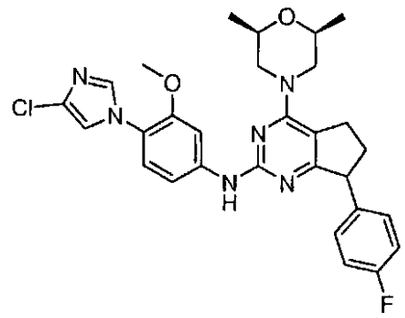


Enantiomer B of *Example 20*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 20*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 45% MeOH (0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (second to elute, enantiomer B, diastereomer 2) as a brown wax. LC-MS $(M+H)^+$ = 519.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.75 (1 H, s), 7.65 (1 H, d, *J*=1.53 Hz), 7.14 - 7.21 (3 H, m), 7.05 - 7.14 (2 H, m), 6.96 - 7.04 (2 H, m), 4.49 - 4.58 (1 H, m), 4.10 (1 H, t, *J*=8.55 Hz), 3.84 - 3.93 (1 H, m), 3.69 - 3.78 (1 H, m), 3.55 - 3.61 (3 H, m), 3.15 - 3.24 (1 H, m), 3.05 - 3.15 (1 H, m), 2.52 (1 H, dddd, *J*=12.67, 8.62, 8.47, 4.12 Hz), 2.02 - 2.17 (2 H, m), 1.83 - 2.02 (2 H, m), 1.65 - 1.77 (1 H, m), 1.23 - 1.32 (3 H, m). The absolute stereochemistry of *Example 20B* was not determined.

Example 21

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

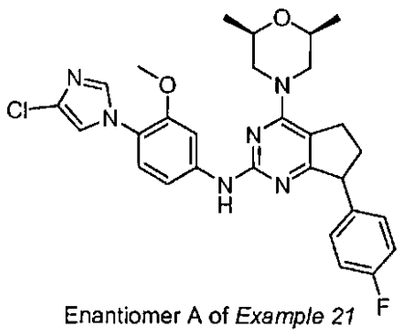


(2S,6R)-4-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-2,6-dimethylmorpholine (*Preparation Hd*) (223 mg, 0.616 mmol) and 4-(4-chloro-

1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (179 mg, 0.801 mmol) were combined and purified as per *Example 16* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (144 mg, 0.217 mmol, 35.2 % yield) as a brown solid. LC-MS $(M+H)^+ = 549.0$. ^1H NMR (500 MHz, *MeOD*) δ ppm 7.81 (1 H, d, *J*=1.53 Hz), 7.41 (1 H, d, *J*=8.55 Hz), 7.28 - 7.38 (4 H, m), 7.09 - 7.20 (3 H, m), 4.62 (2 H, br. s.), 4.45 (1 H, t, *J*=7.93 Hz), 3.83 - 3.89 (3 H, m), 3.69 - 3.80 (2 H, m), 3.25 - 3.30 (1 H, m), 3.13 - 3.23 (1 H, m), 2.94 (2 H, br. s.), 2.75 (1 H, dddd, *J*=13.43, 8.93, 8.77, 4.88 Hz), 2.03 - 2.20 (1 H, m), 1.25 (6 H, d, *J*=6.10 Hz).

Example 21A

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



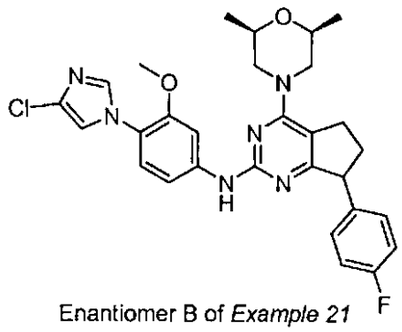
Enantiomer A of *Example 21*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 21*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 35% MeOH (0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (first to elute, enantiomer A) as a brown wax. LC-MS $(M+H)^+ = 549.0$. ^1H NMR (500 MHz, *MeOD*) δ ppm 7.81 (1 H, d, *J*=2.14 Hz), 7.63 (1 H, d, *J*=1.53 Hz), 7.11 - 7.20 (3 H, m), 7.08 (1 H, d, *J*=8.55 Hz), 6.96 - 7.03 (2 H, m), 6.92 (1 H, dd, *J*=8.55, 2.44 Hz), 4.27 - 4.41 (2 H, m), 4.08 (1 H, t, *J*=8.70 Hz), 3.58 - 3.74 (2 H, m), 3.49 (3 H, s), 2.99 - 3.08 (1 H, m), 2.87 - 2.99 (1 H, m), 2.55 - 2.72 (2 H, m),

2.44 - 2.55 (1 H, m), 1.83 - 1.96 (1 H, m, *J*=12.70, 8.55, 8.30, 8.30 Hz), 1.17 - 1.22 (6 H, m). The absolute stereochemistry of *Example 21A* was not determined.

Example 21B

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

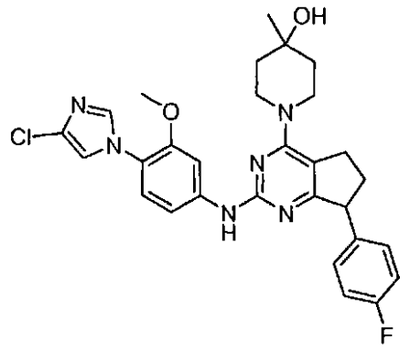


Enantiomer B of *Example 21*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 21*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 35% MeOH (0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (second to elute, enantiomer B) as a brown wax. LC-MS $(M+H)^+$ = 549.0. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.81 (1 H, d, *J*=2.14 Hz), 7.63 (1 H, d, *J*=1.53 Hz), 7.11 - 7.19 (3 H, m), 7.04 - 7.11 (1 H, m), 6.95 - 7.03 (2 H, m), 6.92 (1 H, dd, *J*=8.39, 2.29 Hz), 4.27 - 4.42 (2 H, m), 4.08 (1 H, t, *J*=8.70 Hz), 3.59 - 3.73 (2 H, m), 3.49 (3 H, s), 2.98 - 3.08 (1 H, m), 2.88 - 2.98 (1 H, m), 2.55 - 2.70 (2 H, m), 2.43 - 2.55 (1 H, m), 1.79 - 1.97 (1 H, m, *J*=12.70, 8.55, 8.30, 8.30 Hz), 1.17 - 1.21 (6 H, m). The absolute stereochemistry of *Example 21B* was not determined.

Example 22

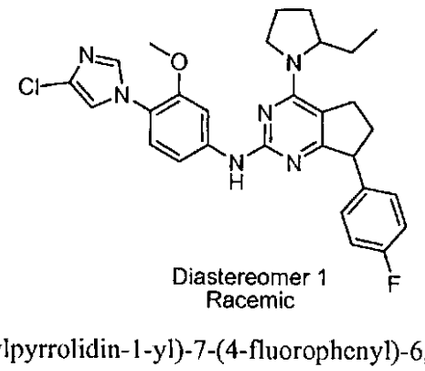
1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-4-methylpiperidin-4-ol



1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-4-methylpiperidin-4-ol (*Preparation He*) (374 mg, 1.034 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (301 mg, 1.344 mmol) were combined and purified as per *Example 17* to give 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-4-methylpiperidin-4-ol (89 mg, 0.162 mmol, 15.68 % yield) as a slightly yellow solid. LC-MS $(M+H)^+$ = 549.3. ^{1}H NMR (500 MHz, *DMSO-d$_6$*) δ ppm 7.82 (1 H, s), 7.64 (1 H, br. s.), 7.50 (1 H, s), 7.27 - 7.43 (3 H, m), 7.20 (3 H, t, *J*=8.70 Hz), 7.06 (1 H, dd, *J*=8.39, 1.68 Hz), 4.36 (3 H, br. s.), 3.73 (3 H, br. s.), 2.98 - 3.26 (3 H, m), 2.59 (1 H, br. s.), 1.88 - 2.06 (1 H, m), 1.62 (4 H, br. s.), 1.25 (2 H, br. s.), 1.19 (3 H, s).

Example 23

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



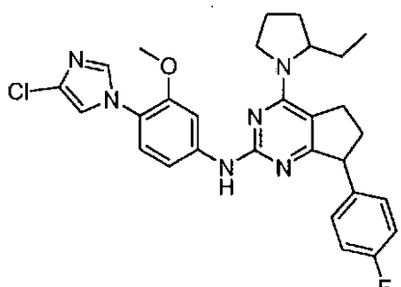
Diastereomer 1
Racemic

2-chloro-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation Hf1*) (77 mg, 0.223 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (64.7 mg, 0.289 mmol) were combined and purified as per *Example 16* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-

methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (racemic, diastereomer 1) (53.31 mg, 0.082 mmol, 37.0 % yield) as a brown solid. LC-MS $(M+H)^+$ = 533.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.79 (1 H, br. s.), 7.36 - 7.61 (2 H, m), 7.34 (3 H, br. s.), 7.17 (3 H, br. s.), 4.44 (2 H, br. s.), 4.00 (2 H, br. s.), 3.88 (3 H, br. s.), 3.16 - 3.27 (1 H, m), 2.73 (2 H, br. s.), 2.09 (5 H, br. s.), 1.32 (2 H, br. s.), 0.93 (3 H, br. s.). The relative stereochemistry of *Example 23* was not determined.

Example 23A

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

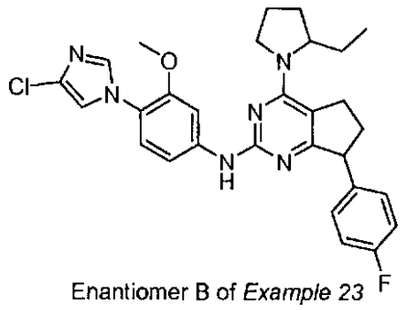


Enantiomer A of *Example 23*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 23*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 45% MeOH (0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (first to elute, enantiomer A) as a brown oil. LC-MS $(M+H)^+$ = 533.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.60 - 7.70 (2 H, m), 7.17 - 7.26 (4 H, m), 7.14 (1 H, d, *J*=8.55 Hz), 6.98 - 7.07 (2 H, m), 4.26 - 4.36 (1 H, m), 4.09 (1 H, t, *J*=8.24 Hz), 3.83 - 3.92 (1 H, m), 3.70 - 3.79 (1 H, m), 3.63 (3 H, s), 3.15 - 3.25 (1 H, m), 3.04 (1 H, ddd, *J*=14.80, 7.63, 7.48 Hz), 2.48 - 2.60 (1 H, m, *J*=12.86, 8.60, 8.60, 4.12 Hz), 1.76 - 2.12 (6 H, m), 1.40 - 1.53 (1 H, m), 0.94 - 1.00 (3 H, m). The absolute stereochemistry of *Example 23A* was not determined.

Example 23B

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

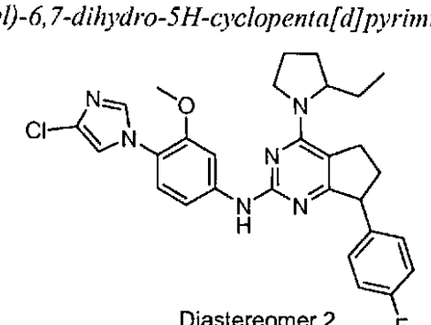


Enantiomer B of *Example 23*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 23*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 45% MeOH (0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (second to elute, enantiomer B) as a brown oil. LC-MS $(M+H)^+$ = 533.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.60 - 7.70 (2 H, m), 7.18 - 7.27 (4 H, m), 7.14 (1 H, d, *J*=8.55 Hz), 7.03 (2 H, t, *J*=8.70 Hz), 4.31 (1 H, br. s.), 4.04 - 4.13 (1 H, m), 3.81 - 3.91 (1 H, m), 3.70 - 3.80 (1 H, m), 3.63 (3 H, s), 3.16 - 3.26 (1 H, m), 3.05 (1 H, ddd, *J*=14.65, 7.78, 7.48 Hz), 2.54 (1 H, dddd, *J*=12.78, 8.70, 8.58, 4.12 Hz), 1.76 - 2.14 (6 H, m), 1.41 - 1.54 (1 H, m), 0.97 (3 H, t, *J*=7.32 Hz). The absolute stereochemistry of *Example 23B* was not determined.

Example 24

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

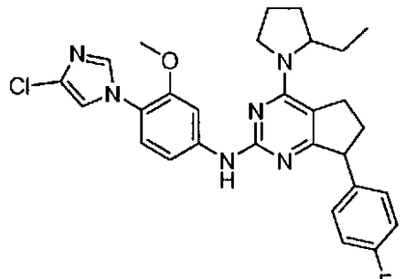


Diastereomer 2
Racemic

2-chloro-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation Hf2*) (80 mg, 0.231 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (67.3 mg, 0.301 mmol) were combined and purified as per *Example 16* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (racemic, diastereomer 2) (39.54 mg, 0.061 mmol, 26.4 % yield) as a brown solid. LC-MS $(M+H)^+ = 533.3$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.78 (1 H, s), 7.28 - 7.44 (5 H, m), 7.17 (3 H, t, *J*=8.09 Hz), 4.46 (2 H, br. s.), 4.00 (2 H, br. s.), 3.88 (3 H, s), 3.37 (1 H, br. s.), 2.73 (2 H, br. s.), 2.09 (6 H, d, *J*=4.27 Hz), 1.27 - 1.73 (1 H, m), 0.87 (3 H, br. s.). The relative stereochemistry of *Example 24* was not determined.

Example 24A

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



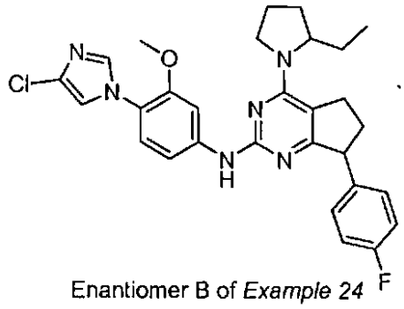
Enantiomer A of *Example 24*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 24*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 45% MeOH (0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (first to elute, enantiomer A) as a brown oil. LC-MS $(M+H)^+ = 533.3$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.58 - 7.71 (2 H, m), 7.16 - 7.26 (4 H, m), 7.10 - 7.16 (1 H, m), 6.97 - 7.08 (2 H, m), 4.29 - 4.39 (1 H, m), 4.14 (1 H, t, *J*=8.39 Hz), 3.82 - 3.93 (1 H, m), 3.72 - 3.82 (1 H, m), 3.61 (3 H, s), 3.17 - 3.26 (1 H, m), 3.12 (1 H, ddd, *J*=14.80, 7.63, 7.48 Hz), 2.56 (1 H, dddd, *J*=12.70, 8.70, 8.51, 3.97 Hz), 1.79 - 2.09 (6 H, m), 1.40 - 1.56 (1 H, m),

0.97 (3 H, t, *J*=7.32 Hz). The absolute stereochemistry of *Example 24A* was not determined.

Example 24B

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

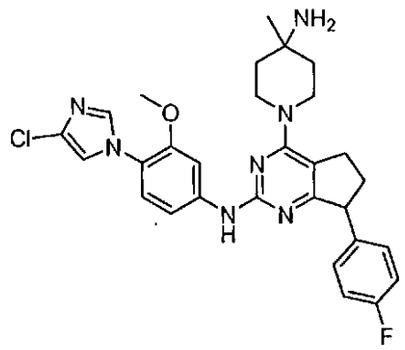


Enantiomer B of *Example 24*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 24*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 45% MeOH (0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (second to elute, enantiomer B) as a brown oil. LC-MS $(M+H)^+$ = 533.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.59 - 7.70 (2 H, m), 7.16 - 7.27 (4 H, m), 7.11 - 7.16 (1 H, m), 7.03 (2 H, t, *J*=8.70 Hz), 4.29 - 4.37 (1 H, m), 4.09 - 4.18 (1 H, m), 3.83 - 3.92 (1 H, m), 3.73 - 3.81 (1 H, m), 3.61 (3 H, s), 3.16 - 3.27 (1 H, m), 3.06 - 3.16 (1 H, m), 2.50 - 2.61 (1 H, m, *J*=12.74, 8.58, 8.58, 3.97 Hz), 1.80 - 2.10 (6 H, m), 1.42 - 1.55 (1 H, m), 0.97 (3 H, t, *J*=7.48 Hz). The absolute stereochemistry of *Example 24B* was not determined.

Example 25

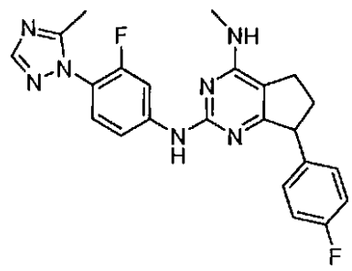
4-(4-amino-4-methylpiperidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



tert-butyl 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-4-methylpiperidin-4-ylcarbamate (*Preparation Hg*) (363 mg, 0.787 mmol) in and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (229 mg, 1.024 mmol) were combined and purified as per *Example 16* to give 4-(4-amino-4-methylpiperidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (66.5 mg, 0.100 mmol, 12.76 % yield) as a slightly yellow solid. LC-MS $(M+H)^+$ = 548.2. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.82 (1 H, d, *J*=2.14 Hz), 7.68 (1 H, s), 7.20 - 7.27 (3 H, m), 7.17 (1 H, d, *J*=8.55 Hz), 7.00 - 7.09 (3 H, m), 4.15 - 4.33 (4 H, m), 3.58 (3 H, s), 3.44 - 3.56 (2 H, m), 3.02 - 3.21 (2 H, m), 2.61 (1 H, dd, *J*=8.55, 4.27 Hz), 2.01 (1 H, dd, *J*=12.51, 8.24 Hz), 1.81 - 1.91 (4 H, m), 1.38 - 1.48 (2 H, m).

Example 26

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

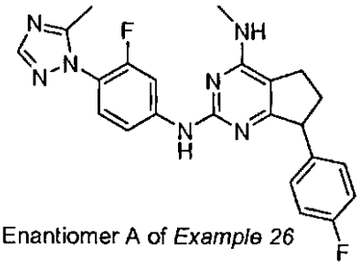


To a solution of 2-chloro-7-(4-fluorophenyl)-N-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (*Preparation Hh*) (144 mg, 0.518 mmol) in Dioxane (2469 μL) was added 3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline (*Preparation C)* (100 mg, 0.518 mmol), Tris(dibenzylideneacetone)dipalladium(0) (23.74 mg, 0.026

mmol), 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (30.0 mg, 0.052 mmol), Na2CO3 (82 mg, 0.778 mmol), and water (494 µL). The resulting mixture was heated to 110 °C and stirred overnight. The reaction was then diluted with water (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by prep HPLC (C18, 50 X 250mm, MeOH/H_2O/TFA) gave N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, TFA (170 mg, 0.311 mmol, 59.9 % yield). LC-MS $(M+H)^+$ = 434.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.06 (1 H, s), 7.96 (1 H, dd, *J*=12.51, 2.14 Hz), 7.48 - 7.59 (2 H, m), 7.26 - 7.33 (2 H, m), 7.09 - 7.18 (2 H, m), 4.46 - 4.54 (1 H, m), 3.17 (3 H, s), 2.87 - 2.97 (1 H, m), 2.74 - 2.85 (2 H, m), 2.40 (3 H, s), 2.09 - 2.21 (1 H, m).

Example 26A

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

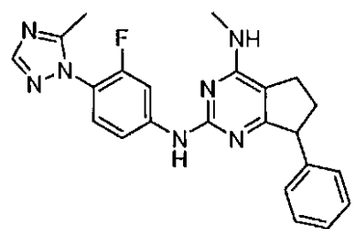


Enantiomer A of *Example 26*

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (*Example 26*) was separated by multiple chiral prep HPLC injections (OJ-H 30 x 250mm, 10 µM, EtOH/Heptane) to give N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, TFA (first to elute, enantiomer A) as a clear, colorless glass. LC-MS $(M+H)^+$ = 434.2. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.03 - 8.13 (2 H, m), 7.41 - 7.47 (2 H, m), 7.23 - 7.30 (2 H, m), 7.04 - 7.14 (2 H, m), 4.33 (1 H, t, *J*=7.93 Hz), 3.12 (3 H, s), 2.81 - 2.92 (1 H, m), 2.67 - 2.81 (2 H, m), 2.40 (3 H, s). The absolute stereochemistry of *Example 26A* was not determined.

Example 26B

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

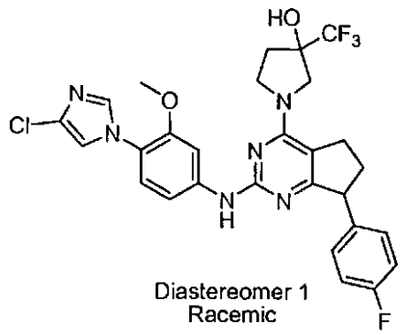


Enantiomer B of *Example 26*

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (*Example 26*) was separated by multiple chiral prep HPLC injections (OJ-H 30 x 250mm, 10 μM, EtOH/Heptane) to give N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, TFA (second to elute, enantiomer B) as a clear, colorless glass. LC-MS $(M+H)^+ = 434.2$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.03 - 8.10 (2 H, m), 7.43 - 7.48 (2 H, m), 7.24 - 7.30 (2 H, m), 7.06 - 7.14 (2 H, m), 4.37 (1 H, t, *J*=7.78 Hz), 3.14 (3 H, s), 2.83 - 2.92 (1 H, m), 2.69 - 2.80 (2 H, m), 2.40 (3 H, s), 2.05 - 2.16 (1 H, m). The absolute stereochemistry of *Example 26B* was not determined.

Example 27

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol

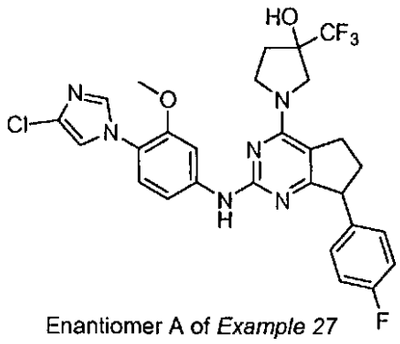


Diastereomer 1
Racemic

1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol (*Preparation Hi*) (245 mg, 0.610 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (177 mg, 0.793 mmol) were combined and purified as per *Example 16* to give 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol, TFA (first to elute, diastereomer A) (51.4 mg, 0.073 mmol) as a clear, colorless glass. LC-MS $(M+H)^+$ = 589.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.97 (1 H, s), 7.67 (1 H, s), 7.17 - 7.26 (3 H, m), 7.14 (1 H, d, *J*=8.55 Hz), 7.04 (2 H, t, *J*=8.70 Hz), 6.91 (1 H, d, *J*=8.55 Hz), 4.14 (2 H, t, *J*=8.85 Hz), 3.93 - 4.06 (3 H, m), 3.58 - 3.68 (3 H, m), 3.21 - 3.31 (1 H, m), 3.09 - 3.21 (1 H, m), 2.51 - 2.63 (1 H, m), 2.28 - 2.41 (1 H, m), 2.16 (1 H, dd, *J*=12.82, 6.41 Hz), 1.95 (1 H, dq, *J*=12.82, 8.55 Hz). The relative stereochemisty of *Example 27* was not determined.

Example 27A

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol

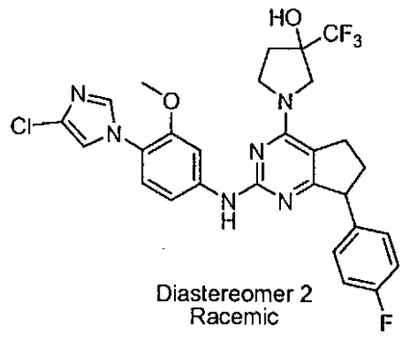


Enantiomer A of *Example 27*

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol (*Example 12*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 45% MeOH (0.1% DEA)/CO_2) to give 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol (first to elute, enantiomer A) (11.34 mg, 0.019 mmol) as an opaque glass. LC-MS $(M+H)^+$ = 589.1. The absolute stereochemistry of *Example 27A* was not determined.

Example 28

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol

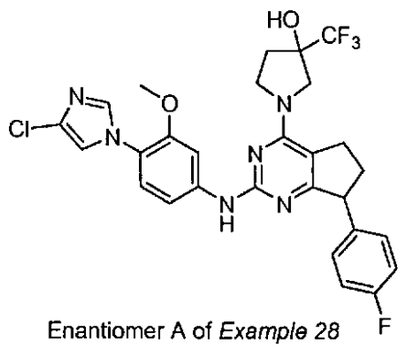


Diastereomer 2
Racemic

1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol (*Preparation Hi*) (245 mg, 0.610 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (177 mg, 0.793 mmol) were combined and purified as per *Example 16* to give 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol, TFA (second to elute, diastereomer 2) (51.1 mg, 0.073 mmol) as a white solid. LC-MS $(M+H)^+ = 589.1$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.96 (1 H, d, *J*=1.83 Hz), 7.68 (1 H, d, *J*=1.53 Hz), 7.19 - 7.27 (3 H, m), 7.15 (1 H, d, *J*=8.55 Hz), 7.04 (2 H, t, *J*=8.70 Hz), 6.95 (1 H, dd, *J*=8.55, 2.14 Hz), 4.10 - 4.21 (2 H, m), 3.95 - 4.04 (3 H, m), 3.61 - 3.69 (3 H, m), 3.27 - 3.32 (1 H, m), 3.08 - 3.20 (1 H, m), 2.57 (1 H, dddd, *J*=13.16, 8.74, 8.62, 4.58 Hz), 2.37 (1 H, dt, *J*=12.89, 9.88 Hz), 2.18 (1 H, dd, *J*=12.82, 6.41 Hz), 1.93 - 2.05 (1 H, m). The relative stereochemistry of *Example 28* was not determined.

Example 28A

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol

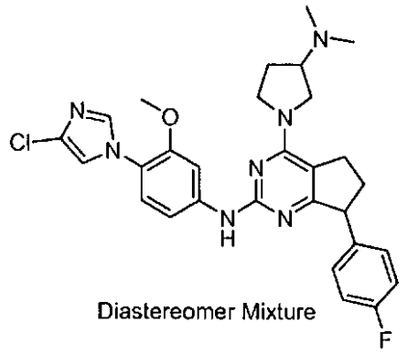


Enantiomer A of *Example 28*

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol (*Example 28*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 45% MeOH (0.1% DEA)/CO_2) to give 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol (first to elute, enantiomer A) (17.18 g, 29.2 mmol) as an opaque glass. LC-MS $(M+H)^+$ = 589.1. The absolute stereochemistry of *Example 28A* was not determined.

Example 29

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



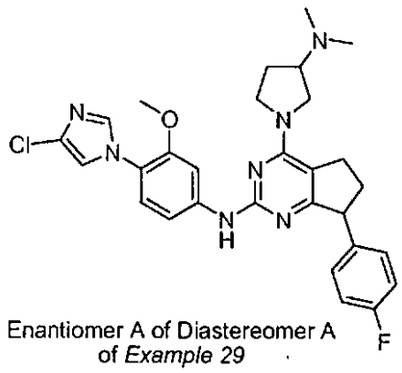
Diastereomer Mixture

1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N,N-dimethylpyrrolidin-3-amine (*Preparation Hj*) (109 mg, 0.302 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (67.6 mg, 0.302 mmol) were combined and purified as per *Example 26* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (88 mg, 0.133 mmol, 44.0 % yield) as a

scrapable tan glass. LC-MS $(M+H)^+$ = 548.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.79 (1 H, s), 7.38 - 7.44 (2 H, m), 7.29 - 7.36 (3 H, m), 7.24 - 7.29 (1 H, m), 7.11 - 7.19 (2 H, m), 4.39 - 4.51 (2 H, m), 4.28 (1 H, br. s.), 4.05 - 4.17 (2 H, m), 4.00 (1 H, d, *J*=2.44 Hz), 3.86 (3 H, s), 3.22 - 3.47 (2 H, m), 3.02 (3 H, s), 2.76 (1 H, br. s.), 2.60 (1 H, br. s.), 2.39 (1 H, br. s.), 2.13 (1 H, br. s.).

Example 29A

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



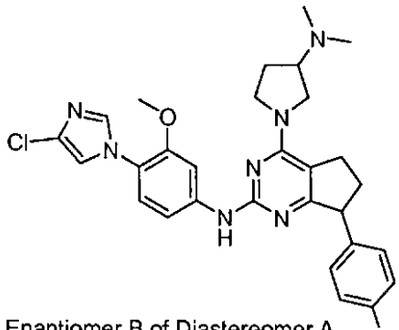
Enantiomer A of Diastereomer A of *Example 29*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 29*) was separated first by multiple chiral HPLC injections (OJ-H 30 x 250mm, 30% EtOH/Heptane) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (first to elute, diastereomer A) which was then separated by multiple chiral SFC injections (IB 30 x 250mm, 5 μM, 35% 50 :50 MeOH:MeCN/(0.1% DEA)CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (first to elute, enantiomer A) as a clear, colorless glass. LC-MS $(M+H)^+$ = 548.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.83 (1 H, d, *J*=2.14 Hz), 7.67 (1 H, d, *J*=1.22 Hz), 7.18 - 7.26 (3 H, m), 7.15 (1 H, d, *J*=8.55 Hz), 7.00 - 7.10 (3 H, m), 4.00 - 4.16 (3 H, m), 3.69 - 3.80 (1 H, m), 3.58 - 3.66 (3 H, m), 3.52 (1 H, t, *J*=9.31 Hz), 3.26 - 3.31 (1 H, m), 3.06 - 3.17 (1 H, m), 2.83 - 2.94 (1 H, m), 2.49 - 2.61 (1 H, m, *J*=13.08, 8.64, 8.64, 4.43 Hz), 2.35 (6 H, s), 2.21 - 2.30 (1

H, m), 1.83 - 2.03 (2 H, m), 1.33 - 1.41 (1 H, m). The absolute stereochemistry of *Example 29A* was not determined.

Example 29B

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

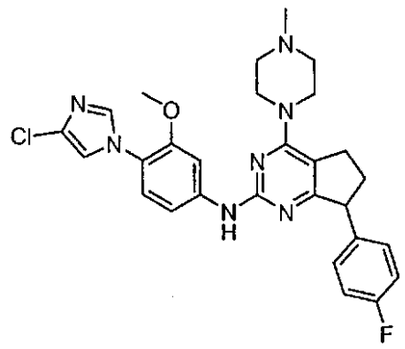


Enantiomer B of Diastereomer A of *Example 29*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 29*) was separated first by multiple chiral HPLC injections (OJ-H 30 x 250mm, 30% EtOH/Heptane) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (first to elute, diastereomer A) which was then separated by multiple chiral SFC injections (IB 30 x 250mm, 5 M, 35% 50 :50 MeOH:MeCN/(0.1% DEA)CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (second to elute, enantiomer B) as a clear, colorless glass. LC-MS $(M+H)^+$ = 548.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.85 (1 H, d, *J*=2.14 Hz), 7.67 (1 H, d, *J*=1.53 Hz), 7.17 - 7.24 (3 H, m), 7.12 - 7.17 (1 H, m), 6.99 - 7.08 (3 H, m), 3.99 - 4.18 (3 H, m), 3.68 - 3.79 (1 H, m), 3.58 (3 H, s), 3.48 - 3.56 (1 H, m), 3.21 - 3.30 (1 H, m), 3.10 - 3.21 (1 H, m), 2.81 - 2.94 (1 H, m), 2.49 - 2.62 (1 H, m), 2.36 (6 H, s), 2.21 - 2.31 (1 H, m), 1.82 - 1.99 (2 H, m). The absolute stereochemistry of *Example 29B* was not determined.

Example 30

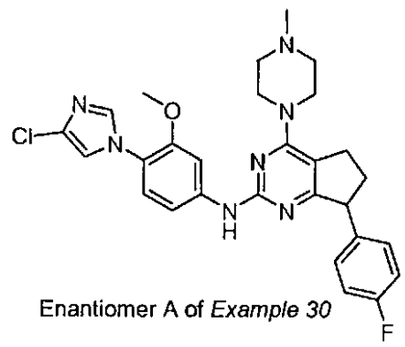
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



2-chloro-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (*Preparation Hk*) (109 mg, 0.314 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (70.3 mg, 0.314 mmol) were combined and purified as per *Example 26* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (104 mg, 0.160 mmol, 51.1 % yield) as a scrapable tan glass. LC-MS $(M+H)^+ = 534.3$. ^1H NMR (500 MHz, *MeOD*) δ ppm 7.79 (1 H, s), 7.52 (1 H, s), 7.26 - 7.36 (4 H, m), 7.08 - 7.16 (3 H, m), 4.41 (1 H, t, *J*=8.09 Hz), 3.73 (3 H, s), 3.37 - 3.63 (7 H, m), 3.09 - 3.28 (3 H, m), 2.97 - 3.03 (3 H, m), 2.67 - 2.79 (1 H, m), 2.05 - 2.20 (1 H, m).

Example 30A

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

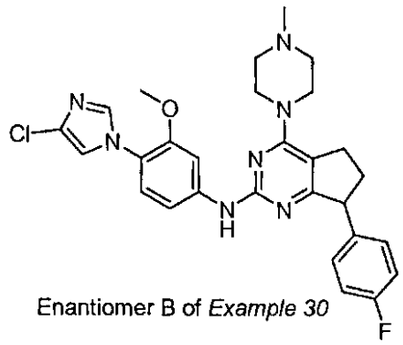


Enantiomer A of *Example 30*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 30*) was separated by multiple chiral prep HPLC injections (OJ-H 30 x 250mm, 10μM, 30% EtOH/Heptane) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (first to elute, enantiomer A) (21.6 mg, 0.033 mmol) as a scrapable tan glass. LC-MS $(M+H)^+$ = 534.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.77 (1 H, br. s.), 7.69 (1 H, s), 7.23 - 7.31 (3 H, m), 7.21 (1 H, d, *J*=8.55 Hz), 6.99 - 7.15 (3 H, m), 4.27 (1 H, t, *J*=8.39 Hz), 3.61 - 3.78 (1 H, m), 3.56 (3 H, s), 3.38 - 3.53 (3 H, m), 3.23 - 3.38 (5 H, m), 3.03 - 3.21 (2 H, m), 2.98 (3 H, s), 2.67 (1 H, dt, *J*=8.47, 4.16 Hz), 1.99 - 2.13 (1 H, m). The absolute stereochemistry of *Example 30A* was not determined.

Example 30B

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



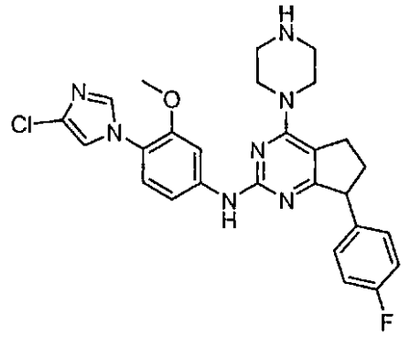
Enantiomer B of *Example 30*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (*Example 30*) was separated by multiple chiral prep HPLC injections (OJ-H 30 x 250mm, 10μM, 30% EtOH/Heptane) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (second to elute, enantiomer B) (21.6 mg, 0.033 mmol) as a scrapable tan glass. LC-MS $(M+H)^+$ = 534.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.81 (1 H, d, *J*=2.14 Hz), 7.68 (1 H, d, *J*=1.53 Hz), 7.22 - 7.29 (3 H, m), 7.16 - 7.21 (1 H, m), 7.00 - 7.11 (3 H, m), 4.24 (1 H, t, *J*=8.55 Hz), 3.57 - 3.70 (1 H, m), 3.53 (3 H, s), 3.46 (3 H, br. s.), 3.27 -

3.36 (5 H, m), 3.02 - 3.18 (2 H, m), 2.98 (3 H, s), 2.60 - 2.72 (1 H, m), 2.00 - 2.10 (1 H, m). The absolute stereochemistry of *Example 30B* was not determined.

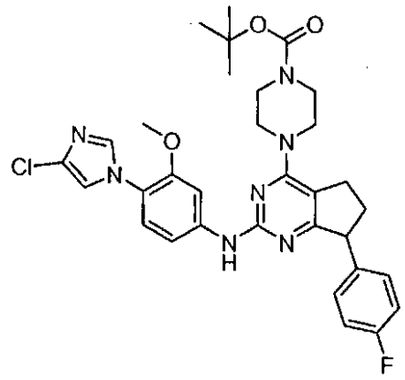
Example 31

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(piperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



Intermediate 31-1

tert-butyl 4-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazine-1-carboxylate



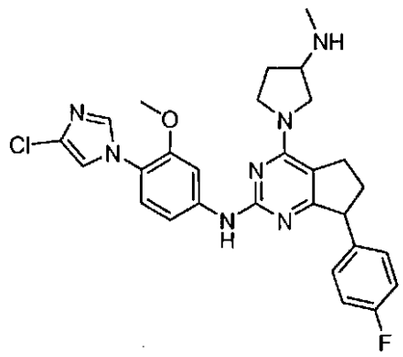
tert-butyl 4-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazine-1-carboxylate (*Preparation HI*) (117 mg, 0.270 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (60.4 mg, 0.270 mmol) were combined as per *Example 26* to give tert-butyl 4-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazine-1-carboxylate (104 mg, 0.168 mmol, 62.1 % yield) crude without purification. LC-MS $(M+H)^+ = 620.4$.

Example 31

To a solution of tert-butyl 4-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazine-1-carboxylate (*Intermediate 31-1*) (167 mg, 0.270 mmol) in DCM (5 mL) was added TFA (500 µL, 6.49 mmol). The reaction mixture was stirred at RT for 1 h. The mixture was then concentrated *in vacuo*. Purification by prep HPLC (Waters Sunfire C18, 50 X 250mm, MeOH/H_2O/TFA) gave N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(piperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (39 mg, 0.062 mmol, 22.78 % yield) as a brown oil. LC-MS $(M+H)^+$ = 520.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.83 (1 H, br. s.), 7.28 - 7.46 (5 H, m), 7.08 - 7.21 (3 H, m), 4.41 - 4.53 (1 H, m), 4.18 - 4.28 (4 H, m), 3.80 (3 H, s), 3.44 (5 H, d, *J*=4.27 Hz), 3.24 - 3.31 (1 H, m), 3.12 - 3.23 (1 H, m), 2.69 - 2.82 (1 H, m), 2.06 - 2.22 (1 H, m).

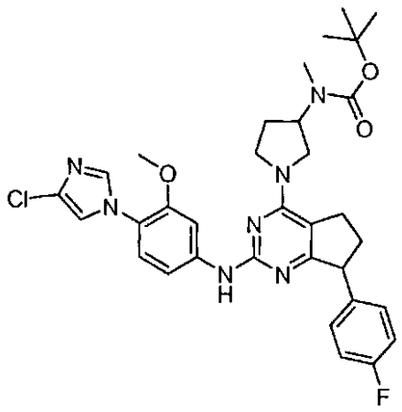
Example 32

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(3-(methylamino)pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



Intermediate 32-1

tert-butyl 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)pyrrolidin-3-yl(methyl)carbamate



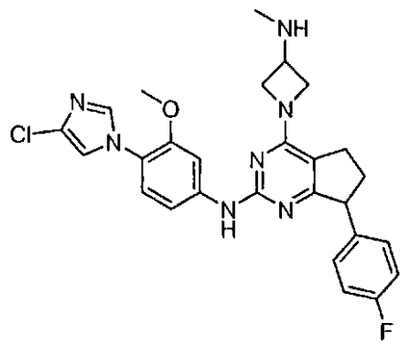
tert-butyl 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)pyrrolidin-3-yl(methyl)carbamate (*Preparation Hm*) (148 mg, 0.331 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (74.1 mg, 0.331 mmol) were combined as per *Example 26* to give the crude tert-butyl 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)pyrrolidin-3-yl(methyl)carbamate (104 mg, 0.164 mmol, 49.5 % yield) which was used without further purification. LC-MS $(M+H)^+$ = 634.4.

Example 32

tert-butyl 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)pyrrolidin-3-yl(methyl)carbamate (Intermediate 32-1) (210 mg, 0.331 mmol) was deprotected and purified as per *Example 31* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(3-(methylamino)pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (50 mg, 0.077 mmol, 23.31 % yield) as a brown oil. LC-MS $(M+H)^+$ = 534.4. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.43 (1 H, s), 7.40 (1 H, d, *J*=8.55 Hz), 7.29 - 7.35 (3 H, m), 7.24 (1 H, dt, *J*=8.62, 2.25 Hz), 7.16 (2 H, t, *J*=8.09 Hz), 4.47 (1 H, br. s.), 4.23 - 4.35 (1 H, m), 4.12 (3 H, br. s.), 4.02 (1 H, br. s.), 3.84 - 3.91 (3 H, m), 3.18 - 3.49 (2 H, m), 2.84 (3 H, s), 2.68 - 2.81 (1 H, m), 2.56 (1 H, br. s.), 2.35 (1 H, br. s.), 2.07 - 2.22 (1 H, m).

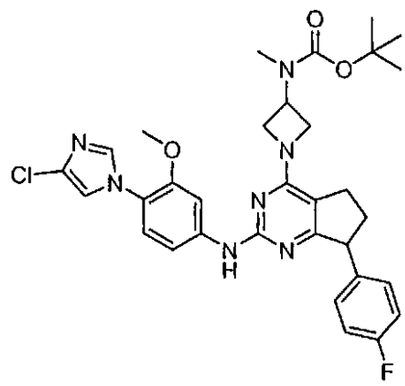
Example 33

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(3-(methylamino)azetidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



Intermediate 33-1

tert-butyl 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)azetidin-3-yl(methyl)carbamate



tert-butyl 1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)azetidin-3-yl(methyl)carbamate (*Preparation Hn*) (147 mg, 0.340 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (76 mg, 0.340 mmol) were combined as per *Example 26* to give the crude tert-butyl 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)azetidin-3-yl(methyl)carbamate (104 mg, 0.168 mmol, 49.4 % yield) which was used without further purification. LC-MS $(M+H)^+ = 620.4$.

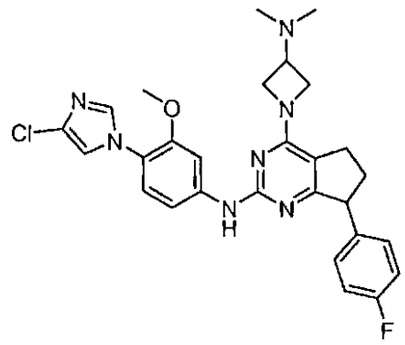
Example 33

tert-butyl 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)azetidin-3-yl(methyl)carbamate (*Intermediate 33-1*) (211 mg, 0.340 mmol) was deprotected and purified as per *Example 31* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-

7-(4-fluorophenyl)-4-(3-(methylamino)azetidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (126 mg, 0.199 mmol, 58.5 % yield) as a slightly yellow oil. LC-MS $(M+H)^+$ = 520.4. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.80 (1 H, s), 7.55 (1 H, d, *J*=2.14 Hz), 7.31 - 7.40 (2 H, m), 7.26 - 7.31 (2 H, m), 7.09 - 7.20 (3 H, m), 4.64 (2 H, br. s.), 4.46 (1 H, t, *J*=7.93 Hz), 4.21 - 4.36 (1 H, m), 3.87 (3 H, s), 3.37 (2 H, s), 3.11 - 3.21 (1 H, m), 3.04 (1 H, t, *J*=14.95 Hz), 2.80 - 2.84 (3 H, m), 2.68 - 2.80 (1 H, m), 2.14 (1 H, dddd, *J*=13.28, 8.85, 6.56, 6.41 Hz).

Example 34

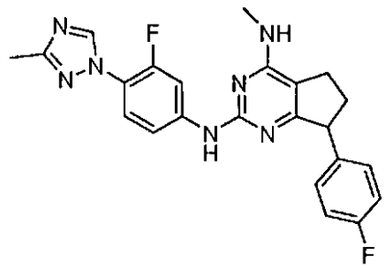
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)azetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



1-(2-chloro-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N,N-dimethylazetidin-3-amine (*Preparation Ho*) (146 mg, 0.421 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (94 mg, 0.421 mmol) were combined and purified as per *Example 26* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)azetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (104 mg, 0.160 mmol, 38.1 % yield) as a slightly brown gum. LC-MS $(M+H)^+$ = 534.4. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.82 (1 H, d, *J*=1.53 Hz), 7.48 (1 H, d, *J*=2.14 Hz), 7.39 (1 H, d, *J*=8.55 Hz), 7.35 (1 H, d, *J*=1.53 Hz), 7.29 - 7.33 (2 H, m), 7.21 (1 H, dd, *J*=8.55, 2.14 Hz), 7.11 - 7.18 (2 H, m), 4.83 (4 H, br. s.), 4.43 - 4.51 (1 H, m), 4.30 - 4.37 (1 H, m), 3.88 (3 H, s), 3.12 - 3.22 (1 H, m), 3.04 (1 H, d, *J*=6.10 Hz), 2.99 (6 H, s), 2.72 - 2.84 (1 H, m, *J*=13.47, 8.98, 8.98, 4.58 Hz), 2.14 (1 H, dddd, *J*=13.16, 8.96, 6.56, 6.41 Hz).

Example 35

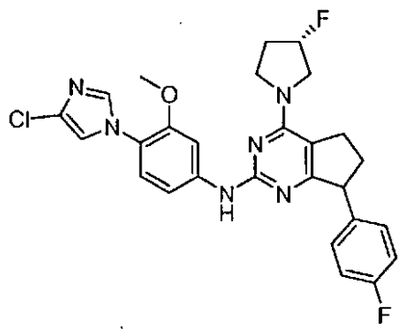
N^2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



2-chloro-7-(4-fluorophenyl)-N-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (*Preparation Hh*) (164 mg, 0.591 mmol) and 3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline (*Preparation B*) (113 mg, 0.591 mmol) were combined and purified as per *Example 26* to give N^2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, TFA (104 mg, 0.190 mmol, 32.2 % yield) as a white solid. LC-MS $(M+H)^+$ = 434.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.75 (1 H, d, *J*=2.44 Hz), 7.94 (1 H, dd, *J*=13.28, 2.29 Hz), 7.79 (1 H, t, *J*=8.70 Hz), 7.48 (1 H, dt, *J*=8.85, 1.22 Hz), 7.27 - 7.35 (2 H, m), 7.10 - 7.19 (2 H, m), 4.51 (1 H, d, *J*=2.44 Hz), 3.18 (3 H, s), 2.89 - 2.98 (1 H, m), 2.74 - 2.87 (2 H, m), 2.46 (3 H, s), 2.09 - 2.23 (1 H, m).

Example 36

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



Diasteriomer A

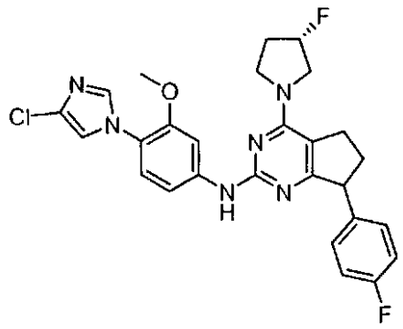
To a solution of 2-chloro-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine (Preparation Hp1)(30.5 mg, 0.091 mmol) and 4-(4-

chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A)(26.4 mg, 0.118 mmol) in THF (272 µL) was added AcOH (272 µL). The solution was heated at 100 °C overnight.

Removed solvent and took residue up in MeOH. Purified by PREP HPLC: (50 X 250 mm HPLC Sunfire C18 10µm 0 to 100% A:B over 40 min, 10 min at 100%B (A is 90:10:0.1 water:MeOH:TFA; B is 90:10:0.1 MeOH:water:TFA)). Speedvac'd appropriate fractions to afford N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine.LC–MS $(M+H)^+ = 523.2$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.74 (1 H, d, *J*=2.14 Hz), 7.49 (1 H, d, *J*=1.53 Hz), 7.12 - 7.19 (2 H, m), 7.05 (1 H, d, *J*=8.24 Hz), 6.95 - 7.01 (4 H, m), 6.84 (1 H, dd, *J*=8.55, 2.44 Hz), 5.35 (1 H, td, *J*=52.87, 3.17 Hz), 4.07 - 4.17 (2 H, m), 4.04 (1 H, t, *J*=9.61 Hz), 3.80 - 3.94 (2 H, m), 3.58 (3 H, s), 3.25 (1 H, ddd, *J*=14.19, 9.00, 4.58 Hz), 3.05 - 3.14 (1 H, m), 2.55 (1 H, dddd, *J*=13.24, 8.74, 8.55, 4.58 Hz), 2.32 - 2.43 (1 H, m), 2.03 - 2.19 (1 H, m), 1.93 - 2.02 (1 H, m).

Example 37

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



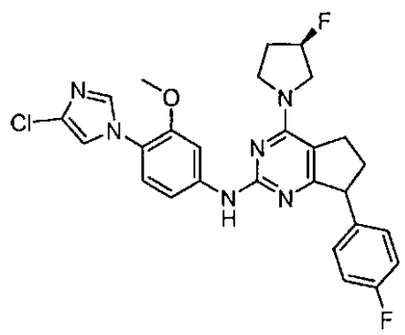
Diastereomer B

The method of Example 36 was used to combine Preparation Hp2 and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to afford N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine.LC–MS $(M+H)^+ = 523.2$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.76 (1 H, d, *J*=1.83 Hz), 7.48 (1 H, s), 7.16 (2 H, dd, *J*=8.24, 5.49

Hz), 6.97 - 7.06 (4 H, m), 6.92 (1 H, s), 6.80 (1 H, dd, *J*=8.39, 1.98 Hz), 5.27 - 5.42 (1 H, m), 4.00 - 4.17 (3 H, m), 3.80 - 3.94 (2 H, m), 3.53 (3 H, s), 3.19 - 3.26 (1 H, m), 3.08 - 3.17 (1 H, m), 2.52 - 2.61 (1 H, m), 2.32 - 2.43 (1 H, m), 2.02 - 2.18 (1 H, m), 1.94 (1 H, dq, *J*=12.97, 8.60 Hz).

Example 38

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

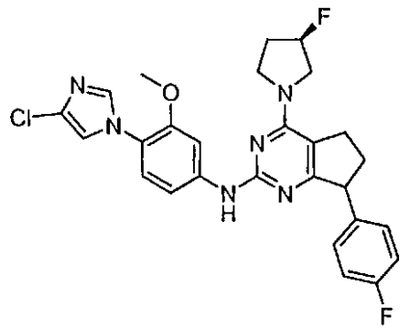


Diasteriomeric mixture

The method of Example 36 was used to combine Preparation Hq and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to afford *N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine* as a mixture of diasteriomers. *LC*–MS $(M+H)^+ = 523.2$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.87 (1 H, s), 7.46 - 7.57 (1 H, m), 7.36 - 7.43 (2 H, m), 7.30 - 7.36 (2 H, m), 7.24 - 7.30 (1 H, m), 7.11 - 7.18 (2 H, m), 5.34 - 5.57 (1 H, m), 4.33 - 4.52 (2 H, m), 4.07 - 4.26 (2 H, m), 3.93 - 4.01 (1 H, m), 3.90 (3 H, s), 3.39 - 3.50 (1 H, m), 3.23 - 3.31 (1 H, m), 2.67 - 2.80 (1 H, m), 2.21 - 2.54 (2 H, m), 2.07 - 2.18 (1 H, m).

Examples 38A and 38B

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



Individual diasteriomers

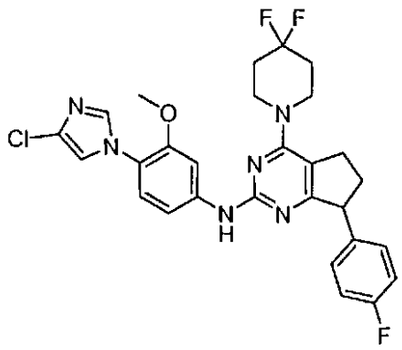
The method of Example 36 was used to combine Preparation Hq and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to afford a mixture of two diasteriomers. After preparative chiral chromatography (25% MeOH, 0.1% DEA; OD-H chiral 30 X 250 nm column), the two diasteriomers were isolated.

38A: LC–MS $(M+H)^+ = 523.2$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.84 (1 H, d, *J*=2.14 Hz), 7.68 (1 H, d, *J*=1.53 Hz), 7.19 - 7.24 (3 H, m), 7.16 (1 H, d, *J*=8.55 Hz), 6.99 - 7.09 (3 H, m), 5.29 - 5.45 (1 H, m), 4.05 - 4.17 (3 H, m), 3.80 - 3.99 (2 H, m), 3.64 (3 H, s), 3.13 (1 H, dt, *J*=14.65, 7.32 Hz), 2.51 - 2.61 (1 H, m, *J*=13.12, 8.70, 8.70, 4.58 Hz), 2.28 - 2.38 (1 H, m), 2.09 - 2.27 (1 H, m), 1.98 (1 H, dddd, *J*=13.20, 8.62, 6.87, 6.71 Hz).

38B: LC–MS $(M+H)^+ = 523.2$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.86 (1 H, d, *J*=2.14 Hz), 7.67 (1 H, s), 7.18 - 7.24 (3 H, m), 7.15 (1 H, d, *J*=8.55 Hz), 7.00 - 7.07 (3 H, m), 5.29 - 5.45 (1 H, m), 4.03 - 4.18 (3 H, m), 3.80 - 4.00 (2 H, m), 3.60 (3 H, s), 3.23 - 3.31 (1 H, m), 3.13 - 3.21 (1 H, m), 2.52 - 2.61 (1 H, m), 2.28 - 2.39 (1 H, m), 2.07 - 2.26 (1 H, m), 1.88 - 1.99 (1 H, m).

Example 39

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(4,4-difluoropiperidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

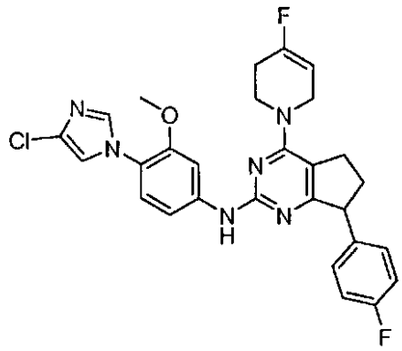


The method of Example 36 was used to combine Preparation Hr and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to afford N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(4,4-difluoropiperidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (Example 39).LC–MS $(M+H)^+$ = 555.0. ^1H NMR (500 MHz, *MeOD*) δ ppm 7.68 (1 H, d, *J*=1.83 Hz), 7.55 - 7.59 (2 H, m), 7.18 (2 H, dd, *J*=8.55, 5.49 Hz), 7.07 - 7.13 (2 H, m), 6.95 - 7.03 (3 H, m), 4.16 (1 H, t, *J*=8.39 Hz), 3.90 (4 H, t, *J*=5.34 Hz), 3.57 (3 H, s), 2.97 - 3.13 (2 H, m), 2.56 - 2.66 (1 H, m, *J*=12.78, 8.49, 8.49, 3.81 Hz), 1.95 - 2.14 (5 H, m).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 39A and 39B, which had identical spectral data.

Example 40

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(4-fluoro-5,6-dihydropyridin-1(2H)-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



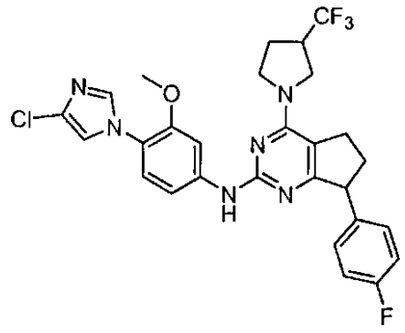
The method of Example 36 was used to combine Preparation Hs and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to afford N-(4-(4-chloro-1H-

imidazol-1-yl)-3-methoxyphenyl)-4-(4-fluoro-5,6-dihydropyridin-1(2H)-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (Example 40).LC–MS $(M+H)^+$ = 535.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.72 (1 H, d, *J*=1.83 Hz), 7.49 (1 H, d, *J*=1.53 Hz), 7.13 - 7.19 (2 H, m), 7.05 (1 H, d, *J*=8.55 Hz), 6.97 - 7.02 (3 H, m), 6.95 (1 H, s), 6.77 (1 H, dd, *J*=8.55, 2.14 Hz), 5.31 (1 H, dt, *J*=14.80, 2.80 Hz), 4.18 - 4.33 (2 H, m), 4.15 (1 H, t, *J*=8.55 Hz), 3.99 - 4.06 (1 H, m), 3.80 - 3.88 (1 H, m), 3.51 (3 H, s), 2.98 - 3.12 (2 H, m), 2.58 (1 H, dddd, *J*=12.63, 8.55, 8.43, 3.66 Hz), 2.37 - 2.53 (2 H, m), 1.99 (1 H, dq, *J*=12.86, 8.33 Hz).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 40A and 40B, which had identical spectral data.

Example 41

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(3-(trifluoromethyl)pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



The method of Example 36 was used to combine Preparation Ht and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to afford *N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(3-(trifluoromethyl)pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine* (Example 41).

The mixture of a pair of racemic diasteriomers were separated by chiral chromatography followed by reverse-phase chromatography to afford the individual enantiomers Examples 41A, 41B, 41C, and 41D.

41A: LC–MS $(M+H)^+$ = 573.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.84 (1 H, d, *J*=1.53 Hz), 7.49 (1 H, s), 7.15 (2 H, dd, *J*=8.39, 5.34 Hz), 7.04 (1 H, d, *J*=8.24 Hz), 6.95 - 7.02 (4 H, m), 6.72 (1 H, dd, *J*=8.39, 1.98 Hz), 4.11 (1 H, t, *J*=8.39 Hz), 3.94 - 4.08 (2

H, m), 3.78 - 3.91 (2 H, m), 3.56 (3 H, s), 3.18 - 3.27 (1 H, m), 2.97 - 3.14 (2 H, m), 2.50 - 2.62 (1 H, m, *J*=12.86, 8.60, 8.60, 4.12 Hz), 2.17 - 2.34 (2 H, m), 1.91 - 2.02 (1 H, m).

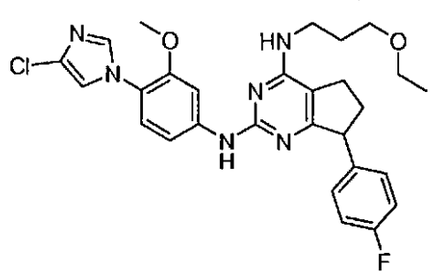
41B: LC–MS $(M+H)^+$ = 573.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.84 (1 H, br. s.), 7.48 (1 H, d, *J*=1.53 Hz), 7.11 - 7.22 (2 H, m), 6.95 - 7.09 (5 H, m), 6.69 - 6.78 (1 H, m), 4.12 (1 H, t, *J*=8.55 Hz), 3.95 - 4.08 (2 H, m), 3.77 - 3.92 (2 H, m), 3.55 (3 H, s), 3.21 (1 H, ddd, *J*=14.11, 8.93, 3.51 Hz), 2.98 - 3.16 (2 H, m), 2.51 - 2.65 (1 H, m), 2.16 - 2.35 (2 H, m), 1.90 - 2.04 (1 H, m).

41C: LC–MS $(M+H)^+$ = 573.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.84 (1 H, br. s.), 7.48 (1 H, d, *J*=1.53 Hz), 7.11 - 7.22 (2 H, m), 6.95 - 7.09 (5 H, m), 6.69 - 6.78 (1 H, m), 4.12 (1 H, t, *J*=8.55 Hz), 3.95 - 4.08 (2 H, m), 3.77 - 3.92 (2 H, m), 3.55 (3 H, s), 3.21 (1 H, ddd, *J*=14.11, 8.93, 3.51 Hz), 2.98 - 3.16 (2 H, m), 2.51 - 2.65 (1 H, m), 2.16 - 2.35 (2 H, m), 1.90 - 2.04 (1 H, m).

41D: LC–MS $(M+H)^+$ = 573.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.84 (1 H, d, *J*=1.53 Hz), 7.49 (1 H, s), 7.15 (2 H, dd, *J*=8.39, 5.34 Hz), 7.04 (1 H, d, *J*=8.24 Hz), 6.95 - 7.02 (4 H, m), 6.72 (1 H, dd, *J*=8.39, 1.98 Hz), 4.11 (1 H, t, *J*=8.39 Hz), 3.94 - 4.08 (2 H, m), 3.78 - 3.91 (2 H, m), 3.56 (3 H, s), 3.18 - 3.27 (1 H, m), 2.97 - 3.14 (2 H, m), 2.50 - 2.62 (1 H, m, *J*=12.86, 8.60, 8.60, 4.12 Hz), 2.17 - 2.34 (2 H, m), 1.91 - 2.02 (1 H, m).

Example 42

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-(3-ethoxypropyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

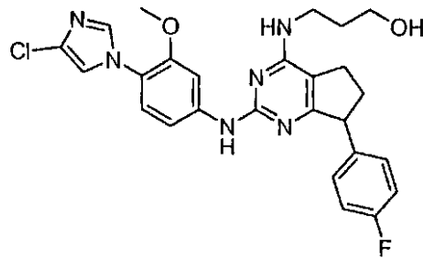


The method of Example 36 was used to combine Preparation Hu and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to afford N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-(3-ethoxypropyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (Example 42).LC–MS $(M+H)^+$ = 537.2. ^{1}H

NMR (500 MHz, $CDCl_3$) δ ppm 7.91 (1 H, d, *J*=2.14 Hz), 7.48 (1 H, d, *J*=1.53 Hz), 7.12 - 7.19 (2 H, m), 7.03 (1 H, d, *J*=8.55 Hz), 6.94 - 7.01 (4 H, m), 6.74 (1 H, dd, *J*=8.55, 2.14 Hz), 5.45 (1 H, t, *J*=4.73 Hz), 4.14 - 4.21 (1 H, m), 3.61 - 3.71 (4 H, m), 3.46 - 3.57 (5 H, m), 2.63 (2 H, dd, *J*=8.85, 6.41 Hz), 1.96 - 2.05 (1 H, m), 1.93 (2 H, quin, *J*=5.72 Hz), 1.25 (3 H, t, *J*=7.02 Hz).

Example 43

3-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-ylamino)propan-1-ol

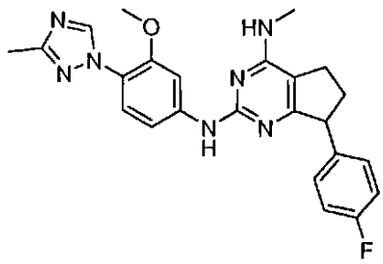


The method of Example 36 was used to combine Preparation Hv and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to afford 3-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-ylamino)propan-1-ol (Example 43).LC–MS $(M+H)^+$ = 509.3. ^1H NMR (500 MHz, *MeOD*) δ ppm 7.87 (1 H, d, *J*=2.14 Hz), 7.68 (1 H, d, *J*=1.53 Hz), 7.19 - 7.26 (3 H, m), 7.16 (1 H, d, *J*=8.55 Hz), 7.01 - 7.09 (3 H, m), 4.19 (1 H, t, *J*=8.09 Hz), 3.64 - 3.72 (4 H, m), 3.61 (3 H, s), 2.77 - 2.86 (1 H, m), 2.60 - 2.74 (2 H, m), 1.96 - 2.06 (1 H, m), 1.90 (2 H, qd, *J*=6.46, 6.26 Hz).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 43A and 43B, which had identical spectral data.

Example 44

7-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



To a solution of 2-chloro-7-(4-fluorophenyl)-N-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (Preparation Hh) (141.2 mg, 0.508 mmol) and 3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline (Preparation D) (208 mg, 1.017 mmol) in N-Methyl-2-pyrrolidinone (4067 µL) was added H_2SO_4 (43.4 µL, 0.813 mmol). The solution was heated to 100 °C. When the reaction was complete, water and $NaHCO_3$ were added. After extraction into CH_2Cl_2, the organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Applied the residue to SG and eluted with a EtOAc/Hex gradient, which yielded 7-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (Example 44).

LC–MS $(M+H)^+$ = 446.1. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 9.43 (1 H, br. s.), 8.47 (1 H, s), 7.77 (1 H, br. s.), 7.54 (1 H, d, *J*=8.85 Hz), 7.14 - 7.20 (2 H, m), 6.99 (2 H, t, *J*=8.55 Hz), 4.88 (1 H, br. s.), 4.24 - 4.31 (1 H, m), 3.71 (3 H, s), 3.15 (3 H, d, *J*=4.90 Hz), 2.73 - 2.82 (1 H, m), 2.63 - 2.72 (2 H, m), 2.46 (3 H, s), 2.06 - 2.16 (1 H, m).

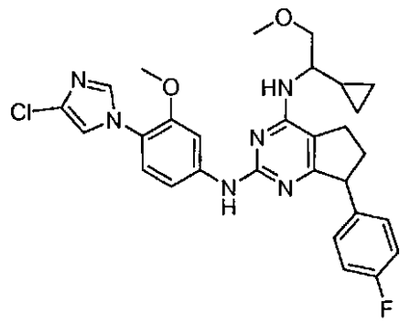
The racemic material above was separated by SFC chiral chromatography to obtain the individual enantiomers (Examples 44A and 44B). SFC Method: Chiralpak OJ-H (30 x 150 mm), 30 % methanol (0.1% diethylamine) in CO_2, 100 bar, flow rate 50 mL/min for 12 min, absorbance 268 nm, injection 2.0 mL of 10 mg/mL solution in methanol, t_R (peak A) = 4.7 min, t_R (peak B) 9.6 min. The absolute stereochemistry of individual enantiomers (Examples 44A and 44B) was not determined.

44A: LC-MS $(M+H)^+$ = 446.2. LC R_t 13.03 min (Waters Sunfire 4.6X150 mm 10 to 100% B in A over 15 min, 1.5 mL/min. (A is 90:10:0.1 water:MeOH:TFA; B is 90:10:0.1 MeOH:water:TFA)). 1H NMR (500 MHz, DMSO-d_6) δ ppm 9.22 (1 H, s), 8.58 (1 H, s), 8.18 (1 H, s), 7.30 (1 H, d, J=8.85 Hz), 7.22 (2 H, t, J=6.26 Hz), 7.08 - 7.16 (3 H, m), 6.93 - 6.99 (1 H, m), 4.17 (1 H, t, J=8.09 Hz), 3.63 (3 H, s), 2.97 (3 H, d, J=4.27 Hz), 2.72 - 2.81 (1 H, m), 2.53 - 2.66 (2 H, m), 2.31 (3 H, s), 1.85 - 1.95 (1 H, m). 13C NMR (126

MHz, DMSO-d_6) δ ppm 170.7, 160.7 (d, J = 241.3 Hz), 159.7, 159.6, 159.2, 151.4, 145.0, 142.9, 140.4 (d, J = 2.7 Hz), 129.8 (d, J = 7.8 Hz, 2C), 124.6, 117.9, 114.9 (d, J = 20.9 Hz, 2C), 109.6, 108.1, 101.5, 55.2, 50.4, 32.7, 27.4, 25.4, 13.5. $[\alpha]_D$ -69.13° (c 2.67, $CHCl_3$).

Example 45

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-(1-cyclopropyl-2-methoxyethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



The method of Example 7 was used to combine Preparation Hw and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to afford N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-(1-cyclopropyl-2-methoxyethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (Example 45). The mixture of a pair of racemic diasteriomers were separated by chiral chromatography followed by reverse-phase chromatography to afford the individual enantiomers Examples 45A, 45B, 45C, and 45D.

45A: LC–MS $(M+H)^+$ = 549.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.75 (1 H, br. s.), 7.40 (1 H, d, *J*=8.24 Hz), 7.22 - 7.29 (3 H, m), 7.15 - 7.21 (3 H, m), 6.99 - 7.08 (2 H, m), 5.97 (1 H, d, *J*=8.24 Hz), 4.42 - 4.50 (1 H, m), 3.84 (3 H, s), 3.78 (1 H, t, *J*=8.09 Hz), 3.63 (2 H, br. s.), 3.43 (3 H, s), 2.86 - 2.97 (1 H, m), 2.82 (2 H, t, *J*=8.55 Hz), 2.21 - 2.32 (1 H, m), 1.15 - 1.27 (1 H, m), 0.62 - 0.70 (1 H, m), 0.53 - 0.62 (1 H, m), 0.39 (1 H, ddd, *J*=9.46, 5.19, 4.88 Hz), 0.26 - 0.33 (1 H, m)

45B: LC–MS $(M+H)^+$ = 549.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.58 (1 H, br. s.), 7.40 (1 H, d, *J*=8.85 Hz), 7.22 - 7.29 (3 H, m), 7.14 - 7.20 (3 H, m), 7.04 (2 H, t, *J*=8.39 Hz), 6.02 (1 H, d, *J*=8.24 Hz), 4.45 (1 H, d, *J*=3.66 Hz), 3.84 (3 H, s), 3.71 - 3.79 (1 H, m), 3.63 (2 H, d, *J*=3.05 Hz), 3.42 (3 H, s), 2.91 (1 H, d, *J*=9.46 Hz), 2.79 (2 H, dd,

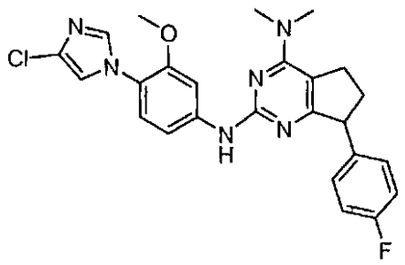
J=8.70, 5.34 Hz), 2.21 - 2.31 (1 H, m), 1.19 (1 H, dt, *J*=8.55, 4.27 Hz), 0.62 - 0.70 (1 H, m), 0.54 - 0.62 (1 H, m), 0.39 (1 H, dq, *J*=9.54, 4.86 Hz), 0.24 - 0.33 (1 H, m).

45C: LC–MS $(M+H)^+ = 549.3$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 10.75 (1 H, br. s.), 7.40 (1 H, d, *J*=8.24 Hz), 7.22 - 7.29 (3 H, m), 7.15 - 7.21 (3 H, m), 6.99 - 7.08 (2 H, m), 5.97 (1 H, d, *J*=8.24 Hz), 4.42 - 4.50 (1 H, m), 3.84 (3 H, s), 3.78 (1 H, t, *J*=8.09 Hz), 3.63 (2 H, br. s.), 3.43 (3 H, s), 2.86 - 2.97 (1 H, m), 2.82 (2 H, t, *J*=8.55 Hz), 2.21 - 2.32 (1 H, m), 1.15 - 1.27 (1 H, m), 0.62 - 0.70 (1 H, m), 0.53 - 0.62 (1 H, m), 0.39 (1 H, ddd, *J*=9.46, 5.19, 4.88 Hz), 0.26 - 0.33 (1 H, m).

45D: LC–MS $(M+H)^+ = 549.3$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 10.58 (1 H, br. s.), 7.40 (1 H, d, *J*=8.85 Hz), 7.22 - 7.29 (3 H, m), 7.14 - 7.20 (3 H, m), 7.04 (2 H, t, *J*=8.39 Hz), 6.02 (1 H, d, *J*=8.24 Hz), 4.45 (1 H, d, *J*=3.66 Hz), 3.84 (3 H, s), 3.71 - 3.79 (1 H, m), 3.63 (2 H, d, *J*=3.05 Hz), 3.42 (3 H, s), 2.91 (1 H, d, *J*=9.46 Hz), 2.79 (2 H, dd, *J*=8.70, 5.34 Hz), 2.21 - 2.31 (1 H, m), 1.19 (1 H, dt, *J*=8.55, 4.27 Hz), 0.62 - 0.70 (1 H, m), 0.54 - 0.62 (1 H, m), 0.39 (1 H, dq, *J*=9.54, 4.86 Hz), 0.24 - 0.33 (1 H, m).

Example 46

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



2-Chloro-7-(4-fluorophenyl)-*N*,*N*-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (268 mg, 0.919 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (205 mg, 0.919 mmol) in THF (1 mL) and acetic acid (1.000 mL). The reaction mixture was stirred overnight at 75°C. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (60.7 mg, 0.095 mmol, 10.36 % yield). LC–MS $(M+H)^+ = 479.4$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.64 - 11.83 (1H, m), 7.62 (1H, d, *J*=1.5 Hz), 7.39 (2H, d,

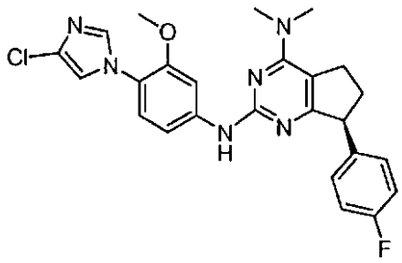
J=2.1 Hz), 7.22 (1H, d, *J*=5.2 Hz), 7.15 (1H, d, *J*=8.5 Hz), 6.96 - 7.07 (3H, m), 5.29 (1H, s), 4.29 - 4.38 (1H, m), 3.81 (3H, s), 3.50 - 3.57 (1H, m), 3.43 - 3.49 (1H, m), 3.31 - 3.39 (3H, m), 3.16 - 3.26 (2H, m), 3.09 - 3.14 (1H, m), 2.58 - 2.72 (1H, m), 2.52 - 2.58 (1H, m), 2.13 - 2.25 (1H, m).

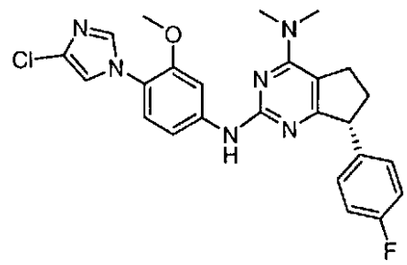
Example 46A & 46B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

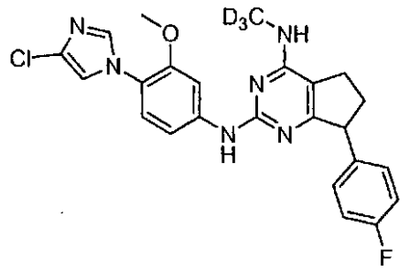




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (*Example 46*) was purified using chiral SFC to afford peak A (*Example 46A*) and peak B (*Example 46B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 35 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 14 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 4.3 min, t_R (peak B) 10.8 min. The absolute stereochemistry of individual enantiomers (*Examples 46A and 46B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 46*).

Example 47

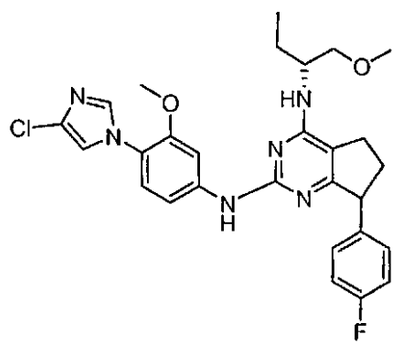
N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-trideuteromethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



A solution of 2-Chloro-7-(4-fluorophenyl)-*N*-trideuteromethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (47.5 mg, 0.169 mmol) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (37.8 mg, 0.169 mmol) in THF (1 mL) and acetic acid (1 mL) was heated at 85°C overnight. The product was purified by a reverse-phase preparative HPLC method to give N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-trideuteromethyl-6,7-dihydro-*5H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (33.3 mg, 0.057 mmol, 33.8 % yield) as brown oil. LC-MS $(M+H)^+$ = 467.9. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.21 (1H, s), 8.35 - 9.96 (1H, m), 8.20 (1H, s), 7.51 (1H, s), 7.43 (1H, d, *J*=8.5 Hz), 7.25 (1H, s), 7.22 (1H, d, *J*=8.9 Hz), 7.14 - 7.20 (2H, m), 7.01 (1H, t, *J*=8.5 Hz), 5.98 (1H, s), 4.43 (1H, d, *J*=4.6 Hz), 3.85 (3H, s), 2.88 (1H, d, *J*=9.5 Hz), 2.69 - 2.83 (2H, m), 2.20 - 2.32 (1H, m).

Example 48

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N4-((R)-1-methoxybutan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, 2 TFA



Diasteriomeric mixture

2-chloro-7-(4-fluorophenyl)-N-((R)-1-methoxybutan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (Preparation Hx) was reacted as described in Example

112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline(Preparation A) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N4-((R)-1-methoxybutan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, 2 TFA as a mixture of two diasteriomers (Example 48). LC–MS $(M+H)^+ = 537.5$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.66 (br. s., 1 H) 7.99 (s, 1 H) 7.51 (d, J=8.85 Hz, 1 H) 7.32 (dd, J=8.85, 1.83 Hz, 1 H) 7.18 - 7.30 (m, 4 H) 7.04 (td, J=8.62, 1.68 Hz, 2 H) 5.83 (t, J=9.61 Hz, 1 H) 4.43 - 4.51 (m, 1 H) 4.28 - 4.39 (m, 1 H) 3.87 (s, 3 H) 3.51 - 3.64 (m, 2 H) 3.38 - 3.49 (m, 3 H) 2.87 - 3.00 (m, 1 H) 2.75 - 2.85 (m, 2 H) 2.24 - 2.35 (m, 1 H) 1.69 - 1.87 (m, 2 H) 0.97 - 1.06 (m, 3 H).

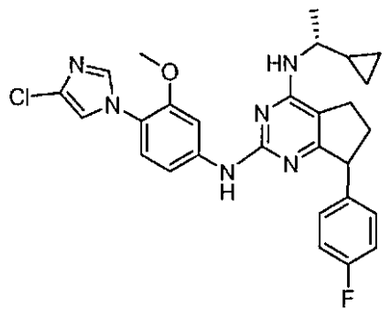
The mixture of two diasteriomers was separated by chiral chromatography to afford two diasteriomers Example 48A and 48B as free amines.

Example 48A: LC–MS $(M+H)^+ = 537.4$. ^1H NMR (500 MHz, MeOD) δ ppm 7.86 (d, J=2.14 Hz, 1 H) 7.66 (d, J=1.53 Hz, 1 H) 7.16 - 7.25 (m, 3 H) 7.10 - 7.16 (m, 1 H) 6.99 - 7.07 (m, 3 H) 4.45 - 4.53 (m, 1 H) 4.17 (t, J=8.24 Hz, 1 H) 3.61 (s, 3 H) 3.56 (dd, J=9.46, 5.80 Hz, 1 H) 3.44 - 3.51 (m, 1 H) 3.37 (d, J=7.02 Hz, 3 H) 2.76 - 2.86 (m, 1 H) 2.59 - 2.75 (m, 2 H) 1.94 - 2.04 (m, 1 H) 1.73 - 1.85 (m, 1 H) 1.54 - 1.66 (m, 1 H) 0.99 (t, J=7.48 Hz, 3 H).

Example 48B: LC–MS $(M+H)^+ = 537.4$. ^1H NMR (500 MHz, MeOD) δ ppm 7.86 (d, J=2.14 Hz, 1 H) 7.67 (d, J=1.53 Hz, 1 H) 7.18 - 7.26 (m, 3 H) 7.11 - 7.16 (m, 1 H) 6.97 - 7.08 (m, 3 H) 4.44 - 4.53 (m, 1 H) 4.17 (t, J=8.09 Hz, 1 H) 3.61 (s, 3 H) 3.55 (dd, J=9.46, 5.49 Hz, 1 H) 3.46 (dd, J=9.61, 5.65 Hz, 1 H) 3.35 - 3.41 (m, 3 H) 2.77 - 2.87 (m, 1 H) 2.67 - 2.76 (m, 1 H) 2.64 (ddd, J=12.44, 8.62, 3.66 Hz, 1 H) 1.93 - 2.07 (m, 1 H) 1.80 (ddd, J=13.50, 7.71, 5.34 Hz, 1 H) 1.56 - 1.68 (m, 1 H) 1.01 (t, J=7.48 Hz, 3 H).

Example 49

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, 2 TFA



Diasteriomeric mixture

2-chloro-N-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (Preparation Hy) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline(Preparation A) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, 2 TFA as a mixture of two diasteriomers (Example 49). LC–MS $(M+H)^+ = 519.5$. ^1H ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.81 (s, 1 H) 7.85 (s, 1 H) 7.38 - 7.48 (m, 2 H) 7.28 (s, 1 H) 7.26 (ddd, J=8.77, 5.11, 1.98 Hz, 1 H) 7.12 (d, J=1.22 Hz, 1 H) 7.04 (td, J=8.62, 1.68 Hz, 2 H) 5.65 (t, J=7.02 Hz, 1 H) 4.41 - 4.52 (m, 1 H) 3.73 - 3.88 (m, 4 H) 2.88 - 3.01 (m, 1 H) 2.71 - 2.88 (m, 2 H) 2.25 - 2.39 (m, 1 H) 1.40 (dd, J=6.56, 4.12 Hz, 3 H) 0.99 - 1.14 (m, 1 H) 0.65 - 0.75 (m, 1 H) 0.53 - 0.64 (m, 1 H) 0.39 (tt, J=9.80, 5.00 Hz, 1 H) 0.27 - 0.35 (m, 1 H).

The mixture of two diasteriomers was separated by chiral chromatography to afford two diasteriomers Example 49A and 49B as free amines.

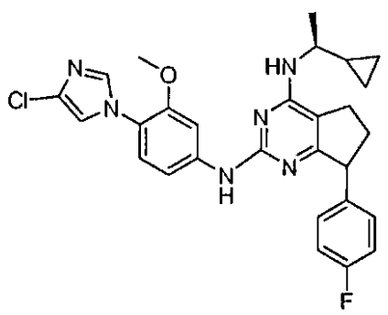
Example 49A: LC–MS $(M+H)^+ = 519.3$. ^1H NMR (500 MHz, MeOD) δ ppm 7.87 (d, J=2.14 Hz, 1 H) 7.66 (d, J=1.53 Hz, 1 H) 7.17 - 7.28 (m, 3 H) 7.08 - 7.17 (m, 1 H) 6.90 - 7.08 (m, 3 H) 4.15 (t, J=8.24 Hz, 1 H) 3.78 - 3.92 (m, 1 H) 3.59 (s, 3 H) 2.75 - 2.85 (m, 1 H) 2.59 - 2.74 (m, 2 H) 1.33 (d, J=6.71 Hz, 3 H) 1.00 - 1.14 (m, 1 H) 0.82 - 1.00 (m, 1 H) 0.39 - 0.59 (m, 3 H) 0.26 (dt, J=9.38, 4.62 Hz, 1 H).

Example 49B: LC–MS $(M+H)^+ = 519.3$. ^1H NMR (500 MHz, MeOD) δ ppm 7.87 (d, J=2.14 Hz, 1 H) 7.66 (d, J=1.53 Hz, 1 H) 7.15 - 7.25 (m, 3 H) 7.13 (d, J=8.55 Hz, 1 H) 7.02 (t, J=8.85 Hz, 2 H) 6.98 (dd, J=8.55, 2.14 Hz, 1 H) 4.16 (t, J=8.09 Hz, 1 H) 3.82 - 3.98 (m, 1 H) 3.60 (s, 3 H) 2.78 - 2.87 (m, 1 H) 2.55 - 2.75 (m, 2 H) 1.91 - 2.04 (m, 1 H)

1.35 (d, J=6.71 Hz, 3 H) 0.79 - 0.98 (m, 1 H) 0.55 (td, J=8.70, 4.27 Hz, 1 H) 0.45 - 0.51 (m, 1 H) 0.32 - 0.43 (m, J=9.65, 5.04, 4.86, 4.86 Hz, 1 H) 0.16 - 0.29 (m, 1 H).

Example 50

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((S)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, TFA



Diasteriomeric mixture

2-chloro-N-((S)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (Preparation Hz) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline(Preparation A) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((S)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, TFA as a mixture of two diasteriomers (Example 50). LC–MS $(M+H)^+$ = 519.5. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.84 (s, 1 H) 7.80 (s, 1 H) 7.43 (s, 1 H) 7.41 (d, J=8.85 Hz, 1 H) 7.28 (s, 1 H) 7.26 (ddd, J=8.70, 5.19, 1.98 Hz, 1 H) 7.19 (d, J=8.55 Hz, 1 H) 7.11 (s, 1 H) 7.04 (td, J=8.62, 1.68 Hz, 2 H) 5.66 (t, J=6.87 Hz, 1 H) 4.40 - 4.52 (m, 1 H) 3.72 - 3.87 (m, 4 H) 2.87 - 3.07 (m, 1 H) 2.67 - 2.86 (m, 2 H) 2.26 - 2.40 (m, 1 H) 1.40 (dd, J=6.56, 4.12 Hz, 3 H) 1.03 - 1.15 (m, 1 H) 0.56 - 0.76 (m, 2 H) 0.29 - 0.49 (m, 2 H).

The mixture of two diasteriomers was separated by chiral chromatography to afford two diasteriomers Example 50A and 50B as free amines.

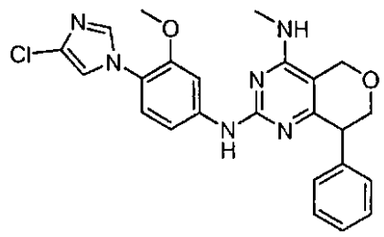
Example 50A: LC–MS $(M+H)^+$ = 519.3. ^1H NMR (500 MHz, MeOD) δ ppm 7.88 (d, J=2.14 Hz, 1 H) 7.67 (d, J=1.53 Hz, 1 H) 7.17 - 7.24 (m, 3 H) 7.14 (d, J=8.55 Hz, 1 H) 6.90 - 7.08 (m, 3 H) 4.18 (t, J=8.09 Hz, 1 H) 3.88 (dd, J=8.09, 6.56 Hz, 1 H) 3.61 (s, 3 H) 2.77 - 2.89 (m, 1 H) 2.58 - 2.77 (m, 2 H) 1.90 - 2.05 (m, 1 H) 1.35 (d, J=6.71 Hz, 3 H)

1.07 (dt, J=8.24, 4.88 Hz, 1 H) 0.51 - 0.57 (m, 1 H) 0.44 - 0.51 (m, 1 H) 0.40 (dd, J=9.61, 4.73 Hz, 1 H) 0.17 - 0.29 (m, 1 H).

Example 50B: LC–MS $(M+H)^+$ = 519.3. ^1H NMR (500 MHz, MeOD) δ ppm 7.87 (d, J=1.83 Hz, 1 H) 7.67 (s, 1 H) 7.20 - 7.27 (m, 3 H) 7.14 (d, J=8.55 Hz, 1 H) 6.93 - 7.08 (m, 3 H) 4.17 (t, J=8.24 Hz, 1 H) 3.75 - 3.93 (m, 1 H) 3.61 (s, 3 H) 2.76 - 2.88 (m, 1 H) 2.54 - 2.73 (m, 2 H) 1.89 - 2.08 (m, 1 H) 1.34 (d, J=6.71 Hz, 3 H) 0.99 - 1.12 (m, 1 H) 0.54 - 0.63 (m, 1 H) 0.46 - 0.54 (m, 1 H) 0.43 (dd, J=9.61, 4.73 Hz, 1 H) 0.18 - 0.28 (m, 1 H).

Example 51

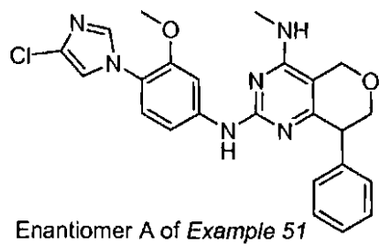
N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



2-chloro-N-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (*Preparation Ia*) (125 mg, 0.453 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (101 mg, 0.453 mmol) were combined and purified as per *Example 26* to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (178 mg, 0.309 mmol, 68.1 % yield) as a slightly yellow, scrapable glass. LC-MS $(M+H)^+$ = 463.2. ^1H NMR (500 MHz, *MeOD*) δ ppm 7.81 (1 H, s), 7.62 (1 H, s), 7.32 - 7.47 (7 H, m), 7.14 (1 H, dd, *J*=8.55, 2.14 Hz), 4.54 - 4.72 (2 H, m), 4.19 (1 H, dd, *J*=11.44, 4.73 Hz), 4.10 (1 H, t, *J*=4.43 Hz), 3.94 (1 H, dd, *J*=11.44, 4.73 Hz), 3.86 (3 H, s), 3.15 - 3.19 (3 H, m).

Example 51A

N^2-(4-(4-chloro-1H-imiazol-1-yl)-3-methoxyphenyl)-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

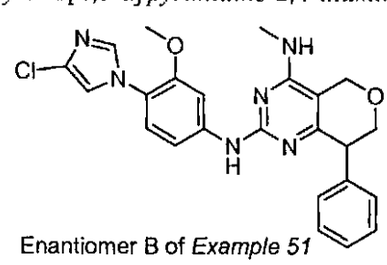


Enantiomer A of *Example 51*

N^2-(4-(4-chloro-1H-imiazol-1-yl)-3-methoxyphenyl)-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine *Example 51* was separated by multiple chiral prep HPLC injections (OJ-H 30 x 250mm, 10μM, EtOH/Heptane) to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (first to elute, enantiomer A) (36.5 mg, 0.063 mmol) as a yellow solid. LC-MS $(M+H)^+ = 463.2$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.83 (1 H, br. s.), 7.70 (1 H, br. s.), 7.35 (2 H, t, *J*=7.32 Hz), 7.24 - 7.33 (4 H, m), 7.21 (1 H, d, *J*=8.55 Hz), 6.97 - 7.05 (1 H, m), 4.52 - 4.71 (2 H, m), 4.16 (1 H, dd, *J*=11.44, 4.73 Hz), 3.98 (1 H, br. s.), 3.87 - 3.96 (1 H, m), 3.61 (3 H, br. s.), 3.06 - 3.14 (3 H, m). The absolute stereochemistry of *Example 51A* was not determined.

Example 51B

N^2-(4-(4-chloro-1H-imiazol-1-yl)-3-methoxyphenyl)-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



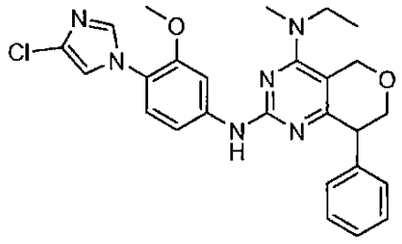
Enantiomer B of *Example 51*

N^2-(4-(4-chloro-1H-imiazol-1-yl)-3-methoxyphenyl)-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine *Example 51* was separated by multiple chiral prep HPLC injections (OJ-H 30 x 250mm, 10μM, EtOH/Heptane) to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (second to elute, enantiomer B) (30.9 mg, 0.054 mmol) as a yellow solid. LC-MS $(M+H)^+ = 463.2$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.74 (2 H, br. s.), 7.24 - 7.48 (7 H, m), 7.01 - 7.13 (1 H, m), 4.52 - 4.73 (2 H, m),

4.17 (1 H, dd, *J*=11.44, 4.73 Hz), 4.00 - 4.11 (1 H, m), 3.88 - 4.00 (1 H, m), 3.71 (3 H, br. s.), 3.12 (3 H, s). The absolute stereochemistry of *Example 51B* was not determined.

Example 52

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



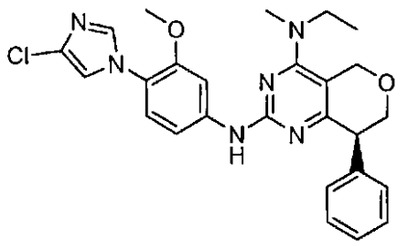
To a solution of 2-chloro-*N*-ethyl-*N*-methyl-8-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidin-4-amine (146 mg, 0.481 mmol) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (107 mg, 0.481 mmol) in THF (1.0 mL) and acetic acid (1.0 mL). The reaction mixture was stirred overnight at 75°C. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidine-2,4-diamine, TFA salt (59.9 mg, 0.092 mmol, 93 % yield). LC–MS $(M+H)^+$ = 491.4. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.77 (1H, s), 7.67 (1H, d, *J*=1.5 Hz), 7.39 (1H, dd, *J*=8.5, 2.1 Hz), 7.26 - 7.35 (5H, m), 7.16 (1H, s), 7.14 (1H, s), 7.06 (1H, d, *J*=1.5 Hz), 4.75 - 4.90 (2H, m), 4.14 - 4.23 (2H, m), 3.90 (1H, d, *J*=7.0 Hz), 3.81 (3H, s), 3.62 (2H, s), 3.27 (3H, s), 1.34 (3H, t, *J*=7.2 Hz).

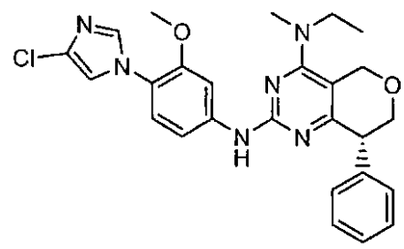
Examples 52A & 52B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

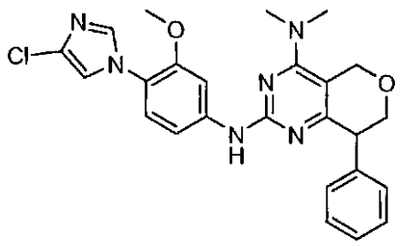




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N^4,N^4-dimethyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine (55.0 mg, 0.112 mmol) (*Example 52*) was purified using chiral SFC to afford peak A (17.2 mg, 0.035 mmol) (*Example 52A*) and peak B (18.8 mg, 0.038 mmol) (*Example 52B*). SFC Method: Chiralpak OJ-H (30 x 250 mm, 5 μM), 35 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 70 mL/min for 13 min, absorbance 268 nm, injection 5μL of 27 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 4.2 min, t_R (peak B) 8.3 min. The absolute stereochemistry of individual enantiomers (*Examples 52A and 52B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 52*).

Example 53

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



To a solution of 2-chloro-*N*,*N*-dimethyl-8-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidin-4-amine (135 mg, 0.466 mmol) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (104 mg, 0.466 mmol) in THF (1.0 mL) and acetic acid (1.0 mL). The reaction mixture was stirred overnight at 75°C. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-8-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidine-2,4-diamine, TFA salt (80.1 mg, 0.130 mmol, 96 % yield). LC–MS $(M+H)^+$ = 477.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.74 (1H, s), 7.74 (1H, d,

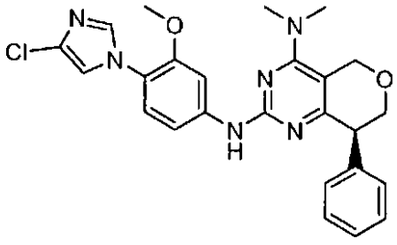
J=1.5 Hz), 7.36 (1H, s), 7.34 - 7.26 (6H, m), 7.15 (1H, d, *J*=8.2 Hz), 7.07 (1H, d, *J*=1.5 Hz), 4.83 (1H, m), 4.13 - 4.21 (1H, m), 3.81 (3H, s), 3.47 (3H, s), 3.32 (6H, s).

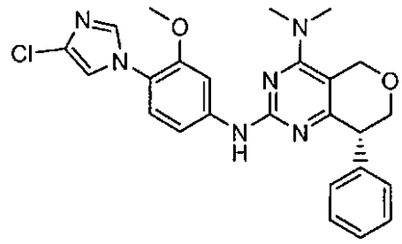
Examples 53A & 53B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

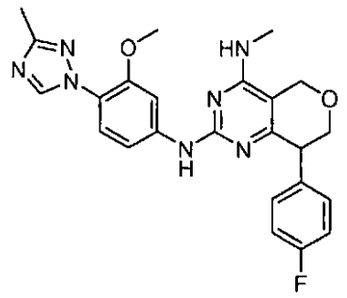




A racemic mixture of N^2-(4-(4-Chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-8-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]pyrimidine-2,4-diamine (80.1 mg, 0.130 mmol) (*Example 53*) was purified using chiral SFC to afford peak A (21.2 mg, 0.044 mmol) (*Example 53A*) and peak B (24.2 mg, 0.051 mmol) (*Example 53B*). SFC Method: Chiralpak OJ-H (30 x 250 mm, 5 μM), 35 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 70 mL/min for 13 min, absorbance 268 nm, injection 5μL of 27 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 4.5 min, t_R (peak B) 9.5 min. The absolute stereochemistry of individual enantiomers (*Examples 53A and 53B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 53*).

Example 54

8-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

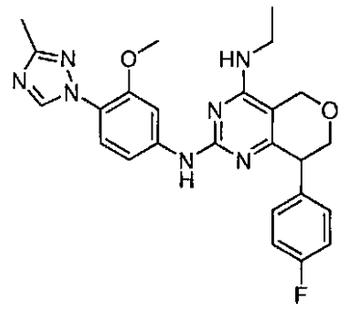


A solution of Preparation D (0.076 g, 0.38 mmol), Preparation Ja (0.11 g, 0.38 mmol), Na_2CO_3 (0.079 g, 0.75 mmol) and xantphos (0.216 g, 0.38 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.17 g, 0.18 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC to give 8-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (0.08 g, 47%) as off-white solid. LC–MS $(M+H)^+ = 462.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 8.70 (1H, s), 7.8 (1H, m), 7.5 (1H, m), 7.34 (2H, m), 7.21 (4H, m), 7.13 (1H, m), 4.60 (1H, d, *J*= 14.0 Hz), 4.46 (1H, d, *J*= 14.0 Hz), 3.83 (2H, m), 3.78 (1H, m), 3.75 (3H, s), 3.01 (3H, d, *J* = 4.0 Hz), 2.32 (3H, s,).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 54A and 54B, which had identical spectral data.

Example 55

N4-ethyl-8-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

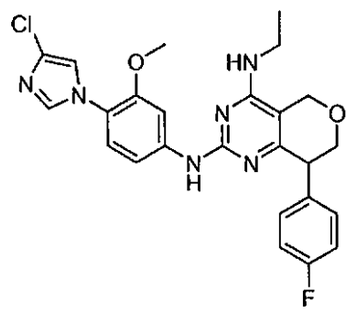


A solution of Preparation D (0.085 g, 0.40 mmol), Preparation Jb (0.16 g, 0.52 mmol), Na_2CO_3 (0.11 g, 1.0 mmol) and xantphos (0.30 g, 0.52 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.26 g, 0.26 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC to give N4-ethyl-8-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (0.90 g, 40%) as off-white solid. LC–MS $(M+H)^+$ = 476.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 8.69 (1H, s), 7.73 (1H, s), 7.48 (1H, s), 7.34 (2H, m), 7.21-7.13 (3H, m), 4.62 (1H, d, *J*= 14.0 Hz), 4.47 (1H, d, *J*= 14.0 Hz), 4.07 (2H, m), 3.92 (2H, m), 3.82 (3H, s), 3.54 (3H, m), 2.33 (3H, s), 1.22 (3H, t, *J* = 7.2.0 Hz).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 55A and 55B, which had identical spectral data.

Example 56

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

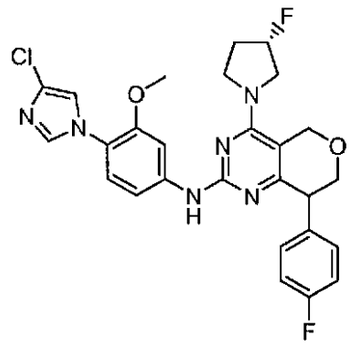


A solution of Preparation A (0.70 g, 0.32 mmol), Preparation Jb (0.11 g, 0.35 mmol), Na_2CO_3 (0.07 g, 0.71 mmol) and xantphos (0.20 g, 0.35 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.18 g, 0.17 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (0.70 g, 40%) as off-white solid. LC–MS $(M-H)^+ = 495.2$. ^1H NMR (400 MHz, -DMSO-*d6*): δ ppm 9.91 (1H, s*b*), 7.83 (1H, m), 7.69 (1H, s), 7.39 (1H, s), 7.22 (4H, m), 7.10 (4H, m), 4.65 (1H, d, *J*= 14.0 Hz), 4.48 (1H, d, *J*= 14.0 Hz), 4.04 (1H, m), 3.83 (1H, m), 3.74 (3H, s), 3.54 (2H, m), 1.22 (3H, t, *J* = 7.2.0 Hz).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 56A and 56B, which had identical spectral data.

Example 57A

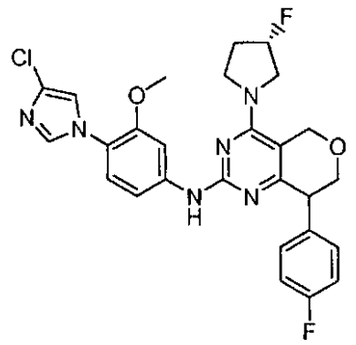
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine



A solution of Preparation A (0.051 g, 0.23 mmol), Preparation Jc1 (0.09 g, 0.25 mmol), Na_2CO_3 (0.050 g, 0.51 mmol) and xantphos (0.148 g, 0.25 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.132 g, 0.12 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 10% methanol in dichloromethane as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine (0.030g, 18%) as an off-white solid.
LC–MS $(M+H)^+$ = 539.0. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.19 (1H, s), 7.89 (1H, s), 7.74 (1H, s), 7.43 (1H, s), 7.27 (2H, m), 7.18-7.11 (4H, m), 5.42 (1H, m), 5.04 (1H, d, *J* = 13.6 Hz), 4.81 (1H, d, *J* = 13.6 Hz), 4.13 (2H, m), 3.91-3.77 (4H, m), 3.66 (1H, m), 3.58 (3H, s), 2.23 (2H, m).

Example 57B

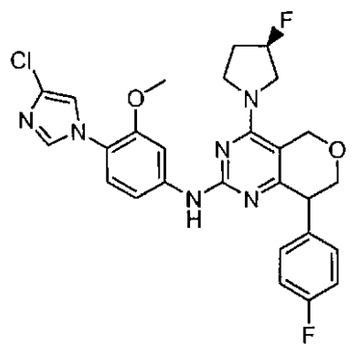
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine



A solution of Preparation A (0.062 g, 0.28 mmol), Preparation Jc2 (0.110 g, 0.31 mmol), Na_2CO_3 (0.066 g, 0.62 mmol) and xantphos (0.181 g, 0.31 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.162 g, 0.15 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 8% methanol in dichloromethane as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine (0.031g, 19%) as an off-white solid. LC–MS $(M+H)^+$ = 539.0. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.21 (1H, s), 7.87 (1H, s), 7.74 (1H, s), 7.43 (1H, s), 7.24 (2H, m), 7.16-7.09 (4H, m), 5.36 (1H, m), 4.95 (2H, m), 5.05 (1H, m), 3.95-3.80 (2H, m), 3.78-3.70 (4H, m), 3.6 (3H, s), 2.22 (2H, m).

Example 58A

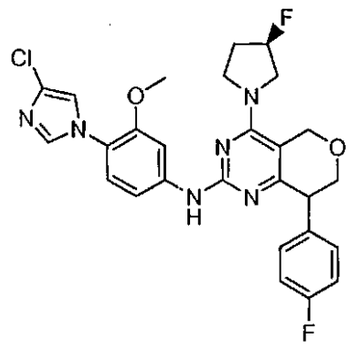
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine



A solution of Preparation A (0.057 g, 0.28 mmol), Preparation Jd1 (0.10 g, 0.28 mmol), Na_2CO_3 (0.06 g, 0.56 mmol) and xantphos (0.16 g, 0.28 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.14 g, 0.14 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 10% methanol in dichloromethane as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine (0.040 g, 27%)as off-white solid. LC–MS $(M+H)^+$ = 539.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.45 (1H, s*b*), 7.79 (1H, s), 7.71 (1H, m), 7.47 (1H, s), 7.34-7.26 (2H, m), 7.21-7.12 (4H, m), 5.41 (1H, m), 5.07 (1H, d, J = 14.0 Hz), 4.85 (1H, d, J = 14.0 Hz), 4.53-4.38 (2H, m), 4.32-4.30 (4H, m), 3.89-3.64 (4H, m), 2.50-2.58 (2H, m).

Example 58B

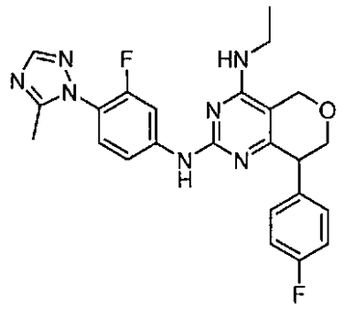
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine



A solution of Preparation A (0.062 g, 0.282 mmol), Preparation Jd2 (0.11 g, 0.310 mmol), Na_2CO_3 (0.065 g, 0.620 mmol) and xantphos (0.179 g, 0.310 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.16 g, 0.155 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 10% methanol in dichloromethane as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine (0.040 g, 27%)as off-white solid. LC–MS $(M+H)^+$ = 539.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.39 (1H, s*b*), 7.78 (1H, s), 7.71 (1H, m), 7.46 (1H, s), 7.28-7.13 (6H, m), 5.40 (1H, m), 4.94 (2H, m), 4.04-3.95 (4H, m), 3.83 (3H, m), 3.67 (3H, m), 2.33-2.08 (2H, m).

Example 59

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

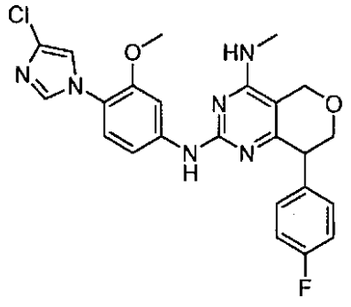


The method of example 56 was used to combine Preparation C and Preparation Jb to afford N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine.LC–MS $(M+H)^+$ = 464.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.99 - 8.06 (2 H, m), 7.24 - 7.34 (4 H, m), 7.04 (2 H, t, *J*=8.70 Hz), 4.65 (1 H, d, *J*=14.30 Hz), 4.56 (1 H, d, *J*=14.30 Hz), 4.16 (1 H, dd, *J*=11.29, 4.58 Hz), 3.94 - 4.00 (1 H, m), 3.92 (1 H, t, *J*=4.88 Hz), 3.57 (2 H, q, *J*=7.12 Hz), 2.37 (3 H, s), 1.29 (3 H, t, *J*=7.17 Hz)

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 59A and 59B, which had identical spectral data.

Example 60

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



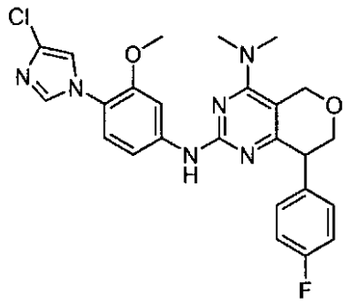
A solution of Preparation A (0.15 g, 0.61 mmol), Preparation Ja (0.20 g, 0.61 mmol), Na_2CO_3 (0.144 g, 1.31 mmol) and xantphos (0.39 g, 0.61 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.31 g, 0.32 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was

evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 2). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (0.12 g, 37%) as off-white solid. LC–MS $(M-H)^+$ = 479.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 12.02 (1H, s*b*), 9.17 (1H, s), 8.06 (1H, s), 7.73 (1H, s), 7.41 (1H, s), 7.25-7.08 (5H, m), 6.77 (1H, m), 4.57 (1H, d, *J*= 14.4 Hz), 4.44 (1H, d, *J*= 14.4 Hz), 4.02 (1H, m), 3.89 (1H, m), 3.80 (1H, m), 3.3 (3H, s), 2.93 (3H, d, *J* = 4.0 Hz).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 60A and 60B, which had identical spectral data.

Example 61

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4,N4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



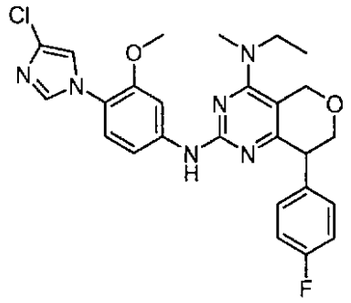
A solution of Preparation A (0.15 g, 0.70 mmol), Preparation Jc (0.24 g, 0.78 mmol), Na_2CO_3 (0.16 g, 1.56 mmol) and xantphos (0.45 g, 0.78 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.35 g, 0.39 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (30 mL x 2). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and evaporated under

reduced pressure to get crude compound. The crude compound was purified by Combiflash (Silica 120 g) using 50% ethyl acetate in pet-ether as mobile phase to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4,N4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (0.15 g, 47%) as off-white solid. LC–MS $(M-H)^+$ = 493.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.21 (1H, s), 7.91 (1H, s), 7.73 (1H, s), 7.41 (1H, s), 7.24 (2H, m), 7.14 (4H, m), 4.83 (1H, d, *J*= 13.6 Hz), 4.70 (1H, d, *J*= 13.6 Hz), 4.16 (1H, m), 4.10 (1H, m), 3.72 (1H, m), 3.56 (3H, s), 3.06 (6H, s).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 61A and 61B, which had identical spectral data.

Example 62

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



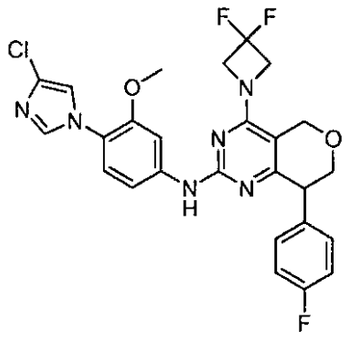
A solution of Preparation A (0.13 g, 0.61 mmol), Preparation Jf (0.20 g, 0.61 mmol), Na_2CO_3 (0.13 g, 1.2 mmol) and xantphos (0.36 g, 0.61 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.28 g, 0.31 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (30 mL x 2). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by Combiflash (Silica 120 g) using 50% ethyl acetate in pet-ether as mobile phase to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-

methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (0.097 g, 47%) as off-white solid. LC–MS $(M+H)^+$ = 509.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.17 (1H, s), 7.83 (1H, s), 7.72 (1H, s), 7.40 (1H, s), 7.24 (2H, m), 7.12 (4H, m), 4.78 (1H, d, *J*= 13.6 Hz), 4.65 (1H, d, *J*= 13.6 Hz), 4.09 (1H, m), 3.73 (1H, m), 3.55 (1H, m), 3.54 (3H, s), 3.38 (2H, m), 3.02 (3H, s), 1.20 (3H, t, *J* = 6.9.0 Hz).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 62A and 62B, which had identical spectral data.

Example 63

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine



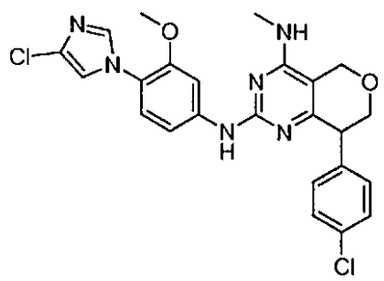
A solution of Preparation A (0.082 g, 0.31 mmol), Preparation Jg (0.13 g, 0.31 mmol), Na_2CO_3 (0.077 g, 0.72 mmol) and xantphos (0.21 g, 0.31 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.16 g, 0.12 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (30 mL x 2). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by Combiflash (Silica 120 g) using 50% ethyl acetate in pet-ether as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine (0.070 g, 35%) as off-white solid. LC–MS $(M-H)^+$ = 541.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.41 (1H,

s), 7.88 (1H, s), 7.73 (1H, s), 7.41 (1H, s), 7.25 (2H, m), 7.17-7.08 (4H, m), 4.78-4.63 (6H, m), 4.04 (2H, m), 3.78 (1H, m), 3.50 (3H, s).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 63A and 63B, which had identical spectral data.

Example 64

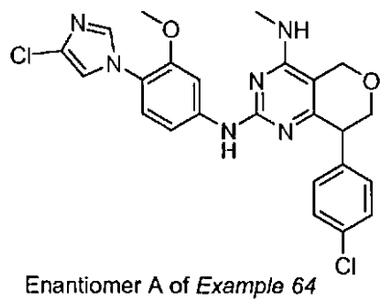
N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



2-chloro-8-(4-chlorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (*Preparation Kb*) (116 mg, 0.374 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (84 mg, 0.374 mmol) were combined and purified as per *Example 26* to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (105 mg, 0.172 mmol, 45.9 % yield) as a white solid. LC-MS $(M+H)^+ = 497.1$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.86 (1 H, br. s.), 7.63 (1 H, br. s.), 7.30 - 7.46 (6 H, m), 7.19 (1 H, dd, *J*=8.55, 2.14 Hz), 4.62 - 4.73 (1 H, m), 4.56 (1 H, d, *J*=14.65 Hz), 4.11 - 4.20 (1 H, m), 4.07 (1 H, d, *J*=3.36 Hz), 3.94 (1 H, dd, *J*=11.44, 3.81 Hz), 3.82 - 3.89 (3 H, m), 3.10 - 3.20 (3 H, m).

Example 64A

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

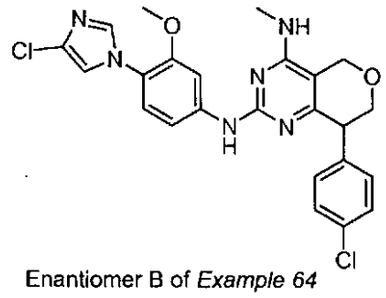


Enantiomer A of *Example 64*

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example 64*) was separated by multiple chiral HPLC injections (OJ-H 30 x 250mm, 10 μM, 35% EtOH/Hexanes) to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (first to elute, enantiomer A) (35 mg, 0.057 mmol) as an off-white solid. LC-MS $(M+H)^+$ = 497.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.80 (1 H, s), 7.71 (1 H, s), 7.36 (2 H, d, *J*=8.24 Hz), 7.25 - 7.30 (3 H, m), 7.22 (1 H, d, *J*=8.55 Hz), 7.03 (1 H, d, *J*=8.55 Hz), 4.50 - 4.68 (2 H, m), 4.15 (1 H, dd, *J*=11.29, 4.27 Hz), 3.97 (1 H, t, *J*=4.27 Hz), 3.87 - 3.94 (1 H, m), 3.66 (3 H, s), 3.08 (3 H, s). The absolute stereochemistry of *Example 64A* was not determined.

Example 64B

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



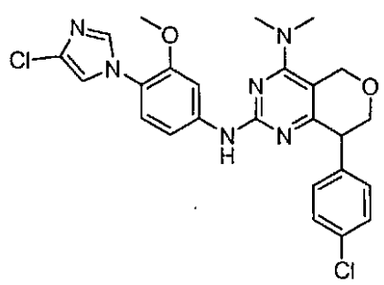
Enantiomer B of *Example 64*

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example 64*) was separated by multiple chiral HPLC injections (OJ-H 30 x 250mm, 10 μM, 35% EtOH/Hexanes) to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA

(second to elute, enantiomer B) (29mg, 0.047 mmol) as an off-white solid. LC-MS $(M+H)^+$ = 497.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.78 (1 H, s), 7.72 (1 H, d, *J*=1.53 Hz), 7.34 - 7.39 (2 H, m), 7.26 - 7.31 (3 H, m), 7.24 (1 H, d, *J*=8.55 Hz), 7.04 (1 H, dd, *J*=8.55, 2.14 Hz), 4.51 - 4.68 (2 H, m), 4.15 (1 H, dd, *J*=11.29, 4.58 Hz), 3.98 (1 H, t, *J*=4.43 Hz), 3.91 (1 H, dd, *J*=11.44, 4.73 Hz), 3.68 (3 H, s), 3.09 (3 H, s). The absolute stereochemistry of *Example 64B* was not determined.

Example 65

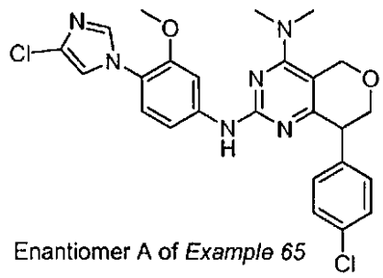
N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



2-chloro-8-(4-chlorophenyl)-N,N-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (*Preparation Kc*) (125 mg, 0.386 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (86 mg, 0.386 mmol) were combined and purified as per *Example 26* to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (110 mg, 0.176 mmol, 45.6 % yield) as a white solid. LC-MS $(M+H)^+$ = 511.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.92 (1 H, br. s.), 7.31 - 7.51 (7 H, m), 7.16 (1 H, dd, *J*=8.39, 1.98 Hz), 4.91 - 5.05 (2 H, m), 4.12 - 4.30 (2 H, m), 3.76 - 3.91 (4 H, m), 3.34 - 3.44 (6 H, m).

Example 65A

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

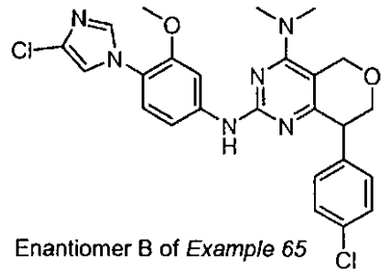


Enantiomer A of *Example 65*

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example 65*) was separated by multiple chiral HPLC injections (OJ-H 30 x 250mm, 10 μM, 35% EtOH/Hexanes) to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (first to elute, enantiomer A) (35 mg, 0.056 mmol) as an off-white solid. LC-MS $(M+H)^+$ = 511.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.71 (1 H, d, *J*=1.22 Hz), 7.67 (1 H, s), 7.36 (2 H, d, *J*=8.55 Hz), 7.24 - 7.30 (3 H, m), 7.22 (1 H, d, *J*=8.55 Hz), 7.01 (1 H, dd, *J*=8.55, 2.14 Hz), 4.77 - 4.96 (2 H, m), 4.23 (1 H, dd, *J*=11.44, 5.65 Hz), 4.11 (1 H, t, *J*=5.65 Hz), 3.84 (1 H, dd, *J*=11.60, 6.10 Hz), 3.60 - 3.66 (3 H, m), 3.18 - 3.23 (6 H, m). The absolute stereochemistry for *Example 65A* was not determined.

Example 65B

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



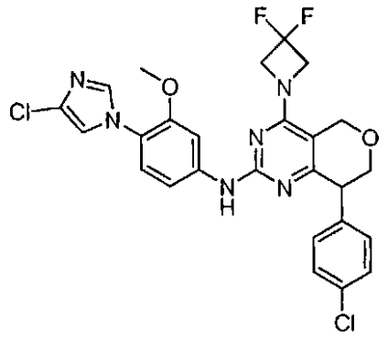
Enantiomer B of *Example 65*

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example 65*) was separated by multiple chiral HPLC injections (OJ-H 30 x 250mm, 10 μM, 35% EtOH/Hexanes) to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (second to elute, enantiomer B) (34 mg, 0.054 mmol) as an off-white solid. LC-MS

$(M+H)^+$ = 511.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.73 (1 H, d, *J*=1.53 Hz), 7.63 (1 H, s), 7.38 (2 H, d, *J*=8.55 Hz), 7.22 - 7.33 (4 H, m), 7.03 (1 H, dd, *J*=8.55, 2.14 Hz), 4.81 - 4.97 (2 H, m), 4.24 (1 H, dd, *J*=11.44, 5.65 Hz), 4.13 (1 H, t, *J*=5.49 Hz), 3.85 (1 H, dd, *J*=11.44, 5.95 Hz), 3.68 (3 H, s), 3.24 (6 H, s). The absolute stereochemistry for *Example 65B* was not determined.

Example 66

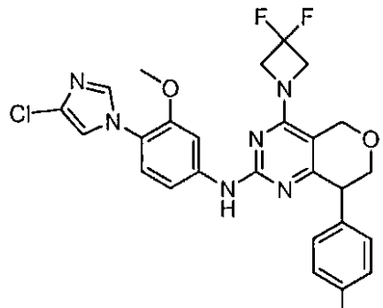
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine



2-chloro-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (*Preparation Ka*) (125 mg, 0.336 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (75 mg, 0.336 mmol) were combined and purified as per *Example 26* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine, TFA (40 mg, 0.059 mmol, 17.69 % yield) as a white solid. LC-MS $(M+H)^+$ = 559.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.83 (1 H, br. s.), 7.39 - 7.45 (3 H, m), 7.31 - 7.39 (4 H, m), 7.17 (1 H, dd, *J*=8.55, 2.14 Hz), 4.88 - 4.97 (5 H, m), 4.74 - 4.81 (1 H, m), 4.08 - 4.19 (2 H, m), 3.91 (1 H, dd, *J*=11.44, 3.81 Hz), 3.81 (3 H, s).

Example 66A

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine

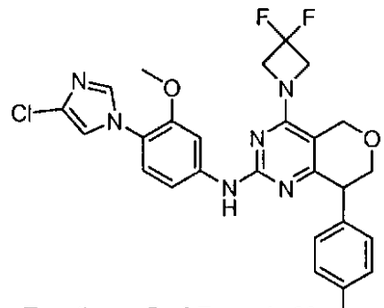


Enantiomer A of *Example 66*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine (*Example* 66) was separated by multiple chiral SFC injections (OD-H 30 x 250mm, 5 μM, 35% MeOH (0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine (first to elute, enantiomer A) (7.8 mg, 0.014 mmol) as a white solid. LC-MS $(M+H)^+$ = 559.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.76 (1 H, s), 7.66 (1 H, s), 7.31 (2 H, d, *J*=8.24 Hz), 7.20 - 7.27 (3 H, m), 7.10 - 7.16 (1 H, m), 6.97 (1 H, d, *J*=8.55 Hz), 4.68 - 4.83 (2 H, m), 4.55 - 4.66 (4 H, m), 4.16 (1 H, dd, *J*=11.44, 5.04 Hz), 4.02 (1 H, t, *J*=4.88 Hz), 3.88 (1 H, dd, *J*=11.29, 5.80 Hz), 3.49 (3 H, s). The absolute stereochemistry of *Example 66A* was not determined.

Example 66B

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine



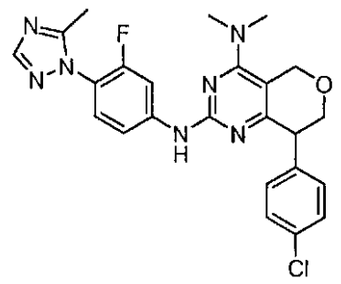
Enantiomer B of *Example 66*

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine (*Example* 66) was separated by multiple chiral SFC injections (OD-H 30 x 250mm, 5 μM, 35% MeOH

(0.1% DEA)/CO_2) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine (second to elute, enantiomer B) (8.1 mg, 0.014 mmol) as a white solid. LC-MS $(M+H)^+$ = 559.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.76 (1 H, d, *J*=2.14 Hz), 7.67 (1 H, d, *J*=1.53 Hz), 7.29 - 7.34 (2 H, m), 7.19 - 7.27 (3 H, m), 7.13 (1 H, d, *J*=8.55 Hz), 6.97 (1 H, dd, *J*=8.55, 2.14 Hz), 4.67 - 4.84 (2 H, m), 4.60 (4 H, t, *J*=12.21 Hz), 4.17 (1 H, dd, *J*=11.44, 5.04 Hz), 4.02 (1 H, t, *J*=5.19 Hz), 3.88 (1 H, dd, *J*=11.29, 5.80 Hz), 3.46 - 3.51 (3 H, m). The absolute stereochemistry of *66B* was not determined.

Example 67

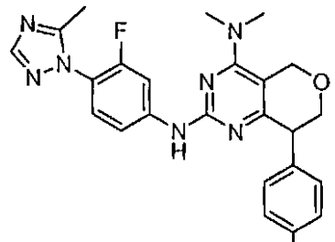
8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



2-chloro-8-(4-chlorophenyl)-N,N-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (*Preparation Kc*) (128 mg, 0.395 mmol) and 3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline (*Preparation C*) (76 mg, 0.395 mmol) were combined and purified as per *Example 26* to give 8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (120 mg, 0.202 mmol, 51.2 % yield) as a white solid. LC-MS $(M+H)^+$ = 480.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.07 (1 H, s), 7.80 (1 H, dd, *J*=12.36, 2.29 Hz), 7.54 (1 H, t, *J*=8.55 Hz), 7.40 - 7.47 (3 H, m), 7.34 - 7.40 (2 H, m), 4.90 - 5.04 (2 H, m), 4.22 - 4.28 (1 H, m), 4.20 (1 H, br. s.), 3.87 (1 H, dd, *J*=11.44, 5.34 Hz), 3.39 (6 H, s), 2.40 (3 H, s).

Example 67A

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

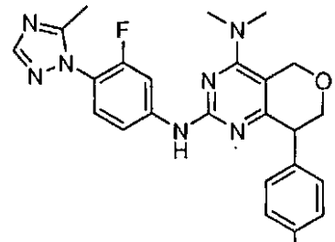


Enantiomer A of *Example 67*

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example 67*) was separated by multiple chiral SFC injections (AD-H 30 x 250mm, 5 μM, 40% MeOH (0.1% DEA)/CO_2) to give 8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (first to elute, enantiomer A) (25.8 mg, 0.054 mmol) as an opaque glass. LC-MS $(M+H)^+$ = 480.1. ^{1}H NMR (400 MHz, *MeOD*) δ ppm 7.99 (1 H, s), 7.87 - 7.95 (1 H, m), 7.19 - 7.33 (6 H, m), 4.72 - 4.83 (2 H, m), 4.22 (1 H, dd, *J*=11.33, 5.54 Hz), 4.02 (1 H, t, *J*=5.67 Hz), 3.87 - 3.95 (1 H, m), 3.09 (6 H, s), 2.33 (3 H, s). The absolute stereochemistry of *Example 67A* was not determined.

Example 67B

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



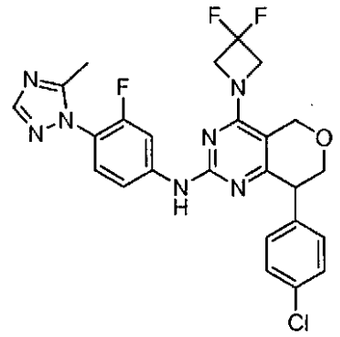
Enantiomer B of *Example 67*

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example 67*) was separated by multiple chiral SFC injections (AD-H 30 x 250mm, 5 μM, 40% MeOH (0.1% DEA)/CO_2) to give 8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (second to elute, enantiomer B) (25.8 mg, 0.054 mmol) as an opaque glass. LC-MS

$(M+H)^+ = 480.1$. ^1H NMR (400 MHz, *MeOD*) δ ppm 7.99 (1 H, s), 7.87 - 7.94 (1 H, m), 7.20 - 7.31 (6 H, m), 4.72 - 4.84 (2 H, m), 4.22 (1 H, dd, *J*=11.33, 5.54 Hz), 4.02 (1 H, t, *J*=5.79 Hz), 3.92 (1 H, dd, *J*=11.33, 6.04 Hz), 3.09 (6 H, s), 2.33 (3 H, s). The absolute stereochemistry of *Example 67B* was not determined.

Example 68

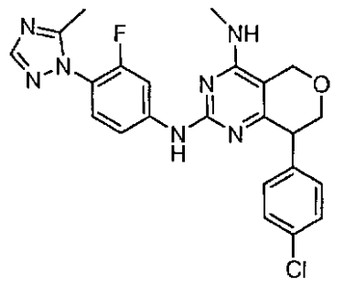
8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine



2-chloro-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (*Preparation Ka*) (128 mg, 0.344 mmol) and 3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline (*Preparation C*) (66.1 mg, 0.344 mmol) were combined and purified as per *Example 26* to give 8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine, TFA (120 mg, 0.187 mmol, 54.4 % yield) as a white solid. LC-MS $(M+H)^+ = 528.1$. ^1H NMR (500 MHz, *MeOD*) δ ppm 8.01 - 8.10 (1 H, m), 7.75 - 7.85 (1 H, m), 7.25 - 7.50 (6 H, m), 4.70 - 4.96 (6 H, m), 4.13 - 4.24 (1 H, m), 4.02 - 4.13 (1 H, m), 3.96 (1 H, dd, *J*=11.44, 4.73 Hz), 2.32 - 2.44 (3 H, m).

Example 69

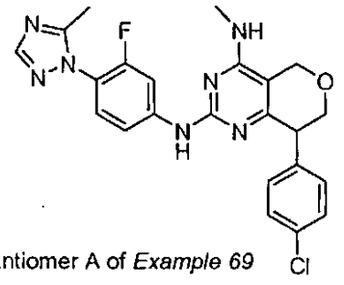
8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



2-chloro-8-(4-chlorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (*Preparation Kb*) (150 mg, 0.484 mmol) and 3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline (*Preparation C*) (93 mg, 0.484 mmol) were combined and purified as per *Example 26* to give 8-(4-chlorophenyl)-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (120 mg, 0.207 mmol, 42.8 % yield) as a clear, colorless glass. LC-MS $(M+H)^+ = 466.1$. ^1H NMR (500 MHz, *MeOD*) δ ppm 8.08 (1 H, s), 7.89 - 7.96 (1 H, m), 7.57 (1 H, t, *J*=8.55 Hz), 7.47 - 7.52 (1 H, m), 7.42 - 7.46 (2 H, m), 7.34 - 7.40 (2 H, m), 4.53 - 4.74 (2 H, m), 4.18 (1 H, dd, *J*=11.44, 4.43 Hz), 4.07 - 4.13 (1 H, m), 3.95 (1 H, dd, *J*=11.44, 4.12 Hz), 3.17 (3 H, s), 2.42 (3 H, s).

Example 69A

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



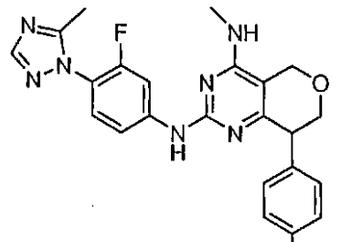
Enantiomer A of *Example 69*

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example* 69) was separated by multiple chiral SFC injections (AD-H 30 x 250mm, 5 μM, 20% MeOH (0.1% DEA)/CO_2) to give 8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (first to elute, enantiomer A) (52.4 mg, 0.112 mmol) as a white solid. LC-MS $(M+H)^+ = 466.1$.

^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.97 - 8.13 (2 H, m), 7.17 - 7.41 (6 H, m), 4.48 - 4.72 (2 H, m), 4.17 (1 H, dd, *J*=11.29, 4.58 Hz), 3.98 (1 H, dd, *J*=11.44, 5.04 Hz), 3.93 (1 H, d, *J*=4.88 Hz), 2.99 - 3.08 (3 H, m), 2.35 - 2.42 (3 H, m). The absolute stereochemistry of *Example 69A* was not determined.

Example 69B

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

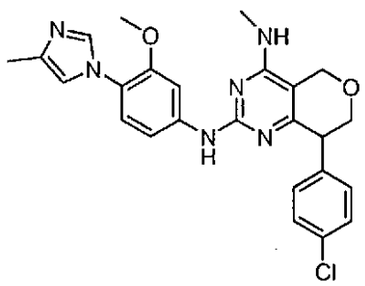


Enantiomer B of *Example 69*

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example* 69) was separated by multiple chiral SFC injections (AD-H 30 x 250mm, 5 μM, 20% MeOH (0.1% DEA)/CO_2) to give 8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (second to elute, enantiomer B) (45.9 mg, 0.099 mmol) as a white solid. LC-MS $(M+H)^+$ = 466.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.00 - 8.06 (2 H, m), 7.25 - 7.35 (6 H, m), 4.52 - 4.68 (2 H, m), 4.17 (1 H, dd, *J*=11.29, 4.88 Hz), 3.96 - 4.02 (1 H, m), 3.92 (1 H, t, *J*=4.88 Hz), 3.05 (3 H, s), 2.38 (3 H, s). The absolute stereochemistry of *Example 69B* was not determined.

Example 70

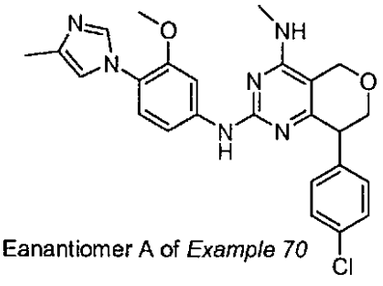
8-(4-chlorophenyl)-N^2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



2-chloro-8-(4-chlorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (*Preparation Kb*) (105.5 mg, 0.340 mmol) and 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)aniline (*Preparation E*) (69.1 mg, 0.340 mmol) were combined and purified as per *Example 26* to give 8-(4-chlorophenyl)-N^2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (120 mg, 0.203 mmol, 59.7 % yield) as a clear, colorless glass. LC-MS $(M+H)^+$ = 477.2. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 9.11 (1 H, s), 7.76 (1 H, br. s.), 7.51 - 7.59 (2 H, m), 7.34 - 7.46 (4 H, m), 7.26 - 7.33 (1 H, m), 4.52 - 4.75 (2 H, m), 4.17 (1 H, dd, *J*=11.44, 4.43 Hz), 4.08 (1 H, br. s.), 3.88 - 4.04 (4 H, m), 3.17 (3 H, s), 2.44 (3 H, s).

Example 70A

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



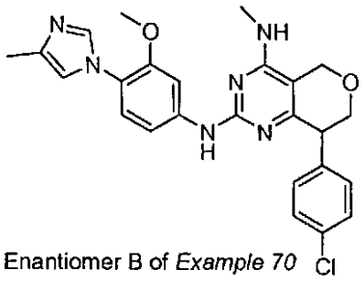
Eanantiomer A of *Example 70*

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example 70*) was separated by multiple chiral SFC injections (AD-H 30 x 250mm, 5 μM, 20% MeOH (0.1% DEA)/CO_2) to give 8-(4-chlorophenyl)-N^2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (first to elute, enantiomer A) as an opaque yellow glass. LC-MS $(M+H)^+$ = 477.2. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.84 (1 H, d, *J*=2.14 Hz), 7.62 (1 H, br. s.), 7.30 (2 H, d, *J*=8.55

Hz), 7.19 - 7.28 (2 H, m), 7.06 - 7.15 (1 H, m), 6.94 (2 H, dd, *J*=8.55, 2.14 Hz), 4.48 - 4.67 (2 H, m), 4.06 - 4.18 (1 H, m), 3.84 - 3.96 (2 H, m), 3.54 (3 H, s), 3.04 (3 H, s), 2.22 (3 H, s). The absolute stereochemistry of *Example 70A* was not determined.

Example 70B

8-(4-chlorophenyl)-N²-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N⁴-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

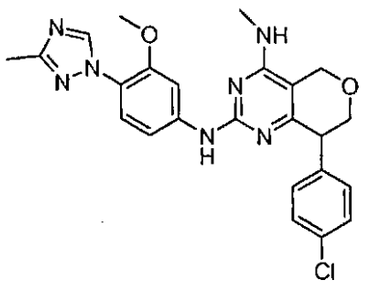


Enantiomer B of *Example 70*

8-(4-chlorophenyl)-N²-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N⁴-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example 70*) was separated by multiple chiral SFC injections (AD-H 30 x 250mm, 5 μM, 20% MeOH (0.1% DEA)/CO_2) to give 8-(4-chlorophenyl)-N²-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N⁴-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (second to elute, enantiomer B) as an opaque yellow glass. LC-MS $(M+H)^+ = 477.2$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.85 (1 H, d, *J*=2.14 Hz), 7.60 - 7.64 (1 H, m), 7.27 - 7.32 (2 H, m), 7.19 - 7.24 (2 H, m), 7.06 - 7.11 (1 H, m), 6.90 - 6.96 (2 H, m), 4.48 - 4.64 (2 H, m), 4.06 - 4.14 (1 H, m), 3.84 - 3.92 (2 H, m), 3.51 - 3.57 (3 H, m), 3.01 - 3.06 (3 H, m), 2.19 - 2.25 (3 H, m). The absolute stereochemistry of *Example 70B* was not determined.

Example 71

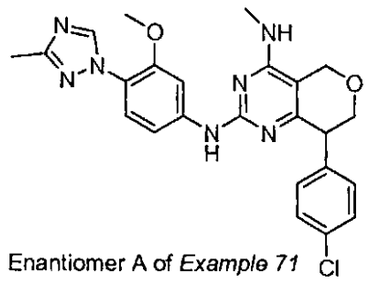
8-(4-chlorophenyl)-N²-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N⁴-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



2-chloro-8-(4-chlorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (*Preparation Kb*) (105.5 mg, 0.340 mmol) and 3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline (*Preparation D*) (69.5 mg, 0.340 mmol) were combined and purified as per *Example 26* to give 8-(4-chlorophenyl)-N^2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (120 mg, 0.203 mmol, 59.6 % yield) as a clear, colorless glass. LC-MS $(M+H)^+$ = 478.2. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.85 (1 H, s), 7.67 (1 H, d, *J*=8.55 Hz), 7.64 (1 H, s), 7.41 - 7.48 (2 H, m), 7.33 - 7.40 (2 H, m), 7.18 (1 H, dd, *J*=8.55, 2.14 Hz), 4.52 - 4.73 (2 H, m), 4.17 (1 H, dd, *J*=11.44, 4.42 Hz), 4.08 (1 H, br. s.), 3.94 (1 H, dd, *J*=11.60, 3.97 Hz), 3.91 (3 H, s), 3.17 (3 H, s), 2.45 (3 H, s).

Example 71A

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



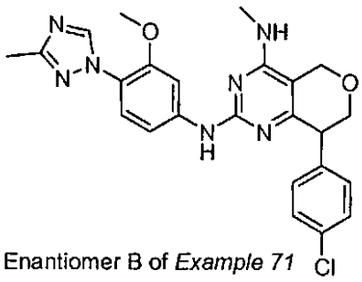
Enantiomer A of *Example 71*

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example 71*) was separated by multiple chiral SFC injections (OD-H 30 x 250mm, 5 μM, 35% MeOH (0.1% DEA)/CO_2) to give 8-(4-chlorophenyl)-N^2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (first to elute, enantiomer A) (24 mg, 0.050 mmol) as a scrapable tan glass. LC-MS

$(M+H)^+$ = 478.2. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.57 (1 H, s), 7.93 (1 H, d, *J*=2.14 Hz), 7.37 (1 H, d, *J*=8.85 Hz), 7.29 - 7.34 (2 H, m), 7.21 - 7.26 (2 H, m), 6.98 (1 H, dd, *J*=8.70, 2.29 Hz), 4.50 - 4.66 (2 H, m), 4.13 (1 H, dd, *J*=10.68, 3.97 Hz), 3.85 - 3.95 (2 H, m), 3.59 (3 H, s), 3.05 (3 H, s), 2.42 (3 H, s). The absolute stereochemistry of *Example 71A* was not determined.

Example 71B

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

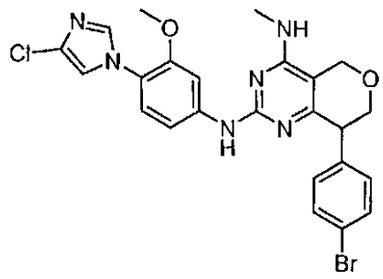


Enantiomer B of *Example 71*

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (*Example 71*) was separated by multiple chiral SFC injections (OD-H 30 x 250mm, 5 μM, 35% MeOH (0.1% DEA)/CO_2) to give 8-(4-chlorophenyl)-N^2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine (second to elute, enantiomer B) (22 mg, 0.046 mmol) as a scrapable tan glass. LC-MS $(M+H)^+$ = 478.2. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.57 (1 H, s), 7.93 (1 H, d, *J*=2.14 Hz), 7.36 (1 H, d, *J*=8.55 Hz), 7.28 - 7.34 (2 H, m), 7.20 - 7.26 (2 H, m), 6.98 (1 H, dd, *J*=8.55, 2.14 Hz), 4.50 - 4.66 (2 H, m), 4.13 (1 H, dd, *J*=10.68, 3.97 Hz), 3.84 - 3.95 (2 H, m), 3.59 (3 H, s), 3.04 (3 H, s), 2.41 (3 H, s). The absolute stereochemistry of *Example 71B* was not determined.

Example 72

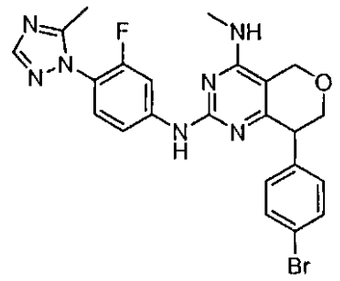
8-(4-bromophenyl)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



8-(4-bromophenyl)-2-chloro-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (*Preparation La*) (95 mg, 0.268 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (90 mg, 0.402 mmol) were combined and purified as per *Example 16* to give 8-(4-bromophenyl)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (38.5 mg, 0.059 mmol, 21.91 % yield) as a tan solid. LC-MS $(M+H)^+$ = 541.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.83 (1 H, br. s.), 7.70 (1 H, br. s.), 7.17 - 7.42 (7 H, m), 6.96 - 7.06 (1 H, m), 4.52 - 4.72 (2 H, m), 4.13 - 4.23 (1 H, m), 3.98 (1 H, br. s.), 3.87 - 3.96 (1 H, m), 3.62 (3 H, d, *J*=7.02 Hz), 3.06 - 3.16 (3 H, m).

Example 73

8-(4-bromophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine

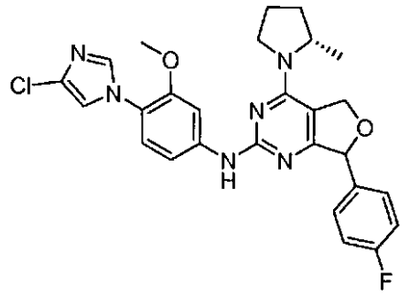


8-(4-bromophenyl)-2-chloro-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (*Preparation La*) (95 mg, 0.268 mmol) and 3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline (*Preparation C*) (77 mg, 0.402 mmol) were combined and purified as per *Example 16* to give 8-(4-bromophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (23 mg, 0.037 mmol, 13.75 % yield). LC-MS $(M+H)^+$ = 510.2. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.74 (2 H, br. s.), 7.25 - 7.45 (7 H, m), 7.00 - 7.12 (1 H, m), 4.53 - 4.73 (2 H, m),

4.17 (1 H, dd, *J*=11.29, 4.88 Hz), 4.00 - 4.09 (1 H, m), 3.89 - 3.99 (1 H, m), 3.71 (3 H, br. s.), 3.12 (3 H, s).

Examples 74A and 74B

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-2-methylpyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine



Discrete diasteriomers

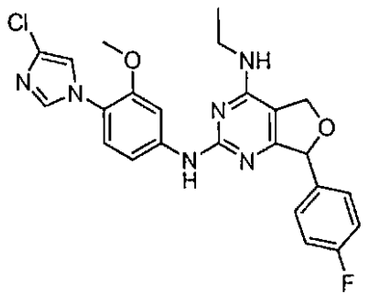
To a mixture of (S)-2-chloro-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation Me) (192.0 mg, 0.575 mmol), 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) (154 mg, 0.690 mmol), XANTPHOS (33.3 mg, 0.058 mmol), Pd2(dba)3 (26.3 mg, 0.029 mmol), and Cs2CO3 (562 mg, 1.726 mmol) was added Dioxane (2397 µL). The mixture was flushed with Nitrogen and placed in a capped vial and heated at 100 °C overnight.

Cooled to rt and diluted with EtOAc. Filtered through a Celite® plug and rotovaped. The residue was placed on Silica Gel and eluted with an EtOAc/Hex gradient to obtain (S)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine (189 mg, 0.363 mmol, 63.1 % yield) as a diasteriomeric mixture. The diasteriomers were separated by chiral SFC chromatography (Chiralcel OJ column, 40% MeOH (.1% DEA) in CO_2) to provide Examples 74A and 74B.

74A: LC–MS $(M+H)^+ = 521.2$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (1 H, d, *J*=1.53 Hz), 7.50 (1 H, d, *J*=1.53 Hz), 7.35 - 7.41 (2 H, m), 7.00 - 7.10 (4 H, m), 6.93 - 6.99 (2 H, m), 5.82 (1 H, t, *J*=2.44 Hz), 5.42 - 5.48 (1 H, m), 5.35 - 5.40 (1 H, m), 5.29 (1 H, s), 3.72 - 3.79 (1 H, m), 3.68 (3 H, s), 3.55 - 3.63 (1 H, m), 1.97 - 2.14 (3 H, m), 1.71 - 1.76 (1 H, m), 1.26 (3 H, d, *J*=6.41 Hz).

Example 75

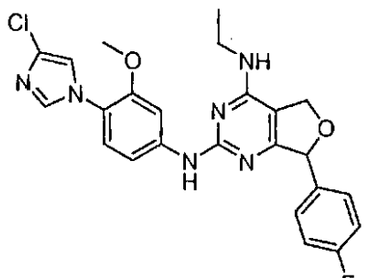
N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine



To a solution of 2-chloro-N-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine (*Preparation Mb*) in Dioxane (619 µL) and Water (124 µL) was added 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (29.1 mg, 0.130 mmol), Tris(dibenzylideneacetone)dipalladium(0) (59.5 mg, 0.065 mmol), 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (75 mg, 0.130 mmol), and Na2CO3 (20.66 mg, 0.195 mmol). The resulting mixture was brought to 110 °C in a sealed tube and stirred overnight The reaction mixture was then diluted with EtOAc (10 mL), washed with water (5 mL), brine (5mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (Silica, MeOH/CHCl3) removed the Xanthene ligand as to not have it ppt out on the prep column. Purification of the resulting oil by prep HPLC (C18, 50 X 250mm, MeOH/H_2O/TFA) gave N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine, TFA (16.94 mg, 0.028 mmol, 21.91 % yield) as a clear glass. LC-MS $(M+H)^+$ = 481.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.86 (1 H, d, *J*=1.53 Hz), 7.56 (1 H, d, *J*=2.14 Hz), 7.43 - 7.49 (2 H, m), 7.40 (1 H, d, *J*=8.85 Hz), 7.37 (1 H, d, *J*=1.22 Hz), 7.21 (1 H, dd, *J*=8.55, 2.14 Hz), 7.17 (2 H, t, *J*=8.70 Hz), 6.10 (1 H, t, *J*=3.20 Hz), 5.17 (1 H, dd, *J*=11.44, 3.81 Hz), 5.04 (1 H, dd, *J*=11.60, 2.14 Hz), 3.86 (3 H, s), 3.66 (2 H, q, *J*=7.32 Hz), 1.32 (3 H, t, *J*=7.32 Hz).

Example 75A

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine

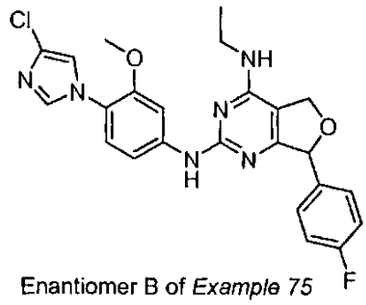


Enantiomer A of *Example 75*

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine (*Example 75*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 35% MeOH (0.1% DEA)/CO_2) to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine (first to elute, enantiomer A) (20.7 mg, 0.043 mmol, 10.71 % yield) as an off-white, scrapable foam. LC-MS $(M+H)^+$ = 481.0. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.87 (1 H, d, *J*=2.14 Hz), 7.68 (1 H, d, *J*=1.22 Hz), 7.36 - 7.42 (2 H, m), 7.22 (1 H, d, *J*=1.53 Hz), 7.13 - 7.17 (1 H, m), 7.04 - 7.11 (3 H, m), 5.79 (1 H, d, *J*=2.14 Hz), 5.09 - 5.15 (1 H, m), 4.96 - 5.03 (1 H, m), 3.71 (3 H, s), 3.57 (2 H, q, *J*=7.02 Hz), 1.25 - 1.30 (3 H, m). The absolute stereochemistry of *Example 75A* was not determined.

Example 75B

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine



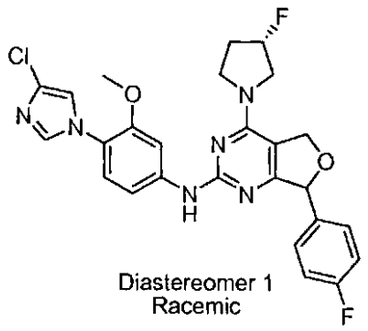
Enantiomer B of *Example 75*

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine (*Example 75*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 35% MeOH (0.1% DEA)/CO_2) to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-

fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine (second to elute, enantiomer B) (19.6 mg, 0.041 mmol, 10.14 % yield) as an off-white, scrapable foam. LC-MS $(M+H)^+$ = 481.0. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.87 (1 H, s), 7.68 (1 H, s), 7.40 (2 H, td, *J*=5.80, 2.44 Hz), 7.23 (1 H, s), 7.14 - 7.18 (1 H, m), 7.06 - 7.12 (3 H, m), 5.80 (1 H, br. s.), 5.13 (1 H, dd, *J*=10.99, 3.05 Hz), 5.00 (1 H, d, *J*=10.99 Hz), 3.72 (3 H, s), 3.57 (2 H, q, *J*=7.02 Hz), 1.25 - 1.31 (3 H, m). The absolute stereochemistry of *Example 75 B* was not determined.

Example 76

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine

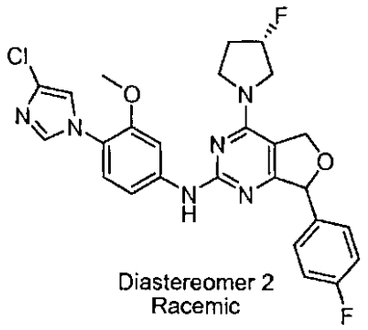


Diastereomer 1
Racemic

2-chloro-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidine (*Preparation Mc1*) (49 mg, 0.145 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (32.4 mg, 0.145 mmol) were combined and purified as per *Example 26* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine, TFA (diastereomer 1, racemate) (24.18 mg, 0.038 mmol, 26.1 % yield) as a slightly yellow glass. LC-MS $(M+H)^+$ = 525.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.92 (1 H, d, *J*=1.53 Hz), 7.54 (1 H, br. s.), 7.47 - 7.52 (2 H, m), 7.38 - 7.42 (2 H, m), 7.28 (1 H, dd, *J*=8.55, 2.14 Hz), 7.15 - 7.21 (2 H, m), 6.07 - 6.11 (1 H, m), 5.62 (1 H, dd, *J*=10.99, 3.97 Hz), 5.35 - 5.53 (2 H, m), 4.09 - 4.23 (2 H, m), 3.89 - 4.08 (2 H, m), 3.87 (3 H, s), 2.44 (1 H, br. s.), 2.12 - 2.38 (1 H, m). The relative stereochemistry of *Example 76* was not determined.

Example 77

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine

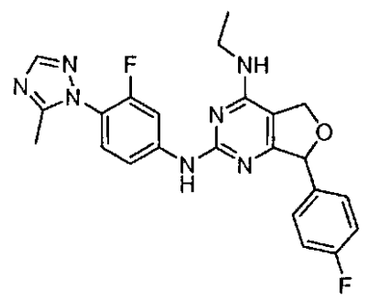


Diastereomer 2
Racemic

2-chloro-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidine (*Preparation Mc2*) (40 mg, 0.118 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (26.5 mg, 0.118 mmol) were combined and purified as per *Example 26* to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine, TFA (diastereomer 2, racemate) (25.75 mg, 0.040 mmol, 34.0 % yield) as a slightly yellow glass. LC-MS $(M+H)^+$ = 525.1. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.88 (1 H, d, *J*=1.22 Hz), 7.54 (1 H, s), 7.46 - 7.51 (2 H, m), 7.36 - 7.42 (2 H, m), 7.16 - 7.25 (3 H, m), 6.08 (1 H, t, *J*=3.20 Hz), 5.52 - 5.60 (1 H, m), 5.36 - 5.52 (2 H, m), 4.02 - 4.20 (2 H, m), 4.00 (2 H, s), 3.88 - 3.99 (1 H, m), 3.86 (3 H, s), 2.37 - 2.51 (1 H, m), 2.14 - 2.37 (1 H, m). The relative stereochemistry of *Example 77* was not determined.

Example 78

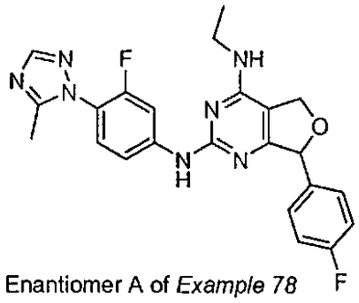
N^4-ethyl-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine



2-chloro-N-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine (*Preparation Mb*) and 3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline (*Preparation C*) (51.6 mg, 0.268 mmol) were combined and purified as per *Example 75* to give N^4-ethyl-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine, TFA (64.1 mg, 0.114 mmol, 42.4 % yield) as a white solid. LC-MS $(M+H)^+ = 450.0$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.08 (1 H, s), 7.96 - 8.02 (1 H, m), 7.42 - 7.53 (4 H, m), 7.17 (2 H, t, *J*=8.85 Hz), 6.04 (1 H, t, *J*=3.05 Hz), 5.18 (1 H, dd, *J*=11.44, 3.51 Hz), 5.02 - 5.08 (1 H, m), 3.64 (2 H, q, *J*=7.12 Hz), 2.42 (3 H, s), 1.34 (3 H, t, *J*=7.17 Hz).

Example 78A

N^4-ethyl-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine

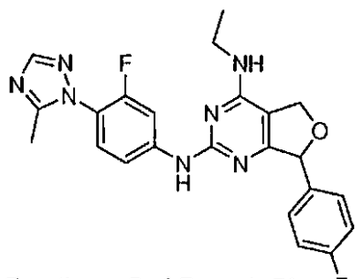


Enantiomer A of *Example 78*

N^4-ethyl-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine (*Example 78*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 30% MeOH (0.1% DEA)/CO_2) to give N^4-ethyl-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine (first to elute, enantiomer A) (25.8 mg, 0.057 mmol, 21.40 % yield) as a white solid. LC-MS $(M+H)^+ = 450.0$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 8.15 (1 H, dd, *J*=13.89, 2.29 Hz), 8.03 (1 H, s), 7.39 - 7.47 (3 H, m), 7.33 (1 H, t, *J*=8.55 Hz), 7.07 - 7.12 (2 H, m), 5.84 (1 H, t, *J*=2.59 Hz), 5.14 (1 H, dd, *J*=11.29, 3.36 Hz), 5.03 (1 H, dd, *J*=11.14, 1.68 Hz), 3.53 - 3.61 (2 H, m), 2.39 (3 H, s), 1.27 - 1.32 (3 H, m). The absolute stereochemistry of *Example 78A* was not determined.

Example 78B

N^4-ethyl-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine

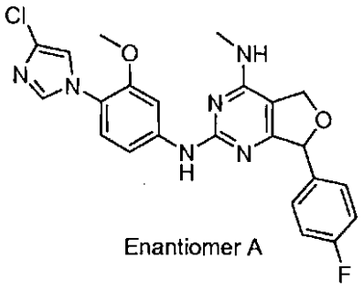


Enantiomer B of *Example 78*

N^4-ethyl-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine (*Example 78*) was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 30% MeOH (0.1% DEA)/CO_2) to give N^4-ethyl-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine (second to elute, enantiomer B) (24.6 mg, 0.055 mmol, 20.40 % yield) as a white solid. LC-MS $(M+H)^+$ = 450.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.99 - 8.06 (1 H, m), 7.94 (1 H, s), 7.36 - 7.42 (2 H, m), 7.23 - 7.29 (1 H, m), 7.12 (1 H, dd, *J*=8.55, 1.83 Hz), 7.02 - 7.08 (2 H, m), 5.86 (1 H, d, *J*=2.44 Hz), 5.01 - 5.21 (2 H, m), 3.50 - 3.60 (2 H, m), 2.40 (3 H, s), 1.27 - 1.33 (3 H, m). The absolute stereochemistry of *Example 78B* was not determined.

Example 79A

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine



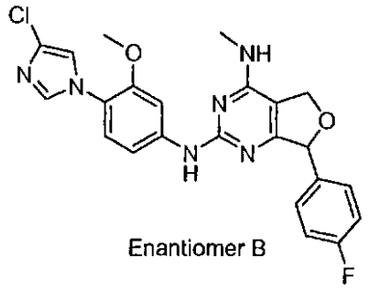
Enantiomer A

2-chloro-7-(4-fluorophenyl)-N-methyl-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine (*Preparation Ma*) (149 mg, 0.533 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (119 mg, 0.533 mmol) were combined and purified as

per *Example 75* to give the racemate N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine which was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 35% MeOH (0.1% DEA)/CO_2) to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine (first to elute, enantiomer A) (18.3 mg, 0.039 mmol, 7.36 % yield) as a white scrapable foam. LC-MS $(M+H)^+$ = 467.0. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.89 - 7.94 (1 H, m), 7.65 - 7.69 (1 H, m), 7.36 - 7.42 (2 H, m), 7.20 - 7.24 (1 H, m), 7.13 - 7.18 (1 H, m), 7.03 - 7.12 (3 H, m), 5.79 (1 H, br. s.), 5.08 - 5.16 (1 H, m), 4.95 - 5.03 (1 H, m), 3.68 - 3.73 (3 H, m), 3.02 - 3.07 (3 H, m). The absolute stereochemistry of *Example 79A* was not determined.

Example 79B

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine



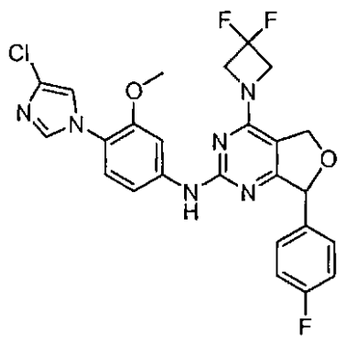
Enantiomer B

2-chloro-7-(4-fluorophenyl)-N-methyl-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine (*Preparation Ma)* (149 mg, 0.533 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (*Preparation A*) (119 mg, 0.533 mmol) were combined and purified as per *Example 75* to give the racemate N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine which was separated by multiple chiral SFC injections (OJ-H 30 x 250mm, 5 μM, 35% MeOH (0.1% DEA)/CO_2) to give N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine (second to elute, enantiomer B) (22.1 mg, 0.047 mmol, 8.89 % yield) as a slightly yellow scrapable foam. LC-MS $(M+H)^+$ = 467.0. ^{1}H NMR (500 MHz, *MeOD*) δ

ppm 7.92 (1 H, d, *J*=2.14 Hz), 7.68 (1 H, d, *J*=1.53 Hz), 7.39 (2 H, dd, *J*=8.70, 5.34 Hz), 7.22 (1 H, d, *J*=1.53 Hz), 7.15 (1 H, d, *J*=8.55 Hz), 7.04 - 7.11 (3 H, m), 5.79 (1 H, br. s.), 5.12 (1 H, dd, *J*=10.99, 3.36 Hz), 4.99 (1 H, d, *J*=10.99 Hz), 3.70 (3 H, s), 3.05 (3 H, s). The absolute stereochemistry of *Example 79B* was not determined.

Example 80

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine

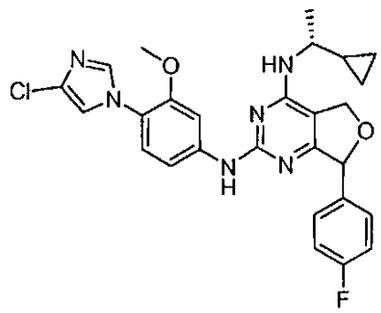


A solution of Preparation A (0.102 g, 0.560 mmol), Preparation Ma (0.160 g, 0.560 mmol), Na_2CO_3 (0.119 g, 0.110 mmol) and xantphos (0.325 g, 0.560 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.310 g, 0.21 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (75 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (Silica gel, 60-120 mesh) using 21% ethyl acetate in pet-ether as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine (0.90 g, 40%) as off-white solid. LC–MS $(M+H)^+$ = 529.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.6 (1H, s), 7.99 (1H, s), 7.98 (1H, s), 7.76-7.41 (3H, m), 7.23-7.13 (4H, m), 5.87 (1H, s), 5.33 (1H, dd, *J* = 11.1, 3.2 Hz), 5.17 (1H, dd, *J* = 11.1, 3.2), 4.67 (4H, m), 3.72 (3H, s).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 80A and 80B, which had identical spectral data.

Example 81

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine, TFA

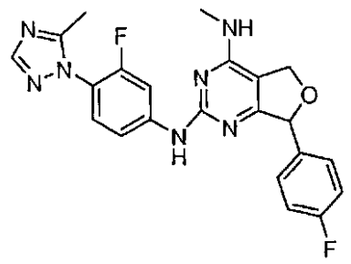


Diasteriomeric mixture

2-chloro-N-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine (Preparation Mf) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine, TFA as a mixture of 2 diasteriomers (Example 81). LC–MS $(M+H)^+$ = 521.3. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.82 (d, J=1.53 Hz, 1 H) 7.44 - 7.51 (m, 3 H) 7.38 (d, J=8.55 Hz, 1 H) 7.35 (d, J=1.53 Hz, 1 H) 7.14 - 7.22 (m, 3 H) 6.08 (br. s., 1 H) 5.21 (dd, J=11.60, 3.05 Hz, 1 H) 5.07 (dd, J=11.44, 2.59 Hz, 1 H) 3.84 (s, 3 H) 3.30(m, 1 H) 1.38 (d, J=6.41 Hz, 3 H) 1.06 - 1.13 (m, 1 H) 0.59 - 0.66 (m, 1 H) 0.54 (d, J=3.97 Hz, 1 H) 0.37 (d, J=4.88 Hz, 1 H) 0.28 (d, J=4.88 Hz, 1 H).

Example 82

N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N4-methyl-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine, TFA

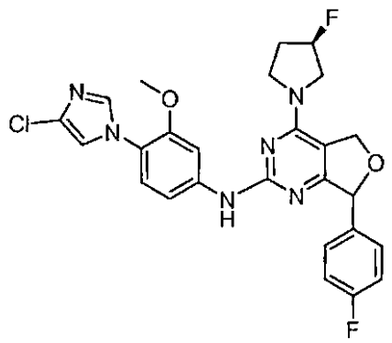


2-chloro-7-(4-fluorophenyl)-N-methyl-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine (Preparation Ma) was reacted as described in Example 112 with 3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline (Preparation C) to give N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N4-methyl-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine, TFA (Example 82). LC–MS $(M+H)^+ = 436.1$. ^1H NMR (500 MHz, MeOD) δ ppm 8.16 (dd, J=13.89, 2.29 Hz, 1 H) 8.03 (s, 1 H) 7.38 - 7.47 (m, 3 H) 7.34 (t, J=8.70 Hz, 1 H) 7.05 - 7.14 (m, 2 H) 5.85 (d, J=1.83 Hz, 1 H) 5.16 (br. s., 1 H) 5.04 (br. s., 1 H) 3.07 (s, 3 H) 2.39 (s, 3 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 82A and 82B as free amines, which had identical spectral data.

Example 83

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine, 2 TFA



Diasteriomeric mixture

2-chloro-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation Mg) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to give N-(4-(4-chloro-1H-

imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine, 2 TFA as a mixture of two diasteriomers (Example 83). LC–MS $(M+H)^+$ = 525.1. ^1H NMR (500 MHz, MeOD) δ ppm 7.83 (br. s., 1 H) 7.57 (br. s., 1 H) 7.43 - 7.52 (m, 2 H) 7.32 - 7.41 (m, 2 H) 7.22 - 7.29 (m, 1 H) 7.10 - 7.22 (m, 2 H) 6.00 - 6.11 (m, 1 H) 5.38 - 5.50 (m, 3 H) 4.10 (br. s., 2 H) 3.90 (br. s., 2 H) 2.31 - 2.51 (m, 2 H).

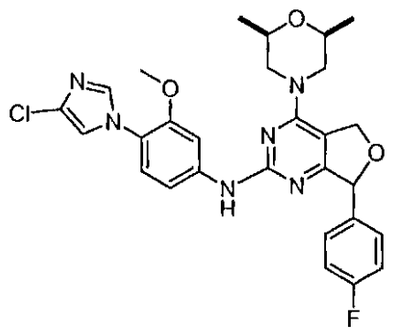
The mixture of two diasteriomers was separated by chiral chromatography to afford two diasteriomers Example 83A and 83B as free amines

Example 83A: LC–MS $(M+H)^+$ = 525.2. ^1H NMR (500 MHz, MeOD) δ ppm 7.80 (d, J=1.83 Hz, 1 H) 7.69 (d, J=1.53 Hz, 1 H) 7.43 (dd, J=8.70, 5.34 Hz, 2 H) 7.23 (d, J=1.22 Hz, 1 H) 7.04 - 7.20 (m, 4 H) 5.77 (br. s., 1 H) 5.50 - 5.59 (m, 1 H) 5.27 - 5.39 (m, 2 H) 4.00 (d, J=11.90 Hz, 1 H) 3.82 - 3.96 (m, 2 H) 3.63 - 3.82 (m, 4 H) 2.26 - 2.42 (m, 2 H).

Example 83B: LC–MS $(M+H)^+$ = 525.2. ^1H NMR (500 MHz, MeOD) δ ppm 7.81 (d, J=1.83 Hz, 1 H) 7.69 (d, J=1.53 Hz, 1 H) 7.39 - 7.47 (m, 2 H) 7.24 (d, J=1.53 Hz, 1 H) 7.16 - 7.21 (m, 1 H) 7.05 - 7.16 (m, 3 H) 5.80 (t, J=2.59 Hz, 1 H) 5.51 (dd, J=10.38, 3.05 Hz, 1 H) 5.36 - 5.46 (m, 2 H) 3.91 (m, 2 H) 3.66 - 3.86 (m, 5 H) 2.23 - 2.42 (m, 2 H).

Example 84

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine, 2 TFA



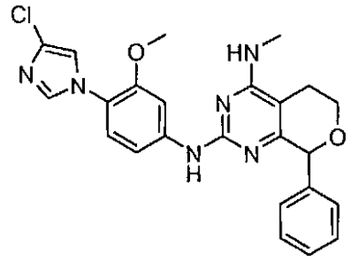
2-chloro-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine (Preparation Mh) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-

fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine, 2 TFA (Example 84). LC–MS $(M+H)^+$ = 551.2. ^1H NMR (400 MHz, MeOD) δ ppm 7.80 (d, J=1.51 Hz, 1 H) 7.55 (d, J=2.27 Hz, 1 H) 7.35 - 7.46 (m, 2 H) 7.23 - 7.33 (m, 2 H) 7.01 - 7.18 (m, 3 H) 5.91 (t, J=2.77 Hz, 1 H) 5.42 (dd, J=10.45, 3.40 Hz, 1 H) 5.28 (dd, J=10.32, 2.27 Hz, 1 H) 4.16 (br. s., 2 H) 3.60 - 3.78 (m, 5 H) 2.81 (ddd, J=13.41, 10.51, 3.53 Hz, 2 H) 1.21 (d, J=6.04 Hz, 6 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 84A and 84B as free amines LC–MS $(M+H)^+$ = 551.2. ^1H NMR (500 MHz, MeOD) δ ppm 7.77 (d, J=2.14 Hz, 1 H) 7.69 (d, J=1.53 Hz, 1 H) 7.35 - 7.50 (m, 2 H) 7.24 (d, J=1.53 Hz, 1 H) 7.18 (d, J=8.55 Hz, 1 H) 7.10 (t, J=8.70 Hz, 2 H) 7.05 (dd, J=8.55, 2.14 Hz, 1 H) 5.80 (d, J=2.44 Hz, 1 H) 5.42 (dd, J=10.38, 3.05 Hz, 1 H) 5.28 (dd, J=10.38, 1.83 Hz, 1 H) 4.16 (br. s., 2 H) 3.61 - 3.76 (m, 5 H) 2.60 - 2.80 (m, 2 H) 1.23 (d, J=6.41 Hz, 6 H).

Example 85

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine

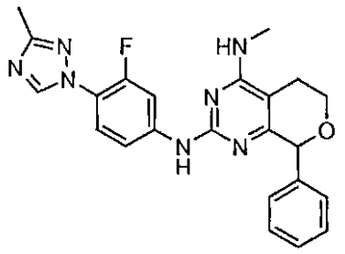


A solution of Preparation A (0.168 g, 0.75 mmol), Preparation Na (0.23 g, 0.834 mmol), Na_2CO_3 (0.176 g, 1.6 mmol) and xantphos (0.482 g, 0.834 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.38 g, 0.417 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through celite bed and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (75 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC

(aqueous 0.1% ammonium acetate in acetonitrile) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine (0.140 g, 36.2%) as off-white solid. LC–MS $(M+H)^+ = 463.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.06 (1H, s), 7.96 (1H, s), 7.72 (1H, s), 7.4 (1H, s), 7.36-7.30 (5H, m), 7.13 (2H, m), 6.94 (1H, m), 5.43 (1H, s), 3.95 (1H, m), 3.81 (1H, s), 3.53 (3H, s), 2.97 (3H, d, $J = 4.4$ Hz), 2.52 (1H, m), 2.45 (1H, m).

Example 86

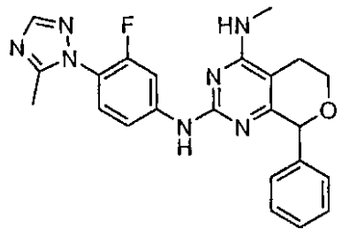
N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine



A solution of Preparation B (0.119 g, 0.62 mmol), Preparation Na (0.19 g, 0.68 mmol), Na_2CO_3 (0.146 g, 1.37 mmol) and xantphos (0.399 g, 0.689 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.315 g, 0.344 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceouse earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (75 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine (0.120 g, 30%) as off-white solid. LC–MS $(M+H)^+ = 432.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.33 (1H, s), 8.68 (1H, s), 8.03 (1H, m), 7.42-7.24 (7H, m), 6.98 (1H, *b*s), 5.44 (1H, s), 4.06 (1H, m), 3.84 (1H, m), 2.95 (3H, d, $J = 4.4$ Hz), 2.59 (1H, m), 2.44 (1H, m), 2.34 (3H, s).

Example 87

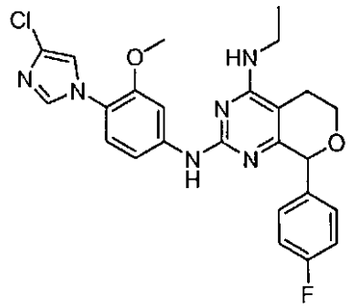
N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine



A solution of Preparation C (0.119 g, 0.62 mmol), Preparation Na (0.19 g, 0.68 mmol), Na_2CO_3 (0.146 g, 1.37 mmol) and xantphos (0.399 g, 0.689 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.315 g, 0.344 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceouse earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (75 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine (0.130 g, 44%) as off-white solid. LC–MS $(M+H)^+ = 432.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.38 (1H, s), 8.04 (1H, s), 8.01 (1H, s), 7.44 (1H, m), 7.34-7.27 (6H, m), 6.99 (1H, *bs*), 5.43 (1H, s), 4.06 (1H, m), 3.83 (1H, m), 2.95 (3H, d, $J = 4.4.0$ Hz), 2.51 (1H, m), 2.44 (1H, m), 2.27 (3H, s).

Example 88

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine

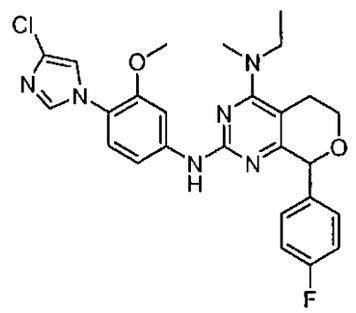


A solution of Preparation A (0.09 g, 0.38 mmol), Preparation Oa (0.15 g, 0.48 mmol), Na_2CO_3 (0.103 g, 0.97 mmol) and xantphos (0.282 g, 0.41 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.270 g, 0.24 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceouse earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (75 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 35% ethyl acetate in pet-ether as mobile phase to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine (0.90 g, 55%) as off-white solid. LC–MS $(M+H)^+$ = 495.2. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.06 (1H, s), 7.88 (1H, s), 7.73 (1H, m), 7.42 (1H, m), 7.33-7.44 (2H, m), 7.14-7.15 (4H, m), 6.92 (1H, m), 5.44 (1H, s), 3.96 (1H, m), 3.82 (1H, m), 3.57 (3H, s), 3.50 (2H, m), 2.45 (2H, m), 1.21 (3H, m).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 88A and 88B, which had identical spectral data.

Example 89

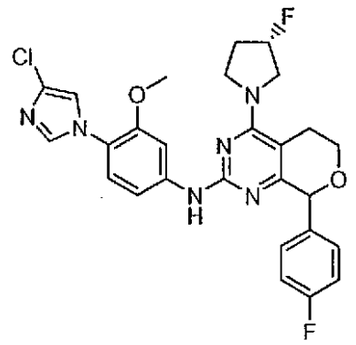
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine



A solution of Preparation A (0.029 g, 0.10 mmol), Preparation Ob (0.050 g, 0.14 mmol), Na_2CO_3 (0.030 g, 0.28 mmol) and xantphos (0.080 g, 0.14 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.078 g, 0.07 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceouse earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (75 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 35% ethyl acetate in pet-ether as mobile phase to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine (0.020 g, 30%) as off-white solid. LC–MS $(M+H)^+ = 509.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.12 (1H, s), 7.75-7.81 (2H, m), 7.38-7.44 (3H, m), 7.15-7.24 (4H, m), 5.51 (1H, s), 4.03 (1H, m), 3.49-3.67 (5H, m), 3.09 (3H, m), 3.01-3.06 (1H, m), 2.51-2.59 (2H, m), 1.22 (3H, t, $J = 7.2$ Hz).

Example 90A

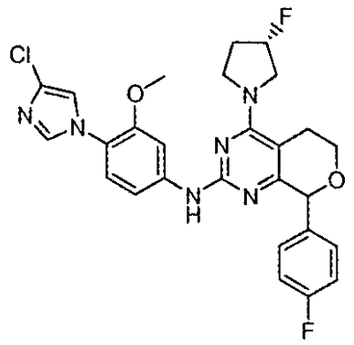
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine



A solution of Preparation A (0.063 g, 0.20 mmol), Preparation Oc1 (0.110 g, 0.3 mmol), Na_2CO_3 (0.066 g, 0.6 mmol) and xantphos (0.181 g, 0.3 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0172 g, 0.10 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceouse earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (75 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 35% ethyl acetate in pet-ether as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine (0.050g, 60%)as off-white solid. LC–MS $(M+H)^+$ = 539.0. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.12 (1H, s), 7.75 (2H, m), 7.39-7.44 (3H, m), 7.15-7.22 (4H, m), 5.50 (1H, s), 5.38 (1H, m), 3.82-4.09 (6H, m), 3.68 (3H, s), 2.98 (2H, m), 2.50-2.43 (2H, m).

Example 90B

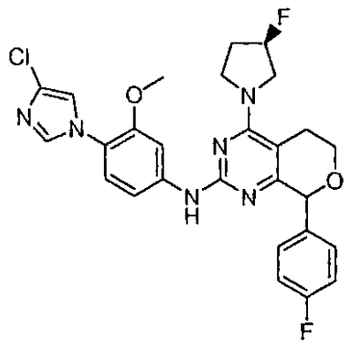
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine



A solution of Preparation A (0.063 g, 0.20 mmol), Preparation Oc2 (0.110 g, 0.3 mmol), Na_2CO_3 (0.066 g, 0.6 mmol) and xantphos (0.181 g, 0.3 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0172 g, 0.10 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceouse earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (75 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 35% ethyl acetate in pet-ether as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine (0.070g, 63%) as off-white solid. LC–MS $(M+H)^+$ = 539.0. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.16 (1H, s), 7.81 (1H, s), 7.74 (1H, s), 7.73 (1H, s), 7.42 (2H, m), 7.17-7.11 (4H, m), 5.54 (1H, s), 5.43 (1H, m), 4.12-3.57 (6H, m), 3.34 (3H, s), 2.97 (2H, m), 2.50-2.43 (2H, m).

Example 91A

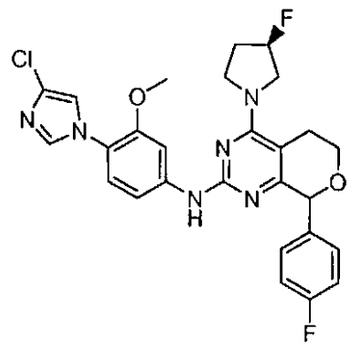
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine



A solution of Preparation A (0.063 g, 0.20 mmol), Preparation Od1 (0.110 g, 0.3 mmol), Na_2CO_3 (0.066 g, 0.6 mmol) and xantphos (0.181 g, 0.3 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0172 g, 0.10 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceouse earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (75 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 35% ethyl acetate in pet-ether as mobile phase to N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine.(0.040 g, 40%)as off-white solid. LC–MS $(M+H)^+$ = 539.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.25 (1H, s), 7.77 (1H, s), 7.77 (1H, s), 7.45 (3H, m), 7.21 (4H, m), 5.53 (1H, s), 5.43 (1H, m), 4.12-3.57 (5H, m), 3.34 (3H, s), 3.33 (1H, m), 3.20 (1H, m), 2.73 (1H, m), 2.31-2.06 (2H, m).

Example 91B

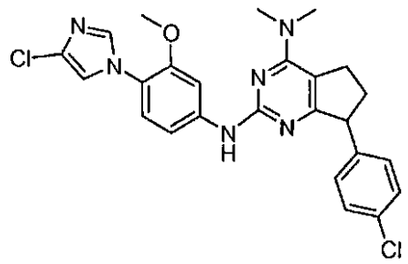
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine



A solution of Preparation A (0.063 g, 0.20 mmol), Preparation Od2 (0.110 g, 0.3 mmol), Na_2CO_3 (0.066 g, 0.6 mmol) and xantphos (0.181 g, 0.3 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0172 g, 0.10 mmol) was added to the reaction mixture and the resulting solution was purged for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diatomaceouse earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (75 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 35% ethyl acetate in pet-ether as mobile phase to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine.(0.039g, 39%) as off-white solid. LC–MS $(M+H)^+ = 539.0$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.15 (1H, s), 7.81 (1H, s), 7.74 (1H, s), 7.43 (1H, s), 7.37 (2H, m), 7.19 (4H, m), 5.54 (1H, s), 5.43 (1H, m), 4.13-3.69 (6H, m), 3.33 (3H, s), 2.96 (2H, m), 2.24-1.91 (2H, m).

Example 92

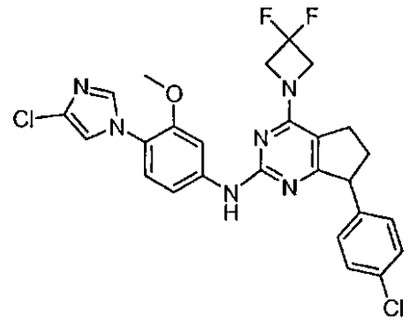
N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



2-Chloro-7-(4-chlorophenyl)-*N*,*N*-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (98 mg, 0.318 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (71.1 mg, 0.318 mmol) in acetic acid (1.000 mL) and THF (1 mL). The reaction mixture was heated at 75°C overnight. Partial conversion to the desired product was observed. The reaction was further heated at 120°C for 6 h. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (17.2 mg, 0.028 mmol, 8.70 % yield). LC–MS $(M+H)^+ = 495.1$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.80 (1H, s), 7.61 - 7.72 (1H, m), 7.34 - 7.42 (2H, m), 7.27 - 7.33 (2H, m), 7.21 (2H, d, *J*=8.5 Hz), 7.16 (1H, d, *J*=9.2 Hz), 7.06 (1H, d, *J*=1.5 Hz), 4.30 - 4.41 (1H, m), 3.82 (6H, s), 3.48 (1H, br. s.), 3.31 - 3.39 (2H, m), 3.18 - 3.27 (1H, m), 2.58 - 2.80 (2H, m), 2.14 - 2.29 (1H, m).

Example 93

N-(4-(4-Chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-6,7-dihydro-5*H*-cyclopenta[d]pyrimidin-2-amine

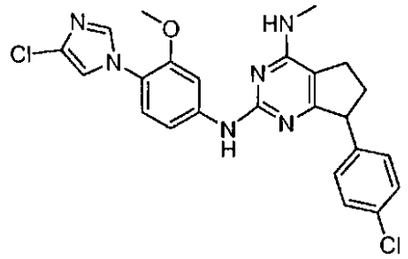


2-Chloro-7-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (70 mg, 0.197 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (52.7 mg, 0.236 mmol) in acetic acid (1 mL) and THF

(1.000 mL). The reaction mixture was heated at 120°C in a microwave for 6 h. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine, TFA salt (8.7 mg, 0.013 mmol, 6.46 % yield). LC–MS $(M+H)^+ = 543.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.85 - 11.99 (1H, m), 7.93 (1H, s), 7.38 - 7.45 (1H, m), 7.31 (2H, d, *J*=8.2 Hz), 7.19 (3H, t, *J*=8.2 Hz), 7.10 (1H, d, *J*=1.5 Hz), 4.37 - 4.47 (1H, m), 3.85 (3H, s), 3.45 - 3.51 (1H, m), 3.07 - 3.18 (2H, m), 2.94 - 3.04 (2H, m), 2.67 - 2.81 (2H, m), 2.19 - 2.37 (2H, m).

Example 94

N^2-(4-(4-Chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-N^4-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine



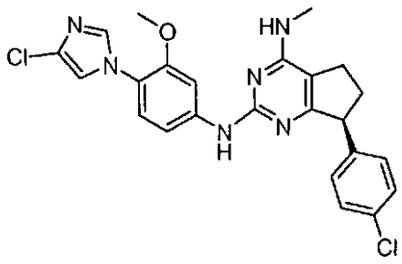
2-Chloro-7-(4-chlorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (101 mg, 0.343 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (77 mg, 0.343 mmol) in acetic acid (2 mL)and THF (2 mL). The reaction mixture was heated at 80°C overnight. Partial conversion to the desired product was observed. The reaction was further heated at 120 °C for 6 h. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-N^4-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (35.5 mg, 0.059 mmol, 17.19 % yield). LC–MS $(M+H)^+ = 481.3$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.08 (1H, s), 8.33 (1H, s), 7.48 (2H, d, *J*=2.1 Hz), 7.30 (2H, d, *J*=8.2 Hz), 7.20 (1H, d, *J*=1.5 Hz), 7.13 (2H, d, *J*=8.5 Hz), 5.83 - 5.93 (1H, m), 4.38 - 4.48 (1H, m), 3.97 (1H, s), 3.86 (3H, s), 3.22 (3H, d, *J*=4.9 Hz), 2.85 - 2.95 (1H, m), 2.77 (2H, dd, *J*=8.7, 5.3 Hz), 2.20 - 2.32 (1H, m).

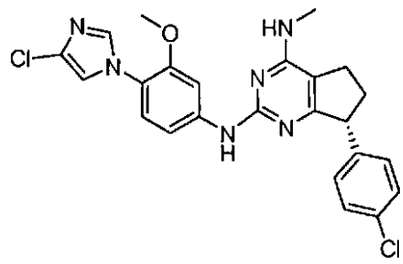
Example 94A & 94B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

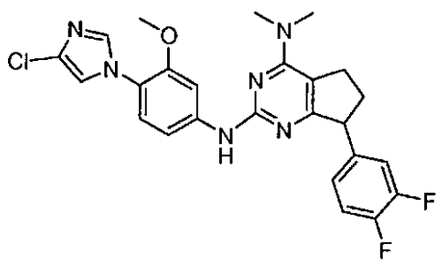




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-N^4-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (37 mg, 0.077 mmol from *Example 94*) was purified using chiral SFC to afford 10.5 mg of peak A (*Example 94A*) and 13.6 mg of peak B (*Example 94B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 35 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 20 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in 50:50 methanol/chloroform (multiple stacked injections), t_R (peak A) = 5.3 min, t_R (peak B) 14.9 min. The absolute stereochemistry of individual enantiomers (*Examples 94A and 94B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 94*).

Example 95

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



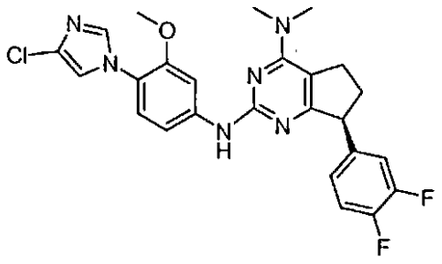
2-Chloro-7-(3,4-difluorophenyl)-*N*,*N*-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (178 mg, 0.575 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (141 mg, 0.632 mmol) in acetic acid (2 mL) and THF (2.000 mL). The reaction mixture was heated at 80°C overnight. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (144.1 mg, 0.233 mmol, 40.6 % yield). LC–MS $(M+H)^+ = 497.0$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.53 - 11.67 (1H, m), 8.96 (1H, br s), 7.85 - 7.96 (1H, m), 7.38 (1H, s), 7.18 (1H, d, *J*=8.2 Hz), 7.00 - 7.16 (4H, m), 4.34 (1H, dd, *J*=9.6, 4.4 Hz), 3.83 (3H, s), 3.30 - 3.57 (6H, m), 3.25 - 3.29 (1H, m), 3.19 - 3.26 (1H, m), 2.61 - 2.72 (1H, m), 2.14 - 2.25 (1H, m).

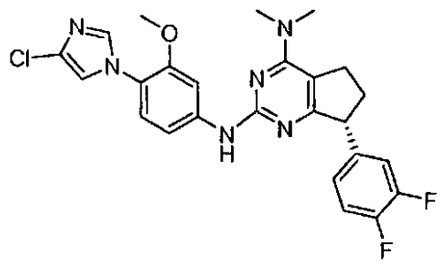
Example 95A & 95B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine





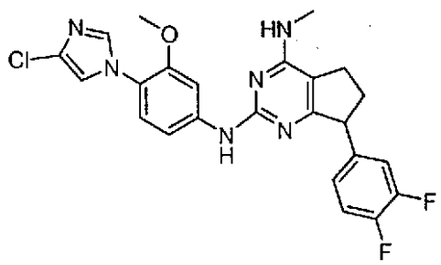
A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (139 mg, 0.28 mmol from *Example 95*) was purified using chiral SFC to afford 47.6 mg of peak A (*Example 95A*) and 47.3 mg of peak B (*Example 95B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 35 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 8 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 4.6 min, t_R (peak B) 6.3 min. The absolute stereochemistry of individual enantiomers (*Examples 95A and 95B*)

- hoja en blanco

was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 95*).

Example 96

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



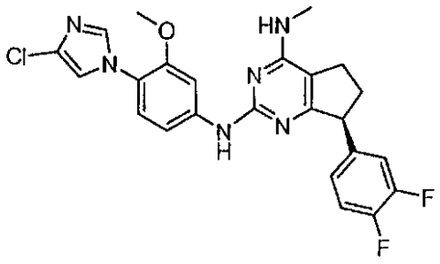
2-Chloro-7-(3,4-difluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (154 mg, 0.521 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (175 mg, 0.781 mmol) in acetic acid (2 mL) and THF (2.000 mL). The reaction mixture was heated at 120°C overnight. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (22.3 mg, 0.034 mmol, 6.46 % yield). LC–MS $(M+H)^+ = 483.2$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.84 (1H, s), 7.83 - 7.89 (1H, m), 7.55 (1H, s), 7.41 - 7.46 (1H, m), 7.17 - 7.21 (1H, m), 7.10 (2H, s), 6.98 - 7.05 (2H, m), 5.79 - 5.90 (1H, m), 4.38 - 4.45 (1H, m), 3.85 (3H, s), 3.20 - 3.25 (3H, m), 2.90 - 3.00 (1H, m), 2.70 - 2.81 (2H, m), 2.20 - 2.32 (1H, m).

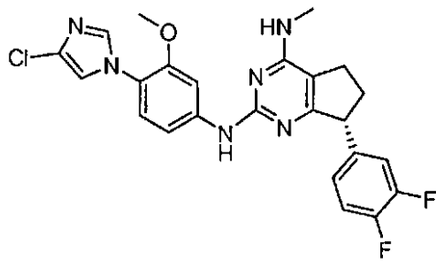
Example 96A & 96B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

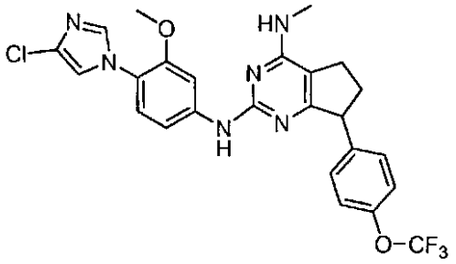




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (1.4 g, 2.345 mmol from *Example 96*) was purified using chiral SFC to afford 475 mg of peak A (*Example 96A*) and 435 mg of peak B (*Example 96B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 25 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 14 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 6.1 min, t_R (peak B) 9.2 min. The absolute stereochemistry of individual enantiomers (*Examples 96A and 96B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 96*).

Example 97

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



2-Chloro-*N*-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (220 mg, 0.640 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (215 mg, 0.960 mmol) in acetic acid (2 mL) and THF (2.000 mL). The reaction mixture was heated at 80°C overnight. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (92

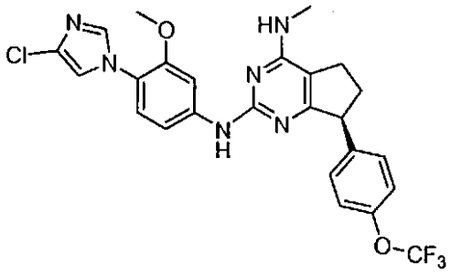
mg, 0.172 mmol, 26.8 % yield). LC–MS $(M+H)^+$ = 531.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.93 (1H, s), 7.66 (1H, br s), 7.50 (1H, s), 7.10 - 7.23 (4H, m), 7.02 (2H, d, *J*=15.3 Hz), 6.83 (1H, d, *J*=8.2 Hz), 4.70 - 4.83 (1H, m), 4.13 - 4.28 (1H, m), 3.12 (3H, d, *J*=4.9 Hz), 2.74 (1H, br. s.), 2.65 (2H, d, *J*=8.2 Hz), 1.97 - 2.08 (1H, m), 1.25 (3H, s).

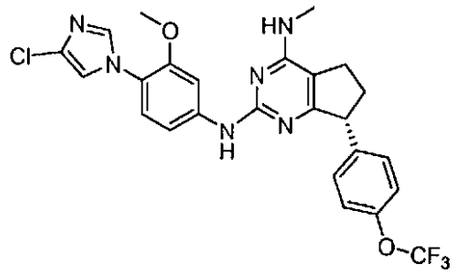
Example 97A & 97B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

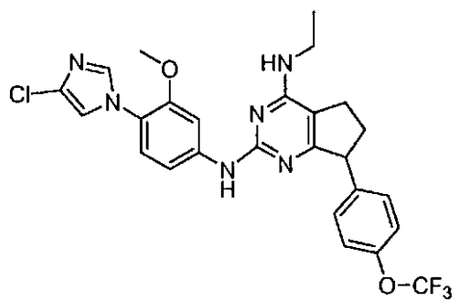




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (86 mg, 0.162 mmol from *Example 97*) was purified using chiral SFC to afford 36.6 mg of peak A (*Example 97A*) and 31.5 mg of peak B (*Example 97B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 30 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 12 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 3.4 min, t_R (peak B) 7.5 min. The absolute stereochemistry of individual enantiomers (*Examples 97A and 97B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 97*).

Example 98

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



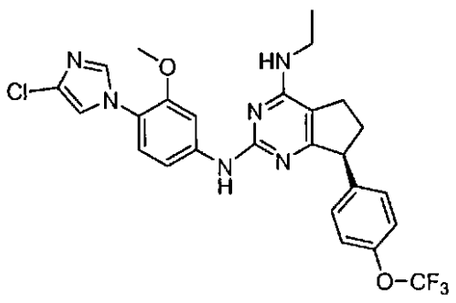
2-Chloro-*N*-ethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (190 mg, 0.531 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (178 mg, 0.797 mmol) in acetic acid (2 mL) and THF (2.000 mL). The reaction mixture was heated at 90°C overnight. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (118 mg, 0.174 mmol, 32.7 % yield). LC–MS $(M+H)^+$ = 545.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.04 (1H, s), 9.01 (1H, br s), 8.29 (1H, s), 7.44 (2H, s), 7.24 (2H, d, *J*=8.5 Hz), 7.19 (2H, d, *J*=5.5 Hz), 7.09 - 7.12 (1H, m), 5.93 - 5.99 (1H, m), 4.43 - 4.51 (1H, m), 3.86 (3H, s), 3.62 - 3.74 (2H, m), 3.46 - 3.55 (1H, m), 2.85 - 2.97 (1H, m), 2.71 - 2.82 (2H, m), 2.26 (1H, m), 1.26 - 1.41 (3H, m).

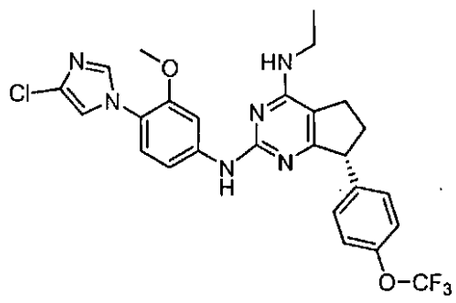
Example 98A & 98B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

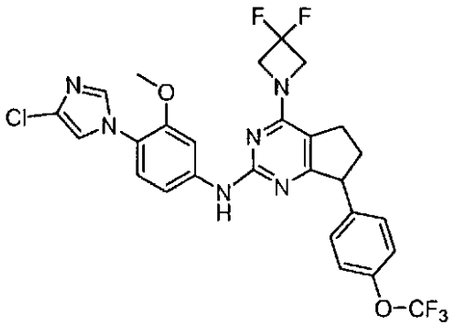




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (111 mg, 0.204 mmol from *Example 98*) was purified using chiral SFC to afford 29.5 mg of peak A (*Example 98A*) and 37.7 mg of peak B (*Example 98B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 30 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 12 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 3.4 min, t_R (peak B) 8.2 min. The absolute stereochemistry of individual enantiomers (*Examples 98A and 98B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 98*).

Example 99

N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



2-Chloro-4-(3,3-difluoroazetidin-1-yl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (244 mg, 0.601 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (202 mg, 0.902 mmol) in acetic acid (2 mL) and THF (2.000 mL). The reaction mixture was heated at 110°C overnight. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine, TFA salt (165.2 mg, 0.229 mmol, 38.1 % yield). LC–MS $(M+H)^+$ = 593.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.83 (1H, s), 8.00 (1H, s), 7.38 - 7.43 (1H, m), 7.30 - 7.33 (1H, m), 7.27 - 7.28 (1H, m), 7.16 - 7.22 (3H, m), 7.09 -

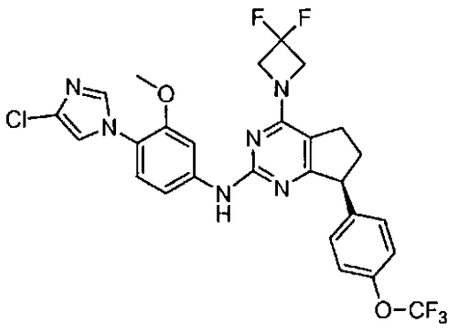
7.12 (1H, m), 4.76 (1H, br s), 4.46 (1H, dd, *J*=9.5, 4.9 Hz), 3.85 (3H, s), 3.07 - 3.17 (2H, m), 2.95 - 3.04 (2H, m), 2.70 - 2.81 (2H, m), 2.21 - 2.34 (2H, m).

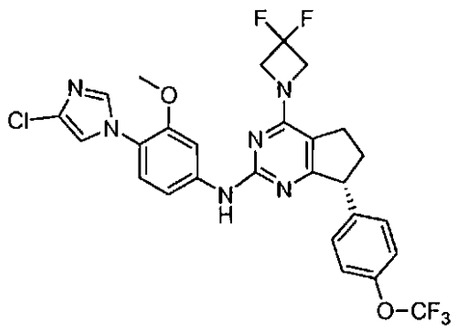
Example 99A & 99B

(S)-N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

and

(R)-N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

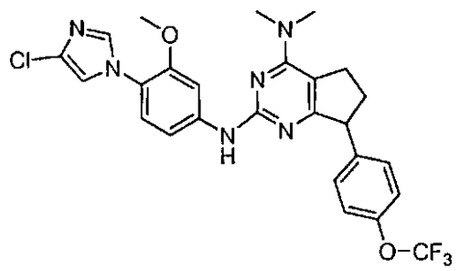




A racemic mixture of *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine (165.2 mg, 0.279 mmol from *Example 99*) was purified using chiral SFC to afford 16.7 mg of peak A (*Example 99A)* and 17.0 mg of peak B (*Example 99B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 30 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 20 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 4.9 min, t_R (peak B) 15.0 min. The absolute stereochemistry of individual enantiomers (*Examples 99A and 99B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 99*).

Example 100

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



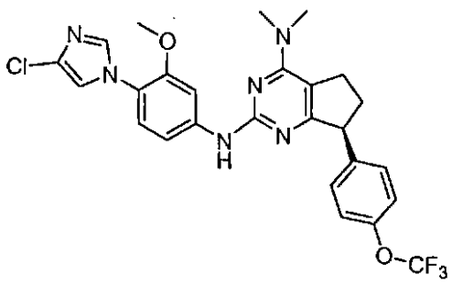
2-Chloro-*N*,*N*-dimethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (250 mg, 0.699 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (234 mg, 1.048 mmol) in acetic acid (1 mL) and THF (1 mL). The reaction mixture was heated at 110°C overnight. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (235 mg, 0.342 mmol, 49.0 % yield). LC–MS $(M+H)^+ = 545.3$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.18 - 11.39 (1H, m), 8.11 (1H, s), 7.40 - 7.45 (1H, m), 7.30 - 7.34 (1H, m), 7.28 (1H, s), 7.17 - 7.23 (3H, m), 7.12 - 7.15 (1H, m), 4.34 - 4.44 (1H, m), 3.84 (3H, s), 3.50 (4H, s), 3.33 - 3.39 (3H, m), 3.18 - 3.27 (1H, m), 2.57 - 2.78 (1H, m), 2.10 - 2.39 (1H, m).

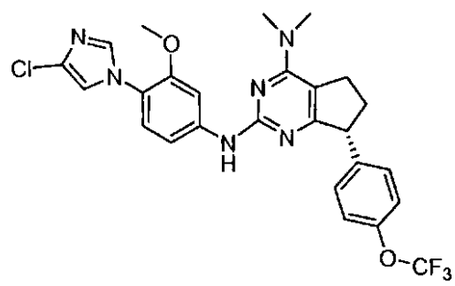
Example 100A & 100B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



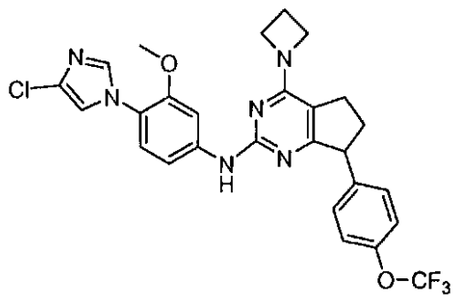


A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-

cyclopenta[*d*]pyrimidine-2,4-diamine (235 mg, 0.431 mmol from *Example 100*) was purified using chiral SFC to afford 29.2 mg of peak A (*Example 100A*) and 29.2 mg of peak B (*Example 100B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 30 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 11 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 3.7 min, t_R (peak B) 8.4 min. The absolute stereochemistry of individual enantiomers (*Examples 100A and 100B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 100*).

Example 101

4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



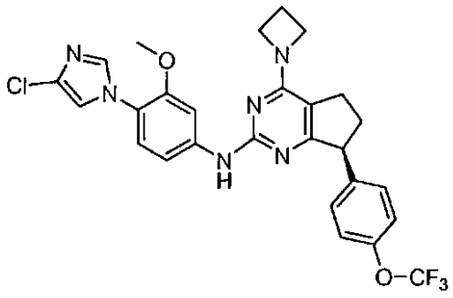
4-(Azetidin-1-yl)-2-chloro-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (238 mg, 0.644 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (216 mg, 0.965 mmol) in acetic acid (2 mL) and THF (2 mL). The reaction mixture was heated at 85°C overnight. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford 4-(azetidin-1-yl)-*N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine, TFA salt (99.3 mg, 0.148 mmol, 22.99 % yield). LC–MS $(M+H)^+$ = 557.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.78 (1H, s), 7.51 - 7.65 (2H, m), 7.33 - 7.40 (1H, m), 7.26 (2H, d, *J*=3.1 Hz), 7.17 (3H, s), 7.04 (1H, s), 4.58 - 4.71 (2H, m), 4.27 - 4.46 (3H, m), 3.82 (3H, s), 2.91 - 3.17 (2H, m), 2.61 - 2.74 (1H, m), 2.50 - 2.60 (2H, m), 2.14 - 2.30 (1H, m).

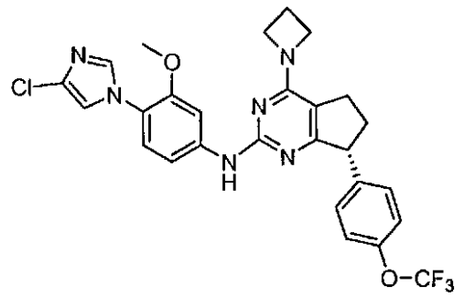
Example 101A & 101B

(S)-4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

and

(R)-4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

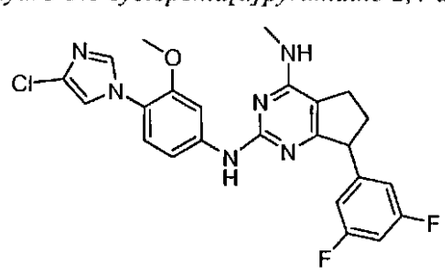




A racemic mixture of 4-(azetidin-1-yl)-*N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine (92 mg, 0.165 mmol from *Example 101*) was purified using chiral SFC to afford 37.6 mg of peak A (*Example 101A*) and 39.1 mg of peak B (*Example 101B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 30 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 18 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 4.7 min, t_R (peak B) 13.6 min. The absolute stereochemistry of individual enantiomers (*Examples 101A and 101B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 101*).

Example 102

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,5-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

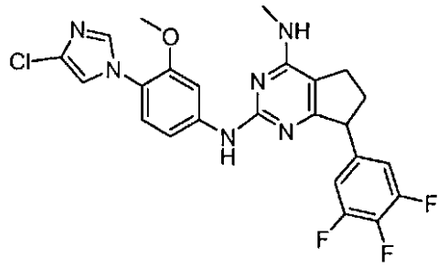


2-Chloro-7-(3,5-difluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (60 mg, 0.203 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (68.1 mg, 0.304 mmol) in acetic acid (2 mL) and THF (2.000 mL). The reaction mixture was heated at 80°C overnight. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(3,5-difluorophenyl)-N^4-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (33.6 mg, 0.056 mmol, 27.5 % yield). LC–MS $(M+H)^+ = 483.0$. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.79 (1H, s), 7.70 (1H, s), 7.29 - 7.45 (2H, m), 7.22 (1H, d, *J*=8.5 Hz), 6.86 - 7.03 (3H, m), 4.27 - 4.60 (1H, m), 3.89 (3H, s), 3.24 - 3.48 (5H, m), 3.17 (1H, s), 2.88 - 3.01 (1H, m), 2.67 - 2.87 (1H, m), 2.03 - 2.32 (1H, m).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 102A and 102B as free amines, which had identical spectral data.

Example 103

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



2-Chloro-*N*-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (100 mg, 0.319 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (107 mg, 0.478 mmol) in acetic acid (2 mL) and THF (2.000 mL). The reaction mixture was heated at 80°C overnight. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (36.3 mg, 0.057 mmol, 17.78 % yield). LC–MS $(M+H)^+ = 501.0$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.88 - 11.96 (1H, m), 7.95 - 8.01 (1H, m), 7.44 - 7.62 (2H, m), 7.09 - 7.19

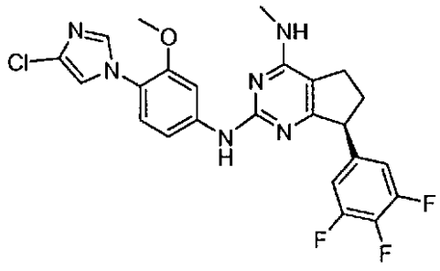
(1H, m), 6.86 - 6.95 (2H, m), 5.55 - 5.66 (1H, m), 5.26 - 5.39 (1H, m), 4.36 - 4.54 (1H, m), 3.90 (3H, s), 3.22 - 3.33 (3H, m), 2.72 - 2.87 (3H, m), 2.18 - 2.38 (1H, m).

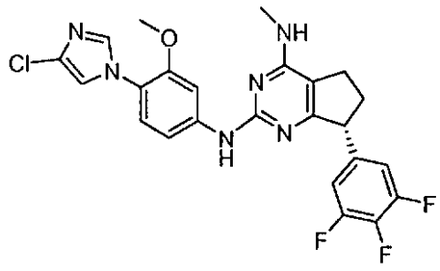
Example 103A & 103B

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

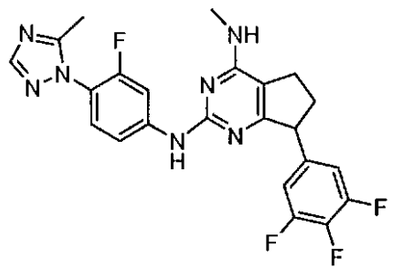




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (59.8 mg, 0.119 mmol from *Example 103*) was purified using chiral SFC to afford 19.5 mg of peak A (*Example 103A*) and 34.8 mg of peak B (*Example 103B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 20 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 16 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 9.7 min, t_R (peak B) 11.9 min. The absolute stereochemistry of individual enantiomers (*Examples 103A and 103B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 103*).

Example 104

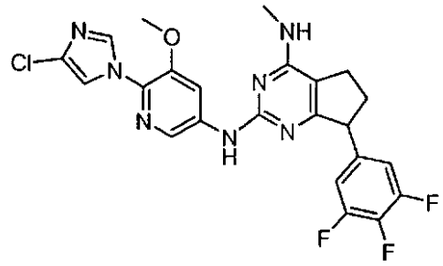
N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



2-Chloro-*N*-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (65.3 mg, 0.208 mmol) was added to a solution of 3-fluoro-4-(5-methyl-1*H*-1,2,4-triazol-1-yl)aniline (40 mg, 0.208 mmol) in acetic acid (2 mL) and THF (2.000 mL). The reaction mixture was heated at 80°C overnight. Partial formation of the desired product was observed. The reaction mixture was heated at 130°C for 6 h. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(3-fluoro-4-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (5.3 mg, 8.99 μmol, 4.32 % yield). LC–MS $(M+H)^+$ = 470.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 12.17 (1 H, s), 8.75 (1 H, d, *J*=1.8 Hz), 8.05 (1 H, dd, *J*=13.7, 2.1 Hz), 7.80 (1 H, t, *J*=8.7 Hz), 7.44 - 7.65 (1 H, m), 6.74 - 6.99 (2 H, m), 5.33 - 5.66 (1 H, m), 4.34 - 4.67 (1 H, m), 3.42 - 3.74 (2 H, m), 3.29 (3 H, d, *J*=4.9 Hz), 2.70 - 2.99 (2 H, m), 2.57 (2 H, s), 2.14 - 2.38 (1 H, m).

Example 105

N^2-(6-(4-Chloro-1H-imidazol-1-yl)-5-methoxypyridin-3-yl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

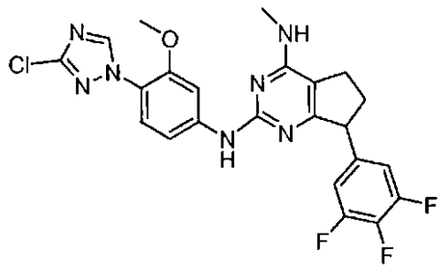


2-Chloro-*N*-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (100 mg, 0.319 mmol) was added to a solution of 6-(4-chloro-1*H*-imidazol-1-yl)-5-methoxypyridin-3-amine (107 mg, 0.478 mmol) in acetic acid (2 mL) and THF (2.000 mL). The reaction mixture was heated at 80°C overnight.

Partial formation of the desired product was observed. The reaction mixture was heated at 130°C for 6 h. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(6-(4-chloro-1*H*-imidazol-1-yl)-5-methoxypyridin-3-yl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (12.9 mg, 0.021 mmol, 6.50 % yield). LC–MS $(M+H)^+$ = 502.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 12.33 (1H, s), 8.75 (1H, s), 8.56 (1H, s), 7.61 - 7.89 (2H, m), 6.85 - 7.00 (2H, m), 5.62 - 5.79 (1H, m), 4.36 - 4.49 (1H, m), 4.02 (3H, s), 3.29 (3H, d, *J*=4.9 Hz), 2.88 - 2.98 (1H, m), 2.76 - 2.85 (2H, m), 2.21 - 2.38 (1H, m).

Example 106

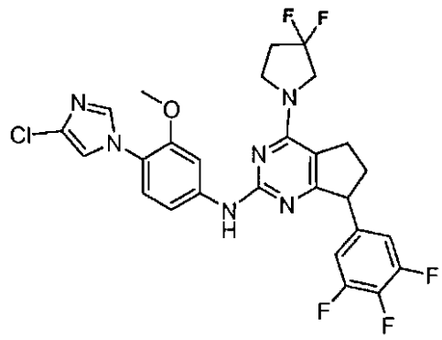
N^2-(4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



2-Chloro-*N*-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (80 mg, 0.255 mmol) was added to a solution of 4-(3-chloro-1*H*-1,2,4-triazol-1-yl)-3-methoxyaniline (86 mg, 0.383 mmol) in acetic acid (2 mL) and THF (2.000 mL). The reaction mixture was heated at 80°C overnight. Partial formation of the desired product was observed. The reaction mixture was heated at 120°C for 4 h. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(3-chloro-1*H*-1,2,4-triazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine, TFA salt (15.5 mg, 0.025 mmol, 9.77 % yield). LC–MS $(M+H)^+$ = 502.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.88 - 12.12 (1H, m), 8.63 (1H, s), 7.68 - 7.81 (1H, m), 7.60 (1H, s), 7.47 (1H, s), 6.92 (1H, t, *J*=7.2 Hz), 3.94 - 3.99 (1H, m), 3.52 (8H, s), 3.22 - 3.29 (1H, m), 2.87 - 3.01 (1H, m), 2.74 - 2.85 (1H, m), 2.22 - 2.38 (1H, m).

Example 107

N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoropyrrolidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



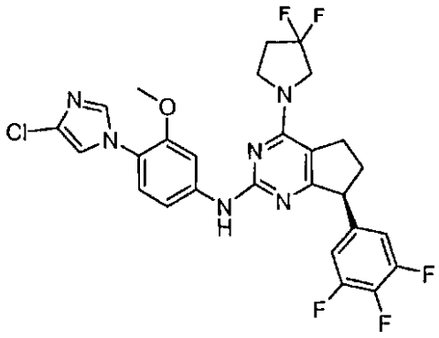
2-Chloro-4-(3,3-difluoropyrrolidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (105 mg, 0.269 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (90 mg, 0.404 mmol) in acetic acid (1 mL) and THF (1.000 mL). The reaction mixture was heated at 80°C overnight. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoropyrrolidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine, TFA salt (54.1 mg, 0.074 mmol, 27.3 % yield). LC–MS $(M+H)^+ = 577.1$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.70 (1H, s), 8.08 - 8.24 (1H, m), 7.40 - 7.57 (1H, m), 7.18 (1H, s), 6.88 - 7.01 (2H, m), 4.37 - 4.45 (1H, m), 4.24 - 4.35 (2H, m), 4.03 - 4.22 (2H, m), 3.98 - 4.03 (1H, m), 3.89 (3H, s), 3.50 - 3.58 (1H, m), 3.15 - 3.42 (2H, m), 2.48 - 2.89 (3H, m), 2.18 - 2.34 (1H, m).

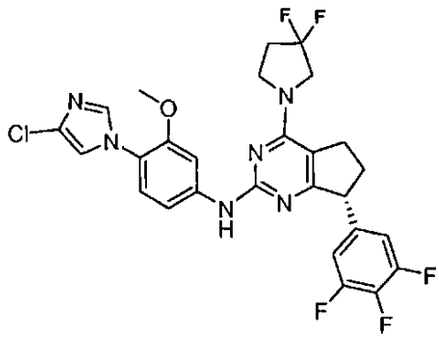
Example 107A & 107B

(S)-N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoropyrrolidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

and

(R)-N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoropyrrolidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

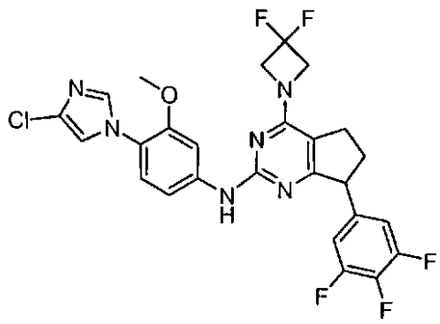




A racemic mixture of *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoropyrrolidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine (48 mg, 0.083 mmol from *Example 107*) was purified using chiral SFC to afford 19.8 mg of peak A (*Example 107A*) and 17.2 mg of peak B (*Example 107B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 25 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 30 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 17.4 min, t_R (peak B) 21.2 min. The absolute stereochemistry of individual enantiomers (*Examples 107A and 107B*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 107*).

Example 108

N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

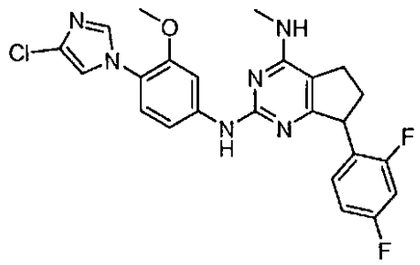


2-Chloro-4-(3,3-difluoroazetidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (105 mg, 0.279 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (94 mg, 0.419 mmol) in acetic acid (1 mL) and THF (1.000 mL). The reaction mixture was heated at 80°C overnight. The crude reaction

mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-amine, TFA salt (31.4 mg, 0.044 mmol, 15.60 % yield). LC–MS $(M+H)^+$ = 563.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.87 (1H, s), 8.09 (1H, s), 7.45 (1H, dd, *J*=8.5, 1.5 Hz), 7.36 (1H, s), 7.29 (2H, s), 7.25 (1H, d, *J*=8.5 Hz), 7.16 (1H, s), 6.91 (2H, t, *J*=6.9 Hz), 4.40 (1H, dd, *J*=9.2, 4.9 Hz), 4.00 (1H, s), 3.89 (3H, s), 3.53 (1 H, s), 3.08 - 3.19 (1H, m), 2.97 - 3.06 (1H, m), 2.72 - 2.84 (1H, m), 2.26 (1H, td, *J*=9.2, 4.3 Hz).

Example 109

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(2,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



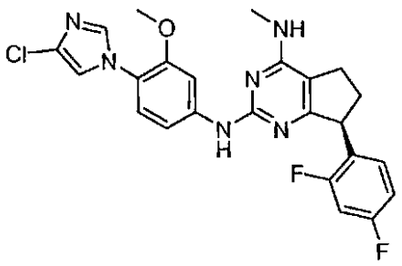
A solution of 2-chloro-7-(2,4-difluorophenyl)-*N*-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (184.6 mg, 0.624 mmol) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (140 mg, 0.624 mmol) in THF (1095 µL) and acetic acid (1095 µL) was heated 80 °C in a capped vial overnight. The solvent was evaporated in vacuum and the residue was partitioned between aqueous sodium bicarbonate solution and dichloromethane. The organic layer was separated and the aqueous layer was extracted with dichloromethane. the combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel to give N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-7-(2,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (179.6 mg, 0.372 mmol, 59.6 % yield) as brown solid. LC-MS $(M+H)^+$ = 483.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.97 (1H, d, *J*=2.1 Hz), 7.49 (1H, d, *J*=1.5 Hz), 7.01 - 7.10 (2H, m), 7.00 (1H, d, *J*=1.5 Hz), 6.73 - 6.84 (3H, m), 4.44 (1H, s), 3.61 (3H, s), 3.11 (3H, d, *J*=4.9 Hz), 2.59 - 2.77 (2H, m), 1.95 - 2.05 (2H, m).

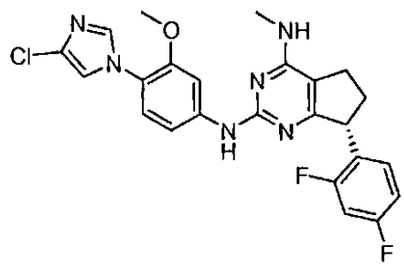
Examples 109A and 109B

(S)- N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(2,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)- N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(2,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

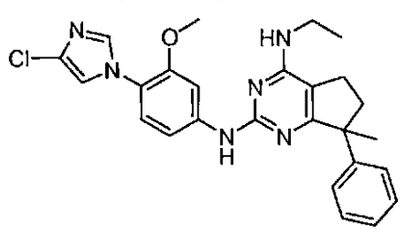




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-tridcutcromethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidinc-2,4-diamine (180 mg, 0.206 mmol from *Example 109*) was purified using chiral supercritical fluid chromatography (SFC) to afford 28.4 mg of peak A (*Example 109A*) and 27.4 mg of peak B (*Example 109B*). SFC Method: Chiralpak OJ-H (21 x 250 mm, 5 μM), 35 % methanol (0.1% diethylamine) in CO_2, 35 °C, flow rate 45 mL/min for 10 min, absorbance 268 nm, injection 0.75mL of 20 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 3.6 min, t_R (peak B) 7.2 min. The absolute stereochemistry of individual enantiomers (*Examples 109A and 109B*) was not determined. LC-MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 109*).

Example 110

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-7-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

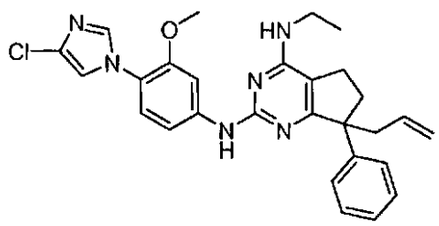


The method of Example 74 was used to combine Preparation Va and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to afford N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-7-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (Example 110).LC–MS $(M+H)^+ = 475.2$. ^{1}H NMR (500 MHz, METHANOL-*d4*) δ ppm 8.03 (1 H, d, *J*=2.14 Hz), 7.65 (1 H, s), 7.22 - 7.30 (4 H, m), 7.20 (1 H, s), 7.10 - 7.16 (2 H, m), 7.02 (1 H, dd, *J*=8.55, 2.14 Hz), 3.66 (3 H, s), 3.56 (2 H, q, *J*=7.32 Hz), 2.56 - 2.69 (2 H, m), 2.30 - 2.38 (1 H, m), 2.14 - 2.22 (1 H, m), 1.25 (3 H, d, *J*=7.20 Hz).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 110A and 110B, which had identical spectral data.

Example 111

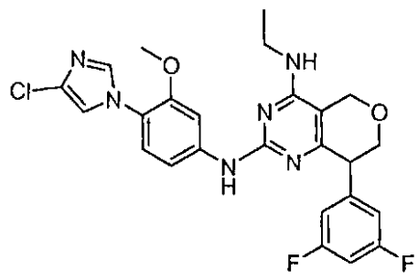
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-7-allyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



The method of Example 74 was used to combine Preparation Wa and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to afford N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-7-allyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (Example 111).LC–MS $(M+H)^+ = 501.2$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.66 (1 H, br. s.), 7.45 - 7.54 (2 H, m), 7.32 - 7.39 (5 H, m), 7.25 - 7.30 (3 H, m), 5.57 - 5.68 (1 H, m, *J*=16.94, 9.92, 7.17, 7.17 Hz), 5.42 (1 H, br. s.), 5.22 (1 H, d, *J*=16.17 Hz), 5.12 (1 H, d, *J*=10.07 Hz), 3.85 (3 H, s), 3.63 - 3.70 (2 H, m), 3.05 - 3.12 (2 H, m), 2.64 - 2.80 (2 H, m), 2.51 - 2.63 (2 H, m), 1.35 (3 H, t, *J*=7.17 Hz).

Example 112

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(3,5-difluorophenyl)-N4-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA

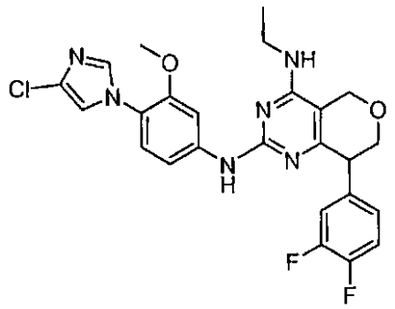


The mixture of 2-chloro-8-(3,5-difluorophenyl)-N-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Xa) (87 mg, 0.267 mmol), 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) (71.7 mg, 0.321 mmol), tris(dibenzylideneacetone)dipalladium(0) (12.23 mg, 0.013 mmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (15.45 mg, 0.027 mmol) and sodium carbonate (42.5 mg, 0.401 mmol) in Dioxane (1272 µL) / Water (254 µL) was heated at 110 °C overnight. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine and concentrated in vacuum. The crude product was purified by Prep-HPLC (Solvent A = 10% Acetonitrile - 90% H2O - 0.1% TFA, Solvent B = 90% Acetonitrile - 10% H2O - 0.1% TFA. Column: PHENOMENEX LUNA 21 x 100mm, 10uC18, Flow rate: 25 ml / min, 30- 100% B, 20 min) to obtain N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(3,5-difluorophenyl)-N4-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (Example 112) (123mg, 0.177 mmol, 66.1 % yield). LC–MS $(M+H)^+$ = 513.2. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.71 (s, 1 H) 8.04 (s, 1 H) 7.49 (d, J=2.14 Hz, 1 H) 7.43 (dd, J=8.55, 2.14 Hz, 1 H) 7.23 (d, J=8.55 Hz, 1 H) 7.17 (d, J=1.53 Hz, 1 H) 7.00 (d, J=5.80 Hz, 2 H) 6.70 - 6.84 (m, 1 H) 6.09 (t, J=5.19 Hz, 1 H) 4.73 (d, J=14.34 Hz, 1 H) 4.54 (d, J=14.34 Hz, 1 H) 3.95 - 4.15 (m, 3 H) 3.88 (s, 3 H) 3.61 - 3.78 (m, 2 H) 1.37 (t, J=7.17 Hz, 3 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 112A and 112B as free amines. LC–MS $(M+H)^+$ = 513.2. ^1H NMR (500 MHz, MeOD) δ ppm 7.84 (d, J=2.14 Hz, 1 H) 7.67 (d, J=1.53 Hz, 1 H) 7.21 (d, J=1.53 Hz, 1 H) 7.13 (d, J=8.55 Hz, 1 H) 6.98 - 7.08 (m, 1 H) 6.89 (d, J=2.14 Hz, 1 H) 6.74 - 6.85 (m, 1 H) 4.65 (d, J=14.34 Hz, 1 H) 4.46 - 4.59 (m, 1 H) 4.11 (dd, J=11.44, 4.43 Hz, 1 H) 3.96 (dd, J=11.44, 4.12 Hz, 1 H) 3.88 (d, J=3.97 Hz, 1 H) 3.66 (s, 3 H) 3.58 (q, J=7.32 Hz, 2 H) 1.27 (t, J=7.17 Hz, 3 H).

Example 113

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(3,4-difluorophenyl)-N4-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA

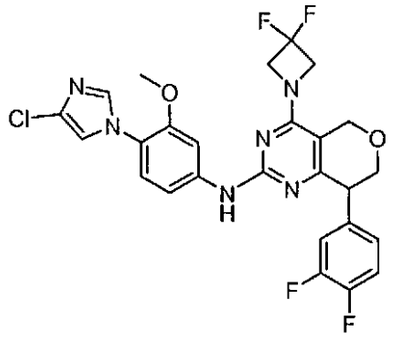


2-chloro-8-(3,4-difluorophenyl)-N-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Ya) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(3,4-difluorophenyl)-N4-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (Example 113). LC–MS $(M+H)^+ = 513.5$. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.84 (d, J=1.22 Hz, 1 H) 7.58 (d, J=2.14 Hz, 1 H) 7.32 - 7.49 (m, 3 H) 7.12 - 7.32 (m, 3 H) 4.71 (d, J=14.95 Hz, 1 H) 4.55 (d, J=14.65 Hz, 1 H) 4.14 (dd, J=11.60, 4.27 Hz, 1 H) 4.06 (br. s., 1 H) 3.92 - 4.02 (m, 1 H) 3.89 (s, 3 H) 3.68 - 3.70 (m, 2 H) 1.32 (t, J=7.17 Hz, 3 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 113A and 113B as free amines. LC–MS $(M+H)^+ = 513.3$. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.83 (d, J=2.14 Hz, 1 H) 7.67 (s, 1 H) 7.09 - 7.25 (m, 4 H) 6.96 - 7.09 (m, 2 H) 4.59 - 4.69 (m, 1 H) 4.47 - 4.57 (m, 1 H) 4.10 (dd, J=11.29, 4.27 Hz, 1 H) 3.92 (dd, J=11.60, 4.27 Hz, 1 H) 3.86 (d, J=3.36 Hz, 1 H) 3.62 - 3.68 (m, 3 H) 3.57 (q, J=7.32 Hz, 2 H) 1.22 - 1.34 (m, 3 H).

Example 114

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8- (3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine, TFA

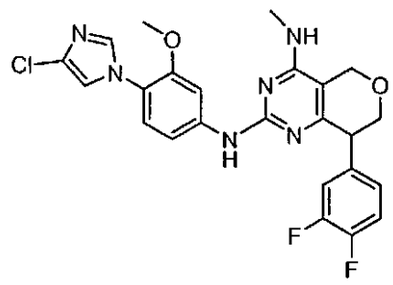


2-chloro-4-(3,3-difluoroazetidin-1-yl)-8-(3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (Preparation Yb) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline(Preparation A) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine, TFA (Example 114). LC–MS $(M+H)^+ = 561.5$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 12.12 (br. s., 1 H) 7.80 (s, 1 H) 7.38 (dd, J=8.55, 1.83 Hz, 1 H) 7.20 - 7.31 (m, 4 H) 7.09 - 7.18 (m, 2 H) 4.69 - 4.89 (m, 6 H) 4.06 (m, 3 H) 3.87 (s, 3 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 114A and 114B as free amines. LC–MS $(M+H)^+ = 561.3$. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.74 (s, 1 H) 7.66 (s, 1 H) 7.10 - 7.24 (m, 4 H) 7.08 (d, J=1.53 Hz, 1 H) 7.02 (d, J=8.55 Hz, 1 H) 4.76 - 4.84 (m, 1 H) 4.68 (d, J=14.04 Hz, 1 H) 4.59 (t, J=12.21 Hz, 4 H) 4.14 (dd, J=11.29, 3.66 Hz, 1 H) 3.98 (br. s., 1 H) 3.86 - 3.94 (m, 1 H) 3.59 (s, 3 H).

Example 115

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(3,4-difluorophenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA

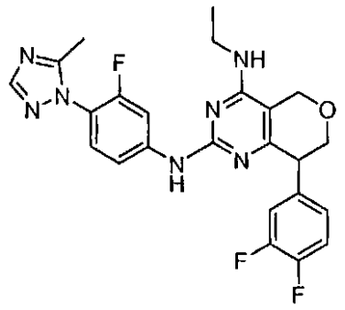


2-chloro-8-(3,4-difluorophenyl)-N-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Yc) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline(Preparation A) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(3,4-difluorophenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (Example 115). LC–MS $(M+H)^+$ = 499.5. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.86 (d, J=1.53 Hz, 1 H) 7.66 (d, J=2.14 Hz, 1 H) 7.26 - 7.41 (m, 4 H) 7.17 - 7.25 (m, 2 H) 4.70 (d, J=14.65 Hz, 1 H) 4.54 (dd, J=14.95, 1.53 Hz, 1 H) 4.15 (dd, J=11.60, 4.27 Hz, 1 H) 4.07 (br. s., 1 H) 3.96 (dd, J=11.60, 3.36 Hz, 1 H) 3.89 (s, 3 H) 3.16 (s, 3 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 115A and 115B as free amines. LC–MS $(M+H)^+$ = 499.3. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.90 (d, J=2.14 Hz, 1 H) 7.67 (d, J=1.53 Hz, 1 H) 7.12 - 7.25 (m, 4 H) 7.07 (d, J=2.14 Hz, 1 H) 6.98 - 7.05 (m, 1 H) 4.63 (d, J=14.34 Hz, 1 H) 4.45 - 4.57 (m, 1 H) 4.11 (dd, J=11.44, 4.43 Hz, 1 H) 3.93 (dd, J=11.44, 4.43 Hz, 1 H) 3.87 (d, J=3.97 Hz, 1 H) 3.61 - 3.70 (m, 3 H) 3.00 - 3.08 (m, 3 H).

Example 116

8-(3,4-difluorophenyl)-N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA



2-chloro-8-(3,4-difluorophenyl)-N-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Ya) was reacted as described in Example 112 with 3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline (Preparation C) to give 8-(3,4-difluorophenyl)-N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (Example 116).

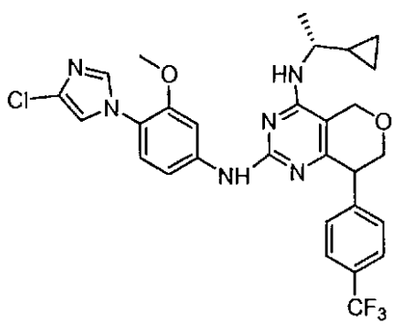
LC–MS $(M+H)^+$ = 482.3 ^{1}H NMR (500 MHz, MeOD) δ ppm 8.13 (s, 1 H) 7.95 (dd, J=12.36, 1.98 Hz, 1 H) 7.47 - 7.62 (m, 2 H) 7.30 - 7.42 (m, 1 H) 7.23 - 7.30 (m, 1 H) 7.21

(br. s., 1 H) 4.72 (d, J=14.95 Hz, 1 H) 4.55 (d, J=14.95 Hz, 1 H) 4.14 (dd, J=11.44, 4.12 Hz, 1 H) 4.07 (br. s., 1 H) 3.91 - 4.01 (m, 1 H) 3.58 - 3.75 (m, 2 H) 2.44 (s, 3 H) 1.26 - 1.43 (m, 3 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 116A and 116B as free amines. LC–MS $(M+H)^+ = 482.3$. ^{1}H NMR ^{1}H NMR (500 MHz, MeOD) δ ppm 8.05 (d, J=2.14 Hz, 1 H) 8.03 (s, 1 H) 7.27 - 7.34 (m, 2 H) 7.17 - 7.25 (m, 2 H) 7.12 (d, J=1.83 Hz, 1 H) 4.61 - 4.68 (m, 1 H) 4.56 (t, J=14.19 Hz, 1 H) 4.15 (dd, J=11.29, 4.58 Hz, 1 H) 4.00 (dd, J=11.44, 4.73 Hz, 1 H) 3.90 (d, J=4.27 Hz, 1 H) 3.58 - 3.66 (m, 2 H) 2.38 (s, 3 H) 1.19 (t, J=7.02 Hz, 3 H).

Example 117

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((R)-1-cyclopropylethyl)-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA

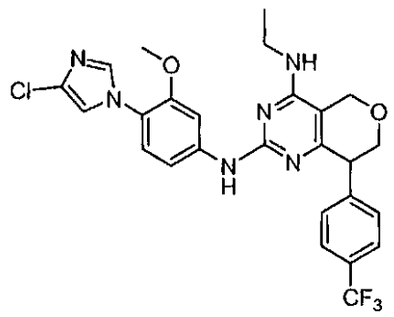


2-chloro-N-((R)-1-cyclopropylethyl)-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Zc) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline(Preparation A) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((R)-1-cyclopropylethyl)-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (Example 117). LC–MS $(M+H)^+ = 585.4$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.95 (s, 1 H) 7.68 (d, J=1.53 Hz, 1 H) 7.52 - 7.65 (m, 4 H) 7.31 - 7.43 (m, 2 H) 7.16 - 7.22 (m, 1 H) 7.10 (d, J=1.53 Hz, 1 H) 5.62 (t, J=7.02 Hz, 1 H) 4.75 (dd, J=14.34, 4.88 Hz, 1 H) 4.58 (dd, J=13.89, 8.39 Hz, 1 H) 4.11 (d, J=2.14 Hz, 3 H) 3.73 - 3.91 (m, 4 H) 1.40 (dd, J=10.38, 6.71 Hz, 3 H) 1.06 (ddd, J=7.78, 3.05, 2.90 Hz, 1 H) 0.69 (dt, J=8.62, 4.39 Hz, 1 H) 0.51 - 0.64 (m, 1 H) 0.38 (ddd, J=14.50, 9.77, 4.73 Hz, 1 H) 0.32 (dd, J=9.61, 4.73 Hz, 1 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 117A and 117B as free amines. LC–MS $(M+H)^+ = 585.1$. ^1H NMR (500 MHz, MeOD) δ ppm 7.73 (d, J=2.14 Hz, 1 H) 7.56 - 7.68 (m, 3 H) 7.44 (d, J=8.24 Hz, 2 H) 7.19 (d, J=1.53 Hz, 1 H) 7.09 (d, J=8.55 Hz, 1 H) 6.94 (dd, J=8.55, 2.14 Hz, 1 H) 4.65 - 4.72 (m, 1 H) 4.52 - 4.62 (m, 1 H) 4.16 (dd, J=11.44, 4.73 Hz, 1 H) 3.92 (dd, J=11.29, 4.88 Hz, 1 H) 3.89 (dd, J=8.24, 6.71 Hz, 1 H) 3.49 (s, 3 H) 3.06 (q, J=7.32 Hz, 1 H) 1.22 - 1.41 (m, 3 H) 1.08 (dt, J=8.24, 4.88 Hz, 1 H) 0.51 - 0.59 (m, 1 H) 0.48 (dd, J=8.39, 5.04 Hz, 1 H) 0.39 (dd, J=9.77, 4.58 Hz, 1 H) 0.19 - 0.33 (m, 1 H).

Example 118

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA



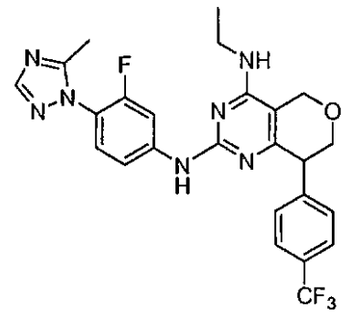
2-chloro-N-ethyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Za) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline(Preparation A) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (Example 118). LC–MS $(M+H)^+ = 545.3$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.87 (s, 1 H) 7.68 (d, J=1.22 Hz, 1 H) 7.59 (m, 4 H) 7.49 (d, J=2.14 Hz, 1 H) 7.40 (dd, J=8.55, 2.14 Hz, 1 H) 7.20 (d, J=8.55 Hz, 1 H) 7.11 (d, J=1.53 Hz, 1 H) 6.38 (br. s., 1 H) 4.76 (d, J=14.34 Hz, 1 H) 4.57 (d, J=13.73 Hz, 1 H) 4.07 - 4.16 (m, 3 H) 3.86 (s, 3 H) 3.59 - 3.77 (m, 2 H) 1.36 (t, J=7.17 Hz, 3 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 118A and 118B as free amines. LC–MS $(M+H)^+ = 545.1$. ^1H NMR (500 MHz, MeOD) δ ppm 7.79 (d, J=1.83 Hz, 1 H) 7.56 - 7.70 (m, 3 H) 7.43 (d, J=7.93 Hz, 2 H) 7.19 (d, J=1.53 Hz, 1 H) 7.11 (d, J=8.55 Hz, 1 H) 6.91 - 7.03 (m, 1 H) 4.60 -

4.72 (m, 1 H) 4.48 - 4.60 (m, 1 H) 4.15 (dd, J=11.14, 4.43 Hz, 1 H) 3.99 (t, J=4.27 Hz, 1 H) 3.87 - 3.97 (m, 1 H) 3.46 - 3.66 (m, 5 H) 1.28 (t, J=7.17 Hz, 3 H).

Example 119

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA

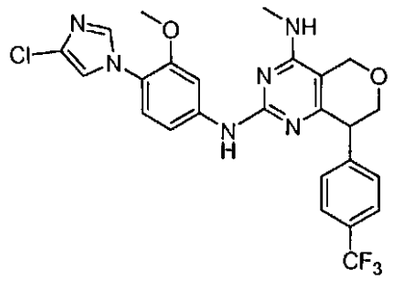


2-chloro-N-ethyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Za) was reacted as described in Example 112 with 3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)aniline (Preparation C) to give N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (Example 119). LC–MS $(M+H)^+ = 514.3$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 12.20 (br. s., 1 H) 8.01 (s, 1 H) 7.93 (dd, J=12.36, 2.29 Hz, 1 H) 7.59 (m, 4 H) 7.52 (dd, J=8.85, 1.53 Hz, 1 H) 7.38 (t, J=8.39 Hz, 1 H) 5.97 (br. s., 1 H) 4.72 (d, J=14.34 Hz, 1 H) 4.54 (d, J=13.73 Hz, 1 H) 3.99 - 4.18 (m, 3 H) 3.57 - 3.75 (m, 2 H) 2.43 (s, 3 H) 1.37 (t, J=7.17 Hz, 3 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 119A and 119B as free amines. LC–MS $(M+H)^+ = 514.1$. ^{1}H NMR (500 MHz, MeOD) δ ppm 8.02 (s, 1 H) 8.00 (dd, J=14.04, 2.14 Hz, 1 H) 7.62 (m, J=8.24 Hz, 2 H) 7.48 (m, J=8.24 Hz, 2 H) 7.21 - 7.34 (m, 2 H) 4.62 - 4.72 (m, 1 H) 4.52 - 4.62 (m, 1 H) 4.15 - 4.27 (m, 1 H) 3.94 - 4.09 (m, 2 H) 3.58 (q, J=7.32 Hz, 2 H) 2.36 (s, 3 H) 1.30 (t, J=7.17 Hz, 3 H).

Example 120

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA

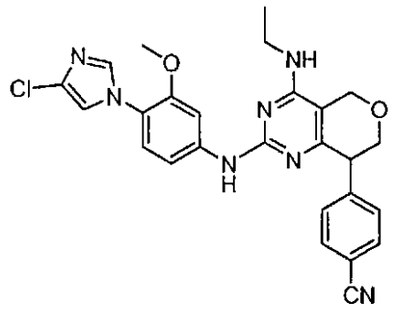


2-chloro-N-methyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (Preparation Zb) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine, TFA (Example 120). LC–MS $(M+H)^+$ = 531.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.80 (s, 1 H) 7.87 (d, J=1.53 Hz, 1 H) 7.51 - 7.63 (m, 5 H) 7.40 (dd, J=8.85, 2.14 Hz, 1 H) 7.28 (s, 1 H) 7.20 (d, J=8.55 Hz, 1 H) 6.56 (d, J=4.58 Hz, 1 H) 4.76 (d, J=14.34 Hz, 1 H) 4.57 (d, J=14.04 Hz, 1 H) 4.01 - 4.14 (m, 3 H) 3.87 (s, 3 H) 3.21 (d, J=4.58 Hz, 3 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 120A and 120B as free amines. LC–MS $(M+H)^+$ = 531.1. ^{1}H NMR (500 MHz, MeOD) δ ppm 7.86 (d, J=2.14 Hz, 1 H) 7.65 (d, J=1.53 Hz, 1 H) 7.60 (m, J=7.93 Hz, 2 H) 7.43 (m, J=7.93 Hz, 2 H) 7.19 (d, J=1.53 Hz, 1 H) 7.11 (d, J=8.55 Hz, 1 H) 6.96 (dd, J=8.55, 2.14 Hz, 1 H) 4.59 - 4.68 (m, 1 H) 4.48 - 4.56 (m, 1 H) 4.15 (dd, J=11.29, 4.58 Hz, 1 H) 3.98 - 4.03 (m, 1 H) 3.92 (dd, J=11.29, 4.88 Hz, 1 H) 3.52 (s, 3 H) 3.04 (s, 3 H).

Example 121

4-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile, TFA



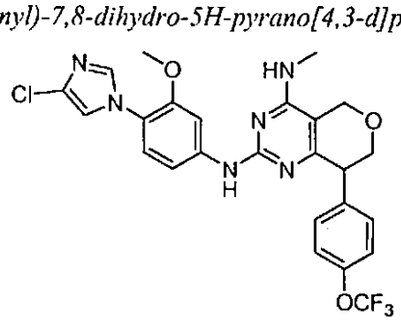
4-(2-chloro-4-(ethylamino)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile

(Preparation AAa) was reacted as described in Example 112 with 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline(Preparation A) to give 4-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile, TFA (Example 121). LC–MS $(M+H)^+ = 502.3$. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 11.80 (s, 1 H) 7.93 (s, 1 H) 7.61 - 7.66 (m, 2 H) 7.55 - 7.61 (m, 2 H) 7.48 (d, J=1.83 Hz, 1 H) 7.41 (dd, J=8.55, 2.14 Hz, 1 H) 7.22 (d, J=8.85 Hz, 1 H) 7.15 (d, J=1.53 Hz, 1 H) 6.22 (t, J=5.34 Hz, 1 H) 4.76 (d, J=14.34 Hz, 1 H) 4.57 (d, J=14.34 Hz, 1 H) 4.09 (s, 3 H) 3.87 (s, 3 H) 3.66 - 3.75 (m, 2 H) 1.37 (t, J=7.32 Hz, 3 H).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 121A and 121B as free amines. LC–MS $(M+H)^+ = 502.1$. ^1H NMR (500 MHz, MeOD) δ ppm 7.80 (d, J=2.14 Hz, 1 H) 7.67 (d, J=2.14 Hz, 2 H) 7.66 (br. s., 1 H) 7.45 (d, J=8.24 Hz, 2 H) 7.22 (s, 1 H) 7.13 (d, J=8.55 Hz, 1 H) 6.98 - 7.05 (m, 1 H) 4.62 - 4.69 (m, 1 H) 4.51 - 4.57 (m, 1 H) 4.15 (dd, J=10.99, 3.97 Hz, 1 H) 3.91 - 4.02 (m, 2 H) 3.54 - 3.64 (m, 5 H) 1.28 (t, J=7.17 Hz, 3 H).

Example 122

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine



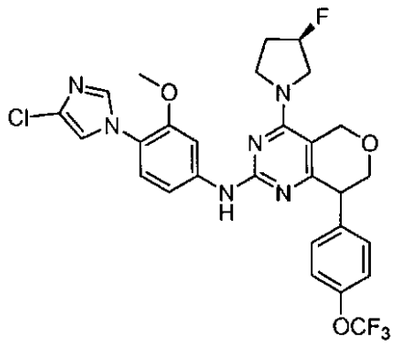
To a mixture of 2-chloro-N-methyl-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-4-amine (69.8 mg, 0.194 mmol), 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A)(52.1 mg, 0.233 mmol), XANTPHOS (11.23 mg, 0.019 mmol), Pd2(dba)3 (8.88 mg, 9.70 μmol), and Cs2CO3 (190 mg, 0.582 mmol) was added Dioxane (808 μL). The mixture was flushed with Nitrogen and placed in a capped vial and heated at 100 °C overnight.

Cooled the reaction to rt and diluted with EtOAc. Filtered through a Celite plug and rotovaped. The residue was placed on Silica gel and eluted with an EtOAc/Hex gradient to obtain N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine. LC–MS $(M+H)^+$ = 547.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.78 (1 H, s), 7.48 (1 H, s), 7.25 - 7.29 (2 H, m), 7.11 - 7.20 (2 H, m), 6.94 - 7.09 (3 H, m), 6.77 (1 H, d, *J*=8.55 Hz), 4.50 - 4.67 (2 H, m), 4.32 (1 H, d, *J*=4.88 Hz), 4.07 - 4.19 (1 H, m), 3.89 - 4.01 (2 H, m), 3.52 (3 H, s), 3.09 (3 H, d, *J*=4.58 Hz).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 122A and 122B, which had identical spectral data.

Examples 123A and 123B

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine



Individual diasteriomers

To a mixture of 2-chloro-4-((R)-3-fluoropyrrolidin-1-yl)-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (57.6 mg, 0.138 mmol), 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) (37.0 mg, 0.165 mmol), XANTPHOS (7.98 mg, 0.014 mmol), Pd2(dba)3 (6.31 mg, 6.89 μmol), and

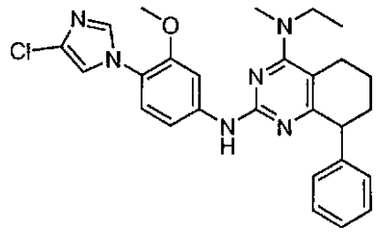
Cs2CO3 (135 mg, 0.414 mmol) was added Dioxane (574 µL). The mixture was flushed with Nitrogen and placed in a capped vial and heated at 100 °C overnight. The reaction was cooled to rt and diluted with EtOAc, then filtered through a Celite plug and concentrated. The residue was placed on Silica gel and eluted with an EtOAc/Hex gradient to obtain 2 diasteriomers (Examples 123A and 123B).

123A: LC–MS $(M+H)^+$ = 605.3. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.79 (1 H, d, *J*=1.53 Hz), 7.46 - 7.53 (3 H, m), 7.32 - 7.41 (4 H, m), 7.19 (1 H, dd, *J*=8.55, 2.14 Hz), 5.43 (1 H, d, *J*=52.50 Hz), 5.12 - 5.18 (1 H, m), 4.99 (1 H, d, *J*=14.34 Hz), 3.98 - 4.33 (6 H, m), 3.87 (3 H, s), 3.81 (1 H, dd, *J*=10.68, 6.41 Hz), 2.37 - 2.49 (1 H, m), 2.15 - 2.33 (1 H, m).

123B: LC–MS $(M+H)^+$ = 605.3. ^{1}H NMR (500 MHz, $CDCl_3$) ppm 7.56 (1 H, d, *J*=1.83 Hz), 7.48 (1 H, d, *J*=1.53 Hz), 7.22 - 7.28 (2 H, m), 7.14 (2 H, d, *J*=8.24 Hz), 7.04 (1 H, d, *J*=8.55 Hz), 6.99 (1 H, d, *J*=1.22 Hz), 6.82 (1 H, dd, *J*=8.55, 1.83 Hz), 5.33 (1 H, d, *J*=52.80 Hz), 4.90 - 5.00 (2 H, m), 4.16 - 4.26 (1 H, m), 4.10 (1 H, dd, *J*=11.44, 4.43 Hz), 3.80 - 4.01 (5 H, m), 3.50 (3 H, s), 2.32 - 2.43 (1 H, m), 2.00 - 2.19 (1 H, m).

Example 124

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine



To a solution of 2-chloro-*N*-ethyl-*N*-methyl-8-phenyl-5,6,7,8-tetrahydroquinazolin-4-amine (42.9 mg, 0.142 mmol) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (31.8 mg, 0.142 mmol) in THF (2 mL) was added 60% suspension of sodium hydride in mineral oil (6.82 mg, 0.284 mmol). The reaction mixture was heated with stirring in a capped vial at 80 °C for 1.5 h. The reaction mixture was carefully partitioned between an aqueous solution of ammonium chloride and dichloromethane. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuum and the residue was purified by

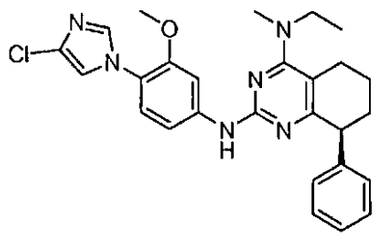
reverse-phase preparative HPLC to give N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine (31.6 mg, 0.048 mmol, 33.5 % yield) as brown oil. LC-MS $(M+H)^+$ = 489.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.50 (1H, br s), 7.74 (1H, d, *J*=1.2 Hz), 7.39 (1H, dd, *J*=8.5, 2.1 Hz), 7.29 (2H, dd, *J*=4.9, 2.7 Hz), 7.21 - 7.27 (2H, m), 7.12 - 7.19 (3H, m), 7.07 (1H, d, *J*=1.5 Hz), 4.20 (1H, t, *J*=7.0 Hz), 3.80 (3H, s), 3.68 - 3.78 (2H, m, *J*=13.8, 7.0, 7.0, 7.0, 7.0 Hz), 3.31 (3H, s), 2.64 - 2.82 (2H, m), 2.27 (1H, ddd, *J*=13.3, 7.5, 5.2 Hz), 1.88 - 1.99 (1H, m), 1.74 - 1.85 (1H, m), 1.54 - 1.67 (1H, m), 1.34 (3H, t, *J*=7.0 Hz).

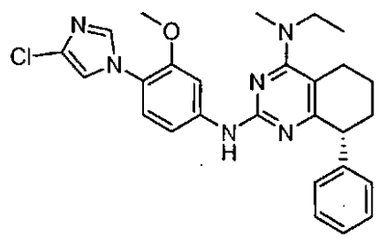
Examples 124A and 124B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine

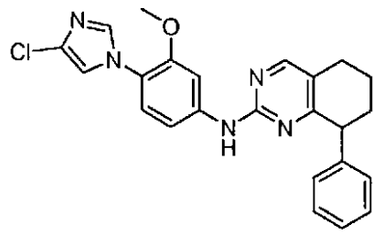




A racemic mixture of N^2-(4-(4-Chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine (183 mg, 0.206 mmol from *Example 124*) was purified using chiral supercritical fluid chromatography (SFC) to afford 54.7 mg of peak A (*Example 124A*) and 53.3 mg of peak B (*Example 124B*). SFC Method: Chiralpak OJ-H (30 x 250 mm, 5 μM), 30 % methanol (0.1% diethylamine) in CO_2, 35 °C, flow rate 70 mL/min for 105 min, absorbance 220 nm, injection 0.75 mL of 26 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 4.9 min, t_R (peak B) 12.0 min. The absolute stereochemistry of individual enantiomers (*Examples 124A and 124B*) were not determined. LC-MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 124*).

Example 125

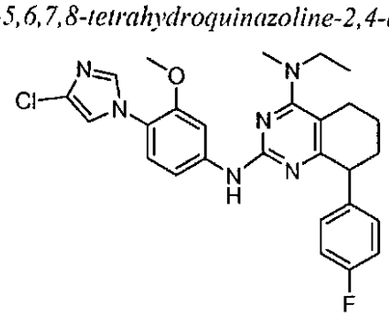
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-phenyl-5,6,7,8-tetrahydroquinazolin-2-amine



To a solution of 2-chloro-8-phenyl-5,6,7,8-tetrahydroquinazoline (33.0 mg, 0.135 mmol) and 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (33.2 mg, 0.148 mmol) in THF (1.5 mL) in a 2.0-5.0 mL microwave tube was added 0.5 M solution of KHMDS in toluene (0.809 mL, 0.405 mmol). The tube was sealed and the reaction mixture was stirred at 100 °C in a microwave for 2 h. The reaction mixture was diluted with methanol and purified using reverse-phase preparative HPLC method. The solvent was removed in vacuum and the residue was purified by reverse-phase preparative HPLC to give N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine (31.6 mg, 0.048 mmol, 33.5 % yield) as brown oil. LC-MS $(M+H)^+ = 432.3$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.68 (1H, s), 8.25 (1H, s), 8.14 (1H, s), 7.32 - 7.39 (3H, m), 7.26 - 7.32 (1H, m), 7.05 - 7.12 (3H, m), 6.96 - 7.04 (2H, m), 4.20 (1H, t, *J*=7.2 Hz), 3.41 (3H, s), 2.80 - 2.94 (2H, m), 2.30 - 2.40 (1H, m), 1.97 - 2.12 (2H, m), 1.81 - 1.93 (1H, m).

Example 126

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-8-(4-fluorophenyl)-N^4-methyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine

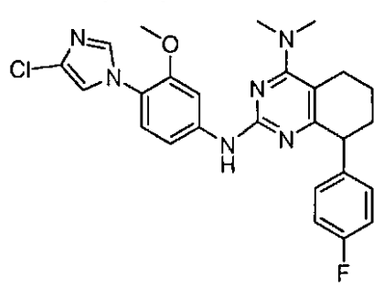


2-Chloro-*N*-ethyl-8-(4-fluorophenyl)-*N*-methyl-5,6,7,8-tetrahydroquinazolin-4-amine (124 mg, 0.388 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-

methoxyaniline (87 mg, 0.388 mmol) in THF (1 mL) and Acetic Acid (1.000 mL). The reaction mixture was stirred overnight at 75 °C. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-8-(4-fluorophenyl)-^{N4}-methyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine, TFA salt (101.3 mg, 0.153 mmol, 39.5 % yield). LC–MS $(M+H)^+$ = 507.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.77 - 11.01 (1H, m), 7.95 - 8.15 (1H, m), 7.33 - 7.44 (1H, m), 7.22 - 7.24 (1H, m), 7.19 (1H, d, *J*=8.5 Hz), 7.12 - 7.16 (2H, m), 6.96 - 7.03 (2H, m), 4.09 - 4.21 (1H, m), 3.96 (1H, s), 3.81 (4H, s), 3.67 - 3.79 (3H, m), 3.32 (3H, s), 2.19 - 2.33 (1H, m), 1.88 - 1.99 (1H, m), 1.71 - 1.81 (1H, m), 1.56 - 1.69 (1H, m), 1.26 - 1.38 (3H, m).

Example 127

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N^4,N^4-dimethyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine



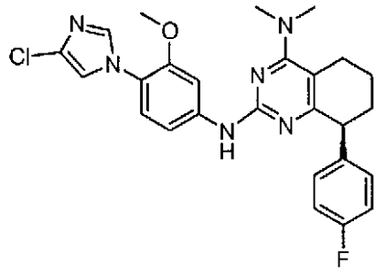
2-Chloro-8-(4-fluorophenyl)-*N*,*N*-dimethyl-5,6,7,8-tetrahydroquinazolin-4-amine (118 mg, 0.386 mmol) was added to a solution of 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (95 mg, 0.424 mmol) in THF (1 mL) and acetic acid (1.000 mL). The reaction mixture was stirred overnight at 75°C. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were evaporated to afford N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N^4,N^4-dimethyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine, TFA salt (74.8 mg, 0.123 mmol, 31.9 % yield). LC–MS $(M+H)^+$ = 493.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.69 (1H, s), 7.59 (1H, d, *J*=1.2 Hz), 7.36 (2H, d, *J*=2.1 Hz), 7.14 (3H, d, *J*=9.2 Hz), 7.05 (1H, d, *J*=1.5 Hz), 6.99 (2H, s), 4.17 - 4.27 (1H, m), 3.81 (3H, s), 3.47 (1H, s), 3.36 (5H, s), 2.65 - 2.84 (2H, m), 2.21 - 2.33 (1H, m), 1.87 - 1.98 (1H, m), 1.69 - 1.81 (1H, m), 1.53 - 1.67 (1H, m).

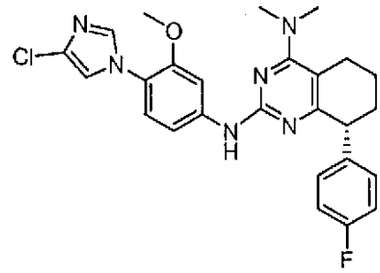
Examples 127A & 127B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N^4,N^4-dimethyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N^4,N^4-dimethyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine

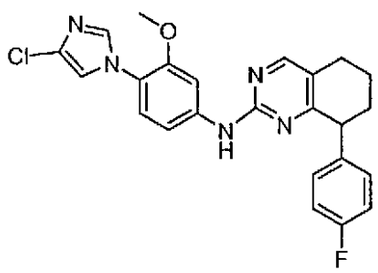




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N^4,N^4-dimethyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine (*Example 127*) was purified using chiral SFC to afford peak A (*Example 127A*) and peak B (*Example 127B*). SFC Method: Chiralpak OJ-H (4.6 x 250 mm, 5 μM), 30 % methanol (0.1% diethylamine) in CO_2, 35°C, flow rate 2.0 mL/min for 13 min, absorbance 268 nm, injection 5μL of 2 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 4.3 min, t_R (peak B) 9.6 min. The absolute stereochemistry of individual enantiomers (*Examples 7 and 8*) was not determined. LC–MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 127*).

Example 128

N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazolin-2-amine

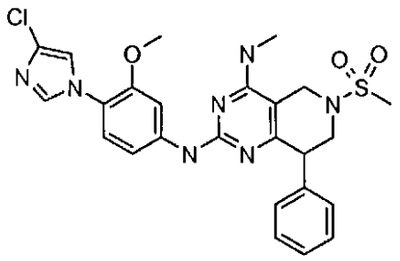


To a solution of 2-chloro-8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazoline (20 mg, 0.076 mmol) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (18.73 mg, 0.084

mmol) in THF (1.5 mL) in a 2.0-5.0 mL microwave tube, was added a 0.5 M solution of KHMDS (0.167 mL, 0.084 mmol). The tube was sealed and the reaction mixture was stirred at 100°C in a microwave for 2 h. The reaction mixture was diluted with methanol and purified using preparative HPLC. The appropriate fractions were evaporated to afford *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydroquinazolin-2-amine, TFA salt (0.7 mg, 1.229 μmol, 1.614 % yield). LC–MS $(M+H)^+ = 450.2$. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.14 - 8.26 (1H, m), 7.56 - 7.62 (1H, m), 7.43 - 7.48 (1H, m), 7.28 - 7.31 (1H, m), 7.21 (1H, s), 6.98 - 7.10 (6H, m), 6.88 - 6.94 (1H, m), 4.08 - 4.18 (1H, m), 2.77 - 2.83 (3H, m), 2.23 - 2.32 (1H, m), 1.91 - 2.13 (3H, m), 1.25 (1H, s).

Example 129

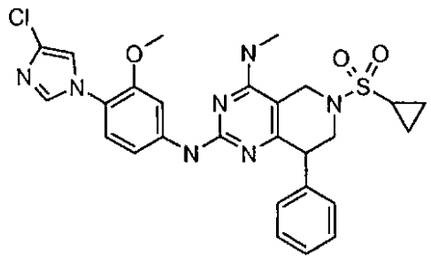
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AEj (0.2 g, 0.433 mmol) in dichloromethane was added diisopropylethylamine (0.11 g, 0.867 mmol) at -10 °C followed by addition of methane sulfonyl chloride (0.055 g, 0.477 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.105 g, 48%) as off-white solid. LC–MS $(M+H)^+ = 540.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.20 (1H, s), 8.03 (1H, s), 7.72 (1H, s), 7.41 (1H, s), 7.31 - 7.03 (8H, m), 4.21 (1H, m), 4.11 (2H, m), 3.60-3.47 (5H, m), 2.96 (3H, d, $J = 4.4$ Hz), 2.89 (3H, s).
The example was separated by chiral chromatography to afford the enantiomers 129A and 129B, which had identical spectral data.

Example 130

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-6-(cyclopropylsulfonyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

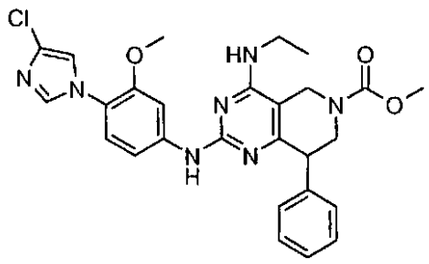


To a solution of Preparation AEj (0.32 g, 0.693 mmol) in dichloromethane was added diisopropylethylamine (0.18 g, 1.38 mmol) at -10 °C followed by addition of cyclopropyl sulfonyl chloride (0.117 g, 0.832 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-6-(cyclopropylsulfonyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.11 g, 35%) as white solid. LC–MS $(M+H)^+$ = 566.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.18 (1H, s), 8.03 (1H, s), 7.72 (1H, s), 7.40 (1H, s), 7.31 - 7.04 (8H, m), 4.26 (1H, m), 4.10 (2H, m), 3.68 (1H, m), 3.68 -3.65 (4H, m), 2.98 (3H, d, *J*= 4.4 Hz), 2.54 (1H, m), 0.95 (4H, m).

The example was separated by chiral chromatography to afford the enantiomers 130A and 130B, which had identical spectral data.

Example 131

Methyl 2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate

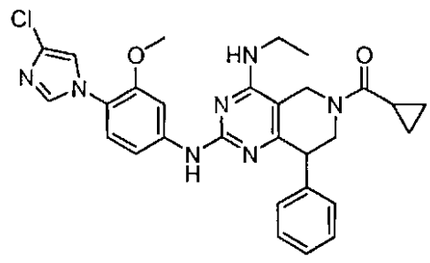


To a solution of Preparation AEk (0.15 g, 0.3 mmol) in dichloromethane was added diisopropylethylamine (0.081 g, 0.6 mmol) at -10 °C followed by addition of methylchloro formate (0.044 g, 0.3 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give methyl 2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (0.12 g, 68%) as white solid. LC–MS $(M-H)^+ = 532.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.16 (1H, s), 7.98 (1H, s), 7.73 (1H, s), 7.42 (1H, s), 7.29 - 7.26 (2H, m), 7.21- 7.12 (5H, m), 7.05 (1H, m), 4.62 (1H, m), 4.23 (1H, m), 3.96-3.87 (3H, m), 3.68 -3.51 (8H, m), 1.23 (3H, t, J = 8.0 Hz).

The example was separated by chiral chromatography to afford the enantiomers 131A and 131B, which had identical spectral data.

Example 132

(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)(cyclopropyl)methanone



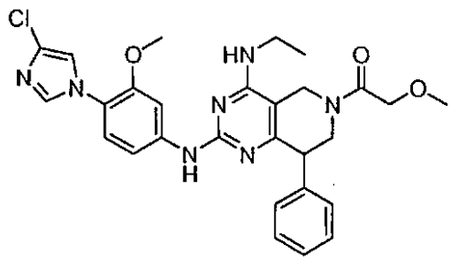
To a solution of Preparation AEk (0.35 g, 0.73 mmol) in dichloromethane was added diisopropylethylamine (0.14 g, 1.1 mmol) at -10 °C followed by addition of cyclopropylcarbonyl chloride (0.085 g, 0.81 mmol). The reaction mixture was stirred at

room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in methanol) to give (2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)(cyclopropyl)methanone (0.12 g, 30%) as white solid. LC–MS $(M+H)^+ = 544.2$. ^1H NMR (400 MHz, $CDCl_3$*6*): δ ppm 7.70 (1H, s), 7.51 (1H, s), 7.31-7.23 (3H, m), 7.12-6.99 (4H, m), 6.93 (1H, *bs*), 5.05 (1H, m), 4.22 (1H, m), 4.07 (1H, m), 3.99 (1H, m), 3.63 (1H, m), 3.59 (5H, m), 1.33 (3H, t, *J* = 7.2 Hz), 1.25 (1H, m), 0.87 (1H, m), 0.84 (2H, m), 0.63 (1H, m).

The example was separated by chiral chromatography to afford the enantiomers 132A and 132B, which had identical spectral data.

Example 133

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-methoxyethanone



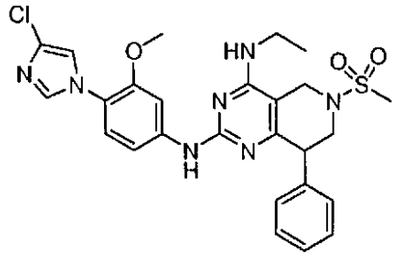
To a solution of Preparation AEk (0.187 g, 0.39 mmol) in dichloromethane was added triethylamine (0.79 g, 0.78 mmol) at -10 oC followed by addition of methoxyacetyl chloride (0.043 g, 0.42 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-methoxyethanone (0.10 g, 57%) as off-white solid. LC–MS $(M+H)^+ = 548.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.19 (1H, s), 7.99 (1H, s), 7.73 (1H, 1), 7.42 (1H, s), 7.32-7.09 (8 H, m), 4.86 (1H, m), 4.20 (2H, m),

4.09 (2H, m), 4.02-3.50 (5H, m), 3.31 (1H, m), 3.18 (1H, m), 2.99 (3H, s), 1.23 (3H, t, J = 7.2 Hz).

The example was separated by chiral chromatography to afford the enantiomers 133A and 133B, which had identical spectral data.

Example 134

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

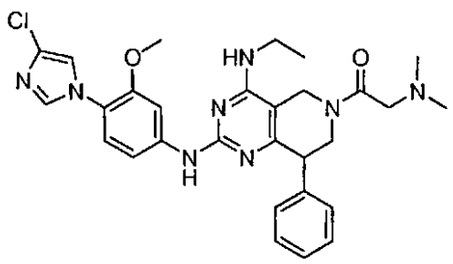


To a solution of Preparation AEk (0.10 g, 0.21 mmol) in dichloromethane was added diisopropylethylamine (0.054 g, 0.42 mmol) at -10 °C followed by addition of methanesulfonyl chloride (0.024 g, 0.21 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.06 g, 54%) as off-white solid. LC–MS $(M+H)^+$ = 554.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.17 (1H, s), 7.96 (1H, s), 7.73 (1H, s), 7.42 (1H, s), 7.32 - 7.20 (5H, m), 7.16 - 7.10 (2H, m), 6.98 (1H, m), 4.22 (1H, m), 4.11-4.03 (2H, m), 3.62-3.49 (7H, m), 2.91 (3H, s), 1.23 (3H, t, J = 7.2 Hz).

The example was separated by chiral chromatography to afford the enantiomers 134A and 134B, which had identical spectral data.

Example 135

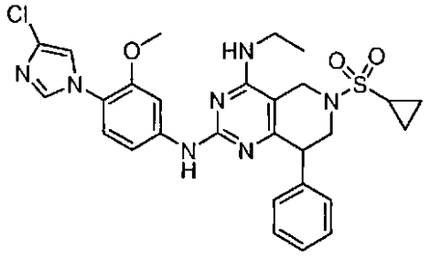
1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-(dimethylamino)ethanone



To a solution of Preparation AEk (0.15 g, 0.31 mmol) in dichloromethane was added triethylamine (0.079 g, 0.78 mmol) at -10 °C followed by addition of N,N-dimethylamionoacetyl chloride.HCl (0.054 g, 0.34 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-(dimethylamino)ethanone (0.11 g, 72%) as off-white solid. LC–MS $(M+H)^+$ = 561.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.16 (1H, s), 7.98 (1H, s), 7.72 (1H, s), 7.40 (1H, s), 7.31 - 7.11 (7H, m), 7.07 (1H, m), 4.77 (1H, m), 4.06 (2H, m), 3.94 (1H, m), 3.60 (1H, m), 3.52-3.42 (5H, m), 2.72 (1H, m), 2.28 (1H, m), 2.15 (6H, s), 1.20 (3H, m). The example was separated by chiral chromatography to afford the enantiomers 135A and 135B, which had identical spectral data.

Example 136

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-6-(cyclopropylsulfonyl)-N4-ethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



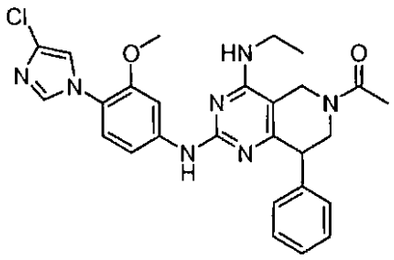
To a solution of Preparation AEk (0.15 g, 0.31 mmol) in dichloromethane was added diisopropylethylamine (0.77 g, 0.62 mmol) at -10 °C followed by addition of cyclopropanesulfonyl chloride (0.042 g, 0.31 mmol). The reaction mixture was stirred at

room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in methanol) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-6-(cyclopropylsulfonyl)-N4-ethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.10 g, 55%) as off-white solid. LC–MS $(M+H)^+ = 578.2$. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 9.15 (1H, s), 7.95 (1H, s), 7.72 (1H, s), 7.41 (1H, s), 7.29 (2H, m), 7.21 (3H, m), 7.14 (2H, m), 7.01 (1H, *bs*), 4.26 (1H, m), 4.11 (2H, m), 3.65 (1H, m), 3.56-3.51 (6H, m), 2.5 (1H, m), 1.23 (5H, m), 0.97 (2H, m).

The example was separated by chiral chromatography to afford the enantiomers 136A and 136B, which had identical spectral data.

Example 137

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)ethanone

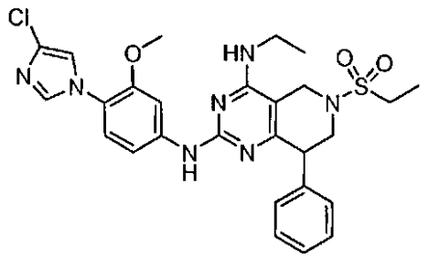


To a solution of Preparation AEk (0.15 g, 0.31 mmol) in dichloromethane was added diisopropylethylamine (0.77 g, 0.62 mmol) at -10 °C followed by addition of acetyl chloride (0.027 g, 0.31 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in methanol) to give 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)ethanone (0.09 g, 57%) as off-white solid. LC–MS $(M+H)^+ = 518.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.19 (1H, s), 8.00 (1H, s), 7.74 (1H, s), 7.42 (1H, s), 7.28 (3H, m), 7.17 - 7.07 (5H, m), 4.91 (1H, m), 4.06 (1H, m), 3.93 (1H, m), 3.82 (2H, m), 3.58-3.50 (5H, m), 1.47 (3 H, s), 1.23 (3H, m).

The example was separated by chiral chromatography to afford the enantiomers 137A and 137B, which had identical spectral data.

Example 138

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-6-(ethylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

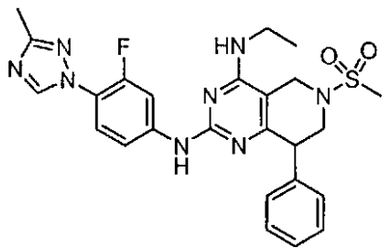


To a solution of Preparation AEk (0.15 g, 0.31 mmol) in dichloromethane was added diisopropylethylamine (0.77 g, 0.62 mmol) at -10 °C followed by addition of ethanesulfonyl chloride (0.038 g, 0.31 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in methanol) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-6-(ethylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.11 g, 62%) as off-white solid. LC–MS $(M-H)^+$ = 566.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.17 (1H, s), 7.96 (1H, s), 7.73 (1H, s), 7.42 (1H, s), 7.31 (2H, m), 7.28 (3H, m), 7.21 (2H, m), 6.97 (1H, m), 4.25 (1H, m), 4.13-4.05 (2H, m), 3.60 (1H, m), 3.58-3.50 (6H, m), 3.05 (2H, m), 1.23 (3H, t, *J*= 8.0 Hz), 1.17 (3H, t, *J* = 7.2 Hz).

The example was separated by chiral chromatography to afford the enantiomers 138A and 138B, which had identical spectral data.

Example 139

N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

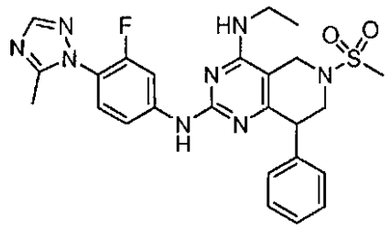


To a solution of Preparation AEm (0.20 g, 0.450 mmol) in dichloromethane was added diisopropylethylamine (0.11 g, 0.90 mmol) at -10 °C followed by addition of methanesulfonyl chloride (0.05 g, 0.450 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.048 g, 20%) as off-white solid. LC–MS $(M+H)^+$ = 523.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.44 (1H, s), 8.67 (1H, s), 8.00 (1H, m), 7.42 (2H, m), 7.39 (2H, m), 7.32 (3H, m), 7.05 (1H, m), 4.20 (1H, m), 4.08 (2H, m), 3.63 (1H, m), 3.55-3.46 (3H, m), 2.92 (3H, s), 2.33 (3H, s), 1.24 (3H, t, J = 7.2 Hz).

The example was separated by chiral chromatography to afford the enantiomers 139A and 139B, which had identical spectral data.

Example 140

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



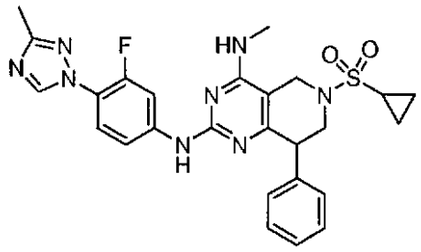
To a solution of Preparation AEo (0.25 g, 0.560 mmol) in dichloromethane was added diisopropylethylamine (0.145 g, 1.120 mmol) at -10 °C followed by addition of methanesulfonyl chloride (0.06 g, 0.560 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed

with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.05 g, 22%) as off-white solid. LC–MS $(M-H)^+$ = 521.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.47 (1H, s), 8.00 (2H, m), 7.44 (1H, m), 7.33-7.22 (6H, m), 7.05 (1H, m), 4.21 (1H, m), 4.11-4.07 (2H, m), 3.63 (1H, m), 3.57-3.50 (3H, m), 2.93 (3H, s), 2.27 (3H, s), 1.24 (3H, t, *J* = 7.2 Hz).

The example was separated by chiral chromatography to afford the enantiomers 140A and 140B, which had identical spectral data.

Example 141

6-(cyclopropylsulfonyl)-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

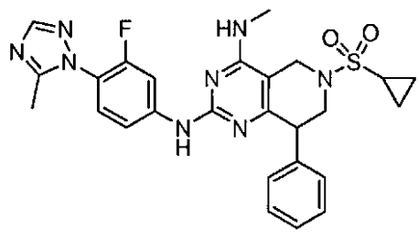


To a solution of Preparation AEI (0.23 g, 0.534 mmol) in dichloromethane was added diisopropylethylamine (0.138 g, 1.060 mmol) at -10 °C followed by addition of cyclopropanesulfonyl chloride (0.089 g, 0.640 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in methanol) to give 6-(cyclopropylsulfonyl)-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.11 g, 50%) as off-white solid. LC–MS $(M+H)^+$ = 535.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.45 (1H, s), 8.68 (1H, s), 8.03 (1H, m), 7.22 (2H, m), 7.32-7.21 (5H, m), 7.11 (1H, m), 4.25 (1H, m), 4.13 (1H, m), 4.08 (1H, m), 3.71 (1H, m), 3.64 (1H, m), 2.96 (3H, d, *J* = 4.0 Hz), 2.58 (1H, m), 2.33 (3H, s), 1.01-0.95 (4H, m).

The example was separated by chiral chromatography to afford the enantiomers 141A and 141B, which had identical spectral data.

Example 142

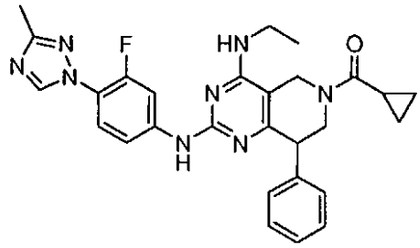
6-(cyclopropylsulfonyl)-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AEm (0.30 g, 0.690 mmol) in dichloromethane was added diisopropylethylamine (0.180 g, 1.39 mmol) at -10 °C followed by addition of cyclopropanesulfonyl chloride (0.117 g, 0.830 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in methanol) to give 6-(cyclopropylsulfonyl)-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.14 g, 45%) as off-white solid. LC–MS $(M+H)^+$ = 535.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.49 (1H, s), 8.02 (2H, m), 7.46 (1H, m), 7.44-7.33 (3H, m), 7.30-7.21 (3H, m), 7.11 (1H, m), 4.26 (1H, m), 4.15 (1H, m), 4.10 (1H, m), 3.73 (1H, m), 3.59 (1H, m), 3.28 (3H, m), 2.59 (1H, m), 2.27 (3H, s), 1.24-1.0 (4H, m).

Example 143

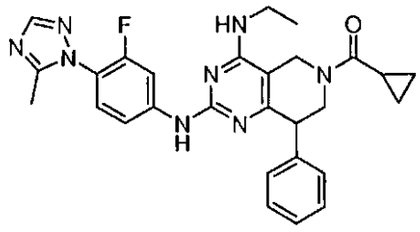
cyclopropyl(4-(ethylamino)-2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone



To a solution of Preparation AEm (0.21 g, 0.49 mmol) in dichloromethane was added diisopropylethylamine (0.12 g, 0.70 mmol) at -10 °C followed by addition of cyclopropylcarbonyl chloride (0.056 g, 0.54 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in methanol) to give cyclopropyl(4-(ethylamino)-2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone (0.090 g, 38%) as white solid. LC–MS $(M+H)^+ = 513.4$. ^{1}H NMR (400 MHz, $CDCl_3$6): δ ppm 8.41 (1H, s), 7.94 (1H, m), 7.63 (1H, m), 7.32 (3H, m), 7.27 (1H, m), 7.10 (2H, m), 4.97 (1H, m), 4.21 (1H, m), 4.10-4.0 (2H, m), 3.91 (1H, m), 3.63 (2H, m), 2.48 (3H, s), 1.35 (3H, t, $J = 7.2$ Hz), 1.22 (1H, m), 0.85 (1H, m), 0.65-0.62 (2H, m), 0.34 (1H, m). The example was separated by chiral chromatography to afford the enantiomers 143A and 143B, which had identical spectral data.

Example 144

cyclopropyl(4-(ethylamino)-2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone



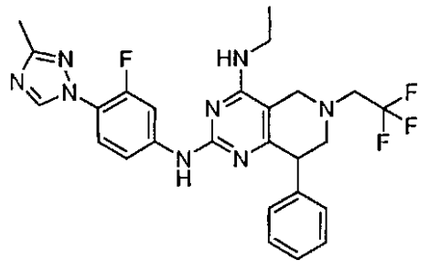
To a solution of Preparation AEo (0.30 g, 0.67 mmol) in dichloromethane was added diisopropylethylamine (0.17 g, 1.35 mmol) at -10 °C followed by addition of cyclopropylcarbonyl chloride (0.084 g, 0.81 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in methanol) to cyclopropyl(4-(ethylamino)-2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone (0.14 g, 41%) as white solid. LC–MS $(M+H)^+ = 513.4$. ^{1}H NMR (400 MHz, $CDCl_3$6): δ ppm

7.94 (2H, m), 7.32-7.25 (4H, m), 7.13 (3H, m), 4.96 (1H, m), 4.22 (1H, m), 4.13-4.04 (2H, m), 3.93 (1H, m), 3.63 (2H, m), 2.39 (3H, s), 1.35 (3H, t, J = 7.2 Hz), 1.26 (1H, m), 0.87 (1H, m), 0.66 (2H, m), 0.38 (1H, m).

The example was separated by chiral chromatography to afford the enantiomers 144A and 144B, which had identical spectral data.

Example 145

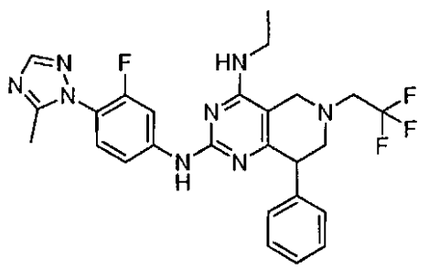
N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-6-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AEp (0.20 g, 0.37 mmol) in THF was added borane-DMS (0.061 g, 0.814 mmol, 2M in diethyl ether) at -0 °C. The reaction mixture was heated at 55 °C for 18 h. The reaction mixture was quenched with methanol and evaporated the solvent under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) get crude to give N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-6-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.025 g, 14%) as yellow solid. LC–MS $(M+H)^+$ = 527.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.32 (1H, s), 8.67 (1H, s), 8.03 (1H, m), 7.41-7.38 (2H, m), 7.27-7.18 (5H, m), 6.83 (1H, m), 3.97 (1H, m), 3.73 (1H, m), 3.57 (1H, m), 3.45 (2H, m), 3.37 (2H, m), 3.18 (1H, m), 2.97 (1H, m), 2.33 (3H., s), 1.23 (3H, t, J = 7.2 Hz).

Example 146

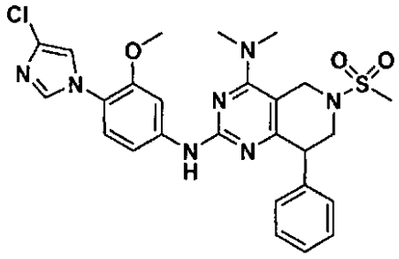
N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-6-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AEq (0.22 g, 0.40 mmol) in THF was added borane-DMS (0.068 g, 0.89 mmol, 2 M in diethyl ether) at -0 °C. The reaction mixture was heated at 55 °C for 18 h. The reaction mixture was quenched with methanol and evaporated the solvent under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) get crude to give N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-6-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.030 g, 15%) as yellow solid. LC–MS $(M+H)^+ = 527.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.37 (1H, s), 8.04 (1H, s), 8.00 (1H, m), 7.42 (1H, m), 7.30-7.20 (6H, m), 6.84 (1H, m), 3.98 (1H, m), 3.73 (1H, m), 3.69 (1H, m), 3.57-3.48 (4H, m), 3.23 (1H, m), 2.99 (1H, m), 2.26 (3H., s), 1.23 (3H, t, $J = 7.2$ Hz).

Example 147

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,N4-dimethyl-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

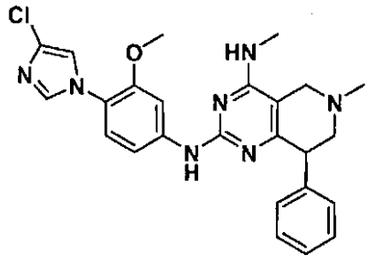


Using the methods of Preparation AEd, Preparation AEj, and Example 134, Preparation AEc was transformed into N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,N4-dimethyl-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine.*LC*–MS $(M-H)^+ = 552.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.27 (1H, s), 7.91 (1H, s), 7.73 (1H, m), 7.42 (1H, m), 7.31 (2H,

m), 7.25-7.10 (5H, m), 4.46 (1H, m), 4.30-4.24 (2H, m), 3.83 (1H, m), 3.53 (3H, s), 3.28 (1H, m), 3.13 (6H, s), 3.09 (3H, s).

Example 148

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,6-dimethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

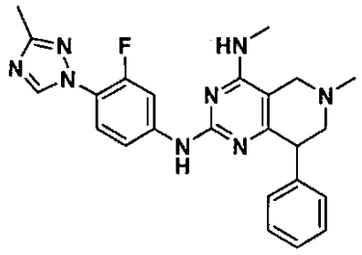


A solution of Preparation A (0.26 g, 1.2 mmol), Preparation AFa (0.35 g, 1.2 mmol), Na_2CO_3 (0.25 g, 2.4 mmol) and xantphos (0.69 g, 1.2 mmol) in dioxane/water (9:1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.55 g, 0.6 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diamataceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (0.5% aqueous ammonium acetate in methanol) give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,6-dimethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.10 g, 18%) as off-white solid. LC–MS $(M+H)^+ = 476.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.05 (1H, s), 8.05 (1H, s), 7.71 (1H, s), 7.40 (1H, s), 7.27-7.17 (5H, m), 7.15-7.06 (2H, m), 6.76 (1H, m), 3.94 (1H, m), 3.50 (3H, s), 3.39 (1H, m), 3.18 (1H, m), 2.95 (3H, d, $J = 4.4$ Hz), 2.51 (1H, m), 2.49 (1H, m), 2.12 (3H, s).

The example was separated by chiral chromatography to afford the enantiomers 148A and 148B, which had identical spectral data.

Example 149

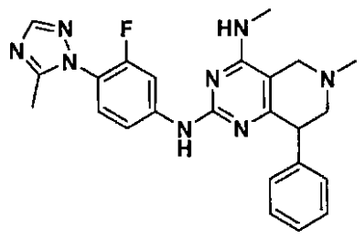
N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



A solution of Preparation B (0.21 g, 1.1 mmol), Preparation AFa (0.35 g, 1.2 mmol), Na_2CO_3 (0.25 g, 2.4 mmol) and xantphos (0.70 g, 1.1 mmol) in dioxane/water (9:1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.55 g, 0.6 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diamataceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (0.5% aqueous ammonium acetate in methanol) give N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.2 g, 38%) as off-white solid. LC–MS $(M+H)^+$ = 445.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.33 (1H, s), 8.67 (1H, s), 8.05 (1H, m), 7.41 (2H, m), 7.3-7.20 (5H, m), 6.84 (1H, m), 3.96 (1H, m), 3.42 (1H, m), 3.25 (1H, m), 2.94 (3H, d, J = 4.4 Hz), 2.92 (1H, m), 2.71 (1H, m), 2.51 (3H, s), 2.40 (3H, s).

Example 150

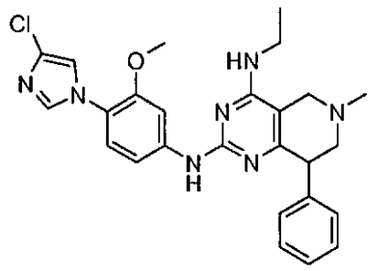
N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



A solution of Preparation C (0.23 g, 1.2 mmol), Preparation AFa (0.35 g, 1.2 mmol), Na_2CO_3 (0.25 g, 2.4 mmol) and xantphos (0.69 g, 1.2 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.55 g, 0.6 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diamataceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (0.5% aqueous ammonium acetate in methanol) give N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.08 g, 15%) as off-white solid. LC–MS $(M+H)^+ = 445.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.38 (1H, s), 8.06 (1H, m), 8.00 (1H, s), 7.44 (1H, m), 7.30-7.23 (5H, m), 7.18 (1H, m), 6.84 (1H, m), 3.95 (1H, m), 3.40 (1H, m), 3.22 (1H, m), 2.93 (3H, d, $J = 4.4$ Hz), 2.90 (1H, m), 2.86 (1H, m), 2.36 (3H, s), 2.26 (3H, s).

Example 151

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

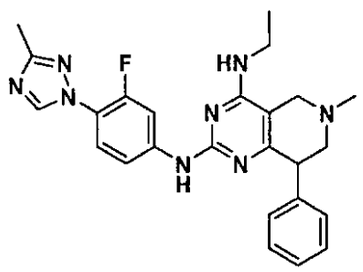


A solution of Preparation A (0.26 g, 1.19 mmol), Preparation AFb (0.4 g, 1.32 mmol), Na_2CO_3 (0.28 g, 2.64 mmol) and xantphos (0.76 g, 1.32 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.60 g, 0.66 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diamataceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (0.5% aqueous ammonium acetate in methanol) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.15 g, 24%) as off-white solid. LC–MS $(M+H)^+ = 490.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.01 (1H, s), 7.97 (1H, s), 7.71 (1H, s), 7.40 (1H, s), 7.39-7.20 (5H, m), 7.18-7.07 (2H, m), 6.70 (1H, m), 3.95 (1H, m), 3.57 (3H, s), 3.56 (2H, m), 3.47 (1H, m), 3.18 (1H, m), 2.85 (1H, m), 2.59 (1H, m), 2.34 (3H, s), 1.22 (3H, t, J = 7.2 Hz).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 151A and 151B, which had identical spectral data.

Example 152

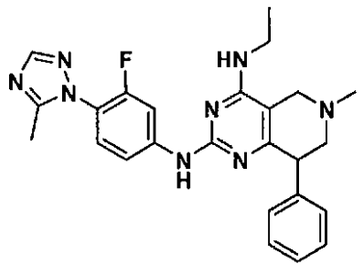
N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



A solution of Preparation B (0.12 g, 0.59 mmol), Preparation AFb (0.20 g, 0.66 mmol), Na_2CO_3 (0.14 g, 1.32 mmol) and xantphos (0.38 g, 0.66 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.30 g, 0.33 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diamataceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (0.5% aqueous ammonium acetate in methanol) give N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.03 g, 11%) as off-white solid. LC–MS $(M+H)^+ = 459.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.31 (1H, s), 8.67 (1H, s), 8.04 (1H, m), 7.40 (2H, m), 7.29-7.17 (5H, m), 6.81 (1H, m), 3.95 (1H, m), 3.48 (2H, m), 3.43 (1H, m), 3.21 (1H, m), 2.91 (1H, m), 2.68 (1H, m), 2.38 (3H, s), 2.33 (3H, s), 1.23 (3H, t, $J = 7.2$ Hz).

Example 153

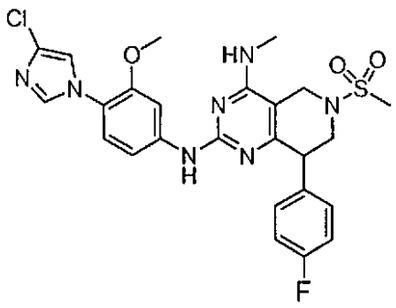
N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



A solution of Preparation C (0.15 g, 0.82 mmol), Preparation AFb (0.25 g, 0.82 mmol), Na_2CO_3 (0.17 g, 1.6 mmol) and xantphos (0.42 g, 0.82 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.37 g, 0.41 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diamataceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (0.5% aqueous ammonium acetate in methanol) give N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.06 g, 17%) as off-white solid. LC–MS $(M+H)^+ = 459.2$. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 7.93 (1H, s), 7.84 (1H, m), 7.34-7.27 (5H, m), 7.26-2.20 (2H, m), 7.05 (1H, m), 4.65 (1H, m), 4.11 (1H, m), 3.61-3.54 (2H, m), 3.39 (2H, m), 3.07 (1H, m), 2.81 (1H, m), 2,51 (3H, s), 2.37 (3H, s), 1.34 (3H, t, $J = 7.2$ Hz).

Example 154

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

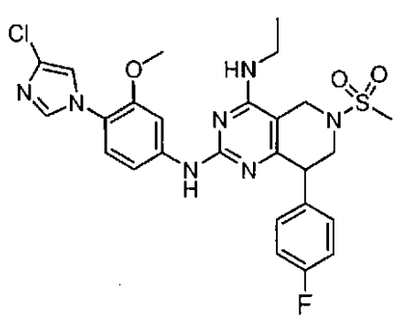


To a solution of Preparation AGk (0.08 g, 0.167 mmol) in dichloromethane was added diisopropylethylamine (0.043 g, 0.33 mmol) followed by methanesulfonyl chloride (0.029 g, 0.167 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.02 g, 23%) as off-white solid. LC–MS $(M+H)^+ = 558.0$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.21 (1H, s), 8.0 (1H, s), 7.73 (1H, s), 7.42 (1H, s), 7.27 - 7.23 (2H, m), 7.16- 7.12 (4H, m), 7.05 (1H, m), 4.20 (1H, m), 4.12 (1H, m), 4.05 (1H, m), 3.56 (3H, s), 3.51-3.47 (2H, m), 2.97 (3H, d, $J = 4.0$ Hz), 2.91 (3H, s).

The example was separated by chiral chromatography to afford the enantiomers 154A and 154B, which had identical spectral data.

Example 155

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

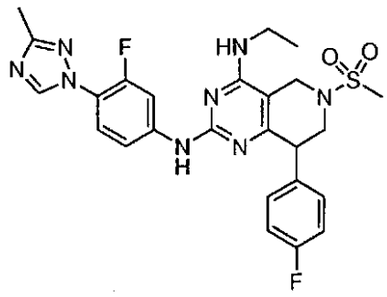


To a solution of Preparation AGl (0.09 g, 0.018 mmol) in dichloromethane was added triethylamine (0.037 g, 0.36 mmol) followed by methanesulfonyl chloride (0.021 g, 0.182 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.04 g, 39%) as off-white solid. LC–MS $(M-H)^+ = 572.0$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.18 (1H, s), 7.95 (1H, s), 7.73 (1H, s), 7.42 (1H, s), 7.27 - 7.23 (2H, m), 7.17- 7.12 (4H, m), 6.99 (1H, m), 4.24 (1H, d, J = 14.0 Hz), 4.12 (1H, m), 4.04 (1H, d, J = 14.0 Hz), 3.56 (3H, s), 3.55-3.47 (4H, m), 2.92 (3H, s), 1.22 (3H, t, J = 7.2 Hz).

The example was separated by chiral chromatography to afford the enantiomers 155A and 155B, which had identical spectral data.

Example 156

N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



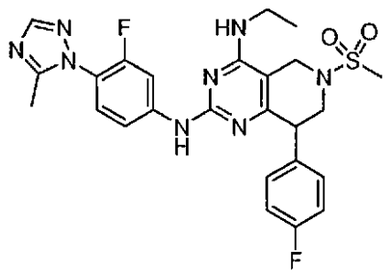
To a solution of Preparation AGm (0.30 g, 0.649 mmol) in dichloromethane was added diisopropylethylamine (0.168 g, 0.29 mmol) followed by methanesulfonyl chloride (0.07 g, 0.649 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.250 g, 71%) as off-

white solid. LC–MS $(M+H)^+ = 541.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.45 (1H, s), 8.69 (1H, s), 8.01 (1H, m), 7.47-7.40 (2H, m), 7.39-7.26 (2H, m), 7.15-7.07 (3H, m), 4.20 (1H, m), 4.12-4.06 (2H, m), 3.63 (1H, m), 3.54-3.48 (3H, m), 2.94 (3H, s), 2.34 (3H, s), 1.22 (3H, t, $J = 7.2$ Hz).

The example was separated by chiral chromatography to afford the enantiomers 156A and 156B, which had identical spectral data.

Example 157

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(methylsulfonyl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

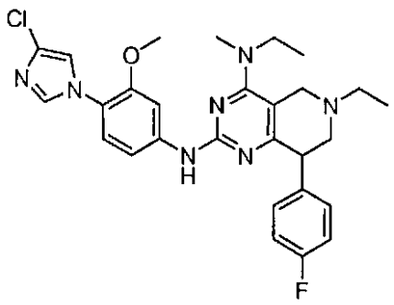


To a solution of Preparation AGn (0.25 g, 0.540 mmol) in dichloromethane was added diisopropylethylamine (0.139 g, 1.080 mmol) followed by methanesulfonyl chloride (0.06 g, 0.540 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(methylsulfonyl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.19 g, 73%) as off-white solid. LC–MS $(M-H)^+ = 541.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.48 (1H, s), 8.01 (1H, m), 7.97 (1H, 1H), 7.43 (1H, m), 7.34-7.27 (3H, m), 7.15-7.11 (2H, m), 7.05 (1H, m), 4.23-4.07 (3H, m), 3.63 (1H, m), 3.55-3.48 (3H, m), 2.94 (3H, s), 2.28 (3H, s), 1.24 (3H, t, $J = 7.2$ Hz).

The example was separated by chiral chromatography to afford the enantiomers 157A and 157B, which had identical spectral data.

Example 158

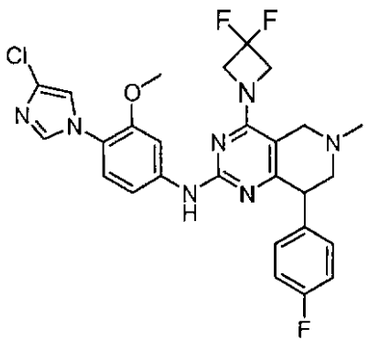
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,6-diethyl-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



To a solution of Preparation AGo (0.010 g, 0.019 mmol) in ethanol was added triethylamine (0.004 g, 0.039 mmol) at 0 °C followed by ethyl iodide (0.030 g, 0.019 mmol). The reaction mixture was heated at 80 °C for 18 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in methanol) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,6-diethyl-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.04 g, 40%) as off-white solid. LC–MS $(M+H)^+$ = 536.2. ^{1}H NMR (400 MHz, methanol-*d4*): δ ppm 7.80 (1H, s), 7.67 (1H, s), 7.26-7.22 (3H, m), 7.13 (1H, m), 7.07-7.00 (2H, m), 6.98 (1H, m), 4.23 (1H, m), 3.75 (1H, m), 3.56-3.48 (6H, m), 3.33 (1H, m), 3.28 (3H, s), 2.69-2.64 (2H, m), 2.53 (1H, m), 1.34 (3H, m), 1.30 (3H, m).

Example 159

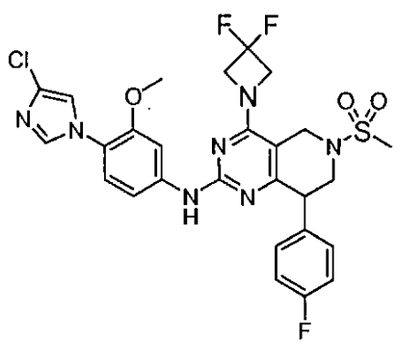
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine



To a solution of Preparation AGp (0.03 g, 0.055 mmol) in acetone was added K_2CO_3 (0.011, 0.083 mmol) followed by methyl iodide (0.012 g, 0.083 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in methanol) to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine (0.007 g, 24%). LC–MS $(M+H)^+ = 556.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 10.50 (1H, s), 9.56 (1H, s), 7.75 (1H, s), 7.43 (1H, s), 7.33-7.30 (2H, m), 7.25-7.18 (2H, m), 7.14 (1H, m), 4.09 (1H, m), 4.82-4.76 (2H, m), 4.64 (3H, m), 4.43 (3H, m), 3.88 (1H, m), 3.51 (3H, s), 2.97 (3H, s).

Example 160

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine

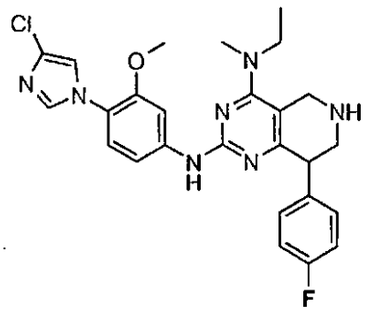


To a solution of Preparation AGp (0.040 g, 0.073 mmol) in acetone was added Cs_2CO_3 (0.036 g, 0.11 mmol) followed by methanesulfonyl chloride (0.012 g, 0.11 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in methanol) to give (0.005 g, 12%) as off-white solid. LC–MS $(M+H)^+$ = 620.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.47 (1H, s), 7.85 (1H, s), 7.74 (1H, s), 7.43 (1H, s), 7.30-7.26 (2H, m), 7.18-7.09 (4H, m), 4.77-4.70 (4H, m), 4.36 (1H, m), 4.24 (2H, m), 3.66 (1H, m), 3.56 (3H, s), 3.44 (1H, m), 3.0 (3H, s).

The example was separated by chiral chromatography to afford the enantiomers 160A and 160B, which had identical spectral data.

Example 161

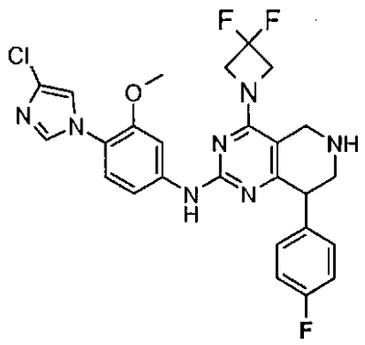
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



This compound is identical to Preparation AGo (vide supra).

Example 162

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine

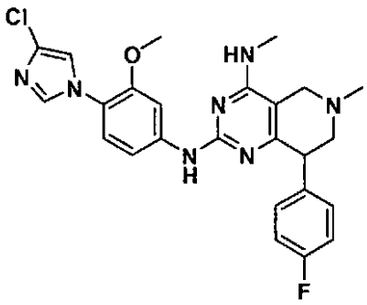


This compound is identical to Preparation AGp (vide supra).

The example was separated by chiral chromatography to yield the individual enantiomers 162A and 162B, which each had identical spectral data.

Example 163

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



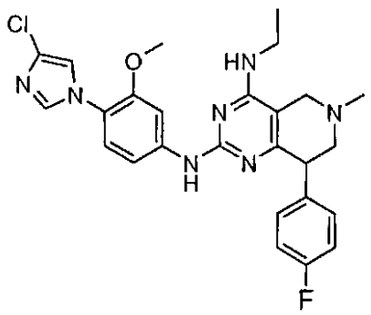
A solution of Preparation A (0.109 g, 0.49 mmol), Preparation AHa (0.15 g, 0.49 mmol), Na_2CO_3 (0.103 g, 0.98 mmol) and xantphos (0.283 g, 0.49 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.253 g, 0.24 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diamataceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (0.5% aqueous ammonium acetate in

methanol) give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.035 g, 14%) as off-white solid. LC–MS $(M+H)^+ = 494.2$. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.07 (1H, s), 8.32 (1H, s), 8.05 (1H, s), 7.72 (1H, s), 7.26 (2H, m), 7.14-7.05 (4H, m), 6.77 (1H, m), 3.96 (1H, m), 3.94 (3H, s), 3.42 (1H, m), 3.11 (1H, m), 2.92 (3H, d, $J = 4.4$ Hz), 2.82 (1H, m), 2.58 (1H, m), 2.33 (3H, s).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 163A and 163B, which had identical spectral data.

Example 164

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



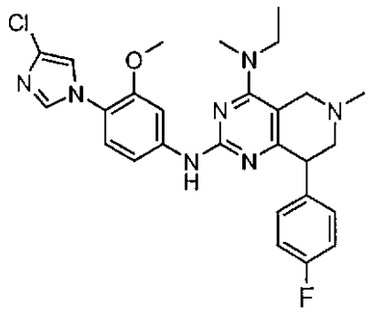
A solution of Preparation A (0.146 g, 0.650 mmol), Preparation AHb (0.210 g, 0.650 mmol), Na_2CO_3 (0.139 g, 1.30 mmol) and xantphos (0.378 g, 0.650 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.338 g, 0.327 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diamataceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (0.5% aqueous ammonium acetate in methanol) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.022 g,

22%) as off-white solid. LC–MS $(M+H)^+ = 508.0$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.07 (1H, s), 7.97 (1H, s), 7.73 (1H, s), 7.41 (1H, s), 7.29-7.23 (2H, m), 7.15-7.05 (4H, m), 6.73 (1H, m), 3.96 (1H, m), 3.56 (3H, s), 3.49-3.40 (3H, m), 3.13 (1H, m), 2.83 (1H, m), 2.62 (1H, m) 2.34 (3H, s), 1.21 (3H, t, $J = 7.2$ Hz).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 164A and 164B, which had identical spectral data.

Example 165

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



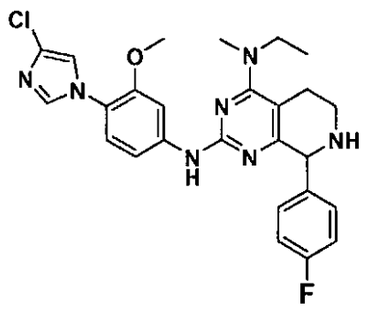
A solution of Preparation A (0.18 g, 0.80 mmol), Preparation AHc (0.30 g, 0.89 mmol), Na_2CO_3 (0.190 g, 1.79 mmol) and xantphos (0.519 g, 0.89 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.465 g, 0.440 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The reaction mass was filtered through a bed of diamataceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine solution (25 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (0.5% aqueous ammonium acetate in methanol) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (0.13 g, 28%) as off-brown solid. LC–MS $(M+H)^+ = 522.0$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.13 (1H, s), 7.86 (1H, s), 7.73 (1H, s), 7.42 (1H, s), 7.24 (2H, m),

7.15-7.07 (4H, m), 4.13 (1H, m), 3.55 (3H, s), 3.47-3.41 (4H, m), 3.04 (3H, s), 2.99 (1H, m), 2.48 (1H, m), 2.34 (3H, s), 1.23 (3H, t, J = 7.2 Hz).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 165A and 165B, which had identical spectral data.

Example 166

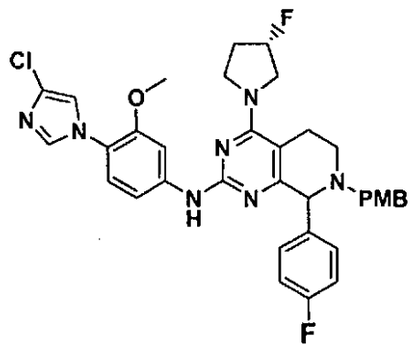
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine



This example is the same compound as Preparation AII (vide supra).

Example 167

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine



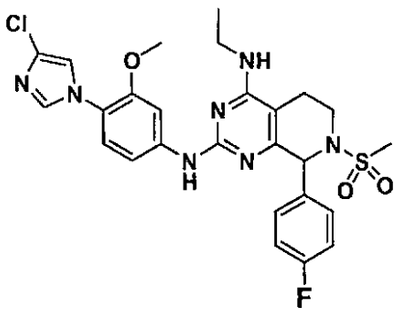
A solution of Preparation A (0.190 g, 0.851 mmol), Preparation AId (0.40 g, 0.851 mmol), Na_2CO_3 (0.180 g, 1.70 mmol) and xantphos (0.491 g, 0.851 mmol) in dioxane/water (9: 1) was purged with argon for 1 h at room temperature. $Pd(dba)_3$ (0.440 g, 0.425 mmol) was added to the reaction mixture and the resulting solution was purged with argon for another 1 h. The reaction mass was heated at 110 °C for 24 h. The

reaction mass was filtered through a bed of diamataceous earth (Celite®) and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate (25 mL x 3). The combined organic layer was washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude compound. The crude compound was purified by column chromatography (60-120 mesh) using 50% ethyl acetate in pet-ether as mobile phase to give a mixture of two diasteriomers N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine (0.40 g, 88%, crude) as off-white solid. LC–MS $(M+H)^+$ = 658.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 8.95 (1H, s), 7.75 (1H, s), 7.74 (1H, s), 7.54 (2H, m), 7.43 (1H, s), 7.29 (1H, m), 7.22-7.14 (5H, m), 6.86 (2H, m), 5.34 (1H, m), 4.38 (1H, s), 4.03 (1H, m), 4.0 (3H, m), 3.72 (6H, s), 3.51 (1H, m), 3.33 (1H, m), 2.95 (2H, m), 2.51 (1H, m), 2.25-2.01 (3H, m).

The diasteriomeric mixture was separated by chiral chromatography to afford two diasteriomers Example 167A and 167B.

Example 168

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine



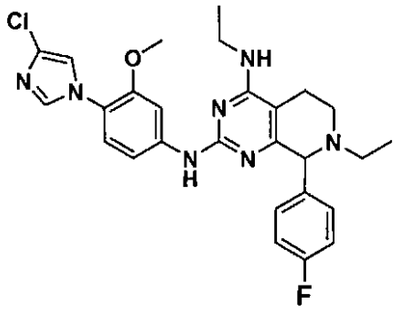
To a solution of Preparation Alk (0.06 g, 0.121 mmol) in dichloromethane was added diisopropylethylamine (0.041 g, 0.243 mmol) at -10 °C followed by methanesulfonyl chloride (0.013 g, 0.121 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in

acetonitrile) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine (0.020 g, 29%) as off-white solid. LC–MS $(M+H)^+$ = 572.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.23 (1H, s), 7.97 (1H, s), 7.74 (1H, s), 7.43 (1H, s), 7.35 (2H, m), 7.23-7.12 (4H, m), 7.0 (1H, m), 5.57 (1H, s), 3.85 (1H, m), 3.79 (3H, s), 3.54 (2H, m), 3.18 (1H, m), 2.88 (3H, s), 2.65 (2H, m), 1.24 (3H, t, *J* = 7.2 Hz).

The racemic mixture was separated by chiral chromatography to afford two enantiomers Example 168A and 168B.

Example 169

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,7-diethyl-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine

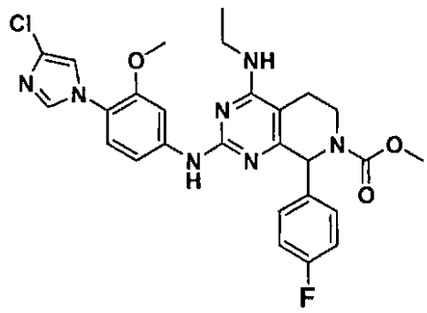


To a solution of Preparation Alk (0.20 g, 0.405 mmol) in dichloromethane was added diisopropylethylamine (0.104 g, 0.806 mmol) at -10 °C followed by ethyl iodide (0.31 g, 0.231 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,7-diethyl-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine (0.110 g, 62%) as off-white solid. LC–MS $(M+H)^+$ = 522.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 8.90 (1H, s), 7.70 (1H, s), 7.73 (1H, s), 7.42 (1H, s), 7.28 (2H, m), 7.17 (4H, m), 6.78 (1H, m), 4.39 (1H, s), 3.65 (3H, s), 3.48 (2H, m), 3.13 (2H, m), 3.08 (1H, m), 2.51 (1H, m), 2.39 (2H, m), 1.22-1.19 (6H, m).

The racemic mixture was separated by chiral chromatography to afford two enantiomers Example 169A and 169B.

Example 170

methyl 2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-(4-fluorophenyl)-5,6-dihydropyrido[3,4-d]pyrimidine-7(8H)-carboxylate

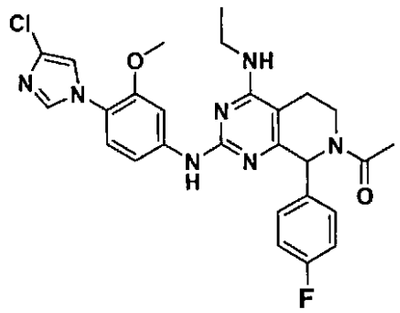


To a solution of Preparation of AIk (0.10 g, 0.20 mmol) in dichloromethane was added triethylamine (0.019 g, 0.20 mmol) at -10 °C followed by methyl chloroformate (0.18 g, 0.20 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give methyl 2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-(4-fluorophenyl)-5,6-dihydropyrido[3,4-d]pyrimidine-7(8H)-carboxylate (0.080 g, 76%) as off-white solid. LC–MS $(M+H)^+ = 552.2$. ^1H NMR (400 MHz, DMSO-*d6*): δ ppm 9.22 (1H, s), 7.96 (1H, s), 7.74 (1H, s), 7.48 (1H, s), 7.33 (2H, m), 7.20-7.13 (4H, m), 6.98 (1H, m), 4.06 (1H, s), 3.82 (1H, m), 3.75 (3H, s), 3.68 (3H, s), 3.56 (2H, m), 3.02 (1H, m), 2.33 (2H, m), 1.21 (3H, t, $J = 7.2$ Hz).

The racemic mixture was separated by chiral chromatography to afford two enantiomers Example 170A and 170B.

Example 171

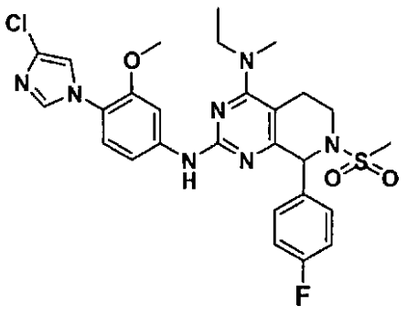
1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-(4-fluorophenyl)-5,6-dihydropyrido[3,4-d]pyrimidin-7(8H)-yl)ethanone



To a solution of Preparation AIk (0.052 g, 0.101 mmol) in dichloromethane was added triethylamine (0.012 g, 0.126 mmol) at -10 °C followed by acetyl chloride (0.007 g, 0.01 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-(4-fluorophenyl)-5,6-dihydropyrido[3,4-d]pyrimidin-7(8H)-yl)ethanone (0.040 g, 72%) as off-white solid. LC–MS $(M+H)^+$ = 536.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.25 (1H, s), 8.0 (1H, s), 7.75 (1H, s), 7.43 (1H, s), 7.32 (2H, m), 7.21-7.14 (4H, m), 6.99 (1H, m), 6.36 (1H, *sb*), 3.95 (1H, m), 3.90 (2H, m), 3.57 (3H, s), 3.49 (1H, m), 3.20 (1H, m), 2.34 (1H, m), 2.12 (3H, s), 1.22 (3H, t, J = 7.2 Hz).

Example 172

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine



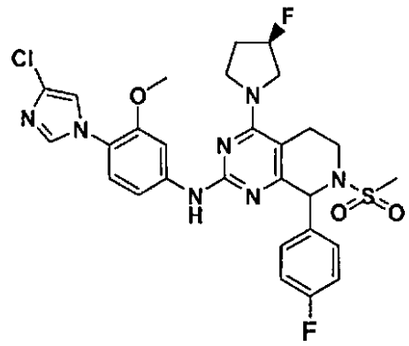
To a solution of Preparation AII (0.070 g, 0.138 mmol) in dichloromethane was added diisopropylethylamine (0.047 g, 0.276 mmol) at -10 °C followed by methanesulfonyl chloride (0.015 g, 0.138 mmol). The reaction mixture was stirred at

room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine (0.030 g, 37%) as off-white solid. LC–MS $(M+H)^+$ = 586.2. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.26 (1H, s), 7.80 (1H, s), 7.74 (1H, s), 7.43 (1H, s), 7.34 (2H, m), 7.32-7.16 (4H, m), 5.65 (1H, s), 3.55 (1H, m), 3.53 (3H, s), 3.51 (2H, m), 3.18 (1H, m), 3.08 (3H, s), 2.91 (3H, s), 2.67 (1H, m), 1.22 (3H, m).

The racemic mixture was separated by chiral chromatography to afford two enantiomers Example 172A and 172B.

Example 173

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine

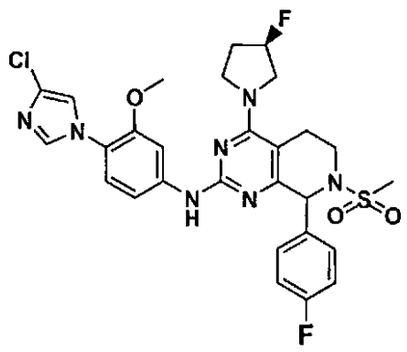


To a solution of Preparation A1m (0.041 g, 0.074 mmol) in dichloromethane was added diisopropylethylamine (0.019 g, 0.148 mmol) at -10 °C followed by addition of methanesulfonyl chloride (0.008 g, 0.074 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine (0.010 g, 20%) as off-white solid. LC–MS $(M+H)^+$ = 616.0. ^{1}H

NMR (400 MHz, DMSO-*d6*): δ ppm 9.27 (1H, s), 7.84 (1H, s), 7.75 (1H, s), 7.43 (1H, s), 7.38 (2H, m), 7.22-7.17 (4H, m), 5.50 (1H, s), 4.11 (1H, m), 4.04 (3H, m), 3.82 (1H, m), 3.51 (3H, s), 3.23 (2H, m), 3.05 (2H, m), 2.95 (3H, s), 2.23 (2H, m).

Example 174

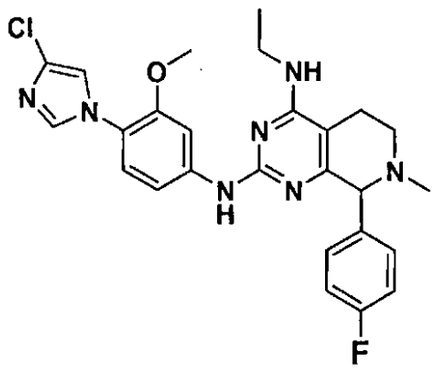
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine



To a solution of Preparation A1n (0.041 g, 0.074 mmol) in dichloromethane was added diisopropylethylamine (0.019 g, 0.148 mmol) at -10 °C followed by addition of methanesulfonyl chloride (0.008 g, 0.074 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, evaporated under reduced pressure to get crude compound. The crude compound was purified by prep-HPLC (aqueous 0.1% ammonium acetate in acetonitrile) to N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine (0.012 g, 20.6%) as off-white solid. LC–MS $(M+H)^+$ = 616.0. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.25 (1H, s), 7.83 (1H, s), 7.74 (1H, s), 7.42 (1H, s), 7.33 (2H, m), 7.22-7.12 (4H, m), 5.76 (1H, s), 5.57 (1H, m), 4.07 (1H, m), 3.99-3.90 (3H, m), 3.88 (1H, m), 3.54 (3H, s), 3.27 (1H, m), 3.11 (1H, m), 2.93 (3H, s), 2.85 (1H, m), 2.23 (2H, m).

Example 175

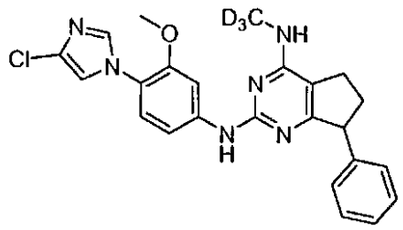
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine



Preparation Alk was combined with methyl iodide in the manner of Example 169 to give N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine.

Example 176

N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-trideuteromethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



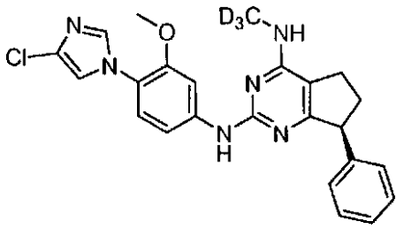
A solution of 2-chloro-*N*-trideuteromethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (121.2 mg, 0.461 mmol) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (103 mg, 0.461 mmol) in THF (1 mL) and acetic acid (1.000 mL) was heated at 80 °C overnight. The reaction mixture was purified by a reverse-phase preparative HPLC method to give N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-trideuteromethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine,TFA salt (114.3 mg, 43%) as brown solid. LC-MS $(M+H)^+$ = 450.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.86 (1H, s), 7.88 (1H, t, *J*=8.4 Hz), 7.22 - 7.31 (4H, m), 7.19 (1H, d, *J*=8.9 Hz), 7.07 (3H, t, *J*=8.7 Hz), 4.27 (1H, t, *J*=8.5 Hz), 3.73 (3H, s), 2.45 - 2.59 (1H, m), 2.38 (1H, d, *J*=7.6 Hz), 2.30 (1H, d, *J*=3.7 Hz), 1.95 - 2.06 (1H, m).

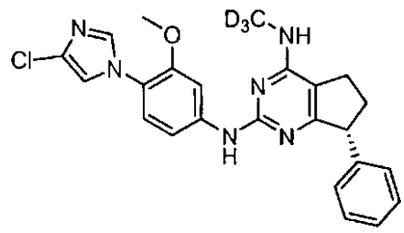
Examples 176A and 176B

(S)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-trideuteromethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)-N^2-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-trideuteromethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

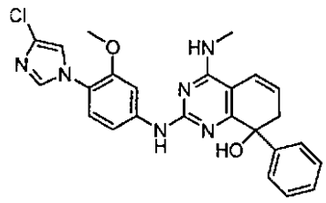




A racemic mixture of N^2-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)-N^4-trideuteromethyl-7-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine-2,4-diamine (133 mg, 0.206 mmol from *Example 176*) was purified using chiral supercritical fluid chromatography (SFC) to afford 28.4 mg of peak A (*Example 176A*) and 27.4 mg of peak B (*Example 176B*). SFC Method: Chiralpak OJ-H (30 x 250 mm, 5 μM), 40 % methanol (0.1% diethylamine) in CO_2, 35 °C, flow rate 70 mL/min for 16 min, absorbance 268 nm, injection 1mL of 22 mg/mL solution in methanol (multiple stacked injections), t_R (peak A) = 5.0 min, t_R (peak B) 11.2 min. The absolute stereochemistry of individual enantiomers (*Examples 176A and 176B*) was not determined. LC-MS and ^{1}H NMR analytical data for the separated enantiomers was identical to the racemate (*Example 176*).

Example 177

2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(methylamino)-8-phenyl-7,8-dihydroquinazolin-8-ol

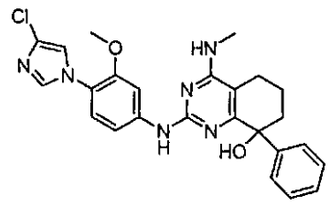


A solution of 2-chloro-4-(methylamino)-8-phenyl-7,8-dihydroquinazolin-8-ol (25 mg) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (29 mg) in dioxane (0.2 mL)

and acetic acid (0.2 mL) was heated at 85 °C for 4 h. THF was removed in vacuo, and the residue was purified by reverse phase preparative to give the title compound (as its TFA salt) as an oil (18 mg). LC–MS $(M+H)^+$ = 475.26. ^1H NMR (TFA salt, 500 MHz, CD_3OD) δ ppm 7.2-7.9 (m), 6.56 (1H, m), 6.18 (1H, m), 3.94 (3H, s), 3.20 (3H, s), 3.10 (2H, m).

Example 178

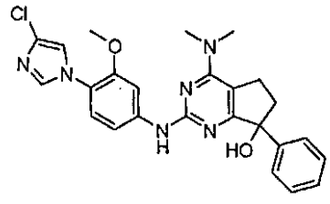
2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(methylamino)-8-phenyl-5,6,7,8-tetrahydroquinazolin-8-ol



The title compound as its TFA salt form was made in the same fashion as described in Example 177. LC–MS $(M+H)^+$ = 477.28. ^1H NMR (TFA salt, 500 MHz, CD_3OD) δ ppm 7.1-8.0 (m), 3.88 (3H, s), 3.18 (3H, s), 1.2-2.5 (6H, m).

Example 179

2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(dimethylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-7-ol

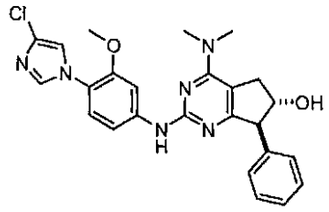


The mixture of 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (37.1 mg, 0.166 mmol), 2-chloro-4-(dimethylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-7-ol (40 mg, 0.138 mmol), $Pd_2(dba)_3$ (5.06 mg, 5.52 μmol), xanphos (7.99 mg, 0.014 mmol) and Cs_2CO_3 (135 mg, 0.414 mmol) was heated at 100 °C overnight. The crude product was purified by Prep-HPLC (Column: PHENOMENEX LUNA C18 30 x100 mm, Solvent A = 10 mM Ammonium Acetate in 95 : 5 H2O / ACN, Solvent B = 10 mM Ammonium Acetate in 5 : 95 H2O / ACN,. Flow rate: 40 ml / min, 35 -100% B, 30 min) to give the title compound as its TFA salt (32 mg). LC–MS $(M+H)^+$ = 477.19. ^1H

NMR (TFA salt, 500 MHz, CD_3OD) δ ppm 6.8-7.8 (m), 3.64 (3H, s), 3.30 (6H, s), 3.0-3.2 (2H, m), and 2.4 (2H, m).

Example 180

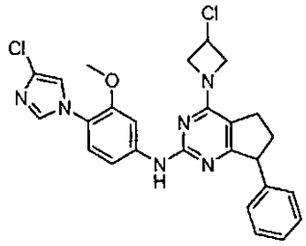
(6S,7S)-2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(dimethylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-ol



The reaction was carried out in the same fashion as described in Example 177, but the purification method is different. The crude product was purified by preparative TLC eluting with 50% acetone/hexanes to give the title compound as an oil. LC–MS $(M+H)^+$ = 477.13. ^1H NMR (500 MHz, $CDCl_3$) δ ppm 6.8-7.9 (m), 4.48 (1H, m), 4.07 (1H, m), 3.58 (1H, m), 3.50 (3H, s), 3.28 (6H, s), 3.12 (1H, m).

Example 181

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-chloroazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

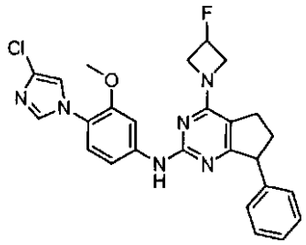


In a manner similar to that described in Example 8, Preparation A and Preparation Gi were reacted to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-chloroazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine. LC–MS $(M+H)^+$ = 507.2. ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 10.71 (d, *J*=19.84 Hz, 1 H) 8.50 (d, *J*=1.53 Hz, 1 H) 7.45 (dd, *J*=8.85, 1.83 Hz, 1 H) 7.24 - 7.40 (m, 5 H) 7.18 - 7.23 (m, 2 H) 5.12 (br. s., 1 H) 4.76 - 4.95 (m, 2 H) 4.71 (d, *J*=10.68 Hz, 1 H) 4.35 - 4.54 (m, 2 H) 3.88 (s, 3 H) 3.12 (d, *J*=14.65 Hz, 1 H) 3.01 (dd, *J*=19.99, 6.26 Hz, 1 H) 2.68 - 2.85 (m, 1 H) 2.24 - 2.42 (m, 1 H).

The individual enantiomers were separated by chiral SFC chromatography to yield examples 181A and 181B.

Example 182

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-fluoroazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

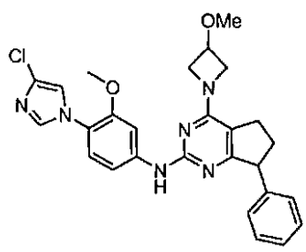


In a manner similar to that described in Example 8, Preparation A and Preparation Gj were reacted to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-fluoroazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine. LC–MS $(M+H)^+ = 491.2$. ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 11.07 (br. s., 1 H) 8.30 (br. s., 1 H) 7.45 (d, *J*=8.55 Hz, 2 H) 7.38 (br. s., 3 H) 7.33 (d, *J*=4.88 Hz, 2 H) 7.13 - 7.31 (m, 1 H) 5.50 – 5.61 (m, 1 H) 4.91 (br. s., 1 H) 4.71 (br. s., 2 H) 4.43 (br. s., 2 H) 3.89 (br. s., 3 H) 3.14 (br. s., 1 H) 3.03 (d, *J*=18.92 Hz, 1 H) 2.75 (br. s., 1 H) 2.20 - 2.39 (m, 1 H).

The individual enantiomers were separated by chiral SFC chromatography to yield examples 182A and 182B.

Example 183

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-methoxyazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



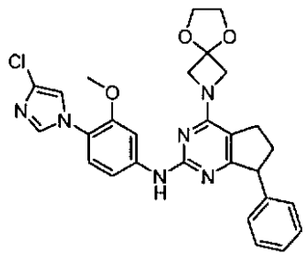
In a manner similar to that described in Example 8, Preparation A and Preparation Gk were reacted to give N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-

methoxyazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine. LC–MS $(M+H)^+$ = 503.2. 1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.73 (1 H, br. s.), 7.49 (1 H, s), 7.30 - 7.35 (2 H, m), 7.22 (4 H, t, *J*=8.24 Hz), 7.04 - 7.07 (1 H, m), 7.00 (1 H, s), 6.90 (1 H, br. s.), 4.45 - 4.52 (2 H, m), 4.33 - 4.39 (1 H, m), 4.16 - 4.23 (3 H, m), 3.57 (3 H, s), 2.98 - 3.07 (1 H, m), 2.85 - 2.96 (1 H, m), 2.55 - 2.67 (1 H, m, *J*=13.28, 8.77, 8.77, 4.58 Hz), 2.06 - 2.16 (1 H, m).

The individual enantiomers were separated by chiral SFC chromatography to yield examples 183A and 183B.

Example 184

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-4-(5,8-dioxa-2-azaspiro[3.4]octan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



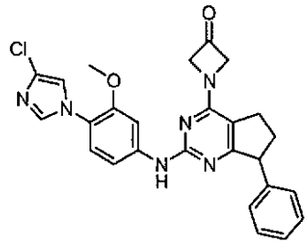
The mixture of 2-(2-chloro-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-5,8-dioxa-2-azaspiro[3.4]octane (Preparation Gl) (23 mg, 0.067 mmol), 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) (17.95 mg, 0.080 mmol), Tris(dibenzylidineacetone)dipalladium(0) (3.06 mg, 3.34 μmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (3.87 mg, 6.69 μmol) and sodium carbonate (14.18 mg, 0.134 mmol) in Dioxane (319 μL) / Water (63.7 μL) was heated at 100 °C overnight. The crude product was purified by Prep-HPLC (Solvent A = 10% MeOH - 90% H2O - 0.1% TFA, Solvent B = 90% MeOH - 10% H2O - 0.1% TFA. Column: PHENOMENEX LUNA 30 x 100mm, S10, Flow rate: 40 ml / min, 30 - 100% B, 30 min) to obtain N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-4-(5,8-dioxa-2-azaspiro[3.4]octan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (17 mg, 0.024 mmol, 35.5 % yield).

LC–MS $(M+H)^+$ = 531.1 ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 11.39 (s, 1 H) 8.09 (s, 1 H) 7.45 (d, *J*=8.55 Hz, 1 H) 7.35 - 7.42 (m, 4 H) 7.19 - 7.34 (m, 1 H) 7.15 (s, 2 H) 4.73 (br. s., 2 H) 4.51 (br. s., 2 H) 4.42 (dd, *J*=8.70, 4.12 Hz, 1 H) 4.09 (d, *J*=3.66 Hz,

4 H) 3.87 (s, 3 H) 3.12 (dd, *J*=14.34, 7.02 Hz, 1 H) 2.90 - 3.05 (m, 1 H) 2.67 - 2.81 (m, 1 H) 2.29 (ddd, *J*=9.16, 4.43, 4.12 Hz, 1 H).

Example 185

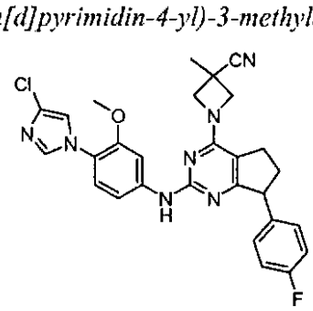
1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)azetidin-3-one



The mixture of N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-4-(5,8-dioxa-2-azaspiro[3.4]octan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (Example 184) (12 mg, 0.023 mmol) in Acetone (161 µL) / Water (32.3 µL)/ HClO4, 70% (32.3 µL) was heated at 50 °C overnight. The crude product was purified by Prep-HPLC to get 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)azetidin-3-one (2.5 mg, 4.62 µmol, 20.5 % yield). LC–MS $(M+H)^+ = 487.2$ ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.57 (s, 1 H) 7.42 (t, *J*=7.63 Hz, 3 H) 7.26 - 7.38 (m, 3 H) 7.12 - 7.26 (m, 2 H) 7.00 - 7.12 (m, 1 H) 5.23 (br. s., 4 H) 4.43 (br. s., 1 H) 3.68 - 3.79 (m, 3 H) 3.10 - 3.27 (m, 1 H) 2.93 - 3.08 (m, 1 H) 2.71 - 2.84 (m, 1 H) 2.37 (br. s., 1 H).

Example 186

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-methylazetidine-3-carbonitrile

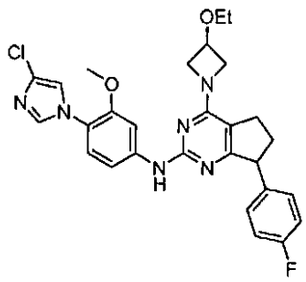


In a manner similar to that described in Example 184, Preparation Hac and Preparation A were combined to obtain 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-

methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-methylazetidine-3-carbonitrile. LC–MS $(M+H)^+$ = 530.1 ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 11.50 (br. s., 1 H) 8.18 (br. s., 1 H) 7.46 (d, *J*=7.63 Hz, 1 H) 7.12 - 7.31 (m, 3 H) 7.06 (br. s., 3 H) 4.99 (br. s., 1 H) 4.72 (br. s., 1 H) 4.43 (br. s., 2 H) 4.28 (br. s., 1 H) 3.88 (s, 3 H) 3.11 (br. s., 1 H) 3.00 (br. s., 1 H) 2.76 (br. s., 1 H) 2.28 (d, *J*=5.49 Hz, 1 H) 1.87 (s, 3 H).

Example 187

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-ethoxyazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

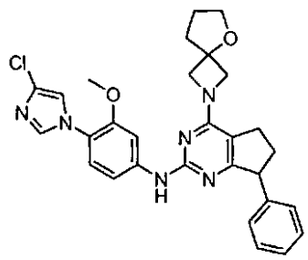


In a manner similar to that described in Example 184, Preparation Had and Preparation A were combined to obtain N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-ethoxyazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine. LC–MS $(M+H)^+$ = 535.1 ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 11.77 (br. s., 1 H) 7.74 (d, *J*=4.58 Hz, 1 H) 7.52 (br. s., 1 H) 7.34 - 7.41 (m, 1 H) 7.12 - 7.30 (m, 2 H) 7.06 - 7.12 (m, 1 H) 7.03 (br. s., 2 H) 4.77 (br. s., 1 H) 4.51 (br. s., 2 H) 4.49 (d, *J*=5.49 Hz, 1 H) 4.36 (br. s., 1 H) 4.24 (br. s., 1 H) 3.85 (d, *J*=4.88 Hz, 3 H) 3.55 (dd, *J*=6.71, 5.49 Hz, 2 H) 3.12 (br. s., 1 H) 2.99 (br. s., 1 H) 2.68 (br. s., 1 H) 2.23 (br. s., 1 H) 1.21 - 1.37 (m, 3 H).

The individual enantiomers were separated by chiral SFC chromatography to yield examples 187A and 187B.

Example 188

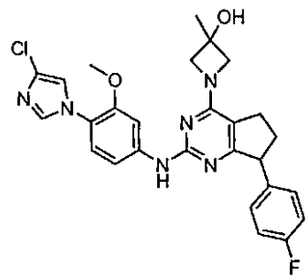
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-4-(5-oxa-2-azaspiro[3.4]octan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



In a manner similar to that described in Example 184, Preparation Gm and Preparation A were combined to obtain N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-4-(5-oxa-2-azaspiro[3.4]octan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine. LC–MS $(M+H)^+ = 529.3$ ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 10.85 (br. s., 1 H) 8.36 (br. s., 1 H) 7.49 (br. s., 4 H) 7.20 - 7.39 (m, 4 H) 4.56 (d, *J*=9.16 Hz, 1 H) 4.41 (br. s., 3 H) 3.92 - 4.10 (m, 3 H) 3.87 (s, 3 H) 3.11 (br. s., 1 H) 3.00 (d, *J*=12.51 Hz, 1 H) 2.73 (br. s., 1 H) 2.26 (t, *J*=6.87 Hz, 3 H) 2.06 (d, *J*=6.41 Hz, 2 H).

Example 189

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-methylazetidin-3-ol

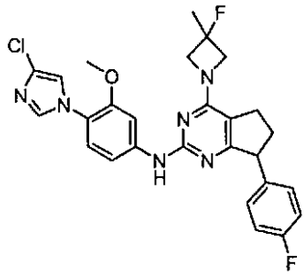


In a manner similar to that described in Example 184, Preparation Hae and Preparation A were combined to obtain 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-methylazetidin-3-ol. LC–MS $(M+H)^+ = 521.1$ ^{1}H NMR (400 MHz, MeOD) δ ppm 7.93 (d, J=1.51 Hz, 1 H) 7.65 (d, J=2.26 Hz, 1 H) 7.26 - 7.44 (m, 4 H) 7.01 - 7.26 (m, 4 H) 4.48 - 4.68 (m, 2 H) 4.44 (dd, J=9.03, 6.78 Hz, 1 H) 4.18 - 4.38 (m, 2 H) 3.90 (s, 3 H) 3.15 (dd, J=5.27, 3.76 Hz, 1 H) 2.96 - 3.06 (m, 1 H) 2.62 - 2.82 (m, 1 H) 2.12 (dddd, J=13.18, 8.85, 6.46, 6.15 Hz, 1 H) 1.55 - 1.66 (m, 3 H).

The individual enantiomers were separated by chiral SFC chromatography to yield examples 189A and 189B.

Example 190

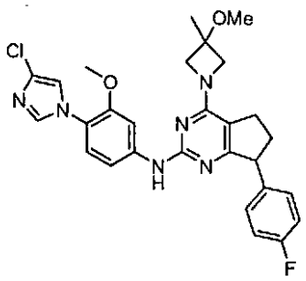
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-fluoro-3-methylazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



A solution of 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-methylazetidin-3-ol (35 mg, 0.067 mmol) in CH2Cl2 (Volume: 274 µl) was cooled to -78 °C. To this mixture was added [Bis(2-methoxyethyl)amino]sulfur trifluoride (13.62 µl, 0.074 mmol) dropwise and the solution was stirred for 30 mins at -78 °C and then warmed to 0 °C and stirred for a further 1 hr. Reaction was quenched with Sat. NaHCO3 solution and brine. The aqueous layer was extracted with CH2Cl2. The organic layer was dried over Na2SO4 and concentrated. The crude product was purified by Prep-HPLC to obtain N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-fluoro-3-methylazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine, TFA (4.0 mg, 5.65 µmol). LC–MS $(M+H)^+$ = 523.1 ^{1}H NMR (500 MHz, CHLOROFORM-d) δ ppm 11.38 (br. s., 1 H) 8.14 (s, 1 H) 7.43 - 7.54 (m, 1 H) 7.30 - 7.38 (m, 1 H) 7.20 - 7.26 (m, 3 H) 7.16 (s, 1 H) 7.06 (t, J=7.78 Hz, 2 H) 4.78 (br. s., 1 H) 4.54 (br. s., 2 H) 4.42 (br. s., 2 H) 3.88 (s, 3 H) 3.12 (d, J=7.93 Hz, 1 H) 3.00 (br. s., 1 H) 2.75 (br. s., 1 H) 2.21 - 2.34 (m, 1 H) 1.78 - 1.82 (br. s, 3 H).

Example 191

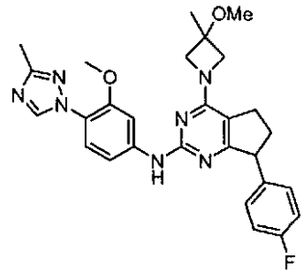
N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(3-methoxy-3-methylazetidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



In a manner similar to that described in Example 184, Preparation Haf and Preparation A were combined to obtain N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(3-methoxy-3-methylazetidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine. LC–MS $(M+H)^+ = 535.1$ ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 11.75 (d, *J*=4.27 Hz, 1 H) 7.83 (d, *J*=1.22 Hz, 1 H) 7.47 (d, *J*=1.83 Hz, 1 H) 7.44 (d, *J*=8.55 Hz, 1 H) 7.15 - 7.33 (m, 4 H) 7.03 (t, *J*=7.63 Hz, 2 H) 4.53 (d, *J*=8.85 Hz, 1 H) 4.24 - 4.43 (m, 3 H) 4.06 - 4.19 (m, 1 H) 3.86 (s, 3 H) 3.34 (s, 3 H) 3.13 (ddd, *J*=12.67, 6.56, 6.41 Hz, 1 H) 3.01 (ddd, *J*=15.95, 4.81, 4.58 Hz, 1 H) 2.70 (td, *J*=9.46, 3.66 Hz, 1 H) 2.24 (tt, *J*=8.96, 4.31 Hz, 1 H) 1.63 (s, 3 H).
The individual enantiomers were separated by chiral SFC chromatography to yield examples 191A and 191B.

Example 192

7-(4-fluorophenyl)-4-(3-methoxy-3-methylazetidin-1-yl)-N-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine



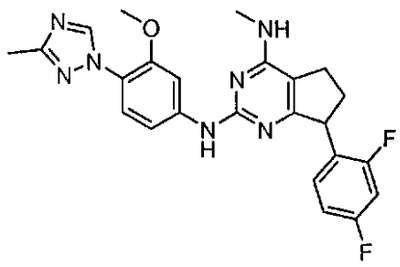
In a manner similar to that described in Example 184, Preparation Haf and Preparation D were combined to obtain 7-(4-fluorophenyl)-4-(3-methoxy-3-methylazetidin-1-yl)-N-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine. LC–MS $(M+H)^+ = 516.1$ ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 11.77 (d, *J*=3.97 Hz, 1 H) 8.88 (s, 1 H) 7.69 (d, *J*=8.55 Hz, 1 H) 7.52 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.47 (s, 1 H) 7.23 (t, *J*=5.49 Hz, 2 H) 7.03 (t,

J=8.39 Hz, 2 H) 4.45 - 4.58 (m, 1 H) 4.35 (d, *J*=4.58 Hz, 2 H) 4.27 (d, *J*=7.63 Hz, 1 H) 4.10 (d, *J*=10.07 Hz, 1 H) 3.85 - 4.04 (m, 3 H) 3.33 (s, 3 H) 3.05 - 3.20 (m, 1 H) 2.92 - 3.05 (m, 1 H) 2.63 - 2.79 (m, 1 H) 2.45 - 2.59 (m, 3 H) 2.23 (td, *J*=8.39, 4.27 Hz, 1 H) 1.57 - 1.72 (m, 3 H).

The individual enantiomers were separated by chiral SFC chromatography to yield examples 192A and 192B.

Example 193

7-(2,4-difluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



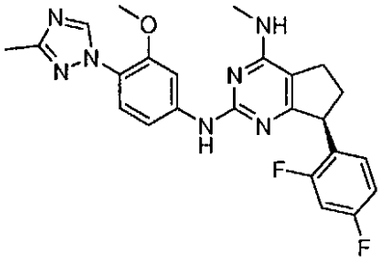
The mixture of 2-chloro-7-(2,4-difluorophenyl)-N-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (153 mg, 0.517 mmol), 3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)aniline (211 mg, 1.035 mmol) and H2SO4 (44.1 µl, 0.828 mmol) in N-Methyl-2-pyrrolidinone (Volume: 2070 µl) was heated at 100 °C overnight. Added Sat.NaHCO3 slowly, and extracted with EtOAc (x3). The combined organic layer was dried over Na2SO4 and concentrated. The crude product was purified by Prep-HPLC (Solvent A = 10% MeOH - 90% H2O - 0.1% TFA, Solvent B = 90% MeOH - 10% H2O - 0.1% TFA. Column: PHENOMENEX LUNA 30 x 100mm, S10, Flow rate: 40 ml / min, 30 - 100% B, 15 min) to get 7-(2,4-difluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, TFA (287 mg, 0.447 mmol, 86 % yield). LC-MS $(M+H)^+$ = 464.1. 1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 11.54 (1 H, s), 9.22 (1 H, s), 7.75 (1 H, d, *J*=8.85 Hz), 7.65 (1 H, s), 7.49 (1 H, d, *J*=8.85 Hz), 7.13 - 7.21 (1 H, m), 6.79 - 6.91 (2 H, m), 6.11 (1 H, d, *J*=4.27 Hz), 4.56 - 4.63 (1 H, m), 3.97 (3 H, s), 3.23 (3 H, d, *J*=4.27 Hz), 2.84 - 2.93 (1 H, m), 2.71 - 2.81 (2 H, m), 2.62 (3 H, s), 2.19 - 2.28 (1 H, m).

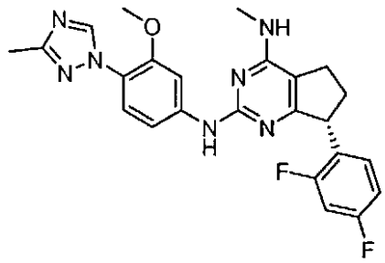
Examples 193A and 193B

(S)- 7-(2,4-difluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

and

(R)- 7-(2,4-difluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

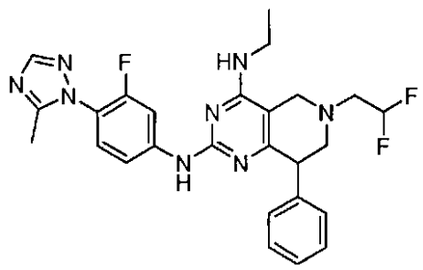




A racemic mixture of *7-(2,4-difluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine* (*Example 193*) was purified using chiral supercritical fluid chromatography (SFC) to afford peak A (*Example 193A*) and peak B (*Example 193B*). SFC Method: Chiralpak OJ-H (30 x 150 mm), 30 % methanol (0.1% diethylamine) in CO_2, 100 bar, flow rate 50 mL/min for 12 min, absorbance 268 nm, injection 2.0 mL of 10 mg/mL solution in methanol, t_R (peak A) = 4.7 min, t_R (peak B) 9.6 min. The absolute stereochemistry of individual enantiomers (*Examples 193A and 193B*) was not determined. 193A: LC-MS $(M+H)^+$ = 446.2. LC R_t 13.03 min (Waters Sunfire 4.6X150 mm 10 to 100% B in A over 15 min, 1.5 mL/min. (A is 90:10:0.1 water:MeOH:TFA; B is 90:10:0.1 MeOH:water:TFA)). 1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.46 (1 H, s), 8.04 (1 H, s), 7.51 (1 H, d, *J*=8.55 Hz), 7.04 - 7.13 (2 H, m), 6.78 - 6.87 (3 H, m), 4.42 - 4.50 (1 H, m), 3.68 (3 H, s), 3.13 (3 H, s), 2.62 - 2.79 (3 H, m), 2.49 (3 H, s), 1.96 - 2.08 (1 H, m).

Example 194

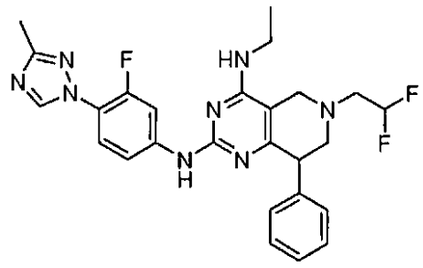
6-(2,2-difluoroethyl)-N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



Preparation AEo was reacted with difluoro-2-iodoethane, potassium carbonate, and sodium iodide in DMF at 80 °C to afford 6-(2,2-difluoroethyl)-N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (Example 194). LC–MS $(M+H)^+ = 509.4$.
The individual enantiomers were separated by chiral SFC chromatography to yield examples 194A and 194B.

Example 195

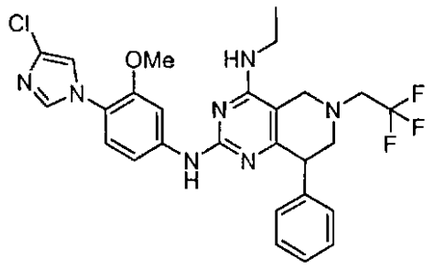
6-(2,2-difluoroethyl)-N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



Preparation AEm was reacted with difluoro-2-iodoethane, potassium carbonate, and sodium iodide in DMF at 80 °C to afford 6-(2,2-difluoroethyl)-N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (Example 195). LC–MS $(M+H)^+ = 509.2$.
The individual enantiomers were separated by chiral SFC chromatography to yield examples 195A and 195B.

Example 196

N4-ethyl-N2-(3-methoxy-4-(4-chloro-1H-13-imidazol-1-yl)phenyl)-8-phenyl-6-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

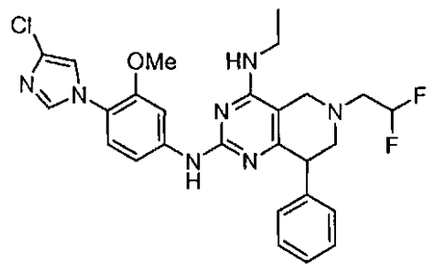


In a manner similar to Preparation AEp and Example 146, Preparation AEk was transformed into N4-ethyl-N2-(3-methoxy-4-(4-chloro-1H-13-imidazol-1-yl)phenyl)-8-phenyl-6-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (Example 196). LC–MS $(M+H)^+ = 558.2$.

The individual enantiomers were separated by chiral SFC chromatography to yield examples 196A and 196B.

Example 197

N4-ethyl-N2-(3-methoxy-4-(4-chloro-1H-13-imidazol-1-yl)phenyl)-8-phenyl-6-(2,2-difluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

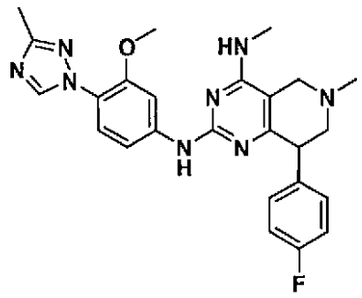


Preparation AEk was reacted with difluoro-2-iodoethane, potassium carbonate, and sodium iodide in DMF at 80 °C to afford N4-ethyl-N2-(3-methoxy-4-(4-chloro-1H-13-imidazol-1-yl)phenyl)-8-phenyl-6-(2,2-difluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine (Example 197). LC–MS $(M+H)^+ = 540.2$.

The individual enantiomers were separated by chiral SFC chromatography to yield examples 197A and 197B.

Example 198

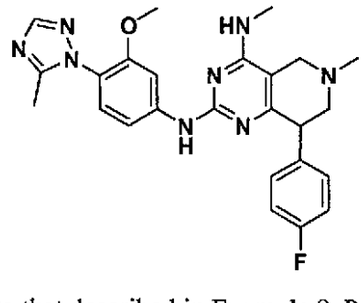
8-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine



In a manner similar to that described in Example 8, Preparation D and Preparation AHa were reacted to give 8-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine. LC–MS $(M+H)^+ = 475.2$. The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 198A and 198B.

Example 199

8-(4-fluorophenyl)-N2-(3-methoxy-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine

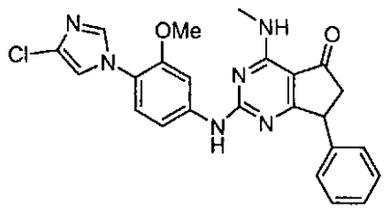


In a manner similar to that described in Example 8, Preparation DD and Preparation AHa were reacted to give 8-(4-fluorophenyl)-N2-(3-methoxy-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine. LC–MS $(M+H)^+ = 475.2$.

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 199A and 199B.

Example 200

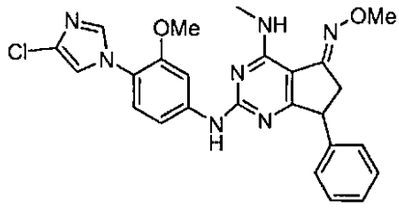
(±)-2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-5-one



A solution of 2-chloro-4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-5-one (Preparation AN) (7 mg) and 4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyaniline (Preparation A) (7 mg) in THF (0.2 mL) and sulfuric acid (4 mg) was heated at 85 °C for 12 h. THF was removed in vacuo, and the residue was purified by reverse phase preparative to give the title compound (as its TFA salt) as a yellowish oil (9 mg). LC–MS $(M+H)^+ = 461.12$. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.80 (m), 7.1-7.4 (m), 4.50 (1H, m), 3.25 (1H, m), 2.56 (1H, m), 3.50 (3H, s), and 3.19 (3H, s). The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 200A and 200B.

Example 201

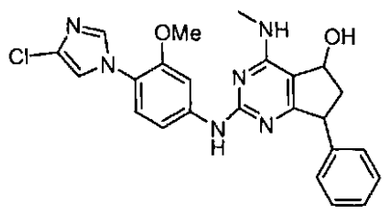
(E)-2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-5-one O-methyl oxime



A 0.15M solution of Example 200 in iPrOH was heated with 4 eq methoxyamine hydrochloride at 85 °C for 3h. Reverse-phase HPLC provided the desired material as a TFA salt. LC–MS $(M+H)^+ = 490.2$. The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 201A and 201B.

Example 202

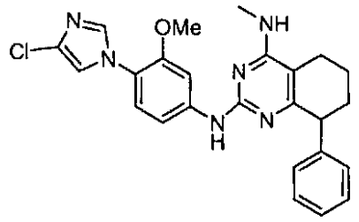
2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-5-ol



To a solution of Example 201 in methanol at rt was added NaBH4, and the rxn mixture was stirred at rt for 1 h. The rxn was worked up with EtOAc/H2O to give the desired pdt as a white solid. LC–MS $(M+H)^+ = 463.1$.

Example 203

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine

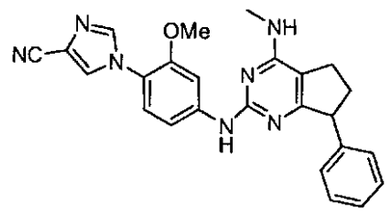


LC–MS $(M+H)^+ = 466.0$. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.86 (1 H, d, J=2.3 Hz), 7.48 (1 H, d, J=1.5 Hz), 7.24 - 7.32 (4 H, m), 7.16 - 7.23 (1 H, m), 7.08 - 7.14 (2 H, m), 7.00 (2 H, s), 6.70 (1 H, dd, J=8.3, 2.0 Hz), 4.71 (1 H, d, J=3.0 Hz), 4.03 (1 H, t, J=5.6 Hz), 3.41 (3 H, s), 3.12 (3 H, d, J=4.8 Hz), 2.30 - 2.48 (2 H, m), 2.09 - 2.22 (1H, m, J=13.0, 9.7, 6.2, 3.3, 3.1 Hz), 1.74 - 1.96 (3 H, m).

The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 203A and 203B.

Example 204

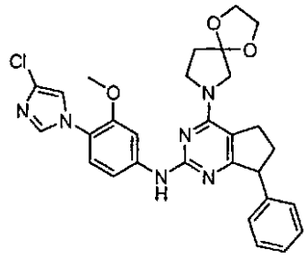
1-(2-methoxy-4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)-1H-imidazole-4-carbonitrile



To a solution of 2-chloro-N-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (Preparation Ga) (150 mg, 0.578 mmol) in Dioxane (Ratio: 1, Volume: 1013 µl) was added 1-(4-amino-2-methoxyphenyl)-1H-imidazole-4-carbonitrile (Preparation AA) (124 mg, 0.578 mmol), and AcOH (Ratio: 1.000, Volume: 1013 µl). The resulting mixture was brought to 100 °C in a sealed vial and stirred overnight. The mixture was brought to pH 8 by the addition of 1 N aqueous sodium Hydroxide. The resulting mixture was extracted with EtOAc(3 x 1 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by prep HPLC (Waters Sunfire C18, 50 X 250mm, acetonitrile/H_2O/ammonium acetate) gave 1-(2-methoxy-4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)-1H-imidazole-4-carbonitrile (57 mg, 0.130 mmol, 22.56 % yield). LC–MS $(M+H)^+$ = 438.2. 1H NMR (500 MHz, *MeOD*) δ ppm 8.02 - 8.08 (2 H, m), 7.90 - 7.94 (1 H, m), 7.31 (2 H, t, *J*=7.63 Hz), 7.16 - 7.24 (4 H, m), 6.99 (1 H, dd, *J*=8.55, 2.14 Hz), 4.18 (1 H, t, *J*=8.09 Hz), 3.56 (3 H, s), 3.07 (3 H, s), 2.76 - 2.84 (1 H, m), 2.59 - 2.74 (2 H, m), 1.98 - 2.05 (1 H, m). The racemic mixture was separated by chiral chromatography to afford the enantiomers Example 204A and 204B.

Example 205

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-4-(1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine

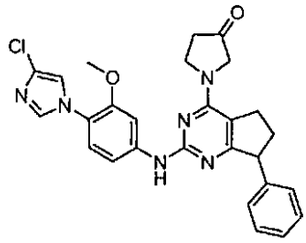


In a manner similar to that described in Example 184, Preparation Go and Preparation A were combined to obtain N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-4-(1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine. LC–MS $(M+H)^+$ = 545.1. 1H NMR (500 MHz, *MeOD*) δ ppm 7.89 (1 H, s), 7.62 (0.5 H, br. s.), 7.53 (0.5 H, br. s.), 7.37 - 7.45 (4 H, m), 7.32 - 7.36 (1 H, m), 7.30 (2 H, d, *J*=7.63 Hz), 7.23 (0.5 H, d, *J*=7.63 Hz), 7.14 (0.5 H, d, *J*=7.32 Hz), 4.40 - 4.47 (1 H, m), 4.25 (1 H, br. s.), 3.96 - 4.14 (6 H, m), 3.88 (4 H, br. s.),

3.34 - 3.46 (1 H, m), 3.28 (1 H, br. s.), 2.69 - 2.79 (1 H, m), 2.24 - 2.32 (1 H, m), 2.09 - 2.23 (2 H, m).

Example 206

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)pyrrolidin-3-one

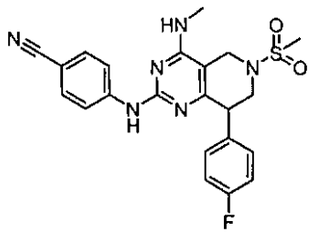


The mixture of N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-4-(1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine (Example 205) (37 mg, 0.068 mmol) and HCl (272 µL, 0.272 mmol) in THF (339 µL) was heated at 60 °C overnight. Concentrated to remove THF and added Acetone (339 µL) and HCl (272 µL, 0.272 mmol) to the mixture. The mixture was heated at 60 °C for 6 h. The crude product was purified by Prep-HPLC (Solvent A = 10% MeOH - 90% H2O - 0.1% TFA, Solvent B = 90% MeOH - 10% H2O - 0.1% TFA. Column: PHENOMENEX LUNA 30 x 100mm, S10, Flow rate: 40 ml / min, 35 - 100% B, 40 min) and then was purified by Prep-HPLC (Column: PHENOMENEX LUNA C18 30 x100 mm, Solvent A = 10 mM Ammonium Acetate in 95 : 5 H2O / ACN, Solvent B = 10 mM Ammonium Acetate in 5 : 95 H2O / ACN,. Flow rate: 40 ml / min, 30 -100% B, 35 min) to get 1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)pyrrolidin-3-one (2.0 mg, 3.59 µmol, 5.29 % yield).

LC–MS $(M+H)^+$ = 501.3.

Example 207

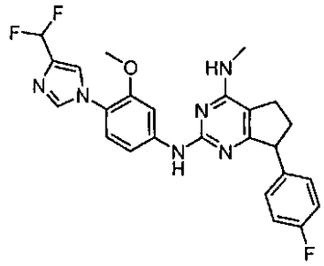
4-(8-(4-fluorophenyl)-4-(methylamino)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-ylamino)benzonitrile



Utilizing 4-aminobenzonitrile and Preparation AGa successively by the general methods described in Preparation AGj, AGk, and AGp, the title compound was obtained. LC–MS $(M+H)^+ = 453.2$. ^{1}H NMR (400 MHz, DMSO-*d*) δ ppm 9.25 (s, 1H) 7.85 (d, *J*= 8.80 Hz, 2H) 7.55 (d, *J*= 8.80 Hz, 2H) 7.25 – 7.29 (m, 2H) 7.10 – 7.17 (m, 3H) 4.05 – 4.24 (m, 3H) 3.53 – 3.63 (m, 2H) 2.95 (d, *J*= 4.4 Hz, 3H) 2.95 (s, 3H).

Example 208

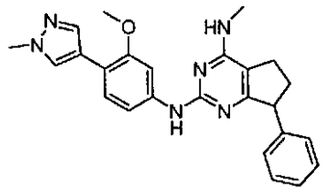
N2-(4-(4-(difluoromethyl)-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



In a manner similar to that described in Example 8, Preparation EE and Preparation Hh were reacted to give N2-(4-(4-(difluoromethyl)-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine. LC–MS $(M+H)^+ = 481.1$ ^{1}H NMR (500 MHz, MeOD) δ ppm 8.19 (s, 1 H) 7.75 (br. s., 1 H) 7.71 (s, 1 H) 7.45 (dd, *J*=8.55, 3.05 Hz, 1 H) 7.31 (ddd, *J*=8.47, 5.26, 2.75 Hz, 2 H) 7.19 - 7.26 (m, 1 H) 7.15 (td, *J*=8.77, 2.90 Hz, 2 H) 6.83 (t, *J*=55 Hz, 1H) 4.51 (d, *J*=2.75 Hz, 1 H) 3.91 (d, *J*=3.05 Hz, 3 H) 3.18 (d, *J*=3.05 Hz, 3 H) 2.92 (d, *J*=9.16 Hz, 1 H) 2.76 - 2.85 (m, 2 H) 2.10 - 2.20 (m, 1 H).

Example 209

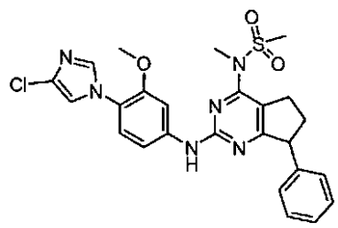
N2-(3-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



In a manner similar to that described in Example 8, Preparation AO and Preparation Ga were reacted to give N2-(3-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine. LC–MS $(M+H)^+$ = 425.4. 1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.84 (1 H, d, *J*=2.01 Hz), 7.81 (1 H, s), 7.74 (1 H, s), 7.32 (3 H, dd, *J*=13.55, 7.78 Hz), 7.19 - 7.26 (3 H, m), 7.07 (1 H, s), 6.78 (1 H, dd, *J*=8.28, 2.01 Hz), 4.60 (1 H, q, *J*=4.52 Hz), 4.16 - 4.23 (1 H, m), 3.91 (3 H, s), 3.64 (3 H, s), 3.11 (3 H, d, *J*=5.02 Hz), 2.58 - 2.76 (3 H, m), 2.00 - 2.11 (1 H, m).

Example 210

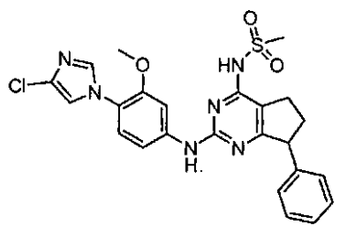
N-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N-methylmethanesulfonamide



Preparation G was reacted with 0.9 eq MeSO2NHMe, 0.1 eq Pd(OAc)2, 0.15 eq xanphos and Cs2CO3 at 110 °C. Preparation A was then added, resulting in the title compound. LC–MS $(M+H)^+$ = 525.4 ^{1}H NMR (400 MHz, DMSO-*d*) δ ppm 9.79 (s, 1 H) 7.75 - 7.77 (m., 2 H) 7.45 (s, 1 H) 7.32 - 7.35 (m, 2 H) 7.23 – 7.27 (m, 4 H) 7.16 – 7.18 (m, 1H) 4.35 (t, *J*=8.80 Hz, 1 H) 3.40 (s, 3 H) 3.31 (s, 3 H) 2.94 – 3.06 (m, 2 H) 2.57 - 2.61 (m, 1 H) 2.51 (s, 3 H) 2.04 – 2.08 (m, 1H).

Example 211

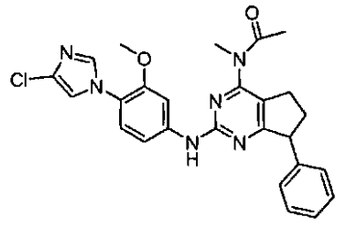
N-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N-methanesulfonamide



The title compound was prepared as for Example 210, substituting MeSO2NH2. LC–MS $(M+H)^+ = 511.0$ ^{1}H NMR (400 MHz, DMSO-*d*) δ ppm 9.51 (s, 1 H) 7.73 – 7.76 (m., 2 H) 7.41 (s, 1 H) 7.16 - 7.31 (m, 8 H) 4.21 (t, *J*=8.40 Hz, 1 H) 3.54 (s, 3 H) 3.41 (s, 3 H) 2.88 – 2.93 (m, 2 H) 2.69 – 2.73 (m, 1 H) 1.91 – 1.97 (m, 1H).

Example 212

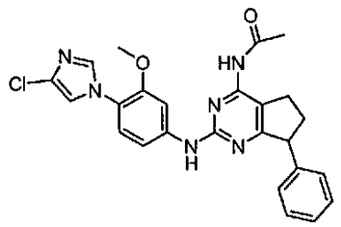
N-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N-methylacetamide



Intermediate Ga was reacted with *p*-methoxybenzylamine in the manner of Preparation Gd. Coupling with Preparation A under the conditions of Example 184, followed by treatment with TFA, led to the C4 NH2 compound. Reaction with AcCl in dichloroethane and DIPEA at ambient temperature for 4h yielded the named compound. LC–MS $(M+H)^+ = 489.2$. ^{1}H NMR (400 MHz, DMSO-*d*) δ ppm 9.89 (s, 1H), 7.92 (s, 1 H), 7.75 (s, 1 H), 7.44 (s, 1 H), 7.36 - 7.12 (m, 7H), 4.38 (t, *J*=8.6 Hz, 1 H), 3.51 (s, 3 H), 3.33 (s, 3H), 2.81 (t, *J*=7.4 Hz, 2 H), 2.59-2.55 (m, 1H), 2.17 (s, 3 H), 2.03 (dd, *J* = 8.8, 12.4 Hz, 1H).

Example 213

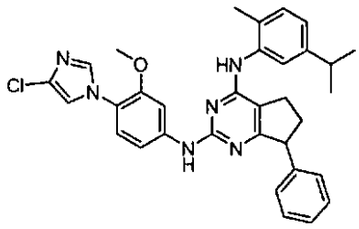
N-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N-acetamide



To a solution of Intermediate Ga was added 1.5 eq AcCl and 2 eq DIPEA and allowed to reflux for 3 days. The product so-obtained was coupled with Preparation A by the method of Example 184 to afford the title compound. LC–MS $(M+H)^+ = 475.2$ ^{1}H NMR (400 MHz, DMSO-*d*) δ ppm 7.86 (s, 1 H) 7.54 (s., 1 H) 7.35 (d, *J*=8.40 1 H) 7.23 - 7.30 (m, 2 H) 7.04 – 7.21 (m, 6 H) 6.73 – 6.76 (m, 1H) 4.26 (t, *J*=8.00 Hz, 1 H) 3.71 (s, 3 H) 2.58 – 2.80 (m, 3 H) 2.02 (s, 3 H) 1.96 – 2.00 (m, 1H).

Example 214

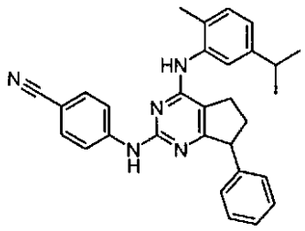
N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-(5-isopropyl-2-methylphenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



To a solution of 2-chloro-N-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine (Preparation Gp) (26.0 mg, 100 μmol) in Dioxane (Ratio: 1, Volume: 175 μl) was added 4-(4-chloro-1H-imidazol-1-yl)-3-methoxyaniline (Preparation A) (22.37 mg, 100 μmol) and AcOH (Ratio: 1.000, Volume: 175 μl). The resulting mixture was brought to 100 °C and stirred overnight. The reaction mixture was brought to pH 10 by the addition of 1 N aqueous NaOH. The resulting mixture was extracted with EtOAc (3 x 4 mL). The combined organic extracts were washed with brine (4 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The product was purified by Prep HPLC to yield the title compound. LC–MS $(M+H)^+ = 565.2$.

Example 215A and 215B

4-(4-(5-isopropyl-2-methylphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile



The method of Example 214 was used to combine 4-aminobenzonitrile and Preparation Gp to afford the title compounds as two distinct and separable atropisomers. LC–MS $(M+H)^+ = 460.3$.

Examples 216-256

The following general methods were used to join the appropriate aniline with Preparation Ga.

Coupling Method A[a]: The method as described in Example 8.

Coupling Method B[a]: The two components were heated at 100 °C in 1:1 HOAc/Dioxane.

Analysis was conducted on one of the following columns[b]:

LC Method A[b]: Phenomenex Luna 3X50 95/5 to 5/95 water/MeOH, 0.1% TFA

LC Method B[b]: Phenomenex Luna 2X50 95/5 to 5/95 water/CH3CN, 0.1% NH4OAc

LC Method C[b]: Phenomenex Luna 2X50 95/5 to 5/95 water/MeOH, 0.1% TFA

LC Method D[b]: Waters 2X50 95/5 to 5/95 water/MeOH, 0.1% NH4OAc

LC Method E[b]: Supelco Ascentis Exp 95/5 to 5/95 water/CH3CN, 0.1% NH4OAc

LC Retention Times[c] are reported along with the gradient run time (rt/grt).

Example	Compound Name	Coupling Method[a]	LC Method[b]	LC Retention time[c]	$(M+H)^+$
216	N4-methyl-N2-(2-methylpyridin-4-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	B	A	1.77/3	332.2
217	N2-(3-methoxyphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	D	3.63/4	347.2

Example	Compound Name	Coupling Method[a]	LC Method[b]	LC Retention time[c]	$(M+H)^+$
218	N2-(4-fluorophenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	D	3.68/4	335.2
219	N2-(3,5-difluorophenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	D	3.87/4	353.2
220	N2-(4-chloro-3-methoxyphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	D	3.83/4	381.2
221	N2-(4-bromo-2-methoxyphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	D	4.10/4	425.1
222	N2-(4-fluoro-3-methoxyphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	D	3.63/4	365.2
223	N4-methyl-7-phenyl-N2-(pyrimidin-5-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	D	3.12/4	319.2

Example	Compound Name	Coupling Method[a]	LC Method[b]	LC Retention time[c]	$(M+H)^+$
224	N4-methyl-7-phenyl-N2-(pyridin-4-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	D	2.85/4	318.2
225	4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile	A	D	3.57/4	342.2
226	4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile	A	C	2.94/4	342.1
227	4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile	A	C	2.92/4	342.1
228	2-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile	A	E	2.64/8	342.2
229	4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-1-naphthonitrile	A	E	5.73/8	392.2
230	5-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)picolinonitrile	A	E	4.54/8	343.2

Example	Compound Name	Coupling Method[a]	LC Method[b]	LC Retention time[c]	$(M+H)^+$
231	2-(4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)acetonitrile	A	E	4.65/8	356.2
232	2-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-1H-benzo[d]imidazole-5-carbonitrile	A	E	4.57/8	382.2
233	3-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile	B	E	4.37/8	342.1
234	N2-(4-tert-butylphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	B	E	5.47/8	373.2
235	N4-methyl-N2-(4-(methylsulfonyl)phenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	B	E	3.79/8	395.1
236	N4-methyl-7-phenyl-N2-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	B	E	5.13/8	400.8

Example	Compound Name	Coupling Method[a]	LC Method[b]	LC Retention time[c]	$(M+H)^+$
237	4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phthalonitrile	B	E	4.47/8	367.2
238	4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-2-(trifluoromethyl)benzonitrile	B	E	4.90/8	410.1
239	N4-methyl-7-phenyl-N2-(4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	B	E	5.13/8	385.1
240	5-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-2,3-dihydro-1H-inden-1-one	B	E	3.89/8	371.2
241	2-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-1H-imidazole-4,5-dicarbonitrile	B	E	4.08/8	357.2
242	2-bromo-5-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile	B	E	4.89/8	420.1

Example	Compound Name	Coupling Method[a]	LC Method[b]	LC Retention time[c]	$(M+H)^+$
243	N,N-dimethyl-4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzamide	B	E	3.50/8	388.2
244	1-(4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)cyclopentanecarbonitrile	B	E	4.91/8	410.2
245	N4-methyl-7-phenyl-N2-(1,2,3,4-tetrahydroisoquinolin-6-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	B	E	4.14/8	372.2
246	4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-2-(trifluoromethoxy)benzonitrile	B	E	5.04/8	426.1
247	1-(4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)cyclopropanecarbonitrile	B	C	3.30/4	382.3

Example	Compound Name	Coupling Method[a]	LC Method[b]	LC Retention time[c]	$(M+H)^+$
248	1-(2-methoxy-4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenylamino)cyclopropanecarbonitrile	B	C	3.06/4	427.1
249	N4-methyl-N2-(2-methyl-1H-indol-5-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	B	1.75/2	370.3
250	N2-(benzofuran-5-yl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	B	1.85/2	357.2
251	N2-(1H-indol-5-yl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	B	1.68/2	356.3
252	N4-methyl-N2-(2-methylbenzo[d]oxazol-6-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	B	1.73/2	372.3

Example	Compound Name	Coupling Method[a]	LC Method[b]	LC Retention time[c]	$(M+H)^+$
253	N2-(1H-benzo[d]imidazol-6-yl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	B	1.47/2	357.2
254	N4-methyl-N2-(1-methyl-1H-indol-5-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	B	1.82/2	370.3
255	N4-methyl-N2-(2-methylbenzo[d]thiazol-6-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	B	1.78/2	388.2
256	N2-(4-bromo-3-methoxyphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine	A	A	2.63/4	425.0/ 427.0

Coupling Method A[a]: The method as described in Example 8.

Coupling Method B[a]: The two components were heated at 100 °C in 1:1 HOAc/Dioxane.

Analysis was conducted on one of the following columns[b]:

LC Method A[b]: Phenomenex Luna 3X50 95/5 to 5/95 water/MeOH, 0.1% TFA

LC Method B[b]: Phenomenex Luna 2X50 95/5 to 5/95 water/CH3CN, 0.1% NH4OAc

LC Method C[b]: Phenomenex Luna 2X50 95/5 to 5/95 water/MeOH, 0.1% TFA

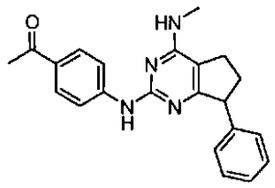
LC Method D[b]: Waters 2X50 95/5 to 5/95 water/MeOH, 0.1% NH4OAc

LC Method E[b]: Supelco Ascentis Exp 95/5 to 5/95 water/CH3CN, 0.1% NH4OAc

LC Retention Times[c] are reported along with the gradient run time (rt/grt).

Example 257

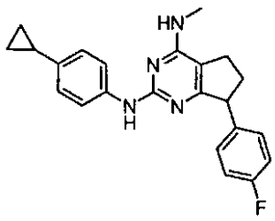
1-(4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)ethanone



A mixture of Example 256 (20 mg, 0.047 mmol), tributyl(1-ethoxyvinyl)stannane (67.9 mg, 0.188 mmol) and Tetrakis(5.43 mg, 4.70 μmol) in toluene(188 μL) was heated at 80°C for 12 hrs. The crude product was purified by prep HPLC. The resulting product was treated with HCl(0.8 eq.) in acetone(0.285 M) and stirred at RT overnight. The mixture was concentrated and added EtOAc, washed with water, brine, dried over Na2SO4 and concentrated to get 1-(2-methoxy-4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)ethanone(4 mg, 10.3 μmol, 22 % yield). LC–MS $(M+H)^+ = 389.2$ ^{1}H NMR (500 MHz, MeOD) δ ppm 7.74 (d, *J*=8.55 Hz, 1 H) 7.66 (s, 1 H) 7.36 - 7.49 (m, 3 H) 7.19 - 7.36 (m, 2 H) 7.08 (dd, *J*=8.55, 1.83 Hz, 1 H) 4.45 (br. s., 1 H) 3.86 - 3.98 (m, 3 H) 3.16 - 3.24 (m, 3 H) 2.93 (br. s., 1 H) 2.73 - 2.86 (m, 2 H) 2.53 - 2.63 (m, 3 H) 2.11 - 2.23 (m, 1 H).

Example 258

N2-(4-cyclopropylphenyl)-7-(4-fluorophenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine

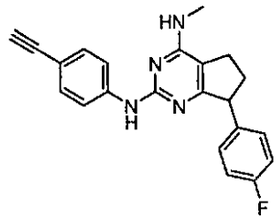


To a solution of the fluorinated analog of Example 256 (150 mg, 0.338 mmol) in Toluene (Ratio: 20, Volume: 1611 μl) was added Cyclopropylboronic acid (37.8 mg, 0.440 mmol), PdOAc2 (3.80 mg, 0.017 mmol), Tricyclohexylphosphine (9.49 mg, 0.034 mmol), Potassium orthophosphate (251 mg, 1.184 mmol), and Water (Ratio: 1.000, Volume: 81 μl). The resulting mixture was brought to 110 °C and stirred overnight. The reaction mixture was diluted with EtOAc (5 mL), washed with water (2 mL), brine (2

mL), dried over MgSO4, filtered and concentrated in vacuo. Purification by flash chromatography (Silica, EtOAc/Hexanes) gave N2-(4-cyclopropyl-3-methoxyphenyl)-7-(4-fluorophenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (15 mg, 0.037 mmol, 10.96 % yield). LC–MS $(M+H)^+ = 405.1$ ^{1}H NMR (500 MHz, MeOD) δ ppm 7.60 (d, *J*=1.83 Hz, 1 H) 7.19 (dd, *J*=7.93, 5.80 Hz, 2 H) 6.97 - 7.14 (m, 3 H) 6.69 – 6.78 (m, 1H) 4.05 - 4.22 (m, 2 H) 3.62 - 3.71 (m, 3 H) 2.98 - 3.11 (m, 3 H) 2.72 - 2.85 (m, 1 H) 2.55 - 2.72 (m, 2 H) 1.90 - 2.05 (m, 2 H) 1.26 (t, *J*=7.17 Hz, 1 H) 0.73 - 0.86 (m, 1 H) 0.46 - 0.61 (m, 1 H).

Example 259

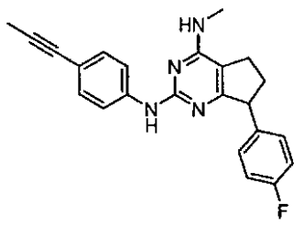
N2-(4-ethynylphenyl)-7-(4-fluorophenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



The mixture of tributyl(ethynyl)stannane (53.3 mg, 0.169 mmol), the fluorinated analog of Example 256 (50 mg, 0.113mmol) and Tetrakis (10.0 mg, 0.011 mmol) in toluene (226 µL) was heated at 110°C for 2 h, and then the solvent was removed in vacuo. The residue was purified by prep HPLC to get N2-(4-ethynyl-3-methoxyphenyl)-7-(4-fluorophenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (1.5 mg, 3.86 µmol). LC–MS $(M+H)^+ = 389.2$ ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.86 (s, 1 H) 7.31 (d, *J*=8.55 Hz, 2 H) 7.16 (dd, *J*=7.78, 5.65 Hz, 3 H) 7.01 (t, *J*=8.70 Hz, 2 H) 6.71 (br. s., 1 H) 4.52 (br. s., 1 H) 3.71 (s, 3 H) 3.15 (d, *J*=4.88 Hz, 3 H) 2.67 (d, *J*=9.77 Hz, 3 H) 1.95 - 2.14 (m, 1 H).

Example 260

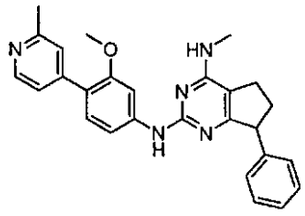
7-(4-fluorophenyl)-N4-methyl-N2-(4-(prop-1-ynyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



The mixture of tributyl(prop-1-ynyl)stannane (55.7 mg, 0.169 mmol), the fluorinated analog of Example 256 (50 mg, 0.113mmol) and Tetrakis (10.0 mg, 0.011 mmol) in toluene (226 µL) was heated at 110°C for 2 h, and then the solvent was removed in vacuo. The residue was purified by prep HPLC to get 7-(4-fluorophenyl)-N2-(3-methoxy-4-(prop-1-ynyl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (2.0 mg, 4.97 µmol). LC–MS $(M+H)^+ = 403.3$ ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.80 (d, *J*=1.76 Hz, 1 H) 7.10 - 7.23 (m, 3 H) 6.93 - 7.08 (m, 2 H) 6.73 (s, 1 H) 4.51 (br. s., 1 H) 4.05 - 4.29 (m, 1 H) 3.70 (s, 3 H) 3.14 (d, *J*=4.77 Hz, 3 H) 2.56 - 2.79 (m, 3 H) 2.09 - 2.14 (m, 3 H) 1.99 - 2.09 (m, 1 H).

Example 261

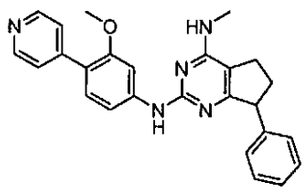
N2-(3-methoxy-4-(2-methylpyridin-4-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



The mixture of 2-methylpyridin-4-ylboronic acid (25.1 mg, 0.183 mmol), Example 256 (26 mg, 0.061mmol), Tetrakis (14.1 mg, 0.012 mmol) and sodium carbonate (13.0 mg, 0.122mmol) in toluene (255 µL)/water (50 µL) was heated at 150°C for 5 h, and then the solvent was removed in vacuo. The residue was purified by prep HPLC to get N2-(3-methoxy-4-(2-methylpyridin-4-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (5.0 mg, 0.011 mmol). LC–MS $(M+H)^+ = 438.2$ ^{1}H NMR (500 MHz, MeOD) δ ppm 8.60 (br. s., 1 H) 8.06 - 8.19 (m, 2 H) 7.75 (d, *J*=1.83 Hz, 1 H) 7.60 - 7.70 (m, 1 H) 7.38 - 7.49 (m, 2 H) 7.22 - 7.38 (m, 4 H) 4.43 - 4.57 (m, 1 H) 3.86 - 3.99 (m, 3 H) 3.17 - 3.26 (m, 3 H) 2.89 - 3.01 (m, 1 H) 2.73 - 2.89 (m, 5 H) 2.19 (dt, *J*=9.16, 6.87 Hz, 1 H).

Example 262

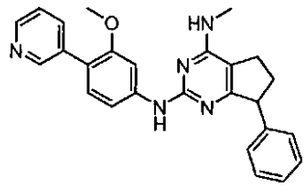
N2-(3-methoxy-4-(pyridin-4-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



The mixture of 4-(tributylstannyl)pyridine (69.2 mg, 0.188 mmol), Example 256 (20 mg, 0.047mmol) and Tetrakis (5.43 mg, 4.70 μmol)in toluene (196 μL)/water (39 μL) was heated at 100°C for 12 h, and then the solvent was removed in vacuo. The residue was purified by prep HPLC to get N2-(3-methoxy-4-(pyridin-4-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (4.0 mg, 9.44 μmol). LC–MS $(M+H)^+$ = 424.2 ^{1}H NMR (500 MHz, MeOD) δ ppm 8.20 – 8.90 (m, 4H) 7.74 (d, *J*=1.83 Hz, 1 H) 7.62 - 7.70 (m, 1 H) 7.39 - 7.47 (m, 2 H) 7.23 - 7.37 (m, 4 H) 4.43 - 4.54 (m, 1 H) 3.94 (s, 3 H) 3.22 (s, 3 H) 2.89 - 3.01 (m, 1 H) 2.75 - 2.87 (m, 2 H) 2.12 - 2.29 (m, 1 H).

Example 263

N2-(3-methoxy-4-(pyridin-3-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine



The mixture of 3-(tributylstannyl)pyridine (55.4 mg, 0.150 mmol), Example 256 (16 mg, 0.061mmol) and Tetrakis (4.35 mg, 3.76 μmol) in toluene (188 μL) was heated at 100°C for 12 h, and then the solvent was removed in vacuo. The residue was purified by prep HPLC to get N2-(3-methoxy-4-(pyridin-3-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine (4.0 mg, 9.44 μmol). LC–MS $(M+H)^+$ = 424.2 ^{1}H NMR (500 MHz, MeOD) δ ppm 8.52 (br. s., 2 H) 7.67 - 7.76 (m, 2 H) 7.55 - 7.64 (m, 1 H) 7.43 - 7.50 (m, 1 H) 7.41 (d, *J*=7.32 Hz, 2 H) 7.32 - 7.37 (m, 1 H) 7.17 - 7.31 (m, 3

H) 4.41 - 4.56 (m, 1 H) 3.88 (s, 3 H) 3.16 - 3.28 (m, 3 H) 2.88 - 3.02 (m, 1 H) 2.73 - 2.88 (m, 2 H) 2.09 - 2.26 (m, 1 H).

BIOLOGICAL METHODS

Cellular assays for inhibition of Aβ1-40 and Aβ1-42 production

H4 cells stably transfected with APP751 containing the Swedish mutation (H4 APP751 SWE clone 8.20, developed at BMS) were maintained in log phase through twice weekly passage at a 1:20 split. For IC_{50} determinations, 30 µl cells (1.5×10^4 cells/well) in DMEM media containing 0.0125% BSA (Sigma A8412) were plated directly into 384-well compound plates (Costar 3709) containing 0.1 µl serially diluted compound in DMSO. Following incubation for 19 h in 5% CO_2 at 37° C, plates were briefly centrifuged (1000 rpm, 5 min). A 10 µl aliquot from each well was transferred to a second assay plate (Costar 3709) for Aβ40 measurements. Antibody cocktails were freshly prepared by dilution into 40 mM Tris-HCl (pH 7.4) with 0.2% BSA and added to assay plates. For Aβ42 measurements, antibodies specific for the Aβ42 neoepitope (565, developed at BMS; conjugated to the Wallac reagent (Perkin Elmer)) and the N-terminal sequence of Aβ peptide (26D6, developed at SIBIA; conjugated to APC (Perkin Elmer)) were mixed and 20 µl of the mixture was added to each well of the incubated cell plate yielding a final concentration of 0.8 ng/well 565 and 75 ng/well 26D6. For the Aβ40 measurements, antibodies specific for the Aβ40 neoepitope (TSD, developed at BMS; conjugated to the Wallac reagent (Perkin Elmer)) and 26D6 as described above were mixed and 20 µl of the mixture was added to the 10 µl aliquots which had been removed previously from the cell plate yielding a final concentration of 1.6 ng/well TSD and 17.5 ng/well 26D6. Assay plates containing antibodies were sealed with aluminum foil and incubated overnight at 4° C. Signal was determined using a Viewlux counter (Perkin Elmer) and IC_{50} values determined using curve fitting in CurveMaster (Excel Fit based).

The activity of representative compounds of the present disclosure, based on Aβ42 cellular IC_{50} values in H4 APP751 SWE clone 8.20, are illustrated in Table 1 (below).

Table 1

Compound of Example	Activity Rating[a]	Compound of Example	Activity Rating[a]
1	+++	85	+++
2	+++	86	++
3	++	87	60 nM
3A	+++	88	++
3B	++	88A	4.5 nM
4	+++	88B	++
4A	+++	89	++
4B	++	90A	++
5	+++	90B	270 nM
5A	+++	91A	+++
5B	++	91B	+
6	++	92	++
6A	+++	93	20 nM
6B	++	94	+++
7A	+++	94A	+++
7B	++	94B	++
8	+++	95	+++
9	8.1 nM	95A	+++
10	+++	95B	++
11	+++	96	+++
11A	3.8	96A	+++
11B	+++	96B	4.6 nM
12	+++	97	+++
12A	+++	97A	+++
13	-	97B	++
14	-	98	++
15	++	98A	+++
16	++	98B	++
16A	+++	99	19 nM
16B	+	99A	++

Compound of Example	Activity Rating[a]	Compound of Example	Activity Rating[a]
17	++	99B	190 nM
17A	120 nM	100	+++
17B	++	100A	4.7 nM
18	++	100B	++
18A	8.8 nM	101	++
18B	++	101A	+++
19	++	101B	++
19A	++	102	+++
19B	59 nM	102A	+++
20	+++	102B	++
20A	+++	103	+++
20B	++	103A	+++
21	++	103B	++
21A	++	104	++
21B	+	105	8.8 nM
23	++	106	++
23A	++	107	++
23B	+	107A	++
24	++	107B	+
24A	++	108	20 nM
24B	200 nM	109A	+++
25	++	109B	+++
26	+++	110A	+++
26A	++	110B	++
26B	++	111	35 nM
27	++	112	+++
28	++	112A	+++
28A	++	112B	++
29	++	113	5.7 nM
29A	++	113A	+++

Compound of Example	Activity Rating[a]	Compound of Example	Activity Rating[a]
29B	++	113B	++
30	++	114	+++
30A	++	114A	++
30B	230 nM	114B	+
31	+	115	+++
32	++	115A	+++
33	100 nM	115B	++
34	++	116	++
35	+++	116A	+++
36	++	116B	+
37	+++	117	45 nM
38	++	117A	++
38A	12 nM	117B	+
38B	++	118	++
39	++	118A	+++
39B	+	118B	+
40A	+++	119	++
40B	+	119A	7.4 nM
41	++	119B	+
41A	++	120	++
41B	++	120A	+++
41C	++	120B	+
41D	++	121	++
42	++	121A	+++
42A	+++	121B	120 nM
43	+++	122A	+++
44	13 nM	123A	++
44A	+++	123B	370 nM
45A	++	124	++
45B	2.5 nM	124A	+++

Compound of Example	Activity Rating[a]	Compound of Example	Activity Rating[a]
45C	++	124B	++
45D	+++	125	++
46	+++	126	++
46A	+++	127	++
46B	++	127A	+++
47	+++	127B	++
48	18 nM	128	+
48A	+++	129	++
48B	130 nM	129A	+++
49	+++	130	+++
49A	+++	130A	+++
49B	++	131	++
50	+++	131A	+++
50A	+++	132	++
50B	++	132A	15 nM
51	4.5 nM	133	++
51A	+++	133A	+++
51B	+++	134	+++
52	++	134A	3.6 nM
52A	+++	135	++
52B	++	135A	++
53	++	136	+++
53A	+++	136A	+++
53B	++	137	11 nM
54	++	137A	+++
54A	++	138	++
54B	+++	138A	+++
55	++	139	++
55B	++	139A	++
56	++	140	++

Compound of Example	Activity Rating[a]	Compound of Example	Activity Rating[a]
56A	+++	140A	+++
56B	++	141	++
57A	14 nM	141A	+++
57B	+	142	++
58A	+++	143	++
58B	120 nM	143B	430 nM
59	++	144	++
59A	+++	144B	540 nM
60	+++	145	++
60A	5.6 nM	146	++
60B	++	147	++
61	++	148A	+++
61A	+++	149	++
61B	++	150	++
62	++	151	+++
62A	+++	151A	+++
62B	86 nM	152	++
63	++	153	++
63A	++	154	++
63B	+	154A	+++
64	++	155A	+++
64A	+++	156	+++
64B	++	156A	9.8 nM
65	++	157	++
65A	5.3 nM	157A	++
65B	160 nM	158	++
66	++	159	++
66A	+	160	++
66B	+++	161	+
67	++	162	++

Compound of Example	Activity Rating[a]	Compound of Example	Activity Rating[a]
67A	++	162A	++
67B	540 nM	163A	+++
68	++	164A	++
69	++	165	++
69A	+++	165A	++
69B	+	165B	180 nM
70	+++	166	+
70A	+++	167A	26 nM
70B	++	168A	+++
71	++	169	++
71A	+++	169A	+++
71B	++	170	++
72	+++	170A	+++
73	3.8 nM	171	16 nM
74A	++	171A	++
75	++	172A	+++
75A	+++	172B	+
75B	++	173	490 nM
76	++	174	++
77	++	175	++
78	++	175A	+++
78A	19 nM	176	+++
78B	++	176A	+++
79A	5.8 nM	176B	+++
79B	++	177	++
80	++	178	+++
80A	++	179	++
81	++	180	++
82	++	181	++
82A	+++	181A	+++

Compound of Example	Activity Rating[a]	Compound of Example	Activity Rating[a]
82B	++	181B	50 nM
83	++	182	++
83A	+++	182A	+++
83B	++	182B	++
84	++	183	11 nM
84A	++	183A	+++
84B	290 nM	183B	++
184	++	211	+++
185	++	212	33 nM
186	++	213	insol
187	++	214	77 nM
187A	++	215A	^
187B	++	215B	173 nM
188	19 nM	216	^
189	+++	217	^
189A	+++	218	3700 nM
189B	++	219	^
190	37 nM	220	550 nM
191	++	221	^
191A	++	222	^
191B	96 nM	223	11000 nM
192	64 nM	224	^
192A	170 nM	225	18 nM
192B	16 nM	226	+
193	++	193B	++
193A	+	227	12 nM
194	++	228	^
194A	++	229	^
194B	175 nM	230	42 nM
195	17 nM	231	+

Compound of Example	Activity Rating[a]	Compound of Example	Activity Rating[a]
195A	26 nM	232	^
195B	+	233	^
196	++	234	^
196A	+++	235	+
196B	54 nM	236	^
197	16 nM	237	29 nM
197A	60 nM	238	+
197B	+++	239	+
198	++	240	Insol
198A	+	241	Insol
198B	15 nM	242	67 nM
199	++	243	+
199A	+	244	^
199B	+++	245	^
200	++	246	31 nM
200A	++	247	+
200B	++	248	^
201	5.3 nM	249	^
201A	10 nM	250	^
201B	++	251	^
202	+++	252	^
203	19 nM	253	5900 nM
203A	+++	254	1000 nM
203B	++	255	^
204	19 nM	256	97 nM
204A	19 nM	257	++
204B	+	258	^
205	++	259	940 nM
206	15 nM	260	860 nM
207	+	261	+++

Compound of Example	Activity Rating[a]	Compound of Example	Activity Rating[a]
208	++	262	+++
209	+++	263	32 nM
210	61 nM		

[a]Activity based on Aβ42 cellular IC_{50} values in H4 APP751 SWE clone 8.20.

+++ = 1.5 nM - 0.0099 M

++ = 0.010 – 0.100 μM

\+ = 0.100 – 1.0 μM

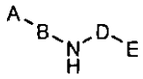
^ = > 1.0 μM

It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

What is claimed is:

1. A compound of formula (I)



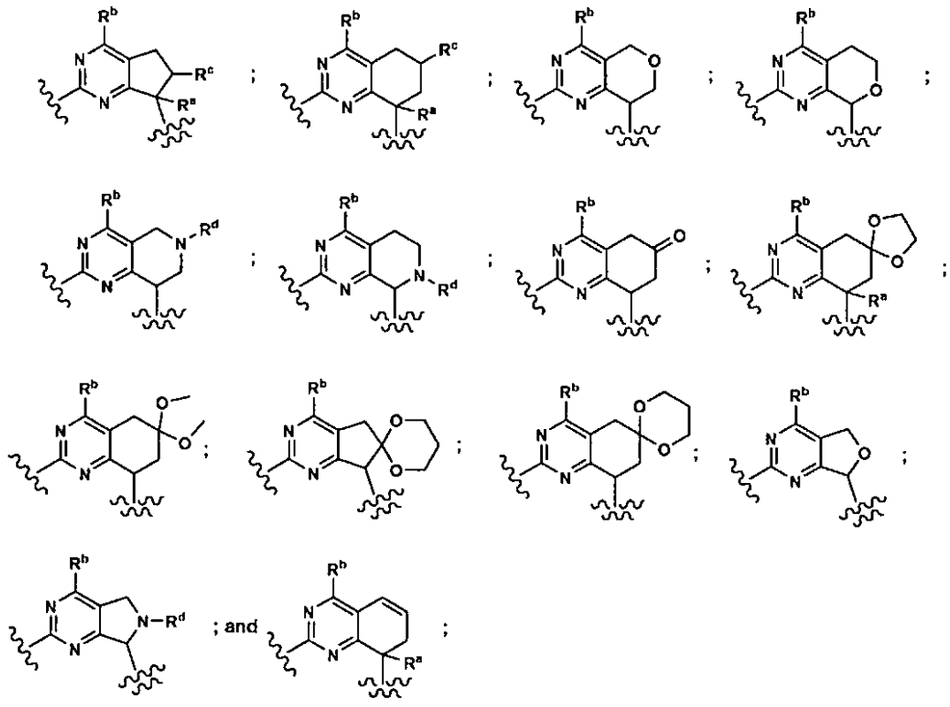
(I),

or a pharmaceutically acceptable salt thereof, wherein

A is a five- or six-membered heteroaromatic ring containing from one to three heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said heteroaromatic ring is optionally substituted with one or two groups selected from halo, haloC_{1-6}alkyl, hydroxy, amino, C_{1-6}alkoxy, and C_{1-6}alkyl;

B is selected from phenyl and pyridinyl, wherein the phenyl and pyridinyl are optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkyl, C_{1-3}alkylamino-C_{1-6}alkoxy, cyano, C_{1-3}dialkylamino-C_{1-6}alkoxy, halo, haloC_{1-6}alkoxy, haloC_{1-6}alkyl, hydroxy, methylamino, and amino;

D is selected from



"  " denotes the point of attachment to the nitrogen atom of the parent molecule;

"  " denotes the point of attachment to the 'E' moiety;

R^a is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, and hydroxy;

R^b is $-NR^xR^y$, wherein R^x and R^y are independently selected from hydrogen, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, (C_{3-7}cycloalkyl)C_{1-4}alkyl, hydroxyC_{1-4}alkyl, and trideuteromethyl, wherein the alkyl part of the (C_{3-7}cycloalkyl)C_{1-4}alkyl can be optionally substituted with a C_{1-4}alkoxy group; or, R^x and R^y, together with the nitrogen atom to which they are attached, form a four- to seven-membered monocyclic or bicyclic ring optionally containing one double bond and optionally containing one additional heteroatom selected from O, NR^z, and S; wherein R^z is selected from hydrogen, C_{1-6}alkyl, and C_{1-4}alkoxycarbonyl; and wherein the ring is optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkyl, halo, haloC_{1-4}alkyl, hydroxy, $-NR^fR^g$, oxo, spirocyclic dioxolanyl; wherein R^f and R^g are independently selected from hydrogen, C_{1-4}alkoxycarbonyl, and C_{1-6}alkyl;

R^c is selected from hydrogen, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfonylamido, amino, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{3-7}cycloalkylamino, hydroxy, and C_{1-4}alkoxy;

R^d is selected from hydrogen, C_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkylcarbonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, C_{3-7}cycloalkylsulfonyl, C_{3-7}cycloalkylcarbonyl, C_{1-6}dialkylaminoC_{1-4}alkylcarbonyl, and haloC_{1-4}alkyl, wherein the alkyl part of the alkoxycarbonyl, the alkylcarbonyl, and the alkylsulfonyl are optionally substituted with one substituent selected from C_{1-4}dialkylamino, and C_{1-4}alkoxy; and

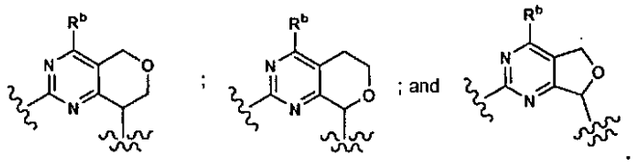
E is selected from C_{1-6}alkyl, C_{4-6}cycloalkyl, (C_{4-7}cycloalkyl)C_{1-4}alkyl, benzyl, phenyl, and a five- to six-membered heteroaromatic ring containing one or two nitrogen atoms, wherein the phenyl, the phenyl part of the benzyl, and the heteroaromatic ring are each optionally substituted with one, two, or three substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo, halo C_{1-6}alkoxy, and haloC_{1-6}alkyl.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is a five-membered heteroaromatic ring containing from one to three nitrogen atoms; wherein said heteroaromatic ring is optionally substituted with one group selected from halo and C_{1-6}alkyl.

3. A compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein B is selected from phenyl and pyridinyl, wherein the phenyl and pyridinyl are optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy and halo.

4. A compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein E is phenyl optionally substituted with one, two, or three substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl.

5. A compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein D is selected from

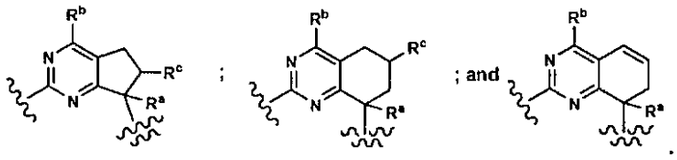


6. A compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^b is $-NR^xR^y$, wherein R^x and R^y are independently selected from hydrogen, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, hydroxyC_{1-4}alkyl, and trideuteromethyl, wherein the alkyl part of the (C_{3-7}cycloalkyl)C_{1-4}alkyl can be optionally substituted with a C_{1-4}alkoxy group.

7. A compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^b is $-NR^xR^y$, wherein R^x and R^y, together with the nitrogen atom to which they are attached, form a four- to seven-membered monocyclic or bicyclic ring optionally containing one additional heteroatom selected from O and NR^z; wherein R^z is selected from C_{1-6}alkyl, and C_{1-4}alkoxycarbonyl; and wherein the ring is

optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkyl, halo, haloC_{1-4}alkyl, hydroxy, -NR^fR^g, oxo, and spirocycle dioxolanyl; wherein R^f and R^g are independently selected from hydrogen, C_{1-4}alkoxycarbonyl, and C_{1-6}alkyl.

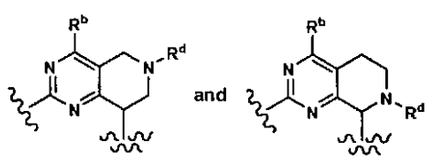
8. A compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein D is selected from



9. A compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein R^b is -NR^xR^y, wherein R^x and R^y are independently selected from hydrogen, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, hydroxyC_{1-4}alkyl, and trideuteromethyl, wherein the alkyl part of the (C_{3-7}cycloalkyl)C_{1-4}alkyl can be optionally substituted with a C_{1-4}alkoxy group.

10. A compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein R^b is -NR^xR^y, wherein R^x and R^y, together with the nitrogen atom to which they are attached, form a four- to seven-membered monocyclic or bicyclic ring optionally containing one additional heteroatom selected from O and NR^z; wherein R^z is selected from C_{1-6}alkyl, and C_{1-4}alkoxycarbonyl; and wherein the ring is optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkyl, halo, haloC_{1-4}alkyl, hydroxy, -NR^fR^g, oxo, and spirocycle dioxolanyl; wherein R^f and R^g are independently selected from hydrogen, C_{1-4}alkoxycarbonyl, and C_{1-6}alkyl.

11. A compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein D is selected from



12. A compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^b is $-NR^xR^y$, wherein R^x and R^y are independently selected from hydrogen, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-6}alkyl, C_{3-7}cycloalkyl, hydroxyC_{1-4}alkyl, and trideuteromethyl, wherein the alkyl part of the (C_{3-7}cycloalkyl)C_{1-4}alkyl can be optionally substituted with a C_{1-4}alkoxy group.

13. A compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R^b is $-NR^xR^y$, wherein R^x and R^y, together with the nitrogen atom to which they are attached, form a four- to seven-membered monocyclic or bicyclic ring optionally containing one additional heteroatom selected from O and NR^z; wherein R^z is selected from C_{1-6}alkyl, and C_{1-4}alkoxycarbonyl; and wherein the ring is optionally substituted with one or two substituents independently selected from C_{1-6}alkoxy, C_{1-6}alkyl, halo, haloC_{1-4}alkyl, hydroxy, $-NR^fR^g$, oxo, and spirocycle dioxolanyl; wherein R^f and R^g are independently selected from hydrogen, C_{1-4}alkoxycarbonyl, and C_{1-6}alkyl.

14. A compound selected from

N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

(S)-4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

(R)-4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-cyclopropyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-cyclobutyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-isopropyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)- N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)- N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(3-Fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(2-Fluoro-5-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-

fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(6-(4-chloro-1H-imidazol-1-yl)-5-methoxypyridin-3-yl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(2-methylpyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-4-methylpiperidin-4-ol;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(2-ethylpyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

4-(4-amino-4-methylpiperidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-

amine;

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-(trifluoromethyl)pyrrolidin-3-ol;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)pyrrolidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-

(4-methylpiperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(piperazin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(3-(methylamino)pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(3-(methylamino)azetidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-(dimethylamino)azetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N^2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine);

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(4,4-difluoropiperidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(4-fluoro-5,6-dihydropyridin-1(2H)-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(3-(trifluoromethyl)pyrrolidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-(3-ethoxypropyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

3-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-ylamino)propan-1-ol;

7-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-(1-cyclopropyl-2-methoxyethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-trideuteromethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N4-((R)-1-methoxybutan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((S)-1-cyclopropylethyl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imiazol-1-yl)-3-methoxyphenyl)-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imiazol-1-yl)-3-methoxyphenyl)-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-

methyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-8-phenyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N4-ethyl-8-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine;

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4,N4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine;

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4,N^4-dimethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-chlorophenyl)-4-(3,3-difluoroazetidin-1-yl)-N-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine;

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-chlorophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-

N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-chlorophenyl)-N^2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-bromophenyl)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(4-bromophenyl)-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-2-methylpyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine ;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine;

N^4-ethyl-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine;

N^4-ethyl-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine;

N^4-ethyl-N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N^4-methyl-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((R)-1-cyclopropylethyl)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine;

N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7-(4-fluorophenyl)-N4-methyl-5,7-dihydrofuro[3,4-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((2S,6R)-2,6-dimethylmorpholino)-7-(4-fluorophenyl)-5,7-dihydrofuro[3,4-d]pyrimidin-2-amine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine;

N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine;

N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-6,8-dihydro-5H-pyrano[3,4-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-6,8-dihydro-5H-pyrano[3,4-d]pyrimidin-2-amine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-4-

(3,3-difluoroazetidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-chlorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4,N^4-dimethyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

(S)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

(R)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4,N^4-dimethyl-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

(S)-4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

(R)-4-(Azetidin-1-yl)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(3,5-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(6-(4-chloro-1H-imidazol-1-yl)-5-methoxypyridin-3-yl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N^2-(4-(3-chloro-1H-1,2,4-triazol-1-yl)-3-methoxyphenyl)-N^4-methyl-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoropyrrolidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

(S)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoropyrrolidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

(R)-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoropyrrolidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-7-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(2,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)- N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(2,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)- N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(2,4-difluorophenyl)-N^4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-7-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-7-allyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(3,5-difluorophenyl)-N4-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(3,4-difluorophenyl)-N4-ethyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8- (3,4-difluorophenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(3,4-difluorophenyl)-N4-methyl-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

8-(3,4-difluorophenyl)-N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-((R)-1-cyclopropylethyl)-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

4-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-8-yl)benzonitrile;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-8-(4-(trifluoromethoxy)phenyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-amine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-N^4-methyl-8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-phenyl-5,6,7,8-tetrahydroquinazolin-2-amine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-ethyl-8-(4-fluorophenyl)-N^4-methyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N^4,N^4-dimethyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N^4,N^4-dimethyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N^4,N^4-dimethyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-

5,6,7,8-tetrahydroquinazolin-2-amine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-6-(cyclopropylsulfonyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

Methyl 2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate;

(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)(cyclopropyl)methanone;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-methoxyethanone;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-2-(dimethylamino)ethanone;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-6-(cyclopropylsulfonyl)-N4-ethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)ethanone;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-6-(ethylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

6-(cyclopropylsulfonyl)-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

6-(cyclopropylsulfonyl)-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-

yl)phenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

cyclopropyl(4-(ethylamino)-2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone;

cyclopropyl(4-(ethylamino)-2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenylamino)-8-phenyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone;

N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-6-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-6-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,N4-dimethyl-6-(methylsulfonyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,6-dimethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-methyl-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4-methyl-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-(4-fluorophenyl)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6-(methylsulfonyl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,6-diethyl-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3,3-difluoroazetidin-1-yl)-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-amine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((S)-3-fluoropyrrolidin-1-yl)-7-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4,7-diethyl-8-(4-fluorophenyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine;

methyl 2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-

(ethylamino)-8-(4-fluorophenyl)-5,6-dihydropyrido[3,4-d]pyrimidine-7(8H)-carboxylate;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(ethylamino)-8-(4-fluorophenyl)-5,6-dihydropyrido[3,4-d]pyrimidin-7(8H)-yl)ethanone;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-N4-methyl-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-8-(4-fluorophenyl)-4-((R)-3-fluoropyrrolidin-1-yl)-7-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-2-amine;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-ethyl-8-(4-fluorophenyl)-7-methyl-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine-2,4-diamine;

N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-trideuteromethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-trideuteromethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)-N^2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N^4-trideuteromethyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(methylamino)-8-phenyl-7,8-dihydroquinazolin-8-ol;

2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(methylamino)-8-phenyl-5,6,7,8-tetrahydroquinazolin-8-ol;

2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(dimethylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-7-ol;

(6S,7S)-2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(dimethylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-6-ol;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-chloroazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-fluoroazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-methoxyazetidin-1-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-4-(5,8-dioxa-2-azaspiro[3.4]octan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)azetidin-3-one;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-methylazetidine-3-carbonitrile;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-ethoxyazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-4-(5-oxa-2-azaspiro[3.4]octan-2-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-3-methylazetidin-3-ol;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(3-fluoro-3-methylazetidin-1-yl)-7-(4-fluorophenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-4-(3-methoxy-3-methylazetidin-1-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

7-(4-fluorophenyl)-4-(3-methoxy-3-methylazetidin-1-yl)-N-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

7-(2,4-difluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(S)- 7-(2,4-difluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

(R)- 7-(2,4-difluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

6-(2,2-difluoroethyl)-N4-ethyl-N2-(3-fluoro-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

6-(2,2-difluoroethyl)-N4-ethyl-N2-(3-fluoro-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-8-phenyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N4-ethyl-N2-(3-methoxy-4-(4-chloro-1H-13-imidazol-1-yl)phenyl)-8-phenyl-6-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

N4-ethyl-N2-(3-methoxy-4-(4-chloro-1H-13-imidazol-1-yl)phenyl)-8-phenyl-6-(2,2-difluoroethyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

8-(4-fluorophenyl)-N2-(3-methoxy-4-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

8-(4-fluorophenyl)-N2-(3-methoxy-4-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)-N4,6-dimethyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine-2,4-diamine;

(±)-2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-5-one;

(E)-2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-5-one O-methyl oxime;

2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-5-ol;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-methyl-8-phenyl-5,6,7,8-tetrahydroquinazoline-2,4-diamine;

1-(2-methoxy-4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)-1H-imidazole-4-carbonitrile;

N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-7-phenyl-4-(1,4-dioxa-7-azaspiro[4.4]nonan-7-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-amine;

1-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)pyrrolidin-3-one;

4-(8-(4-fluorophenyl)-4-(methylamino)-6-(methylsulfonyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-2-ylamino)benzonitrile;

N2-(4-(4-(difluoromethyl)-1H-imidazol-1-yl)-3-methoxyphenyl)-7-(4-fluorophenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(3-methoxy-4-(1-methyl-1H-pyrazol-4-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N-methylmethanesulfonamide;

N-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N-methanesulfonamide;

N-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N-methylacetamide;

N-(2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-N-acetamide;

N2-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-N4-(5-isopropyl-2-methylphenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

4-(4-(5-isopropyl-2-methylphenylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile;

N4-methyl-N2-(2-methylpyridin-4-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(3-methoxyphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-fluorophenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(3,5-difluorophenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-chloro-3-methoxyphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-bromo-2-methoxyphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-fluoro-3-methoxyphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N4-methyl-7-phenyl-N2-(pyrimidin-5-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N4-methyl-7-phenyl-N2-(pyridin-4-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile;

4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile;

4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile;

2-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile;

4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-1-naphthonitrile;

5-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)picolinonitrile;

2-(4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)acetonitrile;

2-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-1H-benzo[d]imidazole-5-carbonitrile;

3-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile;

N2-(4-tert-butylphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N4-methyl-N2-(4-(methylsulfonyl)phenyl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N4-methyl-7-phenyl-N2-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phthalonitrile;

4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-2-(trifluoromethyl)benzonitrile;

N4-methyl-7-phenyl-N2-(4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

5-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-2,3-dihydro-1H-inden-1-one;

2-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-1H-imidazole-4,5-dicarbonitrile;

2-bromo-5-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzonitrile;

N,N-dimethyl-4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)benzamide;

1-(4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)cyclopentanecarbonitrile;

N4-methyl-7-phenyl-N2-(1,2,3,4-tetrahydroisoquinolin-6-yl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)-2-(trifluoromethoxy)benzonitrile;

1-(4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)cyclopropanecarbonitrile;

1-(2-methoxy-4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenylamino)cyclopropanecarbonitrile;

N4-methyl-N2-(2-methyl-1H-indol-5-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(benzofuran-5-yl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(1H-indol-5-yl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N4-methyl-N2-(2-methylbenzo[d]oxazol-6-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(1H-benzo[d]imidazol-6-yl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N4-methyl-N2-(1-methyl-1H-indol-5-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N4-methyl-N2-(2-methylbenzo[d]thiazol-6-yl)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-bromo-3-methoxyphenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

1-(4-(4-(methylamino)-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-ylamino)phenyl)ethanone;

N2-(4-cyclopropylphenyl)-7-(4-fluorophenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(4-ethynylphenyl)-7-(4-fluorophenyl)-N4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

7-(4-fluorophenyl)-N4-methyl-N2-(4-(prop-1-ynyl)phenyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(3-methoxy-4-(2-methylpyridin-4-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine;

N2-(3-methoxy-4-(pyridin-4-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine, and

N2-(3-methoxy-4-(pyridin-3-yl)phenyl)-N4-methyl-7-phenyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine-2,4-diamine; or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition for the treatment of disorders responsive to the reduction of β-amyloid peptide production comprising a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier or diluent.

16. A method for the treatment of disorders responsive to the reduction of β-amyloid peptide production in a mammal in need thereof, which comprises administering to said mammal a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

17. A method of claim 16 wherein said disorder is selected from Alzheimer's Disease (AD), Down Syndrome, mild cognitive impairment (MCI), cerebral amyloid angiopathy (CAA), dementia with Lewy bodies (DLB), amyotrophic lateral sclerosis (ALS-D), inclusion body myositis (IBM), age-related macular degeneration, and cancer.

18. A method of claim 17 wherein said disorder is selected from Alzheimer's Disease and Down Syndrome.

19. A method of claim 18 wherein said disorder is Alzheimer's Disease.

TRADUCCION SOLICITUD

COMPUESTOS PARA LA REDUCCIÓN DE PRODUCCIÓN DE β-AMILOIDE

CAMPO DE LA INVENCIÓN

La presente revelación se refiere a procedimientos para tratar Enfermedad de Alzheimer (AD) y otras afecciones relacionadas con producción de β-amiloide usando compuestos que son inhibidores de producción de péptido β-amiloide (Aβ). La revelación se refiere adicionalmente a composiciones farmacéuticas que comprenden estos compuestos.

ANTECEDENTES DE LA INVENCIÓN

La enfermedad de Alzheimer (AD) es una enfermedad neurodegenerativa progresiva que comienza con pérdida de memoria y progresa para incluir daño cognitivo severo, comportamiento alterado, y función motora decrecida (Grundman, M. *y col., Arch Neurol.* (2004) 61: 59-66; Walsh, D.M. *y col., Neuron* (2004) 44: 181-193). Es la forma más común de demencia y representa la tercera causa principal de muerte después de los trastornos cardiovasculares y el cáncer. El coste de la AD es enorme e incluye el sufrimiento de pacientes y familias y la pérdida de productividad de pacientes y cuidadores. No está disponible actualmente ningún tratamiento que evite de forma efectiva la ADO que revierta de forma efectiva los síntomas clínicos y la patofisiología subyacente.

Un diagnóstico definitivo de AD para un paciente demente requiere una evaluación histopatológica del número y localización de placas neuríticas y enredos neurofibrilares tras la autopsia (recomendaciones consenso para el diagnóstico postmortem de la enfermedad de Alzheimer. *Neurobiol Aging*

(1997) 18: S1-2). Se observan alteraciones similares en pacientes con Trisomía 21 (síndrome de Down). Las placas constan principalmente de péptidos β-amiloides (Aβ) que están formados por una escisión proteolítica por etapas de la proteína precursora de amiloide (APP) mediante enzima de escisión de APP de sitio β (BACE), para generar el extremo N-terminal y γ-secretasa, para generar el extremo C-terminal (Selkoe, D.J., *Physiol Rev.*(2001) 81: 741-766). γ-Secretasa es un complejo de proteína transmembrana que incluye Nicastrin, Aph-1, PEN-2 y bien Presenilina-1 (PS-1) o bien Presenilina-2 (PS-2) (Wolfe, M.S. *y col., Science* (2004) 305: 1119-1123). Se cree que PS-1 y PS-2 contienen los sitios catalíticos de γ-secretasa.

Aβ40 es la forma más abundante de Aβ sintetizada (80-90%), mientras que Aβ42 es la más estrechamente relacionada con la patogénesis de AD. En particular, las mutaciones en los genes APP, PS-1, y PS-2 que conducen a formas familiares, raras de AD implican agregados de Aβ42 como las especies tóxicas fundamentales (Selkoe, D.J., *Physiol Rev.,* (2001) 81: 741-766). La evidencia actual sugiere que la Aβ42 oligomérica, protofibrilar e intracelular juega un papel significativo en el proceso de la enfermedad (Cleary, J.P. *y col., Nat Neurosci.* (2005), 8: 79-84). Los inhibidores de las enzimas que forman Aβ42, tales como γ-secretasa, representan terapias potenciales que modifican la enfermedad para el tratamiento de AD.

La evidencia sugiere que una reducción en los niveles de Aβ en el cerebro mediante inhibición de secretasa-γ puede evitar la aparición y progresión de AD (Selkoe, D. *Physiol. Rev.* (2001) 81: 741-766; Wolfe, M., *J. Med. Chem.* (2001) 44: 2039-2060). Hay datos emergentes para el papel de Aβ en otras enfermedades, incluyendo dificultad cognitiva leve (MCI), síndrome

de Down, angiopatía cerebral amiloide (CAA), demencia con cuerpos de Lewy (DLB), esclerosis lateral amiotrófica (ALS-D), miositis de cuerpos de inclusión (IBM), y degeneración macular relacionada con la edad. Ventajosamente, los compuestos que inhiben secretasa-γ y reducen producción de Aβ se podrían usar para tratar éstas u otras enfermedades dependientes de Aβ.

La producción en exceso y/o la eliminación reducida de Aβ causa CAA (Thal, D. y col., *J. Neuropath. Exp. Neuro.* (2002) 61: 282-293). En estos pacientes, los depósitos amiloides vasculares causan degeneración de paredes vasculares y aneurismas que pueden ser responsables del 10-15% de apoplejías hemorrágicas en pacientes mayores. Como en AD, las mutaciones en el gen que codifica Aβ conducen a una forma de aparición temprana de CAA, referida como hemorragia cerebral con amiloidosis del tipo Dutch, y los ratones que expresan esta proteína mutante desarrollan CAA que es similar para pacientes. Los compuestos que reducen niveles de Aβ podrían reducir o evitar CAA.

DLB se manifiesta con alucinaciones visuales, ilusiones y parkinson. De forma interesante, las mutaciones AD familiares que causan depósitos de Aβ pueden causar también cuerpos de Lewy y síntomas de DLB (Yokota, O. *y col., Acta Neuropathol (Berl)* (2002) 104: 637-648). Adicionalmente, los pacientes esporádicos de DLB tienen depósitos de Aβ similares a aquellos en AD (Deramecourt, V. *y col., J Neuropathol Exp Neurol* (2006) 65: 278-288). En base a estos datos, Aβ probablemente conduce a la patología de los cuerpos de Lewy en DLB y, por lo tanto, los compuestos que reducen los niveles de Aβ podrían reducir o evitar DLB.

Aproximadamente el 25% de los pacientes de ALS tienen demencia o

afasia significativas (Hamilton, R.L. y col., *Acta Neuropathol (Berl)* (2004) 107: 515-522). La mayoría (~60%) de estos pacientes, designados ALS-D, contienen inclusiones positivas de ubiquitina compuestas principalmente de la proteína TDP-43 (Neumann, M. y col., *Science* (2006) 314: 130-133). Aproximadamente el 30% de los pacientes de ALS-D tienen placas amiloides consistentes con que Aβ cause su demencia (Hamilton, R.L. *y col., Acta Neuropathol (Berl)* (2004) 107: 515-522). Estos pacientes serían identificables con los agentes que forman imágenes de amiloide y que potencialmente se pueden tratar con compuestos que reducen niveles de Aβ.

IBM es una enfermedad del músculo esquelético rara, degenerativa relacionada con la edad. La apariencia de depósitos de Aβ en músculo con IBM y la recapitulación de varios aspectos de la enfermedad dirigiendo sobreexpresión de APP en músculo en ratones transgénicos sustenta el papel de Aβ en IBM (revisado en Murphy, M.P. *y col., Neurology* (2006) 66: S65-68). Los compuestos que reducen niveles de Aβ podrían reducir o evitar IBM.

En la degeneración macular asociada con la edad, se ha identificado a Aβ como uno de varios componentes de drusas, depósitos extracelulares debajo del epitelio pigmentario retinal (RPE) (Anderson, D.H. *y col., Exp Eye Res* (2004) 78: 243-256). Un estudio reciente ha mostrado vínculos potenciales entre Aβ y degeneración macular en ratones (Yoshida, T. *y col., J Clin Invest* (2005) 115: 2793-2800). Se han encontrado incrementos en deposición de Aβ y cataratas supranucleares en pacientes de AD (Goldstein, L.E. *y col., Lancet* (2003) 361: 1258-1265). Los compuestos que reducen los niveles de Aβ podrían reducir o evitar la degeneración macular asociada con la edad.

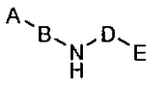
Los compuestos que reducen secretasa gamma pueden ser útiles en tratar afecciones asociadas con pérdida de mielinación, por ejemplo esclerosis múltiple (Watkins, T.A., *y col.*, Neuron (2008) 60: 555-569).

Un reciente estudio de los investigadores del Georgetown University Medical Center sugiere que los inhibidores de gamma-secretasa pueden evitar daño a largo plazo de lesión traumática general (Loane, D. J., *y col., Nature Medicine* (2009): 1-3).

Un enfoque lógico a niveles de Aβ reductores es bloquear la acción de las secretasas. Un enfoque complementario es reducir selectivamente la producción de Aβ1-42 por la acción de ciertos compuestos que sirven para dirigir la escisión medida por γ-secretasa de APP para producir en su lugar formas más cortas de Aβ. Estas formas más cortas parecen agregarse menos fácilmente y las soluciones de las formas más cortas de Aβ son menos neurotóxicas que las soluciones de Aβ1-42 (véase Barten, Donna M.; Meredith, Jere E., Jr.; Zaczek, Robert; Houston, John G.; Albright, Charles F. *Drugs in R&D* (2006), 7 (2), 87-97). Así, los compuestos que reducen selectivamente producción de Aβ1-42 y sus composiciones farmacéuticas son agentes benéficos que evitarán daño de sobreproducción de Aβ y son útiles en tratar enfermedad de Alzheimer, síndrome de Down, CAA y miositis de cuerpos de inclusión, DLB y otros trastornos donde Aβ está sobreproducida.

SUMARIO DE LA INVENCIÓN

En su primer aspecto la presente revelación proporciona un compuesto de fórmula (I)



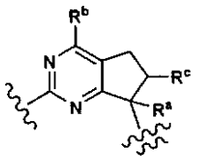
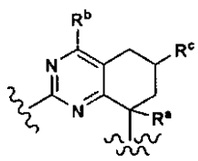
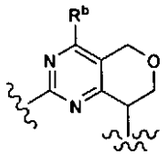
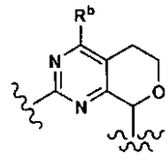
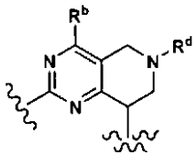
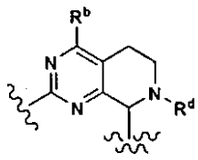
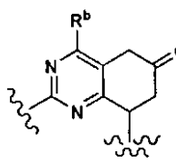
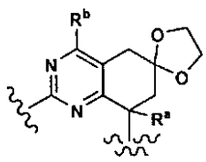
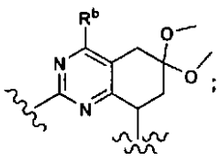
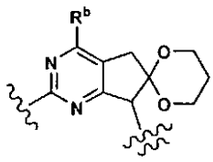
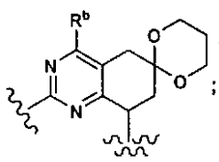
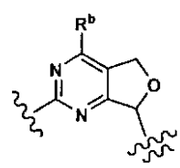
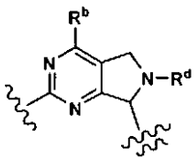
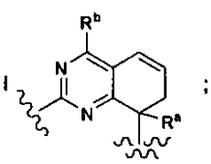
(I),

o una sal farmacéuticamente aceptable del mismo; en la que

A es un anillo heteroaromático de cinco o seis miembros que contiene de uno a tres heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre; en el que dicho anillo heteroaromático está opcionalmente sustituido con uno o dos grupos seleccionados de halo, haloalquilo C_{1-6}, hidroxi, amino, alcoxi C_{1-6} y alquilo C_{1-6};

B se selecciona de fenilo y piridinilo, en el que el fenilo y el piridinilo están opcionalmente sustituidos con uno o dos sustituyentes seleccionados independientemente de alcoxi C_{1-6}, alquilo C_{1-6}, alquilamino C_{1-3}alcoxi-C_{1-6}, ciano, dialquilamino C_{1-3}-alcoxi C_{1-6}, halo, haloalcoxi C_{1-6}, haloalquilo C_{1-6}, hidroxi, metilamino y amino;

D se selecciona de


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y

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" " indica el punto de unión del átomo de nitrógeno a la molécula parental;

" " indica el punto de unión al resto 'E';

R^a se selecciona de hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6} e hidroxi;

R^b es $-NR^xR^y$, en el que R^x y R^y están independientemente seleccionados de hidrógeno, alcoxi C_{1-4}, alcoxi C_{1-4}-alquilo C_{1-4}, alcoxicarbonilo C_{1-4}, alquilo C_{1-6}, cicloalquilo C_{3-7}, (cicloalquilo C_{3-7})alquilo C_{1-4}, hidroxialquilo C_{1-4} y trideuterometilo, en el que la parte alquilo del (cicloalquilo C_{3-7})alquilo C_{1-4} puede estar opcionalmente sustituida con grupo alcoxi C_{1-4}; o, R^x y R^y, conjuntamente con el átomo de nitrógeno al que están unidos, forman un anillo monocíclico o bicíclico de cuatro a siete miembros que contiene opcionalmente un enlace doble y que contiene opcionalmente un heteroátomo adicional

seleccionado de O, NR^z y S; en el que R^z se selecciona de hidrógeno, alquilo C_{1-6} y alcoxicarbonilo C_{1-4}; y en el que el anillo está opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente de alcoxi C_{1-6}, alquilo C_{1-6}, halo, haloalquilo C_{1-4}, hidroxi, $-NR^fR^g$, oxo, dioxolanilo espirocíclico; en el que R^f y R^g están independientemente seleccionados a partir de hidrógeno, alcoxicarbonilo C_{1-4} y alquilo C_{1-6};

R^c se selecciona de hidrógeno, alquilsulfonilo C_{1-4}, alquilsulfonilamido C_{1-4}, amino, alquilamino C_{1-6}, dialquilamino C_{1-6}, cicloalquilamino C_{3-7}, hidroxi y alcoxi C_{1-4};

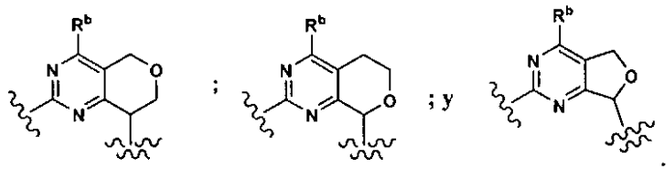
R^d se selecciona de hidrógeno, alquilo C_{1-6}, alcoxi C_{1-4}alquilcarbonilo C_{1-4}, alcoxicarbonilo C_{1-6}, alquilcarbonilo C_{1-6}, alquilsulfonilo C_{1-6}, cicloalquilsulfonilo C_{3-7}, cicloalquilcarbonilo C_{3-7}, dialquilamino C_{1-6}-alquilcarbonilo C_{1-4} y haloalquilo C_{1-4}, en los que la parte alquilo del alcoxicarbonilo, el alquilcarbonilo y el alquilsulfonilo están opcionalmente sustituidos con un sustituyente seleccionado de dialquilamino C_{1-4} y alcoxi C_{1-4}; y

E se selecciona de alquilo C_{1-6}, cicloalquilo C_{4-6}, (cicloalquilo C_{4-7})alquilo C_{1-4}, bencilo, fenilo y un anillo heteroaromático de cinco a seis miembros que contiene uno o dos átomos de nitrógeno, en los que el fenilo, la parte fenílica del bencilo y el anillo heteroaromático están cada uno opcionalmente sustituidos con uno, dos o tres sustituyentes independientemente seleccionados de alquilo C_{1-6}, alcoxi C_{1-6}, ciano, halo, haloalcoxi C_{1-6} y haloalquilo C_{1-6}.

La presente invención se refiere a estos, así como a otros importantes extremos descritos en el presente documento más adelante.

DESCRIPCIÓN DETALLADA DE LAS REALIZACIONES

En una primera realización del primer aspecto la presente revelación proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo como se ha expuesto anteriormente, en la que A es un anillo heteroaromático de cinco miembros que contiene de uno a tres átomos de nitrógeno; y en la que dicho anillo heteroaromático está opcionalmente sustituido con un grupo seleccionado de halo y cicloalquilo C_{1-6}. En una segunda realización, B se selecciona de fenilo y piridinilo, en los que el fenilo y el piridinilo están opcionalmente sustituidos con uno o dos sustituyentes independientemente seleccionados de alcoxi C_{1-6} y halo. En una tercera realización, E es fenilo opcionalmente sustituido con uno, dos, o tres sustituyentes independientemente seleccionados de alquilo C_{1-6}, alcoxi C_{1-6}, ciano, halo, haloalcoxi C_{1-6} y haloalquilo C_{1-6}. En una cuarta realización, D se selecciona de



En una quinta realización, R^b es $-NR^xR^y$, en el que R^x y R^y se seleccionan independientemente de hidrógeno, alcoxi C_{1-4}alquilo C_{1-4}, alquilo C_{1-6}, cicloalquilo C_{3-7}, hidroxialquilo C_{1-4} y trideuterometilo, en el que la parte alquilo del (cicloalquilo C_{3-7})alquilo C_{1-4} puede estar opcionalmente sustituida con un grupo alcoxi C_{1-4}.

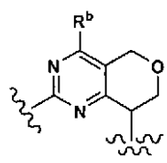
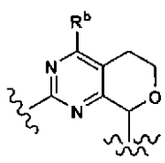
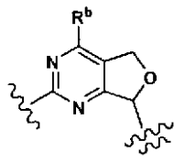
En una sexta realización del primer aspecto, la presente revelación proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que:

A es un anillo heteroaromático de cinco miembros que contiene de uno a tres átomos de nitrógeno; en el que dicho anillo heteroaromático está opcionalmente sustituido con un grupo seleccionado de halo y alquilo C_{1-6};

B se selecciona de fenilo y piridinilo, en el que el fenilo y el piridinilo están opcionalmente sustituidos con uno o dos sustituyentes seleccionados independientemente de alcoxi C_{1-6} y halo;

E es fenilo opcionalmente sustituido con uno, dos, o tres sustituyentes independientemente seleccionados de alquilo C_{1-6}, alcoxi C_{1-6}, ciano, halo, haloalcoxi C_{1-6} y haloalquilo C_{1-6};

D se selecciona de


;

; y

; y

R^b es $-NR^xR^y$, en el que R^x y R^y, conjuntamente con el átomo de nitrógeno al que están unidos, forman un anillo monocíclico o bicíclico de cuatro a siete miembros que contiene opcionalmente un heteroátomo adicional seleccionado de anillo monocíclico o bicíclico de cuatro a cinco miembros que contienen opcionalmente un heteroátomo adicional seleccionado de O y NR^z; en el que R^z se selecciona de alquilo C_{1-6} y alcoxicarbonilo C_{1-4}; y en el que el anillo está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados de alcoxi C_{1-6}, alquilo C_{1-6}, halo, haloalquilo C_{1-4}, hidroxi, $-NR^fR^g$, oxo y dioxolanilo espirocíclico; en los que R^f y R^g están independientemente seleccionados de hidrógeno, alcoxicarbonilo C_{1-4} y alquilo C_{1-6}.

En una séptima realización del primer aspecto, la presente revelación

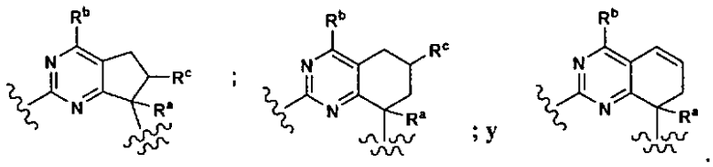
proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que:

A es un anillo heteroaromático de cinco miembros que contiene de uno a tres átomos de nitrógeno; en el que dicho anillo heteroaromático está opcionalmente sustituido con un grupo seleccionado de halo y alquilo C_{1-6};

B se selecciona de fenilo y piridinilo, en el que el fenilo y el piridinilo están opcionalmente sustituidos con uno o dos sustituyentes seleccionados independientemente de alcoxi C_{1-6} y halo;

E es fenilo opcionalmente sustituido con uno, dos, o tres sustituyentes independientemente seleccionados de alquilo C_{1-6}, alcoxi C_{1-6}, ciano, halo, haloalcoxi C_{1-6} y haloalquilo C_{1-6}; y

D se selecciona de



En una octava realización del primer aspecto, la presente revelación proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que:

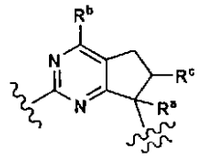
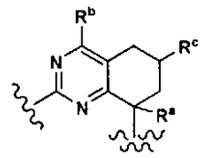
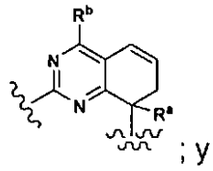
A es un anillo heteroaromático de cinco miembros que contiene de uno a tres átomos de nitrógeno; en el que dicho anillo heteroaromático está opcionalmente sustituido con un grupo seleccionado de halo y alquilo C_{1-6};

B se selecciona de fenilo y piridinilo, en el que el fenilo y el piridinilo están opcionalmente sustituidos con uno o dos sustituyentes seleccionados independientemente de alcoxi C_{1-6} y halo;

E es fenilo opcionalmente sustituido con uno, dos, o tres sustituyentes

independientemente seleccionados de alquilo C_{1-6}, alcoxi C_{1-6}, ciano, halo, haloalcoxi C_{1-6} y haloalquilo C_{1-6};

D se selecciona de




; y

R^b es $-NR^xR^y$, en el que R^x y R^y se seleccionan independientemente de hidrógeno, alcoxi C_{1-4}alquilo C_{1-4}, alquilo C_{1-6}, cicloalquilo C_{3-7}, hidroxialquilo C_{1-4} y trideuterometilo, en el que la parte alquilo del (cicloalquilo C_{3-7})alquilo C_{1-4} puede estar opcionalmente sustituida con un grupo alcoxi C_{1-4}.

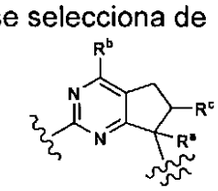
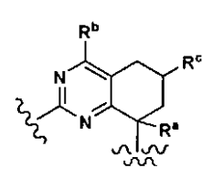
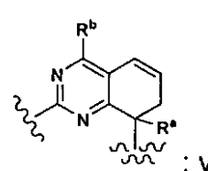
En una novena realización del primer aspecto, la presente revelación proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que:

A es un anillo heteroaromático de cinco miembros que contiene de uno a tres átomos de nitrógeno; en el que dicho anillo heteroaromático está opcionalmente sustituido con un grupo seleccionado de halo y alquilo C_{1-6};

B se selecciona de fenilo y piridinilo, en el que el fenilo y el piridinilo están opcionalmente sustituidos con uno o dos sustituyentes seleccionados independientemente de alcoxi C_{1-6} y halo;

E es fenilo opcionalmente sustituido con uno, dos, o tres sustituyentes independientemente seleccionados de alquilo C_{1-6}, alcoxi C_{1-6}, ciano, halo, haloalcoxi C_{1-6} y haloalquilo C_{1-6};

D se selecciona de




; y

R^b es $-NR^xR^y$, en el que R^x y R^y, conjuntamente con el átomo de nitrógeno al que están unidos, forman un anillo monocíclico o bicíclico de cuatro a siete miembros que contiene opcionalmente un heteroátomo adicional seleccionado de O y NR^z; en el que R^z se selecciona de alquilo C_{1-6} y alcoxicarbonilo C_{1-4}; y en el que el anillo está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados de alcoxi C_{1-6}, alquilo C_{1-6}, halo, haloalquilo C_{1-4}, hidroxi, $-NR^fR^g$, oxo y dioxolanilo espirocíclico; en los que R^f y R^g están independientemente seleccionados de hidrógeno, alcoxicarbonilo C_{1-4} y alquilo C_{1-6}.

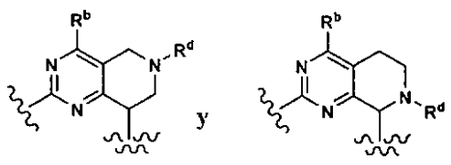
En una décima realización del primer aspecto, la presente revelación proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que:

A es un anillo heteroaromático de cinco miembros que contiene de uno a tres átomos de nitrógeno; en el que dicho anillo heteroaromático está opcionalmente sustituido con un grupo seleccionado de halo y alquilo C_{1-6};

B se selecciona de fenilo y piridinilo, en el que el fenilo y el piridinilo están opcionalmente sustituidos con uno o dos sustituyentes seleccionados independientemente de alcoxi C_{1-6} y halo;

E es fenilo opcionalmente sustituido con uno, dos, o tres sustituyentes independientemente seleccionados de alquilo C_{1-6}, alcoxi C_{1-6}, ciano, halo, haloalcoxi C_{1-6} y haloalquilo C_{1-6}; y

D se selecciona de



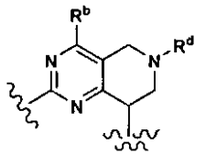
En una undécima realización del primer aspecto, la presente revelación proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que:

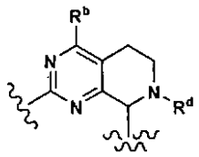
A es un anillo heteroaromático de cinco miembros que contiene de uno a tres átomos de nitrógeno; en el que dicho anillo heteroaromático está opcionalmente sustituido con un grupo seleccionado de halo y alquilo C_{1-6};

B se selecciona de fenilo y piridinilo, en el que el fenilo y el piridinilo están opcionalmente sustituidos con uno o dos sustituyentes seleccionados independientemente de alcoxi C_{1-6} y halo;

E es fenilo opcionalmente sustituido con uno, dos, o tres sustituyentes independientemente seleccionados de alquilo C_{1-6}, alcoxi C_{1-6}, ciano, halo, haloalcoxi C_{1-6} y haloalquilo C_{1-6};

D se selecciona de



y


; y

R^b es $-NR^xR^y$, en el que R^x y R^y se seleccionan independientemente de hidrógeno, alcoxi C_{1-4}alquilo C_{1-4}, alquilo C_{1-6}, cicloalquilo C_{3-7}, hidroxialquilo C_{1-4} y trideuterometilo, en los que la parte alquilo del (cicloalquilo C_{3-7})alquilo C_{1-4} puede estar opcionalmente sustituida con un grupo alcoxi C_{1-4}.

En una duodécima realización del primer aspecto, la presente revelación proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en la que:

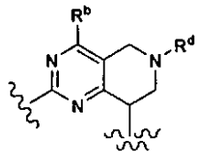
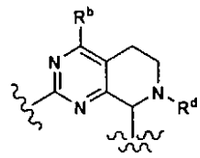
A es un anillo heteroaromático de cinco miembros que contiene de uno a tres átomos de nitrógeno; en el que dicho anillo heteroaromático está

opcionalmente sustituido con un grupo seleccionado de halo y alquilo C_{1-6};

B se selecciona de fenilo y piridinilo, en el que el fenilo y el piridinilo están opcionalmente sustituidos con uno o dos sustituyentes seleccionados independientemente de alcoxi C_{1-6} y halo;

E es fenilo opcionalmente sustituido con uno, dos, o tres sustituyentes independientemente seleccionados de alquilo C_{1-6}, alcoxi C_{1-6}, ciano, halo, haloalcoxi C_{1-6} y haloalquilo C_{1-6};

D se selecciona de

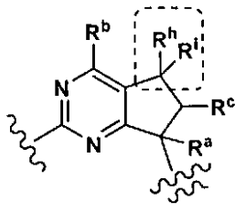

y

; y

R^b es $-NR^xR^y$, en el que R^x y R^y, conjuntamente con el átomo de nitrógeno al que están unidos, forman un anillo monocíclico o bicíclico que contiene opcionalmente un heteroátomo adicional seleccionado de O y NR^z; en el que R^z se selecciona de alquilo C_{1-6} y alcoxicarbonilo C_{1-4}; y en el que el anillo está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados de alcoxi C_{1-6}, alquilo C_{1-6}, halo, haloalquilo C_{1-4}, hidroxi, $-NR^fR^g$, oxo y dioxolanilo espirocíclico; en los que R^f y R^g están independientemente seleccionados de hidrógeno, alcoxicarbonilo C_{1-4} y alquilo C_{1-6}.

En una decimotercera realización del primer aspecto, la definición de A se amplia también para que incluya acilo, acetilo, nitrilo, CF_3, bromo y CH_2CN; y el anillo heteroaromático puede estar adicionalmente sustituido con $CHCF_2$ y/o CN.

En una decimocuarta realización del primer aspecto, B también puede

incluir pirimidinilo.

En una decimoquinta realización del primer aspecto, R^b como parte de D, puede incluir también SO_2alquilo C_{1-6}, acetilo y fenilo, opcionalmente sustituido con 1-3 alquilo C_{1-6}; y en el que además el anillo como parte de R^z también puede incluir tetrahidrofuranilo espirocíclico. Además, D puede incluir también  , en la que Rh, Ri =H, OH, o tomados conjuntamente forman C=O, C=N-OH o C=N-O-alquilo C_{1-6}.

En un segundo aspecto, la presente revelación proporciona una composición farmacéutica para el tratamiento de trastornos que responden a la reducción de producción de péptido β-amiloide que comprende una cantidad terapéuticamente efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en asociación con un vehículo o diluyente farmacéuticamente aceptable.

En un tercer aspecto, la presente revelación proporciona un procedimiento para el tratamiento de trastornos que responden a la reducción de péptido β-amiloide en un mamífero en necesidad de la misma, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo. En una primera realización del primer aspecto dicho trastorno se selecciona de Enfermedad de Alzheimer (AD), Síndrome de Down, alteración cognitiva débil (MCI), angiopatía amiloide cerebral (CAA), demencia con cuerpos de Lewy (DLB), esclerosis lateral amiotrófica (ALS-D), miositis de

cuerpos de inclusión (IBM), degeneración macular relacionada con la edad y cáncer. En una segunda realización del tercer aspecto, dicho trastorno se selecciona de Enfermedad de Alzheimer y Síndrome de Down. En una tercera realización del tercer aspecto, dicho trastorno es Enfermedad de Alzheimer.

Otros aspectos de la presente revelación pueden incluir combinaciones adecuadas de realizaciones reveladas en el presente documento.

Se pueden encontrar aún otros aspectos y realizaciones en la revelación proporcionada en el presente documento.

La descripción de la presente revelación en el presente documento debería interpretarse de forma congruente con las leyes y principios de la formación de enlaces químicos. En algunos casos puede ser necesario retirar un átomo de hidrógeno con el fin de acomodar un sustituyente en cualquier localización dada.

Se entendería que los compuestos comprendidos por la presente revelación son aquellos que son adecuadamente estables para usar como un agente farmacéutico.

Se desea que la definición de cualquier sustituyente o variable en una localización particular en una molécula sea independiente de sus definiciones en otro lugar en esa molécula.

Todas las patentes, solicitudes de patentes, y referencias bibliográficas citadas en la memoria descriptiva se incorporan en el presente documento por referencia en su totalidad. En el caso de inconsistencias, la presente revelación, incluyendo definiciones, prevalecerá.

En algunos casos, el número de átomos de carbono en cualquier grupo particular está designado antes del recitado del grupo. Por ejemplo, el término

"haloalcoxi C_{1-6}" indica un grupo haloalcoxi que contiene uno a seis átomos de carbono y el término "alcoxi C_{1-4}-alquilo C_{1-2}" indica un grupo alcoxi que contiene uno a cuatro grupos alcoxi unidos al resto molecular parental a través de un grupo alquilo de uno o dos átomos de carbono. Donde estas designaciones existen reemplazan a todas las otras definiciones contenidas en el presente documento.

Como se usa en el presente documento, las formas del singular "un", "uno" y "el/la" incluyen referencia al plural a menos que el contexto indique claramente lo contrario.

El término "alcoxi", como se usa en el presente documento, se refiere a un grupo alquilo unido al resto molecular parental a través de un átomo de oxígeno.

El término "alcoxialquilo", como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos alcoxi.

El término "alcoxialquilcarbonilo", como se usa en el presente documento, se refiere a un grupo alcoxialquilo unido al grupo molecular parental a través de un grupo carbonilo.

El término "alcoxicarbonilo", como se usa en el presente documento, se refiere a un grupo alcoxi unido al grupo molecular parental a través de un grupo carbonilo.

El término "alquilo", como se usa en el presente documento, se refiere a un grupo derivado de un hidrocarburo saturado de cadena lineal o ramificada que contiene de uno a diez átomos de carbono.

El término "alquilamino," como se usa en el presente documento, se refiere a $-NHR^x$, en el que R^x es un grupo alquilo.

El término "alquilaminoalcoxi", como se usa en el presente documento, se refiere a un grupo alquilamino unido al resto molecular parental a través de un grupo alcoxi.

El término "alquilcarbonilo", como se usa en el presente documento, se refiere a un grupo alquilo unido al resto molecular parental a través de un grupo carbonilo.

El término "alquilsulfonilo", como se usa en el presente documento, se refiere a un grupo alquilo unido al resto molecular parental a través de un grupo sulfonilo.

El término "alquilsulfonilamido", como se usa en el presente documento se refiere a $-C(O)NHS(O)_2R^x$ en el que R^x es un grupo alquilo.

El término "amino," como se usa en el presente documento, se refiere a $-NH_2$.

El término "carbonilo", como se usa en el presente documento, se refiere a -C(O)-.

El término "ciano", como se usa en el presente documento, se refiere a -CN.

El término "cicloalquilo", como se usa en el presente documento, se refiere a un sistema de anillo monocíclico saturado que tiene de tres a catorce átomos de carbono y cero heteroátomos.

El término "(cicloalquil)alquilo", como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos cicloalquilo.

El término "cicloalquilamino," como se usa en el presente documento, se refiere a $-NHR^x$, en el que Rx es un grupo cicloalquilo.

El término "cicloalquilcarbonilo", como se usa en el presente documento,

se refiere a un grupo cicloalquilo unido al grupo molecular parental a través de un grupo carbonilo.

El término "cicloalquilsulfonilo", como se usa en el presente documento, se refiere a un grupo cicloalquilo unido al grupo molecular parental a través de un grupo sulfonilo.

El término "dialquilamino", como se usa en el presente documento, se refiere a $-NR^xR^y$, en el que R^x y R^y son cada uno grupos alquilo.

El término "dialquilaminoalcoxi", como se usa en el presente documento, se refiere a un grupo dialquilamino unido al resto molecular parental a través de un grupo alcoxi.

El término "dialquilaminoalquilo", como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos dialquilamino.

El término "dialquilaminoalquilcarbonilo", como se usa en el presente documento, se refiere a un grupo dialquilaminoalquilo unido al grupo molecular parental a través de un grupo carbonilo.

Los términos "halo" y "halógeno", como se usan en el presente documento, se refieren a F, Cl, Br e I.

El término "haloalcoxi", como se usa en el presente documento, se refiere a un grupo haloalquilo unido al resto molecular parental a través de un átomo de oxígeno.

El término "haloalquilo", como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, tres o cuatro átomos de halógeno.

El término "hidroxi", como se usa en el presente documento, se refiere a

-OH.

El término "hidroxialquilo", como se usa en el presente documento, se refiere a un grupo alquilo sustituido con uno, dos, o tres grupos hidroxi.

El término "metilamino", como se usa en el presente documento, se refiere a $-NHCH_3$.

El término "oxo", como se usa en el presente documento, se refiere a =O.

El término "sulfonilo", como se usa en el presente documento, se refiere a $-SO_2-$.

Se entendería que la revelación comprende todas las formas estereoquímicas, o mezclas de las mismas, que poseen la capacidad de reducir la producción de péptido β-amiloide.

Ciertos compuestos de la presente revelación pueden existir también en formas conformacionales estables diferentes que pueden ser separables. La asimetría torsional debida a rotación restringida sobre un enlace individual asimétrico, por ejemplo debida a su impedimento estérico o a su tensión de anillo, puede permitir la separación de conformadores diferentes. La presente revelación incluye cada isómero conformacional de estos compuestos y mezclas de los mismos.

La presente invención se desea para incluir todos los isótopos de los átomos que aparecen en los presentes compuestos. Los isótopos incluyen aquellos átomos que tienen el mismo número atómico pero diferentes números másicos. A modo de ejemplo general y sin limitación, los isótopos de hidrógeno incluyen deuterio y tritio. Los isótopos de carbono incluyen ^{13}C y ^{14}C. Los compuestos isotópicamente marcados de la invención pueden

generalmente prepararse por técnicas convencionales conocidas por aquellos expertos en la técnica o por procedimientos análogos a aquellos descritos en el presente documento, usando un reactivo isotópicamente marcado en lugar del reactivo no marcado empleado de lo contrario. Tales compuestos pueden tener una diversidad de usos potenciales, por ejemplo como estándares y reactivos en determinar actividad biológica. En el caso de los isótopos estables, tales compuestos pueden tener el potencial de modificar favorablemente propiedades biológicas, farmacológicas o farmacocinéticas.

Ciertos compuestos de la presente revelación pueden existir en forma híbrida y la presente revelación incluye cada forma híbrida de estos compuestos y mezclas de los mismos.

Los compuestos de la presente revelación pueden existir como sales farmacéuticamente aceptables. La expresión "sal farmacéuticamente aceptable", como se usa en el presente documento, representa sales o formas híbridas de los compuestos de la presente revelación que son solubles en agua o solubles en aceite o dispersables, que son, dentro del alcance del juicio médico bien fundamentado, adecuadas para usar en contacto con los tejidos de pacientes sin excesiva toxicidad, irritación, respuesta alérgica, u otro problema o complicación es proporcional con una relación beneficio/riesgo razonable, y son efectivos para su uso deseado. Las sales se pueden preparar durante el aislamiento y purificación finales de los compuestos o por separado haciendo reaccionar un átomo de nitrógeno adecuado con un ácido adecuado. Las sales de adición representativas incluyen acetato, adipato, alginato, citrato, aspartato, benzoato, bencenosulfonato, bisulfato, butirato, camforato, camforsulfonato; digluconato, glicerofosfato, hemisulfato, heptanoato,

hexanoato, formiato, fumarato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxietanosulfonato, lactato, maleato, mesitilenosulfonato, metanosulfonato, naftilenosulfonato, nicotinato, 2-naftalenosulfonato, oxalato, palmoato, pectinato, persulfato, 3-fenilproprionato, picrato, pivalato, propionato, succinato, tartrato, tricloroacetato, trifluoroacetato, fosfato, glutamato, bicarbonato, para-toluenosulfonato y undecanoato. Ejemplos de ácidos que se pueden emplear para formar sales de adición farmacéuticamente aceptables incluyen ácidos inorgánicos tales como clorhídrico, bromhídrico, sulfúrico y fosfórico, y ácidos orgánicos tales como ácido oxálico, maleico, succínico y cítrico.

Las sales de adición básica se pueden preparar durante el aislamiento y la purificación finales de los compuestos haciendo reaccionar un grupo carboxilo con una base adecuada tal como el hidróxido, carbonato, o bicarbonato de un catión metálico o con amoniaco o una amina primaria, secundaria, o terciaria. Los cationes de sales farmacéuticamente aceptables incluyen litio, sodio, potasio, calcio, magnesio y aluminio, así como cationes de aminas cuaternarias no tóxicas tales como amonio, tetrametilamonio, tetraetilamonio, metilamina, dimetilamina, trimetilamina, trietilamina, dietilamina, etilamina, tributilamina, piridina, N,N-dimetilanilina, N-metilpiperidina, N-metilmorfolina, dicyclohexilamina, procaína, dibencilamina, N,N-dibencilfenetilamina y N,N'-dibenciletilenodiamina. Otras aminas orgánicas representativas útiles para la formación de sales de adición básicas incluyen etilenodiamina, etanolamina, dietanolamina, piperidina y piperazina.

Cuando sea posible que, para usar en terapia, se puedan administrar cantidades terapéuticamente efectivas de un compuesto de fórmula (I), así como que sales farmacéuticamente aceptables de las mismas, se puedan

administrar como la materia prima, es posible presentar el ingrediente activo como una composición farmacéutica. De acuerdo con ello, la revelación proporciona adicionalmente composiciones farmacéuticas, que incluyen cantidades terapéuticamente efectivas de fórmula (I) o sales farmacéuticamente aceptables de las mismas, y uno o más vehículos, diluyentes o excipientes farmacéuticamente aceptables. Los compuestos de fórmula (I) y las sales farmacéuticamente aceptables de los mismos, son como se describen anteriormente. El/los vehículo(s), diluyente(s), o excipiente(s) deben ser aceptables en el sentido de que sean compatibles con los otros ingredientes de la formulación y no deletéreos para el receptor de los mismos. De acuerdo con otro aspecto de la revelación hay proporcionado un procedimiento para la preparación de una formulación farmacéutica incluyendo mezclar un compuesto de fórmula (I), o una sal farmacéuticamente aceptable de la misma, con uno o más vehículos, diluyentes, o excipientes farmacéuticamente aceptables.

La dosificación de los compuestos de Fórmula I para lograr un efecto terapéutico dependerá no sólo de factores tales como la edad, el peso y el sexo del paciente y el modo de administración, sino también en el grado de reducción de β-AP deseado y en la potencia del compuesto particular que se está utilizando para el trastorno particular de la enfermedad implicada. Se contempla también que el tratamiento y la dosificación del compuesto particular se puede administrar en forma de dosificación unitaria y que la forma de de dosificación unitaria se ajustaría de acuerdo con un experto en la técnica para reflejar el nivel de actividad relativo. La decisión en cuanto a la dosificación particular a emplearse (y el número de veces para administrarse por día) está

dentro de la discreción del médico, y se puede variar por valoración de la dosificación en las circunstancias particulares de esta invención para producir el efecto terapéutico deseado.

Una dosis adecuada de un compuesto de Fórmula I o composición farmacéutica del mismo para un mamífero, incluyendo el hombre, que sufre de, o que probablemente sufre de cualquier afección relacionada con producción de β-AP como se describe en el presente documento, generalmente la dosis diaria será de aproximadamente 0,05 mg/kg a aproximadamente 10 mg/kg y preferentemente, aproximadamente 0,1 a 2 mg/kg cuando se administra parenteralmente. Para administración oral, la dosis puede estar en el intervalo de aproximadamente 0,1 a aproximadamente 75 mg/kg y preferentemente de 0,1 a 10 mg/kg de peso corporal. El ingrediente activo se administrará preferentemente en dosis iguales de una a cuatro veces al día. Sin embargo, usualmente se administra una dosis pequeña, y la dosificación se incrementa gradualmente hasta que se determina la dosificación óptima para el huésped en tratamiento. De acuerdo con la buena práctica clínica, se prefieren administrar los compuestos actuales a un nivel de concentración que producirá un efecto antiamiloide efectivo sin causar cualesquiera efectos secundarios dañinos o adversos. Sin embargo, se entenderá que la cantidad del compuesto administrado realmente de determinará por un médico, a la luz de las circunstancias relevantes que incluyen la afección a tratarse, la elección de compuesto para administrarse, la vía elegida de administración, la edad, peso, y respuesta del paciente individual, y la gravedad de los síntomas del paciente.

Las formulaciones farmacéuticas se pueden adaptar para administración por cualquier vía apropiada, por ejemplo por la vía oral (incluyendo la bucal o la

sublingual), rectal, nasal, tópica (incluyendo bucal, sublingual, o transdérmica), vaginal, o parenteral (incluyendo inyecciones o infusiones subcutáneas, intracutáneas, intramusculares, intra-articulares, intrasinoviales, intraesternales, intratecales, intralesionales, intravenosas, o intradérmicas). Tales formulaciones se pueden preparar por cualquier procedimiento conocido en la técnica de farmacia, por ejemplo por unión en asociación del ingrediente activo con el/los vehículo(s) o excipiente(s).

Las formulaciones farmacéuticas adaptadas para administración oral pueden presentarse como unidades discretas tales como cápsulas o comprimidos; polvos o gránulos; soluciones o suspensiones en líquidos acuosos o no acuosos; espumas o batidos comestibles; o emulsiones de aceite-en-agua o emulsiones de agua-en-aceite.

Por ejemplo, para administración oral en la forma de un comprimido o una cápsula, el componente de fármaco activo se puede combinar con un vehículo inerte farmacéuticamente aceptable no tóxico, oral tal como etanol, glicerol, agua y similares. Los polvos se prepararon moliendo el compuesto a un tamaño fino adecuado y mezclando con un vehículo farmacéutico molido de forma similar tal como un carbohidrato comestible, como, por ejemplo, almidón o manitol. También puede estar presente agente aromatizante, conservante, dispersante y colorante.

Las cápsulas se hacen preparando una mezcla en polvo, como se describe anteriormente y cubiertas de gelatina formadas cargadas. Se pueden añadir agentes deslizantes y lubricantes tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio, o polietilenoglicol sólido a la mezcla en polvo antes de la operación de carga. Un agente disgregante o

solubilizante tal como agar-agar, carbonato de calcio, o carbonato de sodio puede también añadirse para incrementar la disponibilidad del medicamento cuando la cápsula es ingerida.

Además, cuando es deseado o necesario, se pueden incorporar aglutinantes, lubricantes, agentes disgregantes, y agentes colorantes adecuados dentro de la mezcla. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales tales como glucosa o beta-lactosa, edulcorantes de maíz, gomas naturales y sintéticas tales como goma arábiga, goma de tragacanto o alginato de sodio, carboximetilcelulosa, polietilenoglicol, ceras, y similares. Los lubricantes usados en estas formas de dosificación incluyen oleato de sodio, cloruro de sodio y similares. Los disgregadores incluyen, sin limitación, almidón, metilcelulosa, agar, bentonita, goma xantana, y similares. Los comprimidos se formularon, por ejemplo, preparando un mezcla en polvo, granulando o soldando con fusión incompleta, añadiendo un lubricante y disgregante, y prensando en comprimidos. Se preparó una mezcla en polvo mezclando el compuesto, molido adecuadamente, con un diluyente o base como se describe anteriormente, y opcionalmente, con un ligando tal como carboximetilcelulosa, un alginato, gelatina, o polivinilpirrolidina, un retardante de solución tal como parafina, un acelerados de resorción tal como una sal cuaternaria y/o agente de absorción tal como bentonita, caolín, o fosfato dicálcico. La mezcla en polvo se puede granular por humectación con un aglutinante tal como jarabe, pasta de almidón, mucílago de goma arábiga, o soluciones de materiales celulósicos o poliméricos y forzándola a pasar a través de un tamiz. Como una alternativa para granular, la mezcla en polvo puede hacerse pasar por la máquina compresora y el resultado son postas

formadas imperfectamente rotas en gránulos. Los gránulos se pueden lubricar para evitar que se adhieran al comprimido formando moldes por medio de la adición de ácido esteárico, una sal de estearato, talco, o aceite mineral. La mezcla lubricada se comprime después en comprimidos. Los compuestos de la presente revelación se pueden combinar también con un vehículo inerte que fluye libre y se pueden comprimir en comprimidos directamente sin ir a través de las etapas de granulación o formación de postas. Se pueden proporcionar un revestimiento protector transparente u opaco constituido por un revestimiento sellante de goma laca, un revestimiento de azúcar o de material polimérico, y un revestimiento pulido de cera. Se pueden añadir tintes a estos recubrimientos para distinguir dosificaciones unitarias diferentes.

Los fluidos orales tales como una solución, jarabes y elixires se pueden preparar en forma de dosificación unitaria tal que una cantidad dada contiene una cantidad predeterminada del compuesto. Los jarabes se pueden preparar disolviendo el compuesto en una solución acuosa adecuadamente aromatizada, mientras que se prepararon elixires por el uso de un vehículo no tóxico. Se pueden añadir también solubilizadores y emulsionantes tales como alcoholes isoestearílicos etoxilados y éteres de polioxietileno sorbitol, conservantes, aditivo aromático tal como aceite de menta o edulcorantes naturales, o sacarina u otros edulcorantes artificiales y similares.

Donde sea apropiado, se pueden microencapsular las formulaciones de dosificación unitaria para administración oral. La formulación se pueden preparar también para prolongar o mantener la liberación como por ejemplo revistiendo o incrustando material particulado en polímeros, ceras, o similares.

Los compuestos de fórmula (I), y las sales farmacéuticamente

aceptables de los mismos, se pueden administrar también en forma de sistemas de administración de liposomas, tales como vesículas unilaminares pequeñas, vesículas unilaminares grandes y vesículas multilaminares. Los liposomas se pueden formar a partir de una diversidad de fosfolípidos, tales como colesterol, estearilamina, o fosfatidilcolinas.

Los compuestos de fórmula (I) y las sales farmacéuticamente aceptables de los mismos se pueden administrar también por el uso de anticuerpos monoclonales como vehículos individuales a los que están acoplados las moléculas de compuestos. Los compuestos pueden estar acoplados también con polímeros solubles como vehículos de fármacos marcables como objetivos. Tales polímeros pueden incluir polivinilpirrolidona, copolímero de pirano, polihidroxipropilmetacrilamidafenol, polihidroxietilaspartamidafenol, o polietilenóxidopolilisina sustituida con residuos de palitoílo. Además, los compuestos pueden acoplarse a una clase de polímeros biodegradables útiles en lograr liberación controlada de un fármaco, por ejemplo, ácido poliláctico, caprolactona poliépsilon, ácido polihidroxibutírico, poliortoésteres, poliacetales, polidihidropiranos, policianoacrilatos, y copolímeros de bloque de hidrogeles reticulados o anfipáticos.

Las formulaciones farmacéuticas adaptadas para administración transdérmica pueden presentarse como parches discretos que se desea que permanezcan en contacto íntimo con la epidermis de un receptor durante un periodo de tiempo prolongado. Por ejemplo, el ingrediente activo se puede administrar a partir del parche por iontoforesis como se describe generalmente en Pharmaceutical Research, 3 (6), 318 (1986).

Las formulaciones farmacéuticas adaptadas para administración tópica

se pueden formular como pomadas, cremas, suspensiones, lociones, polvos, soluciones, pastas, geles, pulverizaciones, aerosoles, o aceites.

Para tratamientos del ojo o de otros tejidos externos, por ejemplo boca y piel, las formulaciones se aplican preferentemente como una pomada o crema tópica. Cuando se formula en una pomada, el ingrediente activo se puede emplear bien con una base parafínica o bien con una base de pomada mezclable en agua. Alternativamente, el ingrediente activo se puede formular en una crema con una base de aceite-en-agua o con una base de agua-en-aceite.

Las formulaciones farmacéuticas adaptadas para administraciones tópicas para el ojo incluyen gotas oculares en las que el ingrediente activo se disuelve o suspende en un vehículo adecuado, especialmente un disolvente acuoso.

Las formulaciones farmacéuticas adaptadas para administración tópica en la boca incluyen tabletas, pastillas, y enjuagues bucales.

Las formulaciones farmacéuticas adaptadas para administración rectal pueden presentarse como supositorios o como enemas.

Las formulaciones farmacéuticas adaptadas para administración nasal en las que el vehículo es un sólido incluyen un polvo de tratamiento que se administra en la manera en la que se toma el rape, es decir por inhalación rápida a través del conducto nasal desde un recipiente del polvo sujetado cerca de la nariz. Las formulaciones adecuadas en las que el vehículo es un líquido, para administración como una pulverización nasal o como gotas nasales, incluyen soluciones acuosas o soluciones aceitosas del ingrediente activo.

Las formulaciones adaptadas para administración por inhalación

incluyen espolvoreados o neblinas de partículas finas, que se pueden generar por medio de diversos tipos de aerosoles, nebulizadores, o insufladores presurizados en dosis medidas.

Las formulaciones farmacéuticas adaptadas para administración vaginal pueden presentarse como pesarios, tampones, cremas, geles, pastas, espumas, o formulaciones de pulverización.

Las formulaciones farmacéuticas adaptadas para administración parenteral incluyen soluciones de inyección estériles acuosas y no acuosas que pueden contener anti-oxidantes, tampones, bacteriostáticos y solutos que vuelven a la formulación isotónica con la sangre del receptor deseado; y suspensiones estériles acuosas y no acuosas que pueden incluir agentes en suspensión y agentes espesantes. Las formulaciones pueden presentarse en recipientes de dosis unitaria o de multidosis, por ejemplo ampollas y viales sellados, 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 usar. Se pueden preparar soluciones y suspensiones de inyección extemporáneas a partir de polvos estériles, gránulos y comprimidos.

Debería entenderse que además de los ingredientes mencionados en particular anteriormente, las formulaciones pueden incluir otros agentes convencionales en la técnica que se han considerado para el tipo de formulación en cuestión, por ejemplo aquellos adecuados para administración oral pueden incluir agentes aromatizantes.

La presente revelación se describirá ahora en conexión con ciertas realizaciones que no se desean para limitar este alcance. Por el contrario, la

presente revelación abarca todas las alternativas, modificaciones y equivalentes y puede incluirse dentro del alcance de las reivindicaciones. Así, los siguientes ejemplos, que incluyen realizaciones específicas, ilustrarán una práctica de la presente revelación, entendiéndose que los ejemplos son para los propósitos de ilustración de ciertas realizaciones y están presentes para proporcionar qué se cree que es la descripción más útil y fácilmente entendible de sus procedimientos y aspectos conceptuales.

Los compuestos de la presente solicitud se pueden sintetizar usando los procedimientos descritos más adelante, conjuntamente con procedimientos de síntesis en la técnica de química orgánica sintética, o variaciones en ella según se aprecian por aquellos expertos en la técnica. Los procedimientos preferidos incluyen, pero no se limitan a, aquellos descritos más adelante. Todas las referencias citadas en el presente documento se incorporan al mismo en su totalidad por referencia.

Los compuestos se pueden preparar usando las reacciones y técnicas descritas en esta sección. Las reacciones se llevan a cabo en disolventes apropiados para los agentes y materiales empleados y son adecuados para las transformaciones que se llevan a cabo. Además, en la descripción de los procedimientos de síntesis descritos más adelante, se entiende que todas las condiciones de reacción propuestas, incluyendo la elección de disolvente, temperatura de reacción, duración del experimento y procedimientos de estimulación, se eligen para ser las condiciones estándar para esa reacción, que se reconocería fácilmente por cualquier experto en la técnica. Se entiende por un experto en la técnica que la funcionalidad presente en diversas partes de la molécula debe ser compatible con los reactivos y reacciones propuestos.

Tales restricciones a los sustituyentes que son compatibles con las condiciones de reacción serán fácilmente patentes para un experto en la técnica y se deben usar después procedimientos alternativos.

Los materiales de partida útiles para sintetizar los compuestos de la presente revelación son conocidos para aquellos expertos en la técnica y pueden elaborarse fácilmente o están disponibles comercialmente.

Los siguientes procedimientos expuestos más adelante se proporcionan para propósitos ilustrativos y no se desean para limitar el alcance de las reivindicaciones. Se reconocerá que puede ser necesario preparar un compuesto tal en el que un grupo funcional esté protegido usando un grupo protector convencional después para retirar el grupo protector para proporcionar un compuesto de la presente revelación. Los detalles que conciernen al uso de grupos protectores de acuerdo con la presente revelación se conocen por aquellos expertos en la técnica.

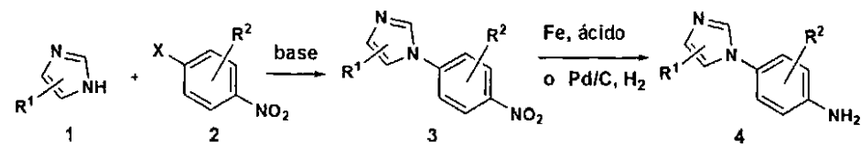
Las abreviaturas usadas en la presente solicitud, que se incluyen en particular en los esquemas ilustrativos y en los ejemplos que siguen, se conocen bien por aquellos expertos en la técnica. Algunas de las abreviaturas usadas son como sigue:

Las abreviaturas químicas usadas en la memoria descriptiva y los Ejemplos se definen como sigue: "dba" para dibencilidenoacetona; "*t*-Bu" para terc-butilo; "DCM" para diclorometano; "LDA" para diisopropilamida de litio; "Ph" para fenilo; "TFA" para ácido trifluoroacético; "Et" para etilo; "DMF" para N,N-dimetilformamida; "OAc" para acetato; "h" para horas, "min" para minutos; y "THF" para tetrahidrofurano.

Los ejemplos de procedimientos útiles para la producción de

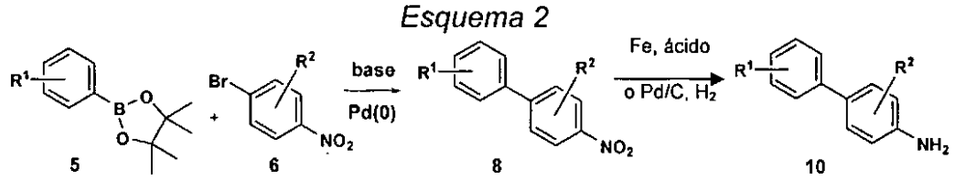
compuestos de esta revelación se ilustran en los *Esquemas 1-24*. *Los Esquemas 1-3* esquematizan diferentes vías para la síntesis de fragmentos de anilina sustituidos usados en la preparación de compuestos del título. Como se ilustra en el *Esquema 1*, se puede añadir una diversidad de heterociclos sustituidos 1, incluyendo pero no limitados a 1*H*-imidazol, 4-metil-1*H*-imidazol, 4-cloro-1*H*-imidazol, 4-(difluorometil)-1*H*-imidazol a cloro- o fluoronitroarenos sustituidos 2, incluyendo pero no limitados a 2-cloro-4-nitroanisol, en condiciones básicas para proporcionar nitroarenos sustituidos con heteroarilos 3. La reducción de los compuestos 3 usando reactivos que incluyen hierro en medio ácido o hidrogenación catalítica, empleando catalizadores tales como paladio en carbono u otros catalizadores conocidos por un experto en la técnica, proporciona anilinas sustituidas 4. Mientras que el *Esquema 1* ilustra la preparación de 4-(1*H*-imidazol-1-ilo)anilinas 4, se reconocería por un experto en la técnica que este procedimiento es ampliamente aplicable a la síntesis de otras 4-heteroarilanilinas, incluyendo pero no limitadas a 4-(1*H*-1,2,4-triazol-1-ilo)anilinas y 4-(1*H*-1,2,3-triazol-1-ilo)anilinas diversamente sustituidas. Además, se pueden usar nitropiridinas sustituidas en lugar de los nitroarenos de fórmula 2 para proporcionar definitivamente piridinas aminosustituidas.

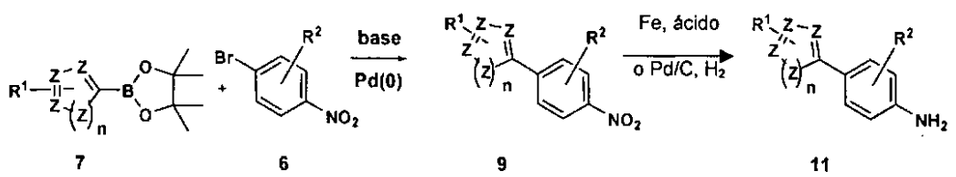
Esquema 1



Los procedimientos adicionales para crear anilinas sustituidas dependen del acoplamiento catalizado por paladio de haluros de arilo o de haluros de heteroarilo a ácidos bóricos (la reacción de acoplamiento de Suzuki). Como se muestra en *Esquema 2*, las biarilanilinas 10 y 11, y sus precursores de nitro 8 y 9, se pueden crear por el acoplamiento de un arilo o de ésteres bóricos de heteroarilo 5 y 7, respectivamente, a haluros de arilo sustituidos 6, incluyendo 1-bromo-2-metoxi-4-nitrobenceno. Alternativamente, los compañeros de acoplamiento pueden revertirse como se muestra en el *Esquema 3*, donde el acoplamiento de un haluro de arilo 12 o de un haluro de heteroarilo 14 al éster bórico del nitroareno 13 crea los nitroarenos sustituidos 8 y 9, respectivamente.

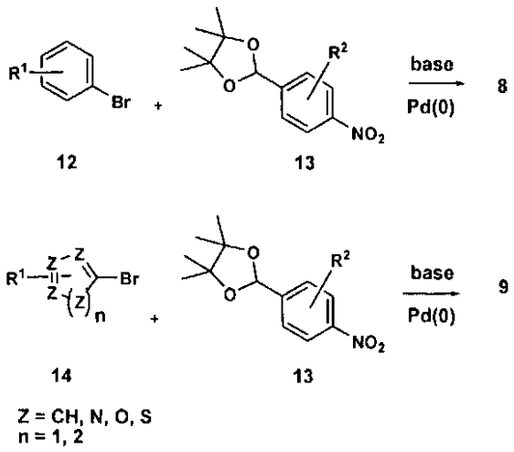
Esquema 2





Z = CH, N, O, S
n = 1, 2

Esquema 3

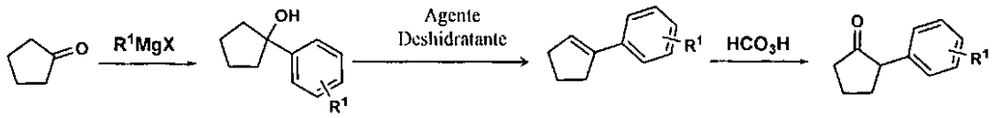


Estos esquemas de reacción generales se desean como ilustraciones de un procedimiento de reacción general que es altamente tolerante de una diversidad de grupos funcionales, y estos procedimientos no están limitados por las estructuras específicas mostradas en los *Esquemas 2* y *3*. Aquellos expertos en la técnica reconocerán también que procedimientos similares que incluyen el acoplamiento de Stille de haluros de arilo o de haluros de heteroarilo son excelentes procedimientos para preparar las anilinas necesarias o sus precursores de nitro.

Los siguientes esquemas esquematizan diferentes vías para la síntesis de 2,4-dicloro-7-aril-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidinas usadas en la preparación de los compuestos del epígrafe. Como se ilustra en el *Esquema 4*, la ciclopentanona 15 puede reaccionar con una diversidad de haluros de arilmagnesio produciendo alcoholes terciarios 16. En la presencia de agentes deshidratantes, tales como ácidos minerales o cloruro de tionilo, estos alcoholes terciarios pueden sufrir eliminación de agua proporcionando olefinas 17. Tras tratamiento con agentes peroxidantes, tales como ácido perfórmico, las olefinas 17 pueden transformarse en 2-arilciclopentanonas 18. Abu Thaher,

B.; Koch, P.; Del Amo, V.; Knochel, P.; Laufer, S. *Synthesis* 2008, *2*, 225-228.

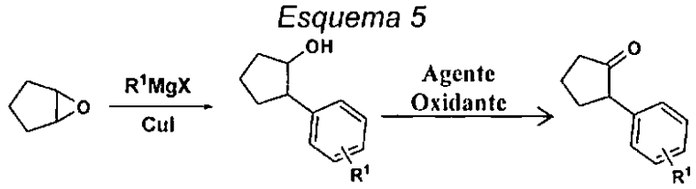
Esquema 4



15 16 17 18

Alternativamente, como se indica en el *Esquema 5*, se pueden preparar 2-arilciclopentanonas 18 por tratamiento de ciclopentenóxido 19 con diversos haluros de alquilmagnesio, en la presencia de sales de cobre, tales como yoduro de cobre, seguidas por oxidación de alcoholes 20 resultantes. La citada oxidación puede llevarse a cabo por un número de agentes de oxidación conocidos por aquellos expertos en la técnica, con resultados superiores logrados por el uso de peryodinano de Dess-Martin. Dess, D. B.; Martin, J.C. *J. Org. Chem.* 1983, 48, 4155-4156.

Esquema 5

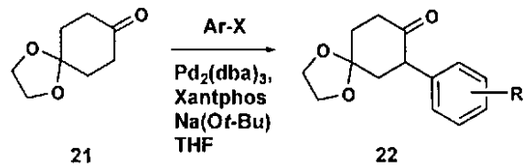


19 20 18

Las cetonas adicionales útiles en la preparación de compuestos de la reivindicación 1 se pueden preparar usando el procedimiento descrito en O. Dirat y col., *Tetrahedron Letters*, 2006,*47*, 1295. Este procedimiento, descrito en el *Esquema 6*, depende de alfa-arilación (Fox y col., *Journal of the American*

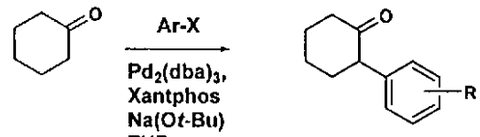
Chemical Society, 2000, *122*, 1360) de cetonas 21 disponibles que incorporan acetales o cetales en la posición 4. Los materiales de partida cetonas 21 correspondientes están comercialmente disponibles o pueden prepararse fácilmente por aquellos expertos en la técnica, y se puede usar una diversidad de acetales, incluyendo los cetales de etilenoglicol mostrados o los cetales de otros alcoholes mostrados incluyendo 1,3-propanodiol, metanol, etanol, y otros. Esta química trabaja igualmente bien produciendo alfa-aril-cetonas 24 insustituidas.

Esquema 6



21 22

donde X = Br, I

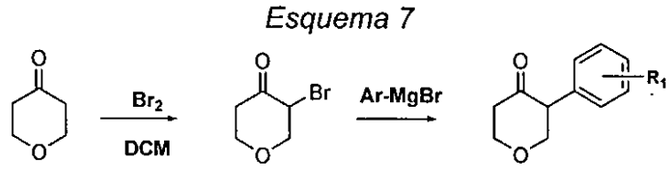


23 24

donde X = Br, I

Se pueden preparar alfa-aril-cetonas adicionales usando la química mostrada en el *Esquema 7*, donde se bromina tetrahidro-4H-piran-4-ona, usando bromo o diclorometano o hidrotribromuro de pirrolidina como un agente de bromination. La alfa-bromocetona resultante se puede hacer reaccionar con un reactivo de Grignard, y después de la migración del grupo arilo se obtiene la alfa-aril-cetona 27 deseada.

Esquema 7

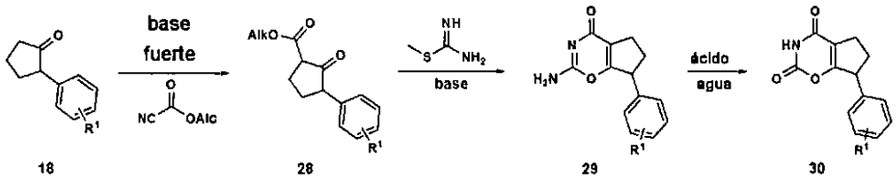


25 26 27

Como se indica en el *Esquema 8*, se pueden desprotonar las 2-arilciclopentanonas 18 con una base fuerte, tal como LDA y se pueden tratar con alquilcianoformiato dando cetoésteres 28, que tras la reacción con 2-metil-

2-tiopseudourea proporcionan 2-amino-7-aril-6,7-dihidrociclopenta[*e*][1,3]oxazin-4(5*H*)-onas 29. Los últimos compuestos sufren hidrólisis catalizada por ácido formando 7-aril-6,7-dihidrociclopenta[*e*][1,3]oxazina-2,4(3*H*,5*H*)-dionas 30. Larsen, J. S.; Christensen, L.; Ludvig, G.; Jørgensen, P. T.; Pedersen, E. B.; Nielsen, C. *J. Chem. Soc., Perkin Trans. I* 2000, *3035-3038.*

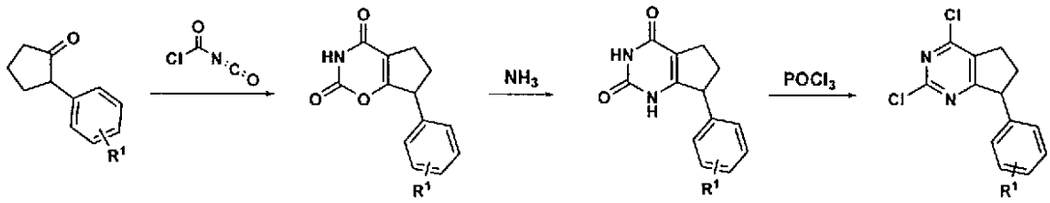
Esquema 8



18 28 29 30

Alternativamente, están disponibles 7-aril-6,7-dihidrociclopenta[*e*][1,3]oxazina-2,4(3*H*,5*H*)-dionas 31 por reacción de 2-arilciclopentanonas 18 con *N*-(clorocarbonil)isocianato (*Esquema 9*). El tratamiento subsiguiente de 7-aril-6,7-dihidrociclopenta[*e*][1,3]oxazina-2,4(3*H*,5*H*)-dionas 31 con amoniaco en agua, seguido por clorinación con oxicloruro de fósforo proporciona 2,4-dicloro-7-aril-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidinas 33.

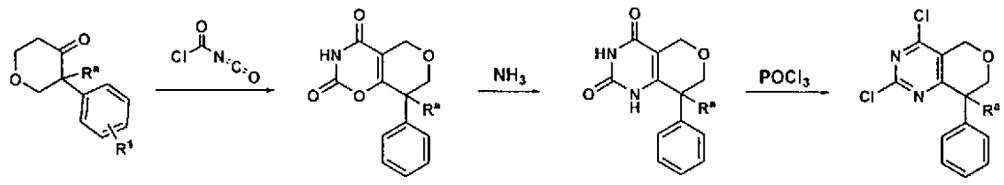
Esquema 9



18 31 32 33

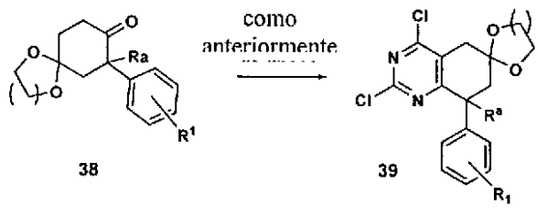
En una manera similar a la síntesis descrita en el *Esquema 9*, se pueden hacer reaccionar cetonas adicionales con *N*-(clorocarbonil)isocianato proporcionando oxazina dionas adicionales 35 que pueden hacerse reaccionar con amoníaco proporcionando las pirimidinadionas 36 (*Esquema 10*). La cloración proporciona después los diclorhidratos intermedios 37. En una manera similar, esta química se puede llevar a cabo usando las cetonas protegidas por cetal producidas en el *Esquema 6* preparando las dicloropirimidinas condensadas correspondientes (*Esquema 11*).

Esquema 10



34 35 36 37

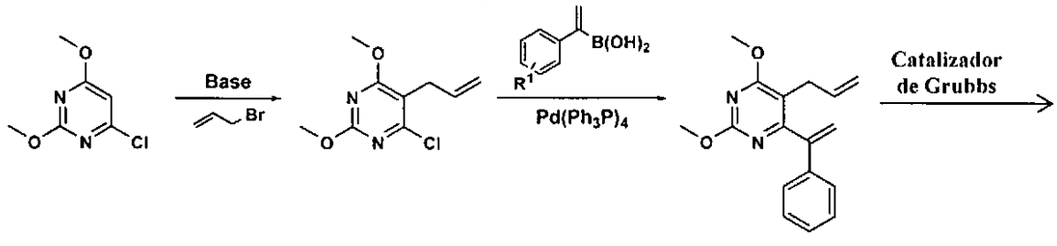
Esquema 11



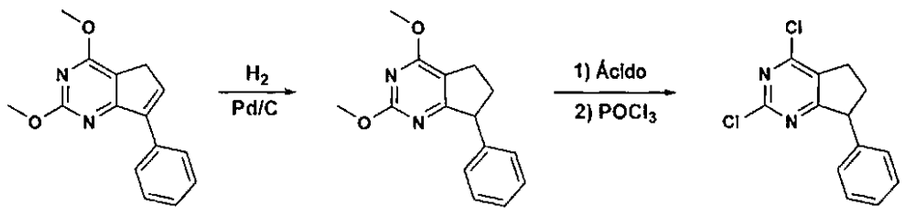
38 39

La síntesis de 2,4-dicloro-7-aril-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidinas 33 podría llevarse a cabo también de acuerdo con la vía descrita en el *Esquema 12*. La 4-cloro-2,6-dimetoxipirimidina 40 podría desprotonarse con una base fuerte, tal como *n*-butillitio o 2,2,6,6-tetrametilpiperidina y desactivarse con bromuro de alilo dando 5-alil-4-cloro-2,6-dimetoxipirimidina 41. Nencka, R.; Votruba, I.; Hřebabecký, H.; Jansa, P.; Tloušťová, E.; Horská, K.; Masojídková, M.; Holý, A. *J. Med. Chem.* 2007, *50*, 6016-6023. El último compuesto puede reaccionar con ácidos α-estirilbóricos en la presencia de un catalizador de paladio, tal como tetrakis(trifenilfosfina)paladio, proporcionando compuestos de fórmula 42 que pueden sufrir metátesis de olefina de cierre de anillo en condiciones de Grubb formando 2,4-dimetoxi-7-aril-5*H*-ciclopenta[*d*]pirimidinas 43. Grubbs, R. H. *Handbook of Metathesis*, 2003, First Edition, Wiley-VCH. El doble enlace en compuestos 43 se puede reducir dando 2,4-dimetoxi-7-aril-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidinas 44, que tras hidrólisis catalizada por ácidos, seguida por clorinación con oxicloruro de fósforo proporcionan intermedios 33.

Esquema 12



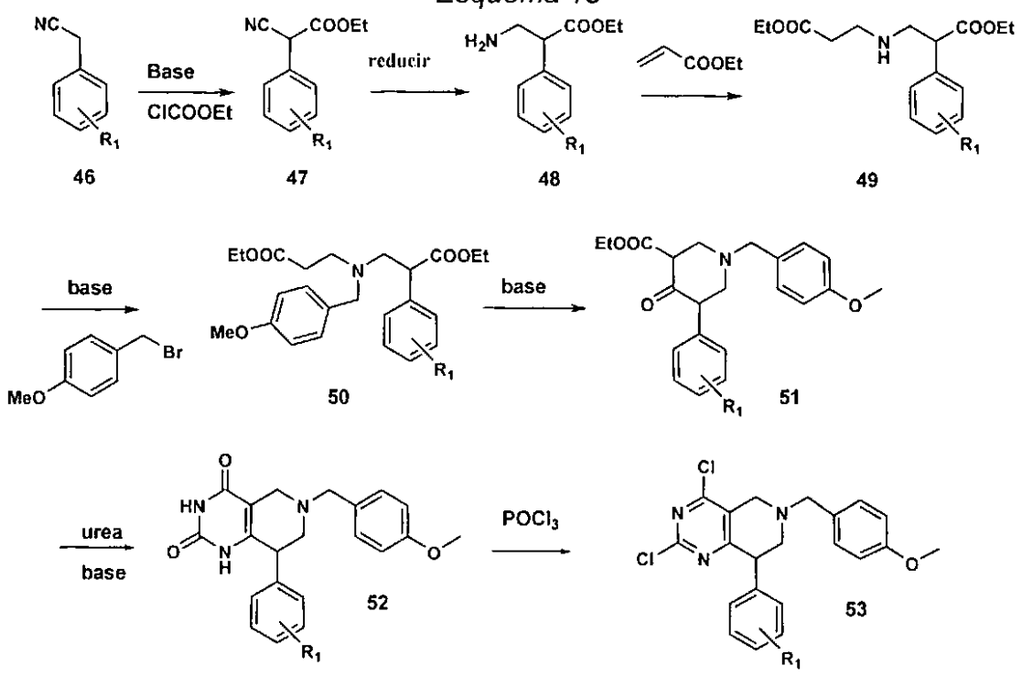
40 41 42



43 44 33

Los miembros adicionales de la clase de compuestos de la reivindicación 1 se pueden preparar como se muestra en el *Esquema 13*. La carboxilación de benzonitrilos seguida de reducción simple usando catálisis metálica (paladio en carbono o procedimientos similares) proporciona el éster beta-amino sustituido 48. La condensación con un éster acrílico proporciona intermedio 49, que puede alquilarse sobre nitrógeno bien proporcionando directamente acceso a sustituyentes R^d, o bien usando la química mostrada puede protegerse con un grupo p-metoxibencilo para posterior desprotección e introducción de R^d. El intermedio 50 se cicla después en la presencia de base (usualmente KO*t*-Bu) proporcionando el beta-cetoéster 51. La condensación del beta-cetoéster 51 con urea en condiciones básicas proporciona el intermedio de pirimidina diona 52, que se puede clorar después en condiciones estándar proporcionando el dicloruro 53. Este dicloruro puede convertirse en compuestos de la reivindicación 1 en el modo usual (véase más adelante).

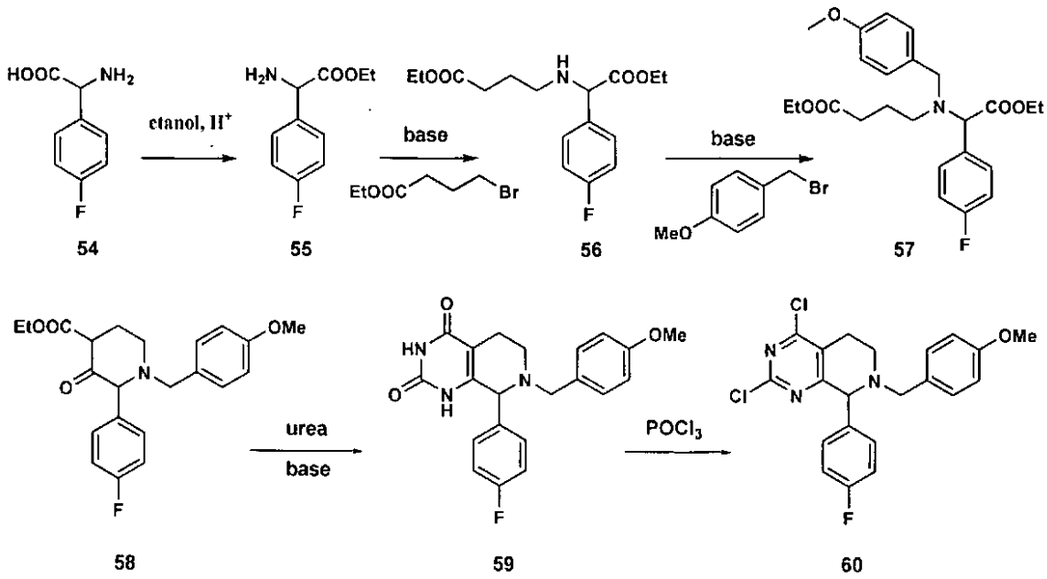
Esquema 13



Los miembros adicionales de la clase de compuestos de la reivindicación 1 se pueden preparar como se muestra en el *Esquema 14*. La esterificación de un aminoácido seguida por la alquilación con 4-bromobutirato de etilo proporciona intermedio 56, que puede alquilarse sobre nitrógeno bien proporcionando directamente acceso a sustituyentes R^d, o bien usando la química mostrada puede protegerse con un grupo p-metoxibencilo para posterior desprotección e introducción de R^d. El intermedio 57 se cicla después en la presencia de base (usualmente KO*t*-Bu) proporcionando el beta-cetoéster 58. La condensación del beta-cetoéster 58 con urea en condiciones básicas proporciona el intermedio de pirimidina diona 59, que se puede clorar después en condiciones estándar proporcionando el dicloruro 60. Este dicloruro puede convertirse en compuestos de la reivindicación 1 en el modo usual (véase más

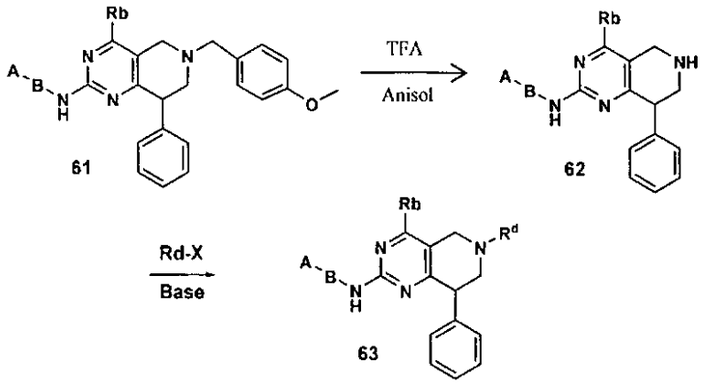
adelante).

Esquema 14

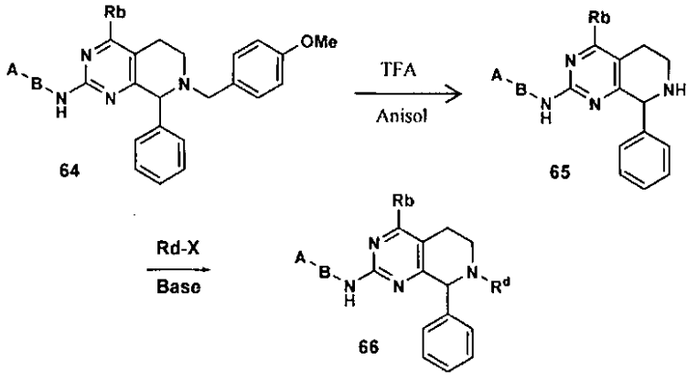


Como se muestra en el *Esquema 15*, el grupo dimetoxibencilo usado protegiendo el átomo de nitrógeno en compuestos de estructura 61 se puede desproteger, por ejemplo por la acción de un ácido fuerte (TFA en la presencia de anisol como un desoxidante de cationes) proporcionando la amina libre, que puede derivatizarse adicionalmente, por ejemplo por acilación, sulfonilación, o alquilación en los modos usuales preparando compuestos adicionales de la reivindicación 1. De forma similar, el isómero posicional 64 amina como se muestra en el *Esquema 16* participa en química idéntica accediendo a una clase adicional de compuestos de la reivindicación 1.

Esquema 15

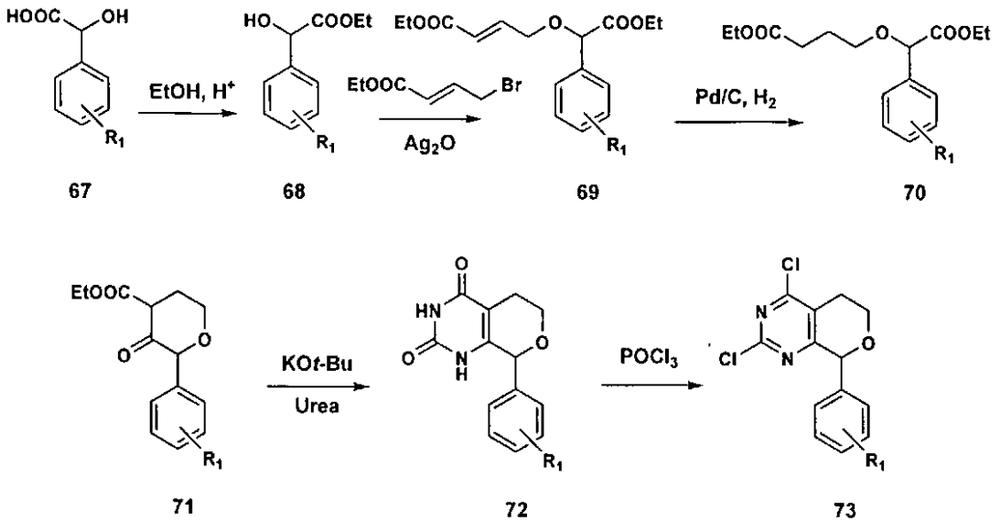


Esquema 16



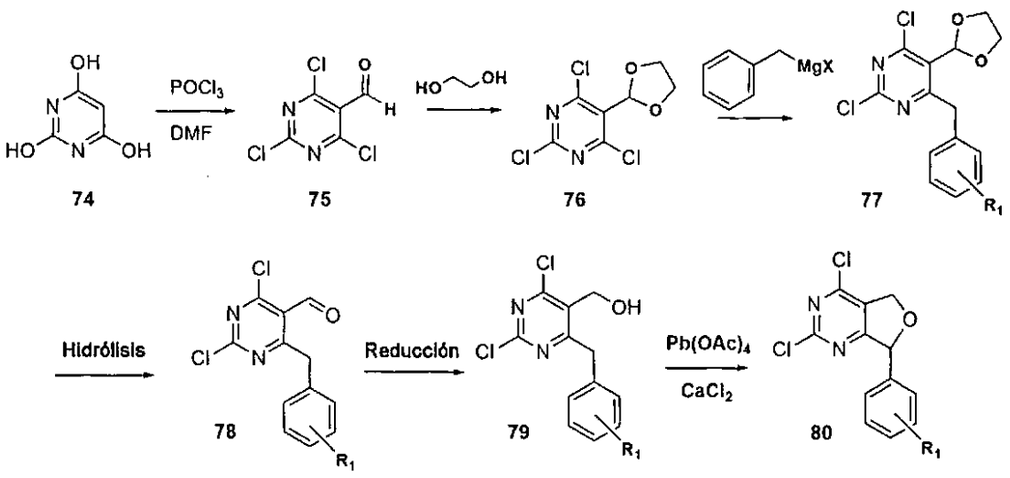
Los análogos adicionales se pueden preparar por la química detallada en el *Esquema 17*. La formación del éster a partir de hidroxiácidos comerciales 67 en condiciones de Fisher está seguida por alquilación del alcohol en catálisis de óxido de plata (I). La reducción de la olefina y la ciclación da el beta-cetoéster 71. La formación de la pirimidina diona con KO*t*-Bu y urea seguida por clorinación con $POCl_3$ da el dicloruro 73, que se transfiere al periodo siguiente para compuestos de la reivindicación 1 como se describe en el *Esquema 22*.

Esquema 17



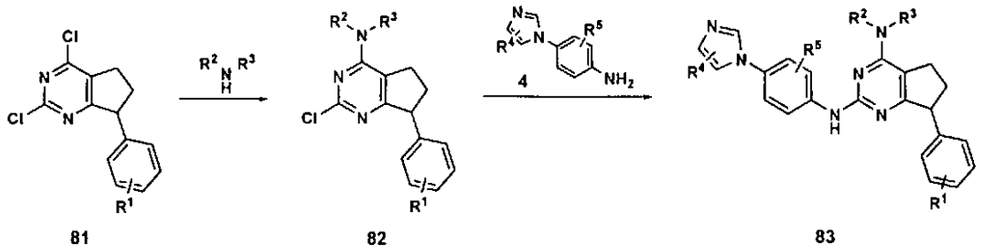
Los análogos adicionales se pueden preparar usando la química mostrada en el *Esquema 18*. La reacción de pirimidina-2,4,6-triol con $POCl_3$ en DMF proporciona el aldehído clorinado 75. La protección del aldehído está seguida por reacción con un agente de Grignard produciendo el reactivo de dicloruro 77. Después de desprotección hidrolítica y de reducción del aldehído al alcohol, el anillo de tetrahidrofurano se puede cerrar por la acción de tetraacetato de plomo proporcionando el dicloruro 80 sustituido que se puede usar de acuerdo con los procedimientos descritos más adelante preparando compuestos adicionales de la reivindicación 1.

Esquema 18



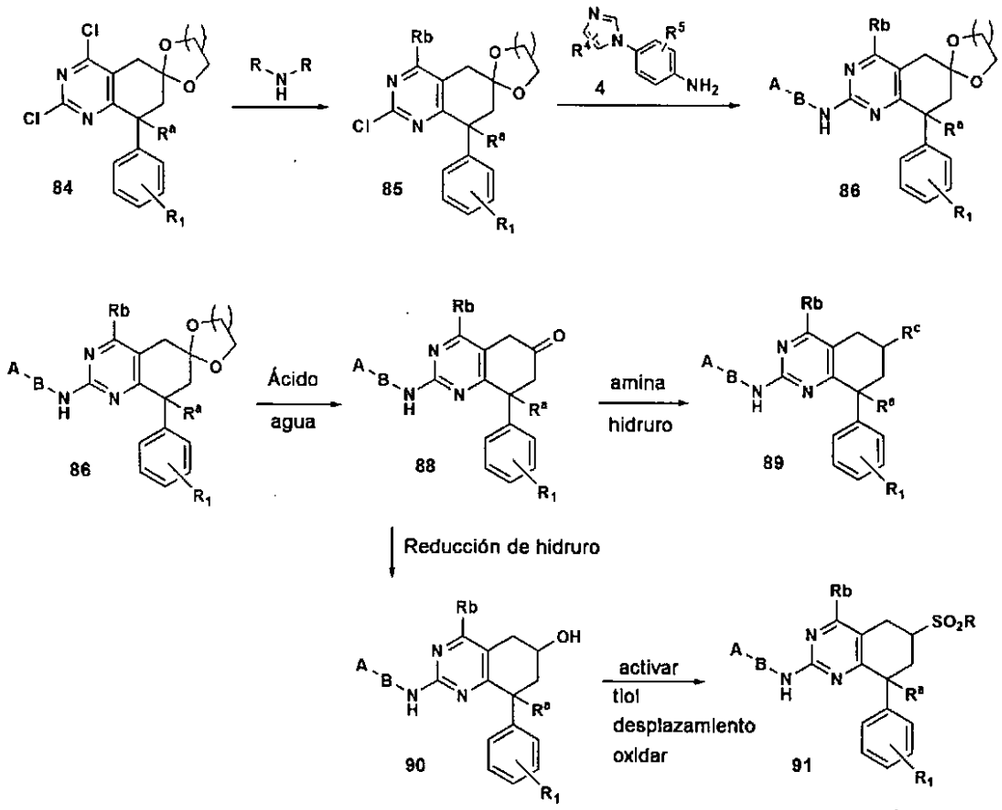
2,4-dicloro-7-aril-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidinas 81 reaccionan selectivamente con aminas primarias y secundarias dando derivados de 2-amino 82, que se pueden acoplar en calentamiento con anilinas 4 formando compuestos del epígrafe 83. (*Esquema 19*). El citado acoplamiento se puede llevar a cabo bien en condiciones ácidas (por ejemplo, usando ácido acético), o bien en condiciones básicas, (por ejemplo, usando hidruro de sodio). Alternativamente, el acoplamiento puede completarse en catálisis metálica, con condiciones conocidas en la bibliografía, por ejemplo el uso de catalizador Xantphos de paladio en la presencia de una base fuerte (NaO*t*-Bu) o Na_2CO_3 en una mezcla codisolvente acuosa (típicamente THF/agua o dioxano/agua).

Esquema 19



Los compuestos adicionales de la reivindicación 1 pueden prepararse por condensación de los dicloruros que contienen cetal apropiados con aminas y anilinas en la manera ya descrita preparando intermedios 86 (*Esquema 20).* La desprotección del cetal, por ejemplo con ácido acuoso produce la cetona 88 que es un intermedio muy útil para la producción de compuestos adicionales. La cetona puede estar directamente condensada con aminas en condiciones reductoras (alquilación reductora) preparando compuestos de amina sustituidos 89. Alternativamente, la cetona se puede reducir con reactivos de hidruro tales como $NaBH_4$ o $LiAlH_4$ proporcionando el alcohol. El alcohol 90 puede activarse, por ejemplo como el metanosulfonato, y después puede desplazarse con nucleófilos que incluyen tioles, azida u otros nucleófilos. La oxidación del tiol prepara el sulfóxido y la sulfona. La reducción de la azida produce una entrada fácil en la amina, que puede también alquilarse adicionalmente produciendo compuestos adicionales de la reivindicación 1.

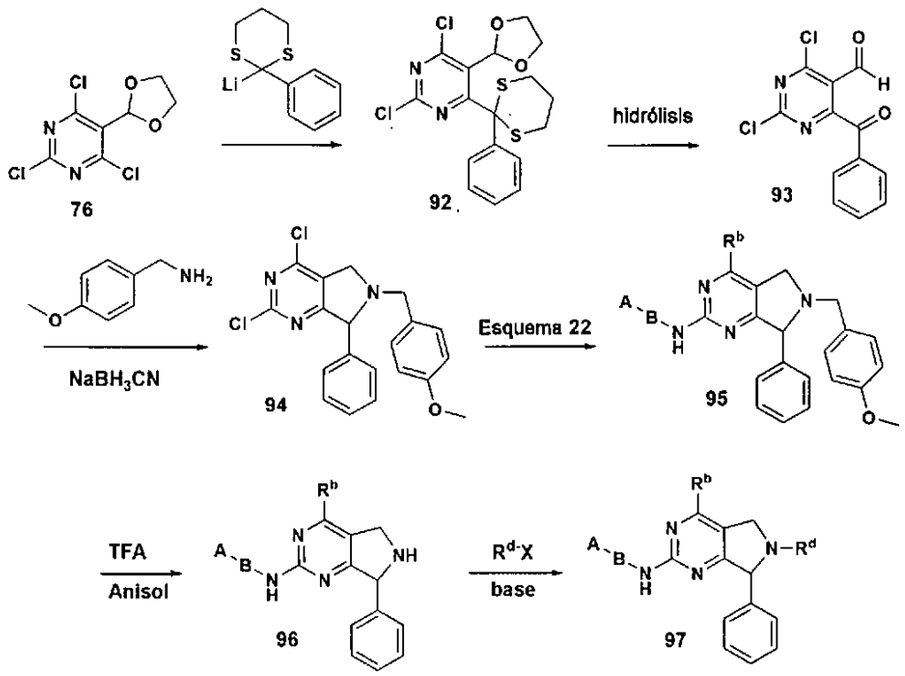
Esquema 20



Un procedimiento adicional para la preparación de análogos de la reivindicación 1 se describe en el *Esquema 21*. Empezando de nuevo con el aldehído 76, la adición del fenilditiano litiado proporciona intermedio 92. La desprotección de los grupos protectores proporciona el cetoaldehído 93, que puede cerrarse a la pirrolidina sustituida 94 por alquilación reductora secuencial. La amina puede bien introducir directamente un sustituyente R^d deseado, o bien como se describe en el esquema se puede usar una amina que introduce un grupo protector (incluyendo 4-metoxibencilo). De acuerdo con

los procedimientos en el presente documento, el dicloruro así obtenido se puede transformar en compuestos de la reivindicación 1. Los análogos adicionales se pueden preparar después por desprotección del grupo 4-metoxibencilo usando procedimientos conocidos para aquellos expertos en la técnica, tales como TFA con anisol como un desoxidante de cationes, seguido por alquilación, acilación, o sulfonilación adicional usando procedimientos conocidos.

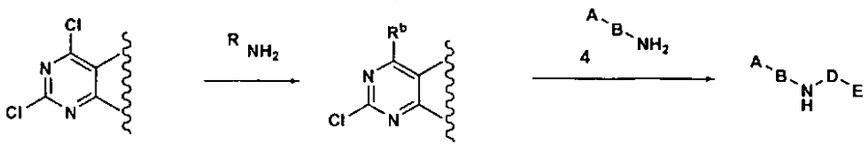
Esquema 21



En un modo general, los dicloruros de pirimidina adicionales preparados usando los procedimientos anteriormente descritos, u otros procedimientos conocidos en la técnica se pueden transformar en análogos adicionales de la

reivindicación 1 como se demuestra en el Esquema 22. Los dicloruros de pirimidina se hacen reaccionar con aminas proporcionando los cloruros 99 que corresponden a las estructuras D-E según se describen en la reivindicación 1, donde el enlace que une la estructura D-E al fragmento ABNH se activa como un grupo cloruro desplazable. Los compuestos del epígrafe de la reivindicación 1 se preparan después condensando los cloruros 99 con las anilinas $ABNH_2$ de acuerdo con los procedimientos anteriormente descritos (*Esquema 19*).

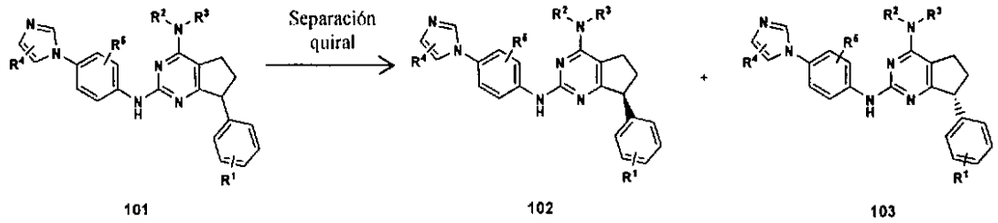
Esquema 22



98 99 100

Los compuestos del epígrafe racémicos se pueden separar por procedimientos quirales conocidos para una persona razonable experta en las técnicas, proporcionando enantiómeros individuales (*Esquema 23*). Esto se demuestra más adelante en las series de ciclopenta[*d*]pirimidina, pero se aplica igualmente a los otros compuestos racémicos descritos en el presente documento.

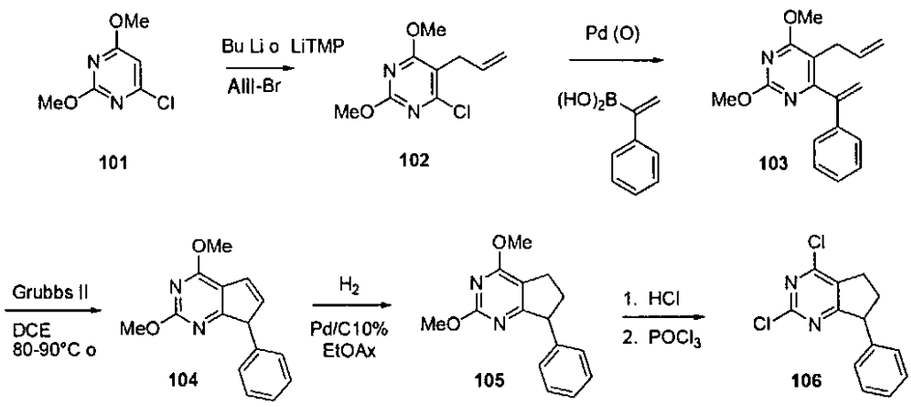
Esquema 23



101 102 103

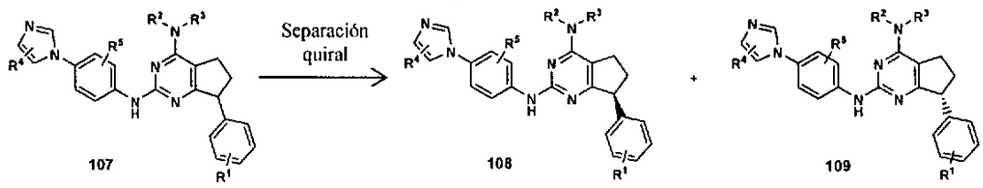
Un procedimiento adicional para producir compuestos de la reivindicación 1 se demuestra en el *Esquema 23*. La 4-cloro-2,6-dimetoxipirimidina 101 comercial se puede desprotonar usando bien butillitio o bien tetrametilpiperidida de litio seguida por alquilación produciendo la pirimidina protegida 102. El acoplamiento de Suzuki de ácido fenilvinilbórico en catálisis de paladio proporciona el dieno 103 que se puede ciclar eficientemente por metátesis de cierre de anillo usando afecciones estándar con catalizador de Grubbs II. La olefina se puede reducir después proporcionando intermedio 105. La desprotección y la cloración en condiciones estándar proporcionan una vía adicional fabricando dicloruros 106 que pueden convertirse a compuestos de la reivindicación 1 usando la química mostrada en el *Esquema 22*.

Esquema 23



Los compuestos del épígrafe racémicos se pueden separar por procedimientos quirales conocidos para una persona razonable experta en las técnicas, proporcionando enantiómeros individuales (*Esquema 24*). Esto se demuestra más adelante en las series de ciclopenta[*d*]pirimidina, pero se aplica igualmente a los otros compuestos racémicos descritos en el presente documento.

Esquema 24



"HPLC" es una abreviatura usada en el presente documento para cromatografía líquida de alta presión. "CL-EM" se refiere a cromatografía líquida de alta presión llevada a cabo de acuerdo con la definición de HPLC con un detector de espectrometría de masas. Condiciones del disolvente de la

HPLC: Cuando se describe como realizados en "condiciones convencionales", las muestras se disolvieron en metanol (1 mg/ml) y se ejecutó usando un programa de gradiente con un caudal de disolvente de 1,0 ml/min. HPLC preparatoria de fase inversa: Cuando se describe que se lleva a cabo en "condiciones convencionales", se disolvieron muestras (aprox. 20 mg) en metanol (10 mg/ml) y se purificó en una columna de 30mm X 100 mm Waters-Atlantis S5 usando una elución con gradiente de 10 minutos desde 0 % hasta 100 % de tampón B en tampón A (tampón A = CH_3OH al 10%/ agua al 90%/TFA al 0,1% y tampón B = MeOH al 90%/agua al 10% /TFA al 0,1%) a 40 ml/minuto.

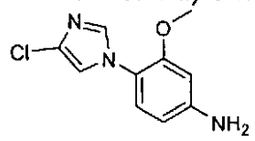
Los espectros de RMN de protón se obtuvieron en un espectrómetro Bruker 400 ó 500. Los datos hacen están referenciados con respecto a la señal del disolvente.

Los ejemplos proporcionados pretenden ayudar a comprender con más detalle la presente divulgación. Los materiales particulares empleados, especies y condiciones pretenden ilustrar con más detalle las realizaciones específicas de la invención y no limitar el alcance razonable de las mismas.

SÍNTESIS DE INTERMEDIOS

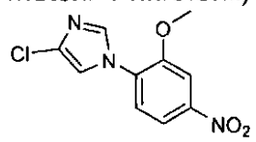
Preparación A

4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina



Intermedio A(1)

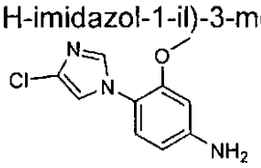
4-cloro-1-(2-metoxi-4-nitrofenil)-1H-imidazol



Una mezcla de 4-cloro-1H-imidazol (5,0 g, 48,8 mmol), 1-cloro-2-metoxi-4-nitrobenceno (9,15 g, 48,8 mmol) y escamas de hidróxido potásico (2,74 g, 48,8 mmol) en DMSO anhidro (50 ml) se calentó a 80 °C durante 20 h. Se dejó enfriar la mezcla de reacción hasta ta y se vertió en 800 ml de agua con agitación vigorosa. El precipitado amarillo-naranja resultante se recogió por filtración a vacío usando un embudo de vidrio sinterizado grueso. El sólido húmedo se transfirió a un matraz de Erlenmeyer de 1 litro. Se añadió etanol absoluto (250 ml) al matraz y la suspensión resultante se calentó hasta que se disolvieron todos los sólidos. La solución transparente se enfrió hasta ta y el producto deseado cristalizó lentamente. Después de 2 h, el sólido cristalino se recogió por filtración a vacío y se aclaró con 100 ml de etanol nuevo. El sólido se secó a alto vacío proporcionando 4-cloro-1-(2-metoxi-4-nitrofenil)-1H-imidazol (5,2 g, 42 % de rendimiento) como un sólido cristalino blanquecino. CL-EM $(M+H)^+$ = 254,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,94 - 8,01 (m, 2 H) 7,76 (d, *J*=1,53 Hz, 1 H) 7,45 (d, *J*=8,55 Hz, 1 H) 7,21 (d, *J*=1,53 Hz, 1 H) 4,02 (s, 3 H).

Preparación A

4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina

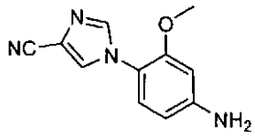


Se añadió polvo de hierro de malla 325 (4,6 g, 82 mmol) a un matraz de

fondo redondo de 500 ml cargado con una mezcla de 4-cloro-1-(2-metoxi-4-nitrofenil)-1H-imidazol (5,2 g, 20,5mmol), etanol absoluto (100 ml), y ácido acético glacial (50 ml). Se unión al matraz un condensador de reflujo enfriado con agua y la mezcla heterogénea se calentó hasta 100 °C con agitación vigorosa durante 30 min. Se dejó enfriar la mezcla de reacción hasta ta y se añadió a una solución enfriada y agitada de NaOH 3 M (291 ml). La mezcla resultante se vertió en un embudo de separación y se extrajo con EtOAc (3 x 250 ml). Las fases orgánicas reunidas se secaron sobre sulfato sódico, se filtraron y se concentraron a vacío proporcionando 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (4,57 g, 97 % de rendimiento) como un sólido. CL-EM $(M+H)^+$ 224,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,47 (d, *J*=1,22 Hz, 1 H) 7,00 (d, *J*=8,24 Hz, 1 H) 6,99 (d, *J*=1,53 Hz, 1 H) 6,32 (d, *J*=2,44 Hz, 1 H) 6,29 (dd, *J*=8,24, 2,44 Hz, 1 H) 3,88 (s ancho, 2 H) 3,78 (s, 3 H).

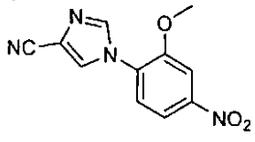
Preparación AA

4-(4-ciano-1H-imidazol-1-il)-3-metoxianilina



Intermedio AA(1)

4-ciano-1-(2-metoxi-4-nitrofenil)-1H-imidazol

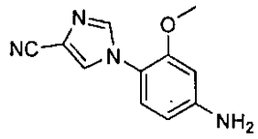


A una solución de 1H-Imidazol-4-carbonitrilo (300 mg, 3,22 mmol) y 4-fluoro-3-metoxinitrobenceno (552 mg, 3,22 mmol) en DMF (Volumen: 6446 µl)

se añadió K_2CO_3 (891 mg, 6,45 mmol). La mezcla resultante se llevó hasta 120 °C y se agitó durante la noche. La mezcla de reacción se diluyó con EtOAc (20 ml), se lavó con agua (2 x 10 ml), salmuera (10 ml), se secó sobre $MgSO_4$, se filtró y se concentró a vacío dando 1-(2-metoxi-4-nitrofenil)-1H-imidazol-4-carbonitrilo (698 mg, 2,86 mmol, 89 % de rendimiento). CL-EM $(M+H)^+$ = 245,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,30 - 8,34 (1 H), 8,19 - 8,23 (1 H), 8,09 - 8,12 (1 H), 8,00 - 8,05 (1 H), 7,71 - 7,79 (1 H), 4,02 - 4,10 (3 H).

Preparación AA

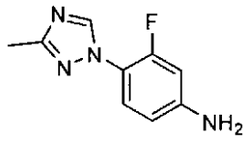
4-(4-ciano-1H-imidazol-1-il)-3-metoxianilina



A una solución de 1-(2-metoxi-4-nitrofenil)-1H-imidazol-4-carbonitrilo (689 mg, 2,82 mmol) en EtOH (Relación: 2, Volumen: 15 ml) se añadió ácido acético (Relación: 1,000, Volumen: 7,50 ml) y hierro (630 mg, 11,29 mmol). La mezcla resultante se llevó hasta 100 °C y se agitó durante 2 h. La reacción se diluyó a continuación con agua y se llevó hasta pH 8 mediante la adición de hidróxido sódico acuoso 1 N. Esta mezcla se extrajo con EtOAc (3 x 5 ml). Los extractos reunidos se lavaron con agua (5 ml), salmuera (5 ml), se secaron sobre $MgSO_4$, se filtraron y se concentraron a vacío. CL-EM $(M+H)^+$ = 215,0.

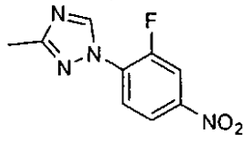
Preparación B

3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)anilina



Intermedio B(1)

1-(2-fluoro-4-nitrofenil)-3-metil-1H-1,2,4-triazol

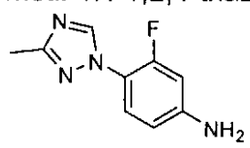


Una mezcla de 3-metil-1H-1,2,4-triazol (15,0 g, 181 mmol), 1,2-difluoro-4-nitrobenceno (28,7 g, 181 mmol) y bicarbonato sódico (15,2 g, 181 mmol) en DMSO (100 ml) se calentó a 80 °C durante 48 h. Se dejó enfriar la mezcla de reacción hasta ta y se vertió en agua (800 ml). La mezcla acuosa se extrajo con EtOAc (3 x 200 ml). Los extractos orgánicos reunidos se lavaron secuencialmente con agua (500 ml) y solución de salmuera (100 ml). La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró a vacío. La mezcla de reacción bruta se purificó usando cromatografía sobre gel de sílice (EtOAc al 30-80%/hexano, gradiente lineal) proporcionando dos productos regioisoméricos. Las fracciones puras del regioisómero menos polar se combinaron y concentraron proporcionando 1-(2-fluoro-4-nitrofenil)-3-metil-1H-1,2,4-triazol (7,2 g, 30,8 mmol, 17 % de rendimiento) como un sólido blanquecino. Las fracciones puras del regioisómero más polar se combinaron y concentraron proporcionando 1-(2-fluoro-4-nitrofenil)-5-metil-1H-1,2,4-triazol (6,23 g, 28,0 mmol, 15 % de rendimiento) como un sólido blanquecino. Datos para 1-(2-fluoro-4-nitrofenil)-3-metil-1H-1,2,4-triazol: CL-EM $(M+H)^+$ = 223,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,73 (d, *J*=2,7 Hz,1 H), 8,15 - 8,26 (m, 3

H), 2,53 (s, 3 H).

Preparación B

3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)anilina

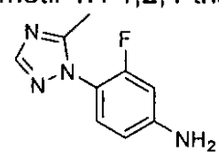


Se añadió paladio al 10% sobre carbón (2,50 g, 23,5 mmol) en una atmósfera de nitrógeno a una solución enfriada (baño de hielo-agua) de 1-(2-fluoro-4-nitrofenil)-5-metil-1H-1,2,4-triazol (15,0 g, 67,5 mmol, de la preparación A, etapa 1) disuelto en metanol (400 ml). El matraz se evacuó repetidas veces y se llenó con hidrógeno gas (doble botella). La mezcla resultante se dejó calentar hasta ta y se dejó agitar durante 72 h en la atmósfera de hidrógeno. El recipiente se purgó a continuación con nitrógeno gas. El recipiente de reacción y su contenido se enfriaron (baño de hielo-agua) y se añadió una porción adicional de paladio al 10% sobre carbón (2,50 g, 23,5 mmol). El matraz se evacuó repetidas veces y se llenó con hidrógeno gas (doble botella). La mezcla resultante se dejó calentar hasta ta y se dejó agitar durante 6 h en la atmósfera de hidrógeno. El recipiente se purgó a continuación con nitrógeno gas. La mezcla de reacción bruta se filtró a través de un lecho corto de tierra de diatomeas (Celite®). El recipiente de reacción y la Celite® se aclararon con metanol nuevo. Los filtrados reunidos se concentraron a vacío. El residuo se secó a alto vacío durante la noche proporcionando 3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)anilina (12,1 g, 63,0 mmol, 93 % de rendimiento) como un sólido negruzco/gris. CL-EM $(M+H)^+$ 193,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,31 (d, *J*=2,4 Hz, 1 H), 7,47 (t, *J*=8,7 Hz, 1 H), 6,47 - 6,58 (m, 2 H), 3,97 (s ancho, 2

H), 2,48 (s, 3 H).

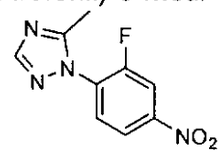
Preparación C

3-Fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina



Intermedio C(1)

1-(2-fluoro-4-nitrofenil)-5-metil-1H-1,2,4-triazol

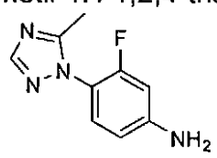


Una mezcla de 3-metil-1H-1,2,4-triazol (15,0 g, 181 mmol), 1,2-difluoro-4-nitrobenceno (28,7 g, 181 mmol) y bicarbonato sódico (15,2 g, 181 mmol) en DMSO (100 ml) se calentó a 80 ºC durante 48 h. Se dejó enfriar la mezcla de reacción hasta ta y se vertió en agua (800 ml). La mezcla acuosa se extrajo con EtOAc (3 x 200 ml). Los extractos orgánicos reunidos se lavaron secuencialmente con agua (500 ml) y solución de salmuera (100 ml). La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró a vacío. La mezcla de reacción bruta se purificó usando cromatografía sobre gel de sílice (EtOAc al 30-80%/hexano, gradiente lineal) proporcionando dos productos regioisoméricos. Las fracciones puras del regioisómero menos polar se combinaron y concentraron proporcionando 1-(2-fluoro-4-nitrofenil)-3-metil-1H-1,2,4-triazol (7,2 g, 30,8 mmol, 17 % de rendimiento) como un sólido blanquecino. Las fracciones puras del regioisómero más polar se combinaron y concentraron proporcionando 1-(2-fluoro-4-nitrofenil)-5-metil-1H-1,2,4-triazol

(6,23 g, 28,0 mmol, 15 % de rendimiento) como un sólido blanquecino. Datos para 1-(2-fluoro-4-nitrofenil)-5-metil-1H-1,2,4-triazol: CL-EM $(M+H)^+$ = 223,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,18 - 8,24 (m, 2 H) 8,04 (s, 1 H) 7,69 - 7,78 (m, 1 H) 2,47-2,53 (m, 3 H).

Preparación C

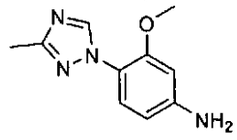
3-Fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina



Se añadió paladio al 10% sobre carbón (1,5 g, 14,1 mmol) en una atmósfera de nitrógeno a una solución enfriada (baño de hielo-agua) de 1-(2-fluoro-4-nitrofenil)-5-metil-1H-1,2,4-triazol (3,7 g, 17 mmol) disuelto en metanol (200 ml). El matraz se evacuó repetidas veces y se llenó con hidrógeno gas (doble botella). La mezcla resultante se dejó calentar hasta ta y se dejó agitar durante 18 h en la atmósfera de hidrógeno. El recipiente se purgó a continuación con nitrógeno gas. La mezcla de reacción bruta se filtró a través de un lecho corto de tierra de diatomeas (Celite®). El recipiente de reacción y Celite® se aclararon con metanol nuevo. Los filtrados reunidos se concentraron a vacío. El residuo se secó a alto vacío proporcionando 3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina (3,14 g, 91 % de rendimiento) como un sólido negruzco/gris. CL-EM $(M+H)^+$ 193,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,91 (s, 1 H) 7,14 (t, *J*=8,55 Hz, 1 H) 6,43 - 6,53 (m, 2 H) 4,04 (s ancho, 2 H) 2,36 (s, 3 H).

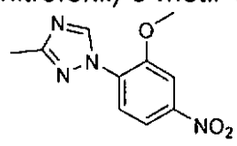
Preparación D

3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)anilina



Intermedio D(1)

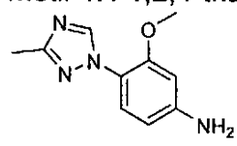
1-(2-metoxi-4-nitrofenil)-3-metil-1H-1,2,4-triazol



Se calentó a 80 °C durante 6 h una mezcla de 3-metil-1H-1,2,4-triazol (5,0 g, 60,2 mmol), 1-cloro-2-metoxi-4-nitrobenceno (11,3 g, 60,2 mmol) y escamas de KOH (3,4 g, 48,1 mmol) en DMSO anhidro (50 ml). Se dejó enfriar la mezcla de reacción hasta ta y se vertió en 800 ml de agua con agitación vigorosa. La mezcla acuosa se extrajo con EtOAc (3 x 200 ml). Los orgánicos reunidos se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron a vacío. El residuo bruto se purificó usando cromatografía sobre gel de sílice (MeOH al 0-2%/cloroformo, gradiente lineal) proporcionando 1-(2-metoxi-4-nitrofenil)-3-metil-1H-1,2,4-triazol (3,7 g, 26 % de rendimiento). CL-EM $(M+H)^+$ = 235,2.

Preparación D

3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)anilina

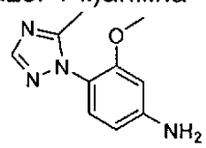


Se añadió paladio al 10% sobre carbón (1,2 g) en una atmósfera de nitrógeno a una solución enfriada (baño de hielo-agua) de 1-(2-metoxi-4-

nitrofenil)-3-metil-1H-1,2,4-triazol (3,7 g, 12,7 mmol) disuelto en metanol (250 ml). El matraz se evacuó repetidas veces y se llenó con hidrógeno gas (doble botella). La mezcla resultante se dejó calentar hasta ta y se dejó agitar durante 18 h en la atmósfera de hidrógeno. Se purgó con nitrógeno gas. La mezcla de reacción bruta se filtró a través de un lecho corto de tierra de diatomeas (Celite®). Se aclaró el recipiente de reacción y se cubrió con metanol. El filtrado se concentró a vacío. El residuo se secó a alto vacío durante la noche proporcionando 3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)anilina (2,44 g, 94 % de rendimiento) como un sólido rojizo. CL-EM $(M+H)^+$ 205,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,35 (s, 1 H) 7,36 (d, *J*=8,55 Hz, 1 H) 6,29 - 6,34 (m, 2 H) 3,80 (s, 3 H) 2,46 (s, 3 H).

Preparación DD

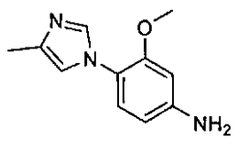
3-metoxi-4-(5-metil-1H-1,2,4-triazol-1-il)anilina



El Intermedio C(1) se hizo reaccionar con NaOMe en DMF proporcionando 1-(2-metoxi-4-nitrofenil)-5-metil-1H-1,2,4-triazol, que se redujo con Fe y cloruro amónico proporcionando el compuesto del epígrafe. CL-EM $(M+H)^+$ 205,1. RMN de ^1H (500 MHz, *CLOROFORMO-d*) δ ppm 7,90 (1 H, s), 7,05 (1 H, d, *J*=7,93 Hz), 6,27 - 6,34 (2 H, m), 3,91 (2 H, s ancho), 3,73 (3 H, s), 2,29 (3 H, s).

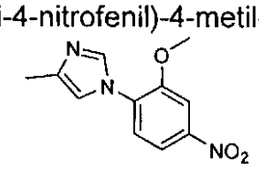
Preparación E

3-metoxi-4-(4-metil-1H-imidazol-1-il)anilina



Intermedio E(1)

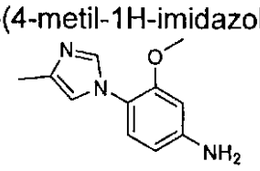
1-(2-metoxi-4-nitrofenil)-4-metil-1H-imidazol



Se calentó a 110 °C durante 24 h una mezcla de 4-metil-1H-imidazol (18,0 g, 53,5 mmol), 1-cloro-2-metoxi-4-nitrobenceno (10,0 g, 53,5 mmol), e hidróxido potásico (4,5 g, 80,3 mmol) en DMSO (50 ml). Se dejó enfriar la mezcla de reacción hasta ta y se vertió en 1000 ml de agua. La mezcla acuosa se extrajo con diclorometano (3 x 250 ml). Los extractos orgánicos reunidos se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron a vacío. La mezcla de reacción bruta se purificó usando cromatografía sobre gel de sílice (cartucho de sílice de 330 g, MeOH al 0-2%/cloroformo, gradiente lineal durante 72 min, caudal 25 ml/min) proporcionando 1-(2-metoxi-4-nitrofenil)-4-metil-1H-imidazol (2,56 g, 20 % de rendimiento) como un sólido amarillo/naranja. CL-EM $(M+H)^+$ = 234,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,97 - 8,00 (m, 1 H) 7,93 - 7,97 (m, 2 H) 7,45 (d, *J*=8,85 Hz, 1 H) 7,02 (s, 1 H) 4,02 (s, 3 H) 2,35 (s, 3 H).

Preparación E

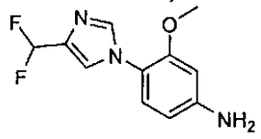
3-metoxi-4-(4-metil-1H-imidazol-1-il)anilina



Se añadió paladio al 10% sobre carbón (250 mg) en una atmósfera de nitrógeno a una solución enfriada (baño de hielo-agua) de 1-(2-metoxi-4-nitrofenil)-4-metil-1H-imidazol (2,56 g, 11,0 mmol) disuelto en metanol (150 ml). El matraz se evacuó repetidas veces y se llenó con hidrógeno gas (doble botella). La mezcla resultante se dejó calentar hasta ta y se dejó agitar durante 18 h en la atmósfera de hidrógeno. Se purgó con nitrógeno gas. La mezcla de reacción bruta se filtró a través de un lecho corto de tierra de diatomeas (Celite®). Se aclaró el recipiente de reacción y se cubrió con metanol. El filtrado se concentró a vacío. El residuo se secó a alto vacío durante la noche proporcionando 3-metoxi-4-(4-metil-1H-imidazol-1-il)anilina (2,25 g, 100 % de rendimiento) como un sólido céreo negruzco/gris. CL-EM $(M+H)^+$ 204,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,69 (s, 1 H) 7,01 (d, *J*=8,55 Hz, 1 H) 6,82 (s, 1 H) 6,33 (d, *J*=2,14 Hz, 1 H) 6,30 (d, *J*=8,55 Hz, 1 H) 3,78 (s, 3 H) 2,33 (s, 3 H).

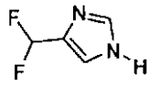
Preparación EE

3-metoxi-4-(4-difluorometil-1H-imidazol-1-il)anilina



Intermedio EE(1)

4-(difluorometil)-1H-imidazol

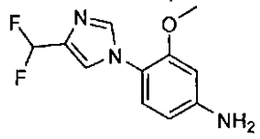


A una solución de 1-tritil-1H-imidazol-4-carbaldehído en diclorometano a 0 °C se añadió desoxiflúor y se agitó durante 3 días. El producto se trató entonces con AcOH/Hcl 1:5 a temperatura ambiente durante la noche

proporcionando 4-(difluorometil)-1H-imidazol.

Preparación EE

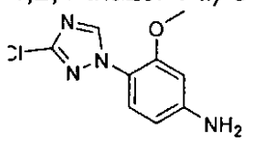
3-metoxi-4-(4-difluorometil-1H-imidazol-1-il)anilina



El Intermedio EE(1) se hizo reaccionar como se describe para la Preparación E proporcionando la Preparación EE deseada. CL-EM $(M+H)^+$ 240,2. RMN de ^1H (400 MHz, DMSO-d6) δ ppm 8,42 (s, 1 H) 7,93 (s, 1 H), 7,48 (d, J = 8,4 Hz, 1 H) 7,19-6,88 (m, 3 H) 3,81 (s, 3 H).

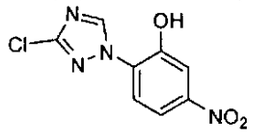
Preparación F

4-(3-cloro-1H-1,2,4-triazol-1-il)-3-metoxianilina



Intermedio F(1)

2-(3-cloro-1H-1,2,4-triazol-1-il)-5-nitrofenol

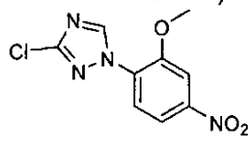


Una mezcla de 3-cloro-1H-1,2,4-triazol (2,76 g, 26,7 mmol), 1-cloro-2-metoxi-4-nitrobenceno (5,0 g, 26,7 mmol), escamas de hidróxido potásico (1,496 g, 26,7 mmol) y DMSO (25 ml) se calentó en un recipiente de reacción herméticamente cerrado a 100 ºC durante 24 h. Se dejó que la reacción se

enfriara hasta ta y se añadieron porciones adicionales de 3-cloro-1H-1,2,4-triazol (1,38 g, 0,5 equiv) e hidróxido potásico (0,75 g, 0,5 equiv). El recipiente de reacción se volvió a cerrar y se calentó hasta 110 °C durante otras 24 h. La mezcla resultante se dejó enfriar hasta ta y se vertió en 500 ml de agua. La mezcla acuosa se extrajo con EtOAc (3 x 100 ml). Los orgánicos reunidos se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron a vacío. El residuo bruto se purificó usando cromatografía sobre gel de sílice (0-5% MeOH/cloroformo, gradiente lineal durante 144 min, caudal 25 ml/min) proporcionando 2-(3-cloro-1H-1,2,4-triazol-1-il)-5-nitrofenol (0,924 g, 3,84 mmol, 14,4 % de rendimiento). CL-EM $(M+H)^+$ = 241,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,97 (s ancho, 1 H) 9,24 (s, 1 H) 7,90 - 7,95 (m, 1 H) 7,89 (d, *J*=2,44 Hz, 1 H) 7,84 (dd, *J*=8,85, 2,44 Hz, 1 H).

Intermedio F(2)

3-cloro-1-(2-metoxi-4-nitrofenil)-1H-1,2,4-triazol

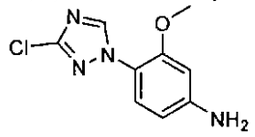


Se añadió yodometano (0,860 ml, 13,82 mmol) a una mezcla de 2-(3-cloro-1H-1,2,4-triazol-1-il)-5-nitrofenol (1,33 g, 5,53 mmol), hidróxido potásico (0,388 g, 6,91 mmol) y DMSO (25 ml). Se dejó agitar la mezcla a ta durante 24 h. La mezcla de reacción se vertió en agua (250 ml) y se extrajo con EtOAc (3x100 ml). Los extractos reunidos se lavaron con agua, se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron a vacío. El residuo bruto se purificó usando cromatografía en columna sobre gel de sílice (MeOH al 0-1%/cloroformo, gradiente lineal durante 72 min, caudal 25

ml/min). Las fracciones puras se reunieron y concentraron proporcionando 3-cloro-1-(2-metoxi-4-nitrofenil)-1H-1,2,4-triazol (0,924 g, 3,63 mmol, 65,6 % de rendimiento) como un sólido amarillo claro. CL-EM $(M+H)^+$ = 255,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,35 (s, 1 H) 7,36 (d, *J*=8,55 Hz, 1 H) 6,29 - 6,34 (m, 2 H) 3,80 (s, 3 H) 2,46 (s, 3 H).

Preparación F

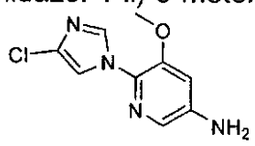
4-(3-cloro-1H-1,2,4-triazol-1-il)-3-metoxianilina



Se añadieron agua (8 ml) y dioxano (8 ml) a una mezcla de 3-cloro-1-(2-metoxi-4-nitrofenil)-1H-1,2,4-triazol (0,900 g, 3,53 mmol) y sulfuro sódico (1,379 g, 17,67 mmol) en un vial de 20 ml. Se tapó el vial y se calentó a 70-80 °C durante 24 horas. La mezcla se enfrió hasta ta, se vertió en agua (300 ml) y se extrajo con EtOAc (2x150 ml). Las fases orgánicas reunidas se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron a vacío proporcionando 4-(3-cloro-1H-1,2,4-triazol-1-il)-3-metoxianilina (577 mg, 73%) como un sólido marrón. CL-EM $(M+H)^+$ 225,1.

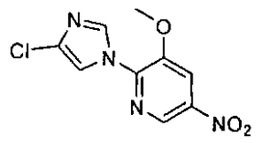
Preparación FF

6-(4-cloro-1H-imidazol-1-il)-5-metoxipiridin-3-amina



Intermedio FF(1)

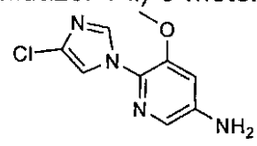
2-(4-cloro-1H-imidazol-1-il)-3-metoxi-5-nitropiridina



Se calentó a 80 °C durante 5 h una mezcla de 4-cloro-1H-imidazol (2,72 g, 26,5 mmol), 2-cloro-3-metoxi-5-nitropiridina (5,0 g, 26,5 mmol) y escamas de KOH 1,488 g, 26,5 mmol) en DMSO anhidro (25 ml). Se dejó enfriar la mezcla de reacción hasta ta y se vertió en 1,0 l de agua con agitación vigorosa. La mezcla se agitó a ta durante 16 h. El precipitado se recogió por filtración a vacío usando un embudo de vidrio sinterizado grueso. El sólido se secó a alto vacío durante 24 h proporcionando 2-(4-cloro-1H-imidazol-1-il)-3-metoxi-5-nitropiridina (5,22 g, 20,50 mmol, 77 % de rendimiento) como un sólido marrón claro. CL-EM $(M+H)^+$ = 255,0. RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 8,94 (d, *J*=2,44 Hz, 1 H) 8,51 (d, *J*=1,83 Hz, 1 H) 8,42 (d, *J*=2,44 Hz, 1 H) 8,02 (d, *J*=1,83 Hz, 1 H) 4,12 (s, 3 H).

Preparación FF

6-(4-cloro-1H-imidazol-1-il)-5-metoxipiridin-3-amina

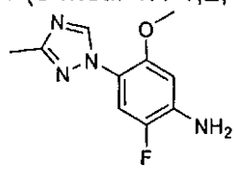


Se añadió polvo de hierro de malla 325 (2,19 g, 39,3 mmol) a un matraz cargado con una mezcla de 2-(4-cloro-1H-imidazol-1-il)-3-metoxi-5-nitropiridina (5,0 g, 19,64 mmol), etanol absoluto (50 ml) y ácido acético glacial (20 ml). Se unión al matraz un condensador de reflujo enfriado con agua y la mezcla heterogénea se calentó hasta 100 °C con agitación vigorosa durante 30 min. Se dejó enfriar la mezcla de reacción hasta ta y se neutralizó tras la adición a una solución enfriada y agitada vigorosamente de NaOH 5 M. La mezcla

resultante se vertió en un embudo de separación y se extrajo con EtOAc. Las fases orgánicas reunidas se secaron sobre sulfato sódico, se filtraron y se concentraron a vacío proporcionando 6-(4-cloro-1H-imidazol-1-il)-5-metoxipiridin-3-amina (3,12 g, 71 % de rendimiento). CL-EM $(M+H)^+$ 225,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,06 (d, *J*=1,83 Hz, 1 H) 7,53 (dd, *J*=13,28, 1,98 Hz, 2 H) 6,70 (d, *J*=2,44 Hz, 1 H) 3,90 (s, 3 H) 3,86 (s ancho, 2 H).

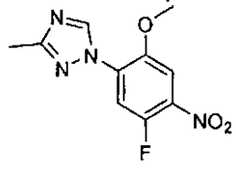
Preparación FFF

2-fluoro-5-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)anilina



Intermedio FFF(1)

1-(5-fluoro-2-metoxi-4-nitrofenil)-3-metil-1H-1,2,4-triazol

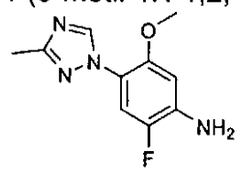


Se calentó a 80 ºC durante 24 h una mezcla de 3-metil-1H-1,2,4-triazol (2,20 g, 26,4 mmol), 1,5-difluoro-2-metoxi-4-nitrobenceno (5,00 g, 26,4 mmol), y carbonato potásico (3,65 g, 26,4 mmol) en DMSO anhidro (50 ml). Se dejó enfriar la mezcla de reacción hasta ta y se vertió en 500 ml de agua/10 ml solución de salmuera. La mezcla acuosa se extrajo con EtOAc (2 x 250 ml). Los extractos orgánicos reunidos se lavaron con agua (500 ml), se secaron

sobre sulfato sódico, se filtraron y se concentraron a vacío. La mezcla de reacción bruta se purificó usando cromatografía en columna sobre gel de sílice (EtOAc al 50%/hexano) proporcionando 1-(5-fluoro-2-metoxi-4-nitrofenil)-3-metil-1H-1,2,4-triazol (1,24 g, 18 % de rendimiento). CL-EM $(M+H)^+$ = 253,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,95 (s, 1 H) 8,00 (d, *J*=11,60 Hz, 1 H) 7,80 (d, *J*=6,10 Hz, 1 H) 4,09 (s, 3 H) 2,50 (s, 3 H).

Preparación FFF

2-fluoro-5-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)anilina

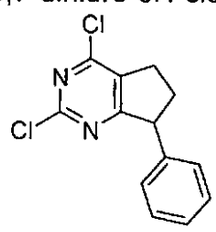


Se añadió paladio al 10% sobre carbón (0,523 g, 4,92 mmol) en una atmósfera de nitrógeno a una solución enfriada (baño de hielo-agua) de 1-(5-fluoro-2-metoxi-4-nitrofenil)-3-metil-1H-1,2,4-triazol (1,24 g, 4,92 mmol) disuelto en metanol (100 ml). El matraz se evacuó repetidas veces y se llenó con hidrógeno gas (doble botella). La mezcla resultante se dejó calentar hasta ta y se dejó agitar durante 18 h en la atmósfera de hidrógeno. El recipiente se purgó a continuación con nitrógeno gas. La mezcla de reacción bruta se filtró a través de un lecho corto de tierra de diatomeas (Celite®). El recipiente de reacción y el lecho corto se aclararon con metanol nuevo. Los filtrados reunidos se concentraron a vacío. El residuo se secó a alto vacío durante la noche proporcionando 2-fluoro-5-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)anilina (1,05 g, 96 % de rendimiento) como un sólido gris. CL-EM $(M+H)^+$ 223,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,46 (s, 1 H) 7,39 (d, *J*=11,29 Hz, 1 H) 6,44 (d, *J*=7,63

Hz, 1 H) 3,89 (s ancho, 2 H) 3,83 (s, 3 H) 2,47 (s, 3 H).

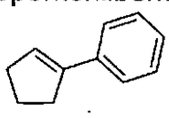
Preparación G

2,4-Dicloro-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Intermedio G(1)

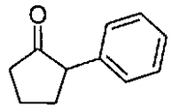
Ciclopentenilbenceno



A una solución de solución 3,0 M de bromuro de fenilmagnesio en éter (49,7 ml, 149 mmol) se añadió THF (300 ml). A esta solución enfriada hasta 0°C se añadió ciclopentanona (13,23 ml, 149 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 min, luego a reflujo durante 2 h. Se añadió hielo (20 g), seguido por HCl 6N, hasta que se disolvió el precipitado. El producto se extrajo con éter. Las fases de éter reunidas se lavaron con solución saturada de bicarbonato sódico, se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando ciclopentenilbenceno (21,49 g, 149 mmol, 100 % de rendimiento) como aceite incoloro. CL-EM $(M+H)^+$ = 145,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,48 (2H, d, *J*=7,3 Hz), 7,35 (2H, t, *J*=7,8 Hz), 7,22 - 7,27 (1H, m), 6,22 (1H, t, *J*=2,1 Hz), 2,70 - 2,80 (2H, m), 2,52 - 2,64 (2H, m), 2,01 - 2,12 (2H, m).

Intermedio G(2)

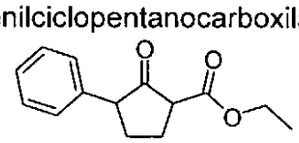
2-Fenilciclopentanona



Una mezcla de peróxido de hidrógeno al 30% (23 ml, 149 mmol) y ácido fórmico al 85% (100 ml, 2619 mmol) se calentó a 40°C durante 15 minutos. La mezcla se añadió cuidadosamente a ciclopentenilbenceno (21,49 g, 149 mmol) y el sistema bifásico resultante se agitó vigorosamente a temperatura ambiente durante 4 h. Se observó una reacción exotérmica al comienzo. Al final de la agitación, la solución se volvió homogénea. La mezcla de reacción se enfrió cuidadosamente con solución acuosa saturada de bicarbonato sódico. El producto se extrajo con éter. Las fases de éter reunidas se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el producto se purificó por cromatografía en columna sobre gel de sílice dando 2-fenilciclopentanona (19,995 g, 125 mmol, 84 % de rendimiento) como aceite marrón. CL-EM $(M+H)^+$ = 161,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,38 (1H, t, *J*=7,3 Hz), 7,30 - 7,35 (2H, m), 7,19 (2H, d, *J*=7,3 Hz), 3,28 - 3,37 (1H, m), 2,71 (1H, td, *J*=4,6, 2,7 Hz), 2,58 - 2,63 (1H, m), 2,43 - 2,55 (1H, m), 2,29 (1H, ddd, *J*=19,0, 10,5, 9,0 Hz), 2,07 - 2,21 (1H, m), 1,88 - 1,99 (1H, m).

Intermedio G(3)

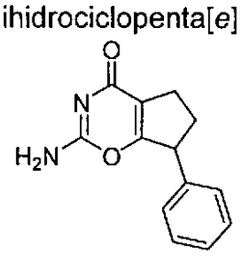
2-oxo-3-fenilciclopentanocarboxilato de etilo



A una solución de diisopropilamina (6,62 ml, 46,8 mmol) en THF (200 ml) a -78 °C se añadió una solución 1,6 M de *n*-butil litio en hexanos (29,3 ml, 46,8 mmol). La solución se agitó durante 30 min a -78 °C y se trató con una solución de 2-fenilciclopentanona (5 g, 31,2 mmol) en 50 ml de THF seco. Después de agitar durante 30 min a -78 °C, se añadió a la mezcla de reacción carbonocianidato de etilo (3,36 ml, 34,3 mmol). La solución resultante se calentó hasta 25 °C con agitación durante 3 h. La mezcla de reacción se enfrió con 10 ml de agua, se lavó con salmuera, se secó sobre sulfato sódico anhidro, se concentró a vacío y se purificó por cromatografía en columna sobre gel de sílice proporcionando 2-oxo-3-fenilciclopentanocarboxilato de etilo (5,3 g, 22,82 mmol, 73 % de rendimiento) como aceite incoloro. CL-EM $(M+K)^+$ = 273,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,32 - 7,39 (2H, m), 7,25 - 7,31 (1H, m), 7,19 - 7,25 (2H, m), 4,18 - 4,32 (2H, m), 3,29 - 3,55 (2H, m), 1,87 - 2,62 (4H, m), 1,28 - 1,39 (3H, m).

Intermedio G(4)

2-Amino-7-fenil-6,7-dihidrociclopenta[*e*][1,3]oxazin-4(5*H*)-ona

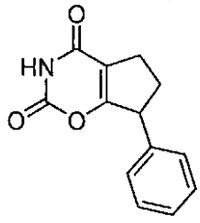


Se disolvió sulfato de 2-metil-2-tiopseudourea (1,336 g, 9,61 mmol) en agua (10 ml) y se añadió KOH (1,128 g, 20,10 mmol). En agitación, se añadió 2-oxo-3-fenilciclopentanocarboxilato de etilo (2,03 g, 8,74 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de

reacción se filtró, se lavó con agua y éter, y se secó sobre sulfato sódico anhidro proporcionando 2-amino-7-fenil-6,7-dihidrociclopenta[*e*][1,3]oxazin-4(5*H*)-ona (1,22 g, 5,35 mmol, 61,2 % de rendimiento) como sólido blanco. CL-EM $(M+H)^+$ = 229,1. RMN de ^1H (500 MHz, dimetilsulfóxido-*d6*) δ ppm 7,57 - 7,85 (2H, m), 7,08 - 7,47 (5H, m), 4,25 - 4,38 (1H, m), 1,72 - 2,73 (3H, m), 1,09 - 1,31 (1H, m).

Intermedio G(5)

7-Fenil-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona



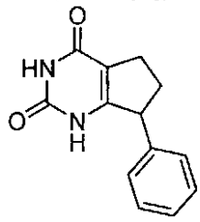
Se disolvió 2-amino-7-fenil-6,7-dihidrociclopenta[*e*][1,3]oxazin-4(5*H*)-ona (900 mg, 3,94 mmol) en una solución acuosa 3M de cloruro de hidrógeno (32 ml, 96 mmol) en agitación. La mezcla se calentó a reflujo durante 1 h. La mezcla de reacción se enfrió y se extrajo con acetato de etilo. La fase orgánica se lavó con solución acuosa saturada de bicarbonato sódico y salmuerase secó sobre sulfato sódico anhidro, se concentró a vacío y se purificó por cromatografía en columna sobre gel de sílice proporcionando 7-fenil-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (350 mg, 1,527 mmol, 38,7 % de rendimiento). CL-EM $(M+H)^+$ = 230,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,34 (1H, s ancho), 7,35 (2H, t, *J*=7,3 Hz), 7,27 - 7,32 (1H, m), 7,18 (2H, d, *J*=7,3 Hz), 4,20 (1H, t, *J*=7,6 Hz), 2,82 - 2,91 (1H, m), 2,61 - 2,79 (2H, m), 2,11 - 2,21 (1H, m).

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Una solución de 2-fenilciclopentanona (19,995 g, 125 mmol) y N-(clorocarbonil)isocianato (23,70 g, 225 mmol) se agitó a 58°C durante 1 h y a 130°C durante 45 min. La mezcla de reacción ensuciada resultante se disolvió en acetato de etilo y se neutralizó con solución acuosa saturada de bicarbonato sódico. La fase orgánica se secó sobre sulfato de magnesio anhidro y se filtró. El producto se purificó por cromatografía en columna sobre gel de sílice dando 7-fenil-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (3,751 g, 16,36 mmol, 13 % de rendimiento) como sólido pardusco. CL-EM $(M+H)^+$ = 230,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,34 (1H, s ancho), 7,35 (2H, t, *J*=7,3 Hz), 7,27 - 7,32 (1H, m), 7,18 (2H, d, *J*=7,3 Hz), 4,20 (1H, t, *J*=7,6 Hz), 2,82 - 2,91 (1H, m), 2,61 - 2,79 (2H, m), 2,11 - 2,21 (1H, m).

Intermedio G(6)

7-Fenil-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona

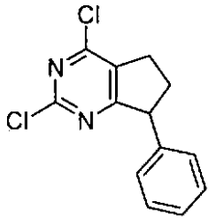


Una solución de 7-fenil-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (3,751 g, 16,36 mmol) en amoníaco concentrado en agua (80 ml, 16,36 mmol) se calentó en un matraz de alta presión de 350 ml durante 5 h. El disolvente se eliminó a vacío dando 7-fenil-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona (3,73 g, 16,34 mmol, 100 % de rendimiento) como sólido marrón. CL-EM $(M+H)^+$ = 229,1. RMN de ^1H (500

MHz, dimetilsulfóxido-*d6*) δ ppm 7,34 (2H, t, *J*=7,5 Hz), 7,26 (1H, t, *J*=7,3 Hz), 7,18 (2H, d, *J*=7,3 Hz), 5,39 (1H, s ancho), 4,14 (1H, d, *J*=7,3 Hz), 2,43 - 2,68 (2H, m), 1,80 - 1,88 (2H, m).

Preparación G

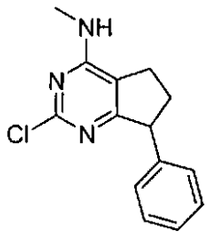
2,4-Dicloro-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Una solución de 7-fenil-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona (1,241 g, 5,44 mmol) en tricloruro de fosforilo (14,93 ml, 163 mmol) se calentó en microondas a 110 °C durante 1 h. Una vez fundido el hielo, el producto se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2,4-dicloro-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (3,132 g, 72%) como sólido marrón claro. CL-EM $(M+H)^+$ = 265,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,31 - 7,37 (2H, m), 7,27 (1H, d, *J*=7,0 Hz), 7,15 (2H, d, *J*=7,9 Hz), 4,44 (1H, t, *J*=8,2 Hz), 3,09 - 3,18 (1H, m), 2,97 - 3,06 (1H, m), 2,73 (1H, ddd, *J*=9,0, 4,7, 4,6 Hz), 2,26 (1H, ddd, *J*=8,5, 7,0, 6,7 Hz).

Preparación Ga

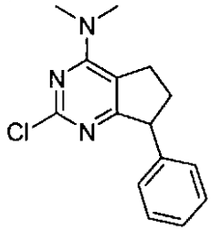
2-cloro-N-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina



A una solución de 2,4-dicloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación G) (395 mg, 1,49 mmol) en THF (3700 µl), se añadió $MeNH_2$ 2 M en THF (3700 µl, 7,45 mmol). Se dejó agitar la reacción a ta. Cuando se completó la reacción, se eliminó el disolvente y se aplicó a gel de sílice. Se eluyó con EtOAc/Hex proporcionando la 2-cloro-N-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina deseada (80,8 mg, 0,220 mmol, 69,1 % de rendimiento). CL-EM $(M+H)^+$ = 260,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,07 (3H, dd, *J*=8,5, 5,5 Hz), 6,96 (2H, t, *J*=8,7 Hz), 4,72 (1H, s ancho), 4,23 (1H, t, *J*=7,2 Hz), 3,09 (3H, d, *J*=4,9 Hz), 2,67 - 2,77 (1H, m), 2,58 - 2,67 (2H, m), 2,01 - 2,11 (1H, m).

Preparación Gb

2-Cloro-*N*,*N*-dimetil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina

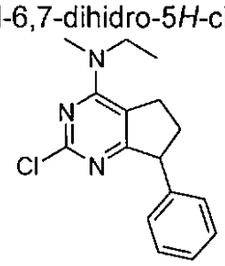


Una solución de 2,4-dicloro-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (200 mg, 0,754 mmol) y dimetilamina en exceso (3,77 ml, 7,54 mmol) en MeOH (2 ml) se agitó a ta durante 1 h. El disolvente se eliminó a vacío proporcionando 2-cloro-*N*,*N*-dimetil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (207

mg, 0,756 mmol, 100 % de rendimiento). CL-EM $(M+H)^+$ = 274,2.

Preparación Gc

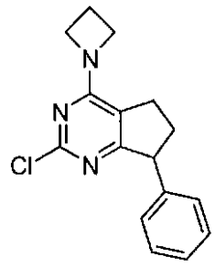
2-Cloro-*N*-etil-*N*-metil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina



Una solución de 2,4-dicloro-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (150 mg, 0,566 mmol) y *N*-metiletanamina en exceso (0,486 ml, 5,66 mmol) en MeOH (2 ml) se agitó a ta durante 1 h. El disolvente se eliminó a vacío proporcionando 2-cloro-*N*-etil-*N*-metil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (163 mg, 0,566 mmol, 100 % de rendimiento). CL-EM $(M+H)^+$ = 288,2.

Preparación Gd

4-(Azetidin-1-il)-2-cloro-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina

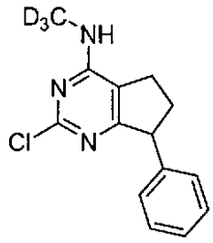


Una solución de 2,4-dicloro-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (150 mg, 0,566 mmol) y azetidina en exceso (162 mg, 2,83 mmol) en metanol (1 ml) se agitó a ta durante 30 min. El disolvente se eliminó a vacío proporcionando 4-(azetidin-1-il)-2-cloro-7-fenil-6,7-dihidro-5*H*-

ciclopenta[*d*]pirimidina (162 mg, 0,567 mmol, 100 % de rendimiento). CL-EM $(M+H)^+$ = 286,3.

Preparación Ge

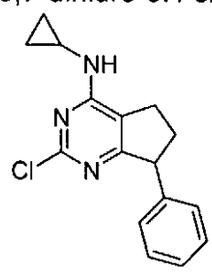
2-Cloro-*N*-trideuterometil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina



A una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (350 mg, 1,236 mmol) y clorhidrato de trideuterometilamina (174 mg, 2,472 mmol) en metanol (3 ml) se añadió DIPEA (0,432 ml, 2,472 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2-cloro-*N*-trideuterometil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina como aceite marrón. CL-EM $(M+H)^+$ = 281,2.

Preparación Gf

2-cloro-N-ciclopropil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina

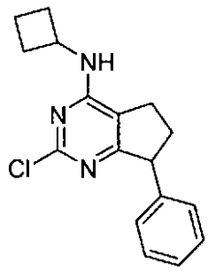


A una solución de 2,4-dicloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina (170 mg, 0,641 mmol) en NMP (2 ml) se añadió

ciclopropanamina (110 mg, 1,924 mmol) gota a gota. La mezcla se agitó a ta durante 3 horas. Se añadieron 8 ml de agua para precipitar el producto. El sólido se separó por filtración y se secó al aire dando una 2-cloro-N-ciclopropil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina bruta (175 mg, 0,612 mmol, 96 % de rendimiento), que se usó para la etapa siguiente sin más purificación. CL-EM $(M+H)^+$ = 286,1

Preparación Gg

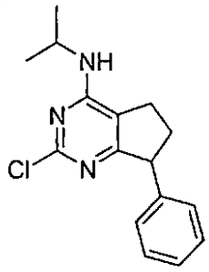
2-cloro-N-ciclobutil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina



A una solución de 2,4-dicloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina (160 mg, 0,60 mmol) en NMP (2 ml) se añadió ciclobutanamina (129 mg, 1,81 mmol) gota a gota. La mezcla se agitó a ta durante 3 hrs. Se añadieron 8 ml de agua para precipitar el producto. El sólido se separó por filtración y se secó al aire dando una 2-cloro-N-ciclobutil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina bruta (177 mg, 0,57 mmol, 94 % de rendimiento), que se usó para la etapa siguiente sin más purificación. CL-EM $(M+H)^+$ = 300,1

Preparación Gh

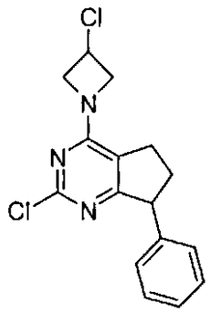
2-cloro-7-fenil-N-isopropil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina



A una solución de 2,4-dicloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina (172 mg, 0,65 mmol) en NMP (2 ml) se añadió propan-2-amina (115 mg, 1,95 mmol) gota a gota. La mezcla se agitó a ta durante 3 hrs. Se añadieron 8 ml de agua para precipitar el producto. El sólido se separó por filtración, se secó al aire y se purificó por Biotage (12 g, hexanos-EtOAc al 70%) dando 2-cloro-N-isopropil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (154 mg, 0,535 mmol, 82 % de rendimiento). RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 7,30 (2 H, t, *J*=7,5 Hz), 7,20 - 7,25 (1 H, m), 7,15 (1 H, d, *J*=1,5 Hz), 7,13 (1 H, s), 4,53 (1 H, d, *J*=7,3 Hz), 4,37 - 4,45 (1 H, m), 4,23 - 4,28 (1 H, m), 2,58 - 2,78 (3 H, m), 2,10 - 2,17 (1 H, m), 1,27 - 1,29 (6 H, m).

Preparación Gi

2-cloro-4-(3-cloroazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina

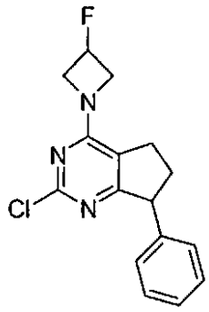


La mezcla de 3-cloroazetidina, HCl (217 mg, 1,697 mmol), 2,4-dicloro-7-

fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina (150 mg, 0,566 mmol) y DIEA (0,395 ml, 2,263 mmol) en N-Metil-2-pirrolidinona (2,0 ml) se agitó a TA durante 3 h. Se añadió agua (8 ml) a la mezcla de reacción. El producto precipitado se filtró, se aclaró con agua se secó al aire. CL-EM $(M+H)^+$ = 320,0. RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 7,21 - 7,39 (m, 3 H) 7,14 (d, *J*=7,02 Hz, 2 H) 4,65 - 4,84 (m, 3 H) 4,34 - 4,48 (m, 2 H) 4,23 (dd, *J*=9,16, 6,41 Hz, 1 H) 3,00 (dd, *J*=8,85, 5,80 Hz, 1 H) 2,83 - 2,93 (m, 1 H) 2,54 - 2,72 (m, 1 H) 2,02 - 2,20 (m, 1 H).

Preparación Gj

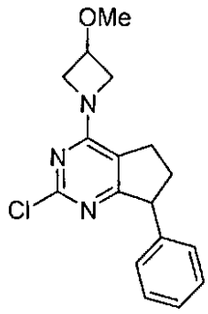
2-cloro-4-(3-fluoroazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina



Se hizo reaccionar 3-fluoroazetidina con la Preparación G en la forma de la Preparación Gi proporcionando el compuesto del epígrafe. CL-EM $(M+H)^+$ = 304,1. RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 7,19 - 7,37 (m, 3 H) 7,15 (d, *J*=7,32 Hz, 2 H) 5,39 – 5,52 (m, 1 H) 4,59 (dddd, *J*=14,88, 10,15, 5,19, 4,88 Hz, 2 H) 4,30 - 4,50 (m, 2 H) 4,23 (dd, *J*=9,00, 6,26 Hz, 1 H) 2,96 - 3,07 (m, 1 H) 2,84 - 2,96 (m, 1 H) 2,56 - 2,70 (m, 1 H) 2,05 - 2,21 (m, 1 H).

Preparación Gk

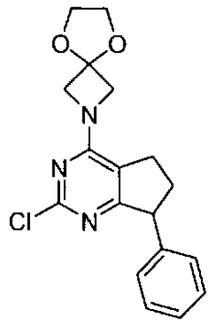
2-cloro-4-(3-metoxiazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina



Se hizo reaccionar 3-metoxiazetidina con la Preparación G en la forma de la Preparación Gi proporcionando el compuesto del epígrafe. CL-EM $(M+H)^+$ = 316,1.

Preparación GI

2-(2-cloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-5,8-dioxa-2-azaspiro[3,4]octano

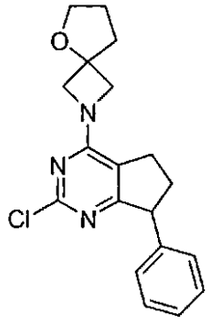


Se hizo reaccionar azetidin-3-ona con la Preparación G en la forma de la Preparación Gi proporcionando 1-(2-cloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)azetidin-3-ona. CL-EM $(M+H)^+$ = 300,0. Se calentó a reflujo durante 24 horas en un aparato de Dean-Stark una mezcla de etilenglicol (119 µl, 2,135 mmol), 1-(2-cloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)azetidin-3-ona (320 mg, 1,068 mmol) y ácido 4-metilbencenosulfónico, H_2O (20,31 mg, 0,107 mmol) en benceno (2965 µl). La mezcla resultante se concentró y se purificó por HPLC Prep proporcionando el

compuesto del epígrafe. CL-EM $(M+H)^+$ = 344,0. RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 7,21 - 7,40 (m, 3 H) 7,15 (d, *J*=7,63 Hz, 2 H) 4,35 - 4,53 (m, 4 H) 4,23 (dd, *J*=9,00, 6,26 Hz, 1 H) 4,03 (s, 4 H) 2,96 - 3,09 (m, 1 H) 2,80 - 2,96 (m, 1 H) 2,51 - 2,70 (m, 1 H) 2,03 - 2,16 (m, 1 H).

Preparación Gm

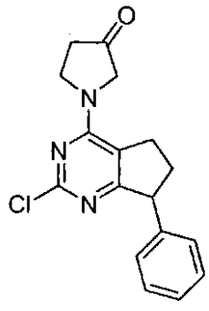
2-(2-cloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-5-oxa-2-azaspiro[3,4]octano



Se hizo reaccionar 5-oxa-2-azaspiro[3,4]octano con la Preparación G en la forma de la Preparación Gi proporcionando el compuesto del epígrafe. CL-EM $(M+H)^+$ = 342,1.

Preparación Gn

1-(2-cloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)pirrolidin-3-ona

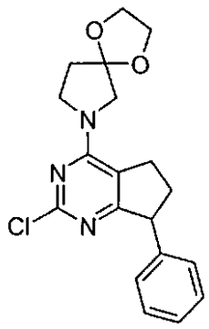


Se hizo reaccionar pirrolidin-3-ona con la Preparación G en la forma de

la Preparación Gi proporcionando el compuesto del epígrafe. CL-EM $(M+H)^+$ = 314,1.

Preparación Go

7-(2-cloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-1,4-dioxa-7-azaspiro[4,4]nonano

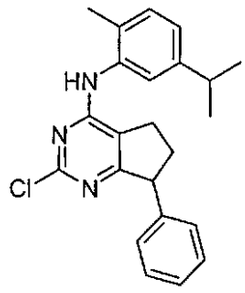


Se calentó a reflujo durante 24 horas en un aparato de Dean-Stark la mezcla de etilenglicol (46,9 µl, 0,841 mmol), 1-(2-cloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)pirrolidin-3-ona (Intermedio Gn) (132 mg, 0,421 mmol) y ácido 4-metilbencenosulfónico, H_2O (8,00 mg, 0,042 mmol) en benceno (1169 µl). La mezcla resultante se concentró y se purificó por HPLC Prep (Columna: PHENOMENEX LUNA C18 30 x100 mm, Disolvente A = Acetato amónico 10 mM en H2O / ACN 95 : 5, Disolvente B = Acetato amónico 10 mM en H2O / ACN 5 : 95. Caudal: 40 ml / min, 30-100, 20 min) obteniendo 7-(2-cloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-1,4-dioxa-7-azaspiro[4,4]nonano (24 mg, 0,067 mmol, 15,94 % de rendimiento). CL-EM $(M+H)^+$ = 358,1. RMN de ^1H (500 MHz, *CLOROFORMO-d*) δ ppm 7,31 (2 H, t, *J*=7,63 Hz), 7,20 - 7,25 (1 H, m), 7,15 (2 H, d, *J*=7,63 Hz), 4,21 (1 H, dd, *J*=9,16, 6,10 Hz), 4,01 - 4,06 (4 H, m), 3,89 - 3,97 (2 H, m), 3,77 - 3,84 (2 H, m), 3,26 (1 H, ddd, *J*=15,03, 8,62, 5,95 Hz), 3,13 (1 H, ddd, *J*=14,95, 8,85, 5,80 Hz), 2,53 - 2,63 (1 H, m), 2,17 (2

H, t, *J*=7,17 Hz), 2,03 - 2,12 (1 H, m).

Preparación Gp

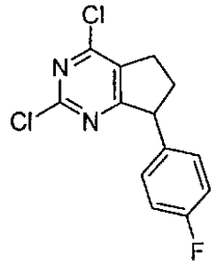
2-cloro-N-(5-isopropil-2-metilfenil)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina



A una solución de 2,4-dicloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina (500 mg, 1,886 mmol) en NMP (Volumen: 7543 µl) se añadió 5-isopropil-2-metilanilina (281 mg, 1,886 mmol) y DIPEA (329 µl, 1,886 mmol). La mezcla resultante se llevó hasta 120 °C y se agitó durante 2 h. La mezcla se diluyó entonces con EtOAc(25 ml), se lavó con agua (2 x 10 ml), salmuera (10 ml), se secó sobre $MgSO_4$, se filtró y se concentró a vacío. La purificación por cromatografía ultrarrápida (Sílice, Thomson 40 g, 0 - 35% EtOAc/Hexanos) dio 2-cloro-N-(5-isopropil-2-metilfenil)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (81421-078-01) (220 mg, 0,582 mmol, 30,9 % de rendimiento). CL-EM $(M+H)^+$ = 378,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,30 - 7,41 (3 H, m), 7,19 - 7,26 (3 H, m), 7,16 (2 H, d, *J*=7,93 Hz), 7,11 (1 H, d, *J*=7,63 Hz), 4,27 (1 H, t, *J*=7,63 Hz), 2,91 (1 H, ddd, *J*=13,89, 6,87, 6,71 Hz), 2,77 - 2,86 (1 H, m), 2,61 - 2,76 (2 H, m), 2,24 (3 H, s), 2,03 - 2,13 (1 H, m), 1,27 (5 H, dd, *J*=7,02, 1,53 Hz).

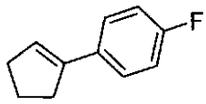
Preparación H

2,4-Dicloro-7-(4-fluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Intermedio H(1)

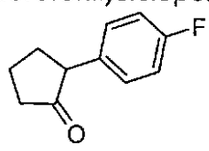
1-Ciclopentenil-4-fluorobenceno



A una solución 0,5 M de 4-fluorobromuro de fenilmagnesio (298 ml, 149 mmol) en THF a 0ºC se añadió cuidadosamente ciclopentanona (13,23 ml, 149 mmol). Una vez terminada la adición, la mezcla de reacción se calentó a reflujo durante 2 h. Se añadieron hielo (10 g) y ácido clorhídrico acuoso 6N. La mezcla de reacción se extrajo con éter. Los extractos orgánicos reunidos se lavaron con una solución acuosa saturada de hidrógeno sulfito sódico, una solución acuosa saturada de bicarbonato sódico y agua. La fase orgánica se secó sobre sulfato de magnesio anhidro y se filtró. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 1-ciclopentenil-4-fluorobenceno (24,155 g, 149 mmol, 100 % de rendimiento) como aceite incoloro. CL-EM $(M+H)^+$ = 163,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,35 - 7,42 (2H, m), 6,95 - 7,02 (2H, m), 6,06 - 6,13 (1H, m), 2,63 - 2,71 (2H, m), 2,47 - 2,56 (2H, m), 1,96 - 2,06 (2H, m).

Intermedio H(2)

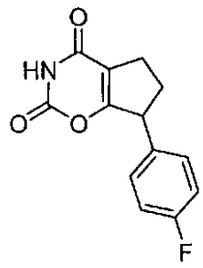
2-(4-Fluorofenil)ciclopentanona



Se calentó a 40ºC durante 10 min una mezcla de ácido fórmico al 80% (100 ml, 2618 mmol) y peróxido de hidrógeno al 30% (23 ml, 149 mmol). La solución resultante se añadió cuidadosamente a 1-ciclopentenil-4-fluorobenceno (24,155 g, 149 mmol) en agitación. El sistema bifásico se agitó inicialmente a temperatura ambiente. Después de un determinado período de tiempo, tuvo lugar una reacción exotérmica espontánea y la temperatura ascendió hasta aproximadamente 50ºC. La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se enfrió mediante la adición cuidadosa de una solución saturada de bicarbonato sódico. Se añadió éter y el contenido del embudo de separación se removió vigorosamente. La fase orgánica se separó y la fase acuosa se extrajo con éter. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2-(4-fluorofenil)ciclopentanona (18,557 g, 104 mmol, 69,9 % de rendimiento) como aceite incoloro. CL-EM $(M+H)^+$ = 177,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,12 - 7,18 (2H, m), 6,98 - 7,04 (2H, m), 3,29 (1H, dd, *J*=11,6, 8,5 Hz), 2,42 - 2,54 (2H, m), 2,27 (1H, ddd, *J*=19,1, 10,5, 8,9 Hz), 2,12 - 2,20 (1H, m), 2,01 - 2,12 (1H, m), 1,87 - 1,99 (1H, m, *J*=11,7, 11,7, 8,2, 6,3 Hz).

Intermedio H(3)

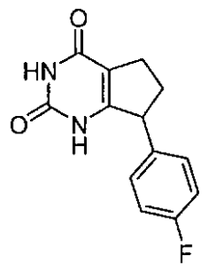
7-(4-Fluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona



Se calentó a 58ºC durante 1 h y a 130ºC durante 2 h una mezcla de 2-(4-fluorofenil)ciclopentanona (18,557 g, 104 mmol) y cloruro carbonisocianatídico (19,77 g, 187 mmol). Tras enfriar hasta temperatura ambiente, la mezcla de reacción ensuciada se disolvió en acetato de etilo y se lavó con solución acuosa saturada de bicarbonato sódico. La fase orgánica se separó y la fase acuosa se extrajo con acetato de etilo. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 7-(4-fluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (13,527 g, 54,7 mmol, 52,5 % de rendimiento) como sólido marrón. CL-EM $(M+H)^+$ = 248,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,80 (1H, s ancho), 7,31 - 7,39 (2H, m), 7,16 - 7,22 (2H, m), 4,30 - 4,38 (1H, m), 2,63 - 2,73 (1H, m), 2,53 - 2,63 (2H, m), 1,84 - 1,95 (1H, m).

Intermedio H(4)

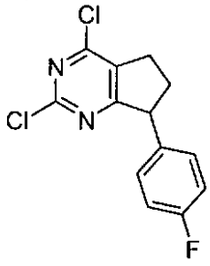
7-(4-Fluorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona



Una solución de 7-(4-fluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (13,527 g, 54,7 mmol) en hidróxido amónico concentrado (150 ml, 3852 mmol) se calentó a 100°C en un recipiente de alta presión (350 ml) durante la noche. La mezcla de reacción se enfrió hasta 0°C y se filtró. El precipitado se lavó consecutivamente con agua y se secó, primero haciendo pasar aire a su través y luego, en una bomba a vacío dando 7-(4-fluorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona (4,670 g, 18,97 mmol, 34,7 % de rendimiento). CL-EM $(M+H)^+$ = 247,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,70 - 11,81 (2H, s ancho), 7,31 - 7,39 (2H, m), 7,16 - 7,22 (2H, m), 4,30 - 4,38 (1H, m), 2,63 - 2,73 (1H, m), 2,53 - 2,63 (2H, m), 1,84 - 1,95 (1H, m).

Preparación H

2,4-Dicloro-7-(4-fluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina

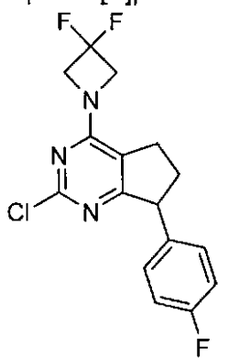


Se agitó a 110 °C durante la noche una solución de 7-(4-fluorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona (1 g, 4,06 mmol) en

oxicloruro de fósforo (11,81 ml, 127 mmol) y *N*,*N*-dimetilanilina (3,94 ml, 31,1 mmol). La mezcla de reacción se vertió cuidadosamente en hielo. Una vez fundido el hielo, la fase acuosa se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (700,0 mg, 2,472 mmol, 60,9 % de rendimiento) como sólido color burdeos oscuro. CL-EM $(M+H)^+$ = 283,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,09 - 7,15 (2H, m), 7,03 (2H, t, *J*=8,5 Hz), 4,42 (1H, t, *J*=8,4 Hz), 3,10 (1H, dd, *J*=9,2, 4,6 Hz), 3,01 (1H, d, *J*=8,2 Hz), 2,73 (1H, d, *J*=8,9 Hz), 2,15 - 2,27 (1H, m).

Preparación Ha

2-cloro-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina

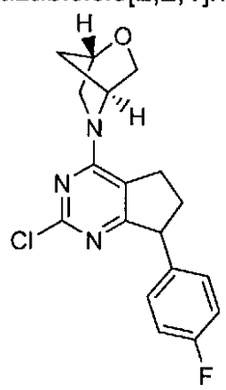


A una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (521 mg, 1,840 mmol) en MeOH (18,400 ml) se añadió DIPEA (0,803 ml, 4,60 mmol), luego 3,3-difluoroazetidina, HCl (358 mg, 2,76 mmol). Se dejó agitar la reacción a ta

durante 2 h y luego se concentró a vacío. La purificación por cromatografía ultrarrápida (sílice, acetato de etilo/hexanos) dio 2-cloro-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (528 mg, 1,554 mmol, 84 % de rendimiento) como un aceite incoloro transparente que cristalizó en reposo. CL-EM $(M+H)^+$ = 340,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,05 - 7,13 (2 H, m), 6,94 - 7,02 (2 H, m), 4,60 (4 H, td, *J*=11,75, 4,27 Hz), 4,18 - 4,30 (1 H, m), 2,93 - 3,06 (1 H, m), 2,80 - 2,95 (1 H, m), 2,56 - 2,70 (1 H, m), 1,96 - 2,18 (1 H, m).

Preparación Hb

(1S,4S)-5-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-2-oxa-5-azabiciclo[2,2,1]heptano

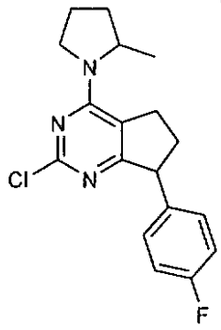


A una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (200 mg, 0,706 mmol) en MeOH (7064 µl) se añadió monoclorhidrato de (1S,4S)-2-oxa-5-azabiciclo[2,2,1]heptano (115 mg, 0,848 mmol) y DIPEA (271 µl, 1,554 mmol). La mezcla resultante se agitó a ta durante la noche. La mezcla de reacción luego se concentró a vacío. El aceite resultante se purificó por cromatografía ultrarrápida (sílice, EtOAc/Hexanos) dando (1S,4S)-5-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-

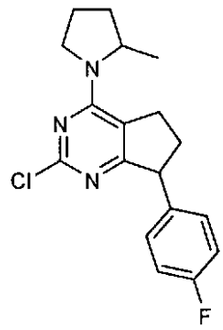
ciclopenta[d]pirimidin-4-il)-2-oxa-5-azabiciclo[2,2,1]heptano (148 mg, 0,428 mmol, 60,6 % de rendimiento). CL-EM $(M+H)^+$ = 346,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,12 - 7,21 (2 H, m), 7,00 - 7,08 (2 H, m), 5,11 - 5,21 (1 H, m), 4,69 - 4,74 (1 H, m), 4,15 - 4,26 (1 H, m), 3,88 - 3,94 (2 H, m), 3,68 - 3,86 (2 H, m), 3,11 - 3,21 (1 H, m), 2,56 - 2,69 (1 H, m), 1,92 - 2,11 (2 H, m), 1,24 - 1,42 (2 H, m).

Preparaciones Hc1 y Hc2

2-cloro-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidina



Hc1
Diastereómero 1
Racémico



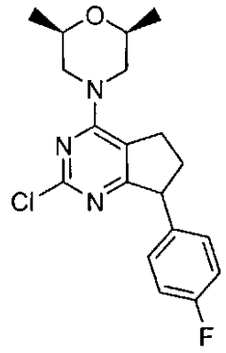
Hc2
Diastereómero 2
Racémico

A una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación *H*) (200 mg, 0,706 mmol) en MeOH (7064 µl) se añadió 2-metilpirrolidina (82 µl, 0,848 mmol). La mezcla resultante se agitó a ta durante 2 días. La mezcla de reacción luego se concentró a vacío. El aceite resultante se purificó por cromatografía ultrarrápida (sílice, EtOAc/Hexanos) dando dos parejas racémicas de diastereómeros 2-cloro-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidina. (*Hc1*, Diastereómero 1, racémico, primero en eluir) (79,5 mg, 0,240 mmol, 33,9 % de

rendimiento). CL-EM $(M+H)^+$ = 332,1; RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,16 (2 H, d, *J*=5,49 Hz), 7,04 (2 H, s), 4,42 - 4,54 (1 H, m), 4,09 - 4,22 (1 H, m), 3,86 - 4,00 (1 H, m), 3,71 - 3,82 (1 H, m), 3,24 - 3,31 (1 H, m), 3,10 - 3,22 (1 H, m), 2,54 - 2,65 (1 H, m), 2,05 - 2,16 (2 H, m), 1,94 - 2,05 (2 H, m), 1,69 - 1,80 (1 H, m), 1,27 (3 H, d, *J*=6,10 Hz). (*Hc2*, Diastereómero 2, racémico, segundo en eluir) (89,5 mg, 0,270 mmol, 38 % de rendimiento). CL-EM $(M+H)^+$ = 332,1; RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,14 (2 H, d, *J*=5,49 Hz), 6,99 - 7,08 (2 H, m), 4,42 - 4,54 (1 H, m), 4,13 - 4,22 (1 H, m), 3,86 - 4,00 (1 H, m), 3,71 - 3,83 (1 H, m), 3,25 - 3,32 (1 H, m), 3,14 - 3,25 (1 H, m), 2,52 - 2,67 (1 H, m), 2,05 - 2,19 (2 H, m), 1,94 - 2,05 (2 H, m), 1,68 - 1,78 (1 H, m), 1,19 - 1,32 (3 H, m). No se determinó la estereoquímica relativa para *Hc1* y *Hc2*.

Preparación Hd

(2S,6R)-4-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-2,6-dimetilmorfolina

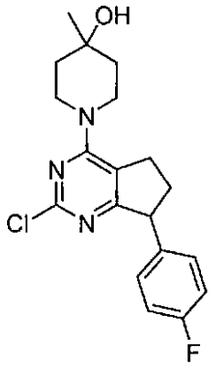


A una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (200 mg, 0,706 mmol) en MeOH (7064 µl) se añadió cis-2,6-dimetilmorfolina (105 µl, 0,848 mmol). La mezcla resultante se agitó a ta durante la noche. Se añadieron entonces otros 2

equivalentes de cis-2,6-dimetilmorfolina y la mezcla se agitó de nuevo durante la noche a ta. La mezcla de reacción luego se concentró a vacío. El aceite resultante se purificó por cromatografía ultrarrápida (sílice, EtOAc/Hexanos) dando (2S,6R)-4-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-2,6-dimetilmorfolina (223 mg, 0,616 mmol, 87 % de rendimiento). CL-EM $(M+H)^+$ = 332,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,11 - 7,24 (2 H, m), 6,99 - 7,09 (2 H, m), 4,39 - 4,51 (2 H, m), 4,20 (1 H, s), 3,70 (2 H, td, *J*=4,12, 2,44 Hz), 3,14 - 3,25 (1 H, m), 3,03 - 3,13 (1 H, m), 2,69 - 2,80 (2 H, m), 2,54 - 2,68 (1 H, m), 1,95 - 2,13 (1 H, m), 1,23 (6 H, d, *J*=6,10 Hz).

Preparación He

1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-4-metilpiperidin-4-ol

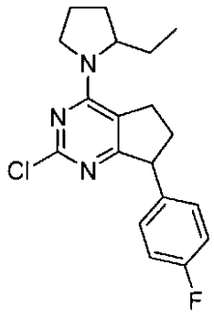


A una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (400 mg, 1,413 mmol) en MeOH (14,100 ml) se añadió 4-metilpiperidin-4-ol (163 mg, 1,413 mmol). La mezcla resultante se agitó a ta durante la noche. La mezcla de reacción luego se concentró a vacío. La purificación por cromatografía ultrarrápida (sílice, EtOAc/Hexanos) dio 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-

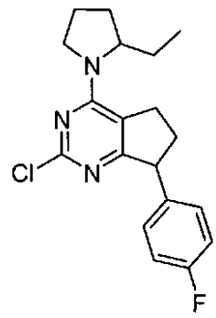
ciclopenta[d]pirimidin-4-il)-4-metilpiperidin-4-ol (374 mg, 1,034 mmol, 73,2 % de rendimiento). CL-EM $(M+H)^+$ = 362,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,12 - 7,21 (2 H, m), 7,04 (2 H, t, *J*=8,85 Hz), 4,11 - 4,30 (3 H, m), 3,48 - 3,63 (2 H, m), 3,14 - 3,23 (1 H, m), 3,00 - 3,12 (1 H, m), 2,54 - 2,66 (1 H, m), 1,94 - 2,09 (1 H, m), 1,68 (4 H, t, *J*=4,12 Hz), 1,28 (3 H, s).

Preparaciones Hf1 y Hf2

2-cloro-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina



Hf1
Diastereómero 1
Racémico



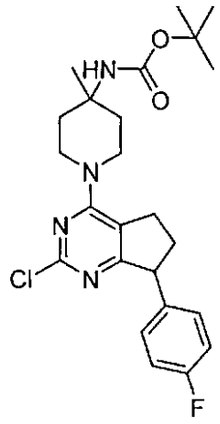
Hf2
Diastereómero 2
Racémico

Se combinaron 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (200 mg, 0,706 mmol) y 2-etilpirrolidina (84 mg, 0,848 mmol) y se purificaron según la *Preparación Hd* dando dos parejas de diastereómeros racémicos 2-cloro-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina. (*Hf1*, Diastereómero 1, racémico, primero en eluir) (77 mg, 0,223 mmol, 32% de rendimiento) CL-EM $(M+H)^+$ = 346. (*Hf2*, Diastereómero 2, racémico, segundo en eluir) (80 mg, 0,232 mmol, 33% de rendimiento); CL-EM $(M+H)^+$ = 346,2. No se determinó la

estereoquímica relativa para *Hf1* y *Hf2*.

Preparación Hg

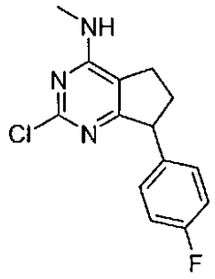
1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-4-metilpiperidin-4-ilcarbamato de terc-butilo



A una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (400 mg, 1,413 mmol) en MeOH (14,100 ml) se añadió 4-metilpiperidin-4-ilcarbamato de terc-butilo (303 mg, 1,413 mmol). La mezcla resultante se agitó a ta durante 7 días. En este momento, la mezcla de reacción se concentró a vacío. La purificación por cromatografía ultrarrápida (sílice, EtOAc/Hexanos) dio 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-4-metilpiperidin-4-ilcarbamato de terc-butilo (159 mg, 0,345 mmol, 24,41 % de rendimiento) como una espuma amarilla. CL-EM $(M+H)^+$ = 461,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,12 - 7,22 (2 H, m), 6,98 - 7,09 (2 H, m), 4,19 (3 H, d, *J*=2,14 Hz), 3,38 - 3,56 (2 H, m), 3,13 - 3,25 (1 H, m), 3,02 - 3,13 (1 H, m), 2,53 - 2,67 (1 H, m), 2,11 - 2,24 (2 H, m), 1,96 - 2,08 (1 H, m), 1,53 - 1,65 (2 H, m), 1,47 (9 H, s), 1,37 (3 H, s).

Preparación Hh

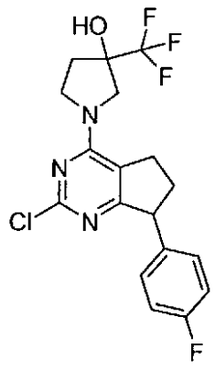
2-cloro-7-(4-fluorofenil)-N-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina



Se combinaron 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (500 mg, 1,766 mmol) y clorhidrato de metanamina (179 mg, 2,65 mmol) y se purificó según la *Preparación Ha* dando 2-cloro-7-(4-fluorofenil)-N-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (344 mg, 1,239 mmol, 70,1 % de rendimiento). CL-EM $(M+H)^+$ = 278,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,03 - 7,12 (2 H, m), 6,91 - 7,03 (2 H, m), 4,53 - 4,79 (1 H, m), 4,19 - 4,29 (1 H, m), 3,09 (3 H, d, *J*=4,88 Hz), 2,56 - 2,80 (3 H, m), 2,00 - 2,15 (1 H, m).

Preparación Hi

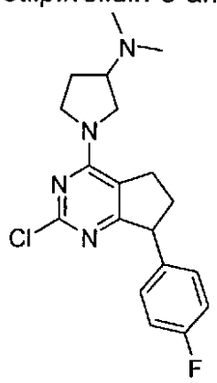
1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol



Se combinaron 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (286 mg, 1,010 mmol) y 3-(trifluorometil)pirrolidin-3-ol (157 mg, 1,010 mmol) y se purificó según la *Preparación Hb* dando 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol (62% de rendimiento). CL-EM $(M+H)^+$ = 402,0.

Preparación Hj

1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N,N-dimetilpirrolidin-3-amina

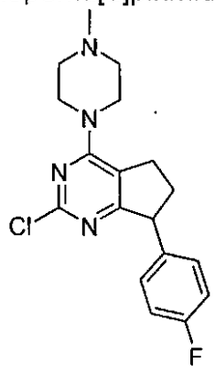


Se combinaron 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (100 mg, 0,353 mmol) y N,N-dimetilpirrolidin-3-amina (44,3 µl, 0,353 mmol) y se purificó según la

Preparación Hb dando 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N,N-dimetilpirrolidin-3-amina (109 mg, 86% de rendimiento). CL-EM $(M+H)^+$ = 361,2.

Preparación Hk

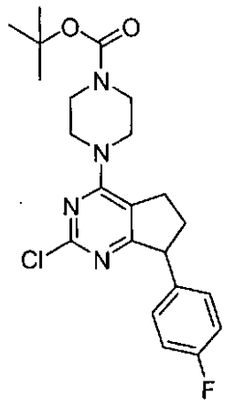
2-cloro-7-(4-fluorofenil)-4-(4-metilpiperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidina



Se combinaron 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (100 mg, 0,353 mmol) y 1-metilpiperazina (39,2 µl, 0,353 mmol) y se purificó según la *Preparación Hb* dando 2-cloro-7-(4-fluorofenil)-4-(4-metilpiperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidina(109 mg, 0,314 mmol, 89 % de rendimiento). CL-EM $(M+H)^+$ = 347,2.

Preparación Hl

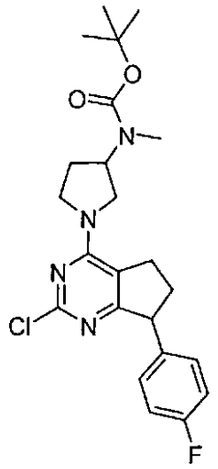
4-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)piperazin-1-carboxilato de terc-butilo



Se combinaron 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (100 mg, 0,353 mmol) y 1-piperazincarboxilato de terc-butilo (65,8 mg, 0,353 mmol) y se purificó según la *Preparación Hb* dando 4-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)piperazin-1-carboxilato de terc-butilo (116,9 mg, 76% de rendimiento). CL-EM $(M+H)^+$ = 433,3.

Preparación Hm

1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)pirrolidin-3-il(metil)carbamato de terc-butilo

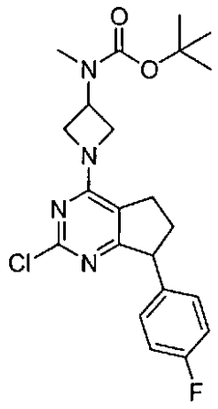


Se combinaron 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-

ciclopenta[d]pirimidina (*Preparación H*) (100 mg, 0,353 mmol) y 3-(N-terc-Butoxicarbonil-N-metilamino)pirrolidina (69,4 µl, 0,353 mmol) y se purificó según la *Preparación Hb* dando 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)pirrolidin-3-il(metil)carbamato de terc-butilo (148 mg, 94% de rendimiento). CL-EM $(M+H)^+$ = 447,2.

Preparación Hn

1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)azetidin-3-il(metil)carbamato de terc-butilo

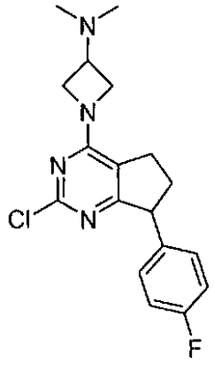


Se combinaron 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (100 mg, 0,353 mmol) y ácido carbámico, 3-azetidinilmetil-, éster 1,1-dimetiletílico (82 mg, 0,441 mmol) y se purificó según la *Preparación Hb* dando 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)azetidin-3-il(metil)carbamato de terc-butilo (147 mg, 96% de rendimiento). CL-EM $(M+H)^+$ = 377,1.

Preparación Ho

1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N,N-

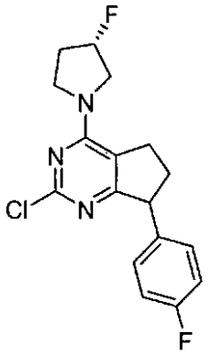
dimetilazetidin-3-amina



Se combinaron 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación H*) (100 mg, 0,353 mmol) y N,N-dimetilazetidin-3-amina, 2 HCl (122 mg, 0,706 mmol) y se purificó según la *Preparación Hb* dando 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N,N-dimetilazetidin-3-amina (cuantitativo). CL-EM $(M+H)^+$ = 347,2.

Preparación Hp1 y Hp2

2-cloro-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-6,7-dihidro-5H ciclopenta[d]pirimidina

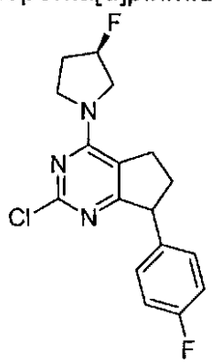


A una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación H) (135 mg, 0,477 mmol) en MeOH (4768

µl) se añadió DIPEA (208 µl, 1,192 mmol), luego (S)-3-fluoropirrolidina (46,7 mg, 0,524 mmol). Se dejó agitar la reacción a temperatura ambiente durante 2 h. Se eliminó el disolvente y el residuo se aplicó a gel de sílice y eluyó con un gradiente de EtOAc/Hex proporcionando dos diastereómeros (Hp1 y Hp2). Hp1: CL-EM $(M+H)^+$ = 336,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,06 - 7,13 (2 H, m), 6,93 - 7,00 (2 H, m), 5,32 (1 H, td, *J*=52,57, 3,17 Hz), 4,17 (1 H, dd, *J*=9,16, 5,49 Hz), 4,06 - 4,14 (1 H, m), 3,98 - 4,06 (1 H, m), 3,76 - 3,90 (2 H, m), 3,25 (1 H, ddd, *J*=15,11, 8,55, 6,26 Hz), 3,08 - 3,16 (1 H, m), 2,51 - 2,60 (1 H, m, *J*=13,20, 9,12, 9,12, 6,41 Hz), 2,32 - 2,42 (1 H, m), 2,00 - 2,17 (2 H, m). Hp2: CL-EM $(M+H)^+$ = 336,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,06 - 7,14 (2 H, m), 6,94 - 7,02 (2 H, m), 5,25 - 5,40 (1 H, m), 3,99 - 4,24 (3 H, m), 3,75 - 3,92 (2 H, m), 3,19 - 3,28 (1 H, m), 3,10 - 3,19 (1 H, m), 2,57 (1 H, dddd, *J*=13,24, 8,74, 8,55, 4,58 Hz), 2,31 - 2,43 (1 H, m), 1,94 - 2,17 (2 H, m)

Preparación Hq

2-cloro-7-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-6,7-dihidro-5H ciclopenta[d]pirimidina



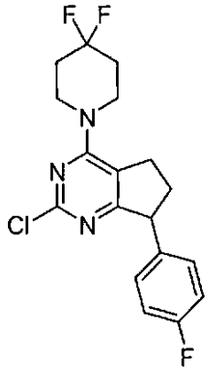
Se hizo reaccionar 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación H) como se describe en la Preparación

Hp1 y Hp2 con (R)-3-fluoropirrolidina. Se eliminó el disolvente y el residuo se aplicó a gel de sílice y eluyó con un gradiente de EtOAc/Hex proporcionando los dos diastereómeros combinados (Hq).

Ha1: CL-EM $(M+H)^+$ = 336,0.

Preparación Hr

2-cloro-4-(4,4-difluoropiperidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina

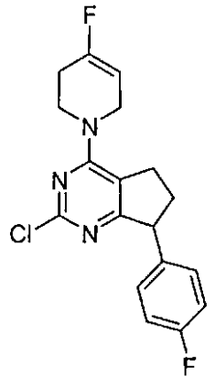


A una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación H) (90 mg, 0,318 mmol) en MeOH (3179 µl), se añadió 4,4-difluoropiperidina (115 mg, 0,95 mmol). Se dejó agitar la reacción a ta. Cuando se completó la reacción, se eliminó el disolvente y se aplicó el residuo a gel de sílice. Se eluyó con EtOAc/Hex proporcionando la 2-cloro-4-(4,4-difluoropiperidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina deseada (80,8 mg, 0,220 mmol, 69,1 % de rendimiento). CL-EM $(M+H)^+$ = 368,0.

Preparación Hs

2-cloro-4-(4-fluoro-5,6-dihidropiridin-1(2H)-il)-7-(4-fluorofenil)-6,7-dihidro-5H-

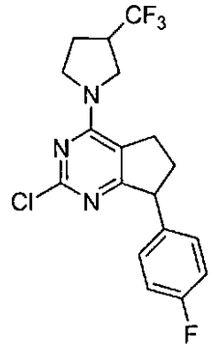
ciclopenta[d]pirimidina



Se hizo reaccionar 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación H) como se describe en la Preparación Hc con 4-fluoro-1,2,3,6-tetrahidropiridina proporcionando 2-cloro-4-(4-fluoro-5,6-dihidropiridin-1(2H)-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación Hs).

Preparación Ht

2-cloro-7-(4-fluorofenil)-4-(3-(trifluorometil)pirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina

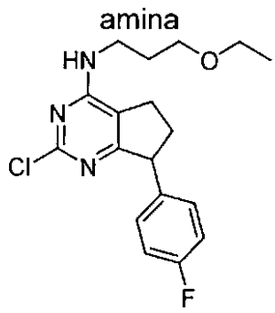


Se hizo reaccionar 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación H) como se describe en la Preparación *Hr* con 3-trifluorometilpirrolidina proporcionando 2-cloro-7-(4-fluorofenil)-4-(3-

(trifluorometil)pirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación Ht) como una mezcla de 4 diastereómeros. CL-EM $(M+H)^+$ = 386,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,05 - 7,11 (2 H, m), 6,96 (2 H, t, *J*=8,70 Hz), 4,14 - 4,20 (1 H, m), 3,89 - 4,02 (2 H, m), 3,75 - 3,86 (2 H, m), 3,17 - 3,28 (1 H, m), 3,06 - 3,16 (1 H, m), 2,99 (1 H, dc, *J*=15,95, 8,01 Hz), 2,50 - 2,61 (1 H, m), 2,13 - 2,30 (2 H, m), 1,95 - 2,06 (1 H, m)

Preparación Hu

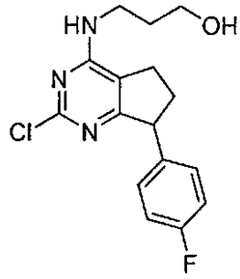
2-cloro-N-(3-etoxipropil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina



Se hizo reaccionar 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación H) como se describe en la Preparación Hr con 3-etoxipropan-1-amina proporcionando 2-cloro-N-(3-etoxipropil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (Preparación Hu). CL-EM $(M+H)^+$ = 350,1.

Preparación Hv

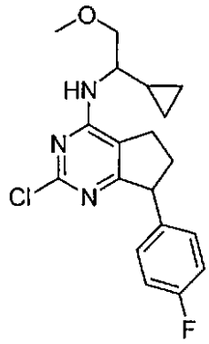
3-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-ilamino)propan-1-ol



Se hizo reaccionar 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación H) como se describe en la Preparación Hr con 3-hidroxipropan-1-amina proporcionando 3-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-ilamino)propan-1-ol (Preparación Hv). CL-EM $(M+H)^+$ = 322,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,08 (2 H, dd, J=8,55, 5,49 Hz), 6,97 (2 H, t, J=8,70 Hz), 5,18 (1 H, s ancho), 4,22 - 4,27 (1 H, m), 3,66 - 3,75 (4 H, m), 3,18 (1 H, s ancho), 2,60 - 2,77 (3 H, m), 2,02 - 2,12 (1 H, m), 1,78 - 1,86 (2 H, m)

Preparación Hw

2-cloro-N-(1-ciclopropil-2-metoxietil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina

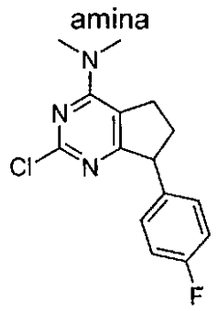


Se hizo reaccionar 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación H) como se describe en la Preparación Hr con 1-ciclopropil-2-metoxietanamina proporcionando 2-cloro-N-(1-ciclopropil-2-

metoxietil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (Preparación Hw) como una mezcla de 4 diastereómeros. CL-EM $(M+H)^+$ = 362,1.

Preparación Hx

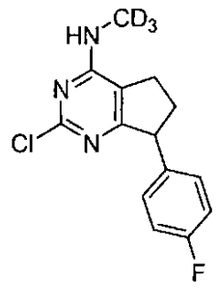
2-Cloro-7-(4-fluorofenil)-*N*,*N*-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina



Una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (260 mg, 0,918 mmol) y dimetilamina en exceso (4,59 ml, 9,18 mmol) en metanol (2 ml) se agitó a ta durante 30 min. El disolvente se eliminó a vacío proporcionando 2-cloro-7-(4-fluorofenil)-*N*,*N*-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina bruta (268 mg, 0,919 mmol, 100 % de rendimiento). CL-EM $(M+H)^+$ = 292,3.

Preparación Hy

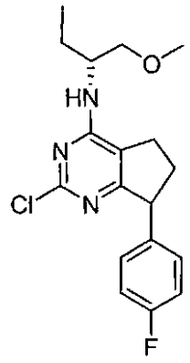
2-Cloro-7-(4-fluorofenil)-*N*-trideuterometil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina



A una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (350 mg, 1,236 mmol) y clorhidrato de trideuterometilamina (174 mg, 2,472 mmol) en metanol (3 ml) se añadió DIPEA (0,432 ml, 2,472 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (350 mg, 1,236 mmol) como aceite marrón. CL-EM $(M+H)^+$ = 281,2.

Preparación Hz

2-cloro-7-(4-fluorofenil)-N-((R)-1-metoxibutan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina

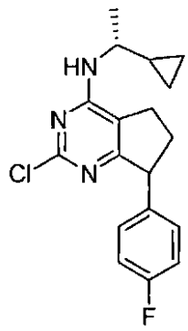


A una mezcla de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación H) (100 mg, 0,353 mmol) en THF (1766 µl)

se añadió (R)-1-metoxibutan-2-amina, HCl (197 mg, 1,413 mmol) y DIEA (493 µl, 2,83 mmol). La mezcla se calentó a 60 °C durante 3 días. El producto bruto se purificó por HPLC preparativa obteniendo 2-cloro-7-(4-fluorofenil)-N-((R)-1-metoxibutan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (Preparación Hz) (78 mg, 0,223 mmol, 63,1 % de rendimiento). CL-EM $(M+H)^+$ = 350,4. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,12 (dd, J=8,24, 5,49 Hz, 2 H) 6,87 - 7,05 (m, 2 H) 4,86 (d, J=7,63 Hz, 1 H) 4,35 (d, J=3,05 Hz, 1 H) 4,18 - 4,30 (m, 1 H) 3,47 - 3,60 (m, 2 H) 3,40 (d, J=6,71 Hz, 3 H) 2,62 - 2,82 (m, 3 H) 2,03 - 2,15 (m, 1 H) 1,58 - 1,78 (m, 2 H) 0,89 - 1,07 (m, 3 H).

Preparación Haa

2-cloro-N-((R)-1-ciclopropiletil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina

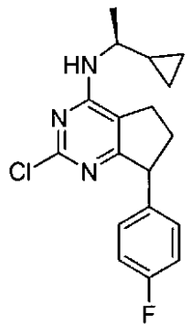


A una solución de 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación H) (100 mg, 0,353 mmol) en THF (1766 µl) se añadió (R)-1-ciclopropiletanamina, HCl (172 mg, 1,413 mmol) y DIEA (493 µl, 2,83 mmol). La mezcla se agitó a 60 °C durante 5 días. El producto bruto se purificó por HPLC preparativa obteniendo 2-cloro-N-((R)-1-ciclopropiletil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (Preparación Haa) (74

mg, 0,223 mmol, 63,1 % de rendimiento). CL-EM $(M+H)^+$ = 332,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,06 - 7,18 (m, 2 H) 7,00 (td, J=8,70, 1,53 Hz, 2 H) 4,65 (d, J=5,80 Hz, 1 H) 4,26 (t, J=7,17 Hz, 1 H) 3,63 - 3,79 (m, 1 H) 2,62 - 2,82 (m, 3 H) 2,04 - 2,16 (m, 1 H) 1,26 - 1,40 (m, 3 H) 0,94 (cd, J=8,24, 3,36 Hz, 1 H) 0,42 - 0,62 (m, 3 H) 0,24 - 0,40 (m, 1 H).

Preparación Hab

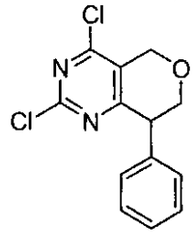
2-cloro-N-((S)-1-ciclopropiletil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina



Se hizo reaccionar 2,4-dicloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación H) como se describe en la Preparación Haa con (S)-1-ciclopropiletanamina, HCl dando 2-cloro-N-((S)-1-ciclopropiletil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (Preparación Hab). CL-EM $(M+H)^+$ = 332,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,07 - 7,21 (m, 2 H) 6,93 - 7,07 (m, 2 H) 4,65 (d, J=5,80 Hz, 1 H) 4,26 (t, J=7,32 Hz, 1 H) 3,61 - 3,79 (m, 1 H) 2,62 - 2,82 (m, 3 H) 2,05 - 2,16 (m, 1 H) 1,25 - 1,39 (m, 3 H) 0,84 - 1,00 (m, 1 H) 0,42 - 0,62 (m, 3 H) 0,29 - 0,40 (m, 1 H).

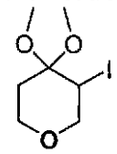
Preparación I

2,4-dicloro-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina



Intermedio I(1)

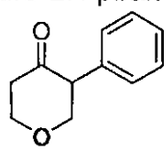
3-yodo-4,4-dimetoxitetrahidro-2H-pirano



A una mezcla de tetrahidro-4H-piran-4-ona (18,52 ml, 200 mmol) y ortoformiato de trimetilo (100 ml, 914 mmol) a 0ºC se añadió yodo (49,2 ml, 200 mmol) lentamente durante 10 min. Cuando se completó la adición, la mezcla de reacción se dejó agitar a 0ºC durante 30 minutos y luego se dejó llegar hasta ta y se agitó hasta que la TLC indicó que se había consumido todo el material de partida (aproximadamente1 h). La reacción se enfrió entonces hasta 0ºC y se enfrió mediante la adición lenta de tiosulfato sódico acuoso saturado (300 ml). La mezcla resultante se extrajo con EtOAc (3 x 75 ml). Las fases orgánicas reunidas se lavaron con salmuera (100 ml), se secaron sobre $MgSO_4$, se filtraron y se concentraron a vacío. La purificación por cromatografía ultrarrápida (sílice, EtOAc/Hexanos) dio 3-yodo-4,4-dimetoxitetrahidro-2H-pirano (43,95 g, 162 mmol, 81 % de rendimiento) como un aceite amarillo. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 4,25 (1 H, c, *J*=2,44 Hz), 3,93 - 4,01 (1 H, m), 3,84 - 3,93 (2 H, m), 3,57 (1 H, td, *J*=11,75, 2,44 Hz), 3,19 - 3,30 (6 H, m), 2,34 (1 H, ddd, *J*=14,34, 12,21, 4,88 Hz), 1,80 (1 H, dc, *J*=14,34, 2,44 Hz).

Intermedio I(2)

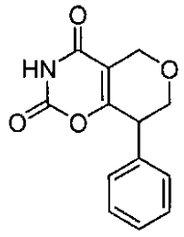
3-fenildihidro-2H-piran-4(3H)-ona



A una mezcla agitada de ácido fenilborónico (16,81 g, 138 mmol), clorhidrato de trans-2-aminociclohexanol (1,393 g, 9,19 mmol) y cloruro de níquel(II) hexahidratado (1,092 g, 4,59 mmol) en THF (92 ml) a 0°C se añadió bis(trimetilsilil)amida de sodio (1,0 M en THF) (184 ml, 184 mmol) gota a gota durante 10 min. Cuando se completó la adición, la mezcla de reacción se purgó con N_2 durante 15 min. A la mezcla de reacción a 0°C se añadió entonces 2-propanol (375 ml) (previamente purgada con N_2). La mezcla resultante se dejó llegar hasta ta, momento en el que se añadió gota a gota durante 5 minutos 3-yodo-4,4-dimetoxitetrahidro-2H-pirano (Intermedio I(1)) (25 g, 92 mmol). La mezcla de reacción se llevó entonces hasta 60°C y se agitó durante la noche. La mezcla de reacción se enfrió entonces hasta 0°C y se enfrió mediante la adición cuidadosa de HCl acuoso 1 N hasta un valor ácido. La mezcla resultante se extrajo con EtOAc (3 x 150 ml). Los extractos orgánicos reunidos se lavaron con salmuera (100 ml), se secaron sobre $MgSO_4$, se filtraron y se concentraron a vacío. La purificación por cromatografía ultrarrápida (sílice, EtOAc/Hexanos) dio 3-fenildihidro-2H-piran-4(3H)-ona (8,37 g, 47,5 mmol, 51,7 % de rendimiento) como un aceite ligeramente naranja. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,32 - 7,39 (2 H, m), 7,26 - 7,31 (1 H, m), 7,21 - 7,26 (2 H, m), 4,17 - 4,31 (2 H, m), 3,91 - 4,05 (2 H, m), 3,78 (1 H, dd, *J*=8,55, 6,10 Hz), 2,61 - 2,74 (1 H, m), 2,51 - 2,61 (1 H, m).

Intermedio I(3)

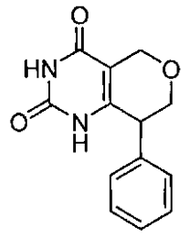
8-fenil-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona



Una mezcla de 3-fenildihidro-2H-piran-4(3H)-ona (Intermedio I(2)) (3 g, 17,02 mmol) y cloruro carbonisocianatídico (10,48 g, 29,8 mmol) en un tubo herméticamente cerrado se calentó hasta 58ºC y se agitó durante 1 h. La mezcla se llevó entonces hasta 130ºC y se agitó durante otras 2 h. La reacción viró a color negro durante este tiempo. Después de enfriar hasta ta, se suspendió el alquitrán en EtOAc (100 ml). La solución resultante se lavó con bicarbonato sódico acuoso saturado (2 x 50 ml), salmuera (50 ml), se secó sobre $MgSO_4$, se filtró y se concentró a vacío. La purificación por cromatografía ultrarrápida (sílice, EtOAc/Hexanos) dio 8-fenil-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona (2,58 g, 10,52 mmol, 61,8 % de rendimiento) como un sólido marrón. CL-EM $(M+H)^+$ = 246,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,34 - 7,41 (4 H, m), 7,29 - 7,34 (1 H, m), 4,42 - 4,63 (2 H, m), 4,08 - 4,15 (1 H, m), 3,94 (1 H, dd, *J*=11,44, 4,12 Hz), 3,85 (1 H, ddd, *J*=4,20, 2,44, 2,21 Hz).

Intermedio I(4)

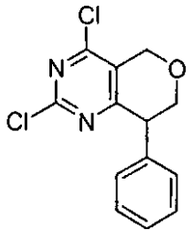
8-fenil-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona



Una solución de 8-fenil-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona (Intermedio I(3)) (2,58 g, 10,52 mmol) en hidróxido amónico (28,7 ml, 736 mmol) se calentó hasta 80 °C en un tubo herméticamente cerrado y se agitó durante la noche. La mezcla de reacción luego se concentró hasta sequedad dando 8-fenil-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona. El material bruto se llevó tal cual. CL-EM $(M+H)^+$ = 245,2.

Preparación I

2,4-dicloro-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina

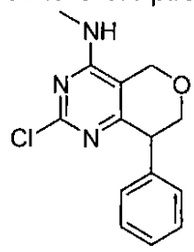


Una mezcla de 8-fenil-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona (Intermedio I(4)) (2569 mg, 10,52 mmol) y $POCl_3$ (29,400 ml, 315 mmol) se calentó hasta 100 °C bajo radiación de microondas en un tubo herméticamente cerrado durante 1h. La mezcla resultante se vertió sobre hielo. Cuando se hubo fundido todo el hielo, la mezcla se extrajo con EtOAc (3 x 15 ml). Los extractos orgánicos reunidos se lavaron con salmuera (20 ml), se secaron sobre $MgSO_4$, se filtraron y se concentraron a vacío. La purificación por cromatografía ultrarrápida (sílice, EtOAc/Hexanos) dio 2,4-dicloro-8-fenil-

7,8-dihidro-5H-pirano[4,3-d]pirimidina (194 mg, 0,690 mmol, 6,56 % de rendimiento). CL-EM $(M+H)^+$ = 281,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,30 - 7,37 (2 H, m), 7,25 - 7,30 (1 H, m), 7,18 - 7,25 (2 H, m), 4,90 - 5,00 (1 H, m), 4,75 - 4,84 (1 H, m), 4,16 - 4,26 (2 H, m), 4,02 - 4,15 (1 H, m).

Preparación Ia

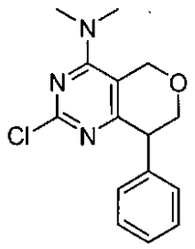
2-cloro-N-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



A una solución de 2,4-dicloro-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación I) (194 mg, 0,690 mmol) en MeOH (6901 µl) se añadió clorhidrato de metanamina (69,9 mg, 1,035 mmol) y N,N-diisopropiletilamina (301 µl, 1,725 mmol). La mezcla resultante se agitó a ta durante 2 h. La mezcla de reacción luego se concentró a vacío. La purificación por cromatografía ultrarrápida (sílice, EtOAc/Hexanos) dio 2-cloro-N-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (126 mg, 0,457 mmol, 66,2 % de rendimiento). CL-EM $(M+H)^+$ = 276,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,28 (2 H, t, *J*=7,32 Hz), 7,20 - 7,25 (1 H, m), 7,14 - 7,20 (2 H, m), 4,47 - 4,62 (2 H, m), 4,47 (1 H, s), 4,00 - 4,11 (2 H, m), 3,95 (1 H, d, *J*=3,36 Hz), 3,08 (3 H, d, *J*=4,88 Hz).

Preparación Ib

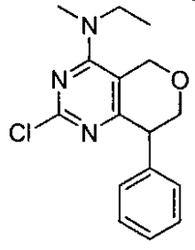
2-Cloro-*N*,*N*-dimetil-8-fenil-7,8-dihidro-5*H*-pirano[4,3-*d*]pirimidin-4-amina



Se agitó a ta durante 1,5 h una solución de 2,4-dicloro-8-fenil-7,8-dihidro-5*H*-pirano[4,3-*d*]pirimidina (135 mg, 0,480 mmol) y dimetilamina en exceso (216 mg, 4,80 mmol) en MeOH (2 ml). El disolvente se eliminó a vacío proporcionando 2-cloro-*N*,*N*-dimetil-8-fenil-7,8-dihidro-5*H*-pirano[4,3-*d*]pirimidin-4-amina (139 mg, 0,480 mmol, 100 % de rendimiento). CL-EM $(M+H)^+$ = 290,3.

Preparación Ic

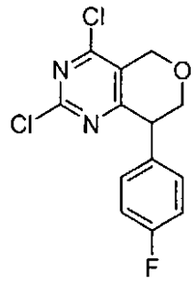
2-Cloro-*N*-etil-*N*-metil-8-fenil-7,8-dihidro-5*H*-pirano[4,3-*d*]pirimidin-4-amina



Se agitó a ta durante 1 h una solución de 2,4-dicloro-8-fenil-7,8-dihidro-5*H*-pirano[4,3-*d*]pirimidina (135 mg, 0,480 mmol) y *N*-metiletanamina en exceso (284 mg, 4,80 mmol) en MeOH (2 ml). El disolvente se eliminó a vacío proporcionando 2-cloro-*N*-etil-*N*-metil-8-fenil-7,8-dihidro-5*H*-pirano[4,3-*d*]pirimidin-4-amina (146 mg, 0,481 mmol, 100 % de rendimiento). CL-EM $(M+H)^+$ = 304,2.

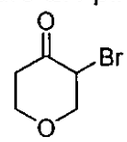
Preparación J:

2,4-dicloro-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



Intermedio J(1):

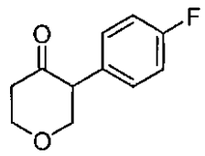
3-bromodihidro-2H-piran-4(3H)-ona



A una solución enfriada de dihidro-2H-piran-4(3H)-ona (10,0 g, 99,8 mmol) en THF se añadió una solución de hidrotribromuro de pirrolidona (49,54 g, 99,8 mmol) en THF durante un período de 10 minutos a °C. La mezcla de reacción se dejó que llegara hasta temperatura ambiente y se agitó durante 2 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con acetato de etilo (300 ml). La solución orgánica se lavó con $NaHCO_3$ acuoso saturado (100 ml), agua (100 ml x 2), solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 3-bromodihidro-2H-piran-4(3H)-ona (12,0 g, 67%) como líquido aceitoso. El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 4,89-4,87 (1H, m) 4,28-4,27 (1H, m) 4,25-4,4,24 (1H, m) 3,85-3,74 (2H, m) 2,71-2,66 (2H, m).

Intermedio J(2):

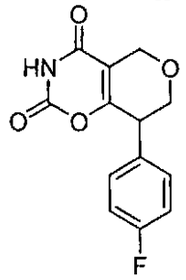
3-(4-fluorofenil)dihidro-2H-piran-4(3H)-ona



A una solución del Intermedio J(1) (12,0 g, 66,9 mmol) en benceno se añadió solución 2 M de bromuro de 4-fluorofenil magnesio en éter (13,34 g, 33,48 ml, 66,9 mmol) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 40 min. La mezcla de reacción se enfrió con HCl acuoso 1,5 N (80 ml). La fase orgánica se separó y la fase acuosa se extrajo con acetato de etilo (100 x 2). La fase orgánica reunida se lavó con agua (100 ml x 2), solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando el compuesto bruto como líquido aceitoso. El compuesto bruto se disolvió en benceno y se añadió una solución de bromuro de 4-fluorofenil magnesio en éter (9,7 g, 24,5 ml, 49,0 mmol) a 0°C. La mezcla de reacción se calentó a reflujo durante 30 min. La mezcla de reacción se enfrió con HCl acuoso 1,5 N (50 ml). La fase orgánica se separó y la fase acuosa se extrajo con acetato de etilo (100 x 2). La fase orgánica reunida se lavó con agua (100 ml x 2), solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando el compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 230-400) usando acetato de etilo al 5% en éter de petróleo como fase móvil dando 3-(4-fluorofenil)dihidro-2H-piran-4(3H)-ona (3,0 g, 36%) como líquido aceitoso. CL-EM $(M+H)^+$ = 195,2. RMN de ^1H (400 MHz, cloroformo-*d*): δ ppm 7,7,21-7,18 (2H, m), 7,06-7,01 (2H, m), 4,28-4,21 (2H, m), 3,99-3,91 (2H, m), 3,79-3,76 (1H, m) 2,72-2,67 (1H, m) 2,64-2,55 (1H, m).

Intermedio J(3)

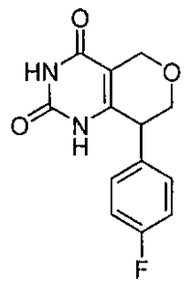
8-(4-fluorofenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona



Se calentó a 58 °C una solución del Intermedio J(2) (1,5 g, 7,72 mmol) e isocianato de N-clorocarbonilo (0,97 g, 9,2 mmol) en atmósfera de nitrógeno durante 1 h. A continuación, se aumentó la temperatura de reacción hasta 130 °C y se mantuvo durante 2 h. La masa de reacción se diluyó con acetato de etilo (50 ml). La solución orgánica resultante se lavó con $NaHCO_3$ saturado (25 ml), solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando 8-(4-fluorofenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona (0,8 g, 38%) como sólido marrón. CL-EM $(M-H)^+$ = 262,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 11,97 (1H, s), 7,43-7,39 (2H, m), 7,21-7,16 (2H, m), 4,48-4,32 (2H, m), 4,05 (2H, m), 3,77 (1H, m).

Intermedio J(4)

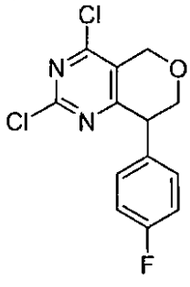
8-(4-fluorofenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona



Se calentó a reflujo durante 18 h una solución del Intermedio J(3) (0,8 g, 3,0 mmol) en amoniaco acuoso (50 ml). Se eliminó el amoníaco en exceso a presión reducida y la solución acuosa se extrajo con acetato de etilo (25 ml x 4). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 8-(4-fluorofenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona (0,4 g, 50%). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 263,4. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 11,16 (1H, s), 10,79 (1H, s), 7,33-7,29 (2H, m), 7,19-7,15 (2H, m), 4,43 (1H, m), 4,25 (1H, m), 3,90 (1H, m), 3,75-3,68 (2H, m).

Preparación J

2,4-dicloro-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina

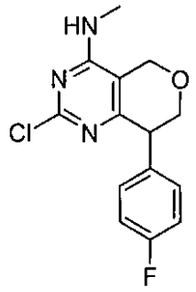


Se calentó a reflujo durante 18 h una solución del Intermedio J(4) (0,7 g, 2,6 mmol) y cantidad catalítica de DMF en $POCl_3$ (20 vol.). Se evaporó el exceso de $POCl_3$ a presión reducida. El residuo se vertió en hielo picado y se

agitó durante 15 min. La solución acuosa se extrajo con acetato de etilo (20 ml x 2). La fase orgánica reunida se lavó con $NaHCO_3$ acuoso saturado (50 ml x 2), solución de salmuera (25 ml), se secó sobre Na_2SO_4 y se evaporó a presión reducida dando 2,4-dicloro-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (0,79 g) como compuesto bruto. El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 299,0.

Preparación Ja

2-cloro-8-(4-fluorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina

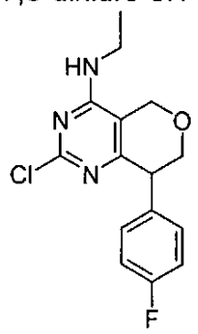


A una solución de la Preparación J (0,7 g, 2,3 mmol) en metanol se añadió Cs_2CO_3 (1,49 g, 4,6 mmol) seguido por adición de clorhidrato de metilamina (0,78 g, 11,7 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con acetato de etilo (25 ml), se lavó con agua (25 ml), solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando 2-cloro-8-(4-fluorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (0,34 g, 49%) como sólido blanquecino. CL-EM $(M+H)^+$ = 294,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm

7,22-7,19 (2H, m), 7,13-7,07 (2H, m), 4,91 (1H, m), 4,75 (1H, m), 4,12-4,08 (2H, m), 3,74 (1H, m), 3,05 (6H, s).

Preparación Jb

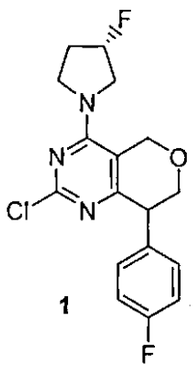
2-cloro-N-etil-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



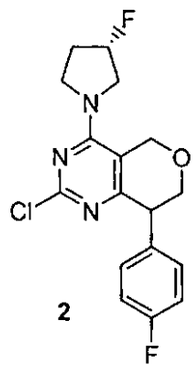
A una solución de la Preparación J (0,350 g, 1,17 mmol) en metanol se añadió diisopropiletilamina (0,30 g, 2,2 mmol) seguida por clorhidrato de etilamina (0,113 g, 1,17 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con acetato de etilo (25 ml), se lavó con agua (25 ml), solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 50-55% en éter de petróleo como fase móvil dando 2-cloro-N-etil-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (0,16 g, 60%) como sólido blanquecino. CL-EM $(M+H)^+$ = 308,2.

Preparación Jc1 y Jc2

2-cloro-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



1

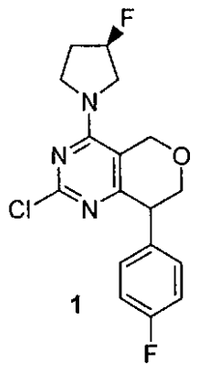


2

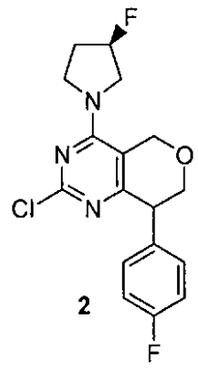
A una solución de la Preparación J (0,70 g, 2,34 mmol) en metanol se añadió diisopropiletilamina (0,60 g, 4,6 mmol) seguida por (R)-3-fluoropirrolidina (0,58 g, 4,6 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por HPLC preparativa (40% etanol en hexano) dando 2-cloro-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (0,90 g, 11% de Isómero 1, 0,110 g, 13% de Isómero 2) como sólido blanquecino. CL-EM $(M+H)^+$ = 352,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,24 (2H, m), 7,13 (2H, m), 5,40 (1H, m), 4,12 (1H, d, *J* = 14,8 Hz), 4,88 (1H, d, *J* = 14,8 Hz), 4,14-4,09 (2H, m), 3,91-3,81 (3H, m), 3,75-3,66 (2H, m), 2,51-2,18 (2H, m).

Preparación Jd 1 y Jd2

2-cloro-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



1



2

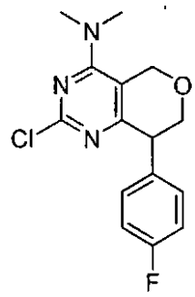
A una solución de la Preparación J (0,70 g, 2,34 mmol) en metanol se añadió diisopropiletilamina (0,60 g, 4,6 mmol) seguida por (S)-3-fluoropirrolidina (0,58 g, 4,6 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por HPLC preparativa (etanol al 40% en hexano) dando 2-cloro-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (0,100 g, 12% de Isómero 1, 0,110 g, 13% de Isómero 2) como sólido blanquecino. CL-EM $(M+H)^+$ = 352,2.

Jd1: RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,24 (2H, m), 7,13 (2H, m), 5,40 (1H, m), 4,12 (1H, d, *J* = 14,4 Hz), 4,88 (1H, d, *J* = 14,4 Hz), 4,11 (2H, m), 3,94-3,89 (3H, m), 3,72-3,58 (2H, m), 2,20-2,01 (2H, m).

Jd2: RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,21 (2H, m), 7,13 (2H, m), 5,39 (1H, m), 5,02 (2H, m), 4,02-3,97 (2H, m), 3,91-3,84 (4H, m), 3,73 (1H, m), 2,23-2,01 (2H, m).

Preparación Je

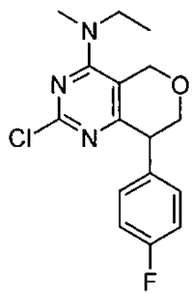
2-cloro-8-(4-fluorofenil)-N,N-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



A una solución de la Preparación J (0,7 g, 2,3 mmol) en metanol se añadió Cs_2CO_3 (1,49 g, 4,6 mmol) seguido por la adición de clorhidrato de metilamina (0,95 g, 11,7 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con acetato de etilo (50 ml), se lavó con agua (25 ml), solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 40% en éter de petróleo como fase móvil dando 2-cloro-8-(4-fluorofenil)-N,N-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (0,35 g, 49%) como sólido blanquecino. CL-EM $(M+H)^+$ = 308,2. Este compuesto se llevó a la etapa siguiente sin purificación posterior.

Preparación Jf

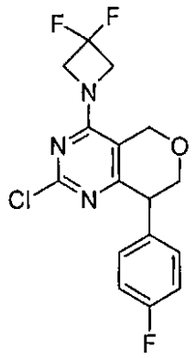
2-cloro-N-etil-8-(4-fluorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



A una solución de la Preparación J (0,7 g, 2,3 mmol) en metanol se añadió Cs_2CO_3 (1,49 g, 4,6 mmol) seguido por la adición de clorhidrato de etilmetilamina (1,1 g, 11,7 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con acetato de etilo (25 ml), se lavó con agua (25 ml), solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando 2-cloro-N-etil-8-(4-fluorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (0,39 g, 52%) como sólido blanquecino. CL-EM $(M+H)^+$ = 322,2. Este compuesto se llevó a la etapa siguiente sin purificación posterior.

Preparación Jg

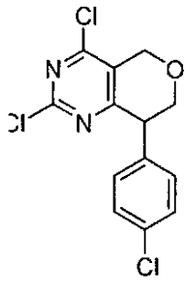
2-cloro-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



A una solución de la Preparación J (0,7 g, 2,3 mmol) en metanol se añadió Cs_2CO_3 (1,49 g, 4,6 mmol) seguido por la adición de clorhidrato de 3,3-difluoroazetidina (0,60 g, 4,6 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con acetato de etilo (25 ml), se lavó con agua (25 ml), solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando 2-cloro-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (0,42 g, 50%) como sólido blanquecino. CL-EM $(M+H)^+$ = 355,2. Este compuesto se llevó a la etapa siguiente sin purificación posterior.

Preparación K

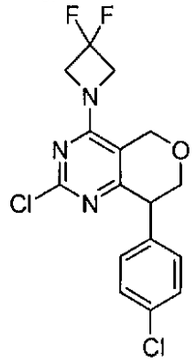
2,4-dicloro-8-(4-clorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



El compuesto del epígrafe se preparó de forma análoga a la Preparación J, como un sólido amarillo pálido. CL-EM $(M+H)^+$ = 315,0. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 7,30 (2H, dd, *J* = 2,0, 6,4 Hz), 7,17 (2H, dd, *J* = 2,0, 6,4 Hz), 4,91 (1H, d, *J* = 16,4 Hz), 4,76 (1H, d, *J* = 16,0 Hz), 4,18 - 4,09 (3H, m).

Preparación Ka

2-cloro-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidina

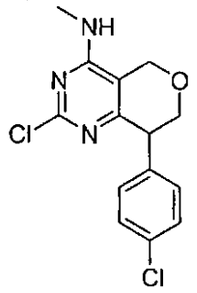


Se combinaron 2,4-dicloro-8-(4-clorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (*Preparación K*) (500 mg, 1,584 mmol) y clorhidrato de 3,3-difluoroazetidina (308 mg, 2,377 mmol) y se purificó según la *Preparación Ha* dando 2-cloro-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (400 mg, 1,075 mmol, 67,8 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 372,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm

7,22 - 7,34 (2 H, m), 7,12 (2 H, d, *J*=8,24 Hz), 4,63 - 4,85 (2 H, m), 4,46 - 4,64 (3 H, m), 4,04 - 4,17 (1 H, m), 3,91 - 4,04 (2 H, m).

Preparación Kb

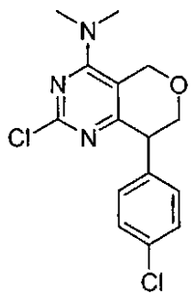
2-cloro-8-(4-clorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



Se combinaron 2,4-dicloro-8-(4-clorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (*Preparación K*) (500 mg, 1,584 mmol) y clorhidrato de metanamina (160 mg, 2,377 mmol) y se purificó según la *Preparación Ha* dando 2-cloro-8-(4-clorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (150 mg, 0,484 mmol, 30,5 % de rendimiento). CL-EM $(M+H)^+$ = 310,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,22 - 7,31 (2 H, m), 7,13 (2 H, d, *J*=8,55 Hz), 4,46 - 4,64 (1 H, m), 4,43 (1 H, s ancho), 3,97 - 4,14 (1 H, m), 3,91 (1 H, d, *J*=3,36 Hz), 3,09 (3 H, d, *J*=4,88 Hz).

Preparación Kc

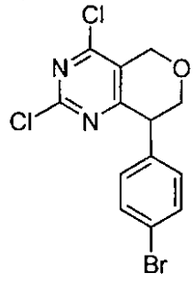
2-cloro-8-(4-clorofenil)-N,N-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



Se combinaron 2,4-dicloro-8-(4-clorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (*Preparación K*) (500 mg, 1,584 mmol) y dimetilamina (2,0 M en THF) (1,188 ml, 2,377 mmol) y se purificaron según la *Preparación Ha* dando 2-cloro-8-(4-clorofenil)-N,N-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (400 mg, 1,234 mmol, 78 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 324,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,20 - 7,31 (2 H, m), 7,04 - 7,15 (2 H, m), 4,70 - 4,89 (2 H, m), 4,17 (1 H, dd, *J*=11,60, 5,49 Hz), 4,05 (1 H, t, *J*=5,49 Hz), 3,87 (1 H, dd, *J*=11,60, 5,49 Hz), 3,05 - 3,19 (6 H, m).

Preparación L

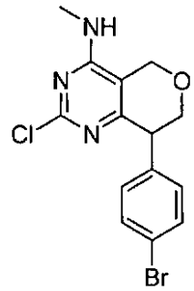
2,4-dicloro-8-(4-bromofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



El compuesto del epígrafe se preparó de forma análoga a la Preparación J, como un sólido amarillo pálido. CL-EM $(M+H)^+$ = 359,0. RMN de ^1H (400 MHz, *CD_3OD*) δ ppm 7,52 (2H, d, *J* = 8,4 Hz), 7,22 (2H, d, *J* = 8,4 Hz), 4,87 (1H, d, *J* = 16,0 Hz), 4,30 (1H, t, *J* = 4,6 Hz), 4,14 (1H, dd, *J* = 4,6, 11,4 Hz), 3,95 (1H, dd, *J* = 4,8, 11,6 Hz).

Preparación La

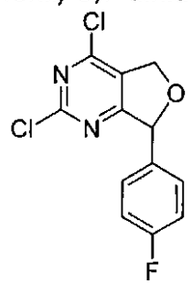
8-(4-bromofenil)-2-cloro-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



Se combinaron 8-(4-bromofenil)-2,4-dicloro-7,8-dihidro-5H-pirano[4,3-d]pirimidina (*Preparación L*) (500 mg, 1,389 mmol) y clorhidrato de metanamina (141 mg, 2,083 mmol) y se purificó según la *Preparación Ha* dando 8-(4-bromofenil)-2-cloro-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (210 mg, 0,592 mmol, 42,6 % de rendimiento). CL-EM $(M+H)^+$ = 356,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,46 (2 H, d, *J*=8,24 Hz), 7,13 (2 H, d, *J*=8,55 Hz), 4,43 - 4,71 (2 H, m), 4,09 (1 H, dd, *J*=11,44, 4,12 Hz), 3,92 - 4,03 (1 H, m), 3,86 (1 H, d, *J*=3,05 Hz), 3,00 (3 H, s).

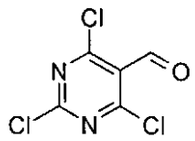
Preparación M

2,4-dicloro-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina



Intermedio M(1)

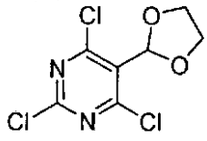
2-hidroxi-2-fenilacetato de etilo



Se calentó a reflujo durante 15 h una solución de pirimidin-2,4,6-triol (10,0 g, 78,2 mmol), DMF (12 ml) en $POCl_3$ (10 vol.). El exceso de $POCl_3$ se evaporó a presión reducida. El residuo se vertió en hielo picado. El sólido precipitado se filtró y se lavó con agua dando 2,4,6-tricloropirimidin-5-carbaldehído (8,0 g, 47%) como sólido amarillo. Este compuesto se llevó a la etapa siguiente sin purificación posterior.

Intermedio M(2)

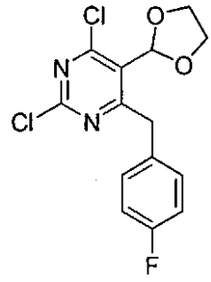
2,4,6-tricloro-5-(1,3-dioxolan-2-il)pirimidina



A una solución del Intermedio M(1) (5,0 g, 23,6 mmol) en benceno seco se añadió etilenglicol (4,0 ml, 64,5 mmol) seguido por ácido *p*-toluenosulfónico (0,15 g, 0,87 mmol) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 20 h. La mezcla de reacción se filtró y se lavó con benceno caliente. El filtrado se evaporó a presión reducida y el residuo se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 10% en éter de petróleo como fase móvil dando (4,5 g, 75%) como sólido blanquecino. CL-EM $(M+H)^+$ = 256,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,6 (1H, s), 7,99 (1H, s), 7,98 (1H, s), 7,76-7,41 (3H, m), 7,23-7,13 (4H, m), 5,87 (1H, s), 5,33 (1H, dd, *J* = 27, 8 Hz), 5,17 (1H, dd, *J* = 27, 8), 4,67 (4H, m), 3,72 (3H, s).

Intermedio M(3)

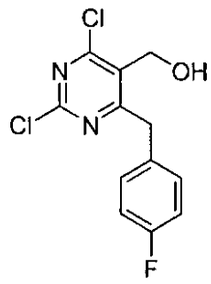
2,4-dicloro-5-(1,3-dioxolan-2-il)-6-(4-fluorobencil)pirimidina



A una solución del Intermedio M(2) (4,0 g, 15,6 mmol) en éter dietílico seco se añadió bromuro de 4-fluorobencil magnesio (75,2 ml, 18,8 mmol, solución 0,25 M en THF) a 0ºC. La mezcla de reacción se dejó que llegara hasta temperatura ambiente y se agitó durante 4 h. La mezcla de reacción se enfrió con cloruro amónico acuoso saturado. La fase orgánica se separó y la fase acuosa se extrajo con éter dietílico (50 ml x 2). La fase orgánica reunida se lavó con agua, se secó sobre Na_2SO_4 anhidro y se evaporó obteniendo compuesto bruto. El compuesto bruto se purificó por combiflash usando acetato de etilo al1,4% en éter de petróleo como fase móvil dando 2,4-dicloro-5-(1,3-dioxolan-2-il)-6-(4-fluorobencil)pirimidina (2,2 g, 43,1%) como sólido blanquecino. CL-EM $(M-H)^+$ = 327,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,26 (2H, m), 7,10 (2H, m), 6,19 (1H, s), 4,25 (2H, s), 4,19 (2H, m), 4,02 (2H, m).

Intermedio M(4)

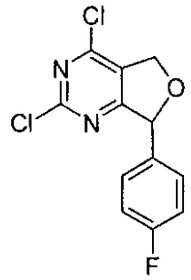
(2,4-dicloro-6-(4-fluorobencil)pirimidin-5-il)metanol



A una solución del Intermedio M(3) (2,0 g, 6,07 mmol) en THF se añadió HCl acuoso 6 N durante un período de 5 minutos a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. El volumen de reacción se redujo a la mitad y la solución se extrajo con éter dietílico (50 ml x 2). La fase orgánica reunida se lavó con agua (50 ml), solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto (1,2 g). El compuesto bruto se disolvió en metanol y se enfrió hasta 0 °C. Se añadió borohidruro sódico (0,234 g) a la mezcla de reacción. La solución resultante se dejó que llegara hasta temperatura ambiente y se agitó durante 1 h. La mezcla de reacción se enfrió con cloruro amónico acuoso saturado, y luego se evaporó el disolvente a presión reducida. El residuo se diluyó con acetato de etilo (50 ml). La solución orgánica se lavó con agua (25 ml), solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 20% en éter de petróleo como fase móvil dando (2,4-dicloro-6-(4-fluorobencil)pirimidin-5-il)metanol (1,0 g, 58%) como líquido aceitoso. CL-EM $(M+H)^+$ = 488,1. RMN de ^1H (300 MHz, $CDCl_3$): δ ppm 7,25 (2H, m), 7,01 (2H, m), 4,82 (2H, m), 4,27 (2H, s).

Preparación M

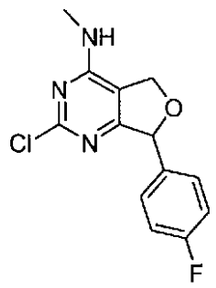
2,4-dicloro-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina



A una solución del Intermedio M(4) (1,0 g, 3,48 mmol) en benceno seco (100 ml) se añadió Cs_2CO_3 (0,4 g, 3,48 mmol) seguido por tetraacetato de plomo (0,3 g, 3,48 mmol) a temperatura ambiente (el color de la mezcla de reacción cambió de incoloro a marrón). La masa de reacción se calentó a reflujo durante 18 h usando un aparato de Dean Stark. La mezcla de reacción se filtró a través de un lecho de Celite y se lavó con éter dietílico. El filtrado se evaporó a presión reducida y el residuo se diluyó con éter dietílico. La solución orgánica se lavó con agua (25 ml x 2), $NaHCO_3$ acuoso saturado, solución de salmuera (10 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por combiflash usando acetato de etilo al 0,9% en éter de petróleo como fase móvil dando 2,4-dicloro-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina (0,250 mg, 30%) como líquido aceitoso. CL-EM $(M+H)^+$ = 485,0. RMN de ^1H (400 MHz, metanol-*d4*): δ ppm 7,48-7,44 (2H, m), 7,16-7,12 (2H, m), 6,15 (1H, s), 5,40 (1H, dd, *J* = 13,6 Hz), 5,27 (1H, dd, *J* = 13,6).

Preparación Ma

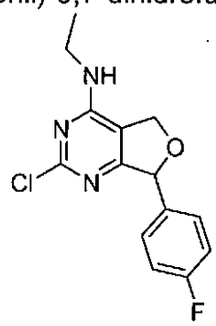
2-cloro-7-(4-fluorofenil)-N-metil-5,7-dihidrofuro[3,4-d]pirimidin-4-amina



Se combinaron 2,4-dicloro-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación M) (250 mg, 0,877 mmol) y clorhidrato de metanamina (89 mg, 1,315 mmol) y se purificó según la Preparación Ia dando 2-cloro-7-(4-fluorofenil)-N-metil-5,7-dihidrofuro[3,4-d]pirimidin-4-amina (149 mg, 0,533 mmol, 60,8 % de rendimiento). CL-EM $(M+H)^+$ = 280,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,31 - 7,44 (2 H, m), 7,05 - 7,17 (2 H, m), 5,80 - 5,95 (1 H, m), 4,94 - 5,21 (2 H, m), 2,93 - 3,07 (3 H, m).

Preparación Mb

2-cloro-N-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-4-amina

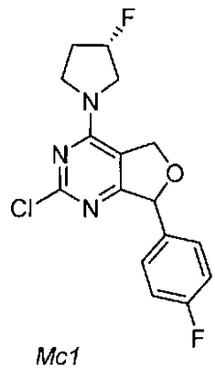


Se combinaron 2,4-dicloro-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación M) (125 mg, 0,438 mmol) y clorhidrato de etilamina (53,6 mg, 0,658 mmol) y se purificó según la Preparación Ha dando 2-cloro-N-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-4-amina (38,17 mg, 0,130 mmol, 29,6 % de rendimiento). CL-EM $(M+H)^+$ = 294,0. RMN de ^1H (500 MHz,

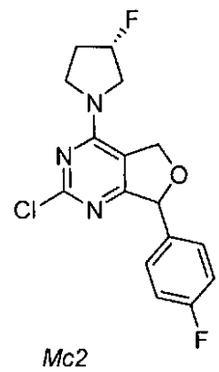
$CDCl_3$) δ ppm 7,24 - 7,38 (2 H, m), 6,92 - 7,08 (2 H, m), 5,73 - 5,98 (1 H, m), 4,83 - 5,21 (2 H, m), 3,36 - 3,63 (2 H, m), 1,13 - 1,28 (3 H, m).

Preparaciones Mc1 y Mc2

2-cloro-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidina



Mc1
Diastereómero 1
Racémico



Mc2
Diastereómero 2
Racémico

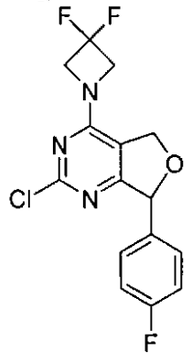
Se combinaron 2,4-dicloro-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación M) (125 mg, 0,438 mmol) y (S)-3-fluoropirrolidina, HCl (83 mg, 0,658 mmol) y se purificó según la Preparación Ha dando 2-cloro-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidina (*Mc1*, Diastereómero 1, primero en eluir) (49 mg, 0,145 mmol, 33,1 % de rendimiento). CL-EM $(M+H)^+$ = 338,0.

(*Mc2*, Diastereómero 2, segundo en eluir) (40 mg, 0,118 mmol, 27,0 % de rendimiento).

CL-EM $(M+H)^+$ = 338,0. No se determinó la estereoquímica relativa de *Mc1* y *Mc2*.

Preparación Md

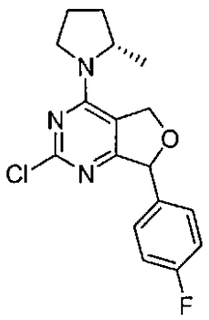
2-cloro-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina



A una solución de la Preparación M (0,05 g, 0,176 mmol) en metanol se añadió diisopropiletilamina (0,045 g, 0,30 mmol) seguido por la adición de clorhidrato de 3,3-difluoroazitidina (0,03 g, 0,193 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 6% en éter de petróleo como fase móvil dando 2-cloro-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina (0,035 g, 46%) como sólido blanco. CL-EM $(M+H)^+$ = 342,2.

Preparación Me

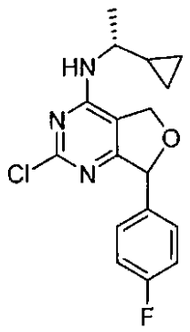
2-cloro-7-(4-fluorofenil)-4-((S)-2-metilpirrolidin-1-il)-5,7-dihidrofuro[3,4-d] pirimidina



Se hizo reaccionar 2,4-dicloro-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación M) como se describe en la Preparación Hp1 y Hp2 con sal *p*-toluenosulfonato de (S)-2-metilpirrolidina proporcionando 2-cloro-7-(4-fluorofenil)-4-((S)-2-metilpirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación Me) como una mezcla de 2 diastereómeros. CL-EM $(M+H)^+$ = 334,1.

Preparación Mf

2-cloro-N-((R)-1-ciclopropiletil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-4-amina

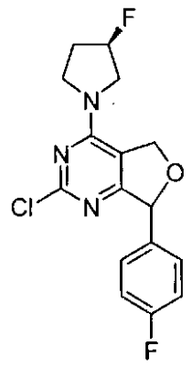


A una solución de 2,4-dicloro-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación M) (150 mg, 0,526 mmol) en THF (2631 µl) se añadió (R)-1-ciclopropiletanamina, HCl (128 mg, 1,052 mmol) y DIEA (368 µl, 2,105 mmol). La mezcla se calentó a 40 °C durante 2 h y se agitó a ta durante la

noche. La mezcla se concentró y se purificó por cromatografía en columna sobre gel de sílice dando 2-cloro-N-((R)-1-ciclopropiletil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-4-amina (Preparación Mf) (25 mg, 0,075 mmol, 14,24 % de rendimiento) como una mezcla de 2 diastereómeros. CL-EM $(M+H)^+$ = 334,1.

Preparación Mg

2-cloro-7-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidina

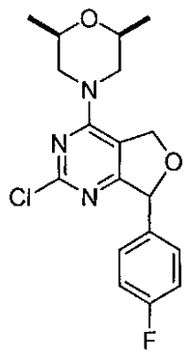


Se hizo reaccionar 2,4-dicloro-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación M) como se describe en la Preparación Xa con (R)-3-fluoropirrolidina, HCl dando 2-cloro-7-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación Mg). CL-EM $(M+H)^+$ = 338,1. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 7,33 - 7,47 (m, 2 H) 7,00 - 7,14 (m, 2 H) 5,83 - 5,97 (m, 1 H) 5,54 (dd, J=11,33, 3,53 Hz, 1 H) 5,36 - 5,49 (m, 2 H) 3,88 - 4,00 (m, 1 H) 3,65 - 3,88 (m, 3 H) 2,30 - 2,52 (m, 1 H) 2,02 - 2,20 (m, 1 H).

Preparación Mh

2-cloro-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-

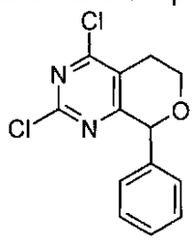
d]pirimidina



Se hizo reaccionar 2,4-dicloro-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación M) como se describe en la Preparación Xa con (2R,6S)-2,6-dimetilmorfolina dando 2-cloro-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación Mh). CL-EM $(M+H)^+$ = 364,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,39 (dd, J=8,70, 5,34 Hz, 2 H) 7,07 (t, J=8,70 Hz, 2 H) 5,90 (s ancho, 1 H) 5,34 - 5,42 (m, 1 H) 5,24 - 5,34 (m, 1 H) 4,14 (q, J=7,02 Hz, 2 H) 3,67 (ddd, J=10,38, 6,41, 2,44 Hz, 4 H), 1,20 (m, 6H).

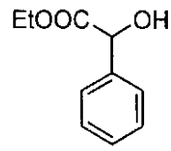
Preparación N

2,4-dicloro-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidina



Intermedio N(1)

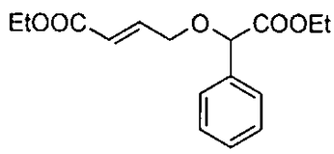
2-hidroxi-2-fenilacetato de etilo



A una solución enfriada de 2-hidroxi-2-fenilacetato de etilo (25,0 g, 164,3 mmol) en etanol se añadió H_2SO_4 concentrado (15 ml) durante un período de 10 min. La mezcla de reacción se calentó a reflujo durante 5 h. El disolvente se evaporó a presión reducida y el residuo se diluyó con acetato de etilo (250 ml). La solución orgánica se lavó con $NaHCO_3$ acuoso saturado (200 ml x 2), agua (100 ml x 2), solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 2-hidroxi-2-fenilacetato de etilo (24,5 g, 83%) como compuesto bruto (líquido oleoso). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H_2O)^+$ = 198,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,41-7,28 (5H, m), 6,04 (1H, d, *J*= 4,0 Hz), 5,11 (1H, d, *J*= 4,0 Hz), 4,13 (2H, m), 1,13 (3H, t, *J* = 7,2 Hz).

Intermedio N(2)

4-(2-etoxi-2-oxo-1-feniletoxi)but-2-enoato de etilo

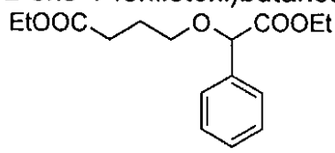


A una solución del Intermedio N(1) (20,0 g, 110,9 mmol) en hexano se añadió óxido de plata (66,75 g, 288,5 mmol) seguido por sulfato de magnesio (2,66 g, 220 mmol) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. La mezcla de reacción se enfrió hasta 0 °C y se añadió óxido de plata (71,8 g, 310,9 mmol) seguido por etil-4-bromocrotonato (32,0 g,

166 mmol). La solución resultante se agitó a temperatura ambiente durante 3 días. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida dando 4-(2-etoxi-2-oxo-1-feniletoxi)but-2-enoato de etilo (20,0 g, 62,5%) como líquido aceitoso. CL-EM $(M+H_2O)^+$ = 310,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,42-7,35 (5H, m), 6,90 (1H, m), 6,05 (1H, m), 5,09 (1H, s), 4,26 (2H, m), 4,16 (4H, m), 1,21 (3H, t, *J*= 7,2 Hz), 1,13 (3H, t, *J* = 7,2 Hz).

Intermedio N(3)

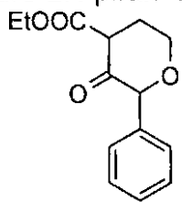
4-(2-etoxi-2-oxo-1-feniletoxi)butanoato de etilo



A una solución del Intermedio N(2) (20,0 g, 68,41 mmol) en etanol se añadió paladio sobre carbón (10%, p/p) a temperatura ambiente. La mezcla de reacción se sometió a hidrogenación bajo una presión de botella de hidrógeno durante 30 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con etanol. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 5% en éter de petróleo como fase móvil dando 4-(2-etoxi-2-oxo-1-feniletoxi)butanoato de etilo (12,0 g, 59,5%) como líquido aceitoso. CL-EM $(M+H)^+$ = 295,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,41-7,27 (5H, m), 4,96 (1H, s), 4,07 (4H, m), 3,62 (1H, m), 3,49 (1H, m), 2,36 (2H, m), 1,79 (2H, m), 1,15 (6H, m).

Intermedio N(4)

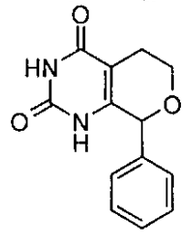
3-oxo-2-feniltetrahidro-2H-piran-4-carboxilato de etilo



A una solución enfriada de Intermedio N(3) (12,0 g, 40,76 mmol) en THF se añadió *t*-BuOK (9,13 g, 81,3 mmol) a 0ºC. La mezcla de reacción se dejó que llegara hasta temperatura ambiente y se agitó durante 1 h. La mezcla de reacción se enfrió con agua y se evaporó el disolvente a presión reducida. El residuo se diluyó con acetato de etilo (200 ml). La fase orgánica se lavó con agua (100 ml x 2), solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando 3-oxo-2-feniltetrahidro-2H-piran-4-carboxilato de etilo (6,0 g, 59,4%) como liquido aceitoso. CL-EM $(M+H)^+$ = 249,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 11,81 (1H, s), 7,36 (5H, m), 5,20 (1H, s), 4,23 (2H, c, *J* = 7,2,0 Hz), 3,71 (1H, m), 3,67 (1H, m), 2,36 (1H, m), 2,32 (1H, m), 1,29 (3H, t, *J* = 7,2 Hz).

Intermedio N(5)

8-fenil-5,6-dihidro-1H-pirano[3,4-d]pirimidin-2,4(3H,8H)-diona

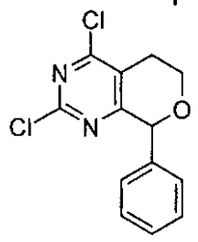


A una solución del Intermedio N(4) (6,0 g, 24,16 mmol) en etanol se

añadió *t*-BuOK (6,76 g, 60,41 mmol) seguido por urea (3,62 g, 60,41 mmol) a temperatura ambiente. La masa de reacción se calentó a reflujo durante 18 h. La mezcla de reacción se enfrió con agua y se evaporó el disolvente a presión reducida. El residuo se diluyó con acetato de etilo (100 ml). La fase orgánica se lavó con agua (100 ml x 2), solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo como fase móvil dando 8-fenil-5,6-dihidro-1H-pirano[3,4-d]pirimidin-2,4(3H,8H)-diona (3,0 g, 50,8%) como sólido amarillo pálido. CL-EM $(M-H)^+$ = 243,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 11,10 (1H, s), 10,57 (1H, s), 7,42-7,39 (3H, m), 7,32 (2H, m), 5,32 (1H, s), 3,71-3,56 (2H, m), 2,38-2,27 (2H, m).

Preparación N

2,4-dicloro-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidina

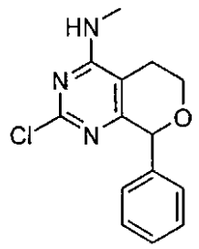


Se calentó a reflujo durante 18 h una solución del Intermedio N(5) (2,0 g, 8,18 mmol) y cantidad catalítica de DMF en $POCl_3$ (10 vol.). El exceso de $POCl_3$ se evaporó a presión reducida. El residuo se vertió en hielo picado y se agitó durante 15 min. La solución acuosa se extrajo con acetato de etilo (50 ml x 3). La fase orgánica reunida se lavó con $NaHCO_3$ acuoso saturado (50 ml x 2), solución de salmuera (50 ml), se secó sobre Na_2SO_4 y se evaporó a presión

reducida dando 2,4-dicloro-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidina (2,0 g, bruto) como sólido marrón. CL-EM $(M+H)^+$ = 281,0.

Preparación Na

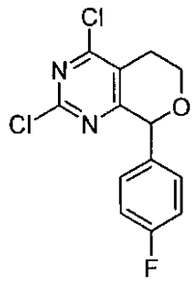
2-cloro-N-metil-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidin-4-amina



A una solución de la Preparación N (2,1 g, bruto) en acetonitrilo se añadió diisopropiletilamina (1,83 g, 14,2 mmol) seguida por la adición de clorhidrato de metilamina (0,96 g, 14,2 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 40% en éter de petróleo como fase móvil dando 2-cloro-N-metil-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidin-4-amina (0,7 g, 35,7%) como sólido blanquecino. CL-EM $(M+H)^+$ = 276,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,49 (1H, m), 7,36-7,31 (3H, m), 7,25-7,23 (2H, m), 5,45 (1H, s), 4,0 (1H, m), 3,79 (1H, m), 2,87 (3H, d, *J* = 4,4 Hz), 2,55 (1H, m), 2,44 (1H, m).

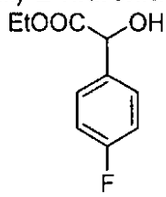
Preparación O

2,4-dicloro-8-(4-fluorofenil)-6,8-dihidro-5H-pirano[3,4-d]pirimidina



Intermedio O(1)

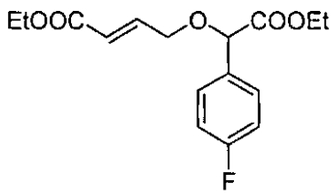
2-(4-fluorofenil)-2-hidroxiacetato de etilo



A una solución enfriada de ácido 2-(4-fluorofenil)-2-hidroxiacético (5,0 g, 29,4 mmol) en etanol se añadió H_2SO_4 concentrado (10 ml) durante un período de 10 min. La mezcla de reacción se calentó a reflujo durante 5 h. El disolvente se evaporó a presión reducida y el residuo se diluyó con acetato de etilo (25 ml). La solución orgánica se lavó con $NaHCO_3$ acuoso saturado (25 ml x 2), agua (20 ml), solución de salmuera (10 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 2-(4-fluorofenil)-2-hidroxiacetato de etilo (5,0 g, 90%) como compuesto bruto (líquido oleoso). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H_2O)^+$ = 216. RMN de ^1H (400 MHz, DMSO-*d6*): δ 7,43-7,46 (2H, m), 7,17-7,20 (2H, m), 6,11-6,13 (1H, m), 5,14 (1H, d, *J* = 5,20 Hz), 3,35-4,13 (2H, m), 1,12-1,15 (3H, m).

Intermedio O(2)

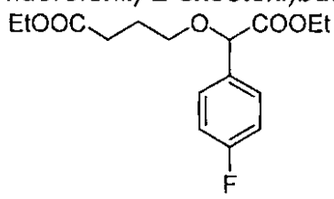
4-(2-etoxi-1-(4-fluorofenil)-2-oxoetoxi)but-2-enoato de etilo



A una solución del Intermedio O(1) (3,0 g, 15,1 mmol) en hexano se añadió óxido de plata (9,1 g, 39,3 mmol) seguido por sulfato de magnesio (1,8 g, 3,0 mmol) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. La mezcla de reacción se enfrió hasta 0 °C y se añadió óxido de plata (9,7 g, 39,9 mmol) seguido por 4-bromocrotonato de etilo (4,3 g, 22,7 mmol). La solución resultante se agitó a temperatura ambiente durante 3 días. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida dando 4-(2-etoxi-1-(4-fluorofenil)-2-oxoetoxi)but-2-enoato de etilo (3,0 g, 90%) como líquido aceitoso. CL-EM $(M+H_2O)^+$= 328,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,42-7,45 (2H, m), 7,04-7,26 (2H, m), 6,95 (1H, m), 6,12 (1H, m), 4,89 (1H, s), 4,13-4,28 (6H, m), 1,30 (3H, t, *J* = 7,20 Hz), 1,26 (3H, *J* = 6,8 Hz).

Intermedio O(3)

4-(2-etoxi-1-(4-fluorofenil)-2-oxoetoxi)butanoato de etilo

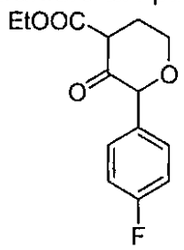


A una solución del Intermedio O(2) (3,0 g, 9,6 mmol) en etanol se añadió paladio sobre carbón (10%, p/p) a temperatura ambiente. La mezcla de reacción se sometió a hidrogenación bajo una presión de botella de hidrógeno

durante 30 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con etanol. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 5% en éter de petróleo como fase móvil dando 4-(2-etoxi-1-(4-fluorofenil)-2-oxoetoxi)butanoato de etilo (3,0 g, 63%) como líquido aceitoso. CL-EM $(M+H)^+$ = 313,2 RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,29-7,46 (2H, m), 7,05-7,09 (2H, m), 4,84 (1H, s), 4,10-4,23 (4H, m), 3,59-3,63 (1H, m), 3,42-3,53 (1H, m), 2,47 (2H, t, *J* = 7,6 Hz), 1,99 (2H, t, *J* = 7,6 Hz), 1,22-1,32 (6H, m).

Intermedio O(4)

2-(4-fluorofenil)-3-oxotetrahidro-2H-piran-4-carboxilato de etilo

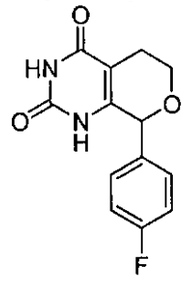


A una solución enfriada de Intermedio O(3) (3,0 g, 9,6 mmol) en THF se añadió *t*-BuOK (2,1 g, 19,0 mmol) a 0 °C. La mezcla de reacción se dejó que llegara hasta temperatura ambiente y se agitó durante 1 h. La mezcla de reacción se enfrió con agua y se evaporó el disolvente a presión reducida. El residuo se diluyó con acetato de etilo (200 ml). La fase orgánica se lavó con agua (100 ml x 2), solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil

dando 2-(4-fluorofenil)-3-oxotetrahidro-2H-piran-4-carboxilato de etilo (1,0 g, 55%) como líquido aceitoso. CL-EM $(M+H)^+$ = 267,1. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 11,81 (1H, s), 7,22-7,42 (2H, m), 7,12-7,20 (2H, m), 5,23 (1H, s), 4,22 (2H, c, *J* = 7,2 Hz), 3,87-3,88 (1H, m), 3,69-3,84 (1H, m), 2,34-2,35 (1H, m), 2,30-2,33 (1H, m), 1,27 (3H, t, *J* = 7,2 Hz).

Intermedio O(5)

8-(4-fluorofenil)-5,6-dihidro-1H-pirano[3,4-d]pirimidin-2,4(3H,8H)-diona

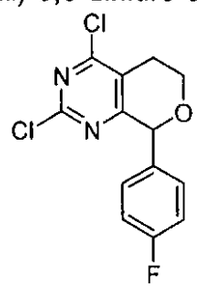


A una solución del Intermedio O(4) (0,30 g, 1,12 mmol) en etanol se añadió *t*-BuOK (0,253 g, 2,2 mmol) seguido por urea (0,135 g, 2,2 mmol) a temperatura ambiente. La masa de reacción se calentó a reflujo durante 18 h. La mezcla de reacción se enfrió con agua y se evaporó el disolvente a presión reducida. El residuo se diluyó con acetato de etilo (100 ml). La fase orgánica se lavó con agua (100 ml x 2), solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo como fase móvil dando 8-(4-fluorofenil)-5,6-dihidro-1H-pirano[3,4-d]pirimidin-2,4(3H,8H)-diona (0,150 g, 40%) como sólido amarillo pálido. CL-EM $(M-H)^+$ = 263,1. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 11,14 (1H, s), 10,57 (1H, s), 7,35-7,36 (2H, m), 7,22 (2H, m), 5,34

(1H, s), 3,66-3,71 (1H, m), 3,58-3,64 (1H, m), 2,33 (2H, m).

Preparación O

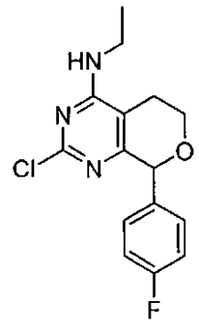
2,4-dicloro-8-(4-fluorofenil)-6,8-dihidro-5H-pirano[3,4-d]pirimidina



Se calentó a reflujo durante 18 h una solución del Intermedio O(5) (0,30 g, 1,1 mmol) y cantidad catalítica de DMF en $POCl_3$ (10 vol.). El exceso de $POCl_3$ se evaporó a presión reducida. El residuo se vertió en hielo picado y se agitó durante 15 min. La solución acuosa se extrajo con acetato de etilo (50 ml x 3). La fase orgánica reunida se lavó con $NaHCO_3$ acuoso saturado (50 ml x 2), solución de salmuera (50 ml), se secó sobre Na_2SO_4 y se evaporó a presión reducida dando 2,4-dicloro-8-(4-fluorofenil)-6,8-dihidro-5H-pirano[3,4-d]pirimidina (0,20 g, bruto) como líquido marrón. CL-EM $(M+H)^+$ = 299,0.

Preparación Oa

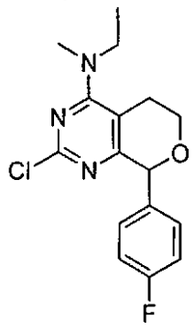
2-cloro-N-etil-8-(4-fluorofenil)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-4-amina



A una solución de la Preparación O (0,35 g, 1,1 mmol) en metanol se añadió diisopropiletilamina (0,30 g, 2,2 mmol) seguida por la adición de clorhidrato de etilamina (0,113 g, 1,1 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 35% en éter de petróleo como fase móvil dando 2-cloro-N-etil-8-(4-fluorofenil)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-4-amina (0,15 g, bruto) como sólido blanquecino. CL-EM $(M+H)^+$ = 308,2,0.

Preparación Ob

2-cloro-N-etil-8-(4-fluorofenil)-N-metil-6,8-dihidro-5H-pirano[3,4-d]pirimidin-4-amina

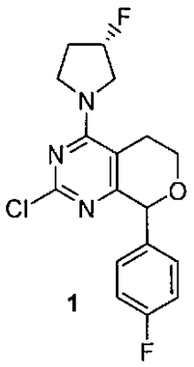


A una solución de la Preparación O (0,20 g, 0,61 mmol) en metanol se añadió diisopropiletilamina (0,172 g, 1,3 mmol) seguida por la adición de clorhidrato de etilmetilamina (0,47 g, 0,81 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 40% en éter de petróleo como fase móvil dando 2-cloro-N-etil-8-(4-fluorofenil)-N-metil-6,8-dihidro-5H-

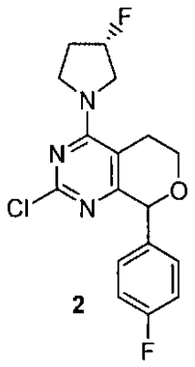
pirano[3,4-d]pirimidin-4-amina (0,020 g bruto) como sólido blanquecino. CL-EM $(M+H)^+$ = 322,2.

Preparación Oc1 y Oc2

2-cloro-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidina



1



2

A una solución de la Preparación O (0,60 g, 2,1 mmol) en metanol se añadió diisopropiletilamina (0,516 g, 4,6 mmol) seguida por la adición de (R)-3-fluoropirrolidina (0,301 g, 2,2 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por HPLC preparativa dando 2-cloro-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidina (0,110 g, 40% de Isómero 1, 0,109 g, 40% de Isómero 2) como sólido blanquecino. CL-EM $(M+H)^+$ = 352,0.

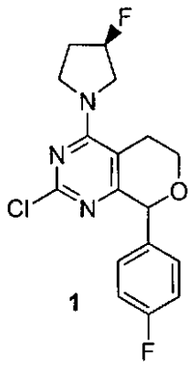
Oc1: RMN de ^{1}H (400 MHz, DMSO-*d6*): δ ppm 7,36-7,36 (2H, m), 7,16 (2H, m), 5,50 (2H, d, *J* = 8,40 Hz), 5,35 (1H, s), 3,58-3,98 (7H, m), 3,24-3,34 (1H, m), 2,78 (1H, m), 2,04-2,28 (2H, m).

Oc2: RMN de ^{1}H (400 MHz, DMSO-*d6*): δ ppm 7,19-7,33 (2H, m), 7,15-7,20 (2H, m), 5,34 (1H, m), 5,40 (1H, m), 3,91-4,10 (2H, m), 3,75-3,90 (2H, m), 3,69-

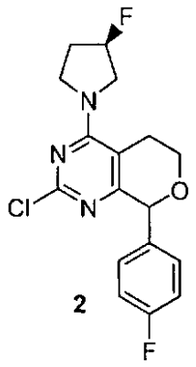
3,75 (2H, m), 3,05 (2H, t, *J* = 5,20 Hz), 2,01 (2H, d, *J* = 8,0 Hz).

Preparación Od1 y Od2

2-cloro-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidina



1



2

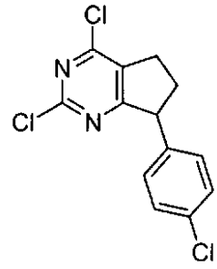
A una solución de la Preparación O (0,60 g, 2,1 mmol) en metanol se añadió diisopropiletilamina (0,516 g, 4,6 mmol) seguida por la adición de (S)-3-fluoropirrolidina (0,301 g, 2,2 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por HPLC preparativa dando 2-cloro-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidina (0,102 g, 39% de Isómero 1, 0,111 g, 40% de Isómero 2) como sólido blanquecino. CL-EM $(M+H)^+$ = 352,0.

Od1: RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,36-7,36 (2H, m), 7,16 (2H, m), 5,50 (2H, d, *J* = 8,4 Hz), 5,35 (1H, s), 3,58-3,98 (7H, m), 3,24-3,34 (1H, m), 2,78 (1H, d, *J* = 8,4 Hz), 2,04-2,28 (2H, m).

Od2: RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,19-7,33 (2H, m), 7,15-7,20 (2H, m), 5,34 (1H, m), 5,40 (1H, m), 3,91-4,10 (2H, m), 3,75-3,90 (2H, m), 3,69-3,75 (m, 2H), 3,05 (2H, t, *J* = 5,20 Hz), 2,01 (2H, d, *J* = 8,0 Hz).

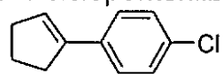
Preparación P

2,4-Dicloro-7-(4-clorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Intermedio P(1)

1-Cloro-4-ciclopentenilbenceno

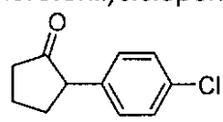


A una solución 1 M de bromuro de 4-clorofenil)magnesio (149 ml, 149 mmol) se añadió ciclopentanona (13,23 ml, 149 mmol). La solución se calentó tras la adición. La mezcla de reacción se agitó a reflujo durante 2 h. La mezcla de reacción se enfrió hasta temperatura ambiente y se enfrió con 10 g de hielo. Se añadió solución de ácido clorhídrico 6N hasta que se disolvió el precipitado completamente. Se añadió éter. La fase orgánica se separó y la fase acuosa se extrajo con éter. Los extractos orgánicos reunidos se lavaron con solución acuosa saturada de hidrógeno sulfito sódico, solución acuosa saturada de bicarbonato sódico y agua. La fase orgánica se secó sobre sulfato de magnesio anhidro y se filtró. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 1-cloro-4-ciclopentenilbenceno (20,0 g, 112 mmol, 75 % de rendimiento) como un aceite incoloro. CL-EM $(M+H)^+$ = 179,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,27 -

7,39 (4H, m), 6,19 (1H, s), 2,66 - 2,74 (2H, m), 2,52 - 2,61 (2H, m), 2,01 - 2,12 (2H, m).

Intermedio P(2)

2-(4-Clorofenil)ciclopentanona

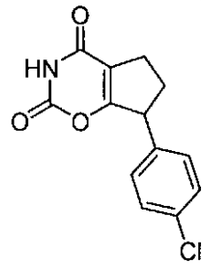


Una mezcla de ácido fórmico (60 ml, 84 mmol) y peróxido de hidrógeno (15 ml, 84 mmol) se calentó a 40°C durante 10 min. La solución resultante se añadió cuidadosamente a 1-cloro-4-ciclopentenilbenceno (15 g, 84 mmol) en agitación. El sistema bifásico se agitó inicialmente a temperatura ambiente. Después de un determinado periodo de tiempo, tuvo lugar una reacción exotérmica espontánea, y la temperatura ascendió hasta aproximadamente 50°C. La mezcla de reacción se agitó a temperatura ambiente durante 1 h. El análisis por CL/EM de la mezcla de reacción muestra la desaparición del material de partida y formación del producto. La mezcla de reacción se enfrió mediante la adición cuidadosa de una solución saturada de bicarbonato sódico. Se añadió éter y la mezcla de reacción se removió vigorosamente. La fase orgánica se separó y la fase acuosa se extrajo con éter. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2-(4-clorofenil)ciclopentanona (5,7 g, 29,3 mmol, 34,9 % de rendimiento) como un aceite incoloro. CL-EM $(M+H)^+$ = 195,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,21 - 7,37 (2H, m), 7,11 (2H, d, *J*=8,5 Hz), 3,25 (1H, dd, *J*=11,6, 8,5 Hz), 2,44 (2H, d, *J*=6,1 Hz), 2,15 - 2,31 (1H, m),

1,96 - 2,15 (3H, m), 1,78 - 1,95 (1H, m).

Intermedio P(3)

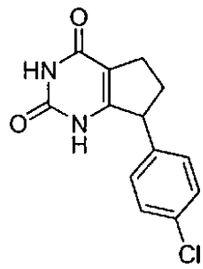
7-(4-Clorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona



Se agitó a 58 °C en un recipiente de alta presión durante 1 h una solución de 2-(4-clorofenil)ciclopentanona (7,80 g, 40,1 mmol) y cloruro carbonisocianatídico (7,61 g, 72,1 mmol). La temperatura se elevó hasta 130 °C y la mezcla de reacción se agitó durante otras 2 h. Después de enfriar hasta ta, la mezcla de reacción solidificó. El residuo sólido se disolvió en acetato de etilo y se lavó con solución acuosa saturada de bicarbonato sódico. La fase orgánica se separó y la fase acuosa se extrajo dos veces con acetato de etilo. Los extractos orgánicos reunidos se secaron sobre sulfato sódico anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo oleoso se purificó por cromatografía en columna sobre gel de sílice proporcionando 7-(4-clorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (5,4 g, 20,48 mmol, 51,1 % de rendimiento). CL-EM $(M+H)^+$ = 264,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,32 (2H, d, *J*=8,5 Hz), 7,12 (2H, d, *J*=8,5 Hz), 4,15 - 4,25 (1H, m), 2,56 - 2,93 (4H, m).

Intermedio P(4)

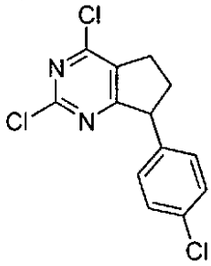
7-(4-Clorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona



Se agitó a 100 °C en un recipiente de alta presión durante 6 h una solución de 7-(4-clorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (5,4 g, 20,48 mmol) en hidróxido amónico concentrado (59,8 ml, 1536 mmol). La formación del precipitado blanco se observó durante el calentamiento. El disolvente se eliminó a vacío proporcionando 7-(4-clorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona (4,9 g, 18,65 mmol, 91 % de rendimiento) como un sólido blanquecino. CL-EM $(M+H)^+$ = 263,2. RMN de ^1H (500 MHz, *DMSO-d*$_6$) δ ppm 7,37 (2H, d, *J*=8,2 Hz), 7,19 (1H, d, *J*=8,5 Hz), 4,16 (1H, d, *J*=5,2 Hz), 3,79 (1H, s ancho), 3,17 (1H, s), 2,51 (2H, d, *J*=1,8 Hz), 1,75 - 1,85 (1H, m).

Preparación P

2,4-Dicloro-7-(4-clorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina

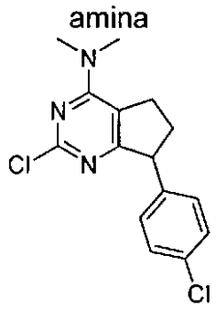


Se calentó a 110 °C durante la noche una mezcla de 7-(4-clorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona (4,7 g, 17,89 mmol), $POCl_3$ (53,4 ml, 573 mmol) y *N*,*N*-dimetilanilina (18,26 ml, 143 mmol). La mezcla de

reacción se vertió en un vaso de precipitados con hielo. Las paredes internas del recipiente de reacción se lavaron con DCM. Tan pronto como el hielo se fundió completamente, la fase orgánica se separó y la fase acuosa se extrajo con DCM. Los extractos orgánicos reunidos se secaron sobre sulfato sódico anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice proporcionando 2,4-dicloro-7-(4-clorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (1,2 g, 4,01 mmol, 22,39 % de rendimiento). CL-EM $(M+H)^+$ = 299,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,41 - 7,99 (2H, m), 7,09 (2H, d, *J*=8,5 Hz), 4,41 (1H, t, *J*=8,4 Hz), 2,94 - 3,18 (2H, m), 2,73 (1H, dt, *J*=8,9, 4,5 Hz), 2,15 - 2,33 (1H, m).

Preparación Pa

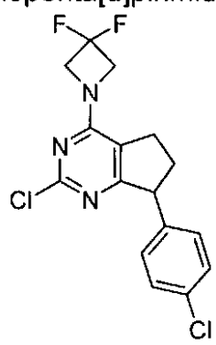
2-Cloro-7-(4-clorofenil)-*N*,*N*-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina



Se agitó a ta durante 30 min una solución de 2,4-dicloro-7-(4-clorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (200 mg, 0,668 mmol) y dimetilamina en exceso (3,34 ml, 6,68 mmol) en MeOH (4 ml). El disolvente se eliminó a vacío y el producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando 2-cloro-7-(4-clorofenil)-*N*,*N*-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (98 mg, 0,318 mmol, 47,6 % de rendimiento). CL-EM $(M+H)^+$ = 308,1.

Preparación Pb

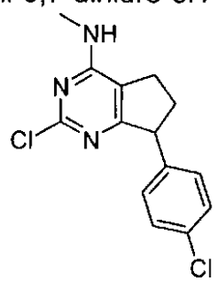
2-Cloro-7-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Se agitó a ta durante 1 h una solución de 2,4-dicloro-7-(4-clorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (325 mg, 1,085 mmol), *N*-etil-*N*-isopropilpropan-2-amina (0,945 ml, 5,42 mmol) y 3,3-difluoroazetidina, sal HCl (281 mg, 2,170 mmol) en MeOH (5 ml). El disolvente se eliminó a vacío y el producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando 2-cloro-7-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (70 mg, 0,197 mmol, 18,12 % de rendimiento). CL-EM $(M+H)^+$ = 356,1.

Preparación Pc

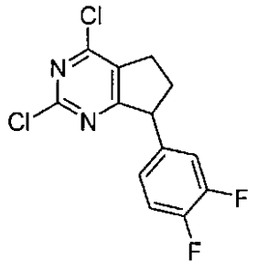
2-Cloro-7-(4-clorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina



Se agitó a ta durante 30 min una solución de 2,4-dicloro-7-(4-clorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (300 mg, 1,001 mmol), metanamina, sal HCl (135 mg, 2,003 mmol) y DIPEA (0,700 ml, 4,01 mmol) en MeOH (6 ml). El disolvente se eliminó a vacío y el producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando 2-cloro-7-(4-clorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (101 mg, 0,343 mmol, 34,3 % de rendimiento). CL-EM $(M+H)^+$ = 294,2.

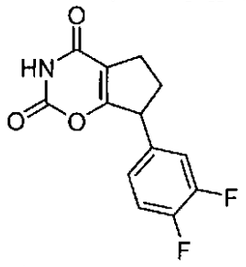
Preparación Q

2,4-Dicloro-7-(3,4-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Intermedio Q(1)

7-(3,4-Difluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona



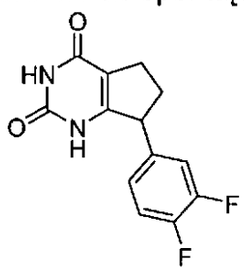
Se agitó a 58 °C una solución de 2-(3,4-difluorofenil)ciclopentanona, (preparada de la forma en que el Intermedio P(1) y P(2)) (1,5 g, 7,65 mmol) y cloruro carbonisocianatídico (1,129 g, 10,70 mmol) en un recipiente de alta presión durante 1 h. La temperatura se elevó hasta 130 °C y la mezcla de

reacción se agitó durante otras 2 h. Después de enfriar hasta ta, la mezcla de reacción solidificó. El residuo sólido se disolvió en acetato de etilo y se lavó con solución acuosa saturada de bicarbonato sódico. La fase orgánica se separó y la fase acuosa se extrajo dos veces con acetato de etilo. Los extractos orgánicos reunidos se secaron sobre sulfato sódico anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo oleoso se purificó por cromatografía en columna sobre gel de sílice proporcionando 7-(3,4-difluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (1,05 g, 3,96 mmol, 51,8 % de rendimiento) como un sólido blanco.

RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 8,16 (1H, s ancho), 7,15 (1H, dt, *J*=10,0, 8,3 Hz), 6,97 - 7,05 (1H, m), 6,88 - 6,95 (1H, m), 2,80 - 2,90 (1H, m), 2,61 - 2,78 (2H, m), 0,78 - 0,86 (2H, m).

Intermedio Q(2)

7-(3,4-Difluorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona

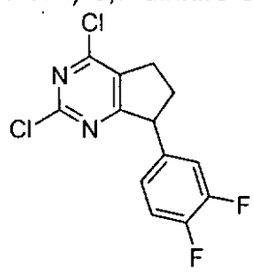


Una solución de 7-(3,4-difluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (1,05 g, 3,96 mmol) en hidróxido amónico concentrado (0,154 ml, 3,96 mmol) se agitó a 100 °C en un recipiente de alta presión (75 ml) durante 6 h. Se observó formación de precipitado blanco durante el calentamiento. El disolvente se eliminó a vacío proporcionando 7-(3,4-difluorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona (1,046 g,

3,96 mmol, 100 % de rendimiento) como un sólido blanquecino. CL-EM $(M+H)^+$ = 265,2.

Preparación Q

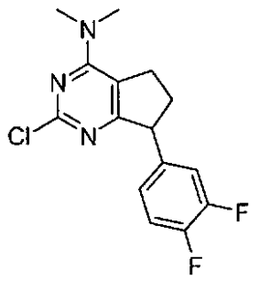
2,4-Dicloro-7-(3,4-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Se calentó a 120 °C durante la noche una mezcla de 7-(3,4-difluorofenil)-6,7-dihidro-*1H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona (500 mg, 1,892 mmol), $POCl_3$ (5644 µl, 60,6 mmol) y *N*,*N*-dimetilanilina (1931 µl, 15,14 mmol). La mezcla de reacción se vertió en un vaso de precipitados con hielo. Las paredes internas del recipiente de reacción se lavaron con DCM. Tan pronto como el hielo se fundió completamente, el contenido del vaso de precipitados se colocó en un embudo de separación. La fase orgánica se separó y la fase acuosa se extrajo con DCM. Los extractos orgánicos reunidos se secaron sobre sulfato sódico anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice proporcionando 2,4-dicloro-7-(3,4-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (446 mg, 1,481 mmol, 78 % de rendimiento). CL-EM $(M+H)^+$ = 301,1.

Preparación Qa

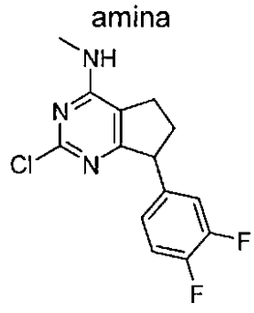
2-Cloro-7-(3,4-difluorofenil)-*N*,*N*-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina



Se agitó a ta durante 30 min una solución de 2,4-dicloro-7-(3,4-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (446 mg, 1,481 mmol) y dimetilamina en exceso (2,222 ml, 4,44 mmol) en MeOH (6 ml). El disolvente se eliminó a vacío y el producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando 2-cloro-7-(3,4-difluorofenil)-*N*,*N*-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (146 mg, 0,471 mmol, 31,8 % de rendimiento). CL-EM $(M+H)^+$ = 310,2.

Preparación Qb

2-Cloro-7-(3,4-difluorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina

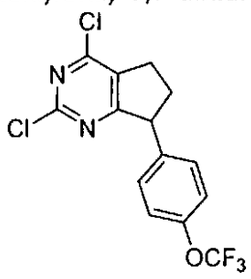


Se agitó a ta durante 1 h una solución de 2,4-dicloro-7-(3,4-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (421 mg, 1,398 mmol), metanamina, HCl (283 mg, 4,19 mmol) y DIPEA (1,465 ml, 8,39 mmol) en metanol (10 ml). El disolvente se eliminó a vacío y el producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando 2-cloro-7-(3,4-difluorofenil)-*N*-

metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (154 mg, 0,521 mmol, 37,2 % de rendimiento). CL-EM $(M+H)^+$ = 296,2.

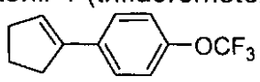
Preparación R

2,4-dicloro-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina



Intermedio R(1)

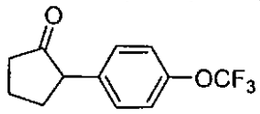
1-ciclopentenil-4-(trifluorometoxi)benceno



Se hizo reaccionar bromuro de (4-(trifluorometoxi)fenil)magnesio en la forma del Intermedio P(1) dando 1-ciclopentenil-4-(trifluorometoxi)benceno.

Intermedio R(2)

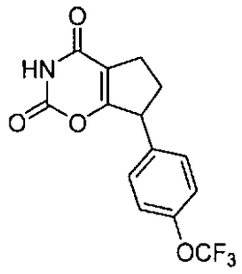
2-(4-(trifluorometoxi)fenil)ciclopentanona



Se hizo reaccionar 1-ciclopentenil-4-(trifluorometoxi)benceno en la forma del Intermedio P(2) dando 2-(4-(trifluorometoxi)fenil)ciclopentanona.

Intermedio R(3)

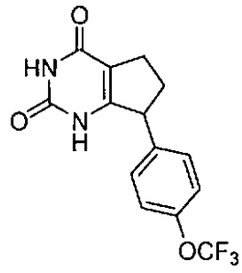
7-(4-(trifluorometoxi)fenil)-6,7-dihidrociclopenta[e][1,3]oxazin-2,4(3H,5H)-diona



Se hizo reaccionar 2-(4-(trifluorometoxi)fenil)ciclopentanona en la forma del Intermedio P(3) proporcionando 7-(4-(trifluorometoxi)fenil)-6,7-dihidrociclopenta[e][1,3]oxazin-2,4(3H,5H)-diona.

Intermedio R(4)

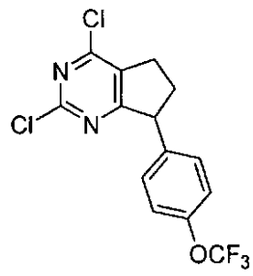
7-(4-(trifluorometoxi)fenil)-6,7-dihidro-1H-ciclopenta[d]pirimidin-2,4(3H,5H)-diona



Se hizo reaccionar 7-(4-(trifluorometoxi)fenil)-6,7-dihidrociclopenta[e][1,3]oxazin-2,4(3H,5H)-diona en la forma del Intermedio P(4) proporcionando 7-(4-(trifluorometoxi)fenil)-6,7-dihidro-1H-ciclopenta[d]pirimidin-2,4(3H,5H)-diona.

Preparación R

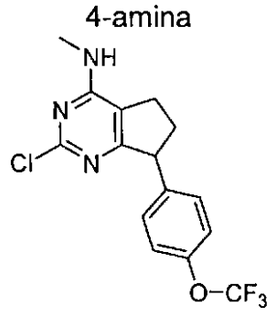
2,4-dicloro-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina



Se hizo reaccionar 7-(4-(trifluorometoxi)fenil)-6,7-dihidro-1H-ciclopenta[d]pirimidin-2,4(3H,5H)-diona en la forma que la Preparación P proporcionando 2,4-dicloro-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina como un sólido rosa. CL-EM $(M+H)^+$ = 349,2. RMN de ^1H (500 MHz, *CD3OD*) δ ppm 7,31 (2H, dd, *J* =2,0, 7,7 Hz), 7,25 (2H, d, *J*=7,4 Hz), 4,56 (1H, t, *J*=8,8 Hz), 3,15 (1H, ddd, *J* = 3,8, 9,1, 16,9 Hz), 3,09-3,00 (1H, m), 2,81-2,72 (1H, m), 2,27-2,22 (1H,m).

Preparación Ra

2-Cloro-*N*-metil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina

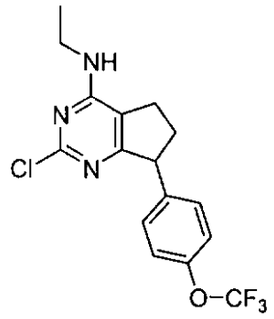


Se agitó a ta durante 1 h una solución de 2,4-dicloro-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (200 mg, 0,573 mmol), y metanamina (0,286 ml, 0,573 mmol) en MeOH (5 ml). El disolvente se eliminó a vacío proporcionando 2-cloro-*N*-metil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina bruta (220 mg, 0,640 mmol, 112 % de

rendimiento). CL-EM $(M+H)^+$ = 343,9.

Preparación Rb

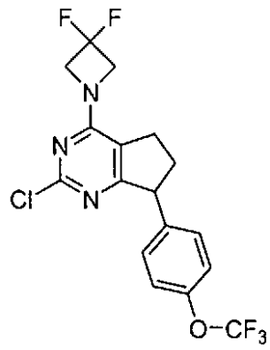
2-Cloro-*N*-etil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina



Se agitó a ta durante 1 h una solución de 2,4-dicloro-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (200 mg, 0,573 mmol), y etanamina (0,286 ml, 0,573 mmol) en MeOH (2 ml). El disolvente se eliminó a vacío y el producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando 2-cloro-*N*-etil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (190 mg, 0,531 mmol, 93 % de rendimiento). CL-EM $(M+H)^+$ = 358,2.

Preparación Rc

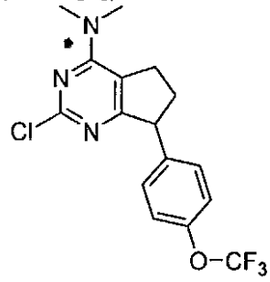
2-Cloro-4-(3,3-difluoroazetidin-1-il)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Se agitó a ta durante 1,5 h una solución de 2,4-dicloro-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (250 mg, 0,716 mmol), 3,3-difluoroazetidina, sal HCl (186 mg, 1,432 mmol) y DIPEA (0,500 ml, 2,86 mmol) en MeOH (3 ml). El disolvente se eliminó a vacío y el producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando 2-cloro-4-(3,3-difluoroazetidin-1-il)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (244 mg, 0,601 mmol, 84 % de rendimiento). CL-EM $(M+H)^+$ = 406,0.

Preparación Rd

2-Cloro-*N*,*N*-dimetil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina

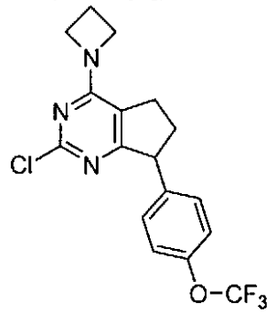


Se agitó a ta durante 1 h una solución de 2,4-dicloro-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (250 mg, 0,716 mmol) y dimetilamina (0,716 ml, 1,432 mmol) en MeOH (2 ml). El disolvente se

eliminó a vacío y el producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando 2-cloro-*N*,*N*-dimetil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (250 mg, 0,699 mmol, 98 % de rendimiento). CL-EM $(M+H)^+$ = 358,0.

Preparación Re

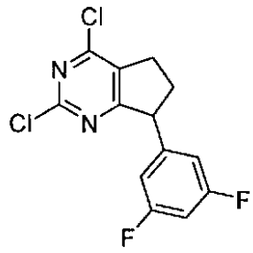
4-(Azetidin-1-il)-2-cloro-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Se agitó a ta durante 1 h una solución de 2,4-dicloro-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (250 mg, 0,716 mmol) y azetidina (82 mg, 1,432 mmol) en MeOH (3 ml). El disolvente se eliminó a vacío y el producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando 4-(azetidin-1-il)-2-cloro-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (238 mg, 0,644 mmol, 90 % de rendimiento). CL-EM $(M+H)^+$ = 371,2.

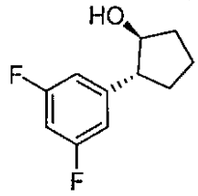
Preparación S

2,4-Dicloro-7-(3,5-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Intermedio S(1)

(1S,2R)-2-(3,5-Difluorofenil)ciclopentanol



Se cargó un matraz con bromuro de (3,5-difluorofenil)magnesio (149 ml, 149 mmol) y yoduro de cobre (I) (1,901 g, 9,98 mmol). A esta mezcla de reacción, se añadió gota a gota 6-oxabiciclo[3,1,0]hexano (12,53 g, 149 mmol) disuelto en THF (25 ml). La mezcla de reacción se calentó tras la adición del epóxido. La reacción se agitó a ta durante 2 h a ta. La mezcla de reacción se enfrió mediante la adición de una solución de cloruro amónico. Se añadió éter y la fase orgánica se recogió, se secó (Na_2SO_4) y se concentró. El producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando (1S,2R)-2-(3,5-difluorofenil)ciclopentanol (26,5 g, 134 mmol, 90 % de rendimiento).

RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 6,72 (2H, dd, *J*=8,7, 2,0 Hz), 6,50 - 6,63 (1H, m), 2,97 (1H, s ancho), 2,78 (1H, d, *J*=10,1 Hz), 1,96 - 2,15 (2H, m), 1,66 - 1,85 (2H, m), 1,53 - 1,65 (2H, m).

Intermedio S(2)

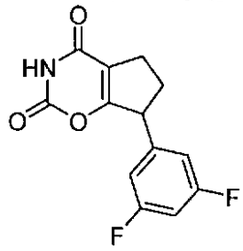
2-(3,5-Difluorofenil)ciclopentanona



A una solución de (1S,2R)-2-(3,5-difluorofenil)ciclopentanol (6 g, 30,3 mmol) en CH_2Cl_2 (150 ml) se añadió peryodinano de Dess-Martin (15,41 g, 36,3 mmol). La mezcla de reacción se agitó a ta durante 3 h. La mezcla de reacción se diluyó con diclorometano y se enfrió con la adición de NaOH 1 N. La fase orgánica se recogió, se secó (Na_2SO_4) y se concentró. El producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando 2-(3,5-difluorofenil)ciclopentanona (4,765 g, 24,29 mmol, 80 % de rendimiento). CL-EM $(M+H)^+$ = 197,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 6,70 (2H, d, *J*=6,7 Hz), 6,52 - 6,67 (1H, m), 3,17 - 3,33 (1H, m), 2,33 - 2,56 (2H, m), 2,06 - 2,26 (2H, m), 2,01 (1H, dd, *J*=11,7, 6,3 Hz), 1,89 (1H, s ancho).

Intermedio S(3)

7-(3,5-difluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona

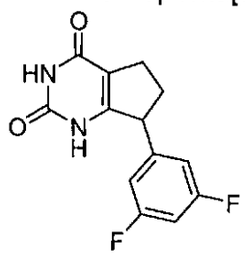


Se calentó a 58ºC durante 1 h y a 130 ºC durante 2 h una mezcla de 2-(3,5-difluorofenil)ciclopentanona (4,765 g, 24,29 mmol) y cloruro carbonisocianatídico (4,61 g, 43,7 mmol). Tras enfriar hasta temperatura ambiente, la mezcla de reacción se disolvió en acetato de etilo y se lavó con solución acuosa saturada de bicarbonato sódico. La fase orgánica se separó y

la fase acuosa se extrajo con acetato de etilo. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 7-(3,5-difluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (700 mg, 2,64 mmol, 10,87 % de rendimiento). CL-EM $(M+H)^+$ = 266,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,79 (1H, s ancho), 6,68 - 6,86 (3H, m), 4,22 (1H, s ancho), 2,87 (1H, dt, *J*=7,0, 4,4 Hz), 2,63 - 2,82 (2H, m), 2,15 (1H, s ancho).

Intermedio S(4)

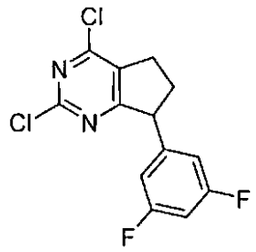
7-(3,5-Difluorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona



Se calentó a 100ºC en un recipiente de alta presión (350 ml) durante la noche una solución de 7-(3,5-difluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (700 mg, 2,64 mmol) en hidróxido amónico concentrado (50 ml, 1284 mmol). La mezcla de reacción se enfrió y se concentró a vacío dando 7-(3,5-difluorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona bruta (740 mg, 2,80 mmol, 106 % de rendimiento). CL-EM $(M+H)^+$ = 265,0.

Preparación S

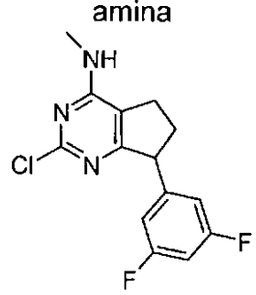
2,4-Dicloro-7-(3,5-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Se calentó en microondas a 110 °C durante 1 h una solución de 7-(3,5-difluorofenil)-6,7-dihidro-1*H*-ciclopenta[d]pirimidin-2,4(3*H*,5*H*)-diona (740 mg, 2,80 mmol) en tricloruro de fosforilo (7,691 ml, 84 mmol). La mezcla de reacción se vertió en hielo. Una vez fundido el hielo, el producto se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2,4-dicloro-7-(3,5-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (200 mg, 0,664 mmol, 23,72 % de rendimiento). CL-EM $(M+H)^+$ = 301,0.

Preparación Sa

2-Cloro-7-(3,5-difluorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina

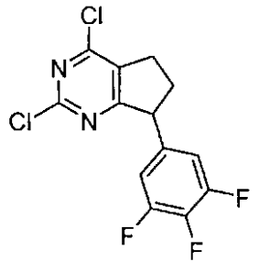


Se agitó a ta durante 1 h una solución de 2,4-dicloro-7-(3,5-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (200 mg, 0,664 mmol) y metanamina (0,664 ml, 1,328 mmol) en MeOH (3 ml). El disolvente se eliminó a vacío y el

producto bruto se purificó por cromatografía en columna sobre gel de sílice dando 2-cloro-7-(3,5-difluorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (60 mg, 0,203 mmol, 30,5 % de rendimiento). CL-EM $(M+H)^+$ = 296,1.

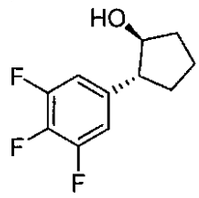
Preparación T

2,4-Dicloro-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Intermedio T(1)

(1S,2R)-2-(3,4,5-Trifluorofenil)ciclopentanol



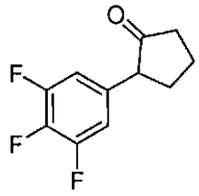
A una suspensión de magnesio (2,88 g, 118 mmol) en THF (110 ml) se añadió lentamente 5-bromo-1,2,3-trifluorobenceno (25 g, 118 mmol). Después de la adición, la mezcla de reacción se calentó a reflujo durante 2 h. A esta mezcla de reacción, se añadieron gota a gota yoduro de cobre (I) (1,506 g, 7,91 mmol) y 6-oxabiciclo[3,1,0]hexano (9,93 g, 118 mmol) disuelto en THF (20 ml). La mezcla de reacción se calentó tras la adición del epóxido. La reacción se agitó a ta durante 2 h a ta. La mezcla de reacción se enfrió mediante la adición de una solución de cloruro de amonio. Se añadió éter y la fase orgánica se recogió, se secó (Na_2SO_4) y se concentró. El producto bruto se purificó por

cromatografía en columna sobre gel de sílice dando (1S,2R)-2-(3,4,5-trifluorofenil)ciclopentanol (20,2 g, 93 mmol, 79 % de rendimiento).

RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 6,79 - 7,02 (2H, m), 4,10 - 4,21 (1H, m), 2,75 - 2,91 (1H, m), 2,08 - 2,24 (2H, m), 1,75 - 1,93 (2H, m), 1,50 - 1,75 (2H, m).

Intermedio T(2)

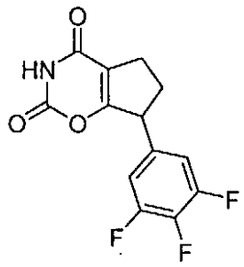
2-(3,4,5-Trifluorofenil)ciclopentanona



A una solución de (1S,2R)-2-(3,4,5-trifluorofenil)ciclopentanol (1 g, 4,63 mmol) en CH_2Cl_2 (20 ml) se añadió peryodinano de Dess-Martin (2,354 g, 5,55 mmol). La mezcla de reacción se agitó a ta durante 1 h. La reacción se diluyó con diclorometano y se enfrió con la adición de NaOH 1 N. La fase orgánica se recogió, se secó (Na_2SO_4) y se concentró. El producto bruto se purificó por cromatografía en columna sobre gel de sílice proporcionando 2-(3,4,5-trifluorofenil)ciclopentanona (310 mg, 1,447 mmol, 31,3 % de rendimiento). CL-EM $(M+H)^+$ = 215,1.

Intermedio T(3)

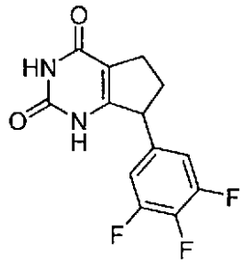
7-(3,4,5-Trifluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona



Se calentó a 58ºC durante 1 h y a 130 ºC durante 2 h una mezcla de 2-(3,4,5-trifluorofenil)ciclopentanona (2 g, 9,34 mmol) y cloruro carbonisocianatídico (1,773 g, 16,81 mmol). Tras enfriar hasta temperatura ambiente, la mezcla de reacción se disolvió en acetato de etilo y se lavó con solución acuosa saturada de bicarbonato sódico. La fase orgánica se separó y la fase acuosa se extrajo con acetato de etilo. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 7-(3,4,5-trifluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (1,227 g, 4,33 mmol, 46,4 % de rendimiento). CL-EM $(M+H)^+$ = 284,0.

Intermedio T(4)

7-(3,4,5-Trifluorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona

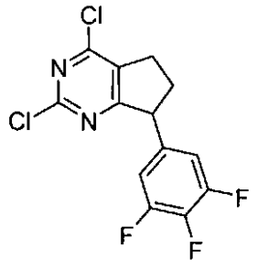


Una solución de 7-(3,4,5-trifluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (1,23 g, 4,34 mmol) en

hidróxido amónico concentrado (75 ml, 1926 mmol) se calentó a 100ºC en un recipiente de alta presión (350 ml) durante la noche. La mezcla de reacción se enfrió y se concentró a vacío dando 7-(3,4,5-trifluorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona bruta (1,3 g, 4,61 mmol, 106 % de rendimiento). CL-EM $(M+H)^+$ = 283,0.

Preparación T

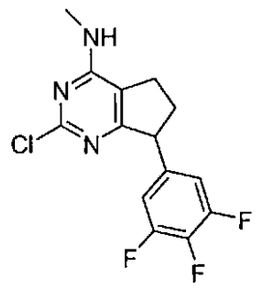
2,4-Dicloro-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Una solución de 7-(3,4,5-trifluorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona (1,3 g, 4,61 mmol) en tricloruro de fosforilo (5 ml, 54,6 mmol) se calentó en microondas a 110 ºC durante 1 h. La reacción se repitió con otros 800 mg del material de partida. Las mezclas de reacción se vertieron en hielo y se combinaron. Una vez fundido el hielo, el producto se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2,4-dicloro-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (498 mg, 1,561 mmol, 33,9 % de rendimiento). CL-EM $(M+H)^+$ = 318,9.

Preparación Ta

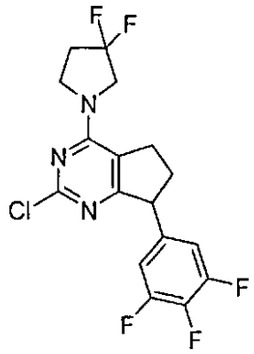
2-Cloro-*N*-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina



Se agitó a ta durante 1 h una solución de 2,4-dicloro-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (498 mg, 1,561 mmol) y metanamina (1,561 ml, 3,12 mmol) en MeOH (10 ml). Se observó reacción incompleta. Se añadieron más porciones de metanamina (1,561 ml, 3,12 mmol) a la mezcla de reacción hasta que se completó la reacción. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2-cloro-7-(3,5-difluorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (60 mg, 0,203 mmol, 30,5 % de rendimiento). CL-EM $(M+H)^+$ = 314,0.

Preparación Tb

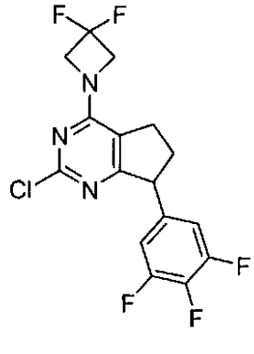
2-Cloro-4-(3,3-difluoropirrolidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Se agitó a ta durante 1 h una solución de 2,4-dicloro-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (100 mg, 0,313 mmol), DIPEA (0,066 ml, 0,376 mmol) y 3,3-difluoropirrolidina, sal HCl (45,0 mg, 0,313 mmol). El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2-cloro-4-(3,3-difluoropirrolidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (105 mg, 0,269 mmol, 86 % de rendimiento). CL-EM $(M+H)^+$ = 390,0.

Preparación Tc

2-Cloro-4-(3,3-difluoroazetidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina

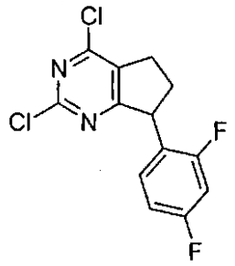


Se agitó a ta durante 1 h una solución de 2,4-dicloro-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (100 mg, 0,313 mmol),

DIPEA (0,109 ml, 0,627 mmol) y 3,3-difluoroazetidina, sal HCl (44,7 mg, 0,345 mmol). El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2-cloro-4-(3,3-difluoroazetidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (105 mg, 0,279 mmol, 89 % de rendimiento). CL-EM $(M+H)^+$ = 376,0.

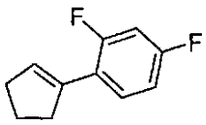
Preparación U

2,4-Dicloro-7-(2,4-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina



Intermedio U(1)

1-Ciclopentenil-2,4-difluorobenceno

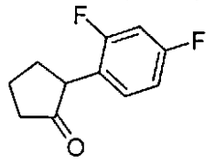


A una solución 0,497M de bromuro de (2,4-difluorofenil)magnesio (32,4 g, 149 mmol) en THF a 0°C se añadió cuidadosamente ciclopentanona (13,23 ml, 149 mmol). Tras terminar la adición, la mezcla de reacción se calentó a reflujo durante 2 h. Se añadieron hielo (10 g) y ácido clorhídrico acuoso 6N. La mezcla de reacción se extrajo con éter. Los extractos orgánicos reunidos se lavaron con una solución acuosa saturada de hidrógeno sulfito sódico, una solución acuosa saturada de bicarbonato sódico y agua. La fase orgánica se secó sobre sulfato de magnesio anhidro y se filtró. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice

dando 1-ciclopentenil-2,4-difluorobenceno (7,064 g, 39,2 mmol, 26,3 % de rendimiento) como aceite incoloro. CL-EM $(M+H)^+$ = 181,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,22 - 7,31 (1H, m), 6,75 - 6,85 (2H, m), 6,26 - 6,31 (1H, m), 2,68 - 2,74 (2H, m), 2,51 - 2,58 (2H, m), 1,93 - 2,02 (2H, m).

Intermedio U(2)

2-(2,4-Difluorofenil)ciclopentanona

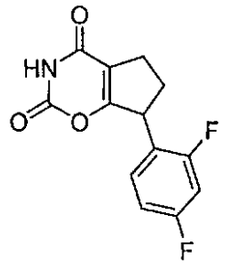


Se calentó a 40°C durante 10 min una mezcla de ácido fórmico al 90% (26,4 ml, 689 mmol) y peróxido de hidrógeno al 30% (6,0 ml, 39,2 mmol). La solución resultante se añadió cuidadosamente a 1-ciclopentenil-2,4-difluorobenceno (7,064 g, 39,2 mmol) en agitación. El sistema bifásico se agitó inicialmente a temperatura ambiente. Después de un determinado período de tiempo, tuvo lugar una reacción exotérmica espontánea, y la temperatura ascendió hasta aproximadamente 50°C. La mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se enfrió mediante la adición cuidadosa de una solución saturada de bicarbonato sódico. Se añadió éter y el contenido del embudo de separación se removió vigorosamente. La fase orgánica se separó y la fase acuosa se extrajo con éter. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2-(2,4-difluorofenil)ciclopentanona (3,503 g, 17,85 mmol, 45,5 % de rendimiento) como aceite incoloro. CL-EM $(M+H)^+$ =

195,2. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 7,08 (1H, td, *J*=8,4, 6,4 Hz), 6,76 - 6,86 (2H, m), 3,42 (1H, dd, *J*=12,2, 8,9 Hz), 2,42 - 2,53 (2H, m), 2,28 - 2,39 (1H, m), 2,13 - 2,23 (1H, m), 1,86 - 2,10 (2H, m).

Intermedio U(3)

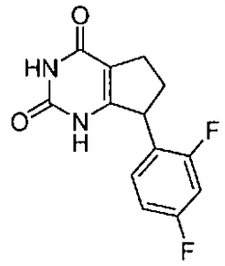
7-(2,4-Difluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona



Se calentó a 58 ºC durante 1 h y a 120ºC durante 3 h una mezcla de 2-(2,4-difluorofenil)ciclopentanona (1,014 g, 5,17 mmol) y solución al 50% en peso de cloruro carbonisocianatídico en tolueno (1,963 g, 9,30 mmol). La mezcla de reacción se disolvió en acetato de etilo y se lavó con una solución acuosa de bicarbonato sódico. La fase orgánica se separó y la fase acuosa se extrajo con acetato de etilo. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 7-(2,4-difluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (499,3 mg, 1,883 mmol, 36,4 % de rendimiento) como sólido marrón. CL-EM $(M+H)^+$ = 266,2. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 8,19 - 8,64 (1H, m), 7,10 (1H, td, *J*=8,5, 6,3 Hz), 6,78 - 6,92 (2H, m), 4,36 - 4,49 (1H, m), 2,79 - 2,92 (1H, m), 2,59 - 2,78 (2H, m), 2,08 (1H, ddd, *J*=9,3, 6,9, 6,7 Hz).

Intermedio U(4)

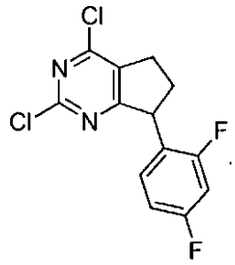
7-(2,4-Difluorofenil)-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-diona



Se calentó a 58 °C durante 1 h y a 120°C durante 3 h una mezcla de 2-(2,4-difluorofenil)ciclopentanona (1,014 g, 5,17 mmol) y solución al 50% en peso de cloruro carbonisocianatídico en tolueno (1,963 g, 9,30 mmol). La mezcla de reacción se disolvió en acetato de etilo y se lavó con una solución acuosa de bicarbonato sódico. La fase orgánica se separó y la fase acuosa se extrajo con acetato de etilo. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtrarón. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 7-(2,4-difluorofenil)-6,7-dihidrociclopenta[*e*][1,3]oxazin-2,4(3*H*,5*H*)-diona (499,3 mg, 1,883 mmol, 36,4 % de rendimiento) como sólido marrón. CL-EM $(M+H)^+$ = 265,1.

Preparación U

2,4-Dicloro-7-(2,4-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina

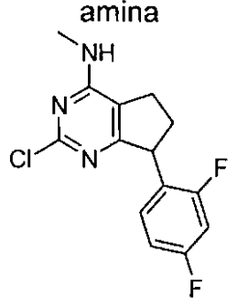


Una solución de 7-fenil-6,7-dihidro-1*H*-ciclopenta[*d*]pirimidin-2,4(3*H*,5*H*)-

diona (248,5 mg, 0,940 mmol) en tricloruro de fosforilo (10 ml) se calentó en microondas a 130 °C durante 2 h. La mezcla de reacción se vertió en un vaso de precipitados con hielo. Una vez fundido el hielo, el producto se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2,4-dicloro-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (267,9 mg, 95%) como sólido marrón claro. CL-EM $(M+H)^+$ = 301,1.

Preparación Ua

2-Cloro-7-(2,4-difluorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina

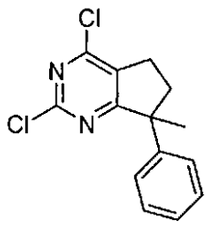


A una solución de 2,4-dicloro-7-(2,4-difluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (267,9 mg, 0,890 mmol) en metanol (5 ml) se añadió una solución 2M de metilamina en metanol (0,890 ml, 1,779 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó a vacío y el residuo se repartió entre acetato de etilo y agua. La fase orgánica se separó y la fase acuosa se extrajo con acetato de etilo. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2-cloro-7-(2,4-difluorofenil)-

N-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (184,6 mg, 0,624 mmol, 70,2 % de rendimiento) como sólido marrón. CL-EM $(M+H)^+$ = 296,1.

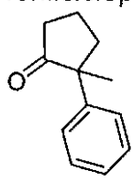
Preparación V

2,4-dicloro-7-metil-7-fenil-6,7-dihidro-5H- ciclopenta[d]pirimidina



Intermedio V(1)

2-metil-2-fenilciclopentanona

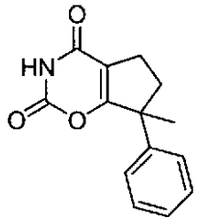


A una suspensión de NaH al 60% (125 mg, 3,12 mmol) en DME (3571 µl) a 0 °C se añadió 2-fenilciclopentanona (500 mg, 3,12 mmol). Después de agitar durante 1h, se añadió MeI (898 µl, 14,36 mmol), y la solución se calentó hasta reflujo durante 2h. La reacción se vertió en hielo y se extrajo 3 veces en Et_2O. Los extractos orgánicos se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron a vacío. Se aplicó sobre gel de sílice y

eluyó con un gradiente de EtOAc/Hex proporcionando 2-metil-2-fenilciclopentanona (401,7 mg, 2,305 mmol, 73,9 % de rendimiento). CL-EM $(M+H)^+$ = 175,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,29 - 7,37 (4 H, m), 7,20 - 7,24 (1 H, m), 2,54 (1 H, dt, *J*=12,51, 6,26 Hz), 2,34 (2 H, t, *J*=7,63 Hz), 1,82 - 2,05 (3 H, m), 1,38 (3 H, s).

Intermedio V(2)

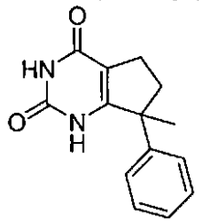
7-metil-7-fenil-6,7-dihidrociclopenta[e][1,3]oxazin-2,4(3H,5H)-diona



Se combinaron 2-metil-2-fenilciclopentanona (Intermedio V(1) (705,5 mg, 4,05 mmol) y cloruro carbonisocianatídico (1700 mg, 8,06 mmol), se llenó con N_2 y se selló en un tubo herméticamente cerrado. Se calentó a 58 °C durante 1 h, luego a 130 °C durante 1,75 h. Se dejó enfriar hasta ta. Se abrió cuidadosamente el tubo (HCl) y se disolvió el residuo en EtOAc. Se repartió con $NaHCO_3$ (ac) y se extrajo 3 veces en EtOAc. Se lavaron las fases orgánicas reunidas con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron a vacío. Se cargó el residuo sobre gel de sílice y se eluyó con un gradiente de EtOAc/Hexano proporcionando 7-metil-7-fenil-6,7-dihidrociclopenta[e][1,3]oxazin-2,4(3H,5H)-diona (43% de rendimiento) CL-EM $(M+H)^+$ = 244,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,12 (1 H, s ancho), 7,32 - 7,38 (2 H, m), 7,26 - 7,30 (3 H, m), 2,69 - 2,75 (2 H, m), 2,43 - 2,52 (1 H, m), 2,21 - 2,29 (1 H, m), 1,68 (3 H, s).

Intermedio V(3)

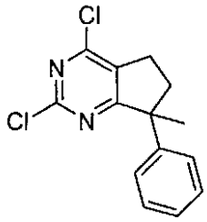
7-metil-7-fenil-6,7-dihidro-1H-ciclopenta[d]pirimidin-2,4(3H,5H)-diona



A 7-metil-7-fenil-6,7-dihidrociclopenta[e][1,3]oxazin-2,4(3H,5H)-diona sólida (420 mg, 1,727 mmol) se añadió hidróxido amónico concentrado (4706 µl, 121 mmol) en un tubo herméticamente cerrado. El tubo se calentó durante 4h a 80 °C. Se enfrió hasta ta. Se eliminó el disolvente bajo una corriente de N_2. Se cargó el residuo sobre gel de sílice y se eluyó con un gradiente de EtOAc/Hexano proporcionando 7-metil-7-fenil-6,7-dihidro-1H-ciclopenta[d]pirimidin-2,4(3H,5H)-diona (293 mg, 1,209 mmol, 70,0 % de rendimiento). CL-EM $(M+H)^+$ = 243,1.

Preparación V

2,4-dicloro-7-metil-7-fenil-6,7-dihidro-5H- ciclopenta[d]pirimidina

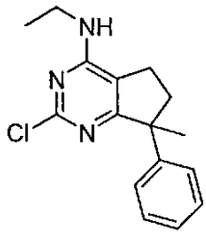


Se disolvió 7-metil-7-fenil-6,7-dihidro-1H-ciclopenta[d]pirimidin-2,4(3H,5H)-diona (48,2 mg, 0,199 mmol) en POCl3 (742 µl, 7,96 mmol) y se colocó en un vial de microondas. Se calentó la reacción durante 1h a 120 °C en el microondas. Se enfrió hasta ta y se vertió en hielo. Tan pronto como se

fundió el hielo, se extrajo 3 veces en EtOAc. Se secó sobre $MgSO_4$, se filtró y se concentró a vacío. Una columna SG rápida de EtOAc/Hex proporcionó 2,4-dicloro-7-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina (43,1 mg, 0,154 mmol, 78 % de rendimiento). CL-EM $(M+H)^+$ = 279,1.

Preparación Va

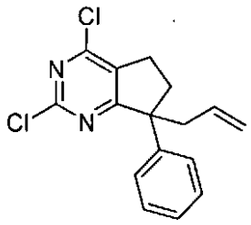
2-cloro-N-etil-7-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina



A una solución de 2,4-dicloro-7-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación V) (43,1 mg, 0,154 mmol) en THF (772 µl) a ta se añadió una solución de etilamina 2M (386 µl, 0,772 mmol) diluida con 390 ul de MeOH (la reacción global es,1M en 1:1 THF/MeOH). Se deja agitar a ta. Se elimina el disolvente y se somete el residuo a una columna de gel de sílice con un gradiente de EtOAc/Hex proporcionando 2-cloro-N-etil-7-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (38,0 mg, 0,132 mmol, 86 % de rendimiento).

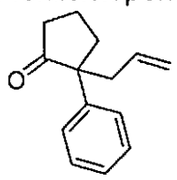
Preparación W

2,4-dicloro-7-alil-7-fenil-6,7-dihidro-5H- ciclopenta[d]pirimidina



Intermedio W(1)

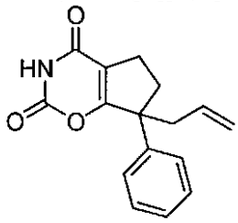
2-alil-2-fenilciclopentanona



Se utilizó el procedimiento del Intermedio V(1) con bromuro de alilo obteniendo 2-alil-2-fenilciclopentanona.

Intermedio W(2)

7-alil-7-fenil-6,7-dihidrociclopenta[e][1,3]oxazin-2,4(3H,5H)-diona

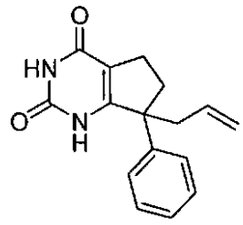


Se utilizó el procedimiento del Intermedio V(2) obteniendo 7-alil-7-fenil-6,7-dihidrociclopenta[e][1,3]oxazin-2,4(3H,5H)-diona.

RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 8,06 (1 H, s ancho), 7,23 - 7,43 (5 H, m), 5,59 - 5,72 (1 H, m, *J*=17,09, 9,99, 7,21, 7,21 Hz), 5,08 - 5,23 (2 H, m), 2,73 - 2,87 (2 H, m), 2,63 - 2,71 (2 H, m), 2,38 - 2,49 (2 H, m)

Intermedio W(3)

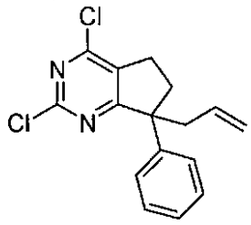
7-alil-7-fenil-6,7-dihidro-1H-ciclopenta[d]pirimidin-2,4(3H,5H)-diona



Se utilizó el procedimiento del Intermedio V(3) obteniendo 7-alil-7-fenil-6,7-dihidro-1H-ciclopenta[d]pirimidin-2,4(3H,5H)-diona. CL-EM $(M+H)^+$ = 269,1.

Preparación W

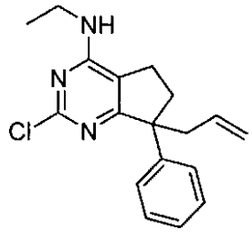
2,4-dicloro-7-alil-7-fenil-6,7-dihidro-5H- ciclopenta[d]pirimidina



Se utilizó el procedimiento del Intermedio V obteniendo 2,4-dicloro-7-alil-7-fenil-6,7-dihidro-5H- ciclopenta[d]pirimidina. CL-EM $(M+H)^+$ = 305,0.

Preparación Wa

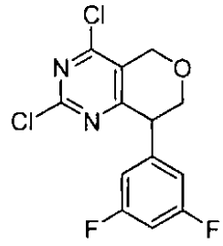
2-cloro-N-etil-7-alil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina



Utilizando el procedimiento para la Preparación Va, se obtuvo 2-cloro-N-etil-7-alil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina. CL-EM $(M+H)^+$ = 314,1.

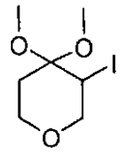
Preparación X

2,4-dicloro-8-(3,5-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



Intermedio X(1)

3-yodo-4,4-dimetoxitetrahidro-2H-pirano



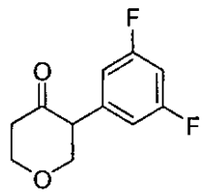
La mezcla de trimetoximetano (82 ml, 745 mmol) y dihidro-2H-piran-4(3H)-ona (14,92 g, 149 mmol) se enfrió hasta 4 °C. Se añadió diyodo (37,8 g, 149 mmol) en lotes y se mantuvo la temperatura de 4 °C a 5 °C. La mezcla de reacción se agitó a 4 °C durante 10 min. Se retiró el baño de enfriamiento, se agitó a 28 °C durante 10 min. La mezcla se enfrió hasta 10 °C y se agitó durante 10 min, y luego se agitó a ta durante 1 h.

La mezcla de reacción se diluyó con CH_2Cl_2 y se enfrió en agua helada. Se enfrió lentamente con solución saturada de $Na_2S_2O_3$. Las fases mezcladas se separaron. La fase acuosa se extrajo con CH_2Cl_2. La fase orgánica reunida se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró. El producto bruto se purificó por cromatografía en columna sobre gel de sílice dando 3-yodo-4,4-dimetoxitetrahidro-2H-pirano (33,05 g, 121 mmol, 82 % de rendimiento). RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 4,24 (1 H, t, J=2,29 Hz), 3,93 - 4,02 (1 H, m), 3,83 - 3,92 (2 H, m), 3,55 (1 H, d, J=2,44 Hz), 3,24 (3 H, s), 3,20 (3 H, s), 2,33

(1 H, dd, J=4,88, 2,14 Hz), 1,79 (1 H, dd, J=14,34, 2,44 Hz)

Intermedio X(2)

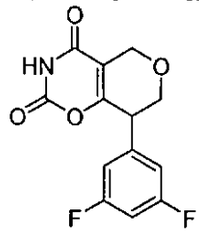
3-(3,5-difluorofenil)dihidro-2H-piran-4(3H)-ona



A una mezcla de (1R,2R)-2-aminociclohexanol clorhidrato de (0,418 g, 2,76 mmol), cloruro de níquel(II) hexahidratado (0,328 g, 1,378 mmol) y ácido 3,5-difluorofenilborónico (6,53 g, 41,3 mmol) se añadió NaHMDS en THF (55,1 ml, 55,1 mmol) a 10 °C gota a gota en N_2. Después de la adición, la mezcla se agitó a 10 °C durante 20 min. Se añadió 2-propanol (113 ml) (previamente infundido con N_2) a 0 °C y luego se agitó la mezcla a ta durante 10 min. Se añadió gota a gota 3-yodo-4,4-dimetoxitetrahidro-2H-pirano (Preparación X1) (7,5 g, 27,6 mmol) en THF y la mezcla se calentó a 60 °C durante la noche. La mezcla de reacción se enfrió en baño de hielo, se añadió HCl 1,0 hasta acidez y se agitó durante 10 min. Se concentró a vacío. Se extrajo con EtOAc y la fase orgánica se lavó con salmuera y se concentró. El residuo se purificó por cromatografía en columna sobre gel de sílice dando 3-(3,5-difluorofenil)dihidro-2H-piran-4(3H)-ona (1,6 g, 7,54 mmol, 27,4 % de rendimiento). RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 6,78 (dd, J=8,24, 2,14 Hz, 2 H) 6,62 - 6,75 (m, 1 H) 4,21 (dd, J=11,44, 5,65 Hz, 2 H) 3,85 - 4,01 (m, 2 H) 3,76 (dd, J=8,55, 6,10 Hz, 1 H) 2,60 - 2,75 (m, 1 H) 2,48 - 2,60 (m, 1 H)

Intermedio X(3)

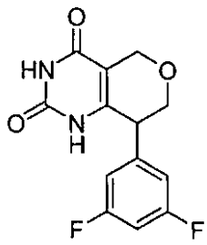
8-(3,5-difluorofenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona



La mezcla de 3-(3,5-difluorofenil) dihidro-2H-piran-4(3H)-ona (Preparación X2) (800 mg, 3,77 mmol) y cloruro carbonisocianatídico (557 mg, 5,28 mmol) se calentó en un frasco herméticamente cerrado a 55 °C durante 1 h y luego a 130 °C durante 2 h. La mezcla se enfrió hasta ta. Se repartió entre EtOAc y solución saturada de $NaHCO_3$. Se extrajo con EtOAc (x 3 veces). Las fases orgánicas reunidas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron. El producto bruto se purificó por cromatografía en columna sobre gel de sílice dando 8-(3,5-difluorofenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona (230 mg, 0,818 mmol, 21,69 % de rendimiento). CL-EM $(M+H)^+$ = 282,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,94 (s ancho, 1 H) 6,85 - 7,01 (m, 2 H) 6,81 (tt, J=8,81, 2,17 Hz, 1 H) 4,70 (d, J=15,56 Hz, 1 H) 4,49 (dd, J=15,56, 2,14 Hz, 1 H) 4,03 - 4,12 (m, 2 H) 3,68 (s ancho, 1 H).

Intermedio X(4)

8-(3,5-difluorofenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona



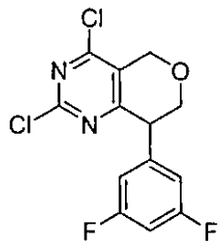
La mezcla de 8-(3,5-difluorofenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-

2,4(3H,5H)-diona (Preparación X3) (230 mg, 0,818 mmol) y hidróxido amónico (2229 µl, 57,3 mmol) en un frasco herméticamente cerrado se calentó a 80 °C durante 4 h. Se insufló N_2 durante la noche obteniendo 8-(3,5-difluorofenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona (191 mg, 0,682 mmol, 83 % de rendimiento) que se usó como tal.

CL-EM $(M+H)^+$ = 281,1.

Preparación X

2,4-dicloro-8-(3,5-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina

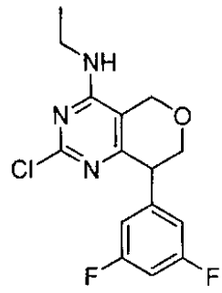


La mezcla de 8-(3,5-difluorofenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona (Intermedio X(4)) (191 mg, 0,682 mmol) y $POCl_3$ (1906 µl, 20,45 mmol) se calentó en un vial de microondas por microondas a 100 °C durante 2,5 h. La mezcla se vertió en hielo, cuando el hielo se fundió se extrajo con EtOAc (x 3 veces), se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró. El producto bruto se purificó por cromatografía en columna sobre gel de sílice dando 2,4-dicloro-8-(3,5-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (117 mg, 0,369 mmol, 54,1 % de rendimiento).

CL-EM $(M+H)^+$ = 317,1. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 6,66 - 6,91 (m, 3 H) 4,87 - 5,01 (m, 1 H) 4,70 - 4,83 (m, 1 H) 4,13 - 4,27 (m, 2 H) 4,10 (t, J=4,03 Hz, 1 H).

Preparación Xa

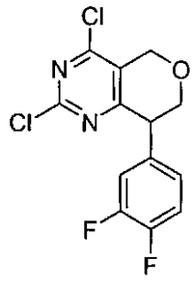
2-cloro-8-(3,5-difluorofenil)-N-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



La mezcla de etanamina (406 µl, 0,812 mmol), 2,4-dicloro-8-(3,5-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación X)(117 mg, 0,369 mmol) y DIEA (161 µl, 0,922 mmol) en THF (1845 µl) se agitó a ta durante 2 h. La mezcla se concentró y se purificó por cromatografía en columna sobre gel de sílice dando 2-cloro-8-(3, 5-difluorofenil)-N-etil-7, 8-dihidro-5H-pirano [4, 3-d] pirimidin-4-amina (104 mg, 0,319 mmol, 87 % de rendimiento). CL-EM $(M+H)^+$ = 326,1.

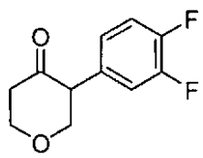
Preparación Y

2,4-dicloro-8-(3,4-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



Intermedio Y(2)

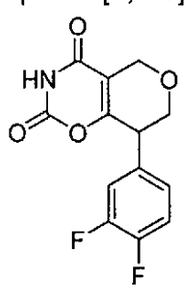
3-(3,4-difluorofenil)dihidro-2H-piran-4(3H)-ona



Se hizo reaccionar ácido 3,4-difluorofenilborónico como se describe en el Intermedio X(2) con 3-yodo-4,4-dimetoxitetrahidro-2H-pirano (Intermedio X(1)) dando 3-(3,4-difluorofenil)dihidro-2H-piran-4(3H)-ona (Intermedio Y(2)). RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 7,03 - 7,22 (m, 2 H) 6,95 (ddd, J=6,33, 4,20, 1,98 Hz, 1 H) 4,17 - 4,32 (m, 2 H) 3,96 (ddd, J=11,52, 9,84, 3,97 Hz, 1 H) 3,91 (dd, J=11,44, 9,00 Hz, 1 H) 3,77 (dd, J=8,85, 5,80 Hz, 1 H) 2,63 - 2,76 (m, 1 H) 2,49 - 2,62 (m, 1 H).

Intermedio Y(3)

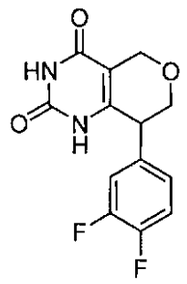
8-(3,4-difluorofenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona



Se hizo reaccionar 3-(3,4-difluorofenil)dihidro-2H-piran-4(3H)-ona (Intermedio Y(2)) como se describe en el Intermedio X(3) con cloruro carbonisocianatídico dando 8-(3,4-difluorofenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona (Intermedio Y(3)). CL-EM $(M+H)^+$ = 282,1. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 7,08 - 7,20 (m, 3 H) 4,67 (d, J=15,26 Hz, 1 H) 4,46 (dd, J=15,56, 2,14 Hz, 1 H) 3,98 - 4,10 (m, 2 H) 3,67 (s ancho, 1H).

Intermedio Y(4)

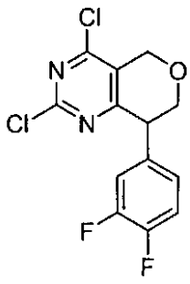
8-(3,4-difluorofenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona



Se hizo reaccionar 8-(3,4-difluorofenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona (Intermedio Y(3)) como se describe en el Intermedio X(4) con hidróxido amónico dando 8-(3,4-difluorofenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona (Intermedio Y(4)). CL-EM $(M-H)^+$ = 279,1.

Preparación Y

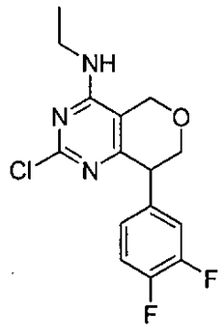
2,4-dicloro-8-(3,4-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



Se hizo reaccionar 2,4-dicloro-8-(3,4-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Intermedio Y(4)) como se describe en la Preparación X con $POCl_3$ dando 2,4-dicloro-8-(3,4-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación Y). CL-EM $(M+H)^+$ = 317,1.

Preparación Ya

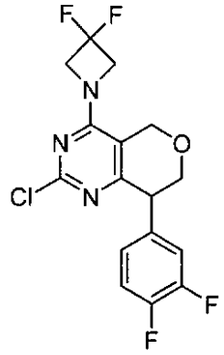
2-cloro-8-(3,4-difluorofenil)-N-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



Se hizo reaccionar 2,4-dicloro-8-(3,4-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación Y) como se describe en la Preparación Xa con etanamina dando 2-cloro-8-(3,4-difluorofenil)-N-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Ya). CL-EM $(M+H)^+$ = 326,1.

Preparación Yb

2-cloro-4-(3,3-difluoroazetidin-1-il)-8-(3,4-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina

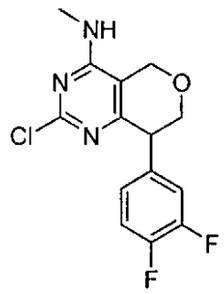


Se hizo reaccionar 2,4-dicloro-8-(3,4-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación Y) como se describe en la Preparación Xa con 3,3-difluoroazetidina, HCl dando 2-cloro-4-(3,3-difluoroazetidin-1-il)-8-(3,4-

difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación Yb). CL-EM $(M+H)^+$ = 374,1.

Preparación Yc

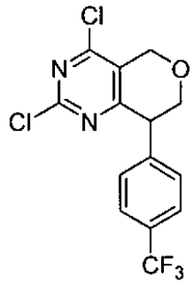
2-cloro-8-(3,4-difluorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



Se hizo reaccionar 2,4-dicloro-8-(3,4-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación Y) como se describe en la Preparación Xa con metanamina dando 2-cloro-8-(3,4-difluorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Yc). CL-EM $(M+H)^+$ = 312,3.

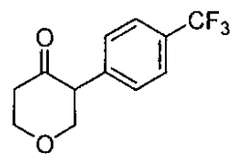
Preparación Z

2,4-dicloro-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



Intermedio Z(2)

3-(4-(trifluorometil)fenil)dihidro-2H-piran-4(3H)-ona

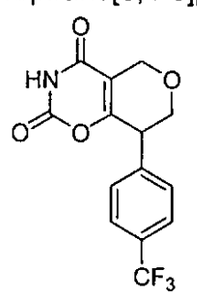


Se hizo reaccionar ácido 4-(trifluorometil)fenilborónico como se describe en el Intermedio X(2) con 3-yodo-4,4-dimetoxitetrahidro-2H-pirano (Intermedio X(1)) dando 3-(4-(trifluorometil)fenil)dihidro-2H-piran-4(3H)-ona (Intermedio Z(2)).

RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 7,61 (m, J=8,24 Hz, 2 H) 7,37 (m, J=7,93 Hz, 2 H) 4,26 (dd, J=11,44, 5,95 Hz, 2 H) 3,93 - 4,05 (m, 2 H) 3,82 - 3,93 (m, 1 H) 2,64 - 2,81 (m, 1 H) 2,49 - 2,64 (m, 1 H)

Intermedio Z(3)

8-(4-(trifluorometil)fenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona



Se hizo reaccionar como 3-(4-(trifluorometil)fenil)dihidro-2H-piran-4(3H)-ona (Intermedio Z(2)) se describe en el Intermedio X(3) con cloruro carbonisocianatídico dando 8-(4-(trifluorometil)fenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona

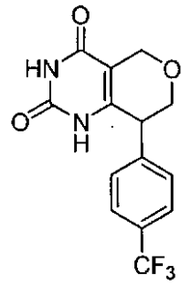
(Intermedio Z(3)).

RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 9,47 (s ancho, 1 H) 7,58 - 7,75 (m, 2 H) 7,42 - 7,55 (m, 2 H) 4,68 (d, J=15,56 Hz, 1 H) 4,42 - 4,57 (m, 1 H) 4,03 - 4,22

(m, 2 H) 3,79 (s ancho, 1 H)

Intermedio Z(4)

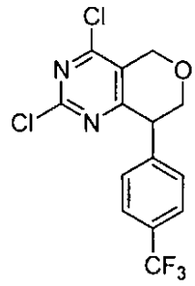
8-(4-(trifluorometil)fenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona



Se hizo reaccionar 8-(4-(trifluorometil)fenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona (Intermedio Z(3)) como se describe en el Intermedio X(4) con hidróxido amónico dando 8-(4-(trifluorometil)fenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona (Intermedio Z(4)). CL-EM $(M-H)^+$ = 313,1.

Preparación Z

2,4-dicloro-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina

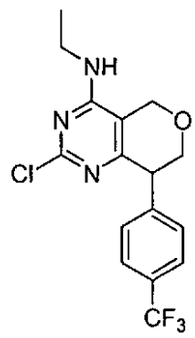


Se hizo reaccionar 8-(4-(trifluorometil)fenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona (Intermedio Z(4)) como se describe en la Preparación X con $POCl_3$ dando 2,4-dicloro-8-(4-(trifluorometil)fenil)-7,8-dihidro-

5H-pirano[4,3-d]pirimidina (Preparación Z). CL-EM $(M+H)^+$ = 349,1.

Preparación Za

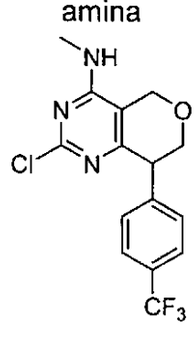
2-cloro-N-etil-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



Se hizo reaccionar 2,4-dicloro-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación Z) como se describe en la Preparación Xa con etanamina dando 2-cloro-N-etil-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Za). CL-EM $(M+H)^+$ = 358,1.

Preparación Zb

2-cloro-N-metil-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina

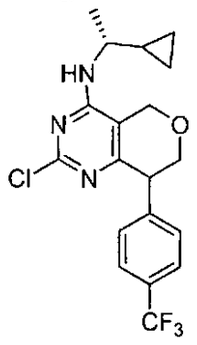


Se hizo reaccionar 2,4-dicloro-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-

pirano[4,3-d]pirimidina (Preparación Z) como se describe en la Preparación Xa con metanamina dando 2-cloro-N-metil-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Zb). CL-EM $(M+H)^+$ = 344,1.

Preparación Zc

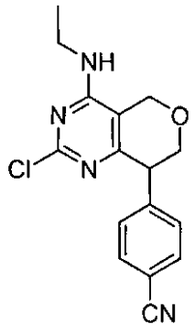
2-cloro-N-((R)-1-ciclopropiletil)-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



Se hizo reaccionar 2,4-dicloro-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación Z) como se describe en la Preparación Xa con (R)-1-ciclopropiletanamina, HCl dando 2-cloro-N-((R)-1-ciclopropiletil)-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Zc). CL-EM $(M+H)^+$ = 398,2.

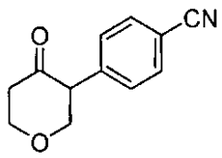
Preparación AAa

4-(2-cloro-4-(etilamino)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-8-il)benzonitrilo



Intermedio AA(2)

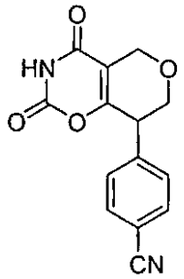
4-(4-oxotetrahidro-2H-piran-3-il)benzonitrilo



Se hizo reaccionar ácido 4-cianofenilborónico como se describe en el Intermedio X(2) con 3-yodo-4,4-dimetoxitetrahidro-2H-pirano (Intermedio X(1)) dando 4-(4-oxotetrahidro-2H-piran-3-il)benzonitrilo (Intermedio AA(2)). CL-EM $(M+H)^+$ = 202,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,66 (d, J=8,24 Hz, 2 H) 7,38 (d, J=8,55 Hz, 2 H) 4,23 - 4,31 (m, 2 H) 3,94 - 4,02 (m, 2 H) 3,85 - 3,92 (m, 1 H) 2,55 - 2,65 (m, 1 H) 2,52 (t, J=5,80 Hz, 1 H).

Intermedio AA(3)

4-(2,4-dioxo-2,3,4,5,7,8-hexahidropirano[3,4-e][1,3]oxazin-8-il)benzonitrilo

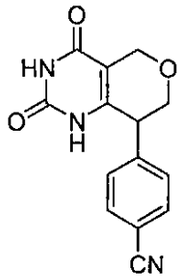


Se hizo reaccionar 4-(4-oxotetrahidro-2H-piran-3-il)benzonitrilo

(Intermedio AA(2)) como se describe en el Intermedio X(3) con cloruro carbonisocianatídico dando 4-(2,4-dioxo-2,3,4,5,7,8-hexahidropirano[3,4-e][1,3]oxazin-8-il)benzonitrilo (Intermedio AA(3)). CL-EM $(M+H)^+$ = 271,1. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 7,57 - 7,78 (m, 2 H) 7,41 - 7,51 (m, 2 H) 4,61 - 4,75 (m, 1 H) 4,50 (dd, J=15,49, 2,14 Hz, 1 H) 4,04 - 4,20 (m, 2 H) 3,78 (s ancho, 1 H).

Intermedio AA(4)

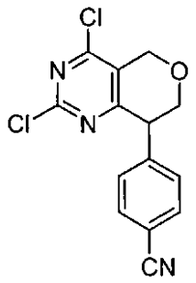
4-(2,4-dioxo-2,3,4,5,7,8-hexahidro-1H-pirano[4,3-d]pirimidin-8-il)benzonitrilo



Se hizo reaccionar 4-(2,4-dioxo-2,3,4,5,7,8-hexahidropirano[3,4-e][1,3]oxazin-8-il)benzonitrilo (Intermedio AA(3)) como se describe en el Intermedio X(4) con hidróxido amónico dando 4-(2,4-dioxo-2,3,4,5,7,8-hexahidro-1H-pirano[4,3-d]pirimidin-8-il)benzonitrilo (Intermedio AA(4)). CL-EM $(M-H)^+$ = 270,2.

Preparación AA

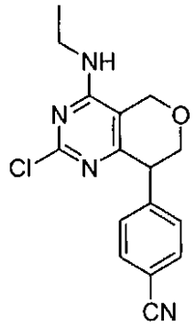
4-(2,4-dicloro-7,8-dihidro-5H-pirano[4,3-d]pirimidin-8-il)benzonitrilo



Se hizo reaccionar 4-(2,4-dioxo-2,3,4,5,7,8-hexahidro-1H-pirano[4,3-d]pirimidin-8-il)benzonitrilo (Intermedio AA(4)) como se describe en la Preparación X con $POCl_3$ dando 4-(2,4-dicloro-7,8-dihidro-5H-pirano[4,3-d]pirimidin-8-il)benzonitrilo (Preparación AA). CL-EM $(M+H)^+$ = 306,1.

Preparación AAa

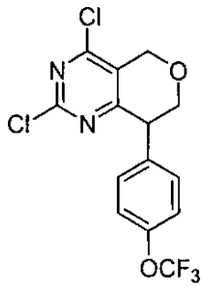
4-(2-cloro-4-(etilamino)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-8-il)benzonitrilo



Se hizo reaccionar 4-(2,4-dicloro-7,8-dihidro-5H-pirano[4,3-d]pirimidin-8-il)benzonitrilo (Preparación AA) como se describe en la Preparación Xa con etanamina dando 4-(2-cloro-4-(etilamino)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-8-il)benzonitrilo (Preparación AAa). CL-EM $(M+H)^+$ = 315,1.

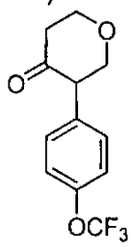
Preparación AB

2,4-dicloro-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



Intermedio AB(2)

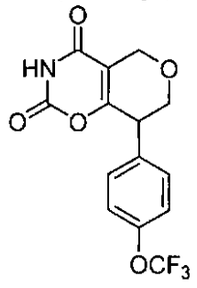
3-(4-(trifluorometoxi)fenil)dihidro-2H-piran-4(3H)-ona



Se utilizó el procedimiento Intermedio X(2) con ácido 4-(trifluorometoxi)fenilborónico obteniendo 3-(4-(trifluorometoxi)fenil)dihidro-2H-piran-4(3H)-ona. RMN de ^{1}H (400 MHz, $CDCl_3$) δ ppm 7,29 (2 H, d, *J*=7,05 Hz), 7,19 - 7,25 (2 H, m), 4,23 - 4,32 (2 H, m), 3,91 - 4,04 (2 H, m), 3,84 (1 H, dd, *J*=8,81, 6,30 Hz), 2,66 - 2,77 (1 H, m), 2,56 - 2,63 (1 H, m)

Intermedio AB(3)

8-(4-(trifluorometoxi)fenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona

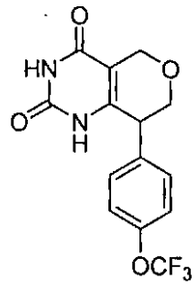


Se utilizó el procedimiento del Intermedio X(3) obteniendo 8-(4-

(trifluorometoxi)fenil)-7,8-dihidropirano[3,4-e][1,3]oxazin-2,4(3H,5H)-diona. RMN de ^{1}H (500 MHz, *DMSO-d*$_6$) δ ppm 11,98 (1 H, s), 7,52 (2 H, d, *J*=8,55 Hz), 7,37 (2 H, d, *J*=7,93 Hz), 4,45 - 4,51 (1 H, m), 4,36 (1 H, dd, *J*=14,95, 2,14 Hz), 4,00 - 4,08 (2 H, m), 3,82 (1 H, dd, *J*=10,68, 3,36 Hz).

Intermedio AB(4)

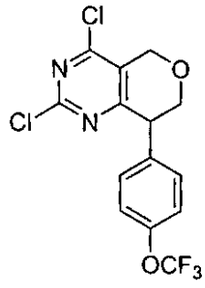
8-(4-(trifluorometoxi)fenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona



Se utilizó el procedimiento del Intermedio X(4) obteniendo 8-(4-(trifluorometoxi)fenil)-7,8-dihidro-1H-pirano[4,3-d]pirimidin-2,4(3H,5H)-diona. CL-EM $(M+H)^+$ = 329,0.

Preparación AB

2,4-dicloro-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina

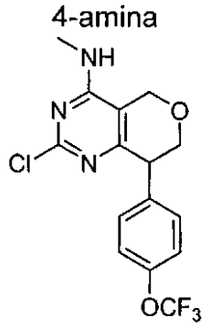


Se utilizó el procedimiento de la Preparación X obteniendo 2,4-dicloro-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina. CL-EM $(M+H)^+$ =

365,0.

Preparación ABa

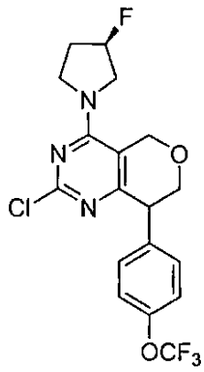
2-cloro-N-metil-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina



A una solución de 2,4-dicloro-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación AB) (80,7 mg, 0,221 mmol) en MeOH (2210 µl) se añadió metilamina (1000 µl, 2,0 mmol) (2M en THF). Se dejó agitar la reacción durante la noche. Se eliminó el disolvente y se aplicó a gel de sílice, eluyendo con un gradiente de EtOAc/Hex proporcionando 2-cloro-N-metil-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (69,8 mg, 0,194 mmol, 88 % de rendimiento). CL-EM $(M+H)^+$ = 360,0.

Preparación ABb

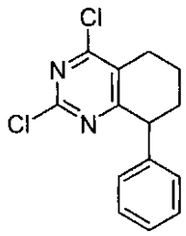
2-cloro-4-((R)-3-fluoropirrolidin-1-il)-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina



A una solución de 2,4-dicloro-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación AB) (56,4 mg, 0,154 mmol) en MeOH (1545 µl) se añadió DIPEA (67,4 µl, 0,386 mmol), luego (R)-3-fluoropirrolidina sólida, HCl (21,34 mg, 0,170 mmol). Se dejó agitar la reacción a ta. Se eliminó el disolvente y se aplicó a gel de sílice. Se eluyó con un gradiente de EtOAc/hex proporcionando la mezcla diastereomérica 2-cloro-4-((R)-3-fluoropirrolidin-1-il)-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (57,6 mg, 0,138 mmol, 89 % de rendimiento). CL-EM $(M+H)^+$ = 418,1.

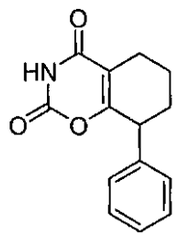
Preparación AC

2,4-Dicloro-8-fenil-5,6,7,8-tetrahidroquinazolina



Intermedio AC(1)

8-Fenil-5,6,7,8-tetrahidro-2*H*-benzo[*e*][1,3]oxazin-2,4(3*H*)-diona



Una solución de 2-fenilciclohexanona (1,500 g, 8,61 mmol) y cloruro carbonisocianatídico (0,966 ml, 12 mmol) se agitó a 58 °C en un recipiente de alta presión (75 ml) durante 1 h. La temperatura se elevó hasta 130 °C y la mezcla de reacción se agitó durante 2 h. Después de enfriar hasta temperatura ambiente, la mezcla de reacción solidificó. El residuo sólido se disolvió en acetato de etilo y se lavó con solución acuosa saturada de bicarbonato sódico. La fase orgánica se separó y la fase acuosa se extrajo dos veces con acetato de etilo. Los extractos orgánicos reunidos se secaron sobre sulfato sódico anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo oleoso se purificó por cromatografía en columna sobre gel de sílice proporcionando 8-fenil-5,6,7,8-tetrahidro-2*H*-benzo[*e*][1,3]oxazin-2,4(3*H*)-diona (415,0 mg, 1,689 mmol, 19,62 % de rendimiento) como sólido blanco y 4*a*-fenil-4*a*,5,6,7-tetrahidro-2*H*-benzo[*e*][1,3]oxazin-2,4(3*H*)-diona (746,4 mg, 3,04 mmol, 35,3 % de rendimiento) como sólido blanco.

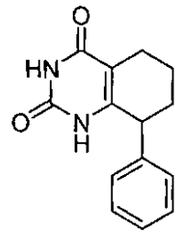
8-fenil-5,6,7,8-tetrahidro-2*H*-benzo[*e*][1,3]oxazin-2,4(3*H*)-diona. CL-EM $(M+H)^+$ = 244,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,61 (1H, s ancho), 7,22 - 7,38 (3H, m), 7,09 - 7,19 (2H, m), 3,81 (1H, t, *J*=4,9 Hz), 2,39 - 2,63 (2H, m), 2,15 (1H, dddd, *J*=13,2, 9,8, 6,3, 3,1 Hz), 1,84 - 1,96 (1H, m), 1,52 - 1,84 (2H, m).

4*a*-fenil-4*a*,5,6,7-tetrahidro-2*H*-benzo[*e*][1,3]oxazin-2,4(3*H*)-diona. CL-EM

$(M+H)^+$ = 244,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,66 (1H, s ancho), 7,40 - 7,46 (2H, m), 7,29 - 7,39 (3H, m), 5,99 - 6,06 (1H, m), 2,37 (1H, ddd, *J*=14,0, 3,4, 3,1 Hz), 2,10 - 2,29 (3H, m), 1,54 - 1,64 (1H, m), 1,21 - 1,36 (1H, m).

Intermedio AC(2)

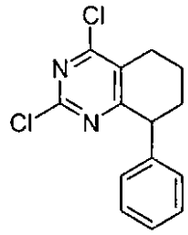
8-Fenil-5,6,7,8-tetrahidroquinazolina-2,4(1*H*,3*H*)-diona



Una solución de 8-fenil-5,6,7,8-tetrahidro-2*H*-benzo[*e*][1,3]oxazin-2,4(3*H*)-diona (415,0 mg, 1,706 mmol) en hidróxido amónico concentrado (35 ml, 899 mmol) se agitó a 100 °C en un recipiente de alta presión (75 ml) durante 6 h. Se observó la formación de precipitado blanco durante el calentamiento. El análisis CL/EM del filtrado mostró la presencia del producto con la masa deseada (M+H) = 243,20. El disolvente se eliminó a vacío proporcionando 8-fenil-5,6,7,8-tetrahidroquinazolina-2,4(1*H*,3*H*)-diona (435 mg, 1,706 mmol, 100 % de rendimiento) como sólido blanquecino. CL-EM $(M+H)^+$ = 243,2. RMN de ^1H (500 MHz, DMSO - d_6) δ ppm 10,2 (2H, s ancho), 7,34 (2H, t, *J*=7,5 Hz), 7,26 (1H, t, *J*=7,3 Hz), 7,14 (2H, d, *J*=7,3 Hz), 3,80 (1H, s ancho), 2,32 - 2,43 (1H, m), 2,15 (1H, ddd, *J*=16,9, 10,5, 6,1 Hz), 1,93 - 2,04 (1H, m), 1,67 - 1,75 (1H, m), 1,56 (1H, ddd, *J*=7,8, 5,2, 2,6 Hz), 1,36 (1H, dt, *J*=13,1, 2,7 Hz).

Preparación AC

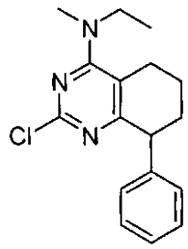
2,4-Dicloro-8-fenil-5,6,7,8-tetrahidroquinazolina



Una mezcla de 8-fenil-5,6,7,8-tetrahidroquinazolina-2,4(1*H*,3*H*)-diona (233,1 mg, 0,962 mmol), oxicloruro de fósforo (2798 µl, 30,0 mmol) y *N*,*N*-dimetilanilina (933 µl, 7,36 mmol) se calentó a 110 °C en un vial tapado durante la noche. La mezcla de reacción se vertió en un vaso de precipitados con hielo y el interior del recipiente de reacción se lavó con diclorometano. Tan pronto como el hielo se fundió completamente, el contenido del vaso de precipitados se colocó en un embudo de separación. La fase orgánica se separó y la fase acuosa se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato sódico anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice proporcionando 2,4-dicloro-8-fenil-5,6,7,8-tetrahidroquinazolina (320,3 mg, 83%) como aceite amarillo. CL-EM $(M+H)^+$ = 279,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,28 (2H, t, *J*=7,5 Hz), 7,19 - 7,24 (1H, m), 6,95 (2H, d, *J*=7,3 Hz), 4,23 (1H, t, *J*=5,6 Hz), 2,82 - 2,92 (1H, m), 2,72 - 2,82 (1H, m), 2,10 - 2,22 (1H, m), 1,97 - 2,06 (1H, m), 1,76 - 1,93 (2H, m).

Preparación ACa

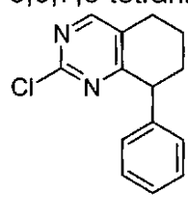
2-Cloro-*N*-etil-*N*-metil-8-fenil-5,6,7,8-tetrahidroquinazolin-4-amina



A una solución de 2,4-dicloro-8-fenil-5,6,7,8-tetrahidroquinazolina (53,9 mg, 0,193 mmol) en metanol (1 ml) se añadió *N*-metiletanamina (0,033 ml, 0,386 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2-cloro-*N*-etil-*N*-metil-8-fenil-5,6,7,8-tetrahidroquinazolin-4-amina (42,9 mg, 0,141 mmol, 72,9 % de rendimiento) como aceite incoloro. CL-EM $(M+H)^+$ = 302,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,25 (2H, t, *J*=7,5 Hz), 7,13 - 7,20 (1H, m), 7,01 (2H, d, *J*=7,3 Hz), 4,06 - 4,14 (1H, m), 3,42 - 3,53 (2H, m), 3,05 (3H, s), 2,56 - 2,74 (2H, m), 2,17 - 2,27 (1H, m), 1,76 - 1,89 (2H, m), 1,52 - 1,64 (1H, m), 1,24 (3H, t, *J*=7,2 Hz).

Preparación ACb

2-Cloro-8-fenil-5,6,7,8-tetrahidroquinazolina

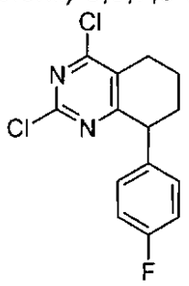


Una mezcla de 2,4-dicloro-8-fenil-5,6,7,8-tetrahidroquinazolina (51,9 mg, 0,186 mmol), cloruro amónico (13,0 mg, 0,243 mmol) y cinc (130 mg, 1,988 mmol) en acetona (0,75 ml) y agua (0,75 ml) se calentó a 90 °C con agitación durante 2 h. La mezcla de reacción se filtró a través de un lecho corto de tierra de diatomeas (Celite®). El disolvente se eliminó a vacío, y el residuo se repartió

entre diclorometano y agua. La fase orgánica se separó y la fase acuosa se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2-cloro-8-fenil-5,6,7,8-tetrahidroquinazolina (24,1 mg, 0,097 mmol, 52,4 % de rendimiento) como sólido blanco. CL-EM $(M+H)^+$ = 245,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,39 (1H, s), 7,27 (2H, t, *J*=7,6 Hz), 7,16 - 7,23 (1H, m), 6,95 (2H, d, *J*=7,3 Hz), 4,21 (1H, t, *J*=6,0 Hz), 2,72 - 2,91 (2H, m), 2,14 - 2,26 (1H, m), 1,95 - 2,06 (1H, m), 1,81 - 1,93 (1H, m), 1,71 - 1,81 (1H, m).

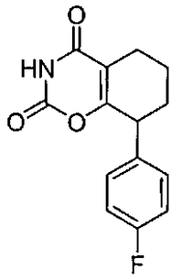
Preparación AD

2,4-dicloro-8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina



Intermedio AD(1)

8-Fenil-5,6,7,8-tetrahidro-2*H*-benzo[*e*][1,3]oxazin-2,4(3*H*)-diona



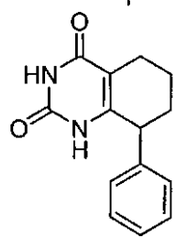
Se hizo reaccionar 2-(4-fluorofenil)ciclohexanona y cloruro carbonisocianatídico (0,966 ml, 12 mmol) como en el Intermedio AC(1)

proporcionando 8-(4-fluorofenil)-5,6,7,8-tetrahidro-2*H*-benzo[*e*][1,3]oxazin-2,4(3*H*)-diona (415,0 mg, 1,689 mmol, 19,62 % de rendimiento) como sólido blanco y 4*a*-(4-fluorofenil)-4*a*,5,6,7-tetrahidro-2*H*-benzo[*e*][1,3]oxazin-2,4(3*H*)-diona (746,4 mg, 3,04 mmol, 35,3 % de rendimiento) como sólido blanco.

8-(4-fluorofenil)-5,6,7,8-tetrahidro-2*H*-benzo[*e*][1,3]oxazin-2,4(3*H*)-diona. CL-EM $(M+H)^+$ = 262,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 9,61 (1H, s ancho), 7,10 (2H, dd, *J* = 5,0,8,5 Hz), 6,98 (2H, t aparente, *J* = 8,5 Hz), 3,77 (1H, t, *J*= 4,9 Hz), 2,38 - 2,53 (2H, m), 2,16-2,07 (1H, m), 1,87 - 1,62 (3H, m).

Intermedio AD(2)

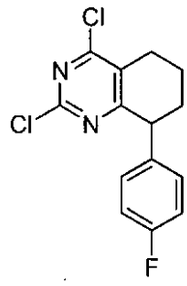
8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina-2,4(1*H*,3*H*)-diona



Se hizo reaccionar una solución de 8-(4-fluorofenil)-5,6,7,8-tetrahidro-2*H*-benzo[*e*][1,3]oxazin-2,4(3*H*)-diona en la forma del Intermedio AC(2) proporcionando 8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina-2,4(1*H*,3*H*)-diona. CL-EM $(M+H)^+$ = 261,2.

Preparación AD

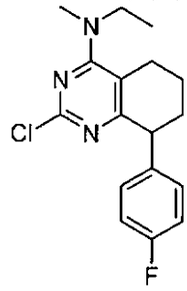
2,4-dicloro-8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina



Se hizo reaccionar una mezcla de 8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina-2,4(1*H*,3*H*)-diona en la forma de la Preparación AC proporcionando 2,4-dicloro-8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina, que no se caracterizó en esta etapa.

Preparación ADa

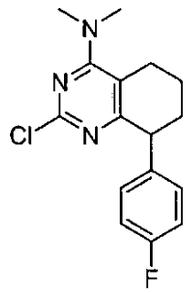
2-Cloro-*N*-etil-8-(4-fluorofenil)-*N*-metil-5,6,7,8-tetrahidroquinazolin-4-amina



Una solución de 2,4-dicloro-8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina (115 mg, 0,387 mmol) y N-metiletanamina en exceso (0,332 ml, 3,87 mmol) en MeOH (2 ml) se agitó a temperatura ambiente durante 30 min. El disolvente se eliminó a vacío proporcionando 2-cloro-*N*-etil-8-(4-fluorofenil)-*N*-metil-5,6,7,8-tetrahidroquinazolin-4-amina (124 mg, 0,388 mmol, 100 % de rendimiento). CL-EM $(M+H)^+$ = 320,2.

Preparación ADb

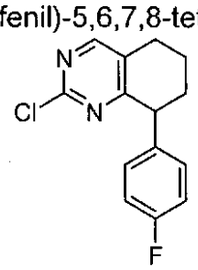
2-Cloro-8-(4-fluorofenil)-*N*,*N*-dimetil-5,6,7,8-tetrahidroquinazolin-4-amina



Se agitó a temperatura ambiente durante 1 h una solución de 2,4-dicloro-8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina (115 mg, 0,387 mmol) y dimetilamina en exceso (1,935 ml, 3,87 mmol) en MeOH (1 ml). El disolvente se eliminó a vacío proporcionando 2-cloro-8-(4-fluorofenil)-*N*,*N*-dimetil-5,6,7,8-tetrahidroquinazolin-4-amina (118 mg, 0,386 mmol, 100 % de rendimiento). CL-EM $(M+H)^+$ = 306,2.

Preparación ADc

2-Cloro-8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina

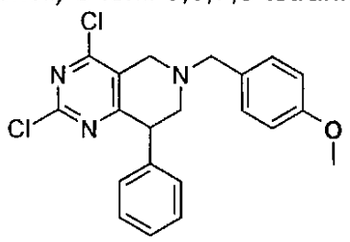


Una mezcla de 2,4-dicloro-8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina (115 mg, 0,387 mmol), cloruro amónico (26,9 mg, 0,503 mmol) y cinc (266 mg, 4,06 mmol) en acetona (1 ml) y agua (1,000 ml) se calentó a 90 °C con agitación durante 2 h. La mezcla de reacción se filtró a través de un lecho corto de Celite. El disolvente se eliminó a vacío, y el residuo se repartió entre diclorometano y agua. La fase orgánica se separó y la fase acuosa se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato

de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando 2-cloro-8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina (20 mg, 0,076 mmol, 19,67 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 263,2.

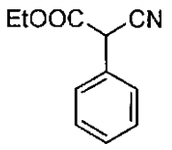
Preparación AE

2,4-dicloro-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina



Intermedio AE(1)

2-ciano-2-fenilacetato de etilo

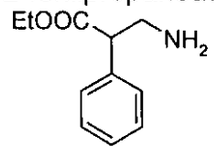


A una solución de hidruro sódico (24,5 g, 1,02 mol) en THF se añadió cianuro de bencilo (50,0 g, 0,426 mol) a -10 °C. La mezcla de reacción se agitó durante 15 min a la misma temperatura. Se añadió a la mezcla de reacción carbonato de dietilo (60,5 g, 0,512 mol) y la mezcla de reacción se dejo alcanzar temperatura ambiente y se calentó hasta 40 °C. (Precaución: la reacción se iniciará repentinamente y de forma exotérmica). Se retiró el baño de calentamiento inmediatamente una vez que la reacción se inició y la mezcla de reacción se enfrió en hielo/acetona. La solución se dejó que llegara hasta temperatura ambiente y se agitó durante 1 h. La masa de reacción se enfrió

hasta 0 °C y se enfrió con cloruro amónico acuoso saturado y se extrajo con acetato de etilo (250 ml x 3). La fase orgánica reunida se lavó con agua (200 ml), solución de salmuera (200 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 2-ciano-2-fenilacetato de etilo como compuesto bruto (71,0 g). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 190,1. RMN de ^1H (400 MHz, DMSO-*d6*) δ ppm 7,45 (5H, m), 5,65 (1H, s), 4,18 (2H, m), 1,18 (3H, t, *J* = 7,2 Hz).

Intermedio AE(2)

3-amino-2-fenilpropanoato de etilo

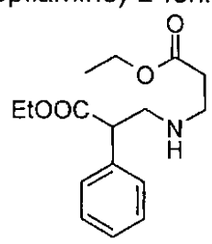


A una solución del Intermedio AE(1) (25,0 g, 0,132 mol) en metanol se añadió paladio sobre carbón (10%, p/p) seguido por ácido trifluoroacético (2,0 volúmenes, 50 ml) a temperatura ambiente. La mezcla de reacción se sometió a hidrogenación bajo una presión de 5 kg de hidrógeno durante 3 h. La mezcla de reacción se filtró a través de un lecho de Celite y se lavó con metanol. El filtrado se evaporó a presión reducida y el residuo se neutralizó con solución acuosa saturada de bicarbonato. La solución acuosa se extrajo con acetato de etilo (200 ml x 4). La fase orgánica reunida se lavó con solución de salmuera (200 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando metanol al 10% en diclorometano como fase móvil dando 3-amino-2-fenilpropanoato de etilo (17,0 g, 67%) como líquido aceitoso. CL-EM $(M+H)^+$ = 194,0. RMN de ^1H (400 MHz,

DMSO-*d6*): δ ppm 7,42-7,2 (7H, m), 4,11 (2H, m), 4,09 (1H, m), 3,44 (1H, m), 3,09 (1H, m), 1,15 (3H, t, *J* = 5,6 Hz).

Intermedio AE(3)

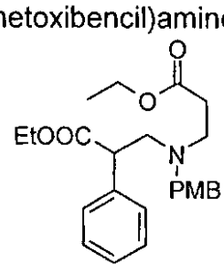
3-(3-etoxi-3-oxopropilamino)-2-fenilpropanoato de etilo



A una solución del Intermedio AE(2) (10,0 g, 51,7 mmol) en etanol se añadió acrilato de etilo (4,1 g, 40,9 mmol) a temperatura ambiente. La mezcla de reacción se agitó a la misma temperatura durante 18 h. El disolvente se evaporó a presión reducida y el compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando 3-(3-etoxi-3-oxopropilamino)-2-fenilpropanoato de etilo (12,1 g, 80%) como líquido oleoso amarillento. CL-EM $(M+H)^+$ = 294,1. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,29 (5H, m), 4,11 (4H, m), 3,76 (1H, m), 3,26 (1H, m), 2,90 (3H, m), 2,44 (2H, m), 1,20 (6H, m).

Intermedio AE(4)

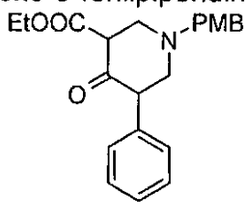
3-((3-etoxi-3-oxopropil)(4-metoxibencil)amino)-2-fenilpropanoato de etilo



A una solución del Intermedio AE(3) (15,0 g, 51,1 mmol) en acetona se añadió K_2CO_3 (8,4 g, 61,4 mmol) seguido por bromuro de *p*-metoxibencilo (15,4 g, 76,7 mmol) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 3 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La fase acuosa se extrajo con acetato de etilo (100 x 3). La fase orgánica reunida se lavó con solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 30% en éter de petróleo como fase móvil dando 3-((3-etoxi-3-oxopropil)(4-metoxibencil)amino)-2-fenilpropanoato de etilo (12,1 g, 60%) como líquido aceitoso. CL-EM $(M+H)^+$ = 414,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,27 (5H, m), 7,13, (2H, m), 6,82 (2H, m), 4,11 (4H, m), 4,08 (3H, s), 4,06 (1H, m), 3,81 (1H, d, *J* = 4,0 Hz), 3,79 (1H, d, *J* = 4,0 Hz), 3,25 (1H, m), 2,73 (3H, m), 2,43 (2H, m), 1,24 (6H, m).

Intermedio AE(5)

1-(4-metoxibencil)-4-oxo-5-fenilpiperidin-3-carboxilato de etilo

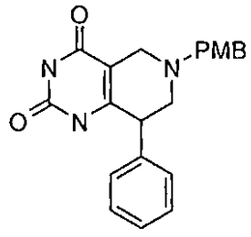


A una solución enfriada de Intermedio AE(4) (12,0 g, 29,0 mmol) en THF se añadió *t*-BuOK (6,5 g, 58,0 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. La masa de reacción se enfrió con agua luego se evaporó el disolvente a presión reducida. El residuo se diluyó con agua y se extrajo con acetato de etilo (100 ml x 2). La fase orgánica reunida se

lavó con solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 25% en éter de petróleo como fase móvil dando 1-(4-metoxibencil)-4-oxo-5-fenilpiperidin-3-carboxilato de etilo (7,1 g, 67%) como líquido aceitoso. CL-EM $(M+H)^+$ = 368,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,26 (4H, m), 7,15 (2H, m), 6,88 (2H, m), 4,15 (2H, m), 4,09 (3H, s), 3,82 (2H, m), 3,66 (2H, m), 2,80 (3H, m), 2,40 (1H, m), 1,24 (3H, m).

Intermedio AE(6)

6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4(1H,3H)-diona

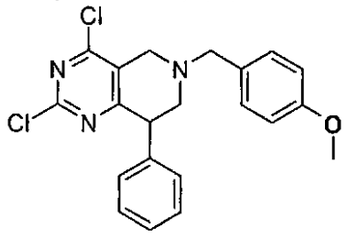


A una solución enfriada de Intermedio AE(5) (7,0 g, 19,0 mmol) en etanol se añadió *t*-BuOK (5,3 g, 47,6 mmol) seguido por urea (2,8 g, 47,6 mmol). La mezcla de reacción se calentó a reflujo durante 24 h. La masa de reacción se enfrió con agua y se evaporó el disolvente a presión reducida. El residuo se diluyó con agua y se extrajo con acetato de etilo (100 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (100 ml), se secó sobre Na_2SO_4 y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando éter de petróleo al 10% en acetato de etilo como fase móvil

dando 6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4(1H,3H)-diona (4,0 g, 57%) como sólido amarillo pálido. CL-EM $(M+H)^+$ = 364,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 11,05 (1H, s), 10,60 (1H, s), 7,30 (5H, m), 6,99 (2H, m), 6,77 (2H, m), 3,72 (2H, m), 3,57 (3H, s), 3,44 (1H, m), 3,34 (1H, m), 2,90 (1H, m), 2,51 (2H, m).

Preparación AE

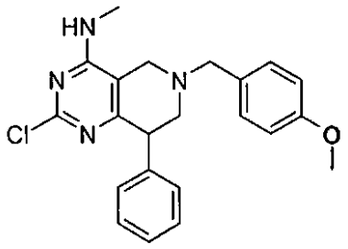
2,4-dicloro-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina



Se calentó a reflujo durante 10 h una solución de Intermedio AE(6) (2,0 g, 5,5 mmol) y cantidad catalítica de DMF en $POCl_3$ (20 vol.). El exceso de $POCl_3$ se evaporó a presión reducida. El residuo se vertió en hielo picado y se agitó durante 15 min. La solución acuosa se extrajo con acetato de etilo (75 ml x 3). La fase orgánica reunida se lavó con $NaHCO_3$ acuoso saturado (50 ml x 2), solución de salmuera (100 ml), se secó sobre Na_2SO_4 y se evaporó a presión reducida dando 2,4-dicloro-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (1,5 g, 69%) como sólido marrón. CL-EM $(M+H)^+$ = 400,0. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,30 (3H, m), 7,26 (4H, m), 6,81 (2H, m), 4,20 (1H, m), 3,79 (2H, m), 3,72 (3H, s), 3,68 (2H, m), 3,57 (1H, m), 3,02 (1H, m), 2,98 (1H, m).

Preparación AEa

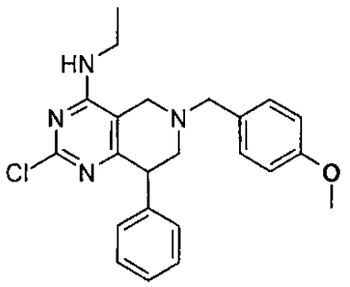
2-cloro-6-(4-metoxibencil)-N-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina



A una solución de la Preparación AE (1,1 g, 2,7 mmol) en acetonitrilo se añadió diisopropiletilamina (1,0 g, 8,3 mmol) seguida por la adición de clorhidrato de metilamina (0,28 g, 4,1 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 30% en éter de petróleo como fase móvil dando 2-cloro-6-(4-metoxibencil)-N-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina (0,8 g, 74%) como sólido blanquecino. CL-EM $(M+H)^+$ = 395,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,29 (4H, m), 7,16 (4H, m), 6,80 (2H, m), 3,93 (1H, m), 3,73 (3H, s), 3,66 (2H, m), 3,57 (1H, m), 3,46 (1H, m), 3,23 (1H, m), 2,67 (3H, d, *J* = 4,0 Hz), 2,51 (1H, m).

Preparación AEb

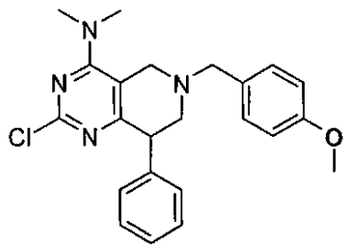
2-cloro-N-etil-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina



A una solución de la Preparación AE (1,6 g, 4,0 mmol) en acetonitrilo se añadió diisopropiletilamina (1,5 g, 12,0 mmol) seguida por la adición de clorhidrato de etilamina (0,52 g, 6,0 mmol) a temperatura ambiente. La mezcla de reacción se agitó a la misma temperatura durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 30% en éter de petróleo como fase móvil dando 2-cloro-N-etil-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina (0,9 g, 56%) como sólido blanquecino. CL-EM $(M-H)^+$ = 407,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,31-7,12 (7H, m), 6,83-6,79 (2H, m), 4,47 (1H, *s ancho)*, 4,06 (1H, m), 3,83 (3H, s), 3,66 (2H, m), 3,58 (2H, m), 3,44 (1H, m), 3,20 (1H, m), 3,08 (1H, m), 2,88 (1H, m), 1,25 (3H, d, *J* = 7,2 Hz).

Preparación AEc

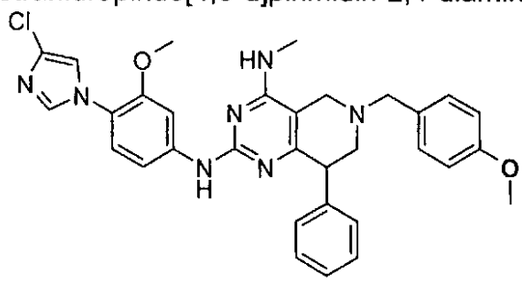
2-cloro-N,N-dimetil-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina



Usando el procedimiento de la Preparación AEb, se utilizó dimetilamina para producir 2-cloro-*N*,*N*-dimetil-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina.

Preparación AEd

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

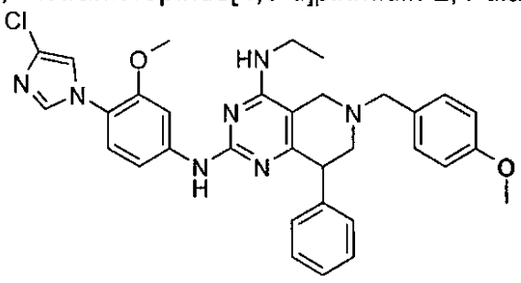


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,229 g, 1,02 mmol), Preparación AEa (0,45 g, 1,14 mmol), Na_2CO_3 (0,24 g, 2,28 mmol) y xantphos (0,659 g, 1,14 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,59 g, 0,57 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (100 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 5% en diclorometano como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-

metoxifenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,28 g, 43%) como sólido blanquecino. CL-EM $(M+H)^+$ = 582,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,06 (1H, s), 8,05 (1H, s), 7,71 (1H, s), 7,4 (1H, s), 7,39-7,06 (11H, m), 6,79 (2H, m), 6,73 (1H, m), 3,93 (1H, m), 3,71 (3H, s), 3,62 (2H, m), 3,55 (3H, s), 3,46 (1H, m), 3,26 (1H, m), 2,92 (3H, d, *J* = 4,4 Hz).

Preparación AEe

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

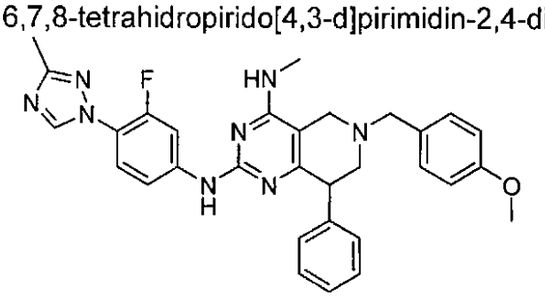


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,442 g, 1,98 mmol), Preparación AEb (0,9 g, 2,2 mmol), Na_2CO_3 (0,467 g, 4,4 mmol) y xantphos (1,27 g, 2,2 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (1,1 g, 1,1 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (100 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía

en columna (gel de sílice, malla 60-120) usando acetato de etilo al 5% en diclorometano como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,71 g, 54%) como sólido blanquecino. CL-EM $(M+H)^+$ = 596,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,03 (1H, s), 7,98 (1H, s), 7,71 (1H, s), 7,40 (1H, s), 7,27-7,10 (9H, m), 6,81-6,78 (2H, m), 6,72 (1H, m), 3,91 (1H, m), 3,71 (3H, s), 3,65 (2H, m), 3,56 (3H, s), 3,51-3,49 (3H, m), 3,28 (1H, m), 2,87 (1H, m), 2,65 (1H, m), 1,18 (3H, t, *J* = 7,2 Hz).

Preparación AEf

N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6-(4-metoxibencil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

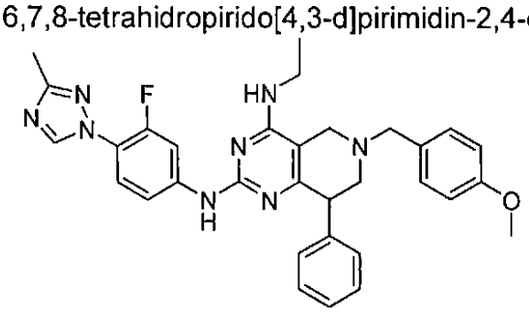


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación B (0,175 g, 0,913 mmol), Preparación AEa (0,40 g, 1,01 mmol), Na_2CO_3 (0,20 g, 2,02 mmol) y xantphos (0,585 g, 1,01 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,525 g, 0,50 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (100 ml x 2). La fase orgánica reunida se lavó con solución de salmuera

(100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 5% en diclorometano como fase móvil dando N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6-(4-metoxibencil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,24 g, 42%) como sólido blanquecino. CL-EM $(M+H)^+$ = 551,1.

Preparación AEg

N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

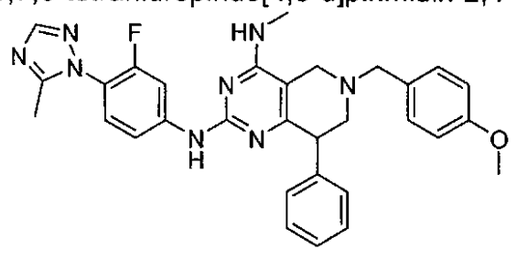


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación B (0,423 g, 2,20 mmol), Preparación AEb (1,0 g, 2,44 mmol), Na_2CO_3 (0,520 g, 4,89 mmol) y xantphos (1,41 g, 2,44 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (1,26 g, 1,22 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (100 ml x 3). La fase orgánica reunida se lavó

con solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 5% en diclorometano como fase móvil dando N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,70 g, 53%) como sólido blanquecino. CL-EM $(M+H)^+$ = 565,2.

Preparación AEh

N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-6-(4-metoxibencil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

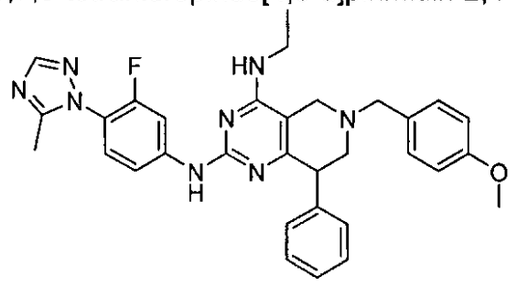


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación C (0,175 g, 0,913 mmol), Preparación AEa (0,40 g, 1,01 mmol), Na_2CO_3 (0,20 g, 2,02 mmol) y xantphos (0,586 g, 1,01 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,525 g, 0,50 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (100 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó

a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 5% en diclorometano como fase móvil dando N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-6-(4-metoxibencil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,27 g, 51%) como sólido blanquecino. CL-EM $(M+H)^+$ = 565,2.

Preparación AEi

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

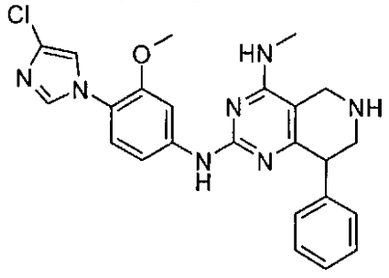


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación C (0,423 g, 2,20 mmol), Preparación AEb (1,0 g, 2,44 mmol), Na_2CO_3 (0,520 g, 4,89 mmol) y xantphos (1,41 g, 2,44 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (1,26 g, 1,22 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (100 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó

a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 5% en diclorometano como fase móvil dando N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-6-(4-metoxibencil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,72 g, 54%) como sólido blanquecino. CL-EM $(M+H)^+$ = 565,4.

Preparación AEj

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

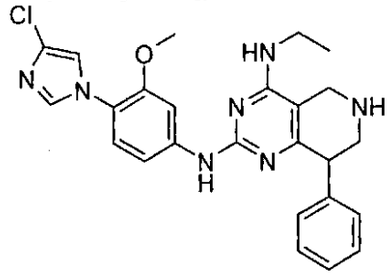


A una solución de la Preparación AEd (0,28 g, 0,48 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (25 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina como compuesto bruto (0,195 g). El compuesto bruto se llevó a la etapa siguiente sin purificación

posterior. CL-EM $(M+H)^+$ = 462,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,03 (1H, s), 8,06 (1H, s), 7,71 (1H, s), 7,39 (1H, s), 7,27-7,24 (2H, m), 7,18-7,05 (5H, m), 6,68 (1H, m), 5,76 (1H, s), 3,81 (1H, m), 3,69-3,63 (2H, m), 3,57 (3H, s), 3,22 (1H, m), 2,95 (3H, d, *J* = 4,0 Hz), 2,84 (1H, m).

Preparación AEk

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

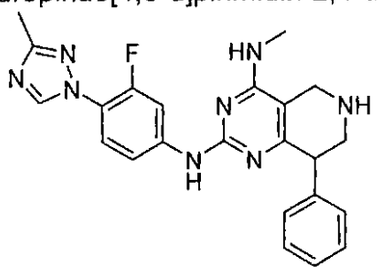


A una solución de la Preparación AEe (0,25 g, 0,42 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (50 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (50 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina como compuesto bruto (0,19 g). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 476,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,00 (1H, s), 7,99 (1H, s), 7,71 (1H, s), 7,40 (1H, s), 7,28-7,24 (2H, m), 7,19-

7,09 (6H, m), 5,76 (1H, m), 3,70 (1H, m), 3,58 (2H, m), 3,51 (3H, s), 3,48 (2H, m), 3,25 (1H, m), 2,80 (1H, m), 1,20 (3H, t, *J* = 7,2 Hz).

Preparación AEI

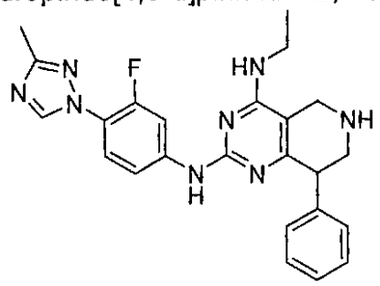
N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



A una solución de la Preparación AEf (0,24 g, 0,436 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (25 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina como compuesto bruto (0,190 g). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 431,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,13 (1H, s), 8,66 (1H, s), 8,00 (1H, m), 7,43-7,36 (2H, m), 7,29-7,26 (3H, m), 7,25-7,17 (3H, m), 6,75 (1H, m), 5,78 (1H, m), 3,83 (1H, m), 3,65 (2H, m), 3,33 (1H, m), 2,94 (3H, d, *J* = 4,4 Hz), 2,33 (3H, s).

Preparación AEm

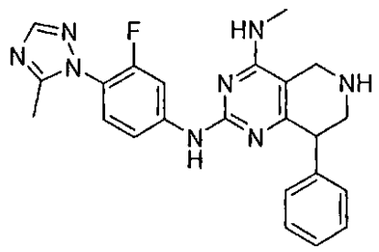
N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



A una solución de la Preparación AEg (0,490 g, 0,868 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (50 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (50 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina como compuesto bruto (0,220 g). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 445,2.

Preparación AEn

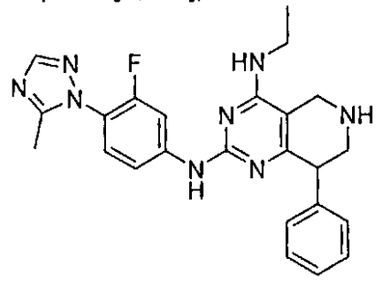
N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



A una solución de la Preparación AEh (0,27 g, 0,490 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (25 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina como compuesto bruto (0,210 g). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 551,2.

Preparación AEo

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

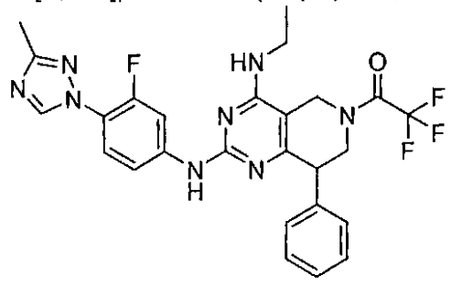


A una solución de la Preparación AEi (0,75 g, 1,32 mmol) en tolueno se

añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (50 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (50 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina como compuesto bruto (0,60 g). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 445,2.

Preparación AEp

1-(4-(etilamino)-2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-2,2,2-trifluoroetanona

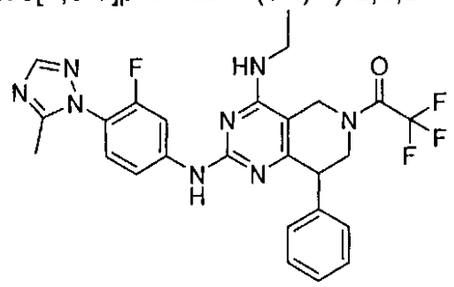


A una solución de la Preparación AEm (0,20 g, 0,449 mmol) en diclorometano se añadió trietilamina (0,068 g, 0,67 mmol) seguida por anhídrido trifluoroacético (0,14 g, 0,67 mmol) y cantidad catalítica de DMAP a 0ºC. La mezcla de reacción se dejó que llegara hasta temperatura ambiente y se agitó durante 18 h. La mezcla de reacción se diluyó con diclorometano, se lavó con $NaHCO_3$ acuoso saturado (25 ml), solución de salmuera (20 ml), se

secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 1-(4-(etilamino)-2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-2,2,2-trifluoroetanona como compuesto bruto (0,18 g, 74%). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 541,2.

Preparación AEq

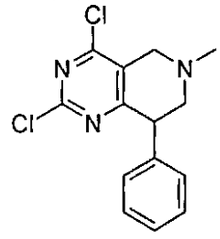
1-(4-(etilamino)-2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-2,2,2-trifluoroetanona



A una solución de la Preparación AEo (0,21 g, 0,47 mmol) en diclorometano se añadió trietilamina (0,071 g, 0,70 mmol) seguida por anhídrido trifluoroacético (0,15 g, 0,70 mmol) y cantidad catalítica de DMAP a 0°C. La mezcla de reacción se dejó que llegara hasta temperatura ambiente y se agitó durante 18 h. La mezcla de reacción se diluyó con diclorometano, se lavó con $NaHCO_3$ acuoso saturado (25 ml), solución de salmuera (20 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 1-(4-(etilamino)-2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-2,2,2-trifluoroetanona como compuesto bruto (0,185 g, 73%). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 541,2.

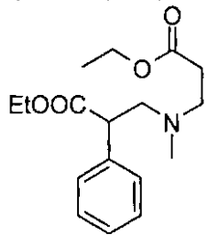
Preparación AF

2,4-dicloro-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina



Intermedio AF(1)

3-((3-etoxi-3-oxopropil)(metil)amino)-2-(4-fluorofenil)propanoato de etilo

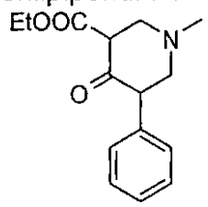


A una solución del Intermedio AE(3) (4,0 g, 13,65 mmol) en acetona se añadió K_2CO_3 (3,7 g, 27,3 mmol) seguido por yoduro de metilo (2,3 g, 16,3 mmol) a 0 °C. La mezcla de reacción se agitó a temperatura ambiente durante 2 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La fase acuosa se extrajo con acetato de etilo (25 x 3). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 40% en éter de petróleo como fase móvil dando 3-((3-etoxi-3-oxopropil)(metil)amino)-2-fenilpropanoato de etilo (0,9 g, 22%) como líquido aceitoso. CL-EM $(M+H)^+$ = 308,0. RMN de ^1H (400 MHz,

DMSO-*d*): δ ppm 7,33-7,26 (5H, m), 4,07-4,01 (4H, m), 3,83 (1H, m), 3,07 (1H, m), 2,69-2,52 (2H, m), 2,47-2,41 (3H, m), 2,21 (3H, s), 1,19-0,10 (6H, m).

Intermedio AF(2)

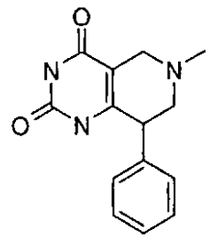
1-metil-4-oxo-5-fenilpiperidin-3-carboxilato de etilo



A una solución enfriada de Intermedio AF(1) (0,9 g, 2,93 mmol) en THF se añadió *t*-BuOK (0,65 g, 5,86 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. La masa de reacción se enfrió con agua, luego se evaporó el disolvente a presión reducida. El residuo se diluyó con agua y se extrajo con acetato de etilo (25 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 10% en éter de petróleo como fase móvil dando 1-metil-4-oxo-5-fenilpiperidin-3-carboxilato de etilo (7,1 g, 67%) como líquido aceitoso. CL-EM $(M+H)^+$ = 262,2.

Intermedio AF(3)

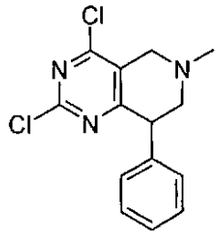
6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4(1H,3H)-diona



A una solución enfriada de Intermedio AF(2) (4,5 g, 17,2 mmol) en etanol se añadió *t*-BuOK (4,8 g, 43,1 mmol) seguida por urea (2,58 g, 43,1 mmol). La mezcla de reacción se calentó a reflujo durante 24 h. La masa de reacción se enfrió con agua y se evaporó el disolvente a presión reducida. El residuo se diluyó con agua y se extrajo con acetato de etilo (50 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando metanol al 10% en diclorometano como fase móvil dando 6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4(1H,3H)-diona (2,5 g, 56%) como sólido amarillo pálido. CL-EM $(M+H)^+$ = 258,2 RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 11,04 (1H, s), 10,56 (1H, s), 7,33-7,23 (5H, m), 3,73 (1H, m), 4,75 (1H, m), 2,83 (1H, m), 2,78 (1H, m), 2,68 (1H, m), 2,22 (3H, s).

Preparación AF

2,4-dicloro-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina

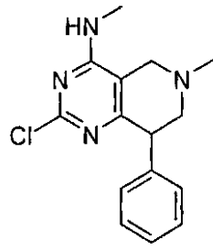


Una solución de Intermedio AF(3) (4,0 g, 15,56 mmol) y cantidad

catalítica de DMF en $POCl_3$ (20 vol.) se calentó a reflujo durante 10 h. El exceso de $POCl_3$ se evaporó a presión reducida. El residuo se vertió en hielo picado y se agitó durante 15 min. La solución acuosa se extrajo con acetato de etilo (75 ml x 3). La fase orgánica reunida se lavó con $NaHCO_3$ acuoso saturado (50 ml x 2), solución de salmuera (75 ml), se secó sobre Na_2SO_4 y se evaporó a presión reducida dando 2,4-dicloro-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (1,2 g, 27%) como sólido marrón. CL-EM $(M+H)^+$ = 294,0.

Preparación AFa

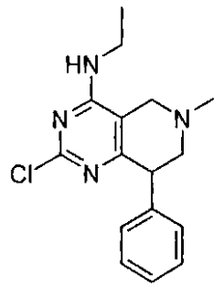
2-cloro-N,6-dimetil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina



A una solución de la Preparación AF (1,0 g, 3,4 mmol) en acetonitrilo se añadió diisopropiletilamina (1,3 g, 10,2 mmol) seguida por la adición de clorhidrato de metilamina (0,34 g, 5,1 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando metanol al 10% en diclorometano como fase móvil dando 2-cloro-N,6-dimetil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina (0,9 g, 91%) como sólido blanquecino. CL-EM $(M+H)^+$ = 289,2.

Preparación AFb

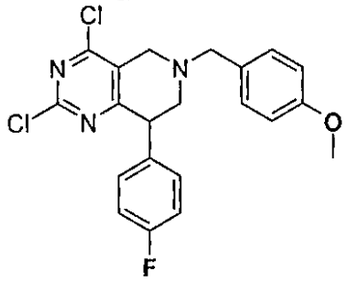
2-cloro-N-etil-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina



A una solución de la Preparación AF (0,4 g, 1,36 mmol) en acetonitrilo se añadió diisopropiletilamina (0,52 g, 4,0 mmol) seguida por la adición de clorhidrato de etilamina (0,16 g, 2,0 mmol) a temperatura ambiente. La mezcla de reacción se agitó a la misma temperatura durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando 2-cloro-N-etil-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina (0,4 g, 97%) como sólido blanquecino. CL-EM $(M-H)^+$ = 303,2.

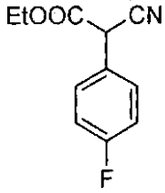
Preparación AG

2,4-dicloro-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina



Intermedio AG(1)

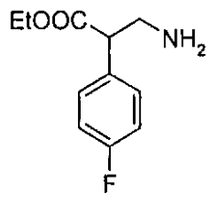
2-ciano-2-(4-fluorofenil)acetato de etilo



A una solución de hidruro sódico (4,2 g, 177,7 mmol) en THF se añadió 4-fluorofenil acetonitrilo (10 g, 74,0 mmol) a -10 °C. La mezcla de reacción se agitó durante 15 min a la misma temperatura. Se añadió carbonato de dietilo (10,5 g, 88,0 mmol) a la mezcla de reacción y la mezcla de reacción se dejó que llegara hasta temperatura ambiente y se calentó hasta 40 °C. (Precaución: La reacción se iniciará rápidamente y de forma exotérmica). El baño de calentamiento se retiró inmediatamente una vez iniciada la reacción y la mezcla de reacción se enfrió en hielo/acetona. La solución se dejó que llegara hasta temperatura ambiente y se agitó durante 1 h. La masa de reacción se enfrió hasta 0 °C y se enfrió con cloruro amónico acuoso saturado y se extrajo con acetato de etilo (50 ml x 3). La fase orgánica reunida se lavó con agua (50 ml), solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 2-ciano-2-(4-fluorofenil)acetato de etilo como compuesto bruto (10 g). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M-H)^+$ = 206,2. RMN de ^1H (400 MHz, $CDCl_3$) δ ppm 7,44 (2H, m), 7,11 (2H, m), 4,69 (1H, s), 4,27-4,22 (2H, c, J = 7,2 Hz),1,26 (3H, m)

Intermedio AG(2)

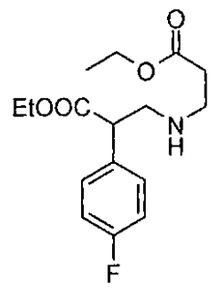
3-amino-2-(4-fluorofenil)propanoato de etilo



A una solución del Intermedio AG(1) (10,0 g, 40,0 mmol) en ácido acético se añadió paladio sobre carbón (10%, p/p) seguido por H_2SO_4 (0,5 volúmenes, 5 ml) a temperatura ambiente. La mezcla de reacción se sometió a hidrogenación bajo 5 kg de presión de hidrógeno durante 18 h. La mezcla de reacción se filtró a través de un lecho de Celite y se lavó con metanol. El filtrado se evaporó a presión reducida y el residuo se neutralizó con solución acuosa saturada de bicarbonato. La solución acuosa se extrajo con acetato de etilo (100 ml x 4). La fase orgánica reunida se lavó con solución de salmuera (100 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando metanol al 10% en diclorometano como fase móvil dando 3-amino-2-(4-fluorofenil)propanoato de etilo (6,0 g, 59%) como líquido aceitoso. CL-EM $(M+H)^+$ = 212,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,26-7,22 (2H, m), 7,04-6,98 (2H, m), 4,15 (2H, m), 3,66 (1H, m), 3,28 (1H, m), 2,99 (1H, m),1,20 (3H, m).

Intermedio AG(3)

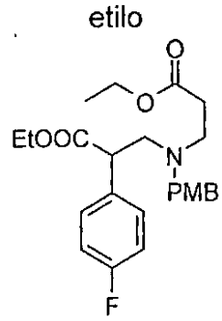
3-(3-etoxi-3-oxopropilamino)-2-(4-fluorofenil)propanoato de etilo



A una solución del Intermedio AG(2) (3,0 g, 14,0 mmol) en etanol se añadió acrilato de etilo (1,7 g, 17,0 mmol) a temperatura ambiente. La mezcla de reacción se agitó a la misma temperatura durante 18 h. El disolvente se evaporó a presión reducida y el compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando 3-(3-etoxi-3-oxopropilamino)-2-(4-fluorofenil)propanoato de etilo (2,5 g, 60%) como líquido oleoso amarilliento. CL-EM $(M+H)^+$ = 313,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,27-7,21 (2H, m), 7,03-6,97 (2H, m), 4,13 (4H, m), 3,77 (1H, m), 3,23(1H, m), 2,89 (3H, m), 2,48 (2H, m). 1,22 (6H, m).

Intermedio AG(4)

3-((3-etoxi-3-oxopropil)(4-metoxibencil)amino)-2-(4-fluorofenil)propanoato de etilo

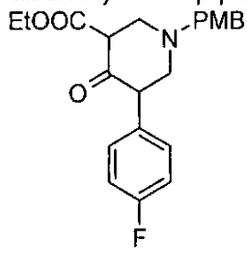


A una solución del Intermedio AG(3) (2,0 g, 6,42 mmol) en acetona se

añadió K_2CO_3 (1,39 g, 9,6 mmol) seguido por bromuro de *p*-metoxibencilo (1,68 g, 8,35 mmol) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 3 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La fase acuosa se extrajo con acetato de etilo (25 x 2). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 30% en éter de petróleo como fase móvil dando 3-((3-etoxi-3-oxopropil)(4-metoxibencil)amino)-2-(4-fluorofenil)propanoato de etilo (1,6 g, 60%) como líquido aceitoso. CL-EM $(M+H)^+$ = 432,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,22 (2H, m), 7,09, (2H, m), 6,95 (2H, m), 6,78 (2H, m) 4,14 (4H, m), 3,80 (3H, s), 3,77 (2H, m), 3,53 (2H, m), 3,16 (1H, m), 2,79 (2H, m), 2,43 (2H, m), 1,24 (6H, m).

Intermedio AG(5)

5-(4-fluorofenil)-1-(4-metoxibencil)-4-oxopiperidin-3-carboxilato de etilo

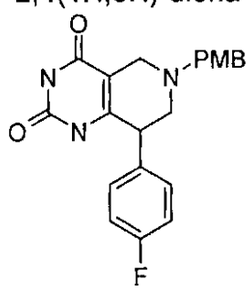


A una solución enfriada de Intermedio AG(4) (1,6 g, 3,71 mmol) en THF se añadió *t*-BuOK (0,62 g, 5,56 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. La masa de reacción se enfrió con agua, luego se evaporó el disolvente a presión reducida. El residuo se diluyó con agua y se extrajo con acetato de etilo (25 ml x 2). La fase orgánica reunida se

lavó con solución de salmuera (30 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 25% en éter de petróleo como fase móvil dando 5-(4-fluorofenil)-1-(4-metoxibencil)-4-oxopiperidin-3-carboxilato de etilo (1,0 g, 70%) como líquido aceitoso. CL-EM $(M+H)^+$ = 386,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 12,0 (1H, s) 7,26 (4H, m), 7,15 (2H, m), 6,88 (2H, m), 4,15 (2H, m), 3,80 (3H, s), 3,77 (2H, m), 3,57 (2H, m), 2,80 (1H, m), 2,40 (1H, m), 1,24 (3H, m).

Intermedio AG(6)

8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4(1H,3H)-diona

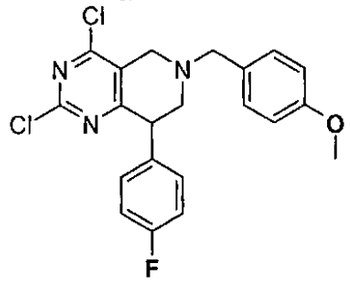


A una solución enfriada de Intermedio AG(5) (1,0 g, 2,59 mmol) en etanol se añadió *t*-BuOK (0,436 g 3,89 mmol) seguido por urea (0,233 g, 3,89 mmol). La mezcla de reacción se calentó a reflujo durante 24 h. La masa de reacción se enfrió con agua y se evaporó el disolvente a presión reducida. El residuo se diluyó con agua y se extrajo con acetato de etilo (25 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (30 ml), se secó sobre Na_2SO_4 y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla

60-120) usando éter de petróleo al 10% en acetato de etilo como fase móvil dando 8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4(1H,3H)-diona (0,6 g, 63%) como sólido amarillo pálido. CL-EM $(M+H)^+$ = 382,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 11,06 (1H, s), 10,60 (1H, s), 7,35 (2H, m), 7,29 (2H, m), 7,05 (2H, m), 6,77 (2H, m), 4,05 (1H m), 3,75 (3H, s), 3,53 (1H, m), 3,44 (2H, m), 2,88 (1H, m), 2,65 (2H, m).

Preparación AG

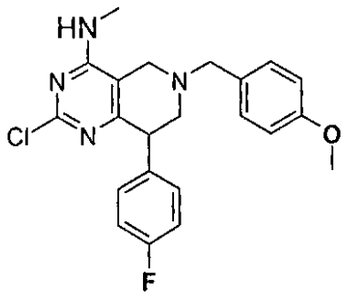
2,4-dicloro-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina



Se calentó a reflujo durante 10 h una solución de Intermedio AG(6) (0,6 g, 1,57 mmol) y cantidad catalítica de DMF en $POCl_3$ (20 vol.). El exceso de $POCl_3$ se evaporó a presión reducida. El residuo se vertió en hielo picado y se agitó durante 15 min. La solución acuosa se extrajo con acetato de etilo (20 ml x 3). La fase orgánica reunida se lavó con $NaHCO_3$ acuoso saturado (10 ml x 2), solución de salmuera (10 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 2,4-dicloro-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (0,35 g,) como sólido marrón. CL-EM $(M+H)^+$ = 418,3.

Preparación AGa

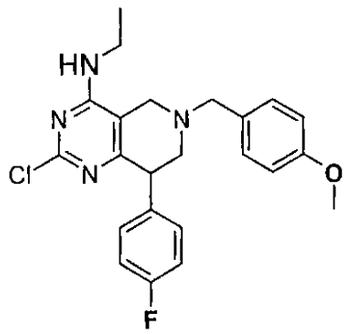
2-cloro-8-(4-fluorofenil)-6-(4-metoxibencil)-N-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina



A una solución de la Preparación AG (1,0 g, 2,39 mmol) en metanol se añadió diisopropiletilamina (0,62 g, 4,79 mmol) seguida por clorhidrato de metilamina (0,192 g, 2,87 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 35% en éter de petróleo como fase móvil dando 2-cloro-8-(4-fluorofenil)-6-(4-metoxibencil)-N-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina (0,408 g, 41%) como sólido blanquecino. CL-EM $(M+H)^+$ = 413,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,32 (1H, m), 7,24-7,20 (2H, m), 7,14-7,06 (4H, m), 6,82 (2H, m), 3,96 (1H, m), 3,72 (3H, s), 3,67 (1H, m), 3,59 (1H, m), 3,50 (1H, m), 3,20 (1H, m), 2,82 (3H, d, *J* = 4,0 Hz), 2,80 (1H, m), 2,51(1H, m).

Preparación AGb

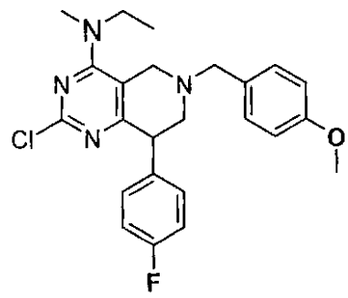
2-cloro-N-etil-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina



A una solución de la Preparación AG (1,0 g, 2,39 mmol) en metanol se añadió diisopropiletilamina (0,61 g, 4,79 mmol) seguida por clorhidrato de etilamina (0,23 g, 2,86 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 30-35% en éter de petróleo como fase móvil dando 2-cloro-N-etil-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina (0,54 g, 54%) como sólido blanquecino. CL-EM $(M+H)^+$ = 427,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,32 (1H, m), 7,30-7,19 (2H, m), 7,13-7,05 (4H, m), 6,80 (2H, m), 3,93 (1H, m), 3,71 (3H, s), 3,68-3,48 (5H, m), 3,22 (1H, m), 2,80 (1H, m), 2,68 (1H, m), 1,15 (3H, m).

Preparación AGc

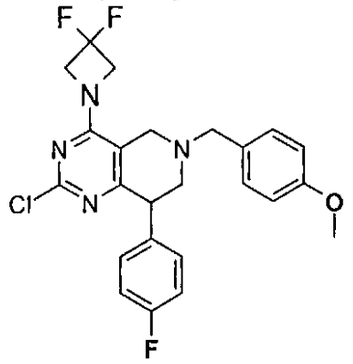
2-cloro-N-etil-8-(4-fluorofenil)-6-(4-metoxibencil)-N-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina



A una solución de la Preparación AG (1,2 g, 2,87 mmol) en metanol se añadió diisopropiletilamina (0,74 g, 5,75 mmol) seguida por etilmetilamina (0,20 g, 3,44 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 30-35% en éter de petróleo como fase móvil dando 2-cloro-N-etil-8-(4-fluorofenil)-6-(4-metoxibencil)-N-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina (0,50 g, 41%) como sólido blanquecino. CL-EM $(M+H)^+$ = 441,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,23-7,16 (4H, m), 7,11-7,07 (2H, m), 6,84 (2H, m), 4,10 (1H, m), 3,73 (3H, s), 3,65-3,56 (3H, m), 3,51-3,40 (3H, m), 3,04 (1H, m), 2,99 (3H, s), 2,58 (1H, m), 1,11 (3H, t, *J* = 7,0 Hz).

Preparación AGd

2-cloro-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina

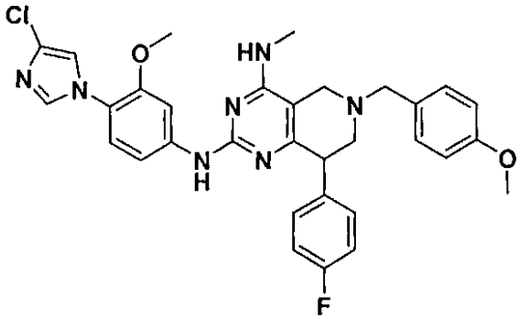


A una solución de la Preparación AG (0,75 g, 1,79 mmol) en metanol se añadió diisopropiletilamina (0,58 g, 4,49 mmol) seguida por 3,3-difluoroazetidina (0,25 g, 1,97 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente

a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 30% en éter de petróleo como fase móvil dando 2-cloro-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (0,4 g, 48%) como sólido blanquecino. CL-EM $(M+H)^+$ = 475,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,25-7,10 (4H, m), 6,97-6,82 (2H, m), 6,80 (2H, m), 4,52 (4H, m), 4,07 (1H, m), 3,80 (3H, s), 3,59 (3H, m), 3,36 (1H, m), 2,93 (1H, m), 2,80 (1H, m).

Preparación AGe

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-6-(4-metoxibencil)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

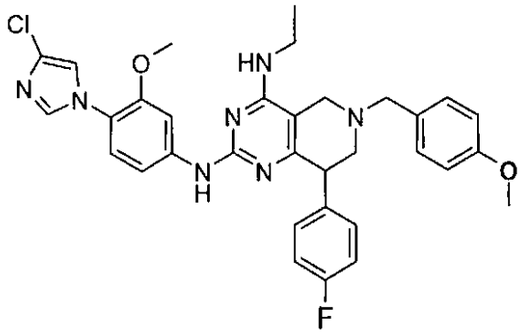


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,215 g, 0,966 mmol), Preparación AGa (0,40 g, 0,966 mmol), Na_2CO_3 (0,205 g, 1,93 mmol) y xantphos (0,558 g, 0,966 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,50 g, 0,48 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con

solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 5% en diclorometano como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-6-(4-metoxibencil)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,20 g, 35%) como sólido blanquecino. CL-EM $(M+H)^+$ = 600,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,09 (1H, s), 8,05 (1H, s), 7,72 (1H, s), 7,41 (1H, s), 7,26-7,22 (2H, m), 7,14-7,05 (7H, m), 6,82-6,75 (2H, m), 3,93 (1H, m), 3,76 (4H, m), 3,74 (2H, m), 3,72 (1H, m), 3,70 (3H, s), 2,92 (3H, d, *J* = 4,0 Hz), 2,90 (1H, m), 2,70 (1H, m).

Preparación AGf

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

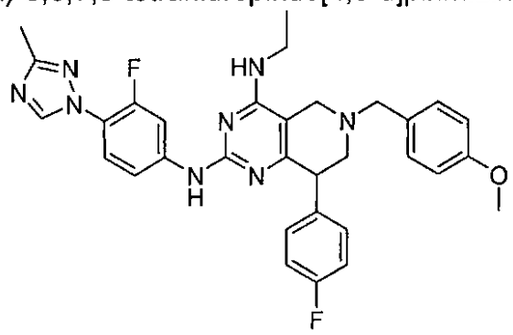


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,283 g, 1,26 mmol), Preparación AGb (0,54 g, 1,26 mmol), Na_2CO_3 (0,26 g, 2,53 mmol) y xantphos (0,73 g, 1,26 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,65 g, 0,63 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción

se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 7% en diclorometano como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,22 g, 29%) como sólido blanquecino. CL-EM $(M+H)^+$ = 614,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,05 (1H, s), 7,97 (1H, s), 7,72 (1H, s), 7,41 (1H, s), 7,39-7,29 (3H, m), 7,25-7,09 (6H, m), 6,81-6,75 (2H, m), 6,72 (1H, m), 3,93 (1H, m), 3,71 (3H, s), 3,67 (1H, m), 3,57 (3H, s), 3,52 (1H, m), 3,49 (2H, m), 3,24 (1H, m) 2,83 (1H, m), 2,65 (1H, m), 1,16 (3H, t, *J* = 7,2 Hz).

Preparación AGg

N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

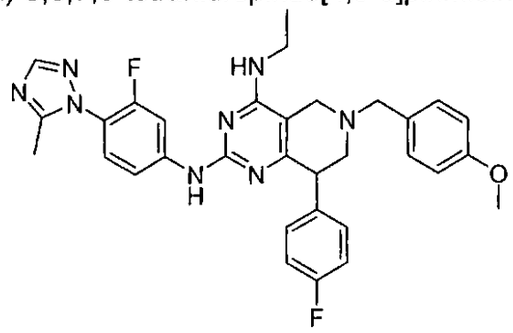


Se purgó con argon durante 1 h a temperatura ambiente una solución de

la Preparación B (0,275 g, 1,43 mmol), Preparación AGb (0,68 g, 1,59 mmol), Na_2CO_3 (0,33 g, 3,19 mmol) y xantphos (0,92 g, 1,59 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,82 g, 0,79 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 10% en diclorometano como fase móvil dando N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,6 g, 65%) como sólido blanquecino. CL-EM $(M+H)^+$ = 583,2.

Preparación AGh

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

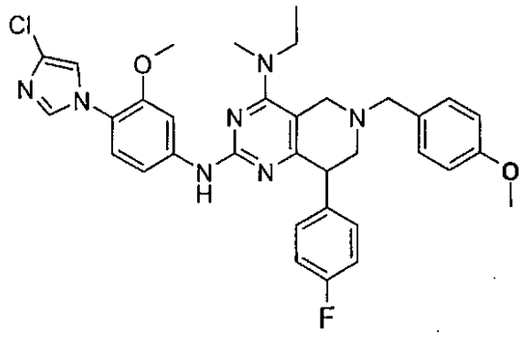


Se purgó con argon durante 1 h a temperatura ambiente una solución de

la Preparación C (0,20 g, 1,05 mmol), Preparación AGb (0,50 g, 1,17 mmol), Na_2CO_3 (0,24 g, 2,34 mmol) y xantphos (0,67 g, 1,17 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,60 g, 0,58 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (20 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 10% en diclorometano como fase móvil dando N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,51 g, 73%) como sólido blanquecino. CL-EM $(M+H)^+$ = 583,2.

Preparación AGi

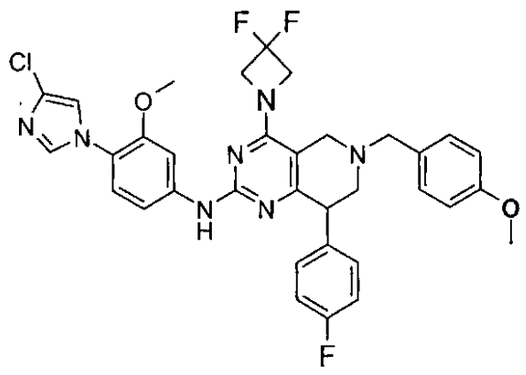
N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-6-(4-metoxibencil)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,25 g, 1,13 mmol), Preparación AGc (0,50 g, 1,13 mmol), Na_2CO_3 (0,24 g, 2,28 mmol) y xantphos (0,65 g, 1,14 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,60 g, 0,560 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (20 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 5-10% en diclorometano como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-6-(4-metoxibencil)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,45 g, 63%) como sólido blanquecino. CL-EM $(M+H)^+$ = 628,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,15 (1H, s), 7,86 (1H, s), 7,73 (1H, s), 7,42 (1H, s), 7,24-7,21 (4H, m), 7,18-7,07 (4H, m), 6,86 (2H, m), 4,11 (1H, m), 3,70 (3H, s), 3,65 (2H, m), 3,56 (3H, s), 3,47 (2H, m), 3,40 (2H, m), 3,07 (1H, m), 2,98 (3H, s), 2,51 (1H, m), 1,24 (3H, t, *J* = 7,2 Hz).

Preparación AGj

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina

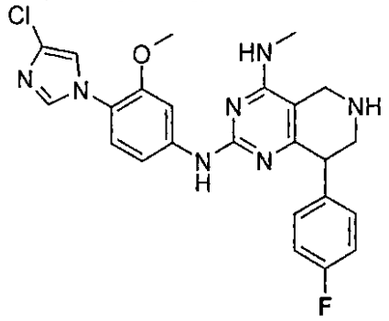


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,20 g, 0,92 mmol), Preparación AGd (0,40 g, 0,84 mmol), Na_2CO_3 (0,18 g, 1,77 mmol) y xantphos (0,48 g, 0,84 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,43 g, 0,420 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 5% en diclorometano como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-6-(4-metoxibencil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina (0,25 g, 49%) como sólido blanquecino. CL-EM $(M+H)^+$ = 663,0.

Preparación AGk

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N4-metil-5,6,7,8-

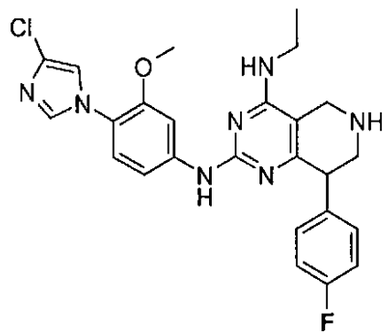
tetrahidropirido[4,3-d]pirimidin-2,4-diamina



A una solución de la Preparación AGe (0,20 g, 0,330 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (25 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,08 g, 51%) como compuesto bruto. El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 480,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,36 (1H, s), 7,86 (1H, s), 7,75 (1H, s), 7,43 (1H, s), 7,32-7,28 (3H, m), 7,23-7,11 (4H, m), 4,30 (1H, m), 4,02 (1H, m), 3,98 (1H, m), 3,71 (1H, m), 3,56 (3H, s), 3,38 (1H, m), 2,98 (3H, d, *J* = 4,0 Hz).

Preparación AGI (BBRC-7610)

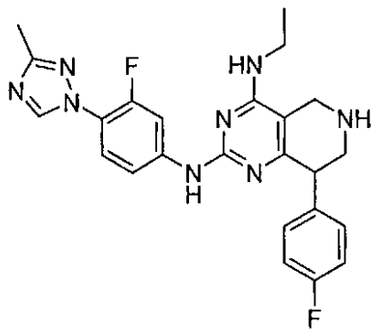
N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



A una solución de la Preparación AGf (0,22 g, 0,35 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (25 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (50 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina como compuesto bruto (0,16 g, 93%). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 494,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,01 (1H, s), 7,98 (1H, s), 7,72 (1H, s), 7,41 (1H, s), 7,21-7,17 (2H, m), 7,13-7,05 (4H, m), 6,67 (1H, m), 3,82 (1H, m), 3,66 (2H, m), 3,56 (3H, s), 3,50 (2H, m), 3,20 (1H, m), 2,85 (1H, m), 1,20 (3H, t, J = 7,2 Hz).

Preparación AGm

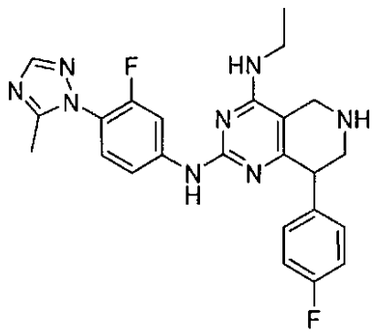
N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



A una solución de la Preparación AGg (0,40 g, 0,68 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (20 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,30 g, 94%) como compuesto bruto. El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 463,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,29 (1H, s), 8,68 (1H, s), 8,03 (1H, m), 7,44-7,37 (2H, m), 7,25-7,21 (2H, m), 7,12-7,07 (2H, m), 6,76 (1H, m), 3,83 (1H, m), 3,68-3,60 (2H, m), 3,55-3,46 (2H, m), 3,22 (1H, m), 2,91 (1H, m), 2,34 (3H, s), 1,20 (3H, t, J = 7,2 Hz).

Preparación AGn

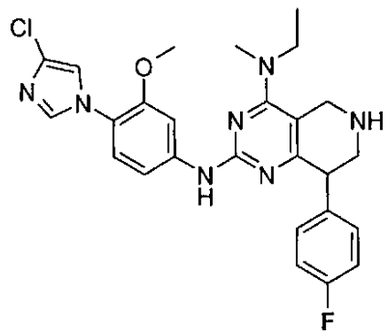
N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



A una solución de la Preparación AGh (0,51 g, 0,87 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (25 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,31 g, 78%) como compuesto bruto. El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 463,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,29 (1H, s), 8,68 (1H, s), 8,02 (1H, m), 7,42 (2H, m), 7,23 (2H, m), 7,28-7,10 (2H, m), 6,75 (1H, m), 3,80 (1H, m), 3,67-3,60 (2H, m), 3,55-3,48 (2H, m), 3,22 (1H, m), 2,89 (1H, m), 2,34 (3H, s), 1,24 (3H, t, *J* = 7,0 Hz).

Preparación AGo(BBRC-4363)

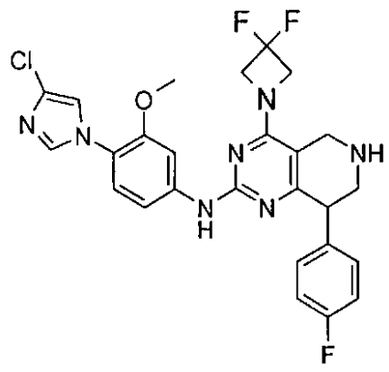
N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



A una solución de la Preparación AGi (0,10 g, 0,15 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (10 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (20 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,03 g) como compuesto bruto. El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 508,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,78 (1H, s), 7,77 (1H, s), 7,37 (1H, s), 7,20-7,16 (3H, m), 7,12-7,06 (4H, m), 4,04 (2H, m), 3,80 (1H, m), 3,50 (3H, s), 3,42-3,32 (3H, m), 3,15 (3H, s), 2,81 (1H, m), 1,17 (3H, t, *J* = 7,2 Hz).

Preparación AGp (BBRC-4364)

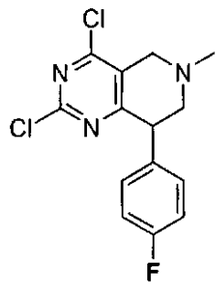
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina



A una solución de la Preparación AGj (0,20 g, 0,30 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (10 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina (0,12 g, 70%) como compuesto bruto. El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 542,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,31 (1H, s), 7,87 (1H, s), 7,73 (1H, s), 7,41 (1H, s), 7,22 (2H, m), 7,15-7,07 (4H, m), 4,74-4,59 (4H, m), 3,97 (1H, m), 3,87 (1H, m), 3,76 (1H, m), 3,51 (3H, s), 3,27 (1H, m), 2,83 (1H, m).

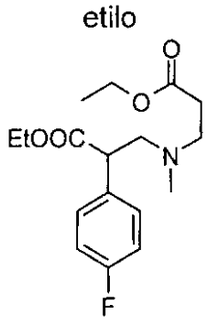
Preparación AH

2,4-dicloro-8-(4-fluorofenil)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina



Intermedio AH(1)

3-((3-etoxi-3-oxopropil)(4-metoxibencil)amino)-2-(4-fluorofenil)propanoato de etilo

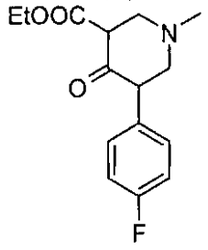


A una solución del Intermedio AG(3) (12,0 g, 38,5 mmol) en acetona se añadió K_2CO_3 (6,38 g, 46,3 mmol) seguido por yoduro de metilo (6,5 g, 46,3 mmol) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 2 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La fase acuosa se extrajo con acetato de etilo (50 x 3). La fase orgánica reunida se lavó con solución de salmuera (75 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 20% en éter de petróleo como fase móvil dando 3-((3-etoxi-3-oxopropil)(metil)amino)-2-fenilpropanoato de etilo (6,0 g, 50%) como líquido aceitoso. CL-EM $(M+H)^+$ = 326,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,01 (2H, m), 6,98, (2H, m), 4,16-4,07 (4H, m), 3,77 (1H, m),

3,13 (1H, t, *J* = 2,4 Hz), 2,75-2,51 (5H, m), 2,17 (3H, s), 1,26-1,19 (6H, m).

Intermedio AH(2)

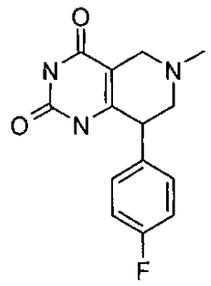
5-(4-fluorofenil)-1-metil-4-oxopiperidin-3-carboxilato de etilo



A una solución enfriada de Intermedio AH(1) (6,0 g, 18,4 mmol) en THF se añadió *t*-BuOK (4,1 g, 36,9 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. La masa de reacción se enfrió con agua, luego se evaporó el disolvente a presión reducida. El residuo se diluyó con agua y se extrajo con acetato de etilo (25 ml x 4). La fase orgánica reunida se lavó con solución de salmuera (30 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 20% en éter de petróleo como fase móvil dando 5-(4-fluorofenil)-1-metil-4-oxopiperidin-3-carboxilato de etilo (3,0 g, 51%) como líquido aceitoso. CL-EM $(M+H)^+$ = 278,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 7,35 (1H, m), 7,15 (1H, m), 7,12 (1H, m), 6,98 (1H, m), 4,01 (2H, m), 3,88 (1H, m), 2,60 (1H, m), 2,38 (2H, m), 2,19 (3H, s), 1,19-1,08 (3H, m).

Intermedio AH(3)

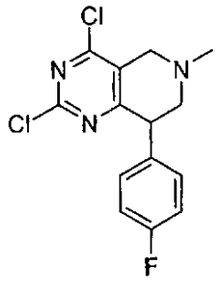
8-(4-fluorofenil)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4(1H,3H)-diona



A una solución enfriada de Intermedio AH(2) (3,0 g, 10,75 mmol) en etanol se añadió *t*-BuOK (3,0 g 26,8 mmol) seguido por urea (1,6 g, 26,8 mmol). La mezcla de reacción se calentó a reflujo durante 36 h. La masa de reacción se enfrió con agua y se evaporó el disolvente a presión reducida. El residuo se diluyó con agua y se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (30 ml), se secó sobre Na_2SO_4 y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 100% como fase móvil dando 8-(4-fluorofenil)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4(1H,3H)-diona (1,5 g, 51%) como sólido amarillo pálido. CL-EM $(M+H)^+$ = 276,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 11,08 (1H, s), 10,59 (1H, s), 7,31 (2H, m), 7,13 (2H, m), 3,74 (1H, m), 3,17 (1H, m), 2,80-2,59 (2H, m), 2,23 (3H, s).

Preparación AH

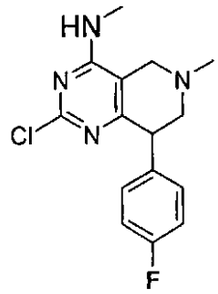
2,4-dicloro-8-(4-fluorofenil)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina



Se calentó a reflujo durante 10 h una solución de Intermedio AH(3) (1,5 g, 5,45 mmol) y cantidad catalítica de DMF en $POCl_3$ (20 vol.). El exceso de $POCl_3$ se evaporó a presión reducida. El residuo se vertió en hielo picado y se agitó durante 15 min. La solución acuosa se extrajo con acetato de etilo (20 ml x 2). La fase orgánica reunida se lavó con $NaHCO_3$ acuoso saturado (10 ml x 2), solución de salmuera (10 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 2,4-dicloro-8-(4-fluorofenil)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina (0,7 g, 56%) como sólido marrón. CL-EM $(M+H)^+$ = 312,2.

Preparación AHa

2-cloro-8-(4-fluorofenil)-N,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina

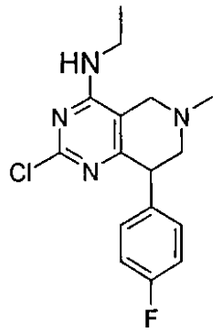


A una solución de la Preparación AH (0,4 g, 1,28 mmol) en metanol se añadió diisopropiletilamina (0,33 g, 2,57 mmol) seguido por clorhidrato de metilamina (0,16 g, 2,57 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando 2-cloro-8-(4-fluorofenil)-N,6-dimetil-5,6,7,8-tetrahidropirido[4,3-

d]pirimidin-4-amina (0,20 g, 51,2%) como sólido blanquecino. CL-EM $(M+H)^+$ = 307,2.

Preparación AHb

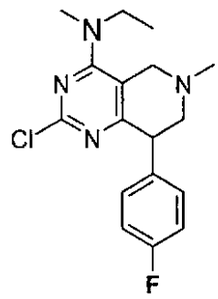
2-cloro-N-etil-8-(4-fluorofenil)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina



A una solución de la Preparación AH (0,7 g, 2,25 mmol) en metanol se añadió diisopropiletilamina (0,58 g, 4,50 mmol) seguido por clorhidrato de etilamina (0,4 g, 4,50 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 30-35% en éter de petróleo como fase móvil dando 2-cloro-N-etil-8-(4-fluorofenil)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina (0,21 g, 29%) como sólido blanquecino. CL-EM $(M+H)^+$ = 321,2.

Preparación AHc

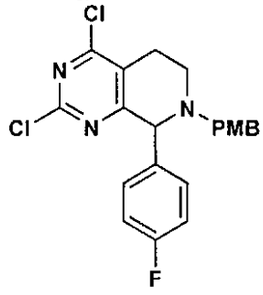
2-cloro-N-etil-8-(4-fluorofenil)-N,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina



A una solución de la Preparación AH (0,35 g, 1,1 mmol) en metanol se añadió diisopropiletilamina (0,29 g, 2,2 mmol) seguido por etilmetilamina (0,67 g, 1,35 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 35% en éter de petróleo como fase móvil dando 2-cloro-N-etil-8-(4-fluorofenil)-N,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-4-amina (0,22 g, 58%) como sólido blanquecino. CL-EM $(M+H)^+$ = 333,9.

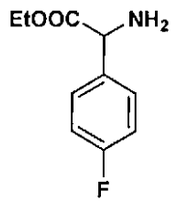
Preparación AI

2,4-dicloro-8-(4-fluorofenil)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidina



Intermedio AI(1)

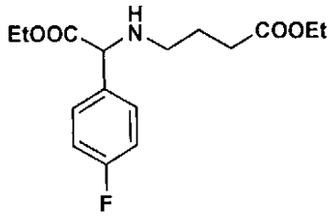
2-amino-2-(4-fluorofenil)acetato de etilo



A una solución enfriada de ácido 2-amino-2-(4-fluorofenil)acético (1,0 g, 6,17 mmol) en etanol se añadió H_2SO_4 concentrado (1 ml) durante un período de 1 min. La mezcla de reacción se calentó a reflujo durante 5 h. El disolvente se evaporó a presión reducida y el residuo se diluyó con acetato de etilo (20 ml). La solución orgánica se lavó con $NaHCO_3$ acuoso saturado (15 ml x 2), agua (20 ml), solución de salmuera (10 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 2-amino-2-(4-fluorofenil)acetato de etilo (0,75 g, 65%) como compuesto bruto (líquido oleoso). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H_2O)^+$ = 198,0. RMN de ^1H (400 MHz, DMSO-d6): δ 7,44-7,40 (2H, m), 7,18-7,13 (2H, m), 4,51 (1H, s), 4,12-4,01 (2H, m), 2,26 (2H, s), 1,12 (3H, t, *J* = 8,0 Hz).

Intermedio AI(2)

4-(2-etoxi-1-(4-fluorofenil)-2-oxoetilamino)butanoato de etilo

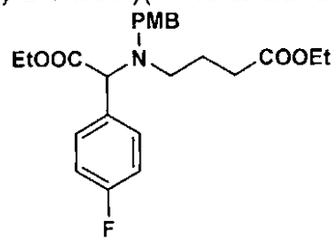


A una solución del Intermedio AI(1) (4,2 g, 21,3 mmol) en DMF se añadió carbonato de cesio (8,3 g, 2,25 mmol) seguido por 4-bromobutiroato de etilo (4,98 g, 2,55 mmol) a temperatura ambiente. La mezcla de reacción se agitó a 70 °C durante 18 h. El disolvente se evaporó a presión reducida y el

compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 25% en éter de petróleo como fase móvil dando 4-(2-etoxi-1-(4-fluorofenil)-2-oxoetilamino)butanoato de etilo (2,0 g, 30%) como líquido oleoso amarillento. CL-EM $(M+H)^+$ = 312,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,33 (2H, m), 7,06 (2H, m), 4,31 (1H, m), 4,18 (4H, m), 2,63 (1H, m), 2,49 (1H, m), 2,35 (2H, m), 1,81 (1H, m), 1,24 (6H, m).

Intermedio AI(3)

4-((2-etoxi-1-(4-fluorofenil)-2-oxoetil)(4-metoxibencil)amino)butanoato de etilo

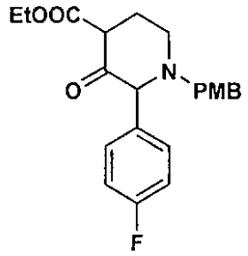


A una solución Intermedio AI(2) (15,0 g, 48,23 mmol) en acetona se añadió K_2CO_3 (7,9 g, 57,8 mmol) seguido por bromuro de 4-metoxibencilo (14,5 g, 72,3 mmol) a 0°C. La mezcla de reacción se calentó a 70 °C durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La fase acuosa se extrajo con acetato de etilo (100 x 2). La fase orgánica reunida se lavó con solución de salmuera (75 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 30% en éter de petróleo como fase móvil dando 4-((2-etoxi-1-(4-fluorofenil)-2-oxoetil)(4-metoxibencil)amino)butanoato de etilo (12,0 g, 60%) como líquido aceitoso. CL-EM $(M+H)^+$ 432,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,30 (2H, m), 7,22 (2H, m), 7,01 (2H, m), 6,99 (2H, m), 4,52 (1H, s), 4,22

(2H, m), 4,04 (2H, m), 3,79 (5H, m), 3,61 (1H, m), 2,71 (1H, m), 2,57 (1H, m), 2,20 (1H, m), 2,07 (1H, m), 1,70 (2H, m), 1,28 (3H, m, *J* = 7,2 Hz), 1,20 (3H, m, *J* = 7,2 Hz).

Intermedio AI(4)

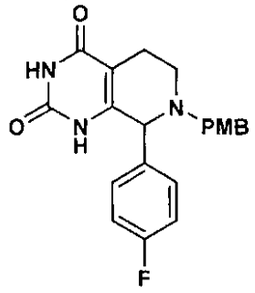
2-(4-fluorofenil)-1-(4-metoxibencil)-3-oxopiperidin-4-carboxilato de etilo



A una solución enfriada de Intermedio AI(3) (12,0 g, 27,7 mmol) en THF se añadió *t*-BuOK (6,2 g, 55,5 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 h. La masa de reacción se enfrió con agua, luego se evaporó el disolvente a presión reducida. El residuo se diluyó con agua y se extrajo con acetato de etilo (50 ml x 4). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 20% en éter de petróleo como fase móvil dando 2-(4-fluorofenil)-1-(4-metoxibencil)-3-oxopiperidin-4-carboxilato de etilo (7,0 g, 67%) como líquido aceitoso. CL-EM $(M+H)^+$ = 386,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 12,02 (1H, s), 7,43 (2H, m), 7,15 (2H, m), 7,04 (2H, m), 6,84 (2H, m), 4,23 (2H, c, *J* = 7,2 Hz), 4,05 (1H, s), 3,79 (3H, s), 3,65 (1H, d, *J* = 13,6 Hz), 3,22 (1H, d, *J* = 13,6 Hz), 2,92 (1H, m), 2,35 (3H, m), 1,32 (3H, t, *J* = 7,2 Hz).

Intermedio AI(5)

8-(4-fluorofenil)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4(1H,3H)-diona

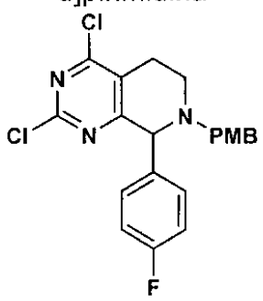


A una solución enfriada de Intermedio AI(4) (7,0 g, 18,1 mmol) en etanol se añadió *t*-BuOK (5,0 g 45,4 mmol) seguido por urea (2,7 g, 45,4 mmol). La mezcla de reacción se calentó a reflujo durante 18 h. La masa de reacción se enfrió con agua y se evaporó el disolvente a presión reducida. El residuo se diluyó con agua y se extrajo con acetato de etilo (50 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (75 ml), se secó sobre Na_2SO_4 y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando éter de petróleo al 50% en acetato de etilo como fase móvil dando 8-(4-fluorofenil)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4(1H,3H)-diona (3,0 g, 45%) como sólido amarillo pálido. CL-EM $(M+H)^+$ = 382,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 11,08 (1H, s), 10,44 (1H, s), 7,26-7,17 (6H, m), 6,92 (2H, m), 4,36 (1H, s), 3,75 (3H, s), 3,73 (1H, d, *J* = 13,2 Hz) 3,58 (1H, d, *J* = 13,2 Hz), 2,63 (2H, m), 2,51 (1H, m), 2,35 (1H, m).

Preparación AI

2,4-dicloro-8-(4-fluorofenil)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-

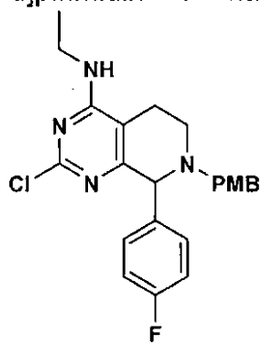
d]pirimidina



Se calentó a 85 °C durante 18 h una solución de Intermedio AI(5) (2,0 g, 5,24 mmol) y cantidad catalítica de DMF en $POCl_3$ (30 vol.). El exceso de $POCl_3$ se evaporó a presión reducida. El residuo se vertió en hielo picado y se agitó durante 15 min. La solución acuosa se extrajo con acetato de etilo (20 ml x 3). La fase orgánica reunida se lavó con $NaHCO_3$ acuoso saturado (10 ml x 4), solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando 2,4-dicloro-8-(4-fluorofenil)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidina (1,4 g, bruto) como sólido marrón. CL-EM $(M+H)^+$ = 418,0.

Preparación AIa

2-cloro-N-etil-8-(4-fluorofenil)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-4-amina

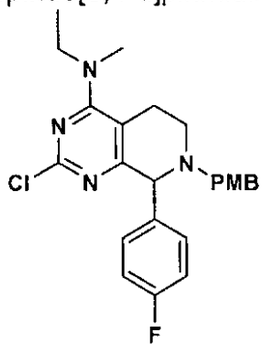


A una solución de la Preparación AI (0,7 g, 1,67 mmol) en metanol se

añadió diisopropiletilamina (0,43 g, 3,35 mmol) seguida por clorhidrato de etilamina (0,27 g, 3,35 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 35% en éter de petróleo como fase móvil dando cloro-N-etil-8-(4-fluorofenil)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-4-amina (0,36 g, 50%) como sólido blanquecino. CL-EM $(M+H)^+$ = 427,2. RMN de ^1H: (400 MHz, DMSO-*d6*): δ ppm 7,38 (2H, m), 7,30 (2H, m), 7,20-7,13 (4H, m), 6,88 (2H, m), 4,45 (1H, s), 3,73 (3H, s), 3,45 (1H, m), 3,40-3,34 (3H, m), 2,88 (1H, m), 2,42 (2H, m), 1,16 (3H, t, *J* = 7,2 Hz).

Preparación Alb

2-cloro-N-etil-8-(4-fluorofenil)-7-(4-metoxibencil)-N-metil-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-4-amina

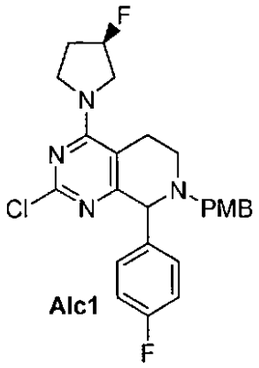


A una solución de la Preparación AI (0,7 g, 1,67 mmol) en metanol se añadió diisopropiletilamina (0,43 g, 3,3 mmol) seguida por etilmetilamina.HCl (0,19 g, 3,35 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida

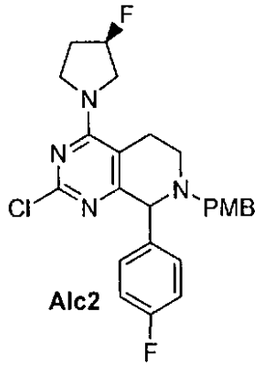
y el residuo se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 20% en éter de petróleo como fase móvil dando 2-cloro-N-etil-8-(4-fluorofenil)-7-(4-metoxibencil)-N-metil-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-4-amina (0,40 g, 54%) como sólido blanquecino. CL-EM $(M+H)^+$ = 441,2. RMN de ^1H: (400 MHz, DMSO-d6) δ ppm 7,49 (2H, m), 7,19-7,14 (4H, m), 6,87 (2H, m), 4,42 (1H, s), 3,73 (3H, s), 3,55 (2H, m), 3,42 (1H, m), 3,21 (1H, m), 3,04 (3H, s), 2,95 (2H, m), 2,56 (1H, m), 2,25 (1H, m), 1,16 (3H, t , *J* = 7,2 Hz).

Preparación Alc1 y Alc2

2-cloro-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidina



Alc1



Alc2

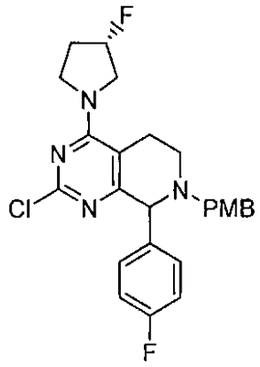
A una solución de la Preparación AI (0,70 g, 1,6 mmol) en metanol se añadió diisopropiletilamina (0,40 g, 3,35 mmol) seguida por (S)-3-fluoropirrolidina (0,25 g, 2,14 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por HPLC preparativa dando 2-cloro-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidina (0,150 g, 37% & 190 mg, 43%).

AIc1: CL-EM $(M+H)^+$ = 471,1. RMN de ^1H (400 MHz, cloroformo-*d*): δ ppm 7,48 (2H, m), 7,15 (2H, m), 7,01 (2H, m), 6,83 (2H, m), 5,30 (1H, m), 4,43 (1H, s), 3,97-3,90 (4H, m), 3,88-3,72 (4H, m), 3,65 (1H, m), 3,17 (1H, m), 3,02 (2H, m), 2,33 (2H, m), 1,95 (1H, m).

AIc2: CL-EM $(M+H)^+$ = 471,1. RMN de ^1H (400 MHz, cloroformo-*d*): δ ppm 7,28 (2H, m), 7,18 (2H, m), 6,99 (2H, m), 6,84 (2H, m), 5,30 (1H, m), 4,58 (1H, s), 4,20-4,11 (2H, m), 3,97-3,80 (6H, m), 3,69 (1H, m), 3,35 (1H, m), 2,88 (2H, m), 2,35 (1H, m), 2,17 (1H, m), 2,05 (1H, m).

Preparación AId

2-cloro-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidina

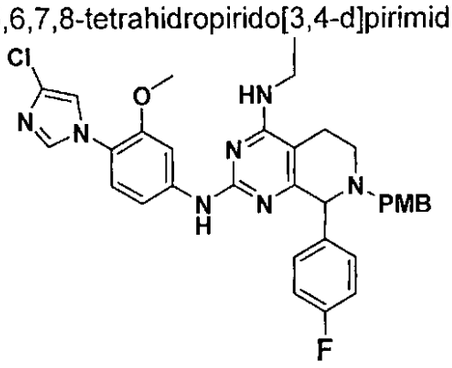


A una solución de la Preparación AI (0,70 g, 1,6 mmol) en metanol se añadió diisopropiletilamina (0,43 g, 3,35 mmol) seguida por (R)-3-fluoropirrolidina (0,25 g, 2,2 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se purificó por HPLC preparativa dando 2-cloro-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidina (0,150 g, 37% & 190 mg, 43%). CL-EM $(M+H)^+$

= 471,2.

Preparación Ale

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina

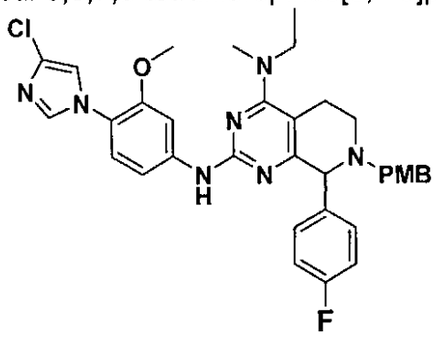


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,36 g, 0,845 mmol), Preparación Ala (0,189 g, 0,845 mmol), Na_2CO_3 (0,179 g, 1,69 mmol) y xantphos (0,488 g, 0,845 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,870 g, 0,845 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (50 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 20% en éter de petróleo como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina (0,30 g, 58%) como sólido

blanquecino. CL-EM $(M+H)^+$ = 614,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 8,96 (1H, s), 7,79 (1H, s), 7,74 (1H, s), 7,43 (1H, s), 7,33 (2H, m), 7,20 (6H, m), 6,89 (2H, m), 6,80 (1H, m), 4,44 (1H, s), 3,74 (3H, s), 3,66 (3H, s), 3,50 (4, m), 2,90 (1H, m), 2,33 (3H, m), 1,24 (3H, t, *J* = 7,2 Hz).

Preparación Alf

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-7-(4-metoxibencil)-N4-metil-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina

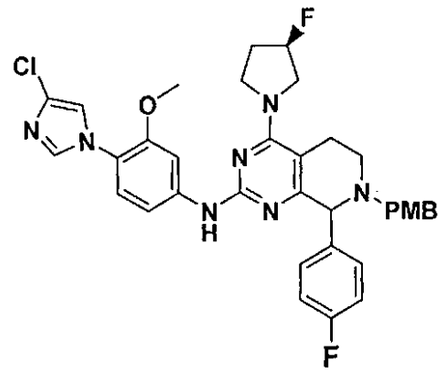


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,20 g, 0,90 mmol), Preparación Alb (0,41 g, 0,90 mmol), Na_2CO_3 (0,192 g, 1,80 mmol) y xantphos (0,525 g, 0,90 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,470 g, 0,45 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (50 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 30% en

éter de petróleo como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-7-(4-metoxibencil)-N4-metil-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina (0,34 g, 59%) como sólido blanquecino. Este compuesto se llevó a la etapa siguiente sin análisis posterior. CL-EM $(M+H)^+$ = 628,2.

Preparación Alg

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina

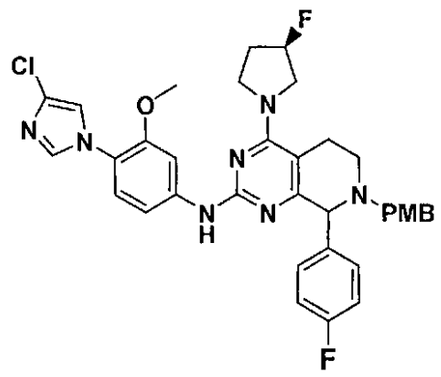


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,070 g, 0,319 mmol), Preparación Alc1 (0,150 g, 0,319 mmol), Na_2CO_3 (0,067 g, 0,63 mmol) y xantphos (0,184 g, 0,319 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,165 g, 0,159 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (20 ml x 3). La fase orgánica

reunida se lavó con solución de salmuera (20 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina (0,1 g, 48%) como sólido blanquecino. CL-EM $(M+H)^+$ = 658,2.

Preparación Alh

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina

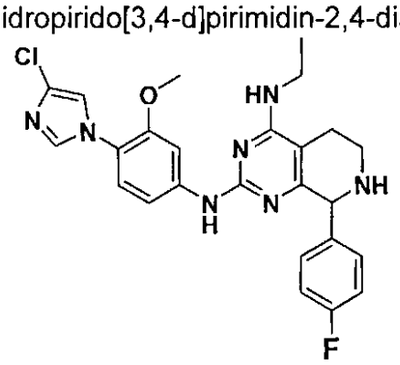


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,09 g, 0,404 mmol), Preparación Alc2 (0,190 g, 0,404 mmol), Na_2CO_3 (0,085 g, 0,80 mmol) y xantphos (0,230 g, 0,404 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,209 g, 0,202 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de

etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (20 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (20 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina (0,120 g, 48%) como sólido blanquecino. CL-EM $(M+H)^+$ = 538,2.

Preparación Alk

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina

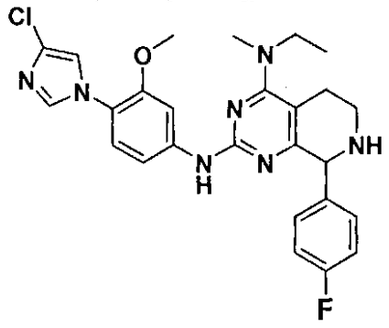


A una solución de la Preparación Ale (0,30 g, 0,489 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (25 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a

presión reducida dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina como compuesto bruto (0,20 g). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 494,2.

Preparación AII (Ejemplo 1)

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina

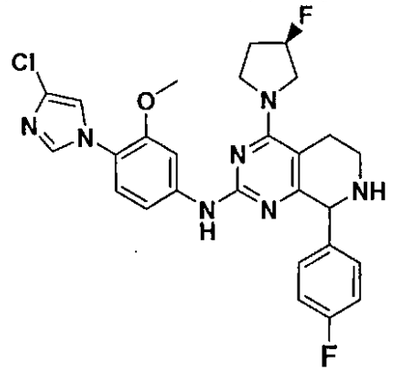


A una solución de la Preparación AIf (0,340 g, 0,541 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (10 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (20 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina como compuesto bruto (0,20 g). El compuesto bruto se llevó a la etapa siguiente sin purificación posterior. CL-EM $(M+H)^+$ = 508,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,05 (1H, s), 7,78 (1H, s), 7,74 (1H, s), 7,43 (1H, s), 7,32 (2H, m),

7,21-7,0 (5H, m), 4,85 (1H, s), 3,59 (3H, s), 3,49 (2H, m), 3,05 (3H, s), 2,68 (2H, m), 2,51 (2H, m), 1,22 (3H, t, *J* = 7,2 Hz).

Preparación AIm

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina

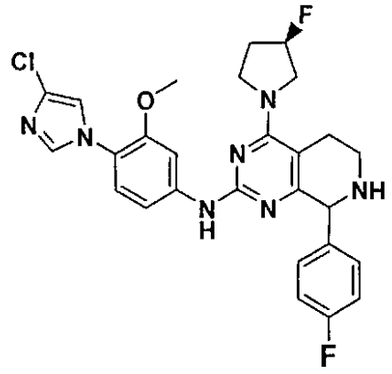


A una solución del Intermedio AIg (0,120 g, 0,182 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (10 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (20 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina (0,040 g, 50%). CL-EM $(M+H)^+$ = 538,2.

Preparación AIn

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-

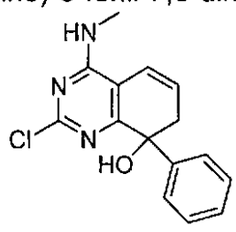
fluoropirrolidin-1-il)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina



A una solución de la Preparación Alh (0,120 g, 0,182 mmol) en tolueno se añadió ácido trifluorometanosulfónico (3,0 vol.) a temperatura ambiente. La mezcla de reacción se calentó a reflujo durante 1 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se lavó con diclorometano (10 ml x 2), se basificó usando $NaHCO_3$ acuoso saturado y se extrajo con acetato de etilo (20 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (20 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina (0,045 g, 51%). CL-EM $(M+H)^+$ = 538,2.

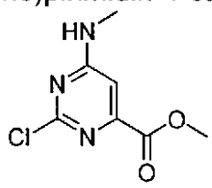
Preparación AJ

2-cloro-4-(metilamino)-8-fenil-7,8-dihidroquinazolin-8-ol



Intermedio AJ(1)

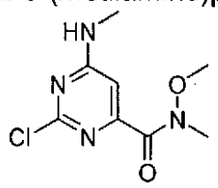
2-cloro-6-(metilamino)pirimidin-4-carboxilato de metilo



A una mezcla de 2,6-dicloropirimidin-4-carboxilato de metilo (2 g), clorhidrato de metilamina (0,72 g) en CH_2Cl_2 (48 ml) a 0 °C se añadió base de Hunig (3,7 ml) gota a gota, y la mezcla de reacción se agitó en baño de hielo durante 1 h y luego a ta durante 1 h. Se eliminó el disolvente a vacío, y el residuo blanco se purificó directamente por Biotage eluyendo con EtOAc al 40-600%/Hexanos (1000 ml) seguido por CH_2Cl_2 al 90%/10% MeOH (4 l) dando el compuesto del epígrafe como un sólido blanco (1,8 g). Estas fracciones se reunieron y se evaporaron a vacío. Durante la eliminación del disolvente, se formo un sólido blanco. Varias filtraciones dieron el compuesto del epígrafe como un sólido blanco (1,8 g, sólido muy blanco). CL-EM $(M+H)^+$ = 202,00

Intermedio AJ(2)

2-cloro-N-metoxi-N-metil-6-(metilamino)pirimidin-4-carboxamida

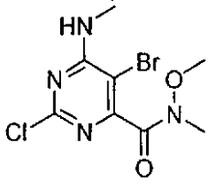


A una suspensión de 2-cloro-6-(metilamino)pirimidin-4-carboxilato de metilo (1,95 g) y clorhidrato de N,O-dimetilhidroxilamina (1,887 g, 19,34 mmol) en THF a -20 °C se añadió cloruro de isopropilmagnesio (23,60 ml, 47,2 mmol) gota a gota mediante un embudo de adición durante un período de 30 min, y la

mezcla de reacción se agitó a -10 °C durante 40 min. La reacción se trató con NH_4Cl saturado y EtOAc, y el producto bruto se purificó por Biotage eluyendo con EtOAc al 40-90%/Hexanos dando el compuesto del epígrafe como un aceite incoloro (786 mg). CL-EM $(M+H)^+$ = 231,01.

Intermedio AJ(3)

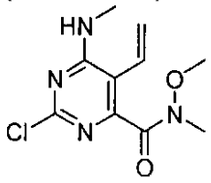
5-bromo-2-cloro-N-metoxi-N-metil-6-(metilamino)pirimidin-4-carboxamida



A una solución de 2-cloro-N-metoxi-N-metil-6-(metilamino)pirimidin-4-carboxamida (959 mg) en MeCN (21 ml) se añadió NBS (814 mg), y la mezcla de reacción se calentó a 60 °C durante 8 h. Se eliminó el disolvente, y se purificó el residuo por Biotage eluyendo con EtOAc al 50%-70/Hexanos (1,2 l) dando el compuesto del epígrafe como un sólido blanco (1,1g). CL-EM $(M+H)^+$ = 310,95.

Intermedio AJ(4)

2-cloro-N-metoxi-N-metil-6-(metilamino)-5-vinilpirimidin-4-carboxamida

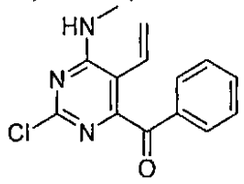


Se calentó a 95 °C durante 12 h una solución de 5-bromo-2-cloro-N-metoxi-N-metil-6-(metilamino)pirimidin-4-carboxamida (100 mg), tributil(vinil)estannano (113 mg), tetraquis (23 mg) en tolueno (1,6 ml) y se

eliminó el disolvente. El residuo se purificó por TLC preparativa eluyendo con EtOAc al 50%/Hexanos dando el compuesto del epígrafe como un aceite incoloro (23 mg). CL-EM $(M+H)^+$ = 257,06.

Intermedio AJ(5)

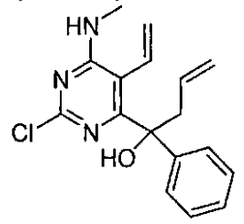
(2-cloro-6-(metilamino)-5-vinilpirimidin-4-il)(fenil)metanona



A una solución de 2-cloro-N-metoxi-N-metil-6-(metilamino)-5-vinilpirimidin-4-carboxamida (136 mg) en THF (1,8 ml) a 0 °C se añadió bromuro de fenilmagnesio (solución 1 M en THF, 1,3 ml)) gota a gota, y la mezcla de reacción se agitó a 0 °C durante 30 min. La reacción se trató con EtOAc/NH_4Cl saturado, y el producto bruto se purificó por TLC preparativa eluyendo con EtOAc al 40%/Hexanos dando el compuesto del epígrafe como un aceite incoloro (87 mg). CL-EM $(M+H)^+$ = 274,03.

Intermedio AJ(6)

1-(2-cloro-6-(metilamino)-5-vinilpirimidin-4-il)-1-fenilbut-3-en-1-ol

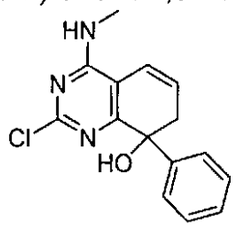


A una solución de (2-cloro-6-(metilamino)-5-vinilpirimidin-4-il)(fenil)metanona (142 mg) en THF (2,6 ml) a ta se añadió bromuro de alil

magnesio (solución 1,0 M en THF, 1,1 ml) gota a gota, y la mezcla de reacción se agitó a ta durante 30 min. La reacción se trató con EtOAc/NH_4Cl saturado, y el producto bruto se purificó por TLC preparativa eluyendo con EtOAc al 30%/Hexanos dando el compuesto del epígrafe como un aceite incoloro (133 mg). CL-EM $(M-H_2O+H)^+$ = 298,18.

Preparación AJ

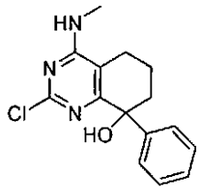
2-cloro-4-(metilamino)-8-fenil-7,8-dihidroquinazolin-8-ol



A una solución de 1-(2-cloro-6-(metilamino)-5-vinilpirimidin-4-il)-1-fenilbut-3-en-1-ol (60 mg) en benceno (5 ml) se añadió Grubbs I (16 mg), y la mezcla de reacción se calentó a 85 °C durante 1 h. Se eliminó el disolvente, y el residuo se purificó por TLC preparativa eluyendo con EtOAc al 40%/Hexanos dando el compuesto del epígrafe como un aceite incoloro (50 mg). RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,4 (5H, m), 6,25 (1H, m), 6,07 (1H, m), 5,14 (1H, s ancho), 4,52 (1H, s), 3,10 (3H, d< J = 5,0 Hz), 2,99 (2H, m). RMN de ^{13}C (125 MHz, $CDCl_3$) 164,32, 159,38, 158,85, 144,15, 128,24, 128,02, 127,83, 125,51, 117,54, 108,14, 60,51, 38,50, y 28,57. EMAR calculado para $C_{15}H_{15}ClN_3O$ (M+H) 288,0904; encontrado: 288,0899.

Preparación AK

2-cloro-4-(metilamino)-8-fenil-5,6,7,8-tetrahidroquinazolin-8-ol

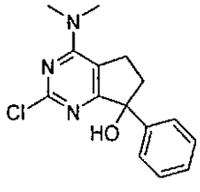


A una solución de 2-cloro-4-(metilamino)-8-fenil-7,8-dihidroquinazolin-8-ol (20 mg) en EtOAc (5 ml) se añadió Pd al 5%/C (6 mg) y la suspensión resultante se agitó bajo una botella de hidrógeno durante 1 h. La mezcla de reacción se filtró a través de una almohadilla de Celite dando el compuesto del epígrafe como un aceite incoloro (20 mg).

RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 7,3 (5H, m), 4,9 (1H, s ancho), 4,02 (1H, s), 3,14 (3H, s ancho), 1,5-2,5 (6H, m) RMN de ^{13}C (125 MHz, $CDCl_3$) 164,82, 162,72, 158,56, 146,54, 128,02, 127,37, 126,72, 110,92, 74,81, 37,58, 28,61, 21,89, 17,47. EMAR calculado para $C_{15}H_{17}ClN_3O$ (M+H) 290,1060; encontrado: 290,1052.

Preparación AL

2-cloro-4-(dimetilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-7-ol

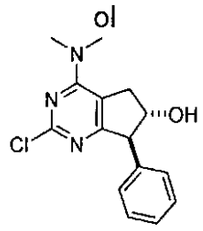


Se preparó 2-cloro-4-(dimetilamino)-7-fenil-7H-ciclopenta[d]pirimidin-7-ol a partir de 2,6-dicloropirimidin-4-carboxilato de metilo usando las mismas transformaciones que las mostradas en la Preparación AJ/AK con las siguientes diferencias: Intermedio AL(1): se usó dimetilamina en lugar de clorhidrato de metilamina, y se usaron 1,1 equiv de base de Hünig; Intermedio AL(6): se usó bromuro de vinilmagnesio en lugar de bromuro de alilmagnesio.

RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,3 (5H, m), 3,28 (6H, s), 1,5-3,4 (5H, m). RMN de ^{13}C (125 MHz, $CDCl_3$) 174,66, 161,76, 159,58, 144,61, 128,49, 127,58, 125,35, 113,92, 82,86, 41,07, 39,00, 28,59. EMAR calculado para $C_{15}H_{17}ClN_3O$ (M+H) 290,1060; encontrado: 290,1050.

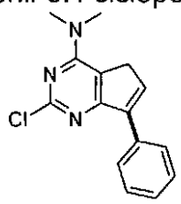
Preparación AM

(6S,7S)-2-cloro-4-(dimetilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-6-ol



Intermedio AM(1)

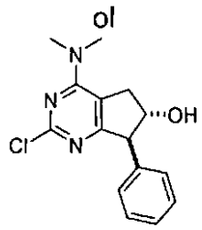
2-cloro-N,N-dimetil-7-fenil-5H-ciclopenta[d]pirimidin-4-amina



A una solución de 2-cloro-4-(dimetilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-7-ol (85 mg) en i-PrOH (5 ml) se añadió HCl en éter (solución 1M), y la mezcla de reacción se calentó a 80 °C durante 3 h. La solución era turbia y viró a solución amarillo transparente al finalizar la reacción. Los disolventes se eliminaron y la mezcla de reacción se trató con EtOAc y $NaHCO_3$ saturado dando el compuesto del epígrafe como un sólido color pardusco (50 mg). CL-EM $(M-H_2O+H)^+$ = 272,07.

Preparación AM

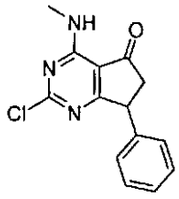
(6S,7S)-2-cloro-4-(dimetilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-6-ol



A una solución de 2-cloro-N,N-dimetil-7-fenil-5H-ciclopenta[d]pirimidin-4-amina (113 mg) en THF (2 ml) a ta se añadió complejo de borano sulfuro de dimetilo en THF (solución 2,0 M, 0,41 ml), y la mezcla de reacción se agitó a ta durante 5 h. Se añadió cuidadosamente agua (0,50 ml), seguido por H_2O_2 al 30% (0,50 ml) y NaOH 1 N (1 ml). Se añadieron 5 ml de EtOAc y la mezcla de reacción se agitó a ta durante 12 h. El producto bruto se purificó por TLC preparativa eluyendo con EtOAc al 50%/Hexanos dando el compuesto del epígrafe como un sólido amarillento (44 mg). CL-EM $(M-H_2O+H)^+$ = 290,05.

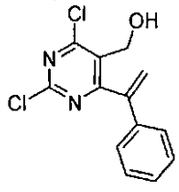
Preparación AN

2-cloro-4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-5-ona



Intermedio AN(1)

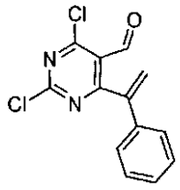
2,4-dicloro-6-(1-fenilvinil)pirimidin-5-il)metanol



Se calentó a 100ºC durante 12 horas una mezcla de 2,4,6-tricloropirimidin-5-il)metanol (1,1 g), ácido 1-fenilvinilborónico (0,8 g), Tetraquis (0,3 g), carbonato sódico (1,64 g) en tolueno (14 ml) y agua (3 ml). Se añadió agua seguido por acetato de etilo, se extrajo la fase acuosa con acetato de etilo (x3) y las fases orgánicas reunidas se secaron sobre sulfato sódico anhidro y luego se filtraron. El filtrado se concentró, y el residuo se purificó por Biotage eluyendo con EtOAc al 10-40%/Hexanos dando el compuesto del epígrafe como un sólido blanco (325 mg). CL-EM $(M+H)^+$ = 281,02. RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 7,5 (5H, m), 6,01 (1H, s), 5,67 (1H, s), 4,62 (2H, s).

Intermedio AN(2)

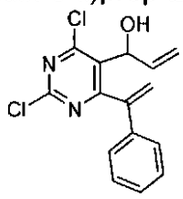
2,4-dicloro-6-(1-fenilvinil)pirimidin-5-carbaldehído



A una solución de 2,4-dicloro-6-(1-fenilvinil)pirimidin-5-il)metanol (327 mg) en CH_2Cl_2 se añadió PCC (600 mg) y tamices moleculares de 4A (600 mg), y la mezcla de reacción se agitó a TA durante 30 min. La solución viró a marrón oscuro desde naranja unos pocos minutos después de la adición de PCC. La mezcla de reacción se filtró a través de una almohadilla de gel de sílice eluyendo con CH_2Cl_2 dando el compuesto del epígrafe as como un sólido parduzco (209 mg) y se usó directamente para la etapa siguiente.

Intermedio AN(3)

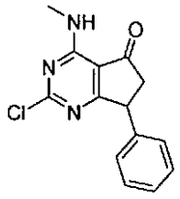
1-(2,4-dicloro-6-(1-fenilvinil)pirimidin-5-il)prop-2-en-1-ol



A una solución de 2,4-dicloro-6-(1-fenilvinil)pirimidin-5-carbaldehído (200 mg) en THF (3,6 ml) a -78C se añadió bromuro de vinilmagnesio (0,79 ml, solución 1M en THF) gota a gota, y la mezcla de reacción se agitó a -78 °C durante 20 min. Se añadió NH_4Cl saturado, seguido por acetato de etilo, la fase acuosa se extrajo con acetato de etilo (x3), y las fases orgánicas reunidas se secaron sobre sulfato sódico anhidro y luego se filtraron. El filtrado se concentró *a vacío* dando el compuesto del epígrafe (156 mg) como un aceite incoloro. El producto bruto se usó directamente para la etapa siguiente.

Preparación AN

2-cloro-4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-5-ona

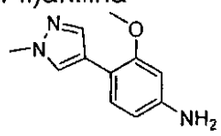


A una solución de 1-(2,4-dicloro-6-(1-fenilvinil)pirimidin-5-il)prop-2-en-1-ol (20 mg) en CH_2Cl_2 (6,5 ml) se añadió catalizador de Grubbs II (6 mg), y la mezcla de reacción se calentó a reflujo durante 30 min. Se eliminó el disolvente, y el residuo se disolvió en EtOAc (4 ml) y se añadió Pd al 10%/C (5 mg). La mezcla de reacción se agitó bajo una botella de hidrógeno durante 35 min. Se retiró la botella de hidrógeno y se añadió a continuación base de Hunig (23 µl) seguida por metilamina (36 µl, solución 2 M en metanol). La mezcla de

reacción se agitó a temperatura ambiente durante 10 min, y los disolventes se eliminaron. El residuo se purificó por TLC preparativa eluyendo con EtOAc al 35%/Hexanos dando el compuesto del epígrafe como un sólido amarillo (6,6 mg, 37% de rendimiento). RMN de ^{1}H (500 MHz, CLOROFORMO-*d*) δ ppm 7,1-7,4 (5H, m), 4,45 (1H, dd, J = 3,0, 8,0 Hz), 3,24 (1H, dd, J = 8,0, 19,5 Hz), 3,20 (3H, s), 3,19 (3H, s), 2,71 (1H, dd, J = 3,0, 19,5 Hz). RMN de ^{13}C (125 MHz, CLOROFORMO-*d*) δ 203,12, 186,69, 166,52, 159,93, 139,88 129,16 (2C), 127,73 (2C), 127,59, 110,98, 46,50, 45,48, y 27,53. EMAR calculado para $C_{14}H_{13}ClN_3O$ (M+H) 274,0742; encontrado: 274,0741.

Preparación AO

3-metoxi-4-(1-metil-1H-pirazol-4-il)anilina



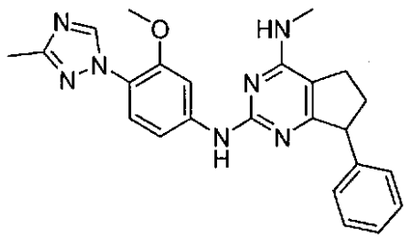
Se calentó a reflujo durante la noche una solución en DMF de 1-metil-1H-pirazol-4-ilboronato de dietilo, 4-bromo-3-metoxi nitrobenceno junto con Pd(dppf) y K_2CO_3. El producto obtenido se redujo con Fe en MeOH/cloruro amónico proporcionando el compuesto del epígrafe. CL-EM $(M+H)^+$ = 204,2. RMN de ^{1}H (400 MHz, DMSO-*d6*): δ ppm 7,84 (1H, s), 7,66 (1H, s), 7,19 (1H, J = 8,2 Hz, d), 6,29 (1H, s), 6,18 (1H, J = 2,0, 8,2 Hz, dd), 5,31 (2H, s ancho), 3,80 (3H, s), 3,75 (3H, s).

EJEMPLOS

Ejemplo 1

N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-7-fenil-6,7-dihidro-

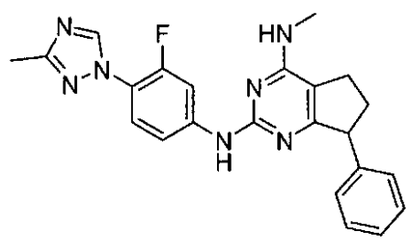
5H-ciclopenta[d]pirimidin-2,4-diamina



Se usó el procedimiento del Ejemplo 74 para combinar la Preparación Ga y 3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)anilina (Preparación D) proporcionando N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (Ejemplo 1). CL-EM $(M+H)^+$ = 428,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,95 (1 H, s ancho), 7,72 (1 H, d, *J*=2,14 Hz), 7,65 (1 H, d, *J*=8,55 Hz), 7,37 - 7,42 (2 H, m), 7,30 - 7,34 (1 H, m), 7,26 (2 H, d, *J*=7,02 Hz), 7,22 (1 H, dd, *J*=8,85, 2,14 Hz), 4,42 - 4,48 (1 H, m), 3,93 (3 H, s), 3,16 (3 H, s), 2,88 - 2,96 (1 H, m), 2,72 - 2,83 (2 H, m), 2,46 (3 H, s), 2,12 - 2,21 (1 H, m).

Ejemplo 2

N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

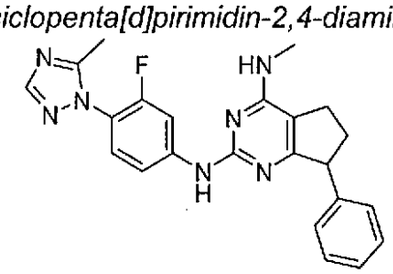


Se usó el procedimiento del Ejemplo 74 para combinar la Preparación

Ga y 3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)anilina (Preparación B) proporcionando N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (Ejemplo 2). CL-EM $(M+H)^+$ = 416,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,77 (1 H, s ancho), 7,95 (1 H, dd, *J*=13,43, 2,14 Hz), 7,77 (1 H, t, *J*=8,70 Hz), 7,48 (1 H, dd, *J*=8,85, 1,53 Hz), 7,40 (2 H, t, *J*=7,48 Hz), 7,33 (1 H, t, *J*=7,48 Hz), 7,28 (2 H, d, *J*=7,02 Hz), 4,49 (1 H, dd, *J*=7,63, 4,58 Hz), 3,18 (3 H, s), 2,88 - 2,98 (1 H, m), 2,77 - 2,86 (2 H, m), 2,46 (3 H, s), 2,14 - 2,24 (1 H, m).

Ejemplo 3

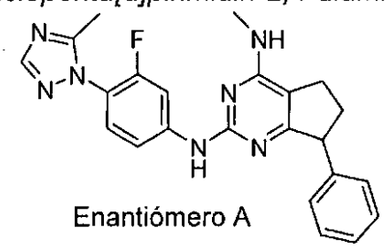
N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se usó el procedimiento del Ejemplo 74 para combinar la Preparación Ga y 3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina (Preparación C) proporcionando N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (Ejemplo 3). CL-EM $(M+H)^+$ = 416,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,11 (1 H, s), 7,99 (1 H, dd, *J*=12,51, 1,83 Hz), 7,51 - 7,60 (2 H, m), 7,41 (2 H, t, *J*=7,48 Hz), 7,31 - 7,36 (1 H, m), 7,28 (2 H, d, *J*=7,02 Hz), 4,47 - 4,54 (1 H, m), 2,90 - 3,00 (1 H, m), 2,76 - 2,87 (2 H, m), 2,42 (3 H, s), 2,15 - 2,26 (1 H, m).

Ejemplo 3A

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

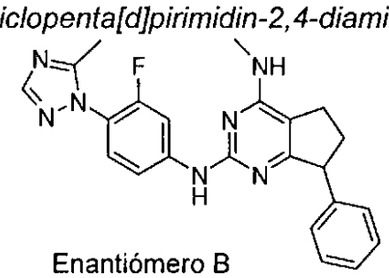


Enantiómero A

El Ejemplo 3 se separó mediante varias inyecciones de HPLC preparativa quiral (OJ-H 30 x 250mm, 10µM, EtOH al 30%/Heptano/DEA al 0,1%) dando N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (primero en eluir, enantiómero A) como vidrio opaco ligeramente amarillo. CL-EM $(M+H)^+$ = 416,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,15 (1 H, dd, *J*=13,73, 2,14 Hz), 8,03 (1 H, s), 7,36 - 7,42 (1 H, m), 7,28 - 7,36 (3 H, m), 7,16 - 7,26 (3 H, m), 4,21 (1 H, t, *J*=7,78 Hz), 3,07 - 3,13 (3 H, m), 2,78 - 2,88 (1 H, m), 2,59 - 2,76 (2 H, m), 2,35 - 2,41 (3 H, m), 1,99 - 2,13 (1 H, m).

Ejemplo 3B

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



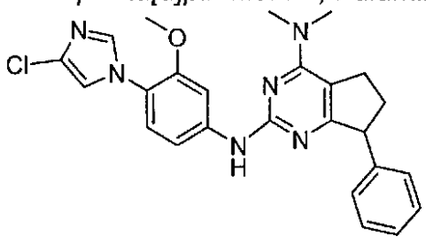
Enantiómero B

Se preparó el Enantiómero B de N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-

1-il)fenil)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina según el *Ejemplo 3A* salvo que éste fue el segundo en eluir de la columna HPLC quiral como vidrio opaco ligeramente amarillo. CL-EM $(M+H)^+$ = 416,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,17 (1 H, dd, *J*=13,89, 2,29 Hz), 8,02 (1 H, s), 7,28 - 7,46 (4 H, m), 7,16 - 7,27 (3 H, m), 4,19 (1 H, t, *J*=7,78 Hz), 3,05 - 3,16 (3 H, m), 2,78 - 2,89 (1 H, m), 2,57 - 2,78 (2 H, m), 2,33 - 2,48 (3 H, m), 1,99 - 2,17 (1 H, m).

Ejemplo 4

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se añadió 2-cloro-*N*,*N*-dimetil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (200 mg, 0,731 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (163 mg, 0,731 mmol) en THF (1 ml) y ácido acético (1,000 ml). La mezcla de reacción se agitó durante la noche a 75°C. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (180,7 mg, 0,308 mmol, 42,2 % de rendimiento). CL-EM $(M+H)^+$ = 461,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,12 (1H, s), 7,98 - 8,17 (2H, m), 7,09 - 7,56 (6H, m), 7,01 - 7,09 (1H, m), 4,31

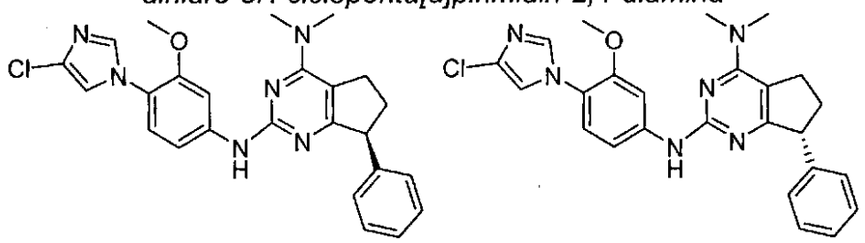
- 4,52 (2H, m), 3,97 (1H, s), 3,81 - 3,89 (2H, m), 3,45 - 3,55 (2H, m), 3,32 - 3,43 (3H, m), 3,16 - 3,29 (2H, m), 2,81 - 3,03 (1H, m), 2,56 - 2,75 (2H, m), 2,07 - 2,32 (2H, m).

Ejemplo 4A & 4B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

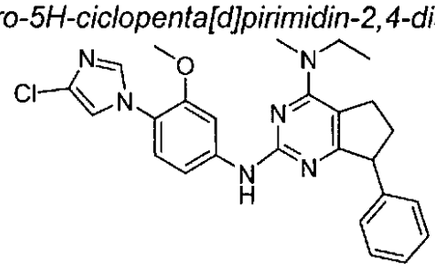
(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (*Ejemplo 4*) usando SFC quiral proporcionando el pico A (*Ejemplo 4A*) y el pico B (*Ejemplo 4B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 µM), metanol al 35% (dietilamina al 0,1%) en CO_2, 35ºC, caudal 2,0 ml/min durante 22 min, absorbancia 268 nm, inyección de 5µl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 5,1 min, t_R (pico B) 18,1 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 4A y 4B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 4*).

Ejemplo 5

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



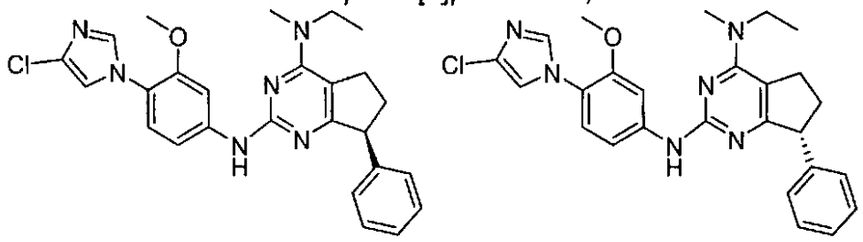
Se añadió 2-cloro-*N*-etil-*N*-metil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (160 mg, 0,556 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (124 mg, 0,556 mmol) en THF (1,5 ml) y ácido acético (1,5 ml). La mezcla de reacción se agitó durante la noche a 80°C. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (85,3 mg, 0,171 mmol, 30,7 % de rendimiento). CL-EM $(M+H)^+$ = 475,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,49 - 7,61 (1 H, m), 7,38 (1 H, s ancho), 7,23 - 7,34 (6 H, m), 7,13 (1 H, d, *J*=8,5 Hz), 7,05 (1 H, s), 4,35 (1 H, dd, *J*=9,3, 4,1 Hz), 3,69 - 3,82 (4 H, m), 3,47 (2 H, s ancho), 3,27 - 3,38 (4 H, m), 3,11 - 3,23 (1 H, m), 2,56 - 2,72 (1 H, m), 2,24 (1 H, ddd, *J*=9,0, 4,4, 4,3 Hz), 1,31 (3 H, t, *J*=7,2 Hz).

Ejemplo 5A y 5B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

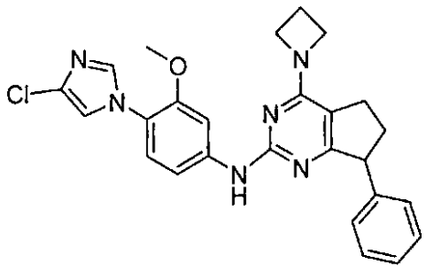
(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (*Ejemplo 5*) usando SFC quiral proporcionando el pico A (*Ejemplo 5A*) y el pico B (*Ejemplo 5B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 μM), metanol al 35% (dietilamina al 0,1%) en CO_2, 35ºC, caudal 2,0 ml/min durante 22 min, absorbancia 268 nm, inyección de 5μl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 4,5 min, t_R (pico B) 16,7 min. So se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 5A y 5B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 5*).

Ejemplo 6

4-(Azetidin-1-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



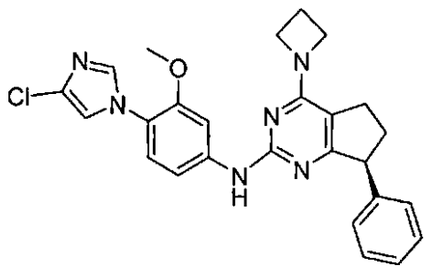
Se añadió 4-(azetidin-1-il)-2-cloro-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (162 mg, 0,567 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (127 mg, 0,567 mmol) en ácido acético (1,000 ml) y THF (1 ml). La mezcla de reacción se calentó a 80°C durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando 4-(azetidin-1-il)-*N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2-amina, sal TFA (39,2 mg, 0,066 mmol, 11,66 % de rendimiento). CL-EM $(M+H)^+$ = 473,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,44 (1H, s), 7,94 (1H, d, *J*=1,5 Hz), 7,52 (1H, d, *J*=2,1 Hz), 7,27 - 7,44 (4H, m), 6,96 - 7,23 (3H, m), 4,64 (3H, s ancho), 4,38 (2H, d, *J*=7,6 Hz), 3,83 (2H, s), 3,29 - 3,52 (1H, m), 3,11 (1H, d, *J*=7,9 Hz), 2,98 (1H, s), 2,62 - 2,76 (1H, m), 2,57 (2H, s), 2,14 - 2,38 (2H, m).

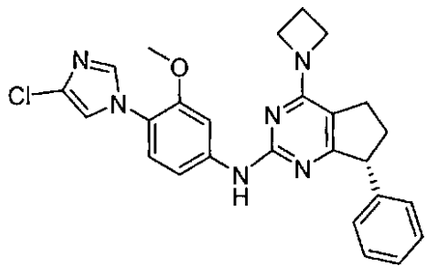
Ejemplo 6A y 6B

(S)-4-(Azetidin-1-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

y

(R)-4-(Azetidin-1-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

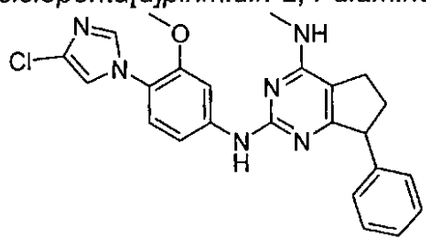




Se purificó una mezcla racémica de 4-(azetidin-1-il)-*N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2-amina (*Ejemplo 6*) usando SFC quiral proporcionando el pico A (*Ejemplo 6A*) y el pico B (*Ejemplo 6B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 µM), metanol al 35% (dietilamina al 0,1%) en CO_2, 35°C, caudal 2,0 ml/min durante 30 min, absorbancia 268 nm, inyección de 5µl de solución de 2 mg/ml en metanol/cloroformo 50/50 (varias inyecciones apiladas), t_R (pico A) = 5,9 min, t_R (pico B) 24,6 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 6A y 6B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 6*).

Ejemplo 7

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Una solución de 2-cloro-*N*-metil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (833 mg, 3,21 mmol) y 4-(4-cloro-1*H*-imidazol-1-

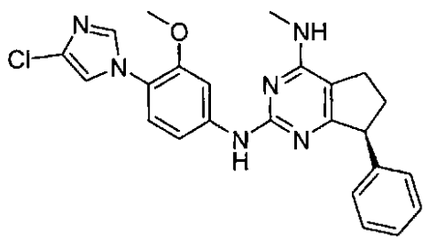
il)-3-metoxianilina (717,9 mg, 3,21 µmol) en THF (5,6 ml) y ácido acético (5,6 ml) se calentó a 85 °C en un recipiente de alta presión de 350 ml durante la noche. El disolvente se eliminó a vacío y el residuo se disolvió en diclorometano y se lavó con solución acuosa saturada de bicarbonato sódico. La fase orgánica se separó y la fase acuosa se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, que estaba contaminada con 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina. El material se trituró con metanol, se enfrió en el frigorífico y se filtró. El residuo se lavó con metanol enfriado en el frigorífico y se secó dando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina pura (673,5 mg, 47%) como sólido marrón claro. CL-EM $(M+H)^+$ = 446,9. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,99 (1H, d, *J*=1,8 Hz), 7,48 (1H, s), 7,27 - 7,33 (2H, m), 7,16 - 7,24 (3H, m), 6,96 - 7,07 (3H, m), 6,71 (1H, dd, *J*=8,4, 1,7 Hz), 4,50 (1H, s ancho), 4,20 (1H, s), 3,48 (3H, s), 3,11 (3H, d, *J*=4,9 Hz), 2,59 - 2,79 (3H, m), 2,01 - 2,13 (1H, m).

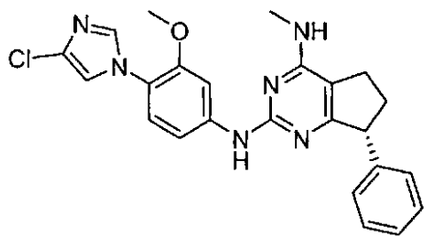
Ejemplos 7A y 7B

(S)-N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)-N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

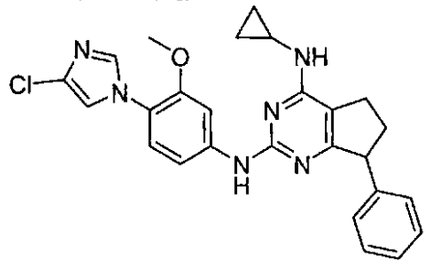




Una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (92 mg, 0,206 mmol del *Ejemplo 7*) se purificó usando cromatografía de fluido supercrítico quiral (SFC) proporcionando 28,4 mg de pico A (*Ejemplo 7A*) y 27,4 mg de pico B (*Ejemplo 7B*). Procedimiento de SFC: Chiralpak OJ-H (30 x 250 mm, 5 μM), metanol al 40 % (dietilamina al 0,1%) en CO_2, 35 °C, caudal 70 ml/min durante 16 min, absorbancia 268 nm, inyección de 1ml de solución de 15 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 5,0 min, t_R (pico B) 12,3 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 7A y 7B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 7*).

Ejemplo 8

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-ciclopropil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

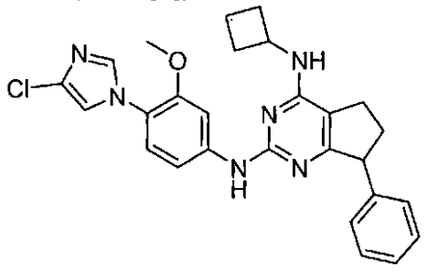


A una mezcla de 2-cloro-N-ciclopropil-7-fenil-6,7-dihidro-5H-

ciclopenta[d]pirimidin-4-amina (175 mg, 0,612 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (151 mg, 0,674 mmol) en NMP (2 ml) se añadió H_2SO_4 concentrado (0,046 ml, 0,857 mmol). La mezcla se agitó a 97°C durante 20 horas. Después de enfriar hasta temperatura ambiente, se añadieron 100 ml de EtOAc, se lavó con $NaHCO_3$ saturado/agua y agua, se secó sobre Na_2SO_4 y finalmente se separó. El residuo se purificó por Biotage (12g, hexanos-EtOAc al 80%) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-ciclopropil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (200 mg, 0,423 mmol, 69,1 % de rendimiento). CL-EM $(M+H)^+$ = 473,10. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,81 (1 H, d, *J*=1,8 Hz), 7,51 (1 H, d, *J*=1,5 Hz), 7,44 (1 H, s), 7,27 - 7,35 (2 H, m), 7,19 - 7,25 (3 H, m), 6,99 - 7,06 (2 H, m), 6,95 (1 H, d, *J*=8,2 Hz), 4,89 (1 H, s ancho), 4,20 (1 H, t, *J*=8,2 Hz), 3,45 (3 H, s), 2,92 (1 H, td, *J*=6,7, 3,1 Hz), 2,76 - 2,86 (1 H, m), 2,59 - 2,75 (2 H, m), 2,07 - 2,14 (1 H, m), 0,85 - 0,91 (2 H, m), 0,63 - 0,70 (2 H, m).

Ejemplo 9

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-ciclobutil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

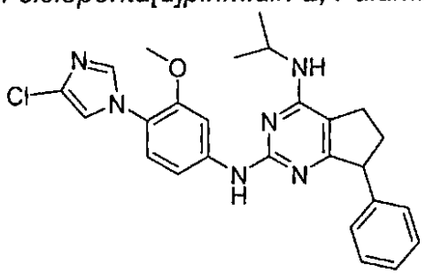


A una mezcla de 2-cloro-N-ciclobutil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (165 mg, 0,55 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (135 mg, 0,605 mmol) en NMP (2 ml) se añadió H_2SO_4

concentrado (0,041 ml, 0,771 mmol). La mezcla se agitó a 97ºC durante 20 horas. Después de enfriar hasta temperatura ambiente, 100 ml de EtOAc se añadió, se lavó con $NaHCO_3$ saturado/agua y agua, se secó sobre Na_2SO_4, y finalmente se separó. El residuo se purificó por Biotage (12 g, hexanos-EtOAc al 80%) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-ciclobutil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (202 mg, 0,394 mmol, 71,6 % de rendimiento). CL-EM $(M+H)^+$ = 487,14. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,92 (1 H, d, *J*=1,8 Hz), 7,51 (1 H, d, *J*=1,2 Hz), 7,28 - 7,33 (2 H, m), 7,18 - 7,24 (3 H, m), 7,13 (1 H, s), 7,03 (1 H, d, *J*=8,5 Hz), 7,01 (1 H, d, *J*=1,2 Hz), 6,74 (1 H, dd, *J*=8,5, 2,1 Hz), 4,64 - 4,80 (2 H, m), 4,17 - 4,23 (1 H, m), 3,49 (3 H, s), 2,72 - 2,81 (1 H, m), 2,61 - 2,71 (2 H, m), 2,43 - 2,53 (2 H, m), 2,09 (1 H, td, *J*=8,0, 2,3 Hz), 1,92 - 2,04 (2 H, m), 1,70 - 1,88 (2 H, m).

Ejemplo 10

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-isopropil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

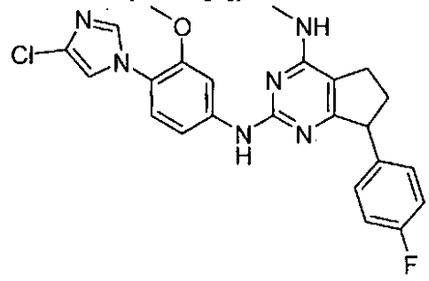


A una solución de 2-cloro-N-isopropil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (154 mg, 0,535 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (114 mg, 0,508 mmol) en DMF (2,5 ml) se añadió H_2SO_4 concentrado (0,040 ml, 0,749 mmol). La mezcla se agitó a 94 ºC durante 20 horas. Después de enfriar hasta temperatura ambiente, 100 ml de EtOAc se

añadió, se lavó con $NaHCO_3$ saturado/H_2O, se secó sobre Na_2SO_4, y se separó. El residuo se purificó por Biotage (12 g, hexanos-EtOAc al 100%) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-isopropil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (120 mg, 0,253 mmol, 47,2 % de rendimiento). CL-EM $(M+H)^+$ = 475,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,92 (1 H, d, *J*=2,1 Hz), 7,51 (1 H, d, *J*=1,5 Hz), 7,31 (2 H, d, *J*=7,3 Hz), 7,22 - 7,25 (2 H, m), 7,22 (1 H, s), 7,08 (1 H, s), 7,04 (1 H, d, *J*=8,5 Hz), 7,01 (1 H, d, *J*=1,5 Hz), 6,74 (1 H, dd, *J*=8,4, 2,3 Hz), 4,38 - 4,46 (1 H, m), 4,33 (1 H, d, *J*=7,9 Hz), 4,18 - 4,24 (1 H, m), 3,49 (3 H, s), 2,72 - 2,80 (1 H, m), 2,61 - 2,71 (2 H, m), 2,07 - 2,14 (1 H, m), 1,33 (6 H, t, *J*=6,6 Hz).

Ejemplo 11

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se calentó a 80 °C durante la noche una solución de 2-cloro-7-(4-fluorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (307,5 mg, 1,107 mmol) y 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (248 mg, 1,107 mmol) en THF (3 ml) y ácido acético (3,00 ml). El disolvente se eliminó a vacío y el residuo se trituró con metanol, se enfrió en el frigorífico y se filtró. El precipitado se lavó concienzudamente con metanol y se secó dando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5*H*-

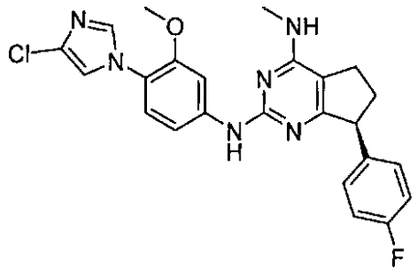
ciclopenta[*d*]pirimidin-2,4-diamina (207,9 mg, 0,447 mmol, 40,4 % de rendimiento) como sólido blanquecino. CL-EM $(M+H)^+$ = 465,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 9,18 (1H, s), 8,15 (1H, d, *J*=1,8 Hz), 7,73 (1H, d, *J*=1,5 Hz), 7,41 (1H, d, *J*=1,5 Hz), 7,18 - 7,26 (2H, m), 7,07 - 7,18 (2H, m), 6,88 - 7,00 (1H, m), 4,12 - 4,20 (1H, m), 4,04 - 4,12 (1H, s ancho), 3,60 (3H, s), 3,17 (1H, s), 2,96 (3H, d, *J*=4,6 Hz), 2,71 - 2,81 (1H, m), 2,52 - 2,66 (2H, m), 1,83 - 1,96 (1H, m).

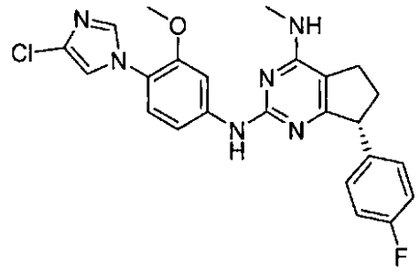
Ejemplos 11A y 11B

(S)- N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)- N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



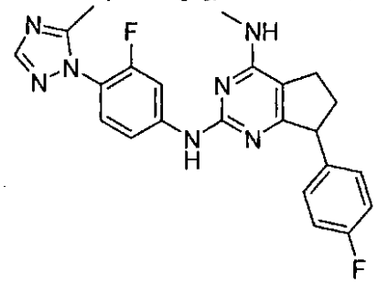


Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-trideuterometil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (150 mg, 0,206 mmol del *Ejemplo 11*) usando cromatografía de fluido supercrítico quiral (SFC) proporcionando 74,6 mg de pico A (*Ejemplo 11A*) y 71,7 mg de pico B (*Ejemplo 11B*). Procedimiento de SFC: Chiralpak OJ-H (30 x 250 mm, 5 μM), metanol al 35% (dietilamina al 0,1%) en CO_2, 35 °C, caudal 70 ml/min durante 12 min, absorbancia 268 nm, inyección de 0,75ml de solución

15 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 4,0 min, t_R (pico B) 8,6 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 11A y 11B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 11*).

Ejemplo 12

N^2-(3-Fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

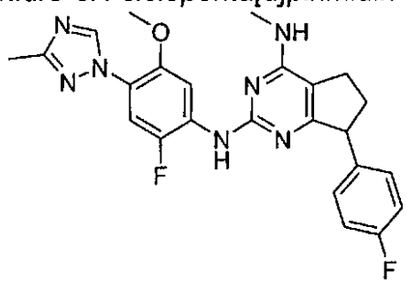


A una solución de 2-cloro-7-(4-fluorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (105,0 mg, 0,378 mmol) y 3-fluoro-4-(3-metil-1*H*-1,2,4-triazol-1-il)anilina (72,7 mg, 0,378 mmol) en THF (2 ml) se añadió suspensión al 60% de hidruro sódico en aceite mineral (30,2 mg, 0,756 mmol). La mezcla de reacción se agitó a 80°C durante 40 minutos. La mezcla de reacción se agitó de nuevo a 80°C durante 4 h. La mezcla de reacción se enfrió con una solución acuosa de cloruro amónico y se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por un sistema de HPLC preparativa de fase inversa dando N^2-(3-fluoro-4-(3-metil-1*H*-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5*H*-

ciclopenta[*d*]pirimidin-2,4-diamina, 2 TFA (45,6 mg, 0,069 mmol, 18,25 % de rendimiento) como aceite marrón. CL-EM $(M+H)^+$ = 434,0. RMN de ^1H (500 MHz, metanol-*d4*) δ ppm 8,86 (1H, s), 7,88 (1H, t, *J*=8,4 Hz), 7,21 - 7,31 (3H, m), 7,19 (1H, d, *J*=8,9 Hz), 7,07 (2H, t, *J*=8,7 Hz), 4,27 (1H, t, *J*=8,5 Hz), 3,73 (3H, s), 3,33 (3H, s), 2,52 (1H, dd, *J*=8,2, 4,0 Hz), 2,49 (3H, s), 2,38 (1H, d, *J*=7,6 Hz), 2,30 (1H, d, *J*=3,7 Hz), 1,95 - 2,07 (1H, m).

Ejemplo 13

N^2-(2-Fluoro-5-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

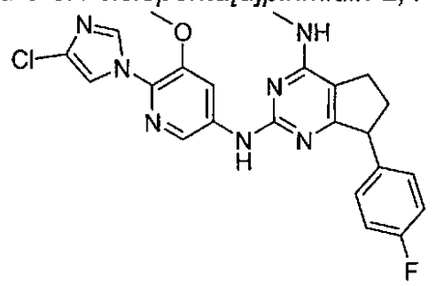


A una solución de 2-cloro-7-(4-fluorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (105,0 mg, 0,378 mmol) y 2-fluoro-5-metoxi-4-(3-metil-1*H*-1,2,4-triazol-1-il)anilina (84 mg, 0,378 mmol) en THF (2 ml) se añadió suspensión al 60% de hidruro sódico en aceite mineral (9,07 mg, 0,378 mmol). La mezcla de reacción se agitó a 80°C durante 40 minutos. La mezcla de reacción se agitó de nuevo a 80°C durante 4 h. La mezcla de reacción se enfrió con una solución acuosa de cloruro amónico y se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por un sistema de HPLC preparativa de fase inversa dando N^2-(2-fluoro-5-metoxi-4-(3-metil-1*H*-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-

5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, 2 TFA (20,2 mg, 0,027 mmol, 7,19 % de rendimiento) como aceite marrón. CL-EM $(M+H)^+$ = 464,0. RMN de ^1H (500 MHz, metanol-*d4*) δ ppm 9,06 (1H, s), 7,74 (1H, d, *J*=10,4 Hz), 7,19 - 7,28 (3H, m), 7,07 (2H, t, *J*=8,5 Hz), 4,24 (1H, s), 4,00 (3H, s), 3,76 (3H, s), 2,48 (3H, s), 2,40 - 2,54 (1H, m), 2,26 - 2,38 (2H, m), 1,89 - 2,02 (1H, m).

Ejemplo 14

N^2-(6-(4-Cloro-1H-imidazol-1-il)-5-metoxipiridin-3-il)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

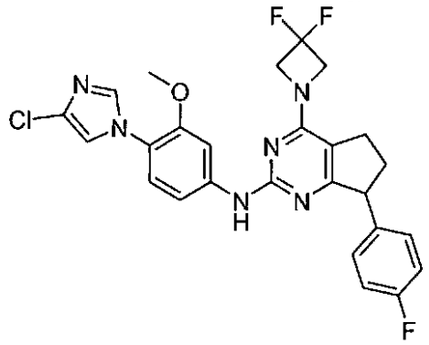


A una solución de 2-cloro-7-(4-fluorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (165,3 mg, 0,595 mmol) y 6-(4-cloro-1*H*-imidazol-1-il)-5-metoxipiridin-3-amina (134 mg, 0,595 mmol) en THF (3,5 ml) se añadió suspensión al 60% de hidruro sódico en aceite mineral (28,6 mg, 1,190 mmol). La mezcla de reacción se calentó a 80°C en un vial tapado durante 6 h. La reacción se enfrió cuidadosamente con solución acuosa de cloruro amónico y el producto se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por un procedimiento de HPLC preparativa de fase inversa proporcionando N^2-(6-(4-cloro-1*H*-imidazol-1-il)-5-metoxipiridin-3-il)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, 2 TFA (26,2 mg, 0,029 mmol, 4,88 % de rendimiento) como aceite

marrón. CL-EM $(M+H)^+$ = 466,0. RMN de ^1H (500 MHz, metanol-*d4*) δ ppm 8,43 (1H, s), 7,96 (1H, s), 7,87 (1H, s), 7,55 (1H, s ancho), 7,19 - 7,32 (2H, m), 7,07 (2H, t, *J*=8,7 Hz), 4,20 - 4,29 (1H, m), 4,06 (3H, s), 3,75 (3H, s), 2,42 - 2,55 (1H, m), 2,21 - 2,39 (2H, m), 1,90 - 2,05 (1H, m).

Ejemplo 15

N-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

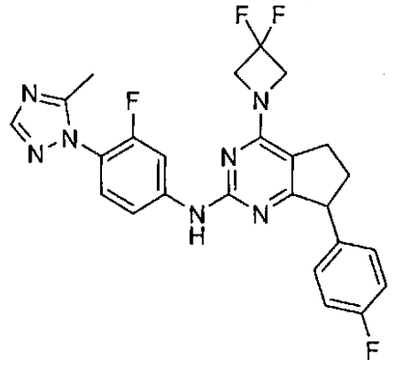


Se calentó a 80°C durante la noche una solución de 2-cloro-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (42,6 mg, 0,125 mmol) y 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (28,0 mg, 0,125 mmol) en THF (1 ml) y ácido acético (1,000 ml). El calentamiento se prolongó a 120°C durante la noche. Tras enfriar, la mezcla de reacción se purificó por cromatografía en columna sobre gel de sílice dando *N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2-amina, TFA (11,8 mg, 0,018 mmol, 14,54 % de rendimiento) como aceite marrón. CL-EM $(M+H)^+$ = 527,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,75 (1H, s), 8,02 (1H, s), 7,40 (1H, dd, *J*=8,5, 2,1 Hz), 7,32 (1H, d, *J*=2,1 Hz), 7,16 - 7,23 (3H, m), 7,12 (1H, s), 7,02 (2H, t, *J*=8,7 Hz),

4,42 (1H, dd, *J*=9,5, 4,9 Hz), 4,80 (4H, s), 3,85 (3H, s), 3,11 (1H, s), 2,98 (1H, s), 2,67 - 2,79 (1H, m), 2,26 (1H, d).

Ejemplo 16

4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

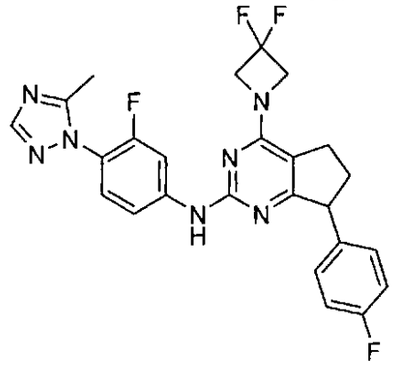


A una solución de 2-cloro-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación Ha*) (170 mg, 0,500 mmol) en THF (1498 µl) se añadió 3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)anilina (*Preparación C*) (125 mg, 0,650 mmol) y ácido acético (1498 µl). La mezcla resultante se calentó hasta 100 °C y se agitó durante la noche. La mezcla de reacción luego se concentró a vacío y se purificó por HPLC preparativa (C18, 30 X 150mm, MeOH/H_2O/TFA) dando 4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (racemato) (101,49 mg, 33,27 % de rendimiento) como un sólido beige. CL-EM $(M+H)^+$ = 496,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,06 - 8,11 (1 H, m), 7,86 (1 H, dd, *J*=12,51, 2,14 Hz), 7,47 - 7,57 (2 H, m), 7,28 - 7,35 (2 H, m), 7,11 - 7,19 (2 H, m), 4,93 (4 H, t, *J*=11,90 Hz), 4,47 (1 H, t, *J*=7,93 Hz), 3,11 - 3,18 (1 H, m), 2,99 - 3,08 (1 H, m), 2,71 -

2,81 (1 H, m, *J*=13,31, 8,91, 8,91, 4,27 Hz), 2,42 (3 H, s), 2,08 - 2,19 (1 H, m, *J*=13,24, 9,04, 6,71, 6,71 Hz).

Ejemplo 16A

4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

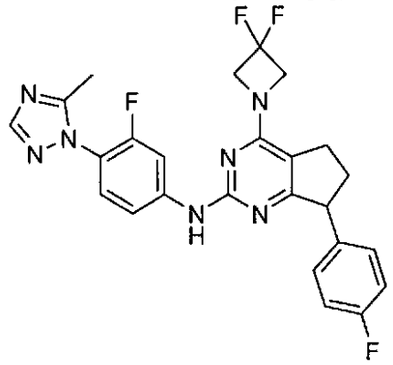


Enantiómero A del *Ejemplo 16*

Se separó 4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 16*) por varias inyecciones sobre SFC quiral (Chiracel OJ-H 30 x 250mm, 5μM, MeOH al 30% (DEA al 0,1%)/CO_2 dando 4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (primero en eluir, enantiómero A) como un sólido blanquecino. CL-EM $(M+H)^+$ = 496,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,87 - 8,08 (2 H, m), 7,35 - 7,44 (1 H, m), 7,31 (1 H, t, *J*=8,70 Hz), 7,24 (2 H, dd, *J*=8,55, 5,49 Hz), 7,04 (2 H, t, *J*=8,70 Hz), 4,64 (4 H, t, *J*=12,05 Hz), 4,19 (1 H, t, *J*=8,24 Hz), 2,98 - 3,08 (1 H, m), 2,86 - 2,98 (1 H, m), 2,55 - 2,68 (1 H, m, *J*=12,86, 8,60, 8,60, 4,12 Hz), 2,37 (3 H, s), 1,97 - 2,12 (1 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 16A*.

Ejemplo 16B

4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

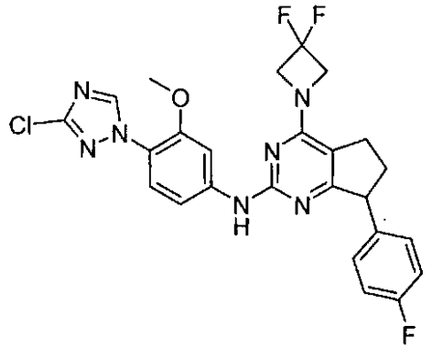


Enantiómero B del *Ejemplo 16*

Se separó 4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 16*) por varias inyecciones sobre SFC quiral (Chiracel OJ-H 30 x 250mm, 5μM, MeOH al 30% (DEA al 0,1%)/CO_2 dando 4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (segundo en eluir, enantiómero B) como un sólido blanquecino. CL-EM $(M+H)^+$ = 496,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,96 - 8,09 (2 H, m), 7,39 (1 H, dd, *J*=9,00, 1,98 Hz), 7,32 (1 H, t, *J*=8,55 Hz), 7,20 - 7,28 (2 H, m), 6,99 - 7,11 (2 H, m), 4,65 (4 H, t, *J*=12,21 Hz), 4,20 (1 H, t, *J*=8,24 Hz), 2,99 - 3,09 (1 H, m), 2,88 - 2,99 (1 H, m), 2,56 - 2,71 (1 H, m), 2,31 - 2,46 (3 H, m), 1,98 - 2,15 (1 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 16B*.

Ejemplo 17

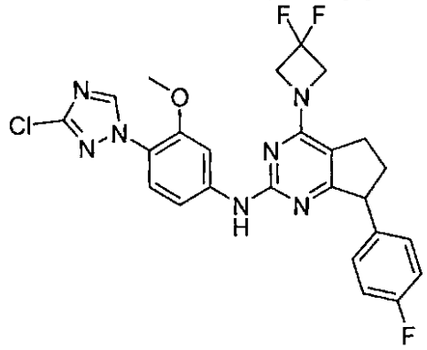
N-(4-(3-cloro-1H-1,2,4-triazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



A una solución de 2-cloro-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación Ha*) (170 mg, 0,500 mmol) y 4-(3-cloro-1H-1,2,4-triazol-1-il)-3-metoxianilina (*Preparación F*) (146 mg, 0,650 mmol) en THF (1498 µl) se añadió ácido acético (1498 µl). La mezcla resultante se calentó hasta 100 °C y se agitó durante la noche. La mezcla de reacción luego se concentró a vacío. Se añadió MeOH al residuo lo cual dio lugar a una suspensión. Esta se filtró dando un sólido que se recogió en MeOH caliente y se filtró. El filtrado luego se concentró a vacío dando N-(4-(3-cloro-1H-1,2,4-triazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (racemato) (130 mg, 49,22 % de rendimiento) como un sólido amarillo. CL-EM $(M+H)^+$ = 528,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,81 (1 H, s), 7,65 (1 H, d, *J*=8,55 Hz), 7,59 (1 H, s), 7,29 - 7,36 (2 H, m), 7,11 - 7,21 (3 H, m), 4,87 - 4,88 (4 H, m), 4,47 (1 H, s), 3,91 (3 H, s), 3,11 - 3,19 (1 H, m), 2,99 - 3,08 (1 H, m), 2,77 (1 H, dddd, *J*=13,47, 8,96, 4,43, 4,27 Hz), 2,13 (1 H, dc, *J*=8,89, 6,70 Hz).

Ejemplo 17A

N-(4-(3-cloro-1H-1,2,4-triazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

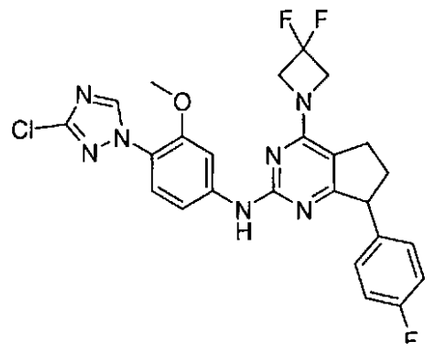


Enantiómero A del *Ejemplo 17*

Se separó N-(4-(3-cloro-1H-1,2,4-triazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 17*) por varias inyecciones sobre SFC quiral (Chiracel AD-H 30 x 250mm, 5μM, MeOH al 45% (DEA al 0,1%)/CO_2 dando 4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (primero en eluir, enantiómero A) como una película amarilla. CL-EM $(M+H)^+$ = 528,1. RMN de ^1H (500 MHz, *DMSO-d*$_6$) δ ppm 8,82 (1 H, d, *J*=1,53 Hz), 8,06 (1 H, s), 7,35 (1 H, d, *J*=8,85 Hz), 7,21 - 7,31 (2 H, m), 7,07 - 7,21 (3 H, m), 4,70 (4 H, t, *J*=12,36 Hz), 4,20 (1 H, t, *J*=8,24 Hz), 3,63 (3 H, s ancho), 3,01 (1 H, s ancho), 2,80 - 2,95 (1 H, m), 2,53 - 2,63 (1 H, m), 1,93 (1 H, d, *J*=8,24 Hz). No se determinó la estereoquímica absoluta del *Ejemplo 17A*.

Ejemplo 17B

N-(4-(3-cloro-1H-1,2,4-triazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

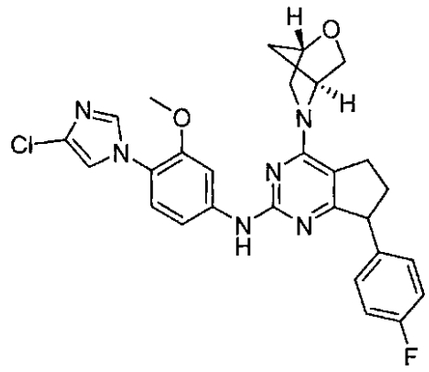


Enantiómero B del *Ejemplo 17*

Se separó N-(4-(3-cloro-1H-1,2,4-triazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 17*) por varias inyecciones sobre SFC quiral (Chiracel AD-H 30 x 250mm, 5μM, MeOH al 45% (DEA al 0,1%)/CO_2 dando 4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (segundo en eluir, enantiómero B) como una película amarilla. CL-EM $(M+H)^+$ = 528,1. RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 8,76 - 8,92 (1 H, m), 8,06 (1 H, s ancho), 7,30 - 7,45 (1 H, m), 7,25 (2 H, d, *J*=5,49 Hz), 7,05 - 7,19 (3 H, m), 4,57 - 4,80 (4 H, m), 4,20 (1 H, s ancho), 3,63 (3 H, s ancho), 3,00 (1 H, s ancho), 2,82 - 2,94 (1 H, m), 2,53 - 2,61 (1 H, m), 1,91 (1 H, s ancho). No se determinó la estereoquímica absoluta del *Ejemplo 17B*.

Ejemplo 18

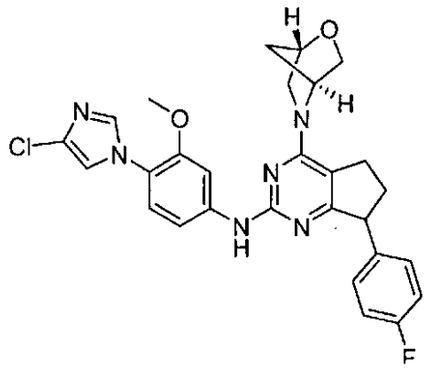
4-((1S,4S)-2-oxa-5-azabiciclo[2,2,1]heptan-5-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Se combinaron (1S,4S)-5-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-2-oxa-5-azabiciclo[2,2,1]heptano (*Preparación Hb*) (148 mg, 0,428 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (124 mg, 0,556 mmol) y se purificó según el *Ejemplo 16* dando 4-((1S,4S)-2-oxa-5-azabiciclo[2,2,1]heptan-5-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (mezcla de diastereómeros) (106 mg, 0,164 mmol, 38,3 % de rendimiento) como un sólido marrón. CL-EM $(M+H)^+$ = 533,1. RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 7,81 (1 H, s), 7,67 (1 H, s ancho), 7,49 (1 H, s), 7,32 (3 H, d, *J*=7,93 Hz), 7,19 (2 H, t, *J*=8,70 Hz), 7,14 (1 H, d, *J*=2,14 Hz), 5,17 (1 H, s ancho), 4,74 (1 H, s), 4,34 (1 H, s ancho), 3,58 - 3,95 (7 H, m), 2,89 - 3,39 (2 H, m), 2,55 (1 H, s), 1,97 (3 H, s ancho).

Ejemplo 18A

4-((1S,4S)-2-oxa-5-azabiciclo[2,2,1]heptan-5-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

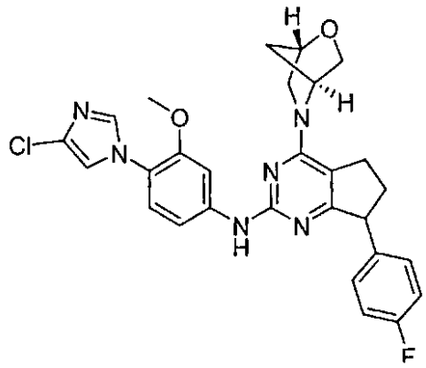


Enantiómero A del *Ejemplo 18*

Se separó 4-((1S,4S)-2-oxa-5-azabiciclo[2,2,1]heptan-5-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 18*) mediante varias inyecciones de SFC quiral (OD-H 30 x 250mm, 5 μM, MeOH al 30% (DEA al 0,1%)/CO_2) dando 4-((1S,4S)-2-oxa-5-azabiciclo[2,2,1]heptan-5-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (primero en eluir, enantiómero A) como un residuo beige. CL-EM $(M+H)^+$ = 532,9. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,82 (1 H, s ancho), 7,67 (1 H, s), 7,18 - 7,30 (3 H, m), 7,11 - 7,18 (1 H, m), 6,96 - 7,09 (3 H, m), 5,14 (1 H, s ancho), 4,72 (1 H, s ancho), 4,18 (1 H, t, *J*=8,55 Hz), 3,94 - 4,01 (1 H, m), 3,92 (1 H, d, *J*=6,41 Hz), 3,78 - 3,86 (1 H, m), 3,69 - 3,78 (1 H, m), 3,57 (3 H, s), 3,01 - 3,15 (2 H, m), 2,51 - 2,69 (1 H, m), 1,84 - 2,11 (3 H, m). No s determinó la estereoquímica absoluta del *Ejemplo 18A*.

Ejemplo 18B

4-((1S,4S)-2-oxa-5-azabiciclo[2,2,1]heptan-5-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

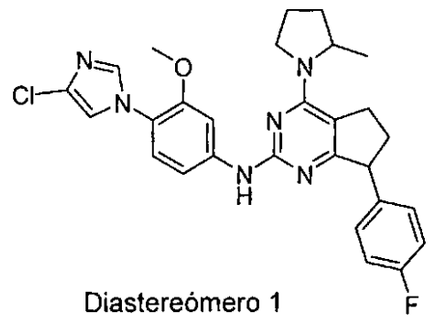


Enantiómero B del *Ejemplo 18*

Se separó 4-((1S,4S)-2-oxa-5-azabiciclo[2,2,1]heptan-5-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 18*) mediante varias inyecciones de SFC quiral (OD-H 30 x 250mm, 5 μM, MeOH al 30% (DEA al 0,1%)/CO_2) dando 4-((1S,4S)-2-oxa-5-azabiciclo[2,2,1]heptan-5-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (segundo en eluir, enantiómero B) como un residuo beige. CL-EM $(M+H)^+$ = 532,9. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,20 - 7,31 (3 H, m), 7,17 (1 H, d, *J*=8,55 Hz), 7,05 (3 H, t, *J*=8,09 Hz), 5,17 (1 H, s ancho), 4,72 (1 H, s), 4,14 (1 H, t, *J*=8,09 Hz), 3,94 - 4,02 (1 H, m), 3,89 - 3,94 (1 H, m), 3,70 - 3,85 (2 H, m), 3,50 - 3,68 (3 H, m), 3,20 - 3,31 (1 H, m), 2,96 (1 H, ddd, *J*=14,65, 7,78, 7,48 Hz), 2,48 - 2,66 (1 H, m, *J*=13,08, 8,72, 8,72, 4,27 Hz), 1,89 - 2,11 (3 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 18B*.

Ejemplo 19

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

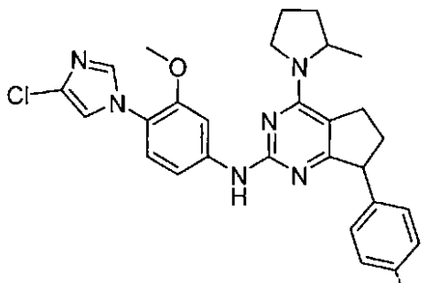


Diastereómero 1
Racémico

Se combinaron 2-cloro-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidinano (*Preparación Hc1*) (159 mg, 0,479 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (139 mg, 0,623 mmol) y se purificó según el *Ejemplo 16* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (racemato, diastereómero 1) (84,37 mg, 0,133 mmol, 27,8 % de rendimiento) como un sólido marrón. CL-EM $(M+H)^+$ = 519,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,80 (1 H, s), 7,41 (1 H, d, *J*=8,55 Hz), 7,30 - 7,37 (4 H, m), 7,21 - 7,32 (1 H, m), 7,17 (2 H, t, *J*=8,55 Hz), 4,68 (1 H, s ancho), 4,44 (1 H, s ancho), 3,94 - 4,23 (2 H, m), 3,88 (3 H, s), 3,37 (3 H, s), 3,18 (1 H, s), 2,72 (1 H, s ancho), 2,11 (4 H, s ancho), 1,83 (1 H, s ancho). No se determinó la estereoquímica relativa del *Ejemplo 19*.

Ejemplo 19A

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

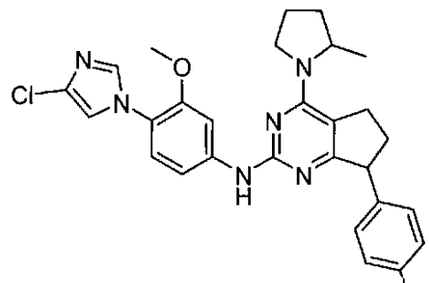


Enantiómero A del *Ejemplo 19*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 19*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 45% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (primero en eluir, enantiómero A, diastereómero 1) como una cera marrón. CL-EM $(M+H)^+$ = 519,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,76 (1 H, s), 7,66 (1 H, d, *J*=1,53 Hz), 7,16 - 7,27 (3 H, m), 7,07 - 7,16 (2 H, m), 7,02 (2 H, t, *J*=8,85 Hz), 4,54 (1 H, t, *J*=5,65 Hz), 4,07 (1 H, t, *J*=8,24 Hz), 3,91 (1 H, dt, *J*=10,45, 4,08 Hz), 3,68 - 3,79 (1 H, m), 3,54 - 3,68 (3 H, m), 3,15 - 3,28 (1 H, m), 2,96 - 3,13 (1 H, m), 2,45 - 2,58 (1 H, m), 2,02 - 2,18 (2 H, m), 1,95 - 2,02 (1 H, m), 1,85 - 1,95 (1 H, m), 1,67 - 1,81 (1 H, m), 1,27 (3 H, d, *J*=6,10 Hz). No se determinó la estereoquímica absoluta del *Ejemplo 19A*.

Ejemplo 19B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

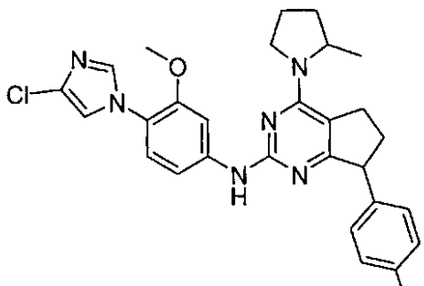


Enantiómero B del *Ejemplo 19*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 19*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 45% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (segundo en eluir, enantiómero B, diastereómero 1) como una cera marrón. CL-EM $(M+H)^+$ = 519,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,76 (1 H, d, *J*=1,53 Hz), 7,65 (1 H, d, *J*=1,22 Hz), 7,15 - 7,23 (3 H, m), 7,06 - 7,14 (2 H, m), 6,96 - 7,05 (2 H, m), 4,48 - 4,57 (1 H, m), 4,05 (1 H, t, *J*=8,39 Hz), 3,85 - 3,94 (1 H, m), 3,66 - 3,76 (1 H, m), 3,60 (3 H, s), 3,16 - 3,26 (1 H, m), 2,95 - 3,08 (1 H, m), 2,44 - 2,55 (1 H, m, *J*=12,78, 8,56, 8,56, 3,97 Hz), 2,01 - 2,14 (2 H, m), 1,94 - 2,01 (1 H, m), 1,85 - 1,94 (1 H, m), 1,68 - 1,77 (1 H, m), 1,26 (3 H, d, *J*=6,10 Hz). No se determinó la estereoquímica absoluta del *Ejemplo 19B*.

Ejemplo 20

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

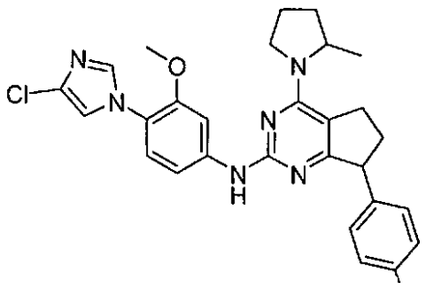


Diastereómero 2
Racémico

Se combinaron 2-cloro-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidinan (*Preparación Hc2*) (179 mg, 0,539 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (157 mg, 0,701 mmol) y se purificó según el *Ejemplo 16* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (racemato, diastereómero 2) (99,55 mg, 0,157 mmol, 29,2 % de rendimiento) como un sólido marrón. CL-EM $(M+H)^+$ = 519,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,80 (1 H, d, *J*=1,53 Hz), 7,41 - 7,60 (1 H, m), 7,40 (1 H, s), 7,30 - 7,37 (3 H, m), 7,21 - 7,29 (1 H, m), 7,16 (2 H, t, *J*=8,70 Hz), 4,68 (1 H, s ancho), 4,45 (1 H, d, *J*=7,93 Hz), 4,17 (1 H, s ancho), 4,00 (1 H, s ancho), 3,88 (3 H, s), 3,34 - 3,48 (2 H, m), 3,17 - 3,30 (1 H, m), 2,73 (1 H, s ancho), 2,11 (4 H, s ancho), 1,81 (1 H, s ancho), 1,35 (3 H, d, *J*=6,41 Hz). No se determinó la estereoquímica relativa del *Ejemplo 20*.

Ejemplo 20A

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

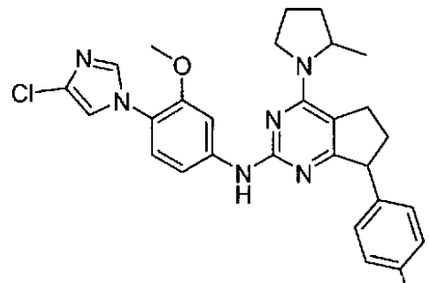


Enantiómero A del *Ejemplo 20*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 20*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 45% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (primero en eluir, enantiómero A, diastereómero 2) como una cera marrón. CL-EM $(M+H)^+$ = 519,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,75 (1 H, d, *J*=1,83 Hz), 7,65 (1 H, d, *J*=1,53 Hz), 7,14 - 7,22 (3 H, m), 7,05 - 7,14 (2 H, m), 6,96 - 7,05 (2 H, m), 4,55 (1 H, td, *J*=6,41, 2,44 Hz), 4,10 (1 H, t, *J*=8,39 Hz), 3,86 - 3,95 (1 H, m), 3,73 (1 H, dt, *J*=10,15, 7,74 Hz), 3,59 (3 H, s), 3,16 - 3,25 (1 H, m), 3,06 - 3,16 (1 H, m), 2,52 (1 H, dddd, *J*=12,70, 8,70, 8,51, 3,97 Hz), 2,02 - 2,16 (2 H, m), 1,82 - 2,02 (2 H, m), 1,65 - 1,78 (1 H, m), 1,27 (3 H, d, *J*=6,10 Hz). No se determinó la estereoquímica absoluta del *Ejemplo 20A*.

Ejemplo 20B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

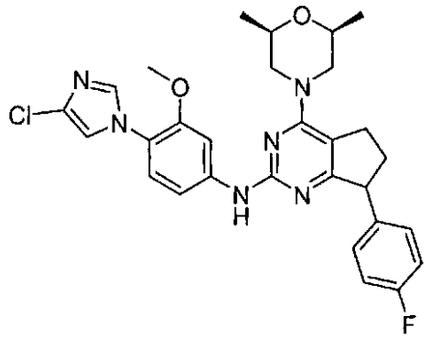


Enantiómero B del *Ejemplo 20*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 20*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 45% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (segundo en eluir, enantiómero B, diastereómero 2) como una cera marrón. CL-EM $(M+H)^+$ = 519,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,75 (1 H, s), 7,65 (1 H, d, *J*=1,53 Hz), 7,14 - 7,21 (3 H, m), 7,05 - 7,14 (2 H, m), 6,96 - 7,04 (2 H, m), 4,49 - 4,58 (1 H, m), 4,10 (1 H, t, *J*=8,55 Hz), 3,84 - 3,93 (1 H, m), 3,69 - 3,78 (1 H, m), 3,55 - 3,61 (3 H, m), 3,15 - 3,24 (1 H, m), 3,05 - 3,15 (1 H, m), 2,52 (1 H, dddd, *J*=12,67, 8,62, 8,47, 4,12 Hz), 2,02 - 2,17 (2 H, m), 1,83 - 2,02 (2 H, m), 1,65 - 1,77 (1 H, m), 1,23 - 1,32 (3 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 20B*.

Ejemplo 21

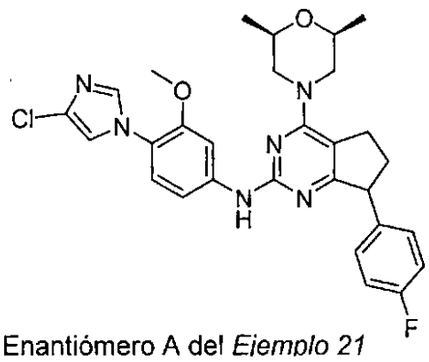
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Se combinaron (2S,6R)-4-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-2,6-dimetilmorfolina (*Preparación Hd*) (223 mg, 0,616 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (179 mg, 0,801 mmol) y se purificó según el *Ejemplo 16* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (144 mg, 0,217 mmol, 35,2 % de rendimiento) como un sólido marrón. CL-EM $(M+H)^+$ = 549,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,81 (1 H, d, *J*=1,53 Hz), 7,41 (1 H, d, *J*=8,55 Hz), 7,28 - 7,38 (4 H, m), 7,09 - 7,20 (3 H, m), 4,62 (2 H, s ancho), 4,45 (1 H, t, *J*=7,93 Hz), 3,83 - 3,89 (3 H, m), 3,69 - 3,80 (2 H, m), 3,25 - 3,30 (1 H, m), 3,13 - 3,23 (1 H, m), 2,94 (2 H, s ancho), 2,75 (1 H, dddd, *J*=13,43, 8,93, 8,77, 4,88 Hz), 2,03 - 2,20 (1 H, m), 1,25 (6 H, d, *J*=6,10 Hz).

Ejemplo 21A

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

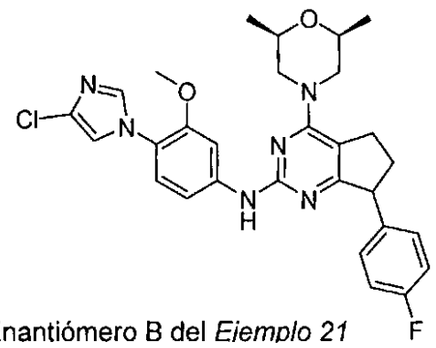


Enantiómero A del *Ejemplo 21*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 21*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 µM, MeOH al 35% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (primero en eluir, enantiómero A) como una cera marrón. CL-EM $(M+H)^+$ = 549,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,81 (1 H, d, *J*=2,14 Hz), 7,63 (1 H, d, *J*=1,53 Hz), 7,11 - 7,20 (3 H, m), 7,08 (1 H, d, *J*=8,55 Hz), 6,96 - 7,03 (2 H, m), 6,92 (1 H, dd, *J*=8,55, 2,44 Hz), 4,27 - 4,41 (2 H, m), 4,08 (1 H, t, *J*=8,70 Hz), 3,58 - 3,74 (2 H, m), 3,49 (3 H, s), 2,99 - 3,08 (1 H, m), 2,87 - 2,99 (1 H, m), 2,55 - 2,72 (2 H, m), 2,44 - 2,55 (1 H, m), 1,83 - 1,96 (1 H, m, *J*=12,70, 8,55, 8,30, 8,30 Hz), 1,17 - 1,22 (6 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 21A*.

Ejemplo 21B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

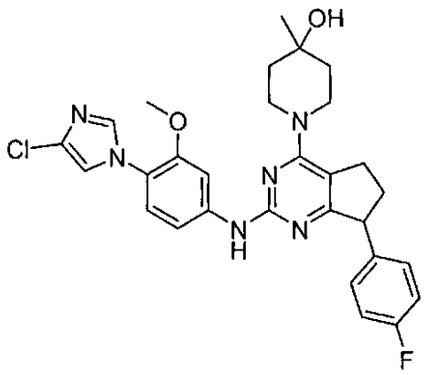


Enantiómero B del *Ejemplo 21*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 21*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 µM, MeOH al 35% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (segundo en eluir, enantiómero B) como una cera marrón. CL-EM $(M+H)^+$ = 549,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,81 (1 H, d, *J*=2,14 Hz), 7,63 (1 H, d, *J*=1,53 Hz), 7,11 - 7,19 (3 H, m), 7,04 - 7,11 (1 H, m), 6,95 - 7,03 (2 H, m), 6,92 (1 H, dd, *J*=8,39, 2,29 Hz), 4,27 - 4,42 (2 H, m), 4,08 (1 H, t, *J*=8,70 Hz), 3,59 - 3,73 (2 H, m), 3,49 (3 H, s), 2,98 - 3,08 (1 H, m), 2,88 - 2,98 (1 H, m), 2,55 - 2,70 (2 H, m), 2,43 - 2,55 (1 H, m), 1,79 - 1,97 (1 H, m, *J*=12,70, 8,55, 8,30, 8,30 Hz), 1,17 - 1,21 (6 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 21B*.

Ejemplo 22

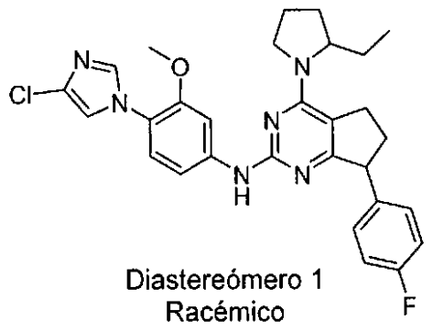
1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-4-metilpiperidin-4-ol



Se combinaron 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-4-metilpiperidin-4-ol (*Preparación He*) (374 mg, 1,034 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (301 mg, 1,344 mmol) y se purificó según el *Ejemplo 17* dando 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-4-metilpiperidin-4-ol (89 mg, 0,162 mmol, 15,68 % de rendimiento) como un sólido ligeramente amarillo. CL-EM $(M+H)^+$ = 549,3. RMN de ^1H (500 MHz, *DMSO-d_6*) δ ppm 7,82 (1 H, s), 7,64 (1 H, s ancho), 7,50 (1 H, s), 7,27 - 7,43 (3 H, m), 7,20 (3 H, t, *J*=8,70 Hz), 7,06 (1 H, dd, *J*=8,39, 1,68 Hz), 4,36 (3 H, s ancho), 3,73 (3 H, s ancho), 2,98 - 3,26 (3 H, m), 2,59 (1 H, s ancho), 1,88 - 2,06 (1 H, m), 1,62 (4 H, s ancho), 1,25 (2 H, s ancho), 1,19 (3 H, s).

Ejemplo 23

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

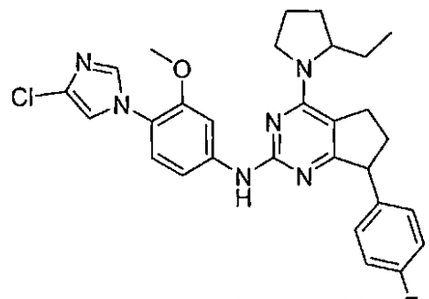


Diastereómero 1
Racémico

Se combinaron 2-cloro-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación Hf1*) (77 mg, 0,223 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (64,7 mg, 0,289 mmol) y se purificó según el *Ejemplo 16* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (racémico, diastereómero 1) (53,31 mg, 0,082 mmol, 37,0 % de rendimiento) como un sólido marrón. CL-EM $(M+H)^+$ = 533,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,79 (1 H, s ancho), 7,36 - 7,61 (2 H, m), 7,34 (3 H, s ancho), 7,17 (3 H, s ancho), 4,44 (2 H, s ancho), 4,00 (2 H, s ancho), 3,88 (3 H, s ancho), 3,16 - 3,27 (1 H, m), 2,73 (2 H, s ancho), 2,09 (5 H, s ancho), 1,32 (2 H, s ancho), 0,93 (3 H, s ancho). No se determinó la estereoquímica relativa del *Ejemplo 23*.

Ejemplo 23A

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

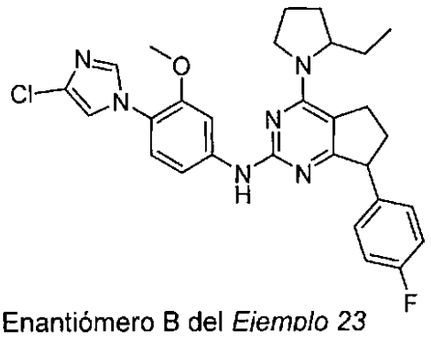


Enantiómero A del *Ejemplo 23*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 23*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 45% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (primero en eluir, enantiómero A) como un aceite marrón. CL-EM $(M+H)^+$ = 533,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,60 - 7,70 (2 H, m), 7,17 - 7,26 (4 H, m), 7,14 (1 H, d, *J*=8,55 Hz), 6,98 - 7,07 (2 H, m), 4,26 - 4,36 (1 H, m), 4,09 (1 H, t, *J*=8,24 Hz), 3,83 - 3,92 (1 H, m), 3,70 - 3,79 (1 H, m), 3,63 (3 H, s), 3,15 - 3,25 (1 H, m), 3,04 (1 H, ddd, *J*=14,80, 7,63, 7,48 Hz), 2,48 - 2,60 (1 H, m, *J*=12,86, 8,60, 8,60, 4,12 Hz), 1,76 - 2,12 (6 H, m), 1,40 - 1,53 (1 H, m), 0,94 - 1,00 (3 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 23A*.

Ejemplo 23B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

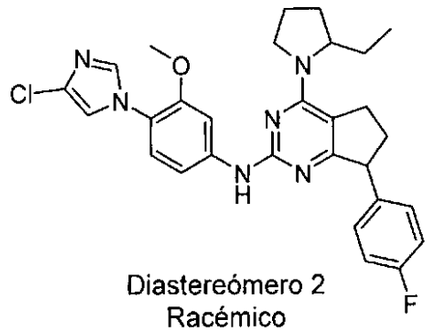


Enantiómero B del *Ejemplo 23*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 23*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 45% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (segundo en eluir, enantiómero B) como un aceite marrón. CL-EM $(M+H)^+$ = 533,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,60 - 7,70 (2 H, m), 7,18 - 7,27 (4 H, m), 7,14 (1 H, d, *J*=8,55 Hz), 7,03 (2 H, t, *J*=8,70 Hz), 4,31 (1 H, s ancho), 4,04 - 4,13 (1 H, m), 3,81 - 3,91 (1 H, m), 3,70 - 3,80 (1 H, m), 3,63 (3 H, s), 3,16 - 3,26 (1 H, m), 3,05 (1 H, ddd, *J*=14,65, 7,78, 7,48 Hz), 2,54 (1 H, dddd, *J*=12,78, 8,70, 8,58, 4,12 Hz), 1,76 - 2,14 (6 H, m), 1,41 - 1,54 (1 H, m), 0,97 (3 H, t, *J*=7,32 Hz). No se determinó la estereoquímica absoluta del *Ejemplo 23B*.

Ejemplo 24

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

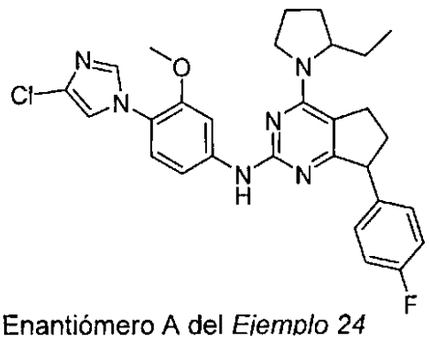


Diastereómero 2
Racémico

Se combinaron 2-cloro-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación Hf2*) (80 mg, 0,231 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (67,3 mg, 0,301 mmol) y se purificó según el *Ejemplo 16* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (racémico, diastereómero 2) (39,54 mg, 0,061 mmol, 26,4 % de rendimiento) como un sólido marrón. CL-EM $(M+H)^+$ = 533,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,78 (1 H, s), 7,28 - 7,44 (5 H, m), 7,17 (3 H, t, *J*=8,09 Hz), 4,46 (2 H, s ancho), 4,00 (2 H, s ancho), 3,88 (3 H, s), 3,37 (1 H, s ancho), 2,73 (2 H, s ancho), 2,09 (6 H, d, *J*=4,27 Hz), 1,27 - 1,73 (1 H, m), 0,87 (3 H, s ancho). No se determinó la estereoquímica relativa del *Ejemplo 24*.

Ejemplo 24A

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

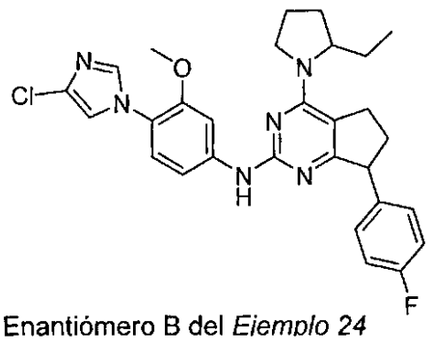


Enantiómero A del *Ejemplo 24*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 24*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 45% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (primero en eluir, enantiómero A) como un aceite marrón. CL-EM $(M+H)^+$ = 533,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,58 - 7,71 (2 H, m), 7,16 - 7,26 (4 H, m), 7,10 - 7,16 (1 H, m), 6,97 - 7,08 (2 H, m), 4,29 - 4,39 (1 H, m), 4,14 (1 H, t, *J*=8,39 Hz), 3,82 - 3,93 (1 H, m), 3,72 - 3,82 (1 H, m), 3,61 (3 H, s), 3,17 - 3,26 (1 H, m), 3,12 (1 H, ddd, *J*=14,80, 7,63, 7,48 Hz), 2,56 (1 H, dddd, *J*=12,70, 8,70, 8,51, 3,97 Hz), 1,79 - 2,09 (6 H, m), 1,40 - 1,56 (1 H, m), 0,97 (3 H, t, *J*=7,32 Hz). No se determinó la estereoquímica absoluta del *Ejemplo 24A*.

Ejemplo 24B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

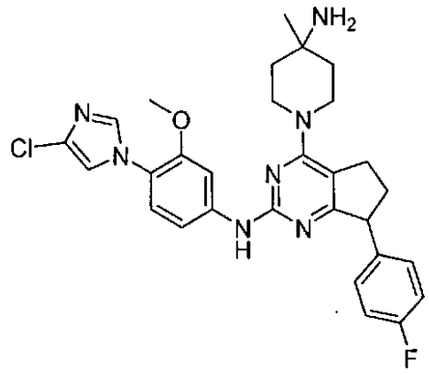


Enantiómero B del *Ejemplo 24*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 24*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 45% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(2-etilpirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (segundo en eluir, enantiómero B) como un aceite marrón. CL-EM $(M+H)^+$ = 533,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,59 - 7,70 (2 H, m), 7,16 - 7,27 (4 H, m), 7,11 - 7,16 (1 H, m), 7,03 (2 H, t, *J*=8,70 Hz), 4,29 - 4,37 (1 H, m), 4,09 - 4,18 (1 H, m), 3,83 - 3,92 (1 H, m), 3,73 - 3,81 (1 H, m), 3,61 (3 H, s), 3,16 - 3,27 (1 H, m), 3,06 - 3,16 (1 H, m), 2,50 - 2,61 (1 H, m, *J*=12,74, 8,58, 8,58, 3,97 Hz), 1,80 - 2,10 (6 H, m), 1,42 - 1,55 (1 H, m), 0,97 (3 H, t, *J*=7,48 Hz). No se determinó la estereoquímica absoluta del *Ejemplo 24B*.

Ejemplo 25

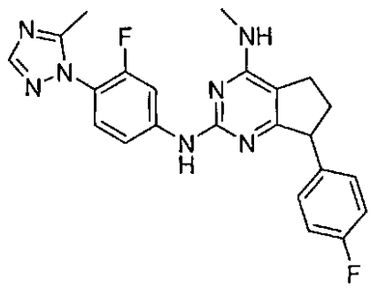
4-(4-amino-4-metilpiperidin-1-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Se combinaron 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-4-metilpiperidin-4-ilcarbamato de *terc*-butilo (*Preparación Hg*) (363 mg, 0,787 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (229 mg, 1,024 mmol) y se purificó según el *Ejemplo 16* dando 4-(4-amino-4-metilpiperidin-1-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (66,5 mg, 0,100 mmol, 12,76 % de rendimiento) como un sólido ligeramente amarillo. CL-EM $(M+H)^+$ = 548,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,82 (1 H, d, *J*=2,14 Hz), 7,68 (1 H, s), 7,20 - 7,27 (3 H, m), 7,17 (1 H, d, *J*=8,55 Hz), 7,00 - 7,09 (3 H, m), 4,15 - 4,33 (4 H, m), 3,58 (3 H, s), 3,44 - 3,56 (2 H, m), 3,02 - 3,21 (2 H, m), 2,61 (1 H, dd, *J*=8,55, 4,27 Hz), 2,01 (1 H, dd, *J*=12,51, 8,24 Hz), 1,81 - 1,91 (4 H, m), 1,38 - 1,48 (2 H, m).

Ejemplo 26

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

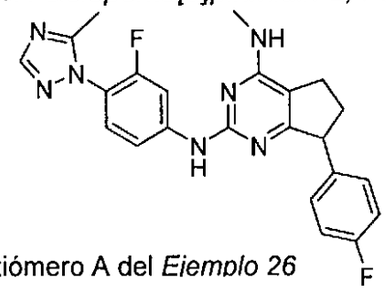


A una solución de 2-cloro-7-(4-fluorofenil)-N-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (*Preparación Hh*) (144 mg, 0,518 mmol) en dioxano (2469 µl) se añadió 3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina (*Preparación C)* (100 mg, 0,518 mmol), tris(dibencilidenacetona)dipaladio(0) (23,74 mg, 0,026 mmol), 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (30,0 mg, 0,052 mmol), Na_2CO_3 (82 mg, 0,778 mmol) y agua (494 µl). La mezcla resultante se calentó hasta 110 °C y se agitó durante la noche. La reacción se diluyó entonces con agua (10 ml) y se extrajo con EtOAc (3 x 5 ml). Los extractos orgánicos reunidos se lavaron con salmuera (10 ml), se secaron sobre $MgSO_4$, se filtraron y concentraron a vacío. Purificación por HLC preparativa (C18, 50 X 250mm, MeOH/H_2O/TFA) dio N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina, TFA (170 mg, 0,311 mmol, 59,9 % de rendimiento). CL-EM $(M+H)^+$ = 434,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,06 (1 H, s), 7,96 (1 H, dd, *J*=12,51, 2,14 Hz), 7,48 - 7,59 (2 H, m), 7,26 - 7,33 (2 H, m), 7,09 - 7,18 (2 H, m), 4,46 - 4,54 (1 H, m), 3,17 (3 H, s), 2,87 - 2,97 (1 H, m), 2,74 - 2,85 (2 H, m), 2,40 (3 H, s), 2,09 - 2,21 (1 H, m).

Ejemplo 26A

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-

dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

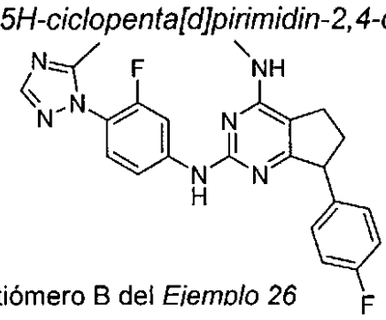


Enantiómero A del *Ejemplo 26*

Se separó N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (*Ejemplo 26*) mediante varias inyecciones de HPLC preparativa quiral (OJ-H 30 x 250mm, 10 μM, EtOH/Heptano) dando N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina, TFA (primero en eluir, enantiómero A) como un vidrio incoloro transparente. CL-EM $(M+H)^+$ = 434,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,03 - 8,13 (2 H, m), 7,41 - 7,47 (2 H, m), 7,23 - 7,30 (2 H, m), 7,04 - 7,14 (2 H, m), 4,33 (1 H, t, *J*=7,93 Hz), 3,12 (3 H, s), 2,81 - 2,92 (1 H, m), 2,67 - 2,81 (2 H, m), 2,40 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 26A*.

Ejemplo 26B

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



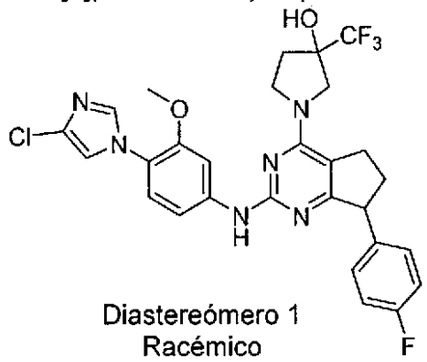
Enantiómero B del *Ejemplo 26*

Se separó N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-

fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (*Ejemplo 26*) mediante varias inyecciones de HPLC preparativa quiral (OJ-H 30 x 250mm, 10 μM, EtOH/Heptano) dando N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina, TFA (segundo en eluir, enantiómero B) como un vidrio incoloro transparente. CL-EM $(M+H)^+$ = 434,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,03 - 8,10 (2 H, m), 7,43 - 7,48 (2 H, m), 7,24 - 7,30 (2 H, m), 7,06 - 7,14 (2 H, m), 4,37 (1 H, t, *J*=7,78 Hz), 3,14 (3 H, s), 2,83 - 2,92 (1 H, m), 2,69 - 2,80 (2 H, m), 2,40 (3 H, s), 2,05 - 2,16 (1 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 26B.*

Ejemplo 27

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol



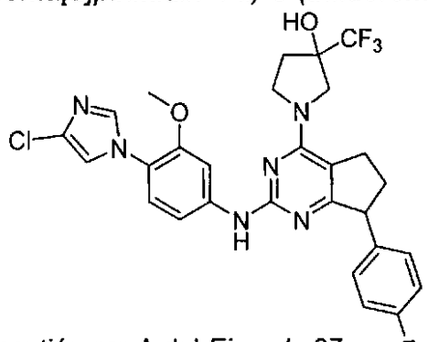
Diastereómero 1
Racémico

Se combinaron 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol (*Preparación Hi*) (245 mg, 0,610 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (177 mg, 0,793 mmol) y se purificó según el *Ejemplo 16* dando 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-

ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol, TFA (primero en eluir, diastereómero A) (51,4 mg, 0,073 mmol) como un vidrio incoloro transparente. CL-EM $(M+H)^+$ = 589,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,97 (1 H, s), 7,67 (1 H, s), 7,17 - 7,26 (3 H, m), 7,14 (1 H, d, *J*=8,55 Hz), 7,04 (2 H, t, *J*=8,70 Hz), 6,91 (1 H, d, *J*=8,55 Hz), 4,14 (2 H, t, *J*=8,85 Hz), 3,93 - 4,06 (3 H, m), 3,58 - 3,68 (3 H, m), 3,21 - 3,31 (1 H, m), 3,09 - 3,21 (1 H, m), 2,51 - 2,63 (1 H, m), 2,28 - 2,41 (1 H, m), 2,16 (1 H, dd, *J*=12,82, 6,41 Hz), 1,95 (1 H, dc, *J*=12,82, 8,55 Hz). No se determinó la estereoquímica relativa del *Ejemplo 27*.

Ejemplo 27A

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol



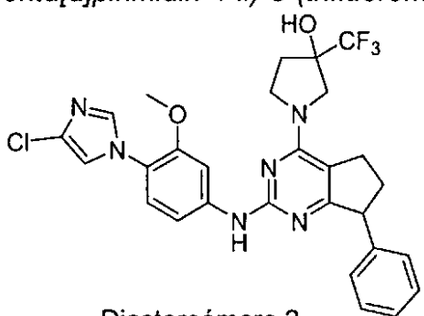
Enantiómero A del *Ejemplo 27*

Se separó 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol (*Ejemplo 12*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 45% (DEA al 0,1%)/CO_2) dando 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol (primero en eluir, enantiómero A) (11,34 mg, 0,019 mmol) como un vidrio opaco. CL-EM $(M+H)^+$ = 589,1. No se determinó la

estereoquímica absoluta del *Ejemplo 27A*.

Ejemplo 28

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol

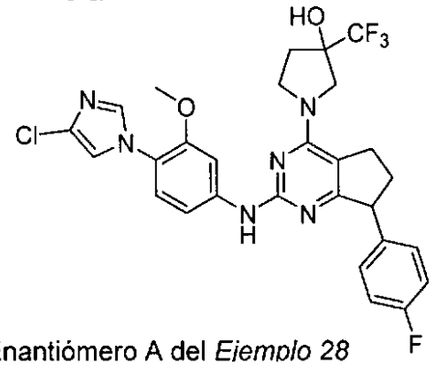


Diastereómero 2
Racémico

Se combinaron 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol (*Preparación Hi*) (245 mg, 0,610 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (177 mg, 0,793 mmol) y se purificó según el *Ejemplo 16* dando 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol, TFA (segundo en eluir, diastereómero 2) (51,1 mg, 0,073 mmol) como un sólido blanco. CL-EM $(M+H)^+$ = 589,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,96 (1 H, d, *J*=1,83 Hz), 7,68 (1 H, d, *J*=1,53 Hz), 7,19 - 7,27 (3 H, m), 7,15 (1 H, d, *J*=8,55 Hz), 7,04 (2 H, t, *J*=8,70 Hz), 6,95 (1 H, dd, *J*=8,55, 2,14 Hz), 4,10 - 4,21 (2 H, m), 3,95 - 4,04 (3 H, m), 3,61 - 3,69 (3 H, m), 3,27 - 3,32 (1 H, m), 3,08 - 3,20 (1 H, m), 2,57 (1 H, dddd, *J*=13,16, 8,74, 8,62, 4,58 Hz), 2,37 (1 H, dt, *J*=12,89, 9,88 Hz), 2,18 (1 H, dd, *J*=12,82, 6,41 Hz), 1,93 - 2,05 (1 H, m). No se determinó la estereoquímica relativa del *Ejemplo 28*.

Ejemplo 28A

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol

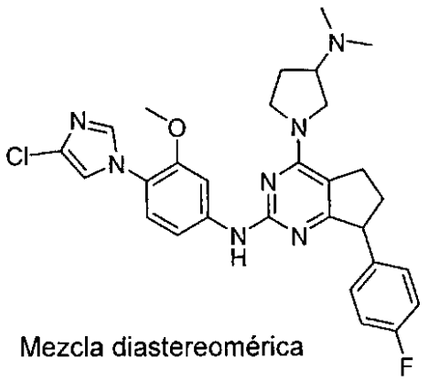


Enantiómero A del *Ejemplo 28*

Se separó 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol (*Ejemplo 28*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 45% (DEA al 0,1%)/CO_2) dando 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-(trifluorometil)pirrolidin-3-ol (primero en eluir, enantiómero A) (17,18 g, 29,2 mmol) como un vidrio opaco. CL-EM $(M+H)^+$ = 589,1. No se determinó la estereoquímica absoluta del *Ejemplo 28A*.

Ejemplo 29

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)pirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

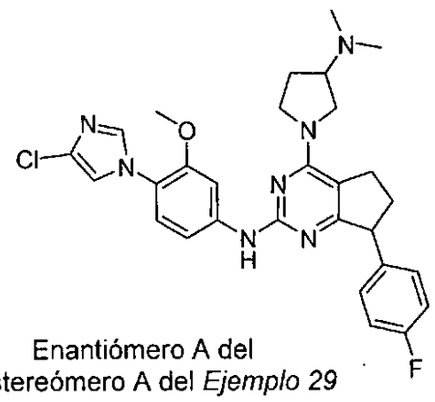


Mezcla diastereomérica

Se combinaron 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N,N-dimetilpirrolidin-3-amina (*Preparación Hj*) (109 mg, 0,302 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (67,6 mg, 0,302 mmol) y se purificó según el *Ejemplo 26* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)pirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (88 mg, 0,133 mmol, 44,0 % de rendimiento) como un vidrio color castaño fragmentado. CL-EM $(M+H)^+$ = 548,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,79 (1 H, s), 7,38 - 7,44 (2 H, m), 7,29 - 7,36 (3 H, m), 7,24 - 7,29 (1 H, m), 7,11 - 7,19 (2 H, m), 4,39 - 4,51 (2 H, m), 4,28 (1 H, s ancho), 4,05 - 4,17 (2 H, m), 4,00 (1 H, d, *J*=2,44 Hz), 3,86 (3 H, s), 3,22 - 3,47 (2 H, m), 3,02 (3 H, s), 2,76 (1 H, s ancho), 2,60 (1 H, s ancho), 2,39 (1 H, s ancho), 2,13 (1 H, s ancho).

Ejemplo 29A

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)pirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

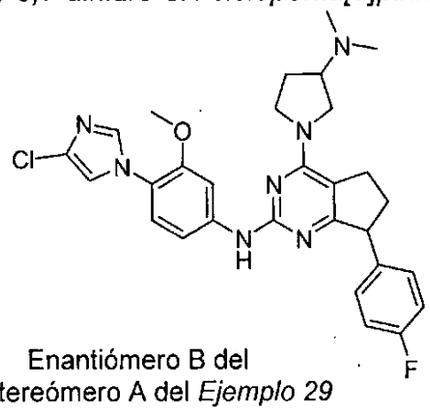


Enantiómero A del
Diastereómero A del *Ejemplo 29*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)pirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 29*) primero mediante varias inyecciones de HPLC quiral (OJ-H 30 x 250mm, EtOH al 30%/Heptano) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)pirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (primero en eluir, diastereómero A) que se separó entonces mediante varias inyecciones de SFC quiral (IB 30 x 250mm, 5 μM, MeOH al 30%:MeCN 50:50/(DEA al 0,1%)CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)pirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (primero en eluir, enantiómero A) como un vidrio incoloro transparente. CL-EM $(M+H)^+$ = 548,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,83 (1 H, d, *J*=2,14 Hz), 7,67 (1 H, d, *J*=1,22 Hz), 7,18 - 7,26 (3 H, m), 7,15 (1 H, d, *J*=8,55 Hz), 7,00 - 7,10 (3 H, m), 4,00 - 4,16 (3 H, m), 3,69 - 3,80 (1 H, m), 3,58 - 3,66 (3 H, m), 3,52 (1 H, t, *J*=9,31 Hz), 3,26 - 3,31 (1 H, m), 3,06 - 3,17 (1 H, m), 2,83 - 2,94 (1 H, m), 2,49 - 2,61 (1 H, m, *J*=13,08, 8,64, 8,64, 4,43 Hz), 2,35 (6 H, s), 2,21 - 2,30 (1 H, m), 1,83 - 2,03 (2 H, m), 1,33 - 1,41 (1 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 29A*.

Ejemplo 29B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)pirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



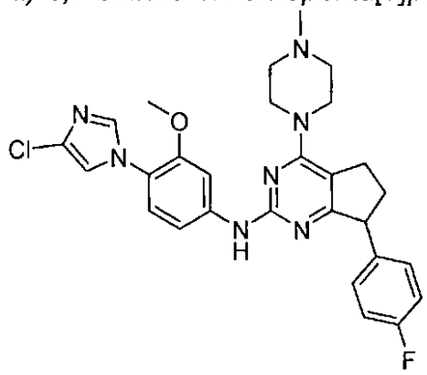
Enantiómero B del
Diastereómero A del *Ejemplo 29*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)pirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 29*) primero mediante varias inyecciones de HPLC quiral (OJ-H 30 x 250mm, EtOH al 30%/Heptano) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)pirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (primero en eluir, diastereómero A) que se separó entonces mediante varias inyecciones de SFC quiral (IB 30 x 250mm, 5 μM, MeOH: MeCN al 35% 50 :50/(DEA al 0,1%)CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)pirrolidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (segundo en eluir, enantiómero B) como un vidrio incoloro transparente. CL-EM $(M+H)^+$ = 548,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,85 (1 H, d, *J*=2,14 Hz), 7,67 (1 H, d, *J*=1,53 Hz), 7,17 - 7,24 (3 H, m), 7,12 - 7,17 (1 H, m), 6,99 - 7,08 (3 H, m), 3,99 - 4,18 (3 H, m), 3,68 - 3,79 (1 H, m), 3,58 (3 H, s), 3,48 - 3,56 (1 H, m), 3,21 - 3,30 (1 H, m), 3,10 -

3,21 (1 H, m), 2,81 - 2,94 (1 H, m), 2,49 - 2,62 (1 H, m), 2,36 (6 H, s), 2,21 - 2,31 (1 H, m), 1,82 - 1,99 (2 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 29B*.

Ejemplo 30

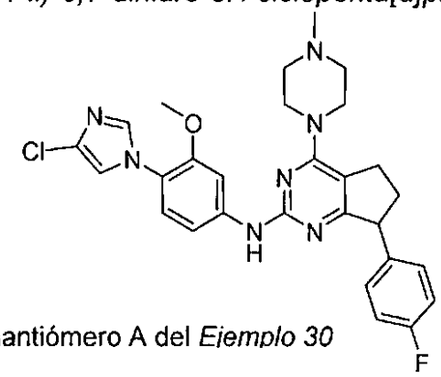
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(4-metilpiperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Se combinaron 2-cloro-7-(4-fluorofenil)-4-(4-metilpiperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidina (*Preparación Hk*) (109 mg, 0,314 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (70,3 mg, 0,314 mmol) y se purificó según el *Ejemplo 26* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(4-metilpiperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (104 mg, 0,160 mmol, 51,1 % de rendimiento) como un vidrio color castaño fragmentado. CL-EM $(M+H)^+$ = 534,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,79 (1 H, s), 7,52 (1 H, s), 7,26 - 7,36 (4 H, m), 7,08 - 7,16 (3 H, m), 4,41 (1 H, t, *J*=8,09 Hz), 3,73 (3 H, s), 3,37 - 3,63 (7 H, m), 3,09 - 3,28 (3 H, m), 2,97 - 3,03 (3 H, m), 2,67 - 2,79 (1 H, m), 2,05 - 2,20 (1 H, m).

Ejemplo 30A

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(4-metilpiperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

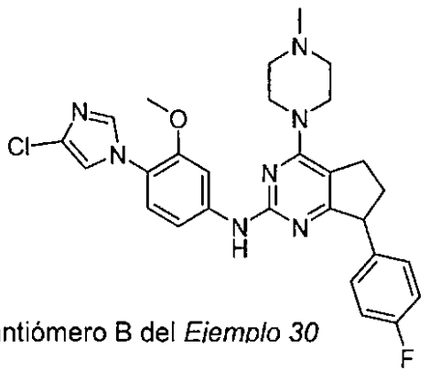


Enantiómero A del *Ejemplo 30*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(4-metilpiperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 30*) mediante varias inyecciones de HPLC preparativa quiral (OJ-H 30 x 250mm, 10μM, EtOH al 30%/Heptano) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(4-metilpiperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (primero en eluir, enantiómero A) (21,6 mg, 0,033 mmol) como un vidrio color castaño fragmentado. CL-EM $(M+H)^+$ = 534,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,77 (1 H, s ancho), 7,69 (1 H, s), 7,23 - 7,31 (3 H, m), 7,21 (1 H, d, *J*=8,55 Hz), 6,99 - 7,15 (3 H, m), 4,27 (1 H, t, *J*=8,39 Hz), 3,61 - 3,78 (1 H, m), 3,56 (3 H, s), 3,38 - 3,53 (3 H, m), 3,23 - 3,38 (5 H, m), 3,03 - 3,21 (2 H, m), 2,98 (3 H, s), 2,67 (1 H, dt, *J*=8,47, 4,16 Hz), 1,99 - 2,13 (1 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 30A*.

Ejemplo 30B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(4-metilpiperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

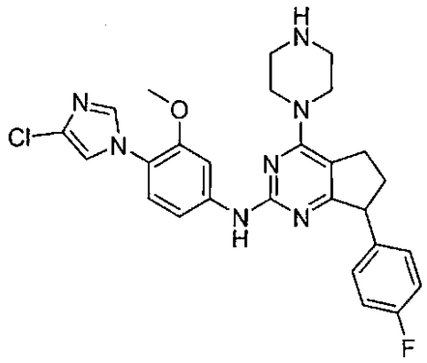


Enantiómero B del *Ejemplo 30*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(4-metilpiperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (*Ejemplo 30*) mediante varias inyecciones de HPLC preparativa quiral (OJ-H 30 x 250mm, 10μM, EtOH al 30%/Heptano) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(4-metilpiperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (segundo en eluir, enantiómero B) (21,6 mg, 0,033 mmol) como un vidrio color castaño en fragmento. CL-EM $(M+H)^+$ = 534,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,81 (1 H, d, *J*=2,14 Hz), 7,68 (1 H, d, *J*=1,53 Hz), 7,22 - 7,29 (3 H, m), 7,16 - 7,21 (1 H, m), 7,00 - 7,11 (3 H, m), 4,24 (1 H, t, *J*=8,55 Hz), 3,57 - 3,70 (1 H, m), 3,53 (3 H, s), 3,46 (3 H, s ancho), 3,27 - 3,36 (5 H, m), 3,02 - 3,18 (2 H, m), 2,98 (3 H, s), 2,60 - 2,72 (1 H, m), 2,00 - 2,10 (1 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 30B*.

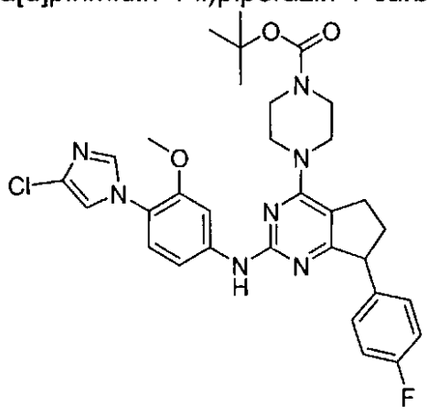
Ejemplo 31

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(piperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Intermedio 31-1

4-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)piperazin-1-carboxilato de terc-butilo



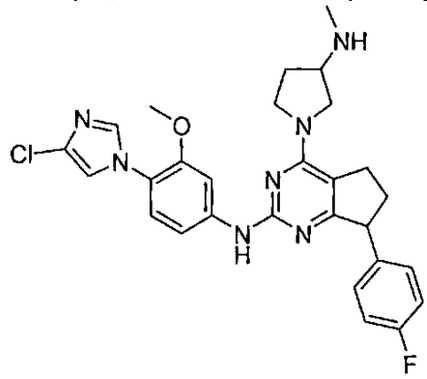
Se combinaron 4-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)piperazin-1-carboxilato de terc-butilo (*Preparación HI*) (117 mg, 0,270 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (60,4 mg, 0,270 mmol) según el *Ejemplo 26* dando 4-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)piperazin-1-carboxilato de terc-butilo (104 mg, 0,168 mmol, 62,1 % de rendimiento) bruto sin purificación. CL-EM $(M+H)^+$ = 620,4.

Ejemplo 31

A una solución de 4-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)piperazin-1-carboxilato de terc-butilo (*Intermedio 31-1*) (167 mg, 0,270 mmol) en DCM (5 ml) se añadió TFA (500 µl, 6,49 mmol). La mezcla de reacción se agitó a ta durante 1 h. La mezcla luego se concentró a vacío. Purificación por HPLC preparativa (Waters Sunfire C18, 50 X 250mm, MeOH/H_2O/TFA) dio N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(piperazin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (39 mg, 0,062 mmol, 22,78 % de rendimiento) como un aceite marrón. CL-EM $(M+H)^+$ = 520,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,83 (1 H, s ancho), 7,28 - 7,46 (5 H, m), 7,08 - 7,21 (3 H, m), 4,41 - 4,53 (1 H, m), 4,18 - 4,28 (4 H, m), 3,80 (3 H, s), 3,44 (5 H, d, *J*=4,27 Hz), 3,24 - 3,31 (1 H, m), 3,12 - 3,23 (1 H, m), 2,69 - 2,82 (1 H, m), 2,06 - 2,22 (1 H, m).

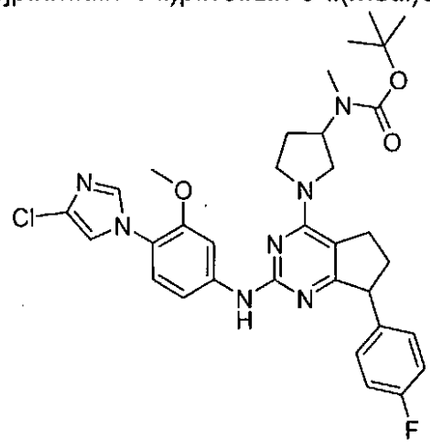
Ejemplo 32

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(3-(metilamino)pirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Intermedio 32-1

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)pirrolidin-3-il(metil)carbamato de terc-butilo



Se combinaron 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)pirrolidin-3-il(metil)carbamato de terc-butilo (*Preparación Hm*) (148 mg, 0,331 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (74,1 mg, 0,331 mmol) según el *Ejemplo 26* dando el 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)pirrolidin-3-il(metil)carbamato de terc-butilo bruto (104 mg, 0,164 mmol, 49,5 % de rendimiento) que se usó sin purificación posterior. CL-EM $(M+H)^+$ = 634,4.

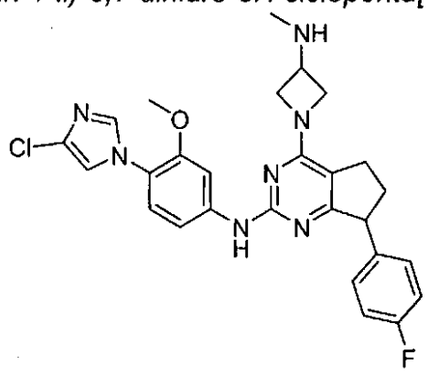
Ejemplo 32

Se desprotegió 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)pirrolidin-3-il(metil)carbamato de terc-butilo (Intermedio 32-1) (210 mg, 0,331 mmol) y se purificó según el *Ejemplo 31* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(3-(metilamino)pirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (50 mg, 0,077 mmol, 23,31 % de

rendimiento) como un aceite marrón. CL-EM $(M+H)^+$ = 534,4. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,43 (1 H, s), 7,40 (1 H, d, *J*=8,55 Hz), 7,29 - 7,35 (3 H, m), 7,24 (1 H, dt, *J*=8,62, 2,25 Hz), 7,16 (2 H, t, *J*=8,09 Hz), 4,47 (1 H, s ancho), 4,23 - 4,35 (1 H, m), 4,12 (3 H, s ancho), 4,02 (1 H, s ancho), 3,84 - 3,91 (3 H, m), 3,18 - 3,49 (2 H, m), 2,84 (3 H, s), 2,68 - 2,81 (1 H, m), 2,56 (1 H, s ancho), 2,35 (1 H, s ancho), 2,07 - 2,22 (1 H, m).

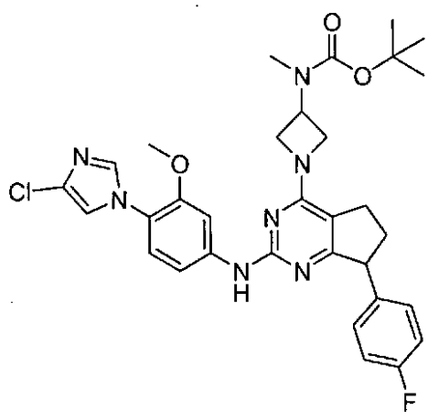
Ejemplo 33

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(3-(metilamino)azetidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Intermedio 33-1

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)azetidin-3-il(metil)carbamato de terc-butilo



Se combinaron 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)azetidin-3-il(metil)carbamato de terc-butilo (*Preparación Hn*) (147 mg, 0,340 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (76 mg, 0,340 mmol) según el *Ejemplo 26* dando el 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)azetidin-3-il(metil)carbamato de terc-butilo bruto (104 mg, 0,168 mmol, 49,4 % de rendimiento) que se usó sin purificación posterior. CL-EM $(M+H)^+$ = 620,4.

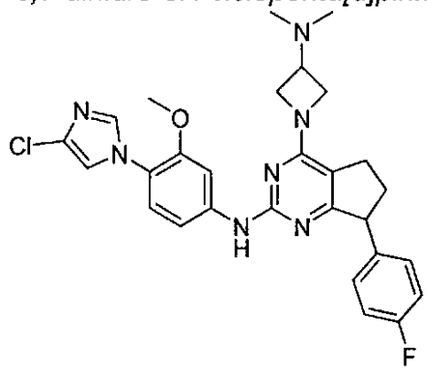
Ejemplo 33

Se desprotegió 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)azetidin-3-il(metil)carbamato de terc-butilo (*Intermedio 33-1*) (211 mg, 0,340 mmol) y se purificó según el *Ejemplo 31* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(3-(metilamino)azetidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (126 mg, 0,199 mmol, 58,5 % de rendimiento) como un aceite ligeramente amarillo. CL-EM $(M+H)^+$ = 520,4. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,80 (1 H, s), 7,55 (1 H, d, *J*=2,14 Hz),

7,31 - 7,40 (2 H, m), 7,26 - 7,31 (2 H, m), 7,09 - 7,20 (3 H, m), 4,64 (2 H, s ancho), 4,46 (1 H, t, *J*=7,93 Hz), 4,21 - 4,36 (1 H, m), 3,87 (3 H, s), 3,37 (2 H, s), 3,11 - 3,21 (1 H, m), 3,04 (1 H, t, *J*=14,95 Hz), 2,80 - 2,84 (3 H, m), 2,68 - 2,80 (1 H, m), 2,14 (1 H, dddd, *J*=13,28, 8,85, 6,56, 6,41 Hz).

Ejemplo 34

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)azetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

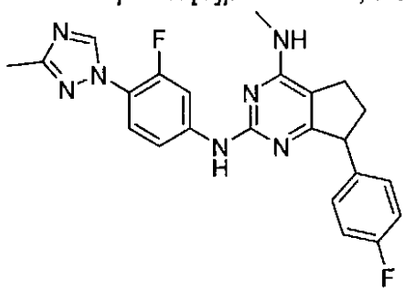


Se combinaron 1-(2-cloro-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N,N-dimetilazetidin-3-amina (*Preparación Ho)* (146 mg, 0,421 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (94 mg, 0,421 mmol) y se purificó según el *Ejemplo 26* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-(dimetilamino)azetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (104 mg, 0,160 mmol, 38,1 % de rendimiento) como una goma ligeramente marrón. CL-EM $(M+H)^+$ = 534,4. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,82 (1 H, d, *J*=1,53 Hz), 7,48 (1 H, d, *J*=2,14 Hz), 7,39 (1 H, d, *J*=8,55 Hz), 7,35 (1 H, d, *J*=1,53 Hz), 7,29 - 7,33 (2 H, m), 7,21 (1 H, dd, *J*=8,55, 2,14 Hz), 7,11 - 7,18 (2 H, m), 4,83 (4 H, s ancho), 4,43 - 4,51 (1 H, m), 4,30 - 4,37 (1 H, m), 3,88 (3 H, s), 3,12 - 3,22 (1 H, m),

3,04 (1 H, d, *J*=6,10 Hz), 2,99 (6 H, s), 2,72 - 2,84 (1 H, m, *J*=13,47, 8,98, 8,98, 4,58 Hz), 2,14 (1 H, dddd, *J*=13,16, 8,96, 6,56, 6,41 Hz).

Ejemplo 35

N^2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

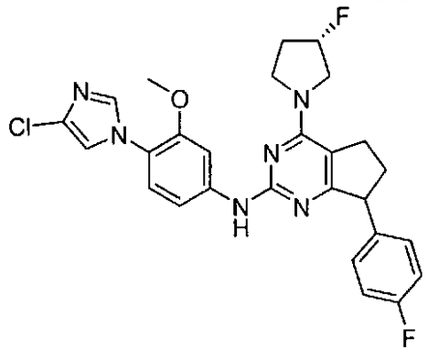


Se combinaron 2-cloro-7-(4-fluorofenil)-N-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (*Preparación Hh*) (164 mg, 0,591 mmol) y 3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)anilina (*Preparación B*) (113 mg, 0,591 mmol) y se purificó según el *Ejemplo 26* dando N^2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina, TFA (104 mg, 0,190 mmol, 32,2 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 434,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,75 (1 H, d, *J*=2,44 Hz), 7,94 (1 H, dd, *J*=13,28, 2,29 Hz), 7,79 (1 H, t, *J*=8,70 Hz), 7,48 (1 H, dt, *J*=8,85, 1,22 Hz), 7,27 - 7,35 (2 H, m), 7,10 - 7,19 (2 H, m), 4,51 (1 H, d, *J*=2,44 Hz), 3,18 (3 H, s), 2,89 - 2,98 (1 H, m), 2,74 - 2,87 (2 H, m), 2,46 (3 H, s), 2,09 - 2,23 (1 H, m).

Ejemplo 36

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((S)-3-

fluoropirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Diastereómero A

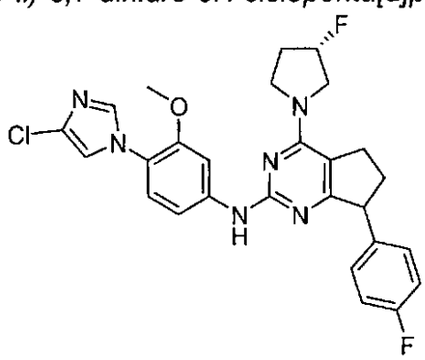
A una solución de 2-cloro-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidina (Preparación Hp1)(30,5 mg, 0,091 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A)(26,4 mg, 0,118 mmol) en THF (272 µl) se añadió AcOH (272 µl). La solución se calentó a 100 °C durante la noche.

Se eliminó el disolvente y se recogió el residuo en MeOH. Se purificó por HPLC prep: (50 X 250 mm HPLC Sunfire C18 10µm 0 hasta 100% A:B durante 40 min, 10 min a 100% de B (A es agua:MeOH:TFA 90:10:0,1; B es MeOH:agua:TFA 90:10:0,1)). Las fracciones apropiadas de Speedvac proporcionaron N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina. CL-EM $(M+H)^+$ = 523,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,74 (1 H, d, *J*=2,14 Hz), 7,49 (1 H, d, *J*=1,53 Hz), 7,12 - 7,19 (2 H, m), 7,05 (1 H, d, *J*=8,24 Hz), 6,95 - 7,01 (4 H, m), 6,84 (1 H, dd, *J*=8,55, 2,44 Hz), 5,35 (1 H, td, *J*=52,87, 3,17 Hz), 4,07 - 4,17 (2 H, m), 4,04 (1 H, t, *J*=9,61 Hz), 3,80 - 3,94 (2 H, m), 3,58 (3 H, s), 3,25 (1 H, ddd, *J*=14,19, 9,00, 4,58 Hz), 3,05 - 3,14 (1 H, m), 2,55 (1 H, dddd, *J*=13,24, 8,74, 8,55, 4,58 Hz), 2,32 - 2,43 (1 H, m), 2,03 - 2,19 (1 H, m), 1,93 -

2,02 (1 H, m).

Ejemplo 37

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

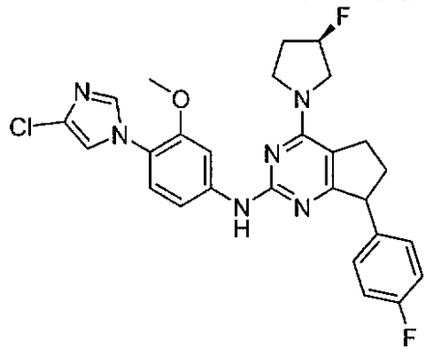


Diastereómero B

Se usó el procedimiento del Ejemplo 36 para combinar la Preparación Hp2 y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) proporcionando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina. CL-EM $(M+H)^+$ = 523,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,76 (1 H, d, *J*=1,83 Hz), 7,48 (1 H, s), 7,16 (2 H, dd, *J*=8,24, 5,49 Hz), 6,97 - 7,06 (4 H, m), 6,92 (1 H, s), 6,80 (1 H, dd, *J*=8,39, 1,98 Hz), 5,27 - 5,42 (1 H, m), 4,00 - 4,17 (3 H, m), 3,80 - 3,94 (2 H, m), 3,53 (3 H, s), 3,19 - 3,26 (1 H, m), 3,08 - 3,17 (1 H, m), 2,52 - 2,61 (1 H, m), 2,32 - 2,43 (1 H, m), 2,02 - 2,18 (1 H, m), 1,94 (1 H, dc, *J*=12,97, 8,60 Hz).

Ejemplo 38

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

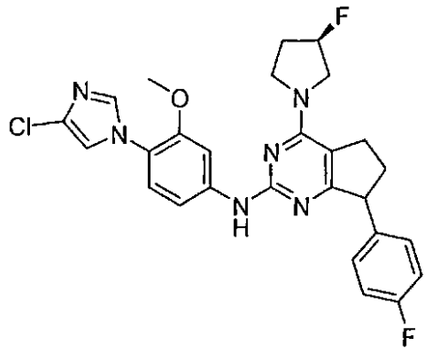


Mezcla diastereomérica

Se usó el procedimiento del Ejemplo 36 para combinar la Preparación Hq y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) proporcionando *N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina* como una mezcla de diastereómeros. *CL-EM* $(M+H)^+$ = 523,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,87 (1 H, s), 7,46 - 7,57 (1 H, m), 7,36 - 7,43 (2 H, m), 7,30 - 7,36 (2 H, m), 7,24 - 7,30 (1 H, m), 7,11 - 7,18 (2 H, m), 5,34 - 5,57 (1 H, m), 4,33 - 4,52 (2 H, m), 4,07 - 4,26 (2 H, m), 3,93 - 4,01 (1 H, m), 3,90 (3 H, s), 3,39 - 3,50 (1 H, m), 3,23 - 3,31 (1 H, m), 2,67 - 2,80 (1 H, m), 2,21 - 2,54 (2 H, m), 2,07 - 2,18 (1 H, m).

Ejemplos 38A y 38B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina)



Diastereómeros individuales

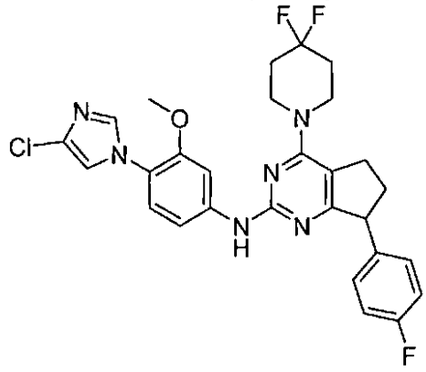
Se usó el procedimiento del Ejemplo 36 para combinar la Preparación Hq y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) proporcionando una mezcla de dos diastereómeros. Después de cromatografía preparativa quiral (MeOH al 25%, DEA al 0,1%; columna OD-H quiral 30 X 250 nm), se aislaron los dos diastereómeros.

38A: CL-EM $(M+H)^+$ = 523,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,84 (1 H, d, *J*=2,14 Hz), 7,68 (1 H, d, *J*=1,53 Hz), 7,19 - 7,24 (3 H, m), 7,16 (1 H, d, *J*=8,55 Hz), 6,99 - 7,09 (3 H, m), 5,29 - 5,45 (1 H, m), 4,05 - 4,17 (3 H, m), 3,80 - 3,99 (2 H, m), 3,64 (3 H, s), 3,13 (1 H, dt, *J*=14,65, 7,32 Hz), 2,51 - 2,61 (1 H, m, *J*=13,12, 8,70, 8,70, 4,58 Hz), 2,28 - 2,38 (1 H, m), 2,09 - 2,27 (1 H, m), 1,98 (1 H, dddd, *J*=13,20, 8,62, 6,87, 6,71 Hz).

38B: CL-EM $(M+H)^+$ = 523,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,86 (1 H, d, *J*=2,14 Hz), 7,67 (1 H, s), 7,18 - 7,24 (3 H, m), 7,15 (1 H, d, *J*=8,55 Hz), 7,00 - 7,07 (3 H, m), 5,29 - 5,45 (1 H, m), 4,03 - 4,18 (3 H, m), 3,80 - 4,00 (2 H, m), 3,60 (3 H, s), 3,23 - 3,31 (1 H, m), 3,13 - 3,21 (1 H, m), 2,52 - 2,61 (1 H, m), 2,28 - 2,39 (1 H, m), 2,07 - 2,26 (1 H, m), 1,88 - 1,99 (1 H, m).

Ejemplo 39

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(4,4-difluoropiperidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

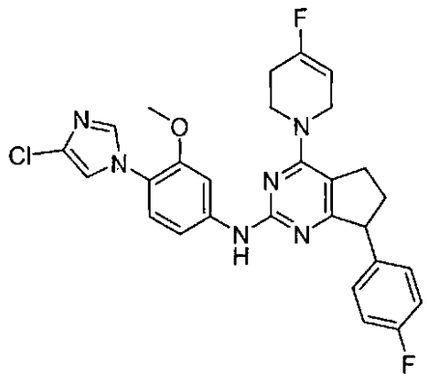


Se usó el procedimiento del Ejemplo 36 para combinar la Preparación Hr y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) proporcionando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(4,4-difluoropiperidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (Ejemplo 39). CL-EM $(M+H)^+$ = 555,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,68 (1 H, d, *J*=1,83 Hz), 7,55 - 7,59 (2 H, m), 7,18 (2 H, dd, *J*=8,55, 5,49 Hz), 7,07 - 7,13 (2 H, m), 6,95 - 7,03 (3 H, m), 4,16 (1 H, t, *J*=8,39 Hz), 3,90 (4 H, t, *J*=5,34 Hz), 3,57 (3 H, s), 2,97 - 3,13 (2 H, m), 2,56 - 2,66 (1 H, m, *J*=12,78, 8,49, 8,49, 3,81 Hz), 1,95 - 2,14 (5 H, m).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 39A y 39B, que tuvieron idénticos datos espectrales.

Ejemplo 40

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(4-fluoro-5,6-dihidropiridin-1(2H)-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

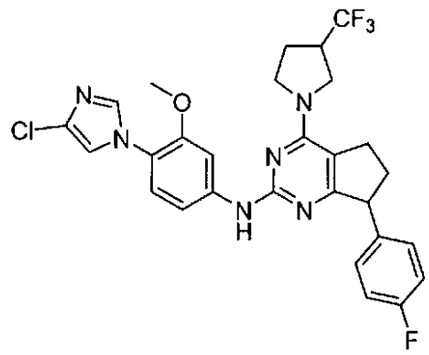


Se usó el procedimiento del Ejemplo 36 para combinar la Preparación Hs y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) proporcionando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(4-fluoro-5,6-dihidropiridin-1(2H)-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (Ejemplo 40). CL-EM $(M+H)^+$ = 535,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,72 (1 H, d, *J*=1,83 Hz), 7,49 (1 H, d, *J*=1,53 Hz), 7,13 - 7,19 (2 H, m), 7,05 (1 H, d, *J*=8,55 Hz), 6,97 - 7,02 (3 H, m), 6,95 (1 H, s), 6,77 (1 H, dd, *J*=8,55, 2,14 Hz), 5,31 (1 H, dt, *J*=14,80, 2,80 Hz), 4,18 - 4,33 (2 H, m), 4,15 (1 H, t, *J*=8,55 Hz), 3,99 - 4,06 (1 H, m), 3,80 - 3,88 (1 H, m), 3,51 (3 H, s), 2,98 - 3,12 (2 H, m), 2,58 (1 H, dddd, *J*=12,63, 8,55, 8,43, 3,66 Hz), 2,37 - 2,53 (2 H, m), 1,99 (1 H, dc, *J*=12,86, 8,33 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 40A y 40B, que tuvieron idénticos datos espectrales.

Ejemplo 41

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(3-(trifluorometil)pirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Se usó el procedimiento del Ejemplo 36 para combinar la Preparación Ht y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) proporcionando *N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(3-(trifluorometil)pirrolidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina* (Ejemplo 41).

La mezcla de una pareja de diastereómeros racémicos se separó por cromatografía quiral seguido por cromatografía de fase inversa proporcionando los enantiómeros individuales Ejemplos 41A, 41B, 41C, y 41D.

41A: CL-EM $(M+H)^+$ = 573,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,84 (1 H, d, *J*=1,53 Hz), 7,49 (1 H, s), 7,15 (2 H, dd, *J*=8,39, 5,34 Hz), 7,04 (1 H, d, *J*=8,24 Hz), 6,95 - 7,02 (4 H, m), 6,72 (1 H, dd, *J*=8,39, 1,98 Hz), 4,11 (1 H, t, *J*=8,39 Hz), 3,94 - 4,08 (2 H, m), 3,78 - 3,91 (2 H, m), 3,56 (3 H, s), 3,18 - 3,27 (1 H, m), 2,97 - 3,14 (2 H, m), 2,50 - 2,62 (1 H, m, *J*=12,86, 8,60, 8,60, 4,12 Hz), 2,17 - 2,34 (2 H, m), 1,91 - 2,02 (1 H, m).

41B: CL-EM $(M+H)^+$ = 573,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,84 (1 H, s ancho), 7,48 (1 H, d, *J*=1,53 Hz), 7,11 - 7,22 (2 H, m), 6,95 - 7,09 (5 H, m), 6,69 - 6,78 (1 H, m), 4,12 (1 H, t, *J*=8,55 Hz), 3,95 - 4,08 (2 H, m), 3,77 - 3,92 (2 H, m), 3,55 (3 H, s), 3,21 (1 H, ddd, *J*=14,11, 8,93, 3,51 Hz), 2,98 - 3,16

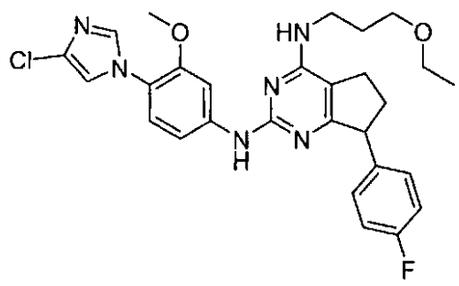
(2 H, m), 2,51 - 2,65 (1 H, m), 2,16 - 2,35 (2 H, m), 1,90 - 2,04 (1 H, m).

41C: CL-EM $(M+H)^+$ = 573,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,84 (1 H, s ancho), 7,48 (1 H, d, *J*=1,53 Hz), 7,11 - 7,22 (2 H, m), 6,95 - 7,09 (5 H, m), 6,69 - 6,78 (1 H, m), 4,12 (1 H, t, *J*=8,55 Hz), 3,95 - 4,08 (2 H, m), 3,77 - 3,92 (2 H, m), 3,55 (3 H, s), 3,21 (1 H, ddd, *J*=14,11, 8,93, 3,51 Hz), 2,98 - 3,16 (2 H, m), 2,51 - 2,65 (1 H, m), 2,16 - 2,35 (2 H, m), 1,90 - 2,04 (1 H, m).

41D: CL-EM $(M+H)^+$ = 573,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,84 (1 H, d, *J*=1,53 Hz), 7,49 (1 H, s), 7,15 (2 H, dd, *J*=8,39, 5,34 Hz), 7,04 (1 H, d, *J*=8,24 Hz), 6,95 - 7,02 (4 H, m), 6,72 (1 H, dd, *J*=8,39, 1,98 Hz), 4,11 (1 H, t, *J*=8,39 Hz), 3,94 - 4,08 (2 H, m), 3,78 - 3,91 (2 H, m), 3,56 (3 H, s), 3,18 - 3,27 (1 H, m), 2,97 - 3,14 (2 H, m), 2,50 - 2,62 (1 H, m, *J*=12,86, 8,60, 8,60, 4,12 Hz), 2,17 - 2,34 (2 H, m), 1,91 - 2,02 (1 H, m).

Ejemplo 42

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-(3-etoxipropil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

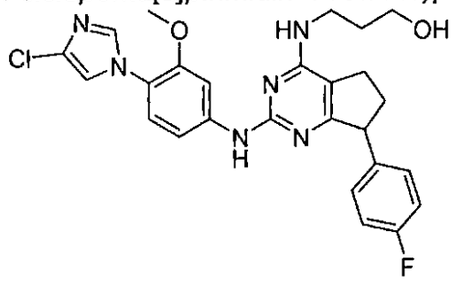


Se usó el procedimiento del Ejemplo 36 para combinar la Preparación Hu y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) proporcionando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-(3-

etoxipropil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (Ejemplo 42). CL-EM $(M+H)^+$ = 537,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,91 (1 H, d, *J*=2,14 Hz), 7,48 (1 H, d, *J*=1,53 Hz), 7,12 - 7,19 (2 H, m), 7,03 (1 H, d, *J*=8,55 Hz), 6,94 - 7,01 (4 H, m), 6,74 (1 H, dd, *J*=8,55, 2,14 Hz), 5,45 (1 H, t, *J*=4,73 Hz), 4,14 - 4,21 (1 H, m), 3,61 - 3,71 (4 H, m), 3,46 - 3,57 (5 H, m), 2,63 (2 H, dd, *J*=8,85, 6,41 Hz), 1,96 - 2,05 (1 H, m), 1,93 (2 H, quintuplete, *J*=5,72 Hz), 1,25 (3 H, t, *J*=7,02 Hz).

Ejemplo 43

3-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-ilamino)propan-1-ol



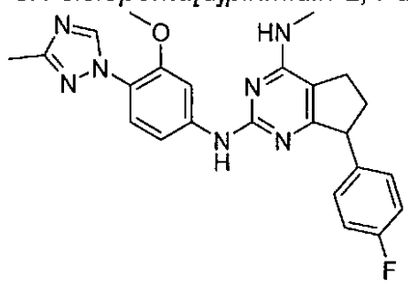
Se usó el procedimiento del Ejemplo 36 para combinar la Preparación Hv y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) proporcionando 3-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-ilamino)propan-1-ol (Ejemplo 43). CL-EM $(M+H)^+$ = 509,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,87 (1 H, d, *J*=2,14 Hz), 7,68 (1 H, d, *J*=1,53 Hz), 7,19 - 7,26 (3 H, m), 7,16 (1 H, d, *J*=8,55 Hz), 7,01 - 7,09 (3 H, m), 4,19 (1 H, t, *J*=8,09 Hz), 3,64 - 3,72 (4 H, m), 3,61 (3 H, s), 2,77 - 2,86 (1 H, m), 2,60 - 2,74 (2 H, m), 1,96 - 2,06 (1 H, m), 1,90 (2 H, cd, *J*=6,46, 6,26 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando

los enantiómeros Ejemplo 43A y 43B, que tuvieron idénticos datos espectrales.

Ejemplo 44

7-(4-fluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



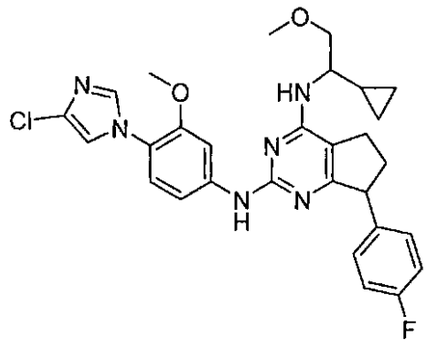
A una solución de 2-cloro-7-(4-fluorofenil)-N-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (Preparación Hh) (141,2 mg, 0,508 mmol) y 3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)anilina (Preparación D) (208 mg, 1,017 mmol) en N-Metil-2-pirrolidinona (4067 µl) se añadió H_2SO_4 (43,4 µl, 0,813 mmol). La solución se calentó hasta 100 °C. Cuando se completó la reacción, se añadieron agua y $NaHCO_3$. Después de extracción en CH_2Cl_2, los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron a vacío. El residuo se aplicó a gel de sílice y eluyó con un gradiente de EtOAc/Hex, que proporcionó 7-(4-fluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (Ejemplo 44). CL-EM $(M+H)^+$ = 446,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 9,43 (1 H, s ancho), 8,47 (1 H, s), 7,77 (1 H, s ancho), 7,54 (1 H, d, *J*=8,85 Hz), 7,14 - 7,20 (2 H, m), 6,99 (2 H, t, *J*=8,55 Hz), 4,88 (1 H, s ancho), 4,24 - 4,31 (1 H, m), 3,71 (3 H, s), 3,15 (3 H, d, *J*=4,90 Hz), 2,73 - 2,82 (1 H, m), 2,63 - 2,72 (2 H, m), 2,46 (3 H, s), 2,06 - 2,16 (1 H, m).

El material racémico se separó por cromatografía quiral SFC obteniendo los enantiómeros individuales (Ejemplos 44A y 44B). Procedimiento SFC: Chiralpak OJ-H (30 x 150 mm), metanol al 30 % (dietilamina al 0,1%) en CO_2, 100 x 10^5 Pa, caudal 50 ml/min durante 12 min, absorbancia 268 nm, inyección de 2,0 ml de solución de 10 mg/ml en metanol, t_R (pico A) = 4,7 min, t_R (pico B) 9,6 min. No se determinó la estereoquímica absoluta de los enantiómeros individuales (Ejemplos 44A y 44B).

44A: CL-EM $(M+H)^+$ = 446,2. CL t_R 13,03 min (Waters Sunfire 4,6X150 mm 10 hasta 100% de B en A durante 15 min, 1,5 ml/min. (A es agua:MeOH:TFA 90:10:0,1 ; B es MeOH:agua:TFA 90:10:0,1)). RMN de ^1H (500 MHz, DMSO-d_6) δ ppm 9,22 (1 H, s), 8,58 (1 H, s), 8,18 (1 H, s), 7,30 (1 H, d, J=8,85 Hz), 7,22 (2 H, t, J=6,26 Hz), 7,08 - 7,16 (3 H, m), 6,93 - 6,99 (1 H, m), 4,17 (1 H, t, J=8,09 Hz), 3,63 (3 H, s), 2,97 (3 H, d, J=4,27 Hz), 2,72 - 2,81 (1 H, m), 2,53 - 2,66 (2 H, m), 2,31 (3 H, s), 1,85 - 1,95 (1 H, m). RMN de ^{13}C (126 MHz, DMSO-d_6) δ ppm 170,7, 160,7 (d, J = 241,3 Hz), 159,7, 159,6, 159,2, 151,4, 145,0, 142,9, 140,4 (d, J = 2,7 Hz), 129,8 (d, J = 7,8 Hz, 2C), 124,6, 117,9, 114,9 (d, J = 20,9 Hz, 2C), 109,6, 108,1, 101,5, 55,2, 50,4, 32,7, 27,4, 25,4, 13,5. $[\alpha]_D$ -69,13° (c 2,67, $CHCl_3$).

Ejemplo 45

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-(1-ciclopropil-2-metoxietil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



El procedimiento del Ejemplo 7 se usó para combinar la Preparación Hw y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) proporcionando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-(1-ciclopropil-2-metoxietil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (Ejemplo 45). La mezcla de una pareja de diastereómeros racémicos se separó por cromatografía quiral seguido por cromatografía de fase inversa proporcionando los enantiómeros individuales Ejemplos 45A, 45B, 45C, y 45D.

45A: CL-EM $(M+H)^+$ = 549,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 10,75 (1 H, s ancho), 7,40 (1 H, d, *J*=8,24 Hz), 7,22 - 7,29 (3 H, m), 7,15 - 7,21 (3 H, m), 6,99 - 7,08 (2 H, m), 5,97 (1 H, d, *J*=8,24 Hz), 4,42 - 4,50 (1 H, m), 3,84 (3 H, s), 3,78 (1 H, t, *J*=8,09 Hz), 3,63 (2 H, s ancho), 3,43 (3 H, s), 2,86 - 2,97 (1 H, m), 2,82 (2 H, t, *J*=8,55 Hz), 2,21 - 2,32 (1 H, m), 1,15 - 1,27 (1 H, m), 0,62 - 0,70 (1 H, m), 0,53 - 0,62 (1 H, m), 0,39 (1 H, ddd, *J*=9,46, 5,19, 4,88 Hz), 0,26 - 0,33 (1 H, m)

45B: CL-EM $(M+H)^+$ = 549,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 10,58 (1 H, s ancho), 7,40 (1 H, d, *J*=8,85 Hz), 7,22 - 7,29 (3 H, m), 7,14 - 7,20 (3 H, m), 7,04 (2 H, t, *J*=8,39 Hz), 6,02 (1 H, d, *J*=8,24 Hz), 4,45 (1 H, d, *J*=3,66 Hz), 3,84 (3 H, s), 3,71 - 3,79 (1 H, m), 3,63 (2 H, d, *J*=3,05 Hz), 3,42 (3 H, s), 2,91

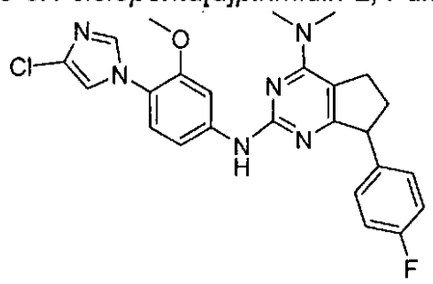
(1 H, d, *J*=9,46 Hz), 2,79 (2 H, dd, *J*=8,70, 5,34 Hz), 2,21 - 2,31 (1 H, m), 1,19 (1 H, dt, *J*=8,55, 4,27 Hz), 0,62 - 0,70 (1 H, m), 0,54 - 0,62 (1 H, m), 0,39 (1 H, dc, *J*=9,54, 4,86 Hz), 0,24 - 0,33 (1 H, m).

45C: CL-EM $(M+H)^+$ = 549,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 10,75 (1 H, s ancho), 7,40 (1 H, d, *J*=8,24 Hz), 7,22 - 7,29 (3 H, m), 7,15 - 7,21 (3 H, m), 6,99 - 7,08 (2 H, m), 5,97 (1 H, d, *J*=8,24 Hz), 4,42 - 4,50 (1 H, m), 3,84 (3 H, s), 3,78 (1 H, t, *J*=8,09 Hz), 3,63 (2 H, s ancho), 3,43 (3 H, s), 2,86 - 2,97 (1 H, m), 2,82 (2 H, t, *J*=8,55 Hz), 2,21 - 2,32 (1 H, m), 1,15 - 1,27 (1 H, m), 0,62 - 0,70 (1 H, m), 0,53 - 0,62 (1 H, m), 0,39 (1 H, ddd, *J*=9,46, 5,19, 4,88 Hz), 0,26 - 0,33 (1 H, m).

45D: CL-EM $(M+H)^+$ = 549,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 10,58 (1 H, s ancho), 7,40 (1 H, d, *J*=8,85 Hz), 7,22 - 7,29 (3 H, m), 7,14 - 7,20 (3 H, m), 7,04 (2 H, t, *J*=8,39 Hz), 6,02 (1 H, d, *J*=8,24 Hz), 4,45 (1 H, d, *J*=3,66 Hz), 3,84 (3 H, s), 3,71 - 3,79 (1 H, m), 3,63 (2 H, d, *J*=3,05 Hz), 3,42 (3 H, s), 2,91 (1 H, d, *J*=9,46 Hz), 2,79 (2 H, dd, *J*=8,70, 5,34 Hz), 2,21 - 2,31 (1 H, m), 1,19 (1 H, dt, *J*=8,55, 4,27 Hz), 0,62 - 0,70 (1 H, m), 0,54 - 0,62 (1 H, m), 0,39 (1 H, dc, *J*=9,54, 4,86 Hz), 0,24 - 0,33 (1 H, m).

Ejemplo 46

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



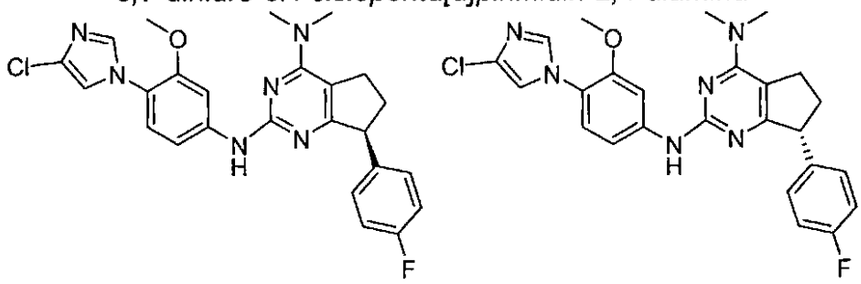
Se añadió 2-cloro-7-(4-fluorofenil)-*N*,*N*-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (268 mg, 0,919 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (205 mg, 0,919 mmol) en THF (1 ml) y ácido acético (1,000 ml). La mezcla de reacción se agitó durante la noche a 75ºC. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4,N^4-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (60,7 mg, 0,095 mmol, 10,36 % de rendimiento). CL-EM $(M+H)^+$ = 479,4. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,64 - 11,83 (1H, m), 7,62 (1H, d, *J*=1,5 Hz), 7,39 (2H, d, *J*=2,1 Hz), 7,22 (1H, d, *J*=5,2 Hz), 7,15 (1H, d, *J*=8,5 Hz), 6,96 - 7,07 (3H, m), 5,29 (1H, s), 4,29 - 4,38 (1H, m), 3,81 (3H, s), 3,50 - 3,57 (1H, m), 3,43 - 3,49 (1H, m), 3,31 - 3,39 (3H, m), 3,16 - 3,26 (2H, m), 3,09 - 3,14 (1H, m), 2,58 - 2,72 (1H, m), 2,52 - 2,58 (1H, m), 2,13 - 2,25 (1H, m).

Ejemplo 46A & 46B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

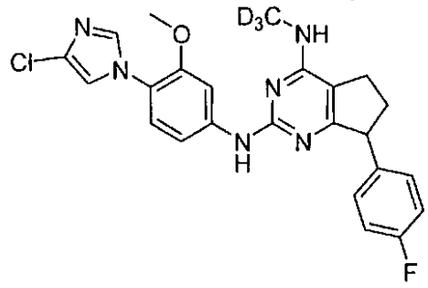
(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4,N^4-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (*Ejemplo 46*) usando SFC quiral proporcionando el pico A (*Ejemplo 46A*) y el pico B (*Ejemplo 46B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 μM), metanol al 35% (dietilamina al 0,1%) en CO_2, 35ºC, caudal 2,0 ml/min durante 14 min, absorbancia 268 nm, inyección de 5μl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 4,3 min, t_R (pico B) 10,8 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 46A y 46B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 46*).

Ejemplo 47

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-trideuterometil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

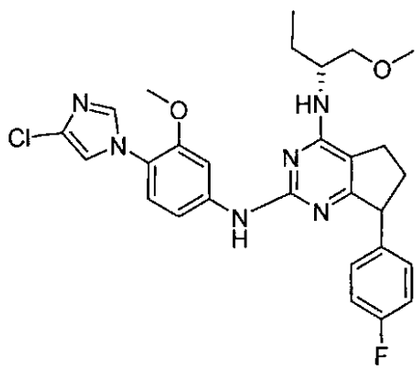


Se calentó a 85ºC durante la noche una solución de 2-Cloro-7-(4-fluorofenil)-*N*-trideuterometil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (47,5 mg, 0,169 mmol) y 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (37,8 mg, 0,169 mmol) en THF (1 ml) y ácido acético (1 ml). El producto se purificó por un procedimiento de HPLC preparativa de fase inversa dando N^2-(4-(4-cloro-1*H*-

imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-trideuterometil-6,7-dihidro-*5H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (33,3 mg, 0,057 mmol, 33,8 % de rendimiento) como aceite marrón. CL-EM $(M+H)^+$ = 467,9. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,21 (1H, s), 8,35 - 9,96 (1H, m), 8,20 (1H, s), 7,51 (1H, s), 7,43 (1H, d, *J*=8,5 Hz), 7,25 (1H, s), 7,22 (1H, d, *J*=8,9 Hz), 7,14 - 7,20 (2H, m), 7,01 (1H, t, *J*=8,5 Hz), 5,98 (1H, s), 4,43 (1H, d, *J*=4,6 Hz), 3,85 (3H, s), 2,88 (1H, d, *J*=9,5 Hz), 2,69 - 2,83 (2H, m), 2,20 - 2,32 (1H, m).

Ejemplo 48

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N4-((R)-1-metoxibutan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina, 2 TFA



Mezcla diastereomérica

Se hizo reaccionar 2-cloro-7-(4-fluorofenil)-N-((R)-1-metoxibutan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (Preparación Hx) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N4-((R)-1-metoxibutan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina, 2 TFA como una mezcla de dos diastereómeros (Ejemplo 48). CL-EM

$(M+H)^+$ = 537,5. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,66 (s ancho, 1 H) 7,99 (s, 1 H) 7,51 (d, J=8,85 Hz, 1 H) 7,32 (dd, J=8,85, 1,83 Hz, 1 H) 7,18 - 7,30 (m, 4 H) 7,04 (td, J=8,62, 1,68 Hz, 2 H) 5,83 (t, J=9,61 Hz, 1 H) 4,43 - 4,51 (m, 1 H) 4,28 - 4,39 (m, 1 H) 3,87 (s, 3 H) 3,51 - 3,64 (m, 2 H) 3,38 - 3,49 (m, 3 H) 2,87 - 3,00 (m, 1 H) 2,75 - 2,85 (m, 2 H) 2,24 - 2,35 (m, 1 H) 1,69 - 1,87 (m, 2 H) 0,97 - 1,06 (m, 3 H).

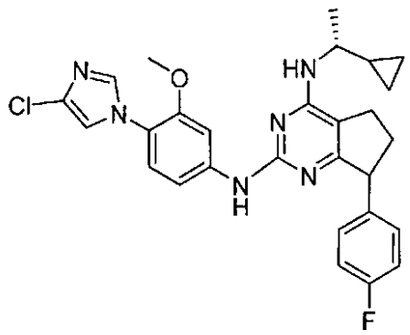
La mezcla de dos diastereómeros se separó por cromatografía quiral proporcionando dos diastereómeros Ejemplo 48A y 48B como aminas libres.

Ejemplo 48A: CL-EM $(M+H)^+$ = 537,4. RMN de ^1H (500 MHz, MeOD) δ ppm 7,86 (d, J=2,14 Hz, 1 H) 7,66 (d, J=1,53 Hz, 1 H) 7,16 - 7,25 (m, 3 H) 7,10 - 7,16 (m, 1 H) 6,99 - 7,07 (m, 3 H) 4,45 - 4,53 (m, 1 H) 4,17 (t, J=8,24 Hz, 1 H) 3,61 (s, 3 H) 3,56 (dd, J=9,46, 5,80 Hz, 1 H) 3,44 - 3,51 (m, 1 H) 3,37 (d, J=7,02 Hz, 3 H) 2,76 - 2,86 (m, 1 H) 2,59 - 2,75 (m, 2 H) 1,94 - 2,04 (m, 1 H) 1,73 - 1,85 (m, 1 H) 1,54 - 1,66 (m, 1 H) 0,99 (t, J=7,48 Hz, 3 H).

Ejemplo 48B: CL-EM $(M+H)^+$ = 537,4. RMN de ^1H (500 MHz, MeOD) δ ppm 7,86 (d, J=2,14 Hz, 1 H) 7,67 (d, J=1,53 Hz, 1 H) 7,18 - 7,26 (m, 3 H) 7,11 - 7,16 (m, 1 H) 6,97 - 7,08 (m, 3 H) 4,44 - 4,53 (m, 1 H) 4,17 (t, J=8,09 Hz, 1 H) 3,61 (s, 3 H) 3,55 (dd, J=9,46, 5,49 Hz, 1 H) 3,46 (dd, J=9,61, 5,65 Hz, 1 H) 3,35 - 3,41 (m, 3 H) 2,77 - 2,87 (m, 1 H) 2,67 - 2,76 (m, 1 H) 2,64 (ddd, J=12,44, 8,62, 3,66 Hz, 1 H) 1,93 - 2,07 (m, 1 H) 1,80 (ddd, J=13,50, 7,71, 5,34 Hz, 1 H) 1,56 - 1,68 (m, 1 H) 1,01 (t, J=7,48 Hz, 3 H).

Ejemplo 49

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-((R)-1-ciclopropiletil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina, 2 TFA



Mezcla diastereomérica

Se hizo reaccionar 2-cloro-N-((R)-1-ciclopropiletil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (Preparación Hy) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-((R)-1-ciclopropiletil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina, 2 TFA como una mezcla de dos diastereómeros (Ejemplo 49). CL-EM $(M+H)^+$ = 519,5. ^{1}H RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 11,81 (s, 1 H) 7,85 (s, 1 H) 7,38 - 7,48 (m, 2 H) 7,28 (s, 1 H) 7,26 (ddd, J=8,77, 5,11, 1,98 Hz, 1 H) 7,12 (d, J=1,22 Hz, 1 H) 7,04 (td, J=8,62, 1,68 Hz, 2 H) 5,65 (t, J=7,02 Hz, 1 H) 4,41 - 4,52 (m, 1 H) 3,73 - 3,88 (m, 4 H) 2,88 - 3,01 (m, 1 H) 2,71 - 2,88 (m, 2 H) 2,25 - 2,39 (m, 1 H) 1,40 (dd, J=6,56, 4,12 Hz, 3 H) 0,99 - 1,14 (m, 1 H) 0,65 - 0,75 (m, 1 H) 0,53 - 0,64 (m, 1 H) 0,39 (tt, J=9,80, 5,00 Hz, 1 H) 0,27 - 0,35 (m, 1 H).

La mezcla de dos diastereómeros se separó por cromatografía quiral proporcionando dos diastereómeros Ejemplo 49A y 49B como aminas libres.

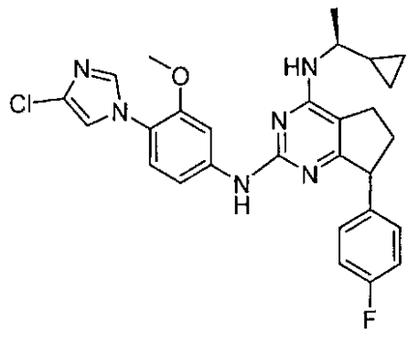
Ejemplo 49A: CL-EM $(M+H)^+$ = 519,3. RMN de ^{1}H (500 MHz, MeOD) δ

ppm 7,87 (d, J=2,14 Hz, 1 H) 7,66 (d, J=1,53 Hz, 1 H) 7,17 - 7,28 (m, 3 H) 7,08 - 7,17 (m, 1 H) 6,90 - 7,08 (m, 3 H) 4,15 (t, J=8,24 Hz, 1 H) 3,78 - 3,92 (m, 1 H) 3,59 (s, 3 H) 2,75 - 2,85 (m, 1 H) 2,59 - 2,74 (m, 2 H) 1,33 (d, J=6,71 Hz, 3 H) 1,00 - 1,14 (m, 1 H) 0,82 - 1,00 (m, 1 H) 0,39 - 0,59 (m, 3 H) 0,26 (dt, J=9,38, 4,62 Hz, 1 H).

Ejemplo 49B: CL-EM $(M+H)^+$ = 519,3. RMN de ^1H (500 MHz, MeOD) δ ppm 7,87 (d, J=2,14 Hz, 1 H) 7,66 (d, J=1,53 Hz, 1 H) 7,15 - 7,25 (m, 3 H) 7,13 (d, J=8,55 Hz, 1 H) 7,02 (t, J=8,85 Hz, 2 H) 6,98 (dd, J=8,55, 2,14 Hz, 1 H) 4,16 (t, J=8,09 Hz, 1 H) 3,82 - 3,98 (m, 1 H) 3,60 (s, 3 H) 2,78 - 2,87 (m, 1 H) 2,55 - 2,75 (m, 2 H) 1,91 - 2,04 (m, 1 H) 1,35 (d, J=6,71 Hz, 3 H) 0,79 - 0,98 (m, 1 H) 0,55 (td, J=8,70, 4,27 Hz, 1 H) 0,45 - 0,51 (m, 1 H) 0,32 - 0,43 (m, J=9,65, 5,04, 4,86, 4,86 Hz, 1 H) 0,16 - 0,29 (m, 1 H).

Ejemplo 50

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-((S)-1-ciclopropiletil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina, TFA



Mezcla diastereomérica

Se hizo reaccionar 2-cloro-N-((S)-1-ciclopropiletil)-7-(4-fluorofenil)-6,7-

dihidro-5H-ciclopenta[d]pirimidin-4-amina (Preparación Hz) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-((S)-1-ciclopropiletil)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina, TFA como una mezcla de dos diastereómeros (Ejemplo 50). CL-EM $(M+H)^+$ = 519,5. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,84 (s, 1 H) 7,80 (s, 1 H) 7,43 (s, 1 H) 7,41 (d, J=8,85 Hz, 1 H) 7,28 (s, 1 H) 7,26 (ddd, J=8,70, 5,19, 1,98 Hz, 1 H) 7,19 (d, J=8,55 Hz, 1 H) 7,11 (s, 1 H) 7,04 (td, J=8,62, 1,68 Hz, 2 H) 5,66 (t, J=6,87 Hz, 1 H) 4,40 - 4,52 (m, 1 H) 3,72 - 3,87 (m, 4 H) 2,87 - 3,07 (m, 1 H) 2,67 - 2,86 (m, 2 H) 2,26 - 2,40 (m, 1 H) 1,40 (dd, J=6,56, 4,12 Hz, 3 H) 1,03 - 1,15 (m, 1 H) 0,56 - 0,76 (m, 2 H) 0,29 - 0,49 (m, 2 H).

La mezcla de dos diastereómeros se separó por cromatografía quiral proporcionando dos diastereómeros Ejemplo 50A y 50B como aminas libres.

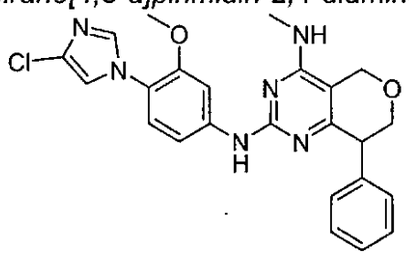
Ejemplo 50A: CL-EM $(M+H)^+$ = 519,3. RMN de ^1H (500 MHz, MeOD) δ ppm 7,88 (d, J=2,14 Hz, 1 H) 7,67 (d, J=1,53 Hz, 1 H) 7,17 - 7,24 (m, 3 H) 7,14 (d, J=8,55 Hz, 1 H) 6,90 - 7,08 (m, 3 H) 4,18 (t, J=8,09 Hz, 1 H) 3,88 (dd, J=8,09, 6,56 Hz, 1 H) 3,61 (s, 3 H) 2,77 - 2,89 (m, 1 H) 2,58 - 2,77 (m, 2 H) 1,90 - 2,05 (m, 1 H) 1,35 (d, J=6,71 Hz, 3 H) 1,07 (dt, J=8,24, 4,88 Hz, 1 H) 0,51 - 0,57 (m, 1 H) 0,44 - 0,51 (m, 1 H) 0,40 (dd, J=9,61, 4,73 Hz, 1 H) 0,17 - 0,29 (m, 1 H).

Ejemplo 50B: CL-EM $(M+H)^+$ = 519,3. RMN de ^1H (500 MHz, MeOD) δ ppm 7,87 (d, J=1,83 Hz, 1 H) 7,67 (s, 1 H) 7,20 - 7,27 (m, 3 H) 7,14 (d, J=8,55 Hz, 1 H) 6,93 - 7,08 (m, 3 H) 4,17 (t, J=8,24 Hz, 1 H) 3,75 - 3,93 (m, 1 H) 3,61 (s, 3 H) 2,76 - 2,88 (m, 1 H) 2,54 - 2,73 (m, 2 H) 1,89 - 2,08 (m, 1 H) 1,34 (d, J=6,71 Hz, 3 H) 0,99 - 1,12 (m, 1 H) 0,54 - 0,63 (m, 1 H) 0,46 - 0,54 (m, 1 H)

0,43 (dd, J=9,61, 4,73 Hz, 1 H) 0,18 - 0,28 (m, 1 H).

Ejemplo 51

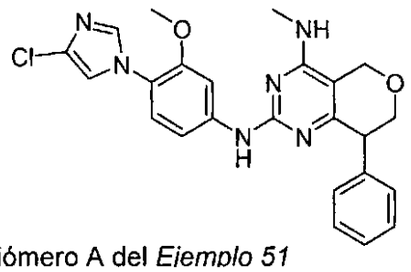
N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



Se combinaron 2-cloro-N-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (*Preparación Ia*) (125 mg, 0,453 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (101 mg, 0,453 mmol) y se purificó según el *Ejemplo 26* dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (178 mg, 0,309 mmol, 68,1 % de rendimiento) como vidrio fragmentado ligeramente amarillo. CL-EM $(M+H)^+$ = 463,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,81 (1 H, s), 7,62 (1 H, s), 7,32 - 7,47 (7 H, m), 7,14 (1 H, dd, *J*=8,55, 2,14 Hz), 4,54 - 4,72 (2 H, m), 4,19 (1 H, dd, *J*=11,44, 4,73 Hz), 4,10 (1 H, t, *J*=4,43 Hz), 3,94 (1 H, dd, *J*=11,44, 4,73 Hz), 3,86 (3 H, s), 3,15 - 3,19 (3 H, m).

Ejemplo 51A

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

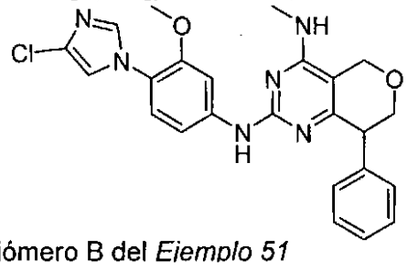


Enantiómero A del *Ejemplo 51*

Se separó N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina *Ejemplo 51* mediante varias inyecciones de HPLC preparativa quiral (OJ-H 30 x 250mm, 10μM, EtOH/Heptano) dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (primero en eluir, enantiómero A) (36,5 mg, 0,063 mmol) como un sólido amarillo. CL-EM $(M+H)^+$ = 463,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,83 (1 H, s ancho), 7,70 (1 H, s ancho), 7,35 (2 H, t, *J*=7,32 Hz), 7,24 - 7,33 (4 H, m), 7,21 (1 H, d, *J*=8,55 Hz), 6,97 - 7,05 (1 H, m), 4,52 - 4,71 (2 H, m), 4,16 (1 H, dd, *J*=11,44, 4,73 Hz), 3,98 (1 H, s ancho), 3,87 - 3,96 (1 H, m), 3,61 (3 H, s ancho), 3,06 - 3,14 (3 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 51A*.

Ejemplo 51B

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



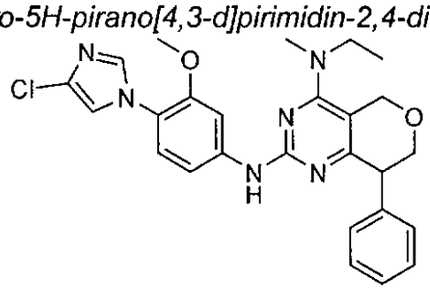
Enantiómero B del *Ejemplo 51*

Se separó N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-8-fenil-

7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina *Ejemplo 51* mediante varias inyecciones de HPLC preparativa quiral (OJ-H 30 x 250mm, 10μM, EtOH/Heptano) dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (segundo en eluir, enantiómero B) (30,9 mg, 0,054 mmol) como un sólido amarillo. CL-EM $(M+H)^+$ = 463,2. RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 7,74 (2 H, s ancho), 7,24 - 7,48 (7 H, m), 7,01 - 7,13 (1 H, m), 4,52 - 4,73 (2 H, m), 4,17 (1 H, dd, *J*=11,44, 4,73 Hz), 4,00 - 4,11 (1 H, m), 3,88 - 4,00 (1 H, m), 3,71 (3 H, s ancho), 3,12 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 51B*.

Ejemplo 52

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



A una solución de 2-cloro-*N*-etil-*N*-metil-8-fenil-7,8-dihidro-5*H*-pirano[4,3-*d*]pirimidin-4-amina (146 mg, 0,481 mmol) y 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (107 mg, 0,481 mmol) en THF (1,0 ml) y ácido acético (1,0 ml). La mezcla de reacción se agitó durante la noche a 75°C. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-8-fenil-7,8-dihidro-5*H*-pirano[4,3-*d*]pirimidin-2,4-diamina, sal TFA (59,9 mg, 0,092 mmol, 93 % de rendimiento). CL-EM $(M+H)^+$ = 491,4. RMN de

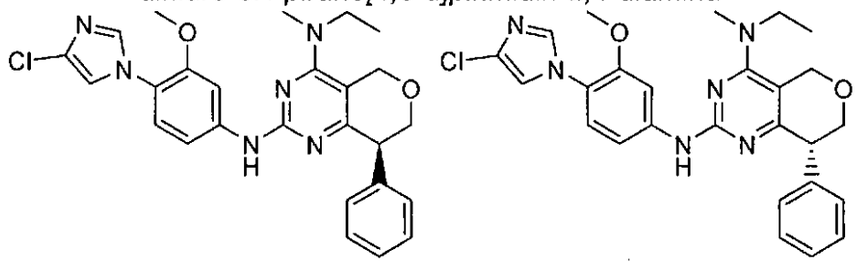
^{1}H (500 MHz, $CDCl_3$) δ ppm 11,77 (1H, s), 7,67 (1H, d, *J*=1,5 Hz), 7,39 (1H, dd, *J*=8,5, 2,1 Hz), 7,26 - 7,35 (5H, m), 7,16 (1H, s), 7,14 (1H, s), 7,06 (1H, d, *J*=1,5 Hz), 4,75 - 4,90 (2H, m), 4,14 - 4,23 (2H, m), 3,90 (1H, d, *J*=7,0 Hz), 3,81 (3H, s), 3,62 (2H, s), 3,27 (3H, s), 1,34 (3H, t, *J*=7,2 Hz).

Ejemplos 52A y 52B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

y

(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

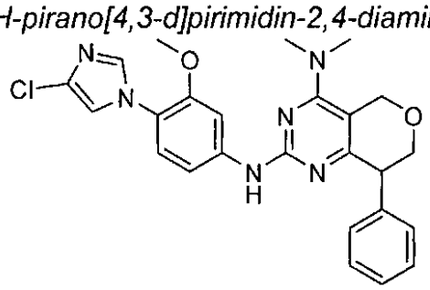


Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N^4,N^4-dimetil-5,6,7,8-tetrahidroquinazolina-2,4-diamina (55,0 mg, 0,112 mmol) (*Ejemplo 52*) usando SFC quiral proporcionando el pico A (17,2 mg, 0,035 mmol) (*Ejemplo 52A*) y el pico B (18,8 mg, 0,038 mmol) (*Ejemplo 52B*). Procedimiento de SFC: Chiralpak OJ-H (30 x 250 mm, 5 μM), metanol al 35% (dietilamina al 0,1%) en CO_2, 35°C, caudal 70 ml/min durante 13 min, absorbancia 268 nm, inyección de 5μl de solución 27 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 4,2 min, t_R (pico B) 8,3 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 52A y 52B*). Los datos analíticos de CL-

EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 52*).

Ejemplo 53

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



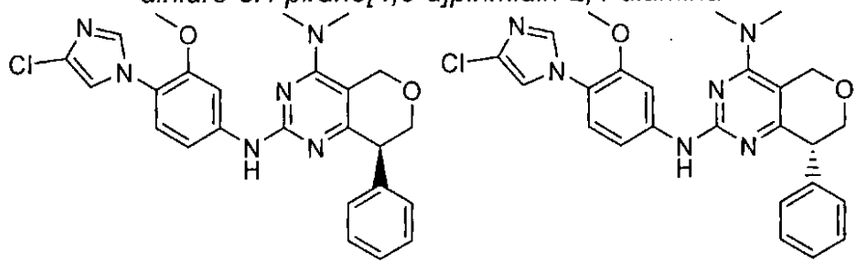
A una solución de 2-cloro-*N*,*N*-dimetil-8-fenil-7,8-dihidro-5*H*-pirano[4,3-*d*]pirimidin-4-amina (135 mg, 0,466 mmol) y 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (104 mg, 0,466 mmol) en THF (1,0 ml) y ácido acético (1,0 ml). La mezcla de reacción se agitó durante la noche a 75°C. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-8-fenil-7,8-dihidro-5*H*-pirano[4,3-*d*]pirimidin-2,4-diamina, sal TFA (80,1 mg, 0,130 mmol, 96 % de rendimiento). CL-EM $(M+H)^+$ = 477,3. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 11,74 (1H, s), 7,74 (1H, d, *J*=1,5 Hz), 7,36 (1H, s), 7,34 - 7,26 (6H, m), 7,15 (1H, d, *J*=8,2 Hz), 7,07 (1H, d, *J*=1,5 Hz), 4,83 (1H, m), 4,13 - 4,21 (1H, m), 3,81 (3H, s), 3,47 (3H, s), 3,32 (6H, s).

Ejemplos 53A y 53B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

y

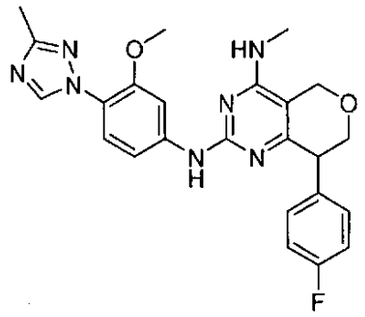
(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



Se purificó una mezcla racémica de N^2-(4-(4-Cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-8-fenil-7,8-dihidro-5*H*-pirano[4,3-*d*]pirimidin-2,4-diamina (80,1 mg, 0,130 mmol) (*Ejemplo 53*) usando SFC quiral proporcionando el pico A (21,2 mg, 0,044 mmol) (*Ejemplo 53A*) y el pico B (24,2 mg, 0,051 mmol) (*Ejemplo 53B*). Procedimiento de SFC: Chiralpak OJ-H (30 x 250 mm, 5 μM), metanol al 35% (dietilamina al 0,1%) en CO_2, 35ºC, caudal 70 ml/min durante 13 min, absorbancia 268 nm, inyección de 5μl de solución 27 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 4,5 min, t_R (pico B) 9,5 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 53A y 53B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 53*).

Ejemplo 54

8-(4-fluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

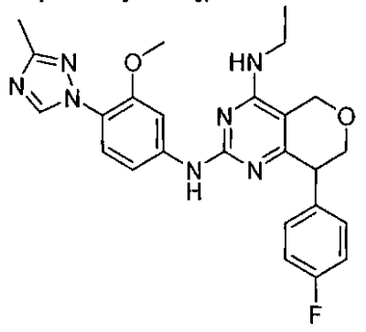


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación D (0,076 g, 0,38 mmol), Preparación Ja (0,11 g, 0,38 mmol), Na_2CO_3 (0,079 g, 0,75 mmol) y xantphos (0,216 g, 0,38 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,17 g, 0,18 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa dando 8-(4-fluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (0,08 g, 47%) como sólido blanquecino. CL-EM $(M+H)^+$ = 462,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 8,70 (1H, s), 7,8 (1H, m), 7,5 (1H, m), 7,34 (2H, m), 7,21 (4H, m), 7,13 (1H, m), 4,60 (1H, d, *J*= 14,0 Hz), 4,46 (1H, d, *J*= 14,0 Hz), 3,83 (2H, m), 3,78 (1H, m), 3,75 (3H, s), 3,01 (3H, d, *J* = 4,0 Hz), 2,32 (3H, s,).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 54A y 54B, que tuvieron idénticos datos espectrales.

Ejemplo 55

N4-etil-8-(4-fluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



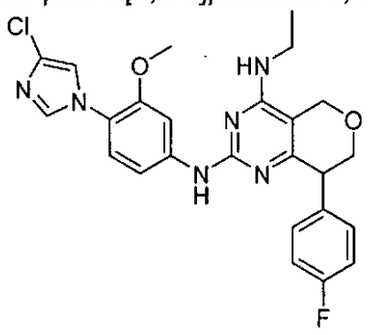
Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación D (0,085 g, 0,40 mmol), Preparación Jb (0,16 g, 0,52 mmol), Na_2CO_3 (0,11 g, 1,0 mmol) y xantphos (0,30 g, 0,52 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,26 g, 0,26 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (10 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (10 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa dando N4-etil-8-(4-fluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (0,90 g, 40%) como sólido blanquecino. CL-EM $(M+H)^+$ = 476,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 8,69 (1H, s), 7,73 (1H, s), 7,48 (1H, s), 7,34 (2H, m), 7,21-7,13 (3H, m), 4,62 (1H, d, *J*= 14,0 Hz), 4,47 (1H, d, *J*= 14,0 Hz),

4,07 (2H, m), 3,92 (2H, m), 3,82 (3H, s), 3,54 (3H, m), 2,33 (3H, s), 1,22 (3H, t, *J* = 7,2,0 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 55A y 55B, que tuvieron idénticos datos espectrales.

Ejemplo 56

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



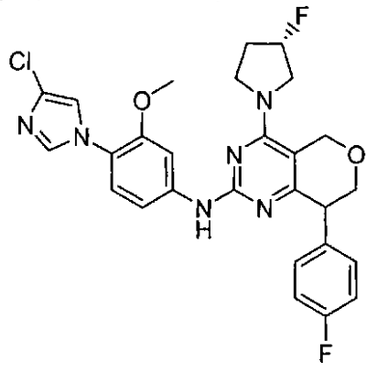
Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,70 g, 0,32 mmol), Preparación Jb (0,11 g, 0,35 mmol), Na_2CO_3 (0,07 g, 0,71 mmol) y xantphos (0,20 g, 0,35 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,18 g, 0,17 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-

etil-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (0,70 g, 40%) como sólido blanquecino. CL-EM $(M-H)^+$ = 495,2. RMN de ^1H (400 MHz, -DMSO-*d6*): δ ppm 9,91 (1H, s ancho), 7,83 (1H, m), 7,69 (1H, s), 7,39 (1H, s), 7,22 (4H, m), 7,10 (4H, m), 4,65 (1H, d, *J*= 14,0 Hz), 4,48 (1H, d, *J*= 14,0 Hz), 4,04 (1H, m), 3,83 (1H, m), 3,74 (3H, s), 3,54 (2H, m), 1,22 (3H, t, *J* = 7,2,0 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 56A y 56B, que tuvieron idénticos datos espectrales.

Ejemplo 57A

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina

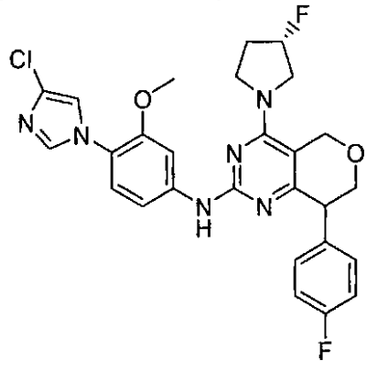


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,051 g, 0,23 mmol), Preparación Jc1 (0,09 g, 0,25 mmol), Na_2CO_3 (0,050 g, 0,51 mmol) y xantphos (0,148 g, 0,25 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,132 g, 0,12 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa

se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando metanol al 10% en diclorometano como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina (0,030g, 18%) como un sólido blanquecino. CL-EM $(M+H)^+$ = 539,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,19 (1H, s), 7,89 (1H, s), 7,74 (1H, s), 7,43 (1H, s), 7,27 (2H, m), 7,18-7,11 (4H, m), 5,42 (1H, m), 5,04 (1H, d, *J* = 13,6 Hz), 4,81 (1H, d, *J* = 13,6 Hz), 4,13 (2H, m), 3,91-3,77 (4H, m), 3,66 (1H, m), 3,58 (3H, s), 2,23 (2H, m).

Ejemplo 57B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina

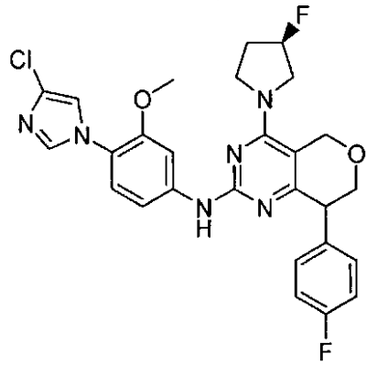


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,062 g, 0,28 mmol), Preparación Jc2 (0,110 g, 0,31 mmol), Na_2CO_3 (0,066 g, 0,62 mmol) y xantphos (0,181 g, 0,31 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,162 g, 0,15 mmol) a la mezcla de reacción y la

solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando metanol al 8% en diclorometano como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina (0,031g, 19%) como un sólido blanquecino. CL-EM $(M+H)^+$ = 539,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,21 (1H, s), 7,87 (1H, s), 7,74 (1H, s), 7,43 (1H, s), 7,24 (2H, m), 7,16-7,09 (4H, m), 5,36 (1H, m), 4,95 (2H, m), 5,05 (1H, m), 3,95-3,80 (2H, m), 3,78-3,70 (4H, m), 3,6 (3H, s), 2,22 (2H, m).

Ejemplo 58A

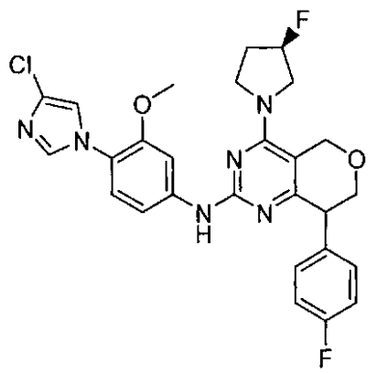
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina



Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,057 g, 0,28 mmol), Preparación Jd1 (0,10 g, 0,28 mmol), Na_2CO_3 (0,06 g, 0,56 mmol) y xantphos (0,16 g, 0,28 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,14 g, 0,14 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando metanol al 10% en diclorometano como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina (0,040 g, 27%) como sólido blanquecino. CL-EM $(M+H)^+$ = 539,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,45 (1H, s ancho), 7,79 (1H, s), 7,71 (1H, m), 7,47 (1H, s), 7,34-7,26 (2H, m), 7,21-7,12 (4H, m), 5,41 (1H, m), 5,07 (1H, d, *J* = 14,0 Hz), 4,85 (1H, d, *J* = 14,0 Hz), 4,53-4,38 (2H, m), 4,32-4,30 (4H, m), 3,89-3,64 (4H, m), 2,50-2,58 (2H, m).

Ejemplo 58B

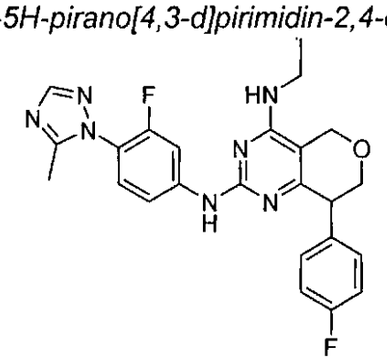
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina



Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,062 g, 0,282 mmol), Preparación Jd2 (0,11 g, 0,310 mmol), Na_2CO_3 (0,065 g, 0,620 mmol) y xantphos (0,179 g, 0,310 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,16 g, 0,155 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando metanol al 10% en diclorometano como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina (0,040 g, 27%) como sólido blanquecino. CL-EM $(M+H)^+$ = 539,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,39 (1H, s *ancho*), 7,78 (1H, s), 7,71 (1H, m), 7,46 (1H, s), 7,28-7,13 (6H, m), 5,40 (1H, m), 4,94 (2H, m), 4,04-3,95 (4H, m), 3,83 (3H, m), 3,67 (3H, m), 2,33-2,08 (2H, m).

Ejemplo 59

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

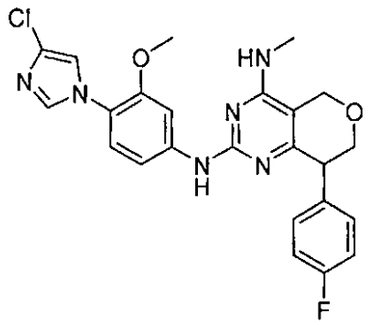


Se usó el procedimiento del *Ejemplo* 56 para combinar la Preparación C y Preparación Jb proporcionando N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina. CL-EM $(M+H)^+$ = 464,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,99 - 8,06 (2 H, m), 7,24 - 7,34 (4 H, m), 7,04 (2 H, t, *J*=8,70 Hz), 4,65 (1 H, d, *J*=14,30 Hz), 4,56 (1 H, d, *J*=14,30 Hz), 4,16 (1 H, dd, *J*=11,29, 4,58 Hz), 3,94 - 4,00 (1 H, m), 3,92 (1 H, t, *J*=4,88 Hz), 3,57 (2 H, c, *J*=7,12 Hz), 2,37 (3 H, s), 1,29 (3 H, t, *J*=7,17 Hz)

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 59A y 59B, que tuvieron idénticos datos espectrales.

Ejemplo 60

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



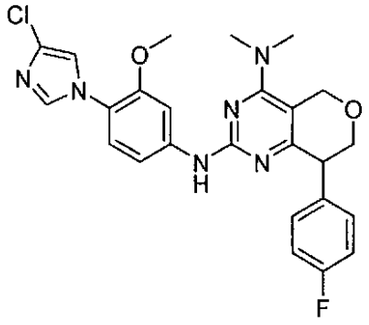
Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,15 g, 0,61 mmol), Preparación Ja (0,20 g, 0,61 mmol), Na_2CO_3 (0,144 g, 1,31 mmol) y xantphos (0,39 g, 0,61 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,31 g, 0,32 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (0,12 g, 37%) como sólido blanquecino. CL-EM $(M-H)^+$ = 479,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 12,02 (1H, s ancho), 9,17 (1H, s), 8,06 (1H, s), 7,73 (1H, s), 7,41 (1H, s), 7,25-7,08 (5H, m), 6,77 (1H, m), 4,57 (1H, d, *J*= 14,4 Hz), 4,44 (1H, d, *J*= 14,4 Hz), 4,02 (1H, m), 3,89 (1H, m), 3,80 (1H, m), 3,3 (3H, s), 2,93 (3H, d, *J* = 4,0 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando

los enantiómeros Ejemplo 60A y 60B, que tuvieron idénticos datos espectrales.

Ejemplo 61

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N4,N4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



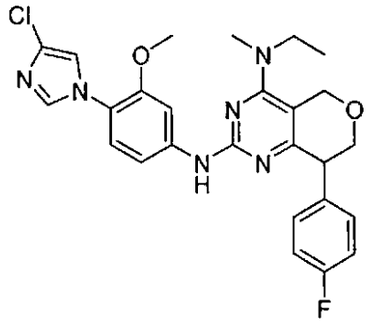
Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,15 g, 0,70 mmol), Preparación Je (0,24 g, 0,78 mmol), Na_2CO_3 (0,16 g, 1,56 mmol) y xantphos (0,45 g, 0,78 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,35 g, 0,39 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (30 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (20 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por combiflash (Sílice 120 g) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N4,N4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (0,15 g, 47%) como sólido blanquecino. CL-EM $(M-H)^+$ = 493,0. RMN de ^1H

(400 MHz, DMSO-*d6*): δ ppm 9,21 (1H, s), 7,91 (1H, s), 7,73 (1H, s), 7,41 (1H, s), 7,24 (2H, m), 7,14 (4H, m), 4,83 (1H, d, *J*= 13,6 Hz), 4,70 (1H, d, *J*= 13,6 Hz), 4,16 (1H, m), 4,10 (1H, m), 3,72 (1H, m), 3,56 (3H, s), 3,06 (6H, s).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 61A y 61B, que tuvieron idénticos datos espectrales.

Ejemplo 62

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



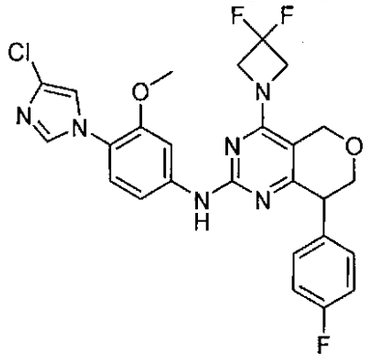
Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,13 g, 0,61 mmol), Preparación Jf (0,20 g, 0,61 mmol), Na_2CO_3 (0,13 g, 1,2 mmol) y xantphos (0,36 g, 0,61 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,28 g, 0,31 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (30 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (20 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó

por combiflash (Sílice 120 g) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (0,097 g, 47%) como sólido blanquecino. CL-EM $(M+H)^+$ = 509,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,17 (1H, s), 7,83 (1H, s), 7,72 (1H, s), 7,40 (1H, s), 7,24 (2H, m), 7,12 (4H, m), 4,78 (1H, d, *J*= 13,6 Hz), 4,65 (1H, d, *J*= 13,6 Hz), 4,09 (1H, m), 3,73 (1H, m), 3,55 (1H, m), 3,54 (3H, s), 3,38 (2H, m), 3,02 (3H, s), 1,20 (3H, t, *J* = 6,9,0 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 62A y 62B, que tuvieron idénticos datos espectrales.

Ejemplo 63

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina



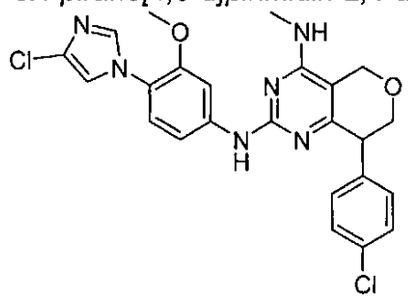
Se purgó con argon durante 1 h a temperatura ambiente Una solución de la Preparación A (0,082 g, 0,31 mmol), Preparación Jg (0,13 g, 0,31 mmol), Na_2CO_3 (0,077 g, 0,72 mmol) y xantphos (0,21 g, 0,31 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,16 g, 0,12 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a

110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (30 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (20 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por combiflash (Sílice 120 g) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina (0,070 g, 35%) como sólido blanquecino. CL-EM $(M-H)^+$ = 541,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,41 (1H, s), 7,88 (1H, s), 7,73 (1H, s), 7,41 (1H, s), 7,25 (2H, m), 7,17-7,08 (4H, m), 4,78-4,63 (6H, m), 4,04 (2H, m), 3,78 (1H, m), 3,50 (3H, s).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 63A y 63B, que tuvieron idénticos datos espectrales.

Ejemplo 64

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

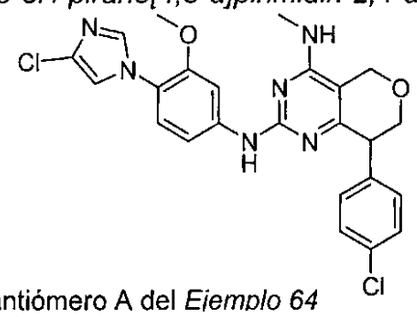


Se combinaron 2-cloro-8-(4-clorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-

d]pirimidin-4-amina (*Preparación Kb*) (116 mg, 0,374 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (84 mg, 0,374 mmol) y se purificó según el *Ejemplo 26* dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (105 mg, 0,172 mmol, 45,9 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 497,1. RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 7,86 (1 H, s ancho), 7,63 (1 H, s ancho), 7,30 - 7,46 (6 H, m), 7,19 (1 H, dd, *J*=8,55, 2,14 Hz), 4,62 - 4,73 (1 H, m), 4,56 (1 H, d, *J*=14,65 Hz), 4,11 - 4,20 (1 H, m), 4,07 (1 H, d, *J*=3,36 Hz), 3,94 (1 H, dd, *J*=11,44, 3,81 Hz), 3,82 - 3,89 (3 H, m), 3,10 - 3,20 (3 H, m).

Ejemplo 64A

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



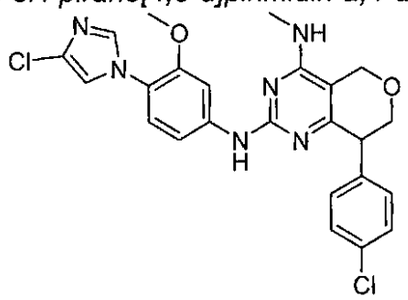
Enantiómero A del *Ejemplo 64*

Se separó N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo 64*) mediante varias inyecciones de HPLC quiral (OJ-H 30 x 250mm, 10 μM, EtOH al 35%/Hexanos) dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (primero en eluir, enantiómero A) (35 mg, 0,057 mmol) como un sólido blanquecino. CL-EM $(M+H)^+$ = 497,1. RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 7,80

(1 H, s), 7,71 (1 H, s), 7,36 (2 H, d, *J*=8,24 Hz), 7,25 - 7,30 (3 H, m), 7,22 (1 H, d, *J*=8,55 Hz), 7,03 (1 H, d, *J*=8,55 Hz), 4,50 - 4,68 (2 H, m), 4,15 (1 H, dd, *J*=11,29, 4,27 Hz), 3,97 (1 H, t, *J*=4,27 Hz), 3,87 - 3,94 (1 H, m), 3,66 (3 H, s), 3,08 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 64A*.

Ejemplo 64B

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

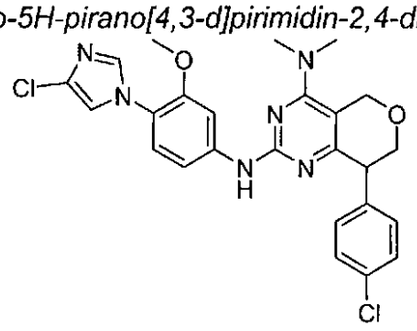


Enantiómero B del *Ejemplo 64*

Se separó N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo 64*) mediante varias inyecciones de HPLC quiral (OJ-H 30 x 250mm, 10 μM, EtOH al 35%/Hexanos) dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (segundo en eluir, enantiómero B) (29mg, 0,047 mmol) como un sólido blanquecino. CL-EM $(M+H)^+$ = 497,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,78 (1 H, s), 7,72 (1 H, d, *J*=1,53 Hz), 7,34 - 7,39 (2 H, m), 7,26 - 7,31 (3 H, m), 7,24 (1 H, d, *J*=8,55 Hz), 7,04 (1 H, dd, *J*=8,55, 2,14 Hz), 4,51 - 4,68 (2 H, m), 4,15 (1 H, dd, *J*=11,29, 4,58 Hz), 3,98 (1 H, t, *J*=4,43 Hz), 3,91 (1 H, dd, *J*=11,44, 4,73 Hz), 3,68 (3 H, s), 3,09 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 64B*.

Ejemplo 65

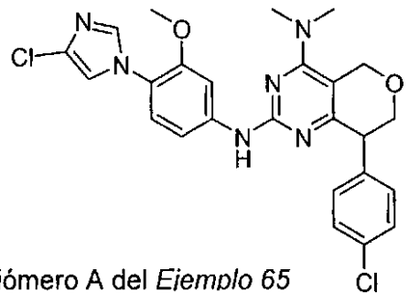
N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



Se combinaron 2-cloro-8-(4-clorofenil)-N,N-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (*Preparación Kc*) (125 mg, 0,386 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (86 mg, 0,386 mmol) y se purificó según el *Ejemplo 26* dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (110 mg, 0,176 mmol, 45,6 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 511,1. RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 7,92 (1 H, s ancho), 7,31 - 7,51 (7 H, m), 7,16 (1 H, dd, *J*=8,39, 1,98 Hz), 4,91 - 5,05 (2 H, m), 4,12 - 4,30 (2 H, m), 3,76 - 3,91 (4 H, m), 3,34 - 3,44 (6 H, m).

Ejemplo 65A

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

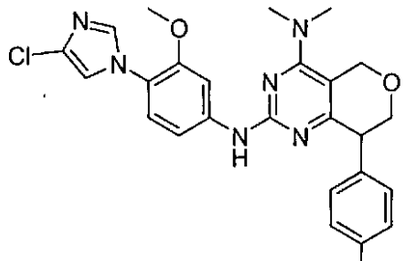


Enantiómero A del *Ejemplo 65*

Se separó N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo 65*) mediante varias inyecciones de HPLC quiral (OJ-H 30 x 250mm, 10 μM, EtOH al 35%/Hexanos) dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (primero en eluir, enantiómero A) (35 mg, 0,056 mmol) como un sólido blanquecino. CL-EM $(M+H)^+$ = 511,1. RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 7,71 (1 H, d, *J*=1,22 Hz), 7,67 (1 H, s), 7,36 (2 H, d, *J*=8,55 Hz), 7,24 - 7,30 (3 H, m), 7,22 (1 H, d, *J*=8,55 Hz), 7,01 (1 H, dd, *J*=8,55, 2,14 Hz), 4,77 - 4,96 (2 H, m), 4,23 (1 H, dd, *J*=11,44, 5,65 Hz), 4,11 (1 H, t, *J*=5,65 Hz), 3,84 (1 H, dd, *J*=11,60, 6,10 Hz), 3,60 - 3,66 (3 H, m), 3,18 - 3,23 (6 H, m). No se determinó la estereoquímica absoluta para el *Ejemplo 65A*.

Ejemplo 65B

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

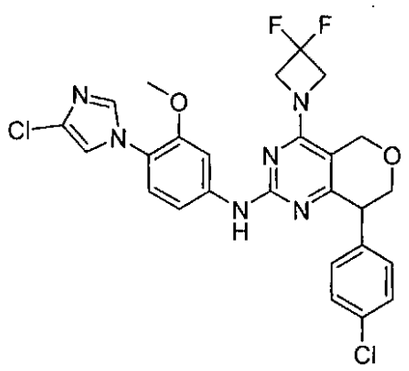


Enantiómero B del *Ejemplo 65*

Se separó N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo 65*) mediante varias inyecciones de HPLC quiral (OJ-H 30 x 250mm, 10 μM, EtOH al 35%/Hexanos) dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (segundo en eluir, enantiómero B) (34 mg, 0,054 mmol) como un sólido blanquecino. CL-EM $(M+H)^+$ = 511,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,73 (1 H, d, *J*=1,53 Hz), 7,63 (1 H, s), 7,38 (2 H, d, *J*=8,55 Hz), 7,22 - 7,33 (4 H, m), 7,03 (1 H, dd, *J*=8,55, 2,14 Hz), 4,81 - 4,97 (2 H, m), 4,24 (1 H, dd, *J*=11,44, 5,65 Hz), 4,13 (1 H, t, *J*=5,49 Hz), 3,85 (1 H, dd, *J*=11,44, 5,95 Hz), 3,68 (3 H, s), 3,24 (6 H, s). No se determinó la estereoquímica absoluta para el *Ejemplo 65B*.

Ejemplo 66

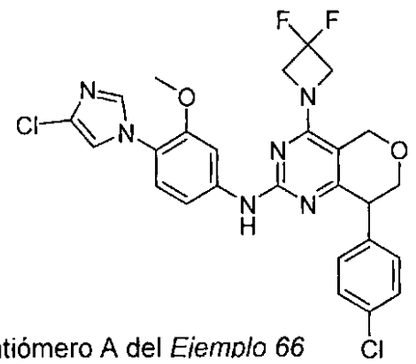
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina



Se combinaron 2-cloro-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (*Preparación Ka*) (125 mg, 0,336 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (75 mg, 0,336 mmol) y se purificó según el *Ejemplo 26* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina, TFA (40 mg, 0,059 mmol, 17,69 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 559,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,83 (1 H, s ancho), 7,39 - 7,45 (3 H, m), 7,31 - 7,39 (4 H, m), 7,17 (1 H, dd, *J*=8,55, 2,14 Hz), 4,88 - 4,97 (5 H, m), 4,74 - 4,81 (1 H, m), 4,08 - 4,19 (2 H, m), 3,91 (1 H, dd, *J*=11,44, 3,81 Hz), 3,81 (3 H, s).

Ejemplo 66A

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina

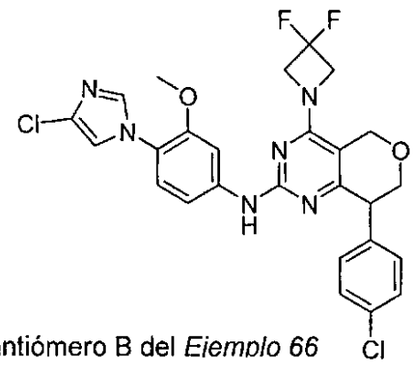


Enantiómero A del *Ejemplo 66*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina (*Ejemplo* 66) mediante varias inyecciones de SFC quiral (OD-H 30 x 250mm, 5 µM, MeOH al 35% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina (primero en eluir, enantiómero A) (7,8 mg, 0,014 mmol) como un sólido blanco. CL-EM $(M+H)^+$ = 559,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,76 (1 H, s), 7,66 (1 H, s), 7,31 (2 H, d, *J*=8,24 Hz), 7,20 - 7,27 (3 H, m), 7,10 - 7,16 (1 H, m), 6,97 (1 H, d, *J*=8,55 Hz), 4,68 - 4,83 (2 H, m), 4,55 - 4,66 (4 H, m), 4,16 (1 H, dd, *J*=11,44, 5,04 Hz), 4,02 (1 H, t, *J*=4,88 Hz), 3,88 (1 H, dd, *J*=11,29, 5,80 Hz), 3,49 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 66A*.

Ejemplo 66B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina

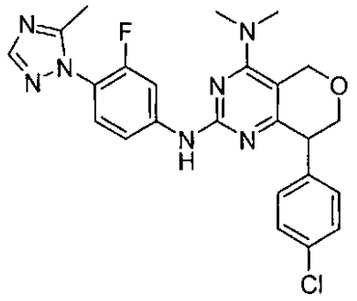


Enantiómero B del *Ejemplo 66*

Se separó N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina (*Ejemplo* 66) mediante varias inyecciones de SFC quiral (OD-H 30 x 250mm, 5 μM, MeOH al 35% (DEA al 0,1%)/CO_2) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina (segundo en eluir, enantiómero B) (8,1 mg, 0,014 mmol) como un sólido blanco. CL-EM $(M+H)^+$ = 559,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,76 (1 H, d, *J*=2,14 Hz), 7,67 (1 H, d, *J*=1,53 Hz), 7,29 - 7,34 (2 H, m), 7,19 - 7,27 (3 H, m), 7,13 (1 H, d, *J*=8,55 Hz), 6,97 (1 H, dd, *J*=8,55, 2,14 Hz), 4,67 - 4,84 (2 H, m), 4,60 (4 H, t, *J*=12,21 Hz), 4,17 (1 H, dd, *J*=11,44, 5,04 Hz), 4,02 (1 H, t, *J*=5,19 Hz), 3,88 (1 H, dd, *J*=11,29, 5,80 Hz), 3,46 - 3,51 (3 H, m). No se determinó la estereoquímica absoluta de *66B*.

Ejemplo 67

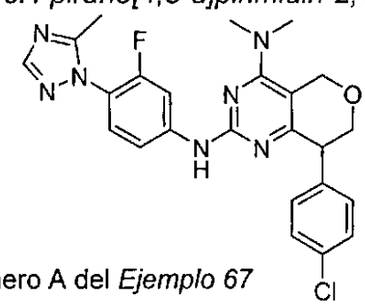
8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



Se combinaron 2-cloro-8-(4-clorofenil)-N,N-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (*Preparación Kc*) (128 mg, 0,395 mmol) y 3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina (*Preparación C*) (76 mg, 0,395 mmol) y se purificó según el *Ejemplo 26* dando 8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (120 mg, 0,202 mmol, 51,2 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 480,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,07 (1 H, s), 7,80 (1 H, dd, *J*=12,36, 2,29 Hz), 7,54 (1 H, t, *J*=8,55 Hz), 7,40 - 7,47 (3 H, m), 7,34 - 7,40 (2 H, m), 4,90 - 5,04 (2 H, m), 4,22 - 4,28 (1 H, m), 4,20 (1 H, s ancho), 3,87 (1 H, dd, *J*=11,44, 5,34 Hz), 3,39 (6 H, s), 2,40 (3 H, s).

Ejemplo 67A

8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

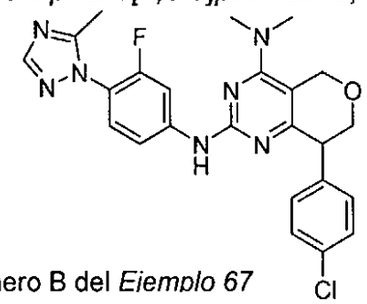


Enantiómero A del *Ejemplo 67*

Se separó 8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo 67*) mediante varias inyecciones de SFC quiral (AD-H 30 x 250mm, 5 μM, 40% MeOH (DEA al 0,1%)/CO_2) dando 8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (primero en eluir, enantiómero A) (25,8 mg, 0,054 mmol) como un vidrio opaco. CL-EM $(M+H)^+$ = 480,1. RMN de ^1H (400 MHz, *MeOD*) δ ppm 7,99 (1 H, s), 7,87 - 7,95 (1 H, m), 7,19 - 7,33 (6 H, m), 4,72 - 4,83 (2 H, m), 4,22 (1 H, dd, *J*=11,33, 5,54 Hz), 4,02 (1 H, t, *J*=5,67 Hz), 3,87 - 3,95 (1 H, m), 3,09 (6 H, s), 2,33 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 67A*.

Ejemplo 67B

8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



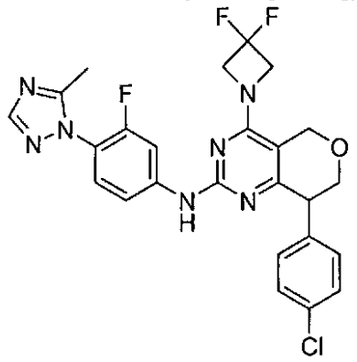
Enantiómero B del *Ejemplo 67*

Se separó 8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo 67*) mediante varias inyecciones de SFC quiral (AD-H 30 x 250mm, 5 μM, 40% MeOH (DEA al 0,1%)/CO_2) dando 8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-

diamina (segundo en eluir, enantiómero B) (25,8 mg, 0,054 mmol) como un vidrio opaco. CL-EM $(M+H)^+$ = 480,1. RMN de ^1H (400 MHz, *MeOD*) δ ppm 7,99 (1 H, s), 7,87 - 7,94 (1 H, m), 7,20 - 7,31 (6 H, m), 4,72 - 4,84 (2 H, m), 4,22 (1 H, dd, *J*=11,33, 5,54 Hz), 4,02 (1 H, t, *J*=5,79 Hz), 3,92 (1 H, dd, *J*=11,33, 6,04 Hz), 3,09 (6 H, s), 2,33 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 67B*.

Ejemplo 68

8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina

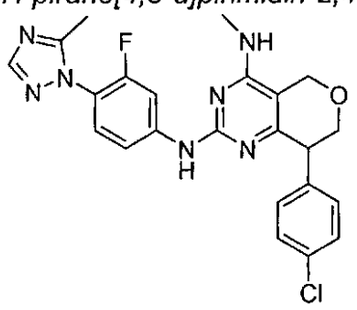


Se combinaron 2-cloro-8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (*Preparación Ka*) (128 mg, 0,344 mmol) y 3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina (*Preparación C*) (66,1 mg, 0,344 mmol) y se purificó según el *Ejemplo 26* dando 8-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina, TFA (120 mg, 0,187 mmol, 54,4 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 528,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,01 - 8,10 (1 H, m), 7,75 - 7,85 (1 H, m), 7,25 - 7,50 (6 H, m), 4,70 - 4,96 (6 H, m), 4,13 - 4,24 (1 H, m), 4,02 - 4,13 (1 H, m), 3,96 (1 H,

dd, *J*=11,44, 4,73 Hz), 2,32 - 2,44 (3 H, m).

Ejemplo 69

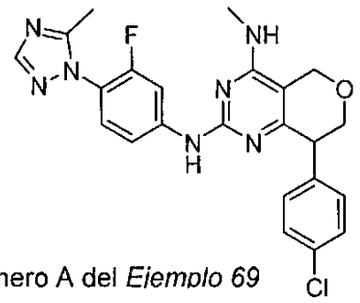
8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



Se combinaron 2-cloro-8-(4-clorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (*Preparación Kb*) (150 mg, 0,484 mmol) y 3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina (*Preparación C*) (93 mg, 0,484 mmol) y se purificó según el *Ejemplo 26* dando 8-(4-clorofenil)-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (120 mg, 0,207 mmol, 42,8 % de rendimiento) como un vidrio incoloro transparente. CL-EM $(M+H)^+$ = 466,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,08 (1 H, s), 7,89 - 7,96 (1 H, m), 7,57 (1 H, t, *J*=8,55 Hz), 7,47 - 7,52 (1 H, m), 7,42 - 7,46 (2 H, m), 7,34 - 7,40 (2 H, m), 4,53 - 4,74 (2 H, m), 4,18 (1 H, dd, *J*=11,44, 4,43 Hz), 4,07 - 4,13 (1 H, m), 3,95 (1 H, dd, *J*=11,44, 4,12 Hz), 3,17 (3 H, s), 2,42 (3 H, s).

Ejemplo 69A

8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

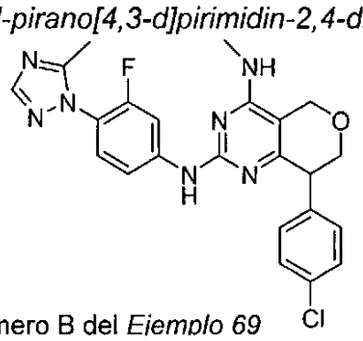


Enantiómero A del *Ejemplo 69*

Se separó 8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo* 69) mediante varias inyecciones de SFC quiral (AD-H 30 x 250mm, 5 μM, 20% MeOH (DEA al 0,1%)/CO_2) dando 8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (primero en eluir, enantiómero A) (52,4 mg, 0,112 mmol) como un sólido blanco. CL-EM $(M+H)^+$ = 466,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,97 - 8,13 (2 H, m), 7,17 - 7,41 (6 H, m), 4,48 - 4,72 (2 H, m), 4,17 (1 H, dd, *J*=11,29, 4,58 Hz), 3,98 (1 H, dd, *J*=11,44, 5,04 Hz), 3,93 (1 H, d, *J*=4,88 Hz), 2,99 - 3,08 (3 H, m), 2,35 - 2,42 (3 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 69A*.

Ejemplo 69B

8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

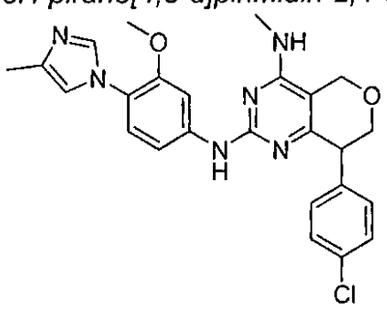


Enantiómero B del *Ejemplo 69*

Se separó 8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo* 69) mediante varias inyecciones de SFC quiral (AD-H 30 x 250mm, 5 μM, 20% MeOH (DEA al 0,1%)/CO_2) dando 8-(4-clorofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (segundo en eluir, enantiómero B) (45,9 mg, 0,099 mmol) como un sólido blanco. CL-EM $(M+H)^+$ = 466,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,00 - 8,06 (2 H, m), 7,25 - 7,35 (6 H, m), 4,52 - 4,68 (2 H, m), 4,17 (1 H, dd, *J*=11,29, 4,88 Hz), 3,96 - 4,02 (1 H, m), 3,92 (1 H, t, *J*=4,88 Hz), 3,05 (3 H, s), 2,38 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 69B*.

Ejemplo 70

8-(4-clorofenil)-N^2-(3-metoxi-4-(4-metil-1H-imidazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

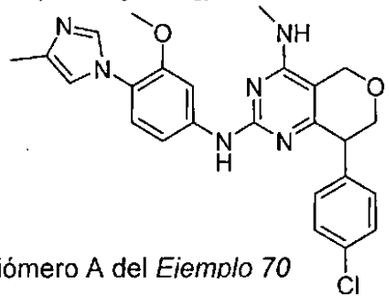


Se combinaron 2-cloro-8-(4-clorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (*Preparación Kb*) (105,5 mg, 0,340 mmol) y 3-metoxi-4-(4-metil-1H-imidazol-1-il)anilina (*Preparación E*) (69,1 mg, 0,340 mmol) y se purificó según el *Ejemplo 26* dando 8-(4-clorofenil)-N^2-(3-metoxi-4-(4-metil-1H-imidazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (120 mg, 0,203 mmol, 59,7 % de rendimiento) como un vidrio incoloro

transparente. CL-EM $(M+H)^+$ = 477,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 9,11 (1 H, s), 7,76 (1 H, s ancho), 7,51 - 7,59 (2 H, m), 7,34 - 7,46 (4 H, m), 7,26 - 7,33 (1 H, m), 4,52 - 4,75 (2 H, m), 4,17 (1 H, dd, *J*=11,44, 4,43 Hz), 4,08 (1 H, s ancho), 3,88 - 4,04 (4 H, m), 3,17 (3 H, s), 2,44 (3 H, s).

Ejemplo 70A

8-(4-clorofenil)-N^2-(3-metoxi-4-(4-metil-1H-imidazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

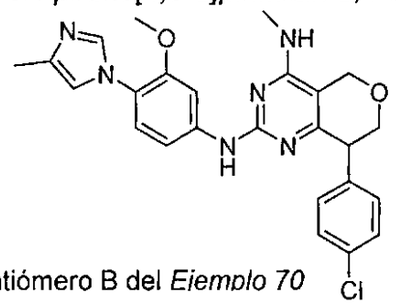


Enantiómero A del *Ejemplo 70*

Se separó 8-(4-clorofenil)-N^2-(3-metoxi-4-(4-metil-1H-imidazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo 70*) mediante varias inyecciones de SFC quiral (AD-H 30 x 250mm, 5 μM, 20% MeOH (DEA al 0,1%)/CO_2) dando 8-(4-clorofenil)-N^2-(3-metoxi-4-(4-metil-1H-imidazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (primero en eluir, enantiómero A) como un vidrio amarillo opaco. CL-EM $(M+H)^+$ = 477,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,84 (1 H, d, *J*=2,14 Hz), 7,62 (1 H, s ancho), 7,30 (2 H, d, *J*=8,55 Hz), 7,19 - 7,28 (2 H, m), 7,06 - 7,15 (1 H, m), 6,94 (2 H, dd, *J*=8,55, 2,14 Hz), 4,48 - 4,67 (2 H, m), 4,06 - 4,18 (1 H, m), 3,84 - 3,96 (2 H, m), 3,54 (3 H, s), 3,04 (3 H, s), 2,22 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 70A*.

Ejemplo 70B

8-(4-clorofenil)-N^2-(3-metoxi-4-(4-metil-1H-imidazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

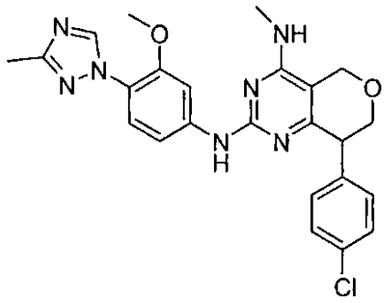


Enantiómero B del *Ejemplo 70*

Se separó 8-(4-clorofenil)-N^2-(3-metoxi-4-(4-metil-1H-imidazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo 70*) mediante varias inyecciones de SFC quiral (AD-H 30 x 250mm, 5 μM, 20% MeOH (DEA al 0,1%)/CO_2) dando 8-(4-clorofenil)-N^2-(3-metoxi-4-(4-metil-1H-imidazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (segundo en eluir, enantiómero B) como un vidrio amarillo opaco. CL-EM $(M+H)^+$ = 477,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,85 (1 H, d, *J*=2,14 Hz), 7,60 - 7,64 (1 H, m), 7,27 - 7,32 (2 H, m), 7,19 - 7,24 (2 H, m), 7,06 - 7,11 (1 H, m), 6,90 - 6,96 (2 H, m), 4,48 - 4,64 (2 H, m), 4,06 - 4,14 (1 H, m), 3,84 - 3,92 (2 H, m), 3,51 - 3,57 (3 H, m), 3,01 - 3,06 (3 H, m), 2,19 - 2,25 (3 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 70B*.

Ejemplo 71

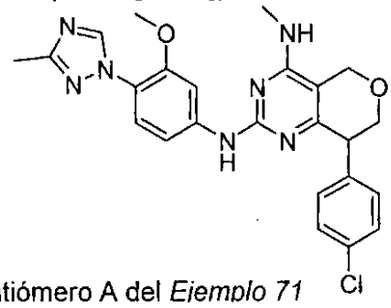
8-(4-clorofenil)-N^2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



Se combinaron 2-cloro-8-(4-clorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (*Preparación Kb*) (105,5 mg, 0,340 mmol) y 3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)anilina (*Preparación D*) (69,5 mg, 0,340 mmol) y se purificó según el *Ejemplo 26* dando 8-(4-clorofenil)-N^2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (120 mg, 0,203 mmol, 59,6 % de rendimiento) como un vidrio incoloro transparente. CL-EM $(M+H)^+$ = 478,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,85 (1 H, s), 7,67 (1 H, d, *J*=8,55 Hz), 7,64 (1 H, s), 7,41 - 7,48 (2 H, m), 7,33 - 7,40 (2 H, m), 7,18 (1 H, dd, *J*=8,55, 2,14 Hz), 4,52 - 4,73 (2 H, m), 4,17 (1 H, dd, *J*=11,44, 4,42 Hz), 4,08 (1 H, s ancho), 3,94 (1 H, dd, *J*=11,60, 3,97 Hz), 3,91 (3 H, s), 3,17 (3 H, s), 2,45 (3 H, s).

Ejemplo 71A

8-(4-clorofenil)-N^2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

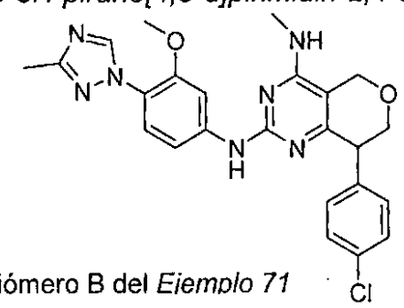


Enantiómero A del *Ejemplo 71*

Se separó 8-(4-clorofenil)-N^2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo 71*) mediante varias inyecciones de SFC quiral (OD-H 30 x 250mm, 5 μM, MeOH al 35% (DEA al 0,1%)/CO_2) dando 8-(4-clorofenil)-N^2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (primero en eluir, enantiómero A) (24 mg, 0,050 mmol) como un vidrio color castaño fragmentado. CL-EM $(M+H)^+$ = 478,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,57 (1 H, s), 7,93 (1 H, d, *J*=2,14 Hz), 7,37 (1 H, d, *J*=8,85 Hz), 7,29 - 7,34 (2 H, m), 7,21 - 7,26 (2 H, m), 6,98 (1 H, dd, *J*=8,70, 2,29 Hz), 4,50 - 4,66 (2 H, m), 4,13 (1 H, dd, *J*=10,68, 3,97 Hz), 3,85 - 3,95 (2 H, m), 3,59 (3 H, s), 3,05 (3 H, s), 2,42 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 71A*.

Ejemplo 71B

8-(4-clorofenil)-N^2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



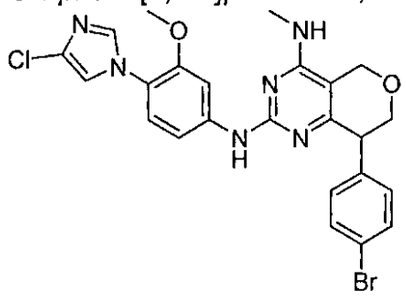
Enantiómero B del *Ejemplo 71*

Se separó 8-(4-clorofenil)-N^2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (*Ejemplo 71*) mediante varias inyecciones de SFC quiral (OD-H 30 x 250mm, 5 μM, MeOH al 35% (DEA al 0,1%)/CO_2) dando 8-(4-clorofenil)-N^2-(3-metoxi-4-(3-metil-1H-

1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina (segundo en eluir, enantiómero B) (22 mg, 0,046 mmol) como un vidrio color castaño fragmentado. CL-EM $(M+H)^+$ = 478,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,57 (1 H, s), 7,93 (1 H, d, *J*=2,14 Hz), 7,36 (1 H, d, *J*=8,55 Hz), 7,28 - 7,34 (2 H, m), 7,20 - 7,26 (2 H, m), 6,98 (1 H, dd, *J*=8,55, 2,14 Hz), 4,50 - 4,66 (2 H, m), 4,13 (1 H, dd, *J*=10,68, 3,97 Hz), 3,84 - 3,95 (2 H, m), 3,59 (3 H, s), 3,04 (3 H, s), 2,41 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 71B*.

Ejemplo 72

8-(4-bromofenil)-N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina

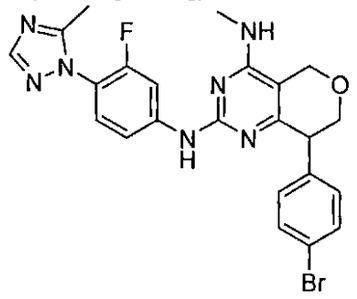


Se combinaron 8-(4-bromofenil)-2-cloro-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (*Preparación La*) (95 mg, 0,268 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (90 mg, 0,402 mmol) y se purificó según el *Ejemplo 16* dando 8-(4-bromofenil)-N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (38,5 mg, 0,059 mmol, 21,91 % de rendimiento) como un sólido color castaño. CL-EM $(M+H)^+$ = 541,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,83 (1 H, s ancho), 7,70 (1 H, s ancho), 7,17 - 7,42 (7 H, m), 6,96 - 7,06 (1 H,

m), 4,52 - 4,72 (2 H, m), 4,13 - 4,23 (1 H, m), 3,98 (1 H, s ancho), 3,87 - 3,96 (1 H, m), 3,62 (3 H, d, *J*=7,02 Hz), 3,06 - 3,16 (3 H, m).

Ejemplo 73

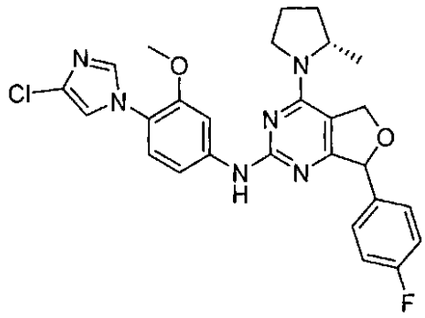
8-(4-bromofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



Se combinaron 8-(4-bromofenil)-2-cloro-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (*Preparación La*) (95 mg, 0,268 mmol) y 3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina (*Preparación C*) (77 mg, 0,402 mmol) y se purificó según el *Ejemplo 16* dando 8-(4-bromofenil)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (23 mg, 0,037 mmol, 13,75 % de rendimiento). CL-EM $(M+H)^+$ = 510,2. RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 7,74 (2 H, s ancho), 7,25 - 7,45 (7 H, m), 7,00 - 7,12 (1 H, m), 4,53 - 4,73 (2 H, m), 4,17 (1 H, dd, *J*=11,29, 4,88 Hz), 4,00 - 4,09 (1 H, m), 3,89 - 3,99 (1 H, m), 3,71 (3 H, s ancho), 3,12 (3 H, s).

Ejemplos 74A y 74B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((S)-2-metilpirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina



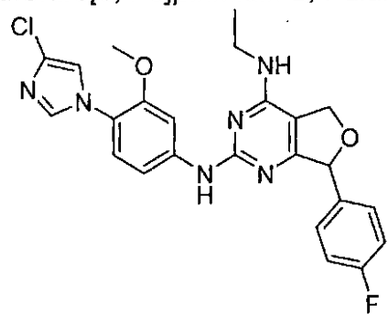
Diastereómeros discretos

A una mezcla de (S)-2-cloro-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación Me) (192,0 mg, 0,575 mmol), 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) (154 mg, 0,690 mmol), XANTPHOS (33,3 mg, 0,058 mmol), Pd2(dba)3 (26,3 mg, 0,029 mmol), y Cs2CO3 (562 mg, 1,726 mmol) se añadió dioxano (2397 µl). La mezcla se purgó con nitrógeno y se colocó en un vial tapado y se calentó a 100 °C durante la noche. Se enfrió hasta ta y se diluyó con EtOAc. Se filtró a través de un lecho corto de Celite® y se sometió a evaporación rotatoria. El residuo se colocó sobre gel de sílice y eluyó con un gradiente de EtOAc/Hex obteniendo (S)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(2-metilpirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina (189 mg, 0,363 mmol, 63,1 % de rendimiento) as a mezcla diastereomérica. Los diastereómeros se separaron por cromatografía quiral SFC (columna Chiralcel OJ, MeOH al 40% MeOH (DEA al 0,1%) en CO_2) proporcionando los Ejemplos 74A y 74B.

74A: CL-EM $(M+H)^+$ = 521,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,60 (1 H, d, *J*=1,53 Hz), 7,50 (1 H, d, *J*=1,53 Hz), 7,35 - 7,41 (2 H, m), 7,00 - 7,10 (4 H, m), 6,93 - 6,99 (2 H, m), 5,82 (1 H, t, *J*=2,44 Hz), 5,42 - 5,48 (1 H, m), 5,35 - 5,40 (1 H, m), 5,29 (1 H, s), 3,72 - 3,79 (1 H, m), 3,68 (3 H, s), 3,55 - 3,63 (1 H, m), 1,97 - 2,14 (3 H, m), 1,71 - 1,76 (1 H, m), 1,26 (3 H, d, *J*=6,41 Hz).

Ejemplo 75

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina

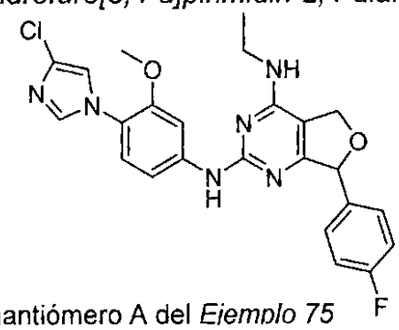


A una solución de 2-cloro-N-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-4-amina (*Preparación Mb*) en dioxano (619 µl) y agua (124 µl) se añadió 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (29,1 mg, 0,130 mmol), tris(dibencilidenacetona)dipaladio(0) (59,5 mg, 0,065 mmol), 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (75 mg, 0,130 mmol) y Na_2CO_3 (20,66 mg, 0,195 mmol). La mezcla resultante se llevó hasta 110 °C en un tubo herméticamente cerrado y se agitó durante la noche. La mezcla de reacción se diluyó entonces con EtOAc (10 ml), se lavó con agua (5 ml), salmuera (5ml), se secó sobre $MgSO_4$, se filtró y se concentró a vacío. La purificación por cromatografía ultrarrápida (sílice, MeOH/$CHCl_3$) eliminó el ligando Xanteno ya que no precipitó en la columna preparativa. La purificación del aceite resultante por HPLC preparativa (C18, 50 X 250mm, MeOH/H_2O/TFA) dio N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina, TFA (16,94 mg, 0,028 mmol, 21,91 % de rendimiento) como un vidrio transparente. CL-EM $(M+H)^+$ = 481,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,86 (1 H, d, *J*=1,53 Hz), 7,56 (1 H, d, *J*=2,14 Hz), 7,43 - 7,49 (2 H, m), 7,40 (1 H, d, *J*=8,85 Hz), 7,37 (1 H, d, *J*=1,22 Hz), 7,21 (1 H, dd, *J*=8,55,

2,14 Hz), 7,17 (2 H, t, *J*=8,70 Hz), 6,10 (1 H, t, *J*=3,20 Hz), 5,17 (1 H, dd, *J*=11,44, 3,81 Hz), 5,04 (1 H, dd, *J*=11,60, 2,14 Hz), 3,86 (3 H, s); 3,66 (2 H, c, *J*=7,32 Hz), 1,32 (3 H, t, *J*=7,32 Hz).

Ejemplo 75A

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina

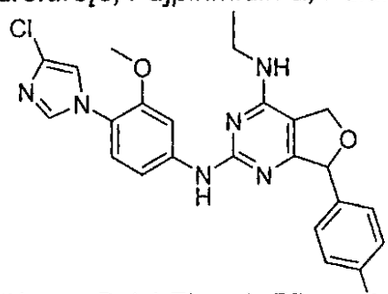


Enantiómero A del *Ejemplo 75*

Se separó N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina (*Ejemplo 75*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 35% (DEA al 0,1%)/CO_2) dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina (primero en eluir, enantiómero A) (20,7 mg, 0,043 mmol, 10,71 % de rendimiento) como una espuma blanquecina fragmentada. CL-EM $(M+H)^+$ = 481,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,87 (1 H, d, *J*=2,14 Hz), 7,68 (1 H, d, *J*=1,22 Hz), 7,36 - 7,42 (2 H, m), 7,22 (1 H, d, *J*=1,53 Hz), 7,13 - 7,17 (1 H, m), 7,04 - 7,11 (3 H, m), 5,79 (1 H, d, *J*=2,14 Hz), 5,09 - 5,15 (1 H, m), 4,96 - 5,03 (1 H, m), 3,71 (3 H, s), 3,57 (2 H, c, *J*=7,02 Hz), 1,25 - 1,30 (3 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 75A*.

Ejemplo 75B

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina

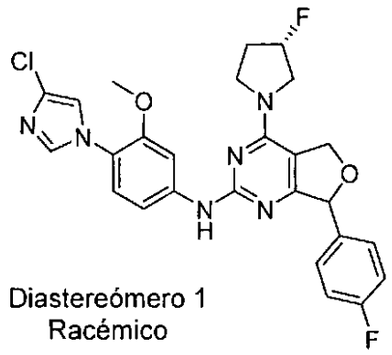


Enantiómero B del *Ejemplo 75*

Se separó N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina (*Ejemplo 75*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 35% (DEA al 0,1%)/CO_2) dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina (segundo en eluir, enantiómero B) (19,6 mg, 0,041 mmol, 10,14 % de rendimiento) como espuma blanquecina fragmentada. CL-EM $(M+H)^+$ = 481,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,87 (1 H, s), 7,68 (1 H, s), 7,40 (2 H, td, *J*=5,80, 2,44 Hz), 7,23 (1 H, s), 7,14 - 7,18 (1 H, m), 7,06 - 7,12 (3 H, m), 5,80 (1 H, s ancho), 5,13 (1 H, dd, *J*=10,99, 3,05 Hz), 5,00 (1 H, d, *J*=10,99 Hz), 3,72 (3 H, s), 3,57 (2 H, c, *J*=7,02 Hz), 1,25 - 1,31 (3 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 75 B*.

Ejemplo 76

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina

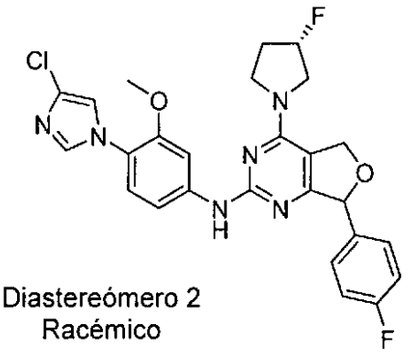


Diastereómero 1
Racémico

Se combinaron 2-cloro-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidina (*Preparación Mc1*) (49 mg, 0,145 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (32,4 mg, 0,145 mmol) y se purificó según el *Ejemplo 26* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina, TFA (diastereómero 1, racemato) (24,18 mg, 0,038 mmol, 26,1 % de rendimiento) como vidrio ligeramente amarillo. CL-EM $(M+H)^+$ = 525,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,92 (1 H, d, *J*=1,53 Hz), 7,54 (1 H, s ancho), 7,47 - 7,52 (2 H, m), 7,38 - 7,42 (2 H, m), 7,28 (1 H, dd, *J*=8,55, 2,14 Hz), 7,15 - 7,21 (2 H, m), 6,07 - 6,11 (1 H, m), 5,62 (1 H, dd, *J*=10,99, 3,97 Hz), 5,35 - 5,53 (2 H, m), 4,09 - 4,23 (2 H, m), 3,89 - 4,08 (2 H, m), 3,87 (3 H, s), 2,44 (1 H, s ancho), 2,12 - 2,38 (1 H, m). No se determinó la estereoquímica relativa del *Ejemplo 76*.

Ejemplo 77

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina

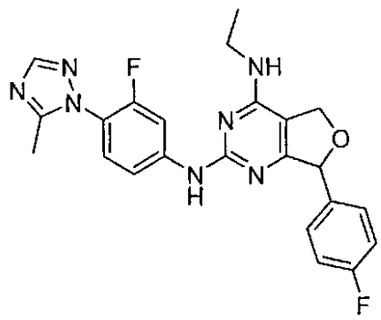


Diastereómero 2
Racémico

Se combinaron 2-cloro-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidina (*Preparación Mc2*) (40 mg, 0,118 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (26,5 mg, 0,118 mmol) y se purificó según el *Ejemplo 26* dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina, TFA (diastereómero 2, racemato) (25,75 mg, 0,040 mmol, 34,0 % de rendimiento) como un vidrio ligeramente amarillo. CL-EM $(M+H)^+$ = 525,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,88 (1 H, d, *J*=1,22 Hz), 7,54 (1 H, s), 7,46 - 7,51 (2 H, m), 7,36 - 7,42 (2 H, m), 7,16 - 7,25 (3 H, m), 6,08 (1 H, t, *J*=3,20 Hz), 5,52 - 5,60 (1 H, m), 5,36 - 5,52 (2 H, m), 4,02 - 4,20 (2 H, m), 4,00 (2 H, s), 3,88 - 3,99 (1 H, m), 3,86 (3 H, s), 2,37 - 2,51 (1 H, m), 2,14 - 2,37 (1 H, m). No se determinó la estereoquímica relativa del *Ejemplo 77*.

Ejemplo 78

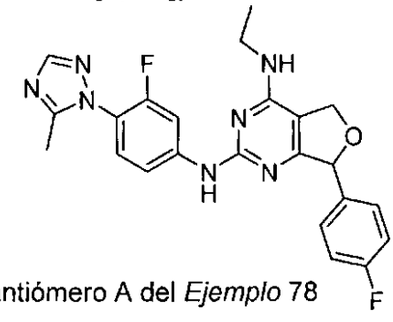
N^4-etil-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina



Se combinaron 2-cloro-N-etil-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-4-amina (*Preparación Mb*) y 3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina (*Preparación C*) (51,6 mg, 0,268 mmol) y se purificó según el *Ejemplo 75* dando N^4-etil-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina, TFA (64,1 mg, 0,114 mmol, 42,4 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 450,0. RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 8,08 (1 H, s), 7,96 - 8,02 (1 H, m), 7,42 - 7,53 (4 H, m), 7,17 (2 H, t, *J*=8,85 Hz), 6,04 (1 H, t, *J*=3,05 Hz), 5,18 (1 H, dd, *J*=11,44, 3,51 Hz), 5,02 - 5,08 (1 H, m), 3,64 (2 H, c, *J*=7,12 Hz), 2,42 (3 H, s), 1,34 (3 H, t, *J*=7,17 Hz).

Ejemplo 78A

N^4-etil-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina

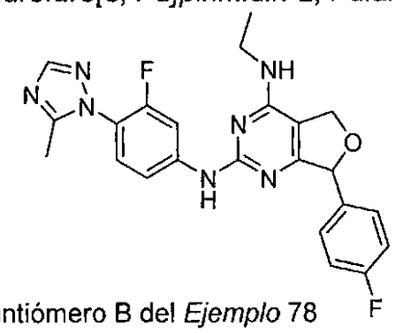


Enantiómero A del *Ejemplo* 78

Se separó N^4-etil-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina (*Ejemplo 78*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 30% (DEA al 0,1%)/CO_2) dando N^4-etil-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina (primero en eluir, enantiómero A) (25,8 mg, 0,057 mmol, 21,40 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 450,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,15 (1 H, dd, *J*=13,89, 2,29 Hz), 8,03 (1 H, s), 7,39 - 7,47 (3 H, m), 7,33 (1 H, t, *J*=8,55 Hz), 7,07 - 7,12 (2 H, m), 5,84 (1 H, t, *J*=2,59 Hz), 5,14 (1 H, dd, *J*=11,29, 3,36 Hz), 5,03 (1 H, dd, *J*=11,14, 1,68 Hz), 3,53 - 3,61 (2 H, m), 2,39 (3 H, s), 1,27 - 1,32 (3 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 78A*.

Ejemplo 78B

N^4-etil-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina



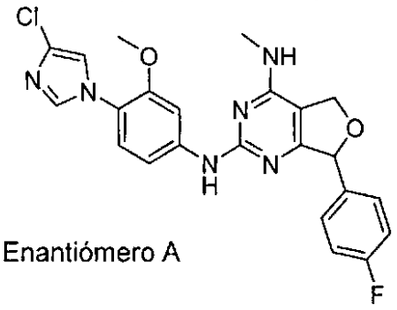
Enantiómero B del *Ejemplo* 78

Se separó N^4-etil-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina (*Ejemplo 78*) mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 30%

(DEA al 0,1%)/CO_2) dando N^4-etil-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina (segundo en eluir, enantiómero B) (24,6 mg, 0,055 mmol, 20,40 % de rendimiento) como un sólido blanco. CL-EM $(M+H)^+$ = 450,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,99 - 8,06 (1 H, m), 7,94 (1 H, s), 7,36 - 7,42 (2 H, m), 7,23 - 7,29 (1 H, m), 7,12 (1 H, dd, *J*=8,55, 1,83 Hz), 7,02 - 7,08 (2 H, m), 5,86 (1 H, d, *J*=2,44 Hz), 5,01 - 5,21 (2 H, m), 3,50 - 3,60 (2 H, m), 2,40 (3 H, s), 1,27 - 1,33 (3 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 78B*.

Ejemplo 79A

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-metil-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina



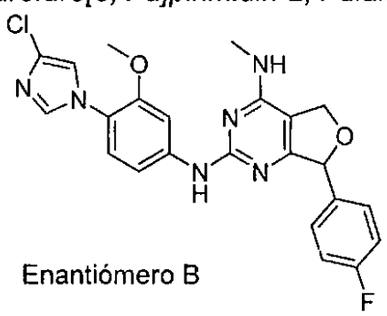
Enantiómero A

Se combinaron 2-cloro-7-(4-fluorofenil)-N-metil-5,7-dihidrofuro[3,4-d]pirimidin-4-amina (*Preparación Ma*) (149 mg, 0,533 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (119 mg, 0,533 mmol) y se purificó según el *Ejemplo 75* dando el racemato N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-metil-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina que se separó mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 35% (DEA al 0,1%)/CO_2) dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-metil-5,7-dihidrofuro[3,4-

d]pirimidin-2,4-diamina (primero en eluir, enantiómero A) (18,3 mg, 0,039 mmol, 7,36 % de rendimiento) como una espuma blanca fragmentada. CL-EM $(M+H)^+$ = 467,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,89 - 7,94 (1 H, m), 7,65 - 7,69 (1 H, m), 7,36 - 7,42 (2 H, m), 7,20 - 7,24 (1 H, m), 7,13 - 7,18 (1 H, m), 7,03 - 7,12 (3 H, m), 5,79 (1 H, s ancho), 5,08 - 5,16 (1 H, m), 4,95 - 5,03 (1 H, m), 3,68 - 3,73 (3 H, m), 3,02 - 3,07 (3 H, m). No se determinó la estereoquímica absoluta del *Ejemplo 79A*.

Ejemplo 79B

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-metil-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina



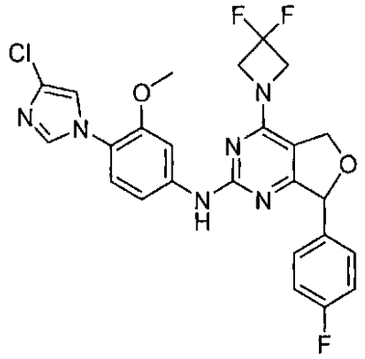
Enantiómero B

Se combinaron 2-cloro-7-(4-fluorofenil)-N-metil-5,7-dihidrofuro[3,4-d]pirimidin-4-amina (*Preparación Ma)* (149 mg, 0,533 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (*Preparación A*) (119 mg, 0,533 mmol) y se purificó según el *Ejemplo 75* dando el racemato N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-metil-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina que se separó mediante varias inyecciones de SFC quiral (OJ-H 30 x 250mm, 5 μM, MeOH al 35% (DEA al 0,1%)/CO_2) dando N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N^4-metil-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina (segundo en eluir, enantiómero B) (22,1 mg, 0,047

mmol, 8,89 % de rendimiento) como una espuma ligeramente amarilla fragmentada. CL-EM $(M+H)^+$ = 467,0. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,92 (1 H, d, *J*=2,14 Hz), 7,68 (1 H, d, *J*=1,53 Hz), 7,39 (2 H, dd, *J*=8,70, 5,34 Hz), 7,22 (1 H, d, *J*=1,53 Hz), 7,15 (1 H, d, *J*=8,55 Hz), 7,04 - 7,11 (3 H, m), 5,79 (1 H, s ancho), 5,12 (1 H, dd, *J*=10,99, 3,36 Hz), 4,99 (1 H, d, *J*=10,99 Hz), 3,70 (3 H, s), 3,05 (3 H, s). No se determinó la estereoquímica absoluta del *Ejemplo 79B*.

Ejemplo 80

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina



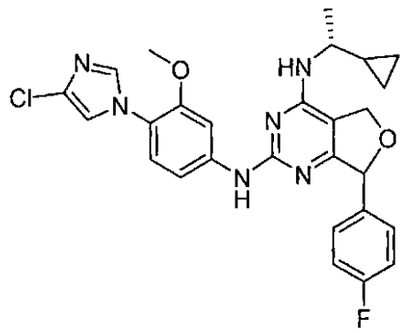
Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,102 g, 0,560 mmol), Preparación Ma (0,160 g, 0,560 mmol), Na_2CO_3 (0,119 g, 0,110 mmol) y xantphos (0,325 g, 0,560 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,310 g, 0,21 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa

se extrajo con acetato de etilo (75 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (gel de sílice, malla 60-120) usando acetato de etilo al 21% en éter de petróleo como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina (0,90 g, 40%) como sólido blanquecino. CL-EM $(M+H)^+$ = 529,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,6 (1H, s), 7,99 (1H, s), 7,98 (1H, s), 7,76-7,41 (3H, m), 7,23-7,13 (4H, m), 5,87 (1H, s), 5,33 (1H, dd, *J* = 11,1, 3,2 Hz), 5,17 (1H, dd, *J* = 11,1, 3,2), 4,67 (4H, m), 3,72 (3H, s).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 80A y 80B, que tuvieron idénticos datos espectrales.

Ejemplo 81

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-((R)-1-ciclopropiletil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina, TFA

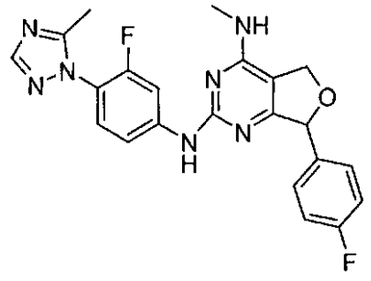


Mezcla diastereomérica

Se hizo reaccionar 2-cloro-N-((R)-1-ciclopropiletil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-4-amina (Preparación Mf) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-((R)-1-ciclopropiletil)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina, TFA como una mezcla de 2 diastereómeros (Ejemplo 81). CL-EM $(M+H)^+$ = 521,3. RMN de ^1H (500 MHz, MeOD) δ ppm 7,82 (d, J=1,53 Hz, 1 H) 7,44 - 7,51 (m, 3 H) 7,38 (d, J=8,55 Hz, 1 H) 7,35 (d, J=1,53 Hz, 1 H) 7,14 - 7,22 (m, 3 H) 6,08 (s ancho, 1 H) 5,21 (dd, J=11,60, 3,05 Hz, 1 H) 5,07 (dd, J=11,44, 2,59 Hz, 1 H) 3,84 (s, 3 H) 3,30(m, 1 H) 1,38 (d, J=6,41 Hz, 3 H) 1,06 - 1,13 (m, 1 H) 0,59 - 0,66 (m, 1 H) 0,54 (d, J=3,97 Hz, 1 H) 0,37 (d, J=4,88 Hz, 1 H) 0,28 (d, J=4,88 Hz, 1 H).

Ejemplo 82

N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N4-metil-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina, TFA



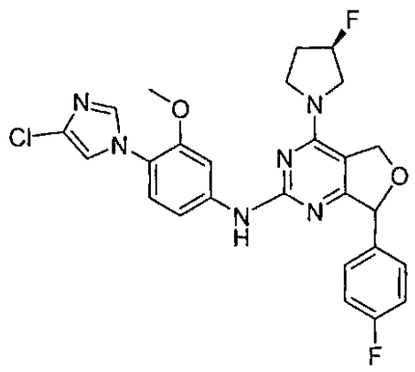
Se hizo reaccionar 2-cloro-7-(4-fluorofenil)-N-metil-5,7-dihidrofuro[3,4-d]pirimidin-4-amina (Preparación Ma) como se describe en el Ejemplo 112 con 3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina (Preparación C) dando N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7-(4-fluorofenil)-N4-metil-5,7-dihidrofuro[3,4-d]pirimidin-2,4-diamina, TFA (Ejemplo 82). CL-EM $(M+H)^+$ =

436,1. RMN de ^{1}H (500 MHz, MeOD) δ ppm 8,16 (dd, J=13,89, 2,29 Hz, 1 H) 8,03 (s, 1 H) 7,38 - 7,47 (m, 3 H) 7,34 (t, J=8,70 Hz, 1 H) 7,05 - 7,14 (m, 2 H) 5,85 (d, J=1,83 Hz, 1 H) 5,16 (s ancho, 1 H) 5,04 (s ancho, 1 H) 3,07 (s, 3 H) 2,39 (s, 3 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 82A y 82B como aminas libres, que tuvieron idénticos datos espectrales.

Ejemplo 83

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina, 2 TFA



Mezcla diastereomérica

Se hizo reaccionar 2-cloro-7-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación Mg) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina, 2 TFA como una mezcla de dos diastereómeros (Ejemplo 83). CL-EM $(M+H)^+$ = 525,1. RMN de

^{1}H (500 MHz, MeOD) δ ppm 7,83 (s ancho, 1 H) 7,57 (s ancho, 1 H) 7,43 - 7,52 (m, 2 H) 7,32 - 7,41 (m, 2 H) 7,22 - 7,29 (m, 1 H) 7,10 - 7,22 (m, 2 H) 6,00 - 6,11 (m, 1 H) 5,38 - 5,50 (m, 3 H) 4,10 (s ancho, 2 H) 3,90 (s ancho, 2 H) 2,31 - 2,51 (m, 2 H).

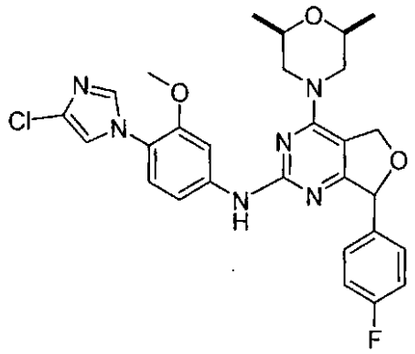
La mezcla de dos diastereómeros se separó por cromatografía quiral proporcionando dos diastereómeros Ejemplo 83A y 83B como aminas libres

Ejemplo 83A: CL-EM $(M+H)^+$ = 525,2. RMN de ^{1}H (500 MHz, MeOD) δ ppm 7,80 (d, J=1,83 Hz, 1 H) 7,69 (d, J=1,53 Hz, 1 H) 7,43 (dd, J=8,70, 5,34 Hz, 2 H) 7,23 (d, J=1,22 Hz, 1 H) 7,04 - 7,20 (m, 4 H) 5,77 (s ancho, 1 H) 5,50 - 5,59 (m, 1 H) 5,27 - 5,39 (m, 2 H) 4,00 (d, J=11,90 Hz, 1 H) 3,82 - 3,96 (m, 2 H) 3,63 - 3,82 (m, 4 H) 2,26 - 2,42 (m, 2 H).

Ejemplo 83B: CL-EM $(M+H)^+$ = 525,2. RMN de ^{1}H (500 MHz, MeOD) δ ppm 7,81 (d, J=1,83 Hz, 1 H) 7,69 (d, J=1,53 Hz, 1 H) 7,39 - 7,47 (m, 2 H) 7,24 (d, J=1,53 Hz, 1 H) 7,16 - 7,21 (m, 1 H) 7,05 - 7,16 (m, 3 H) 5,80 (t, J=2,59 Hz, 1 H) 5,51 (dd, J=10,38, 3,05 Hz, 1 H) 5,36 - 5,46 (m, 2 H) 3,91 (m, 2 H) 3,66 - 3,86 (m, 5 H) 2,23 - 2,42 (m, 2 H).

Ejemplo 84

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina, 2 TFA



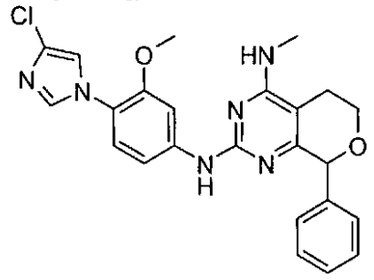
Se hizo reaccionar 2-cloro-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidina (Preparación Mh) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenil)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina, 2 TFA (Ejemplo 84). CL-EM $(M+H)^+$ = 551,2. RMN de ^1H (400 MHz, MeOD) δ ppm 7,80 (d, J=1,51 Hz, 1 H) 7,55 (d, J=2,27 Hz, 1 H) 7,35 - 7,46 (m, 2 H) 7,23 - 7,33 (m, 2 H) 7,01 - 7,18 (m, 3 H) 5,91 (t, J=2,77 Hz, 1 H) 5,42 (dd, J=10,45, 3,40 Hz, 1 H) 5,28 (dd, J=10,32, 2,27 Hz, 1 H) 4,16 (s ancho, 2 H) 3,60 - 3,78 (m, 5 H) 2,81 (ddd, J=13,41, 10,51, 3,53 Hz, 2 H) 1,21 (d, J=6,04 Hz, 6 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 84A y 84B como aminas libres.

CL-EM $(M+H)^+$ = 551,2. RMN de ^1H (500 MHz, MeOD) δ ppm 7,77 (d, J=2,14 Hz, 1 H) 7,69 (d, J=1,53 Hz, 1 H) 7,35 - 7,50 (m, 2 H) 7,24 (d, J=1,53 Hz, 1 H) 7,18 (d, J=8,55 Hz, 1 H) 7,10 (t, J=8,70 Hz, 2 H) 7,05 (dd, J=8,55, 2,14 Hz, 1 H) 5,80 (d, J=2,44 Hz, 1 H) 5,42 (dd, J=10,38, 3,05 Hz, 1 H) 5,28 (dd, J=10,38, 1,83 Hz, 1 H) 4,16 (s ancho, 2 H) 3,61 - 3,76 (m, 5 H) 2,60 - 2,80 (m, 2 H) 1,23 (d, J=6,41 Hz, 6 H).

Ejemplo 85

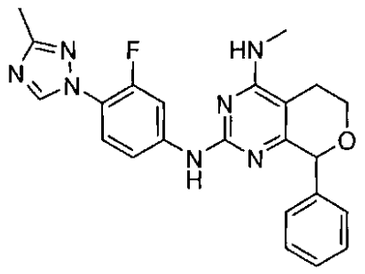
N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2,4-diamina



Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,168 g, 0,75 mmol), Preparación Na (0,23 g, 0,834 mmol), Na_2CO_3 (0,176 g, 1,6 mmol) y xantphos (0,482 g, 0,834 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,38 g, 0,417 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de Celite y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (75 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2,4-diamina (0,140 g, 36,2%) como sólido blanquecino. CL-EM $(M+H)^+$ = 463,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,06 (1H, s), 7,96 (1H, s), 7,72 (1H, s), 7,4 (1H, s), 7,36-7,30 (5H, m), 7,13 (2H, m), 6,94 (1H, m), 5,43 (1H, s), 3,95 (1H, m), 3,81 (1H, s), 3,53 (3H, s), 2,97 (3H, d, *J* = 4,4 Hz), 2,52 (1H, m), 2,45 (1H, m).

Ejemplo 86

N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2,4-diamina

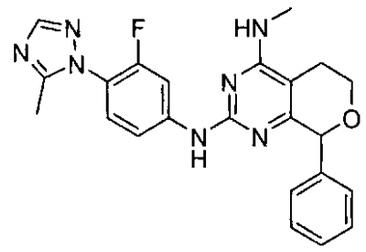


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación B (0,119 g, 0,62 mmol), Preparación Na (0,19 g, 0,68 mmol), Na_2CO_3 (0,146 g, 1,37 mmol) y xantphos (0,399 g, 0,689 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,315 g, 0,344 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (75 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2,4-diamina (0,120 g, 30%) como sólido blanquecino. CL-EM $(M+H)^+$ = 432,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,33 (1H, s), 8,68 (1H, s), 8,03 (1H, m), 7,42-7,24 (7H, m),

6,98 (1H, *s ancho)*, 5,44 (1H, s), 4,06 (1H, m), 3,84 (1H, m), 2,95 (3H, d, *J* = 4,4 Hz), 2,59 (1H, m), 2,44 (1H, m), 2,34 (3H, s).

Ejemplo 87

N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2,4-diamina

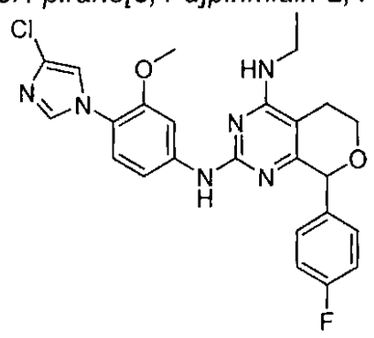


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación C (0,119 g, 0,62 mmol), Preparación Na (0,19 g, 0,68 mmol), Na_2CO_3 (0,146 g, 1,37 mmol) y xantphos (0,399 g, 0,689 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,315 g, 0,344 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (75 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2,4-diamina (0,130 g, 44%) como sólido blanquecino. CL-EM $(M+H)^+$ = 432,2. RMN de ^1H (400 MHz,

DMSO-*d6*): δ ppm 9,38 (1H, s), 8,04 (1H, s), 8,01 (1H, s), 7,44 (1H, m), 7,34-7,27 (6H, m), 6,99 (1H, *s ancho)*, 5,43 (1H, s), 4,06 (1H, m), 3,83 (1H, m), 2,95 (3H, d, *J* = 4,4,0 Hz), 2,51 (1H, m), 2,44 (1H, m), 2,27 (3H, s).

Ejemplo 88

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2,4-diamina



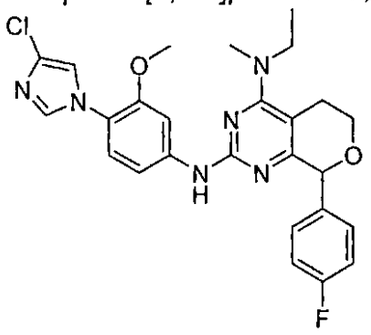
Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,09 g, 0,38 mmol), Preparación Oa (0,15 g, 0,48 mmol), Na_2CO_3 (0,103 g, 0,97 mmol) y xantphos (0,282 g, 0,41 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,270 g, 0,24 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (75 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 35% en éter de petróleo como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-

metoxifenil)-N4-etil-8-(4-fluorofenil)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2,4-diamina (0,90 g, 55%) como sólido blanquecino. CL-EM $(M+H)^+$ = 495,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,06 (1H, s), 7,88 (1H, s), 7,73 (1H, m), 7,42 (1H, m), 7,33-7,44 (2H, m), 7,14-7,15 (4H, m), 6,92 (1H, m), 5,44 (1H, s), 3,96 (1H, m), 3,82 (1H, m), 3,57 (3H, s), 3,50 (2H, m), 2,45 (2H, m), 1,21 (3H, m).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 88A y 88B, que tuvieron idénticos datos espectrales.

Ejemplo 89

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2,4-diamina

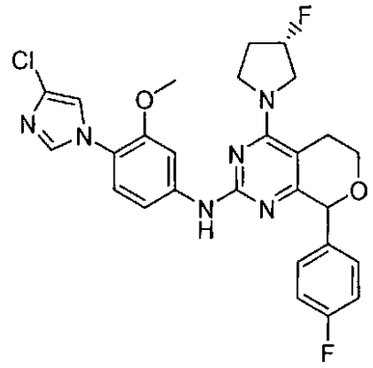


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,029 g, 0,10 mmol), Preparación Ob (0,050 g, 0,14 mmol), Na_2CO_3 (0,030 g, 0,28 mmol) y xantphos (0,080 g, 0,14 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,078 g, 0,07 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa

se extrajo con acetato de etilo (75 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 35% en éter de petróleo como fase móvil dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2,4-diamina (0,020 g, 30%) como sólido blanquecino. CL-EM $(M+H)^+$ = 509,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,12 (1H, s), 7,75-7,81 (2H, m), 7,38-7,44 (3H, m), 7,15-7,24 (4H, m), 5,51 (1H, s), 4,03 (1H, m), 3,49-3,67 (5H, m), 3,09 (3H, m), 3,01-3,06 (1H, m), 2,51-2,59 (2H, m), 1,22 (3H, t, *J* = 7,2 Hz).

Ejemplo 90A

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina

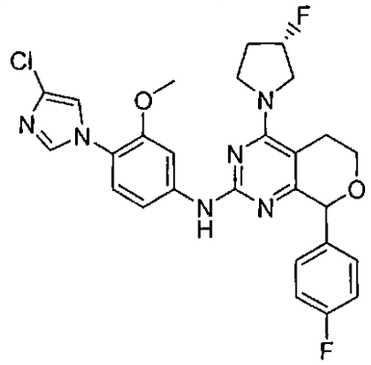


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,063 g, 0,20 mmol), Preparación Oc1 (0,110 g, 0,3 mmol), Na_2CO_3 (0,066 g, 0,6 mmol) y xantphos (0,181 g, 0,3 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0172 g, 0,10 mmol) a la mezcla de reacción y la

solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (75 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 35% en éter de petróleo como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina (0,050g, 60%) como sólido blanquecino. CL-EM $(M+H)^+$ = 539,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,12 (1H, s), 7,75 (2H, m), 7,39-7,44 (3H, m), 7,15-7,22 (4H, m), 5,50 (1H, s), 5,38 (1H, m), 3,82-4,09 (6H, m), 3,68 (3H, s), 2,98 (2H, m), 2,50-2,43 (2H, m).

Ejemplo 90B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina

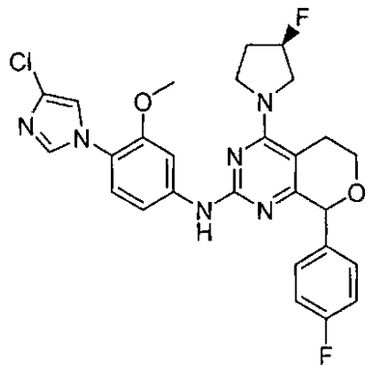


Se purgó con argon durante 1 h a temperatura ambiente una solución de

la Preparación A (0,063 g, 0,20 mmol), Preparación Oc2 (0,110 g, 0,3 mmol), Na_2CO_3 (0,066 g, 0,6 mmol) y xantphos (0,181 g, 0,3 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0172 g, 0,10 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (75 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 35% en éter de petróleo como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina (0,070g, 63%) como sólido blanquecino. CL-EM $(M+H)^+$ = 539,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,16 (1H, s), 7,81 (1H, s), 7,74 (1H, s), 7,73 (1H, s), 7,42 (2H, m), 7,17-7,11 (4H, m), 5,54 (1H, s), 5,43 (1H, m), 4,12-3,57 (6H, m), 3,34 (3H, s), 2,97 (2H, m), 2,50-2,43 (2H, m).

Ejemplo 91A

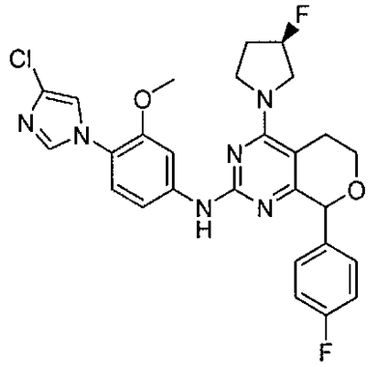
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina



Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,063 g, 0,20 mmol), Preparación Od1 (0,110 g, 0,3 mmol), Na_2CO_3 (0,066 g, 0,6 mmol) y xantphos (0,181 g, 0,3 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0172 g, 0,10 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (75 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 35% en éter de petróleo como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina (0,040 g, 40%) como sólido blanquecino. CL-EM $(M+H)^+$ = 539,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,25 (1H, s), 7,77 (1H, s), 7,77 (1H, s), 7,45 (3H, m), 7,21 (4H, m), 5,53 (1H, s), 5,43 (1H, m), 4,12-3,57 (5H, m), 3,34 (3H, s), 3,33 (1H, m), 3,20 (1H, m), 2,73 (1H, m), 2,31-2,06 (2H, m).

Ejemplo 91B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina

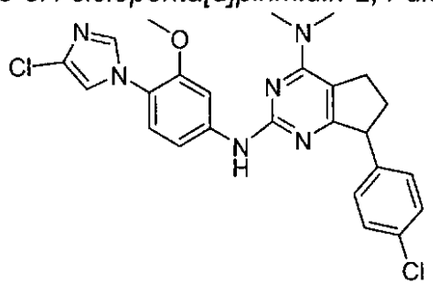


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,063 g, 0,20 mmol), Preparación Od2 (0,110 g, 0,3 mmol), Na_2CO_3 (0,066 g, 0,6 mmol) y xantphos (0,181 g, 0,3 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0172 g, 0,10 mmol) a la mezcla de reacción y la solución resultante se purgó durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (75 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 35% en éter de petróleo como fase móvil dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina (0,039g, 39%) como sólido blanquecino. CL-EM $(M+H)^+$ = 539,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,15 (1H, s), 7,81

(1H, s), 7,74 (1H, s), 7,43 (1H, s), 7,37 (2H, m), 7,19 (4H, m), 5,54 (1H, s), 5,43 (1H, m), 4,13-3,69 (6H, m), 3,33 (3H, s), 2,96 (2H, m), 2,24-1,91 (2H, m).

Ejemplo 92

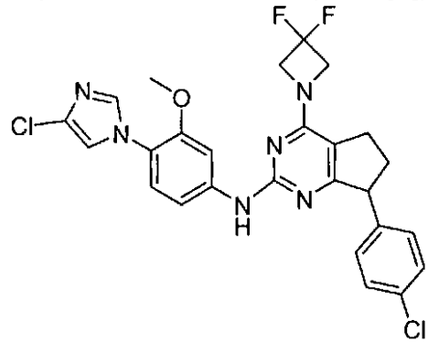
N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-clorofenil)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se añadió 2-cloro-7-(4-clorofenil)-*N*,*N*-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (98 mg, 0,318 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (71,1 mg, 0,318 mmol) en ácido acético (1,000 ml) y THF (1 ml). La mezcla de reacción se calentó a 75°C durante la noche. Se observó conversión parcial al producto deseado. La reacción se calentó de nuevo a 120°C durante 6 h. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(4-clorofenil)-N^4,N^4-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (17,2 mg, 0,028 mmol, 8,70 % de rendimiento). CL-EM $(M+H)^+$ = 495,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,80 (1H, s), 7,61 - 7,72 (1H, m), 7,34 - 7,42 (2H, m), 7,27 - 7,33 (2H, m), 7,21 (2H, d, *J*=8,5 Hz), 7,16 (1H, d, *J*=9,2 Hz), 7,06 (1H, d, *J*=1,5 Hz), 4,30 - 4,41 (1H, m), 3,82 (6H, s), 3,48 (1H, s ancho), 3,31 - 3,39 (2H, m), 3,18 - 3,27 (1H, m), 2,58 - 2,80 (2H, m), 2,14 - 2,29 (1H, m).

Ejemplo 93

N-(4-(4-Cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-6,7-dihidro-5*H*-ciclopenta[d]pirimidin-2-amina

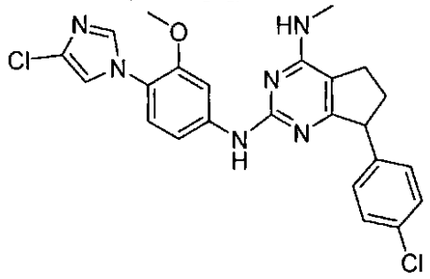


Se añadió 2-cloro-7-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (70 mg, 0,197 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (52,7 mg, 0,236 mmol) en ácido acético (1 ml) y THF (1,000 ml). La mezcla de reacción se calentó a 120ºC en un microondas durante 6 h. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando *N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(4-clorofenil)-4-(3,3-difluoroazetidin-1-il)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2-amina, sal TFA (8,7 mg, 0,013 mmol, 6,46 % de rendimiento). CL-EM $(M+H)^+$ = 543,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,85 - 11,99 (1H, m), 7,93 (1H, s), 7,38 - 7,45 (1H, m), 7,31 (2H, d, *J*=8,2 Hz), 7,19 (3H, t, *J*=8,2 Hz), 7,10 (1H, d, *J*=1,5 Hz), 4,37 - 4,47 (1H, m), 3,85 (3H, s), 3,45 - 3,51 (1H, m), 3,07 - 3,18 (2H, m), 2,94 - 3,04 (2H, m), 2,67 - 2,81 (2H, m), 2,19 - 2,37 (2H, m).

Ejemplo 94

N^2-(4-(4-Cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(4-clorofenil)-N^4-metil-6,7-

dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina



Se añadió 2-cloro-7-(4-clorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (101 mg, 0,343 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (77 mg, 0,343 mmol) en ácido acético (2 ml)y THF (2 ml). La mezcla de reacción se calentó a 80°C durante la noche. Se observó conversión parcial al producto deseado. La reacción se calentó de nuevo a 120 °C durante 6 h. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(4-clorofenil)-N^4-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (35,5 mg, 0,059 mmol, 17,19 % de rendimiento). CL-EM $(M+H)^+$ = 481,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,08 (1H, s), 8,33 (1H, s), 7,48 (2H, d, *J*=2,1 Hz), 7,30 (2H, d, *J*=8,2 Hz), 7,20 (1H, d, *J*=1,5 Hz), 7,13 (2H, d, *J*=8,5 Hz), 5,83 - 5,93 (1H, m), 4,38 - 4,48 (1H, m), 3,97 (1H, s), 3,86 (3H, s), 3,22 (3H, d, *J*=4,9 Hz), 2,85 - 2,95 (1H, m), 2,77 (2H, dd, *J*=8,7, 5,3 Hz), 2,20 - 2,32 (1H, m).

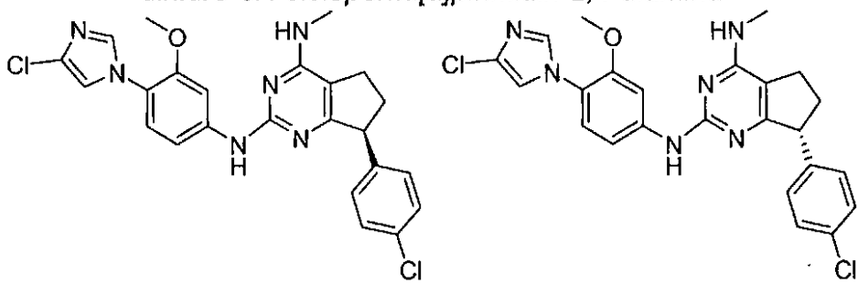
Ejemplo 94A y 94B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-clorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-clorofenil)-N^4-metil-6,7-

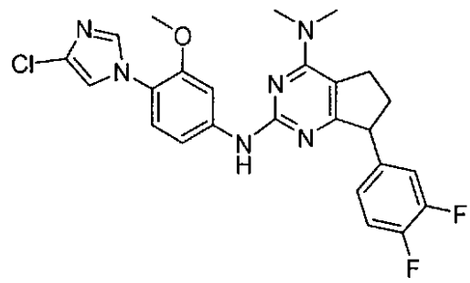
dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se purificó una mezcla racémica de *N*^{2}-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(4-clorofenil)-*N*^{4}-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (37 mg, 0,077 mmol del *Ejemplo 94*) usando SFC quiral proporcionando 10,5 mg de pico A (*Ejemplo 94A*) y 13,6 mg de pico B (*Ejemplo 94B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 μM), metanol al 35% (dietilamina al 0,1%) en CO_2, 35ºC, caudal 2,0 ml/min durante 20 min, absorbancia 268 nm, inyección de 5μl de solución de 2 mg/ml en metanol/cloroformo 50/50 (varias inyecciones apiladas), t_R (pico A) = 5,3 min, t_R (pico B) 14,9 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 94A y 94B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 94*).

Ejemplo 95

N^2*-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(3,4-difluorofenil)-N*^{4}*,N*^{4}*-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina*



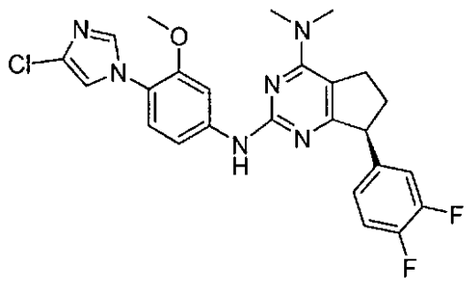
Se añadió 2-cloro-7-(3,4-difluorofenil)-*N*,*N*-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (178 mg, 0,575 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (141 mg, 0,632 mmol) en ácido acético (2 ml) y THF (2,000 ml). La mezcla de reacción se calentó a 80°C durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(3,4-difluorofenil)-N^4,N^4-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (144,1 mg, 0,233 mmol, 40,6 % de rendimiento). CL-EM $(M+H)^+$ = 497,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,53 - 11,67 (1H, m), 8,96 (1H, s ancho), 7,85 - 7,96 (1H, m), 7,38 (1H, s), 7,18 (1H, d, *J*=8,2 Hz), 7,00 - 7,16 (4H, m), 4,34 (1H, dd, *J*=9,6, 4,4 Hz), 3,83 (3H, s), 3,30 - 3,57 (6H, m), 3,25 - 3,29 (1H, m), 3,19 - 3,26 (1H, m), 2,61 - 2,72 (1H, m), 2,14 - 2,25 (1H, m).

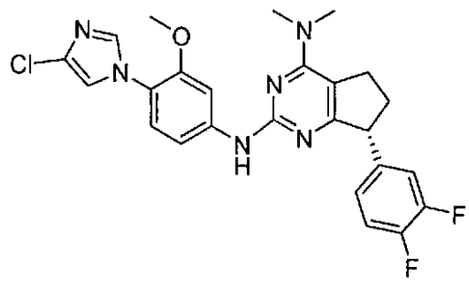
Ejemplo 95A y 95B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(3,4-difluorofenil)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(3,4-difluorofenil)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

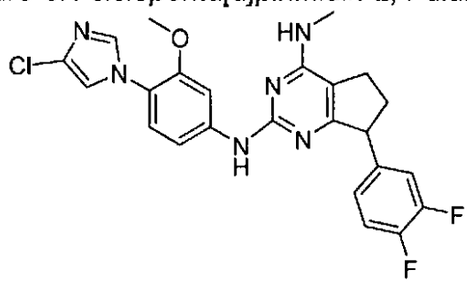




Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(3,4-difluorofenil)-N^4,N^4-dimetil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (139 mg, 0,28 mmol del *Ejemplo 95*) usando SFC quiral proporcionando 47,6 mg de pico A (*Ejemplo 95A*) y 47,3 mg de pico B (*Ejemplo 95B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 µM), metanol al 35% (dietilamina al 0,1%) en CO_2, 35ºC, caudal 2,0 ml/min durante 8 min, absorbancia 268 nm, inyección de 5µl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 4,6 min, t_R (pico B) 6,3 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 95A y 95B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 95*).

Ejemplo 96

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(3,4-difluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se añadió 2-cloro-7-(3,4-difluorofenil)-*N*-metil-6,7-dihidro-5*H*-

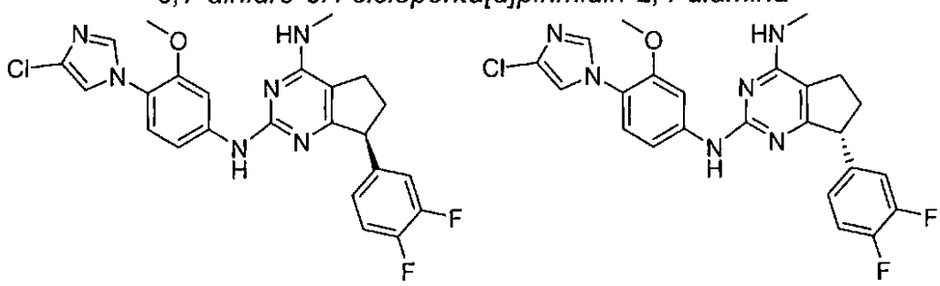
ciclopenta[*d*]pirimidin-4-amina (154 mg, 0,521 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (175 mg, 0,781 mmol) en ácido acético (2 ml) y THF (2,000 ml). La mezcla de reacción se calentó a 120°C durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(3,4-difluorofenil)-N^4-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (22,3 mg, 0,034 mmol, 6,46 % de rendimiento). CL-EM $(M+H)^+$ = 483,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,84 (1H, s), 7,83 - 7,89 (1H, m), 7,55 (1H, s), 7,41 - 7,46 (1H, m), 7,17 - 7,21 (1H, m), 7,10 (2H, s), 6,98 - 7,05 (2H, m), 5,79 - 5,90 (1H, m), 4,38 - 4,45 (1H, m), 3,85 (3H, s), 3,20 - 3,25 (3H, m), 2,90 - 3,00 (1H, m), 2,70 - 2,81 (2H, m), 2,20 - 2,32 (1H, m).

Ejemplo 96A y 96B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(3,4-difluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(3,4-difluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

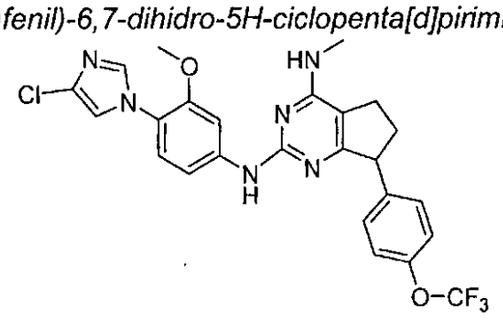


Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(3,4-difluorofenil)-N^4-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-

2,4-diamina (1,4 g, 2,345 mmol del *Ejemplo 96*) usando SFC quiral proporcionando 475 mg de pico A (*Ejemplo 96A*) y 435 mg de pico B (*Ejemplo 96B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 μM), 25 % metanol (dietilamina al 0,1%) en CO_2, 35ºC, caudal 2,0 ml/min durante 14 min, absorbancia 268 nm, inyección de 5μl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 6,1 min, t_R (pico B) 9,2 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 96A y 96B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 96*).

Ejemplo 97

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se añadió 2-cloro-*N*-metil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (220 mg, 0,640 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (215 mg, 0,960 mmol) en ácido acético (2 ml) y THF (2,000 ml). La mezcla de reacción se calentó a 80ºC durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-

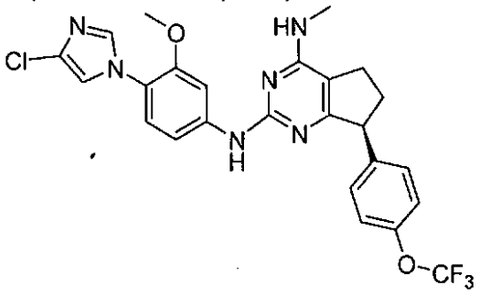
ciclopenta[*d*]pirimidin-2,4-diamina (92 mg, 0,172 mmol, 26,8 % de rendimiento). CL-EM $(M+H)^+$ = 531,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,93 (1H, s), 7,66 (1H, s ancho), 7,50 (1H, s), 7,10 - 7,23 (4H, m), 7,02 (2H, d, *J*=15,3 Hz), 6,83 (1H, d, *J*=8,2 Hz), 4,70 - 4,83 (1H, m), 4,13 - 4,28 (1H, m), 3,12 (3H, d, *J*=4,9 Hz), 2,74 (1H, s ancho), 2,65 (2H, d, *J*=8,2 Hz), 1,97 - 2,08 (1H, m), 1,25 (3H, s).

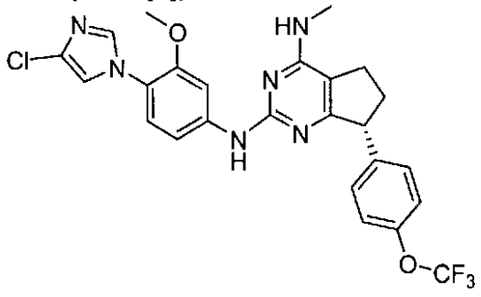
Ejemplo 97A y 97B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



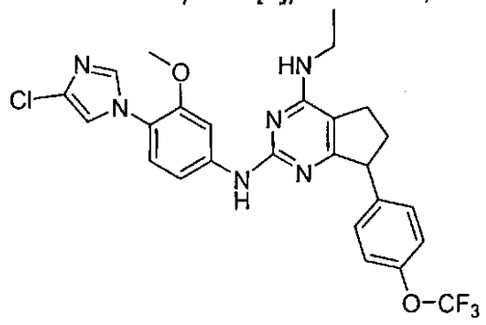


Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (86 mg, 0,162 mmol del *Ejemplo 97*) usando SFC quiral proporcionando 36,6 mg de pico A (*Ejemplo 97A*) y 31,5 mg de pico B (*Ejemplo 97B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 μM), metanol al 30% (dietilamina al 0,1%) en CO_2, 35°C, caudal 2,0 ml/min durante 12 min, absorbancia 268 nm, inyección de 5μl de solución de 2 mg/ml en

metanol (varias inyecciones apiladas), t_R (pico A) = 3,4 min, t_R (pico B) 7,5 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 97A y 97B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 97*).

Ejemplo 98

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se añadió 2-cloro-*N*-etil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (190 mg, 0,531 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (178 mg, 0,797 mmol) en ácido acético (2 ml) y THF (2,000 ml). La mezcla de reacción se calentó a 90°C durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (118 mg, 0,174 mmol, 32,7 % de rendimiento). CL-EM $(M+H)^+$ = 545,0. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 11,04 (1H, s), 9,01 (1H, s ancho), 8,29 (1H, s), 7,44 (2H, s), 7,24 (2H, d, *J*=8,5 Hz), 7,19 (2H, d, *J*=5,5 Hz), 7,09 - 7,12 (1H, m), 5,93 - 5,99 (1H, m), 4,43 - 4,51 (1H, m), 3,86 (3H, s), 3,62 - 3,74 (2H, m), 3,46 - 3,55 (1H, m), 2,85 - 2,97 (1H,

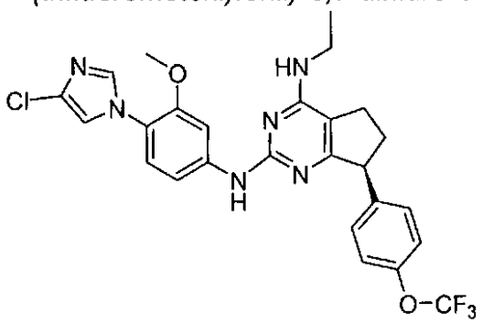
m), 2,71 - 2,82 (2H, m), 2,26 (1H, m), 1,26 - 1,41 (3H, m).

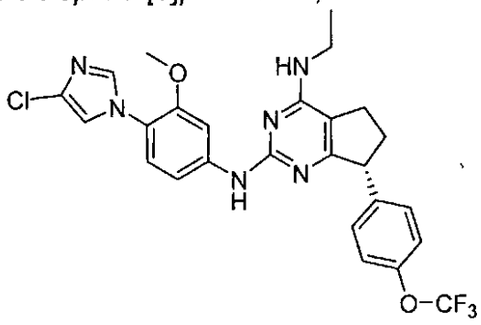
Ejemplo 98A y 98B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

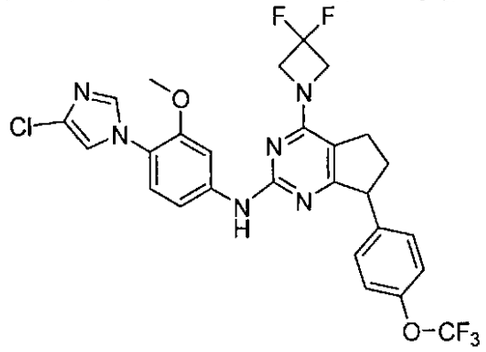




Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (111 mg, 0,204 mmol del *Ejemplo 98*) usando SFC quiral proporcionando 29,5 mg de pico A (*Ejemplo 98A*) y 37,7 mg de pico B (*Ejemplo 98B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 μM), metanol al 30% (dietilamina al 0,1%) en CO_2, 35°C, caudal 2,0 ml/min durante 12 min, absorbancia 268 nm, inyección de 5μl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 3,4 min, t_R (pico B) 8,2 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 98A y 98B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 98*).

Ejemplo 99

N-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Se añadió 2-cloro-4-(3,3-difluoroazetidin-1-il)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (244 mg, 0,601 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (202 mg, 0,902 mmol) en ácido acético (2 ml) y THF (2,000 ml). La mezcla de reacción se calentó a 110ºC durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando *N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2-amina, sal TFA (165,2 mg, 0,229 mmol, 38,1 % de rendimiento). CL-EM $(M+H)^+$ = 593,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,83 (1H, s), 8,00 (1H, s), 7,38 - 7,43 (1H, m), 7,30 - 7,33 (1H, m), 7,27 - 7,28 (1H, m), 7,16 - 7,22 (3H, m), 7,09 - 7,12 (1H, m), 4,76 (1H, s ancho), 4,46 (1H, dd, *J*=9,5, 4,9 Hz), 3,85 (3H, s), 3,07 - 3,17 (2H, m), 2,95 - 3,04 (2H, m), 2,70 - 2,81 (2H, m), 2,21 - 2,34 (2H, m).

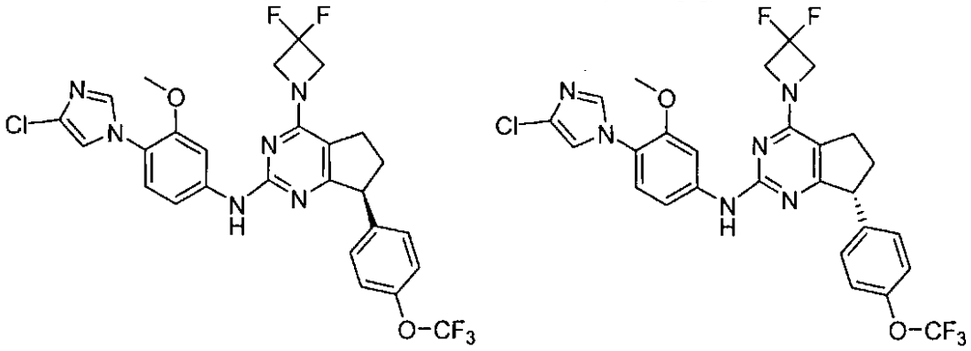
Ejemplo 99A y 99B

(S)-N-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-

(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

y

(R)-N-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

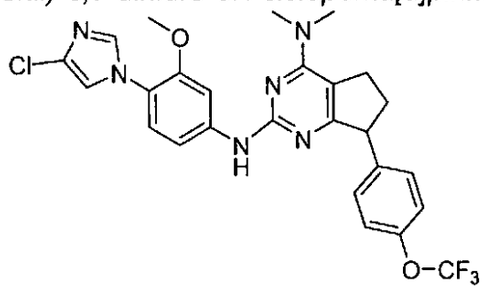


Se purificó una mezcla racémica de *N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2-amina (165,2 mg, 0,279 mmol del *Ejemplo 99*) usando SFC quiral proporcionando 16,7 mg de pico A (*Ejemplo 99A)* y 17,0 mg de pico B (*Ejemplo 99B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 μM), metanol al 30% (dietilamina al 0,1%) en CO_2, 35ºC, caudal 2,0 ml/min durante 20 min, absorbancia 268 nm, inyección de 5μl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 4,9 min, t_R (pico B) 15,0 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 99A y 99B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 99*).

Ejemplo 100

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-7-(4-

(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se añadió 2-cloro-*N*,*N*-dimetil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (250 mg, 0,699 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (234 mg, 1,048 mmol) en ácido acético (1 ml) y THF (1 ml). La mezcla de reacción se calentó a 110ºC durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (235 mg, 0,342 mmol, 49,0 % de rendimiento). CL-EM $(M+H)^+$ = 545,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,18 - 11,39 (1H, m), 8,11 (1H, s), 7,40 - 7,45 (1H, m), 7,30 - 7,34 (1H, m), 7,28 (1H, s), 7,17 - 7,23 (3H, m), 7,12 - 7,15 (1H, m), 4,34 - 4,44 (1H, m), 3,84 (3H, s), 3,50 (4H, s), 3,33 - 3,39 (3H, m), 3,18 - 3,27 (1H, m), 2,57 - 2,78 (1H, m), 2,10 - 2,39 (1H, m).

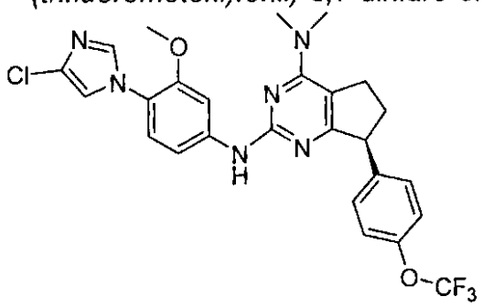
Ejemplo 100A y 100B

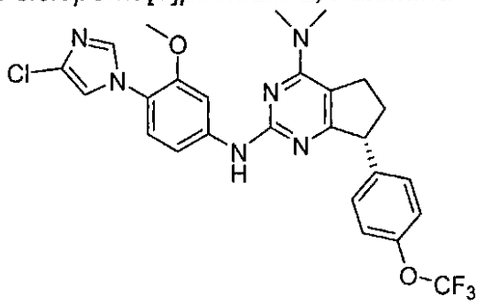
(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-7-(4-

(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

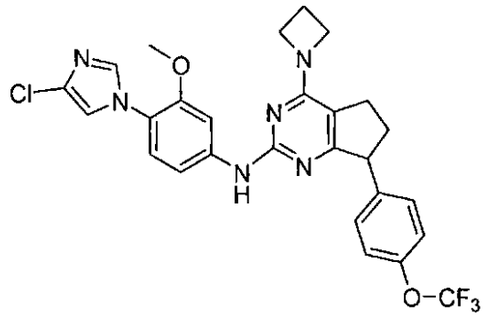




Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4,N^4-dimetil-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (235 mg, 0,431 mmol del *Ejemplo 100*) usando SFC quiral proporcionando 29,2 mg de pico A (*Ejemplo 100A*) y 29,2 mg de pico B (*Ejemplo 100B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 µM), metanol al 30% (dietilamina al 0,1%) en CO_2, 35ºC, caudal 2,0 ml/min durante 11 min, absorbancia 268 nm, inyección de 5µl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 3,7 min, t_R (pico B) 8,4 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 100A y 100B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 100*).

Ejemplo 101

4-(Azetidin-1-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



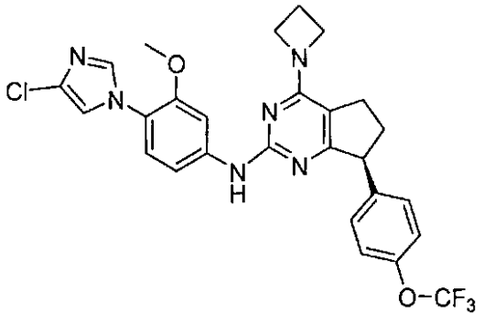
Se añadió 4-(azetidin-1-il)-2-cloro-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (238 mg, 0,644 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (216 mg, 0,965 mmol) en ácido acético (2 ml) y THF (2 ml). La mezcla de reacción se calentó a 85ºC durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando 4-(azetidin-1-il)-*N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2-amina, sal TFA (99,3 mg, 0,148 mmol, 22,99 % de rendimiento). CL-EM $(M+H)^+$ = 557,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,78 (1H, s), 7,51 - 7,65 (2H, m), 7,33 - 7,40 (1H, m), 7,26 (2H, d, *J*=3,1 Hz), 7,17 (3H, s), 7,04 (1H, s), 4,58 - 4,71 (2H, m), 4,27 - 4,46 (3H, m), 3,82 (3H, s), 2,91 - 3,17 (2H, m), 2,61 - 2,74 (1H, m), 2,50 - 2,60 (2H, m), 2,14 - 2,30 (1H, m).

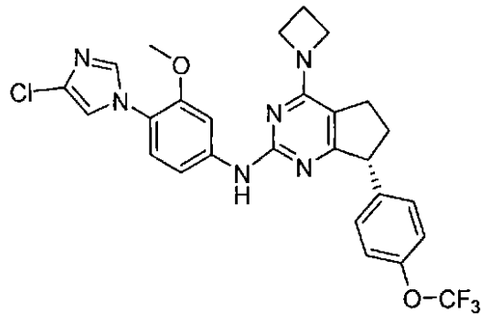
Ejemplo 101A y 101B

(S)-4-(Azetidin-1-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

y

(R)-4-(Azetidin-1-il)-N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

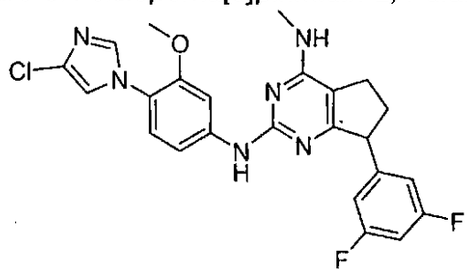




Se purificó una mezcla racémica de 4-(azetidin-1-il)-*N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(4-(trifluorometoxi)fenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2-amina (92 mg, 0,165 mmol del *Ejemplo 101*) usando SFC quiral proporcionando 37,6 mg de pico A (*Ejemplo 101A*) y 39,1 mg de pico B (*Ejemplo 101B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 μM), metanol al 30% (dietilamina al 0,1%) en CO_2, 35°C, caudal 2,0 ml/min durante 18 min, absorbancia 268 nm, inyección de 5μl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 4,7 min, t_R (pico B) 13,6 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 101A y 101B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 101*).

Ejemplo 102

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(3,5-difluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

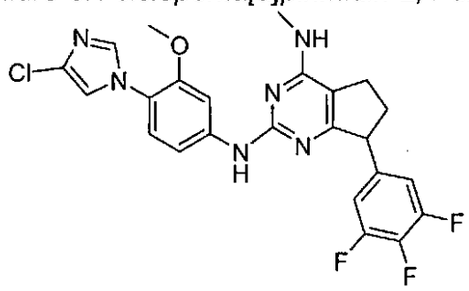


Se añadió 2-cloro-7-(3,5-difluorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (60 mg, 0,203 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (68,1 mg, 0,304 mmol) en ácido acético (2 ml) y THF (2,000 ml). La mezcla de reacción se calentó a 80ºC durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(3,5-difluorofenil)-N^4-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (33,6 mg, 0,056 mmol, 27,5 % de rendimiento). CL-EM $(M+H)^+$ = 483,0. RMN de ^{1}H (500 MHz, *MeOD*) δ ppm 7,79 (1H, s), 7,70 (1H, s), 7,29 - 7,45 (2H, m), 7,22 (1H, d, *J*=8,5 Hz), 6,86 - 7,03 (3H, m), 4,27 - 4,60 (1H, m), 3,89 (3H, s), 3,24 - 3,48 (5H, m), 3,17 (1H, s), 2,88 - 3,01 (1H, m), 2,67 - 2,87 (1H, m), 2,03 - 2,32 (1H, m).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 102A y 102B como aminas libres, que tuvieron idénticos datos espectrales.

Ejemplo 103

N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se añadió 2-cloro-*N*-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-

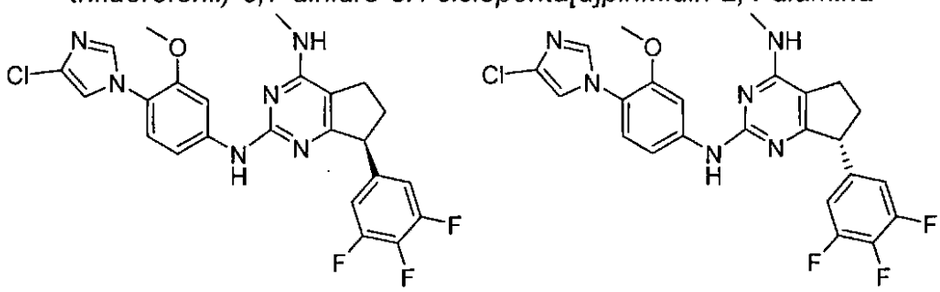
ciclopenta[*d*]pirimidin-4-amina (100 mg, 0,319 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (107 mg, 0,478 mmol) en ácido acético (2 ml) y THF (2,000 ml). La mezcla de reacción se calentó a 80ºC durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (36,3 mg, 0,057 mmol, 17,78 % de rendimiento). CL-EM $(M+H)^+$ = 501,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,88 - 11,96 (1H, m), 7,95 - 8,01 (1H, m), 7,44 - 7,62 (2H, m), 7,09 - 7,19 (1H, m), 6,86 - 6,95 (2H, m), 5,55 - 5,66 (1H, m), 5,26 - 5,39 (1H, m), 4,36 - 4,54 (1H, m), 3,90 (3H, s), 3,22 - 3,33 (3H, m), 2,72 - 2,87 (3H, m), 2,18 - 2,38 (1H, m).

Ejemplo 103A y 103B

(S)-N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)-N^2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

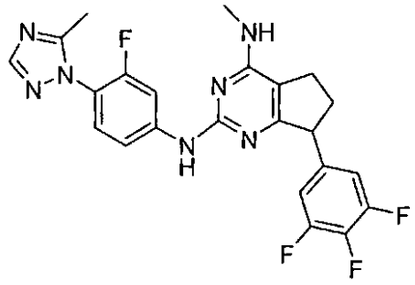


Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-

metoxifenil)-N^4-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (59,8 mg, 0,119 mmol del *Ejemplo 103*) usando SFC quiral proporcionando 19,5 mg de pico A (*Ejemplo 103A*) y 34,8 mg de pico B (*Ejemplo 103B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 µM), 20 % metanol (dietilamina al 0,1%) en CO_2, 35°C, caudal 2,0 ml/min durante 16 min, absorbancia 268 nm, inyección de 5µl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 9,7 min, t_R (pico B) 11,9 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 103A y 103B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 103*).

Ejemplo 104

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N^4-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

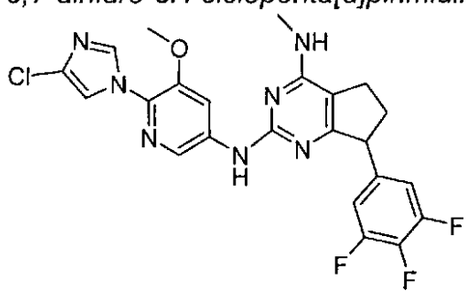


Se añadió 2-cloro-*N*-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (65,3 mg, 0,208 mmol) a una solución de 3-fluoro-4-(5-metil-1*H*-1,2,4-triazol-1-il)anilina (40 mg, 0,208 mmol) en ácido acético (2 ml) y THF (2,000 ml). La mezcla de reacción se calentó a 80°C durante la noche. Se observó formación parcial del producto deseado. La mezcla de reacción se calentó a 130°C durante 6 h. La mezcla de reacción

bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(3-fluoro-4-(3-metil-1*H*-1,2,4-triazol-1-il)fenil)-N^4-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (5,3 mg, 8,99 µmol, 4,32 % de rendimiento). CL-EM $(M+H)^+$ = 470,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 12,17 (1 H, s), 8,75 (1 H, d, *J*=1,8 Hz), 8,05 (1 H, dd, *J*=13,7, 2,1 Hz), 7,80 (1 H, t, *J*=8,7 Hz), 7,44 - 7,65 (1 H, m), 6,74 - 6,99 (2 H, m), 5,33 - 5,66 (1 H, m), 4,34 - 4,67 (1 H, m), 3,42 - 3,74 (2 H, m), 3,29 (3 H, d, *J*=4,9 Hz), 2,70 - 2,99 (2 H, m), 2,57 (2 H, s), 2,14 - 2,38 (1 H, m).

Ejemplo 105

N^2-(6-(4-Cloro-1H-imidazol-1-il)-5-metoxipiridin-3-il)-N^4-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

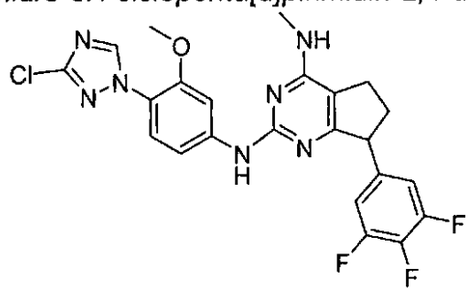


Se añadió 2-cloro-*N*-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (100 mg, 0,319 mmol) a una solución de 6-(4-cloro-1*H*-imidazol-1-il)-5-metoxipiridin-3-amina (107 mg, 0,478 mmol) en ácido acético (2 ml) y THF (2,000 ml). La mezcla de reacción se calentó a 80°C durante la noche. Se observó formación parcial del producto deseado. La mezcla de reacción se calentó a 130°C durante 6 h. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(6-(4-cloro-1*H*-imidazol-1-il)-5-metoxipiridin-3-il)-

N^4-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (12,9 mg, 0,021 mmol, 6,50 % de rendimiento). CL-EM $(M+H)^+$ = 502,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 12,33 (1H, s), 8,75 (1H, s), 8,56 (1H, s), 7,61 - 7,89 (2H, m), 6,85 - 7,00 (2H, m), 5,62 - 5,79 (1H, m), 4,36 - 4,49 (1H, m), 4,02 (3H, s), 3,29 (3H, d, *J*=4,9 Hz), 2,88 - 2,98 (1H, m), 2,76 - 2,85 (2H, m), 2,21 - 2,38 (1H, m).

Ejemplo 106

N^2-(4-(3-cloro-1H-1,2,4-triazol-1-il)-3-metoxifenil)-N^4-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

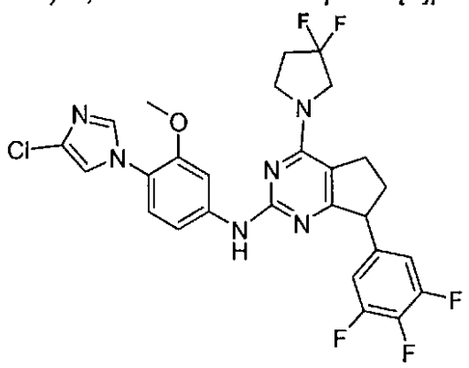


Se añadió 2-cloro-*N*-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (80 mg, 0,255 mmol) a una solución de 4-(3-cloro-1*H*-1,2,4-triazol-1-il)-3-metoxianilina (86 mg, 0,383 mmol) en ácido acético (2 ml) y THF (2,000 ml). La mezcla de reacción se calentó a 80°C durante la noche. Se observó formación parcial del producto deseado. La mezcla de reacción se calentó a 120°C durante 4 h. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(3-cloro-1*H*-1,2,4-triazol-1-il)-3-metoxifenil)-N^4-metil-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (15,5 mg, 0,025 mmol, 9,77 % de rendimiento). CL-EM $(M+H)^+$ = 502,0. RMN

de ^{1}H (500 MHz, $CDCl_3$) δ ppm 11,88 - 12,12 (1H, m), 8,63 (1H, s), 7,68 - 7,81 (1H, m), 7,60 (1H, s), 7,47 (1H, s), 6,92 (1H, t, *J*=7,2 Hz), 3,94 - 3,99 (1H, m), 3,52 (8H, s), 3,22 - 3,29 (1H, m), 2,87 - 3,01 (1H, m), 2,74 - 2,85 (1H, m), 2,22 - 2,38 (1H, m).

Ejemplo 107

N-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoropirrolidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Se añadió 2-cloro-4-(3,3-difluoropirrolidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (105 mg, 0,269 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (90 mg, 0,404 mmol) en ácido acético (1 ml) y THF (1,000 ml). La mezcla de reacción se calentó a 80ºC durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando *N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoropirrolidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2-amina, sal TFA (54,1 mg, 0,074 mmol, 27,3 % de rendimiento). CL-EM $(M+H)^+$ = 577,1. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 11,70 (1H, s), 8,08 - 8,24 (1H, m), 7,40 - 7,57 (1H, m), 7,18 (1H, s), 6,88 - 7,01 (2H, m), 4,37 - 4,45 (1H, m), 4,24 - 4,35 (2H, m), 4,03 - 4,22 (2H, m),

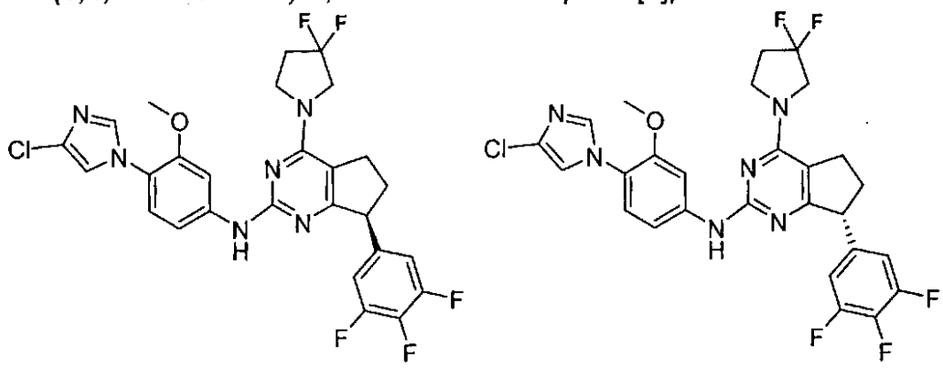
3,98 - 4,03 (1H, m), 3,89 (3H, s), 3,50 - 3,58 (1H, m), 3,15 - 3,42 (2H, m), 2,48 - 2,89 (3H, m), 2,18 - 2,34 (1H, m).

Ejemplo 107A y 107B

(S)-N-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoropirrolidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

y

(R)-N-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoropirrolidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

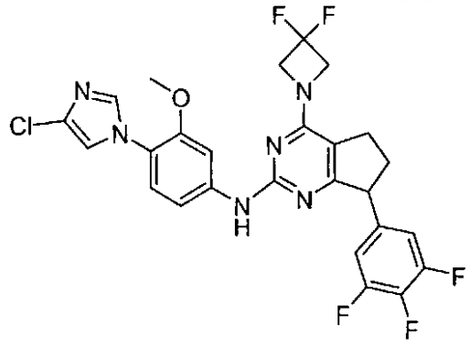


Se purificó una mezcla racémica de *N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoropirrolidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2-amina (48 mg, 0,083 mmol del *Ejemplo 107*) usando SFC quiral proporcionando 19,8 mg de pico A (*Ejemplo 107A*) y 17,2 mg de pico B (*Ejemplo 107B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 μM), 25 % metanol (dietilamina al 0,1%) en CO_2, 35°C, caudal 2,0 ml/min durante 30 min, absorbancia 268 nm, inyección de 5μl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 17,4 min, t_R (pico B) 21,2 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 107A y 107B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los

enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 107*).

Ejemplo 108

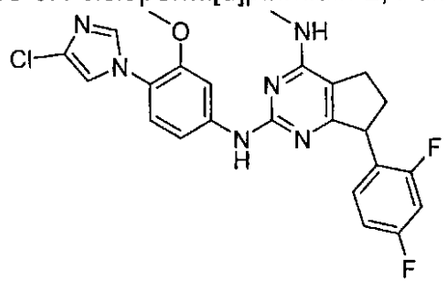
N-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Se añadió 2-cloro-4-(3,3-difluoroazetidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidina (105 mg, 0,279 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (94 mg, 0,419 mmol) en ácido acético (1 ml) y THF (1,000 ml). La mezcla de reacción se calentó a 80°C durante la noche. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando *N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-7-(3,4,5-trifluorofenil)-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2-amina, sal TFA (31,4 mg, 0,044 mmol, 15,60 % de rendimiento). CL-EM $(M+H)^+$ = 563,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,87 (1H, s), 8,09 (1H, s), 7,45 (1H, dd, *J*=8,5, 1,5 Hz), 7,36 (1H, s), 7,29 (2H, s), 7,25 (1H, d, *J*=8,5 Hz), 7,16 (1H, s), 6,91 (2H, t, *J*=6,9 Hz), 4,40 (1H, dd, *J*=9,2, 4,9 Hz), 4,00 (1H, s), 3,89 (3H, s), 3,53 (1 H, s), 3,08 - 3,19 (1H, m), 2,97 - 3,06 (1H, m), 2,72 - 2,84 (1H, m), 2,26 (1H, td, *J*=9,2, 4,3 Hz).

Ejemplo 109

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(2,4-difluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se calentó 80 °C en un vial tapado durante la noche una solución de 2-cloro-7-(2,4-difluorofenil)-*N*-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (184,6 mg, 0,624 mmol) y 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (140 mg, 0,624 mmol) en THF (1095 µl) y ácido acético (1095 µl). El disolvente se evaporó a vacío y el residuo se repartió entre solución acuosa de bicarbonato sódico y diclorometano. La fase orgánica se separó y la fase acuosa se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por cromatografía en columna sobre gel de sílice dando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-7-(2,4-difluorofenil)-N^4-metil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (179,6 mg, 0,372 mmol, 59,6 % de rendimiento) como sólido marrón. CL-EM $(M+H)^+$ = 483,1. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,97 (1H, d, *J*=2,1 Hz), 7,49 (1H, d, *J*=1,5 Hz), 7,01 - 7,10 (2H, m), 7,00 (1H, d, *J*=1,5 Hz), 6,73 - 6,84 (3H, m), 4,44 (1H, s), 3,61 (3H, s), 3,11 (3H, d, *J*=4,9 Hz), 2,59 - 2,77 (2H, m), 1,95 - 2,05 (2H, m).

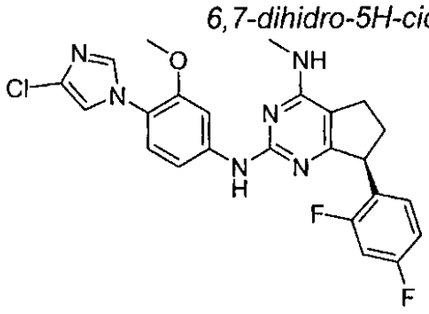
Ejemplos 109A y 109B

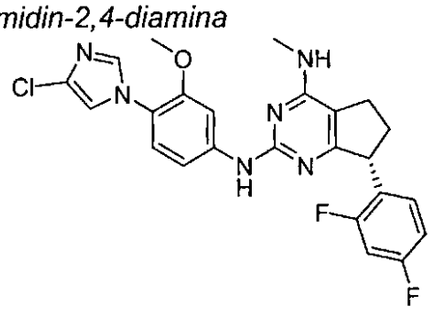
(S)- N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(2,4-difluorofenil)-N^4-metil-

6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)- N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(2,4-difluorofenil)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

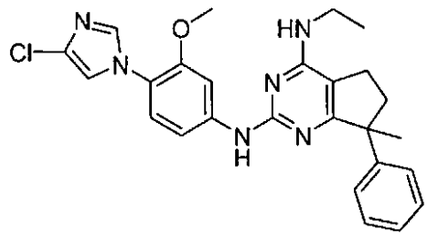




Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-trideuterometil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (180 mg, 0,206 mmol del *Ejemplo 109*) usando cromatografía de fluido supercrítico quiral (SFC) proporcionando 28,4 mg de pico A (*Ejemplo 109A*) y 27,4 mg de pico B (*Ejemplo 109B*). Procedimiento de SFC: Chiralpak OJ-H (21 x 250 mm, 5 μM), metanol al 35% (dietilamina al 0,1%) en CO_2, 35 °C, caudal 45 ml/min durante 10 min, absorbancia 268 nm, inyección de 0,75ml de solución 20 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 3,6 min, t_R (pico B) 7,2 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 109A y 109B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 109*).

Ejemplo 110

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-7-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

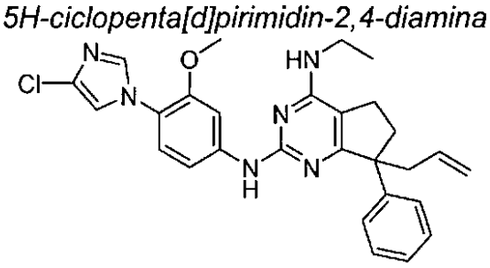


Se usó el procedimiento del Ejemplo 74 para combinar la Preparación Va y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) proporcionando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-7-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (Ejemplo 110). CL-EM $(M+H)^+$ = 475,2. RMN de ^1H (500 MHz, METANOL-*d4*) δ ppm 8,03 (1 H, d, *J*=2,14 Hz), 7,65 (1 H, s), 7,22 - 7,30 (4 H, m), 7,20 (1 H, s), 7,10 - 7,16 (2 H, m), 7,02 (1 H, dd, *J*=8,55, 2,14 Hz), 3,66 (3 H, s), 3,56 (2 H, c, *J*=7,32 Hz), 2,56 - 2,69 (2 H, m), 2,30 - 2,38 (1 H, m), 2,14 - 2,22 (1 H, m), 1,25 (3 H, d, *J*=7,20 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 110A y 110B, que tuvieron idénticos datos espectrales.

Ejemplo 111

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-7-alil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

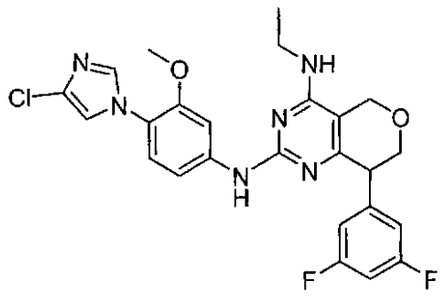


Se usó el procedimiento del Ejemplo 74 para combinar la Preparación

Wa y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) proporcionando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-7-alil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (Ejemplo 111). CL-EM $(M+H)^+$ = 501,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,66 (1 H, s ancho), 7,45 - 7,54 (2 H, m), 7,32 - 7,39 (5 H, m), 7,25 - 7,30 (3 H, m), 5,57 - 5,68 (1 H, m, *J*=16,94, 9,92, 7,17, 7,17 Hz), 5,42 (1 H, s ancho), 5,22 (1 H, d, *J*=16,17 Hz), 5,12 (1 H, d, *J*=10,07 Hz), 3,85 (3 H, s), 3,63 - 3,70 (2 H, m), 3,05 - 3,12 (2 H, m), 2,64 - 2,80 (2 H, m), 2,51 - 2,63 (2 H, m), 1,35 (3 H, t, *J*=7,17 Hz).

Ejemplo 112

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(3,5-difluorofenil)-N4-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA



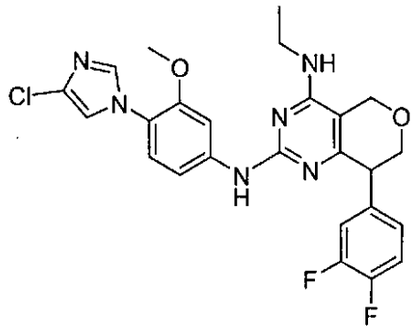
Se calentó a 110 ºC durante la noche la mezcla de 2-cloro-8-(3,5-difluorofenil)-N-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Xa) (87 mg, 0,267 mmol), 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) (71,7 mg, 0,321 mmol), tris(dibencilidenacetona)dipaladio(0) (12,23 mg, 0,013 mmol), (9,9-dimetil-9H-xanteno-4,5-diil)bis(difenilfosfina) (15,45 mg, 0,027 mmol) y carbonato sódico (42,5 mg, 0,401 mmol) en dioxano (1272 µl) / agua (254 µl). La mezcla de reacción se diluyó con agua y se extrajo con EtOAc. Las fases orgánicas reunidas se lavaron con salmuera y se

concentraron a vacío. El producto bruto se purificó por HPLC preparativa (Disolvente A = Acetonitrilo al 10% - H2O al 90% - TFA al 0,1%, Disolvente B = Acetonitrilo al 90% - H2O al 10% - TFA al 0,1%. Columna: PHENOMENEX LUNA 21 x 100mm, 10uC18, Caudal: 25 ml / min, 30 - 100% de B, 20 min) obteniendo N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(3,5-difluorofenil)-N4-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (Ejemplo 112) (123mg, 0,177 mmol, 66,1 % de rendimiento). CL-EM $(M+H)^+$ = 513,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,71 (s, 1 H) 8,04 (s, 1 H) 7,49 (d, J=2,14 Hz, 1 H) 7,43 (dd, J=8,55, 2,14 Hz, 1 H) 7,23 (d, J=8,55 Hz, 1 H) 7,17 (d, J=1,53 Hz, 1 H) 7,00 (d, J=5,80 Hz, 2 H) 6,70 - 6,84 (m, 1 H) 6,09 (t, J=5,19 Hz, 1 H) 4,73 (d, J=14,34 Hz, 1 H) 4,54 (d, J=14,34 Hz, 1 H) 3,95 - 4,15 (m, 3 H) 3,88 (s, 3 H) 3,61 - 3,78 (m, 2 H) 1,37 (t, J=7,17 Hz, 3 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 112A y 112B como aminas libres. CL-EM $(M+H)^+$ = 513,2. RMN de ^1H (500 MHz, MeOD) δ ppm 7,84 (d, J=2,14 Hz, 1 H) 7,67 (d, J=1,53 Hz, 1 H) 7,21 (d, J=1,53 Hz, 1 H) 7,13 (d, J=8,55 Hz, 1 H) 6,98 - 7,08 (m, 1 H) 6,89 (d, J=2,14 Hz, 1 H) 6,74 - 6,85 (m, 1 H) 4,65 (d, J=14,34 Hz, 1 H) 4,46 - 4,59 (m, 1 H) 4,11 (dd, J=11,44, 4,43 Hz, 1 H) 3,96 (dd, J=11,44, 4,12 Hz, 1 H) 3,88 (d, J=3,97 Hz, 1 H) 3,66 (s, 3 H) 3,58 (q, J=7,32 Hz, 2 H) 1,27 (t, J=7,17 Hz, 3 H).

Ejemplo 113

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(3,4-difluorofenil)-N4-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA



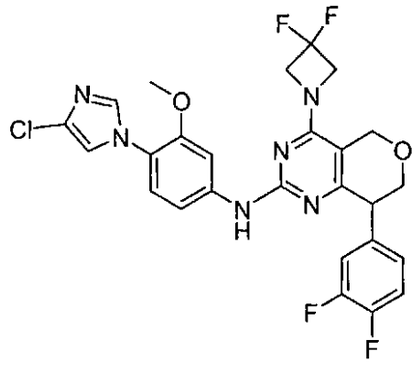
Se hizo reaccionar 2-cloro-8-(3,4-difluorofenil)-N-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Ya) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(3,4-difluorofenil)-N4-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (Ejemplo 113). CL-EM $(M+H)^+$ = 513,5. RMN de ^1H (500 MHz, MeOD) δ ppm 7,84 (d, J=1,22 Hz, 1 H) 7,58 (d, J=2,14 Hz, 1 H) 7,32 - 7,49 (m, 3 H) 7,12 - 7,32 (m, 3 H) 4,71 (d, J=14,95 Hz, 1 H) 4,55 (d, J=14,65 Hz, 1 H) 4,14 (dd, J=11,60, 4,27 Hz, 1 H) 4,06 (s ancho, 1 H) 3,92 - 4,02 (m, 1 H) 3,89 (s, 3 H) 3,68 - 3,70 (m, 2 H) 1,32 (t, J=7,17 Hz, 3 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 113A y 113B como aminas libres. CL-EM $(M+H)^+$ = 513,3. RMN de ^1H (500 MHz, MeOD) δ ppm 7,83 (d, J=2,14 Hz, 1 H) 7,67 (s, 1 H) 7,09 - 7,25 (m, 4 H) 6,96 - 7,09 (m, 2 H) 4,59 - 4,69 (m, 1 H) 4,47 - 4,57 (m, 1 H) 4,10 (dd, J=11,29, 4,27 Hz, 1 H) 3,92 (dd, J=11,60, 4,27 Hz, 1 H) 3,86 (d, J=3,36 Hz, 1 H) 3,62 - 3,68 (m, 3 H) 3,57 (q, J=7,32 Hz, 2 H) 1,22 - 1,34 (m, 3 H).

Ejemplo 114

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8- (3,4-

difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina, TFA



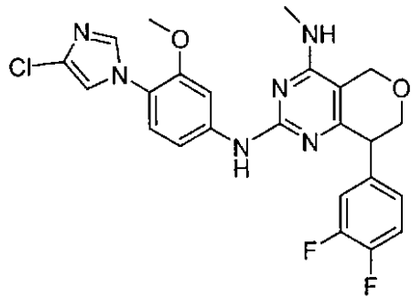
Se hizo reaccionar 2-cloro-4-(3,3-difluoroazetidin-1-il)-8-(3,4-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (Preparación Yb) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8-(3,4-difluorofenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina, TFA (Ejemplo 114). CL-EM $(M+H)^+$ = 561,5. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 12,12 (s ancho, 1 H) 7,80 (s, 1 H) 7,38 (dd, J=8,55, 1,83 Hz, 1 H) 7,20 - 7,31 (m, 4 H) 7,09 - 7,18 (m, 2 H) 4,69 - 4,89 (m, 6 H) 4,06 (m, 3 H) 3,87 (s, 3 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 114A y 114B como aminas libres. CL-EM $(M+H)^+$ = 561,3. RMN de ^1H (500 MHz, MeOD) δ ppm 7,74 (s, 1 H) 7,66 (s, 1 H) 7,10 - 7,24 (m, 4 H) 7,08 (d, J=1,53 Hz, 1 H) 7,02 (d, J=8,55 Hz, 1 H) 4,76 - 4,84 (m, 1 H) 4,68 (d, J=14,04 Hz, 1 H) 4,59 (t, J=12,21 Hz, 4 H) 4,14 (dd, J=11,29, 3,66 Hz, 1 H) 3,98 (s ancho, 1 H) 3,86 - 3,94 (m, 1 H) 3,59 (s, 3 H).

Ejemplo 115

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(3,4-difluorofenil)-N4-metil-7,8-

dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA

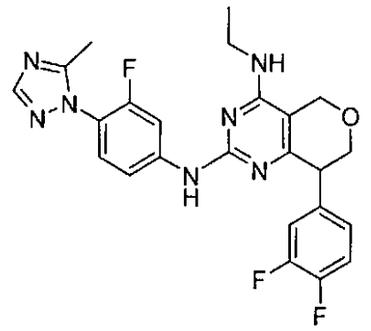


Se hizo reaccionar 2-cloro-8-(3,4-difluorofenil)-N-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Yc) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(3,4-difluorofenil)-N4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (Ejemplo 115). CL-EM $(M+H)^+$ = 499,5. RMN de ^1H (500 MHz, MeOD) δ ppm 7,86 (d, J=1,53 Hz, 1 H) 7,66 (d, J=2,14 Hz, 1 H) 7,26 - 7,41 (m, 4 H) 7,17 - 7,25 (m, 2 H) 4,70 (d, J=14,65 Hz, 1 H) 4,54 (dd, J=14,95, 1,53 Hz, 1 H) 4,15 (dd, J=11,60, 4,27 Hz, 1 H) 4,07 (s ancho, 1 H) 3,96 (dd, J=11,60, 3,36 Hz, 1 H) 3,89 (s, 3 H) 3,16 (s, 3 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 115A y 115B como aminas libres. CL-EM $(M+H)^+$ = 499,3. RMN de ^1H (500 MHz, MeOD) δ ppm 7,90 (d, J=2,14 Hz, 1 H) 7,67 (d, J=1,53 Hz, 1 H) 7,12 - 7,25 (m, 4 H) 7,07 (d, J=2,14 Hz, 1 H) 6,98 - 7,05 (m, 1 H) 4,63 (d, J=14,34 Hz, 1 H) 4,45 - 4,57 (m, 1 H) 4,11 (dd, J=11,44, 4,43 Hz, 1 H) 3,93 (dd, J=11,44, 4,43 Hz, 1 H) 3,87 (d, J=3,97 Hz, 1 H) 3,61 - 3,70 (m, 3 H) 3,00 - 3,08 (m, 3 H).

Ejemplo 116

8-(3,4-difluorofenil)-N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA

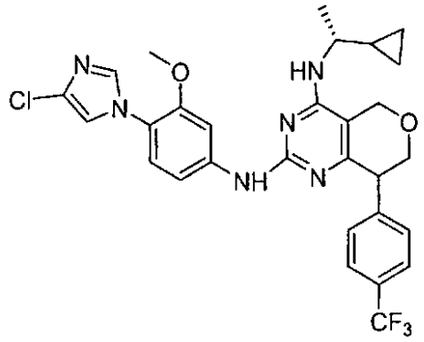


Se hizo reaccionar 2-cloro-8-(3,4-difluorofenil)-N-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Ya) como se describe en el Ejemplo 112 con 3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina (Preparación C) dando 8-(3,4-difluorofenil)-N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (Ejemplo 116). CL-EM $(M+H)^+$ = 482,3 RMN de ^1H (500 MHz, MeOD) δ ppm 8,13 (s, 1 H) 7,95 (dd, J=12,36, 1,98 Hz, 1 H) 7,47 - 7,62 (m, 2 H) 7,30 - 7,42 (m, 1 H) 7,23 - 7,30 (m, 1 H) 7,21 (s ancho, 1 H) 4,72 (d, J=14,95 Hz, 1 H) 4,55 (d, J=14,95 Hz, 1 H) 4,14 (dd, J=11,44, 4,12 Hz, 1 H) 4,07 (s ancho, 1 H) 3,91 - 4,01 (m, 1 H) 3,58 - 3,75 (m, 2 H) 2,44 (s, 3 H) 1,26 - 1,43 (m, 3 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 116A y 116B como aminas libres. CL-EM $(M+H)^+$ = 482,3. RMN de ^1H RMN de ^1H (500 MHz, MeOD) δ ppm 8,05 (d, J=2,14 Hz, 1 H) 8,03 (s, 1 H) 7,27 - 7,34 (m, 2 H) 7,17 - 7,25 (m, 2 H) 7,12 (d, J=1,83 Hz, 1 H) 4,61 - 4,68 (m, 1 H) 4,56 (t, J=14,19 Hz, 1 H) 4,15 (dd, J=11,29, 4,58 Hz, 1 H) 4,00 (dd, J=11,44, 4,73 Hz, 1 H) 3,90 (d, J=4,27 Hz, 1 H) 3,58 - 3,66 (m, 2 H) 2,38 (s, 3 H) 1,19 (t, J=7,02 Hz, 3 H).

Ejemplo 117

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-((R)-1-ciclopropiletil)-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA



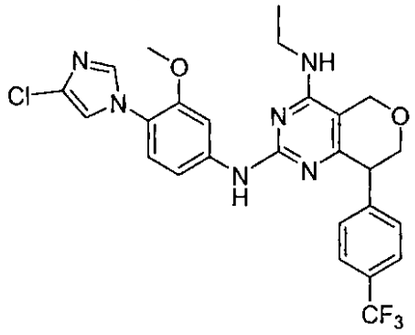
Se hizo reaccionar 2-cloro-N-((R)-1-ciclopropiletil)-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Zc) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-((R)-1-ciclopropiletil)-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (Ejemplo 117). CL-EM $(M+H)^+$ = 585,4. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,95 (s, 1 H) 7,68 (d, J=1,53 Hz, 1 H) 7,52 - 7,65 (m, 4 H) 7,31 - 7,43 (m, 2 H) 7,16 - 7,22 (m, 1 H) 7,10 (d, J=1,53 Hz, 1 H) 5,62 (t, J=7,02 Hz, 1 H) 4,75 (dd, J=14,34, 4,88 Hz, 1 H) 4,58 (dd, J=13,89, 8,39 Hz, 1 H) 4,11 (d, J=2,14 Hz, 3 H) 3,73 - 3,91 (m, 4 H) 1,40 (dd, J=10,38, 6,71 Hz, 3 H) 1,06 (ddd, J=7,78, 3,05, 2,90 Hz, 1 H) 0,69 (dt, J=8,62, 4,39 Hz, 1 H) 0,51 - 0,64 (m, 1 H) 0,38 (ddd, J=14,50, 9,77, 4,73 Hz, 1 H) 0,32 (dd, J=9,61, 4,73 Hz, 1 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 117A y 117B como aminas libres. CL-EM $(M+H)^+$ = 585,1. RMN de ^1H (500 MHz, MeOD) δ ppm 7,73 (d, J=2,14 Hz, 1 H) 7,56 -

7,68 (m, 3 H) 7,44 (d, J=8,24 Hz, 2 H) 7,19 (d, J=1,53 Hz, 1 H) 7,09 (d, J=8,55 Hz, 1 H) 6,94 (dd, J=8,55, 2,14 Hz, 1 H) 4,65 - 4,72 (m, 1 H) 4,52 - 4,62 (m, 1 H) 4,16 (dd, J=11,44, 4,73 Hz, 1 H) 3,92 (dd, J=11,29, 4,88 Hz, 1 H) 3,89 (dd, J=8,24, 6,71 Hz, 1 H) 3,49 (s, 3 H) 3,06 (q, J=7,32 Hz, 1 H) 1,22 - 1,41 (m, 3 H) 1,08 (dt, J=8,24, 4,88 Hz, 1 H) 0,51 - 0,59 (m, 1 H) 0,48 (dd, J=8,39, 5,04 Hz, 1 H) 0,39 (dd, J=9,77, 4,58 Hz, 1 H) 0,19 - 0,33 (m, 1 H).

Ejemplo 118

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA



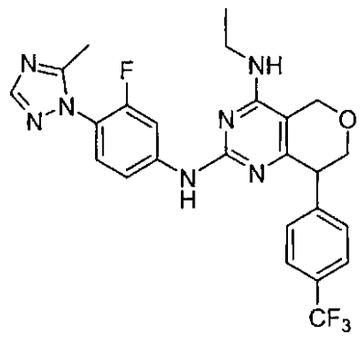
Se hizo reaccionar 2-cloro-N-etil-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Za) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (Ejemplo 118). CL-EM $(M+H)^+$ = 545,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,87 (s, 1 H) 7,68 (d, J=1,22 Hz, 1 H) 7,59 (m, 4 H) 7,49 (d, J=2,14 Hz, 1 H) 7,40 (dd, J=8,55, 2,14 Hz, 1 H) 7,20 (d, J=8,55 Hz, 1 H) 7,11 (d, J=1,53 Hz, 1 H) 6,38 (s ancho, 1 H) 4,76 (d, J=14,34 Hz, 1 H) 4,57 (d, J=13,73 Hz, 1 H) 4,07

- 4,16 (m, 3 H) 3,86 (s, 3 H) 3,59 - 3,77 (m, 2 H) 1,36 (t, J=7,17 Hz, 3 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 118A y 118B como aminas libres. CL-EM $(M+H)^+$ = 545,1. RMN de ^1H (500 MHz, MeOD) δ ppm 7,79 (d, J=1,83 Hz, 1 H) 7,56 - 7,70 (m, 3 H) 7,43 (d, J=7,93 Hz, 2 H) 7,19 (d, J=1,53 Hz, 1 H) 7,11 (d, J=8,55 Hz, 1 H) 6,91 - 7,03 (m, 1 H) 4,60 - 4,72 (m, 1 H) 4,48 - 4,60 (m, 1 H) 4,15 (dd, J=11,14, 4,43 Hz, 1 H) 3,99 (t, J=4,27 Hz, 1 H) 3,87 - 3,97 (m, 1 H) 3,46 - 3,66 (m, 5 H) 1,28 (t, J=7,17 Hz, 3 H).

Ejemplo 119

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA



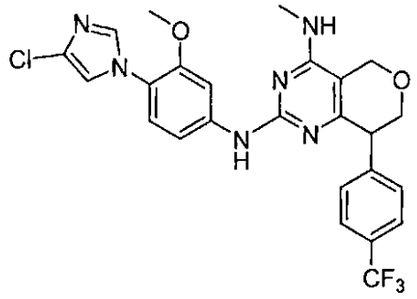
Se hizo reaccionar 2-cloro-N-etil-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Za) como se describe en el Ejemplo 112 con 3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)anilina (Preparación C) dando N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (Ejemplo 119). CL-EM $(M+H)^+$ = 514,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 12,20 (s ancho, 1 H) 8,01 (s, 1 H) 7,93 (dd, J=12,36, 2,29 Hz, 1 H) 7,59 (m, 4

H) 7,52 (dd, J=8,85, 1,53 Hz, 1 H) 7,38 (t, J=8,39 Hz, 1 H) 5,97 (s ancho, 1 H) 4,72 (d, J=14,34 Hz, 1 H) 4,54 (d, J=13,73 Hz, 1 H) 3,99 - 4,18 (m, 3 H) 3,57 - 3,75 (m, 2 H) 2,43 (s, 3 H) 1,37 (t, J=7,17 Hz, 3 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 119A y 119B como aminas libres. CL-EM $(M+H)^+$ = 514,1. RMN de ^1H (500 MHz, MeOD) δ ppm 8,02 (s, 1 H) 8,00 (dd, J=14,04, 2,14 Hz, 1 H) 7,62 (m, J=8,24 Hz, 2 H) 7,48 (m, J=8,24 Hz, 2 H) 7,21 - 7,34 (m, 2 H) 4,62 - 4,72 (m, 1 H) 4,52 - 4,62 (m, 1 H) 4,15 - 4,27 (m, 1 H) 3,94 - 4,09 (m, 2 H) 3,58 (q, J=7,32 Hz, 2 H) 2,36 (s, 3 H) 1,30 (t, J=7,17 Hz, 3 H).

Ejemplo 120

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA



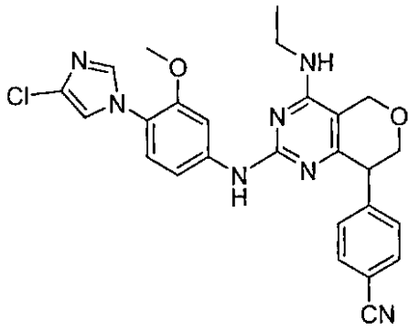
Se hizo reaccionar 2-cloro-N-metil-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (Preparación Zb) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-8-(4-(trifluorometil)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina, TFA (Ejemplo 120). CL-EM $(M+H)^+$ = 531,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,80 (s, 1 H) 7,87 (d, J=1,53 Hz, 1 H) 7,51 - 7,63 (m, 5 H) 7,40 (dd, J=8,85,

2,14 Hz, 1 H) 7,28 (s, 1 H) 7,20 (d, J=8,55 Hz, 1 H) 6,56 (d, J=4,58 Hz, 1 H) 4,76 (d, J=14,34 Hz, 1 H) 4,57 (d, J=14,04 Hz, 1 H) 4,01 - 4,14 (m, 3 H) 3,87 (s, 3 H) 3,21 (d, J=4,58 Hz, 3 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 120A y 120B como aminas libres. CL-EM $(M+H)^+$ = 531,1. RMN de ^1H (500 MHz, MeOD) δ ppm 7,86 (d, J=2,14 Hz, 1 H) 7,65 (d, J=1,53 Hz, 1 H) 7,60 (m, J=7,93 Hz, 2 H) 7,43 (m, J=7,93 Hz, 2 H) 7,19 (d, J=1,53 Hz, 1 H) 7,11 (d, J=8,55 Hz, 1 H) 6,96 (dd, J=8,55, 2,14 Hz, 1 H) 4,59 - 4,68 (m, 1 H) 4,48 - 4,56 (m, 1 H) 4,15 (dd, J=11,29, 4,58 Hz, 1 H) 3,98 - 4,03 (m, 1 H) 3,92 (dd, J=11,29, 4,88 Hz, 1 H) 3,52 (s, 3 H) 3,04 (s, 3 H).

Ejemplo 121

4-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-8-il)benzonitrilo, TFA



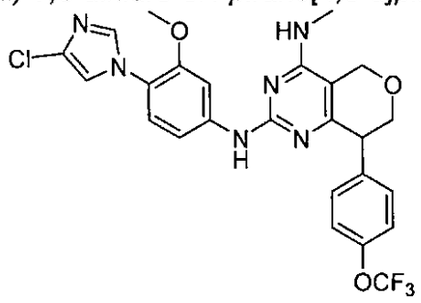
Se hizo reaccionar 4-(2-cloro-4-(etilamino)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-8-il)benzonitrilo (Preparación AAa) como se describe en el Ejemplo 112 con 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) dando 4-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-8-il)benzonitrilo, TFA (Ejemplo 121). CL-EM $(M+H)^+$ = 502,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,80 (s, 1 H) 7,93 (s, 1 H) 7,61 -

7,66 (m, 2 H) 7,55 - 7,61 (m, 2 H) 7,48 (d, J=1,83 Hz, 1 H) 7,41 (dd, J=8,55, 2,14 Hz, 1 H) 7,22 (d, J=8,85 Hz, 1 H) 7,15 (d, J=1,53 Hz, 1 H) 6,22 (t, J=5,34 Hz, 1 H) 4,76 (d, J=14,34 Hz, 1 H) 4,57 (d, J=14,34 Hz, 1 H) 4,09 (s, 3 H) 3,87 (s, 3 H) 3,66 - 3,75 (m, 2 H) 1,37 (t, J=7,32 Hz, 3 H).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 121A y 121B como aminas libres. CL-EM $(M+H)^+$ = 502,1. RMN de ^1H (500 MHz, MeOD) δ ppm 7,80 (d, J=2,14 Hz, 1 H) 7,67 (d, J=2,14 Hz, 2 H) 7,66 (s ancho, 1 H) 7,45 (d, J=8,24 Hz, 2 H) 7,22 (s, 1 H) 7,13 (d, J=8,55 Hz, 1 H) 6,98 - 7,05 (m, 1 H) 4,62 - 4,69 (m, 1 H) 4,51 - 4,57 (m, 1 H) 4,15 (dd, J=10,99, 3,97 Hz, 1 H) 3,91 - 4,02 (m, 2 H) 3,54 - 3,64 (m, 5 H) 1,28 (t, J=7,17 Hz, 3 H).

Ejemplo 122

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina



A una mezcla de 2-cloro-N-metil-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-4-amina (69,8 mg, 0,194 mmol), 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) (52,1 mg, 0,233 mmol), XANTPHOS (11,23 mg, 0,019 mmol), Pd2(dba)3 (8,88 mg, 9,70 µmol), y Cs_2CO_3 (190 mg, 0,582 mmol) se añadió dioxano (808 µl). La mezcla se purgó

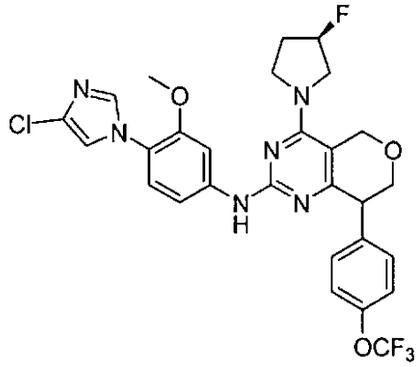
con nitrógeno y se colocó en un vial cerrado y se calentó a 100 °C durante la noche.

La reacción se enfrió hasta ta y se diluyó con EtOAc. Se filtró a través de un lecho corto de Celite y se sometió a evaporación rotatoria. El residuo se colocó sobre gel de sílice y eluyó con un gradiente de EtOAc/Hex obteniendo N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2,4-diamina. CL-EM $(M+H)^+$ = 547,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,78 (1 H, s), 7,48 (1 H, s), 7,25 - 7,29 (2 H, m), 7,11 - 7,20 (2 H, m), 6,94 - 7,09 (3 H, m), 6,77 (1 H, d, *J*=8,55 Hz), 4,50 - 4,67 (2 H, m), 4,32 (1 H, d, *J*=4,88 Hz), 4,07 - 4,19 (1 H, m), 3,89 - 4,01 (2 H, m), 3,52 (3 H, s), 3,09 (3 H, d, *J*=4,58 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 122A y 122B, que tuvieron idénticos datos espectrales.

Ejemplos 123A y 123B

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-((R)-3-fluoropirrolidin-1-il)-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina



Diastereómeros individuales

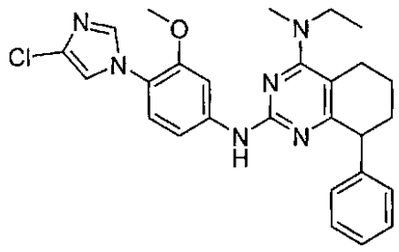
A una mezcla de 2-cloro-4-((R)-3-fluoropirrolidin-1-il)-8-(4-(trifluorometoxi)fenil)-7,8-dihidro-5H-pirano[4,3-d]pirimidina (57,6 mg, 0,138 mmol), 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) (37,0 mg, 0,165 mmol), XANTPHOS (7,98 mg, 0,014 mmol), $Pd_2(dba)_3$ (6,31 mg, 6,89 µmol) y Cs_2CO_3 (135 mg, 0,414 mmol) se añadió dioxano (574 µl). La mezcla se purgó con nitrógeno y se colocó en un vial tapado y se calentó a 100 °C durante la noche. La reacción se enfrió hasta ta y se diluyó con EtOAc, luego se filtró a través de un lecho corto de Celite y se concentró. El residuo se colocó sobre gel de sílice y eluyó con un gradiente de EtOAc/Hex obteniendo 2 diastereómeros (Ejemplos 123A y 123B).

123A: CL-EM $(M+H)^+$ = 605,3. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,79 (1 H, d, *J*=1,53 Hz), 7,46 - 7,53 (3 H, m), 7,32 - 7,41 (4 H, m), 7,19 (1 H, dd, *J*=8,55, 2,14 Hz), 5,43 (1 H, d, *J*=52,50 Hz), 5,12 - 5,18 (1 H, m), 4,99 (1 H, d, *J*=14,34 Hz), 3,98 - 4,33 (6 H, m), 3,87 (3 H, s), 3,81 (1 H, dd, *J*=10,68, 6,41 Hz), 2,37 - 2,49 (1 H, m), 2,15 - 2,33 (1 H, m).

123B: CL-EM $(M+H)^+$ = 605,3. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 7,56 (1 H, d, *J*=1,83 Hz), 7,48 (1 H, d, *J*=1,53 Hz), 7,22 - 7,28 (2 H, m), 7,14 (2 H, d, *J*=8,24 Hz), 7,04 (1 H, d, *J*=8,55 Hz), 6,99 (1 H, d, *J*=1,22 Hz), 6,82 (1 H, dd, *J*=8,55, 1,83 Hz), 5,33 (1 H, d, *J*=52,80 Hz), 4,90 - 5,00 (2 H, m), 4,16 - 4,26 (1 H, m), 4,10 (1 H, dd, *J*=11,44, 4,43 Hz), 3,80 - 4,01 (5 H, m), 3,50 (3 H, s), 2,32 - 2,43 (1 H, m), 2,00 - 2,19 (1 H, m).

Ejemplo 124

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-8-fenil-5,6,7,8-tetrahidroquinazolina-2,4-diamina



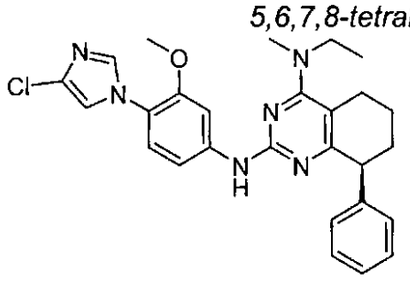
A una solución de 2-cloro-*N*-etil-*N*-metil-8-fenil-5,6,7,8-tetrahidroquinazolin-4-amina (42,9 mg, 0,142 mmol) y 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (31,8 mg, 0,142 mmol) en THF (2 ml) se añadió suspensión al 60% de hidruro sódico en aceite mineral (6,82 mg, 0,284 mmol). La mezcla de reacción se calentó con agitación en un vial tapado a 80 °C durante 1,5 h. La mezcla de reacción se repartió cuidadosamente entre una solución acuosa de cloruro amónico y diclorometano. La fase orgánica se separó y la fase acuosa se extrajo con diclorometano. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio anhidro y se filtraron. El disolvente se eliminó a vacío y el residuo se purificó por HPLC preparativa de fase inversa dando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-8-fenil-5,6,7,8-tetrahidroquinazolina-2,4-diamina (31,6 mg, 0,048 mmol, 33,5 % de rendimiento) como aceite marrón. CL-EM $(M+H)^+$ = 489,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 11,50 (1H, s ancho), 7,74 (1H, d, *J*=1,2 Hz), 7,39 (1H, dd, *J*=8,5, 2,1 Hz), 7,29 (2H, dd, *J*=4,9, 2,7 Hz), 7,21 - 7,27 (2H, m), 7,12 - 7,19 (3H, m), 7,07 (1H, d, *J*=1,5 Hz), 4,20 (1H, t, *J*=7,0 Hz), 3,80 (3H, s), 3,68 - 3,78 (2H, m, *J*=13,8, 7,0, 7,0, 7,0, 7,0 Hz), 3,31 (3H, s), 2,64 - 2,82 (2H, m), 2,27 (1H, ddd, *J*=13,3, 7,5, 5,2 Hz), 1,88 - 1,99 (1H, m), 1,74 - 1,85 (1H, m), 1,54 - 1,67 (1H, m), 1,34 (3H, t, *J*=7,0 Hz).

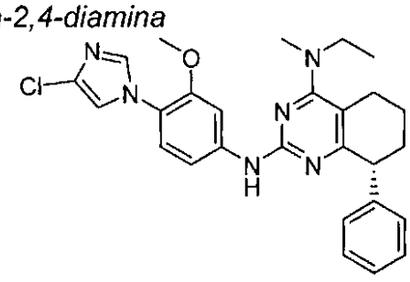
Ejemplos 124A y 124B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-8-fenil-5,6,7,8-tetrahidroquinazolina-2,4-diamina

y

(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-8-fenil-5,6,7,8-tetrahidroquinazolina-2,4-diamina

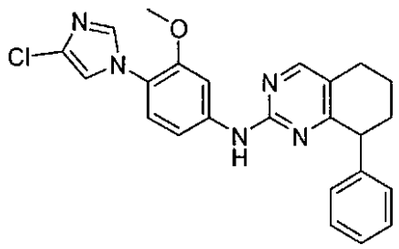




Se purificó una mezcla racémica de N^2-(4-(4-Cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-etil-N^4-metil-8-fenil-5,6,7,8-tetrahidroquinazolina-2,4-diamina (183 mg, 0,206 mmol del *Ejemplo 124*) usando cromatografía de fluido supercrítico quiral (SFC) proporcionando 54,7 mg de pico A (*Ejemplo 124A*) y 53,3 mg de pico B (*Ejemplo 124B)*. Procedimiento de SFC: Chiralpak OJ-H (30 x 250 mm, 5 μM), metanol al 30% (dietilamina al 0,1%) en CO_2, 35 °C, caudal 70 ml/min durante 105 min, absorbancia 220 nm, inyección de 0,75 ml de solución 26 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 4,9 min, t_R (pico B) 12,0 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 124A y 124B*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 124*).

Ejemplo 125

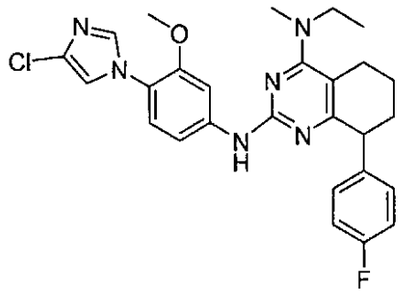
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-fenil-5,6,7,8-tetrahidroquinazolin-2-amina



A una solución de 2-cloro-8-fenil-5,6,7,8-tetrahidroquinazolina (33,0 mg, 0,135 mmol) y 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (33,2 mg, 0,148 mmol) en THF (1,5 ml) en un tubo de microondas de 2,0-5,0 ml se añadió solución 0,5 M de KHMDS en tolueno (0,809 ml, 0,405 mmol). El tubo se cerró herméticamente y la mezcla de reacción se agitó a 100 °C en un microondas durante 2 h. La mezcla de reacción se diluyó con metanol y se purificó usando un procedimiento de HPLC preparativa de fase inversa. El disolvente se eliminó a vacío y el residuo se purificó por HPLC preparativa de fase inversa dando *N*^{2}-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-*N*^{4}-etil-*N*^{4}-metil-8-fenil-5,6,7,8-tetrahidroquinazolina-2,4-diamina (31,6 mg, 0,048 mmol, 33,5 % de rendimiento) como aceite marrón. CL-EM $(M+H)^+$ = 432,3. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 11,68 (1H, s), 8,25 (1H, s), 8,14 (1H, s), 7,32 - 7,39 (3H, m), 7,26 - 7,32 (1H, m), 7,05 - 7,12 (3H, m), 6,96 - 7,04 (2H, m), 4,20 (1H, t, *J*=7,2 Hz), 3,41 (3H, s), 2,80 - 2,94 (2H, m), 2,30 - 2,40 (1H, m), 1,97 - 2,12 (2H, m), 1,81 - 1,93 (1H, m).

Ejemplo 126

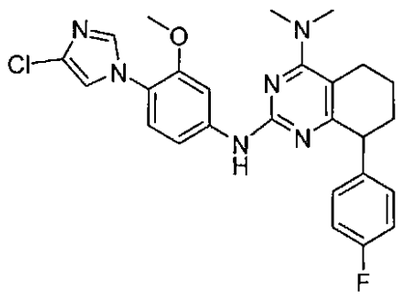
N^2*-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N*^{4}*-etil-8-(4-fluorofenil)-N*^{4}*-metil-5,6,7,8-tetrahidroquinazolina-2,4-diamina*



Se añadió 2-cloro-*N*-etil-8-(4-fluorofenil)-*N*-metil-5,6,7,8-tetrahidroquinazolin-4-amina (124 mg, 0,388 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (87 mg, 0,388 mmol) en THF (1 ml) y ácido acético (1,000 ml). La mezcla de reacción se agitó durante la noche a 75 °C. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-etil-8-(4-fluorofenil)-^{N4}-metil-5,6,7,8-tetrahidroquinazolina-2,4-diamina, sal TFA (101,3 mg, 0,153 mmol, 39,5 % de rendimiento). CL-EM $(M+H)^+$ = 507,2. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 10,77 - 11,01 (1H, m), 7,95 - 8,15 (1H, m), 7,33 - 7,44 (1H, m), 7,22 - 7,24 (1H, m), 7,19 (1H, d, *J*=8,5 Hz), 7,12 - 7,16 (2H, m), 6,96 - 7,03 (2H, m), 4,09 - 4,21 (1H, m), 3,96 (1H, s), 3,81 (4H, s), 3,67 - 3,79 (3H, m), 3,32 (3H, s), 2,19 - 2,33 (1H, m), 1,88 - 1,99 (1H, m), 1,71 - 1,81 (1H, m), 1,56 - 1,69 (1H, m), 1,26 - 1,38 (3H, m).

Ejemplo 127

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N^4,N^4-dimetil-5,6,7,8-tetrahidroquinazolina-2,4-diamina



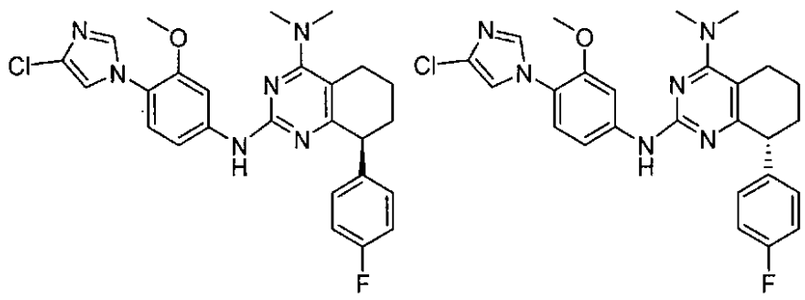
Se añadió 2-cloro-8-(4-fluorofenil)-*N*,*N*-dimetil-5,6,7,8-tetrahidroquinazolin-4-amina (118 mg, 0,386 mmol) a una solución de 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (95 mg, 0,424 mmol) en THF (1 ml) y ácido acético (1,000 ml). La mezcla de reacción se agitó durante la noche a 75ºC. La mezcla de reacción bruta se purificó por HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N^4,N^4-dimetil-5,6,7,8-tetrahidroquinazolina-2,4-diamina, sal TFA (74,8 mg, 0,123 mmol, 31,9 % de rendimiento). CL-EM $(M+H)^+$ = 493,2. RMN de ^{1}H (500 MHz, $CDCl_3$) δ ppm 11,69 (1H, s), 7,59 (1H, d, *J*=1,2 Hz), 7,36 (2H, d, *J*=2,1 Hz), 7,14 (3H, d, *J*=9,2 Hz), 7,05 (1H, d, *J*=1,5 Hz), 6,99 (2H, s), 4,17 - 4,27 (1H, m), 3,81 (3H, s), 3,47 (1H, s), 3,36 (5H, s), 2,65 - 2,84 (2H, m), 2,21 - 2,33 (1H, m), 1,87 - 1,98 (1H, m), 1,69 - 1,81 (1H, m), 1,53 - 1,67 (1H, m).

Ejemplos 127A y 127B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N^4,N^4-dimetil-5,6,7,8-tetrahidroquinazolina-2,4-diamina

y

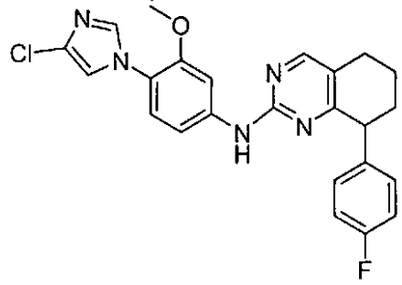
(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N^4,N^4-dimetil-5,6,7,8-tetrahidroquinazolina-2,4-diamina



Una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N^4,N^4-dimetil-5,6,7,8-tetrahidroquinazolina-2,4-diamina (*Ejemplo 127*) se purificó usando SFC quiral proporcionando el pico A (*Ejemplo 127A*) y el pico B (*Ejemplo 127B*). Procedimiento de SFC: Chiralpak OJ-H (4,6 x 250 mm, 5 μM), metanol al 30% (dietilamina al 0,1%) en CO_2, 35ºC, caudal 2,0 ml/min durante 13 min, absorbancia 268 nm, inyección de 5μl de solución de 2 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 4,3 min, t_R (pico B) 9,6 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 7 y 8*). Los datos analíticos de CL-EM y RMN de ^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 127*).

Ejemplo 128

N-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolin-2-amina

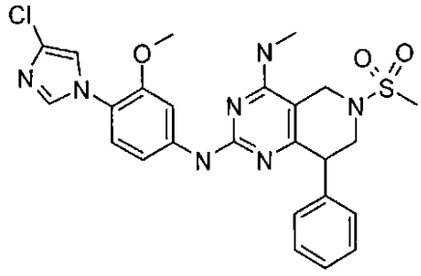


A una solución de 2-cloro-8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolina (20 mg, 0,076 mmol) y 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (18,73 mg,

0,084 mmol) en THF (1,5 ml) en un tubo de microondas de 2,0-5,0 ml, se añadió una solución 0,5 M de KHMDS (0,167 ml, 0,084 mmol). El tubo se cerró herméticamente y la mezcla de reacción se agitó a 100ºC en un microondas durante 2 h. La mezcla de reacción se diluyó con metanol y purificó usando HPLC preparativa. Las fracciones apropiadas se evaporaron proporcionando *N*-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-5,6,7,8-tetrahidroquinazolin-2-amina, sal TFA (0,7 mg, 1,229 µmol, 1,614 % de rendimiento). CL-EM $(M+H)^+$ = 450,2. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,14 - 8,26 (1H, m), 7,56 - 7,62 (1H, m), 7,43 - 7,48 (1H, m), 7,28 - 7,31 (1H, m), 7,21 (1H, s), 6,98 - 7,10 (6H, m), 6,88 - 6,94 (1H, m), 4,08 - 4,18 (1H, m), 2,77 - 2,83 (3H, m), 2,23 - 2,32 (1H, m), 1,91 - 2,13 (3H, m), 1,25 (1H, s).

Ejemplo 129

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-6-(metilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



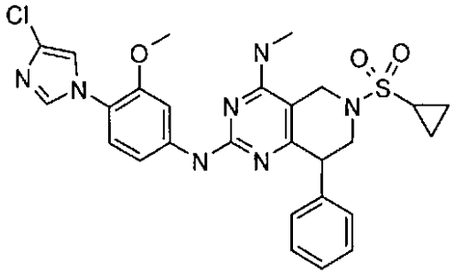
A una solución de la Preparación AEj (0,2 g, 0,433 mmol) en diclorometano se añadió diisopropiletilamina (0,11 g, 0,867 mmol) a -10 ºC seguido por la adición de cloruro de metanosulfonilo (0,055 g, 0,477 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión

reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-6-(metilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,105 g, 48%) como sólido blanquecino. CL-EM $(M+H)^+$ = 540,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,20 (1H, s), 8,03 (1H, s), 7,72 (1H, s), 7,41 (1H, s), 7,31 - 7,03 (8H, m), 4,21 (1H, m), 4,11 (2H, m), 3,60-3,47 (5H, m), 2,96 (3H, d, *J* = 4,4 Hz), 2,89 (3H, s).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 129A y 129B, que tuvieron idénticos datos espectrales.

Ejemplo 130

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-6-(ciclopropilsulfonil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



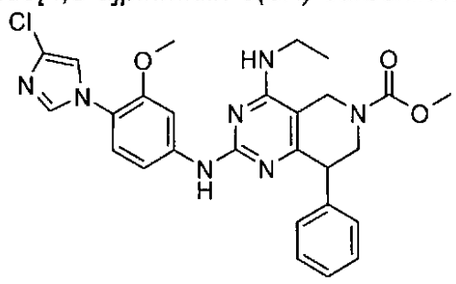
A una solución de la Preparación AEj (0,32 g, 0,693 mmol) en diclorometano se añadió diisopropiletilamina (0,18 g, 1,38 mmol) a -10 °C seguido por la adición de cloruro de ciclopropilsulfonilo (0,117 g, 0,832 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-6-(ciclopropilsulfonil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,11 g, 35%) como sólido blanco. CL-EM $(M+H)^+$ = 566,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,18 (1H, s), 8,03 (1H, s), 7,72 (1H, s), 7,40 (1H, s), 7,31 - 7,04 (8H, m), 4,26 (1H, m), 4,10 (2H, m), 3,68 (1H, m), 3,68 -3,65 (4H, m), 2,98 (3H, d, *J*= 4,4 Hz), 2,54 (1H, m), 0,95 (4H, m).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 130A y 130B, que tuvieron idénticos datos espectrales.

Ejemplo 131

2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-carboxilato de metilo



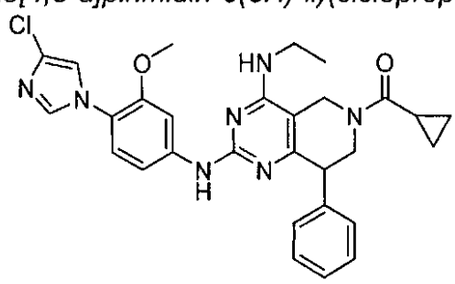
A una solución de la Preparación AEk (0,15 g, 0,3 mmol) en diclorometano se añadió diisopropiletilamina (0,081 g, 0,6 mmol) a -10 °C seguido por la adición de cloroformiato de metilo (0,044 g, 0,3 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando 2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-

dihidropirido[4,3-d]pirimidin-6(5H)-carboxilato de metilo (0,12 g, 68%) como sólido blanco. CL-EM $(M-H)^+$ = 532,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,16 (1H, s), 7,98 (1H, s), 7,73 (1H, s), 7,42 (1H, s), 7,29 - 7,26 (2H, m), 7,21-7,12 (5H, m), 7,05 (1H, m), 4,62 (1H, m), 4,23 (1H, m), 3,96-3,87 (3H, m), 3,68 - 3,51 (8H, m), 1,23 (3H, t, *J* = 8,0 Hz).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 131A y 131B, que tuvieron idénticos datos espectrales.

Ejemplo 132

(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)(ciclopropil)metanona



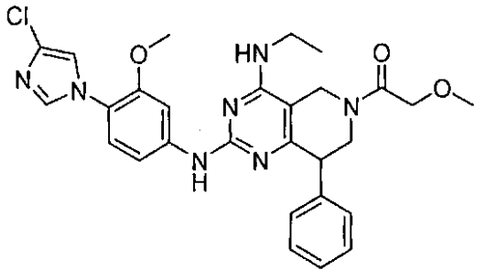
A una solución de la Preparación AEk (0,35 g, 0,73 mmol) en diclorometano se añadió diisopropiletilamina (0,14 g, 1,1 mmol) a -10 °C seguido por la adición de cloruro de ciclopropilcarbonilo (0,085 g, 0,81 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en metanol) dando (2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)(ciclopropil)metanona (0,12 g, 30%) como sólido blanco. CL-EM $(M+H)^+$ = 544,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm

7,70 (1H, s), 7,51 (1H, s), 7,31-7,23 (3H, m), 7,12-6,99 (4H, m), 6,93 (1H, *s ancho)*, 5,05 (1H, m), 4,22 (1H, m), 4,07 (1H, m), 3,99 (1H, m), 3,63 (1H, m), 3,59 (5H, m), 1,33 (3H, t, *J* = 7,2 Hz), 1,25 (1H, m), 0,87 (1H, m), 0,84 (2H, m), 0,63 (1H, m).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 132A y 132B, que tuvieron idénticos datos espectrales.

Ejemplo 133

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-2-metoxietanona



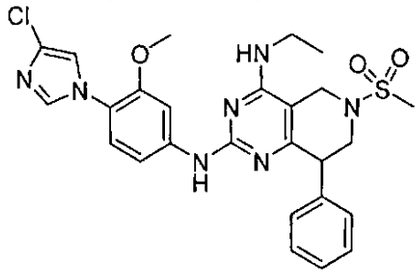
A una solución de la Preparación AEk (0,187 g, 0,39 mmol) en diclorometano se añadió trietilamina (0,79 g, 0,78 mmol) a -10 °C seguido por la adición de cloruro de metoxiacetilo (0,043 g, 0,42 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-2-metoxietanona (0,10 g, 57%) como sólido blanquecino. CL-EM $(M+H)^+$ = 548,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,19 (1H, s), 7,99 (1H, s), 7,73 (1H, 1), 7,42 (1H, s), 7,32-7,09 (8 H, m),

4,86 (1H, m), 4,20 (2H, m), 4,09 (2H, m), 4,02-3,50 (5H, m), 3,31 (1H, m), 3,18 (1H, m), 2,99 (3H, s), 1,23 (3H, t, *J* = 7,2 Hz).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 133A y 133B, que tuvieron idénticos datos espectrales.

Ejemplo 134

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-6-(metilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

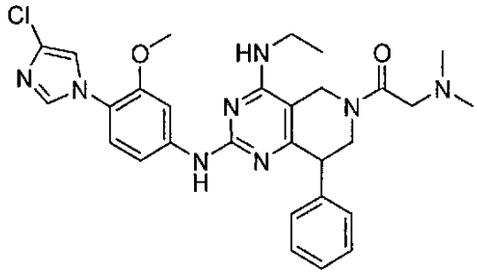


A una solución de la Preparación AEk (0,10 g, 0,21 mmol) en diclorometano se añadió diisopropiletilamina (0,054 g, 0,42 mmol) a -10 °C seguido por la adición de cloruro de metanosulfonilo (0,024 g, 0,21 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-6-(metilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,06 g, 54%) como sólido blanquecino. CL-EM $(M+H)^+$ = 554,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,17 (1H, s), 7,96 (1H, s), 7,73 (1H, s), 7,42 (1H, s), 7,32 - 7,20 (5H, m), 7,16 - 7,10 (2H, m), 6,98 (1H, m), 4,22 (1H, m), 4,11-4,03 (2H, m), 3,62-3,49 (7H, m), 2,91 (3H, s), 1,23 (3H, t, *J* = 7,2 Hz).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 134A y 134B, que tuvieron idénticos datos espectrales.

Ejemplo 135

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-2-(dimetilamino)etanona

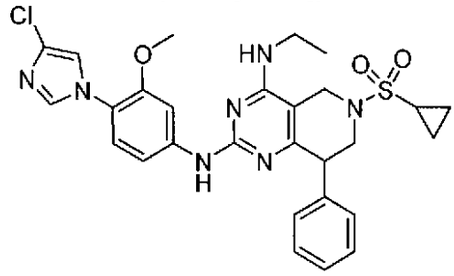


A una solución de la Preparación AEk (0,15 g, 0,31 mmol) en diclorometano se añadió trietilamina (0,079 g, 0,78 mmol) a -10 ºC seguido por la adición de cloruro de N,N-dimetilamionoacetilo.HCl (0,054 g, 0,34 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)-2-(dimetilamino)etanona (0,11 g, 72%) como sólido blanquecino. CL-EM $(M+H)^+$ = 561,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,16 (1H, s), 7,98 (1H, s), 7,72 (1H, s), 7,40 (1H, s), 7,31 - 7,11 (7H, m), 7,07 (1H, m), 4,77 (1H, m), 4,06 (2H, m), 3,94 (1H, m), 3,60 (1H, m), 3,52-3,42 (5H, m), 2,72 (1H, m), 2,28 (1H, m), 2,15 (6H, s), 1,20 (3H, m).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 135A y 135B, que tuvieron idénticos datos espectrales.

Ejemplo 136

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-6-(ciclopropilsulfonil)-N4-etil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



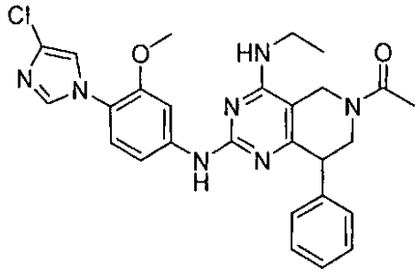
A una solución de la Preparación AEk (0,15 g, 0,31 mmol) en diclorometano se añadió diisopropiletilamina (0,77 g, 0,62 mmol) a -10 °C seguido por la adición de cloruro de ciclopropanosulfonilo (0,042 g, 0,31 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en metanol) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-6-(ciclopropilsulfonil)-N4-etil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,10 g, 55%) como sólido blanquecino. CL-EM $(M+H)^+$ = 578,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 9,15 (1H, s), 7,95 (1H, s), 7,72 (1H, s), 7,41 (1H, s), 7,29 (2H, m), 7,21 (3H, m), 7,14 (2H, m), 7,01 (1H, *s ancho)*, 4,26 (1H, m), 4,11 (2H, m), 3,65 (1H, m), 3,56-3,51 (6H, m), 2,5 (1H, m), 1,23 (5H, m), 0,97 (2H, m).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 136A y 136B, que tuvieron idénticos datos espectrales.

Ejemplo 137

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-

dihidropirido[4,3-d]pirimidin-6(5H)-il)etanona

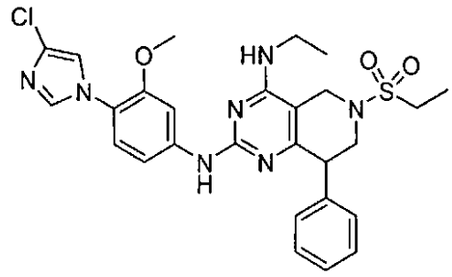


A una solución de la Preparación AEk (0,15 g, 0,31 mmol) en diclorometano se añadió diisopropiletilamina (0,77 g, 0,62 mmol) a -10 °C seguido por la adición de cloruro de acetilo (0,027 g, 0,31 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en metanol) dando 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)etanona (0,09 g, 57%) como sólido blanquecino. CL-EM $(M+H)^+$ = 518,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,19 (1H, s), 8,00 (1H, s), 7,74 (1H, s), 7,42 (1H, s), 7,28 (3H, m), 7,17 - 7,07 (5H, m), 4,91 (1H, m), 4,06 (1H, m), 3,93 (1H, m), 3,82 (2H, m), 3,58-3,50 (5H, m), 1,47 (3 H, s), 1,23 (3H, m).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 137A y 137B, que tuvieron idénticos datos espectrales.

Ejemplo 138

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-6-(etilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

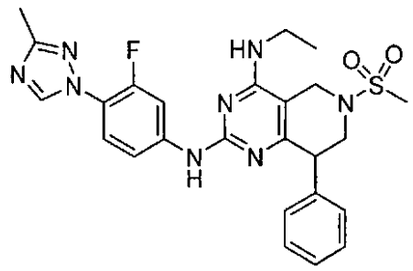


A una solución de la Preparación AEk (0,15 g, 0,31 mmol) en diclorometano se añadió diisopropiletilamina (0,77 g, 0,62 mmol) a -10 °C seguido por la adición de cloruro de etanosulfonilo (0,038 g, 0,31 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en metanol) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-6-(etilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,11 g, 62%) como sólido blanquecino. CL-EM $(M-H)^+$ = 566,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,17 (1H, s), 7,96 (1H, s), 7,73 (1H, s), 7,42 (1H, s), 7,31 (2H, m), 7,28 (3H, m), 7,21 (2H, m), 6,97 (1H, m), 4,25 (1H, m), 4,13-4,05 (2H, m), 3,60 (1H, m), 3,58-3,50 (6H, m), 3,05 (2H, m), 1,23 (3H, t, *J*= 8,0 Hz), 1,17 (3H, t, *J* = 7,2 Hz).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 138A y 138B, que tuvieron idénticos datos espectrales.

Ejemplo 139

N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6-(metilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

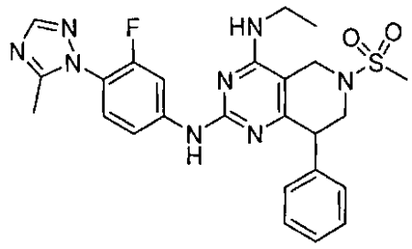


A una solución de la Preparación AEm (0,20 g, 0,450 mmol) en diclorometano se añadió diisopropiletilamina (0,11 g, 0,90 mmol) a -10 °C seguido por la adición de cloruro de metanosulfonilo (0,05 g, 0,450 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6-(metilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,048 g, 20%) como sólido blanquecino. CL-EM $(M+H)^+$ = 523,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,44 (1H, s), 8,67 (1H, s), 8,00 (1H, m), 7,42 (2H, m), 7,39 (2H, m), 7,32 (3H, m), 7,05 (1H, m), 4,20 (1H, m), 4,08 (2H, m), 3,63 (1H, m), 3,55-3,46 (3H, m), 2,92 (3H, s), 2,33 (3H, s), 1,24 (3H, t, *J* = 7,2 Hz).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 139A y 139B, que tuvieron idénticos datos espectrales.

Ejemplo 140

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-6-(metilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

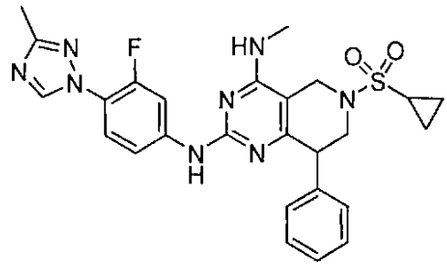


A una solución de la Preparación AEo (0,25 g, 0,560 mmol) en diclorometano se añadió diisopropiletilamina (0,145 g, 1,120 mmol) a -10 °C seguido por la adición de cloruro de metanosulfonilo (0,06 g, 0,560 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-6-(metilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,05 g, 22%) como sólido blanquecino. CL-EM $(M-H)^+$ = 521,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,47 (1H, s), 8,00 (2H, m), 7,44 (1H, m), 7,33-7,22 (6H, m), 7,05 (1H, m), 4,21 (1H, m), 4,11-4,07 (2H, m), 3,63 (1H, m), 3,57-3,50 (3H, m), 2,93 (3H, s), 2,27 (3H, s), 1,24 (3H, t, *J* = 7,2 Hz).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 140A y 140B, que tuvieron idénticos datos espectrales.

Ejemplo 141

6-(ciclopropilsulfonil)-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

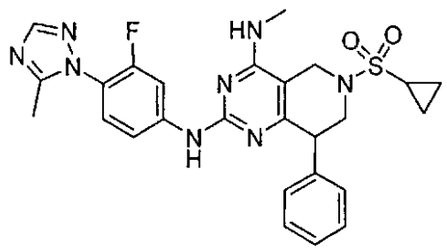


A una solución de la Preparación AEI (0,23 g, 0,534 mmol) en diclorometano se añadió diisopropiletilamina (0,138 g, 1,060 mmol) a -10 °C seguido por la adición de cloruro de ciclopropanosulfonilo (0,089 g, 0,640 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en metanol) dando 6-(ciclopropilsulfonil)-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,11 g, 50%) como sólido blanquecino. CL-EM $(M+H)^+$ = 535,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,45 (1H, s), 8,68 (1H, s), 8,03 (1H, m), 7,22 (2H, m), 7,32-7,21 (5H, m), 7,11 (1H, m), 4,25 (1H, m), 4,13 (1H, m), 4,08 (1H, m), 3,71 (1H, m), 3,64 (1H, m), 2,96 (3H, d, *J* = 4,0 Hz), 2,58 (1H, m), 2,33 (3H, s), 1,01-0,95 (4H, m).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 141A y 141B, que tuvieron idénticos datos espectrales.

Ejemplo 142

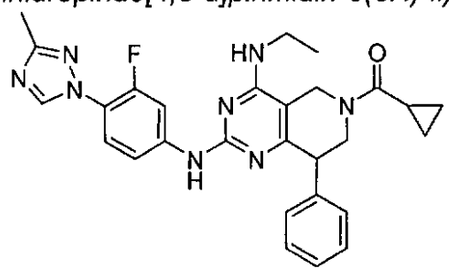
6-(ciclopropilsulfonil)-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



A una solución de la Preparación AEm (0,30 g, 0,690 mmol) en diclorometano se añadió diisopropiletilamina (0,180 g, 1,39 mmol) a -10 °C seguido por la adición de cloruro de ciclopropanosulfonilo (0,117 g, 0,830 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en metanol) dando 6-(ciclopropilsulfonil)-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,14 g, 45%) como sólido blanquecino. CL-EM $(M+H)^+$ = 535,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,49 (1H, s), 8,02 (2H, m), 7,46 (1H, m), 7,44-7,33 (3H, m), 7,30-7,21 (3H, m), 7,11 (1H, m), 4,26 (1H, m), 4,15 (1H, m), 4,10 (1H, m), 3,73 (1H, m), 3,59 (1H, m), 3,28 (3H, m), 2,59 (1H, m), 2,27 (3H, s), 1,24-1,0 (4H, m).

Ejemplo 143

ciclopropil(4-(etilamino)-2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)metanona

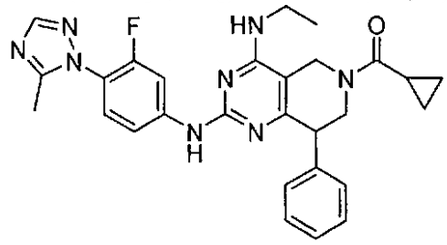


A una solución de la Preparación AEm (0,21 g, 0,49 mmol) en diclorometano se añadió diisopropiletilamina (0,12 g, 0,70 mmol) a -10 °C seguido por la adición de cloruro de ciclopropilcarbonilo (0,056 g, 0,54 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en metanol) dando ciclopropil(4-(etilamino)-2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)metanona (0,090 g, 38%) como sólido blanco. CL-EM $(M+H)^+$ = 513,4. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 8,41 (1H, s), 7,94 (1H, m), 7,63 (1H, m), 7,32 (3H, m), 7,27 (1H, m), 7,10 (2H, m), 4,97 (1H, m), 4,21 (1H, m), 4,10-4,0 (2H, m), 3,91 (1H, m), 3,63 (2H, m), 2,48 (3H, s), 1,35 (3H, t, *J* = 7,2 Hz), 1,22 (1H, m), 0,85 (1H, m), 0,65-0,62 (2H, m), 0,34 (1H, m).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 143A y 143B, que tuvieron idénticos datos espectrales.

Ejemplo 144

ciclopropil(4-(etilamino)-2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)metanona



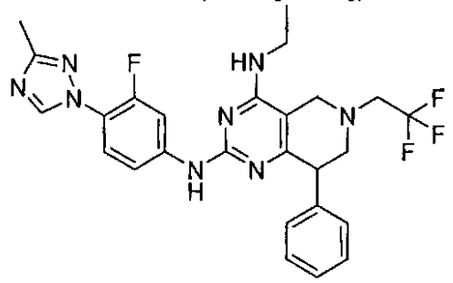
A una solución de la Preparación AEo (0,30 g, 0,67 mmol) en

diclorometano se añadió diisopropiletilamina (0,17 g, 1,35 mmol) a -10 °C seguido por la adición de cloruro de ciclopropilcarbonilo (0,084 g, 0,81 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en metanol) dando ciclopropil(4-(etilamino)-2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-il)metanona (0,14 g, 41%) como sólido blanco. CL-EM $(M+H)^+$ = 513,4. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,94 (2H, m), 7,32-7,25 (4H, m), 7,13 (3H, m), 4,96 (1H, m), 4,22 (1H, m), 4,13-4,04 (2H, m), 3,93 (1H, m), 3,63 (2H, m), 2,39 (3H, s), 1,35 (3H, t, *J* = 7,2 Hz), 1,26 (1H, m), 0,87 (1H, m), 0,66 (2H, m), 0,38 (1H, m).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 144A y 144B, que tuvieron idénticos datos espectrales.

Ejemplo 145

N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-6-(2,2,2-trifluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

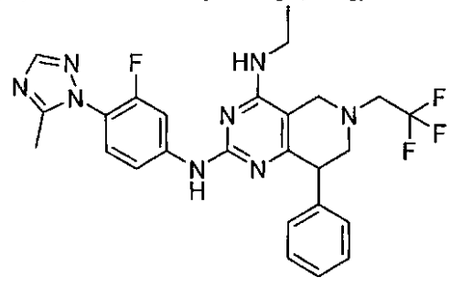


A una solución de la Preparación AEp (0,20 g, 0,37 mmol) en THF se añadió borano-DMS (0,061 g, 0,814 mmol, 2M en éter dietílico) a -0 °C. La

mezcla de reacción se calentó a 55 °C durante 18 h. La mezcla de reacción se enfrió con metanol y se evaporó el disolvente a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-6-(2,2,2-trifluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina bruta (0,025 g, 14%) como sólido amarillo. CL-EM $(M+H)^+$ = 527,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,32 (1H, s), 8,67 (1H, s), 8,03 (1H, m), 7,41-7,38 (2H, m), 7,27-7,18 (5H, m), 6,83 (1H, m), 3,97 (1H, m), 3,73 (1H, m), 3,57 (1H, m), 3,45 (2H, m), 3,37 (2H, m), 3,18 (1H, m), 2,97 (1H, m), 2,33 (3H, s), 1,23 (3H, t, *J* = 7,2 Hz).

Ejemplo 146

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-6-(2,2,2-trifluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

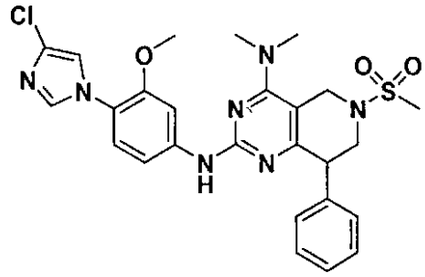


A una solución de la Preparación AEq (0,22 g, 0,40 mmol) en THF se añadió borano-DMS (0,068 g, 0,89 mmol, 2 M en éter dietílico) a -0 °C. La mezcla de reacción se calentó a 55 °C durante 18 h. La mezcla de reacción se enfrió con metanol y se evaporó el disolvente a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N4-etil-N2-(3-fluoro-4-(5-metil-

1H-1,2,4-triazol-1-il)fenil)-8-fenil-6-(2,2,2-trifluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina bruta (0,030 g, 15%) como sólido amarillo. CL-EM $(M+H)^+$ = 527,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,37 (1H, s), 8,04 (1H, s), 8,00 (1H, m), 7,42 (1H, m), 7,30-7,20 (6H, m), 6,84 (1H, m), 3,98 (1H, m), 3,73 (1H, m), 3,69 (1H, m), 3,57-3,48 (4H, m), 3,23 (1H, m), 2,99 (1H, m), 2,26 (3H, s), 1,23 (3H, t, *J* = 7,2 Hz).

Ejemplo 147

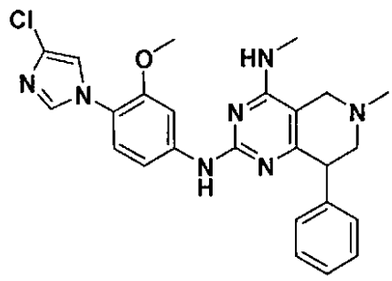
N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4,N4-dimetil-6-(metilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



Usando los procedimientos de la Preparación AEd, la Preparación AEj y el Ejemplo 134, se transformó la Preparación AEc en N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4,N4-dimetil-6-(metilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina. CL-EM $(M-H)^+$ = 552,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,27 (1H, s), 7,91 (1H, s), 7,73 (1H, m), 7,42 (1H, m), 7,31 (2H, m), 7,25-7,10 (5H, m), 4,46 (1H, m), 4,30-4,24 (2H, m), 3,83 (1H, m), 3,53 (3H, s), 3,28 (1H, m), 3,13 (6H, s), 3,09 (3H, s).

Ejemplo 148

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4,6-dimetil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

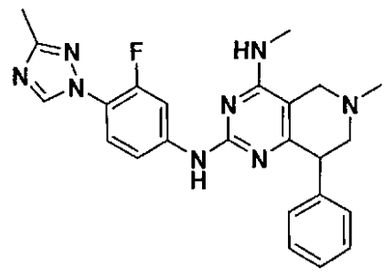


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,26 g, 1,2 mmol), Preparación AFa (0,35 g, 1,2 mmol), Na_2CO_3 (0,25 g, 2,4 mmol) y xantphos (0,69 g, 1,2 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,55 g, 0,6 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 ºC durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico al 0,5% en metanol) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4,6-dimetil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,10 g, 18%) como sólido blanquecino. CL-EM $(M+H)^+$ = 476,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,05 (1H, s), 8,05 (1H, s), 7,71 (1H, s), 7,40 (1H, s), 7,27-7,17 (5H, m), 7,15-7,06 (2H, m), 6,76 (1H, m), 3,94 (1H, m), 3,50 (3H, s), 3,39 (1H, m), 3,18 (1H, m), 2,95 (3H, d, *J* = 4,4 Hz), 2,51 (1H, m), 2,49 (1H, m), 2,12 (3H, s).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 148A y 148B, que tuvieron idénticos datos espectrales.

Ejemplo 149

N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4,6-dimetil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

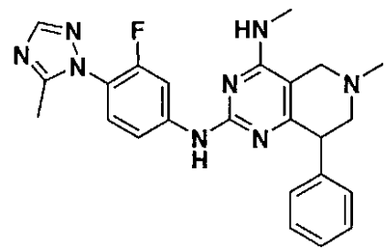


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación B (0,21 g, 1,1 mmol), Preparación AFa (0,35 g, 1,2 mmol), Na_2CO_3 (0,25 g, 2,4 mmol) y xantphos (0,70 g, 1,1 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,55 g, 0,6 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 ºC durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,5% en metanol) dando N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4,6-dimetil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,2 g, 38%) como sólido blanquecino. CL-EM $(M+H)^+$ = 445,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,33 (1H, s), 8,67 (1H, s), 8,05 (1H, m), 7,41 (2H, m), 7,3-7,20 (5H, m), 6,84 (1H, m), 3,96 (1H, m), 3,42 (1H, m), 3,25 (1H, m), 2,94 (3H, d, *J* = 4,4 Hz), 2,92

(1H, m), 2,71 (1H, m), 2,51 (3H, s), 2,40 (3H, s).

Ejemplo 150

N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4,6-dimetil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

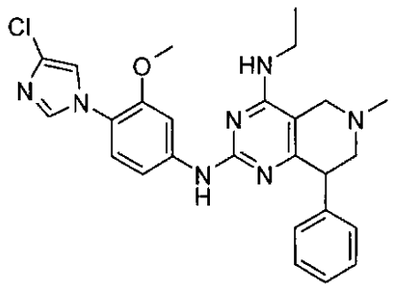


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación C (0,23 g, 1,2 mmol), Preparación AFa (0,35 g, 1,2 mmol), Na_2CO_3 (0,25 g, 2,4 mmol) y xantphos (0,69 g, 1,2 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,55 g, 0,6 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 ºC durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,5% en metanol) dando N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4,6-dimetil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,08 g, 15%) como sólido blanquecino. CL-EM $(M+H)^+$ = 445,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm

9,38 (1H, s), 8,06 (1H, m), 8,00 (1H, s), 7,44 (1H, m), 7,30-7,23 (5H, m), 7,18 (1H, m), 6,84 (1H, m), 3,95 (1H, m), 3,40 (1H, m), 3,22 (1H, m), 2,93 (3H, d, *J* = 4,4 Hz), 2,90 (1H, m), 2,86 (1H, m), 2,36 (3H, s), 2,26 (3H, s).

Ejemplo 151

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



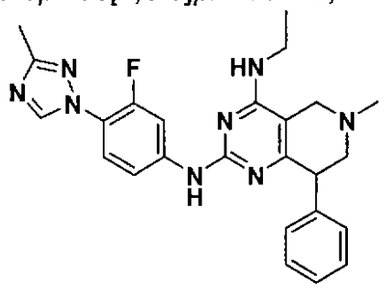
Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,26 g, 1,19 mmol), Preparación AFb (0,4 g, 1,32 mmol), Na_2CO_3 (0,28 g, 2,64 mmol) y xantphos (0,76 g, 1,32 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,60 g, 0,66 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,5% en metanol) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-6-metil-8-fenil-

5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,15 g, 24%) como sólido blanquecino. CL-EM $(M+H)^+$ = 490,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,01 (1H, s), 7,97 (1H, s), 7,71 (1H, s), 7,40 (1H, s), 7,39-7,20 (5H, m), 7,18-7,07 (2H, m), 6,70 (1H, m), 3,95 (1H, m), 3,57 (3H, s), 3,56 (2H, m), 3,47 (1H, m), 3,18 (1H, m), 2,85 (1H, m), 2,59 (1H, m), 2,34 (3H, s), 1,22 (3H, t, *J* = 7,2 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 151A y 151B, que tuvieron idénticos datos espectrales.

Ejemplo 152

N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

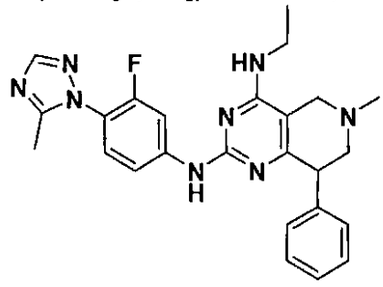


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación B (0,12 g, 0,59 mmol), Preparación AFb (0,20 g, 0,66 mmol), Na_2CO_3 (0,14 g, 1,32 mmol) y xantphos (0,38 g, 0,66 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,30 g, 0,33 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado

se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,5% en metanol) dando N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,03 g, 11%) como sólido blanquecino. CL-EM $(M+H)^+$ = 459,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,31 (1H, s), 8,67 (1H, s), 8,04 (1H, m), 7,40 (2H, m), 7,29-7,17 (5H, m), 6,81 (1H, m), 3,95 (1H, m), 3,48 (2H, m), 3,43 (1H, m), 3,21 (1H, m), 2,91 (1H, m), 2,68 (1H, m), 2,38 (3H, s), 2,33 (3H, s), 1,23 (3H, t, *J* = 7,2 Hz).

Ejemplo 153

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

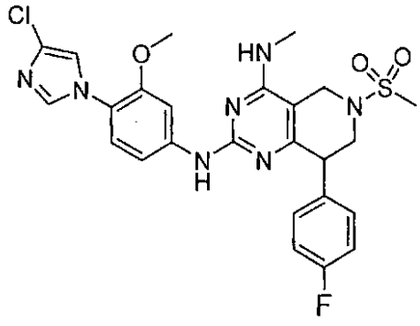


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación C (0,15 g, 0,82 mmol), Preparación AFb (0,25 g, 0,82 mmol), Na_2CO_3 (0,17 g, 1,6 mmol) y xantphos (0,42 g, 0,82 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,37 g, 0,41 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción

se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,5% en metanol) dando N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,06 g, 17%) como sólido blanquecino. CL-EM $(M+H)^+$ = 459,2. RMN de ^1H (400 MHz, $CDCl_3$): δ ppm 7,93 (1H, s), 7,84 (1H, m), 7,34-7,27 (5H, m), 7,26-2,20 (2H, m), 7,05 (1H, m), 4,65 (1H, m), 4,11 (1H, m), 3,61-3,54 (2H, m), 3,39 (2H, m), 3,07 (1H, m), 2,81 (1H, m), 2,51 (3H, s), 2,37 (3H, s), 1,34 (3H, t, *J* = 7,2 Hz).

Ejemplo 154

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N4-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



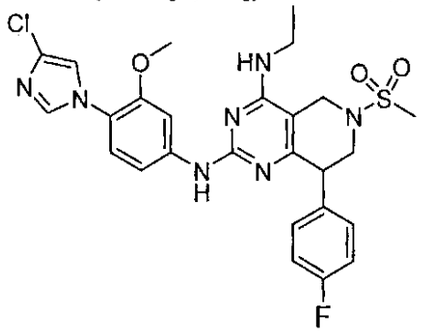
A una solución de la Preparación AGk (0,08 g, 0,167 mmol) en diclorometano se añadió diisopropiletilamina (0,043 g, 0,33 mmol) seguido por cloruro de metanosulfonilo (0,029 g, 0,167 mmol) a 0°C. La mezcla de reacción

se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N4-metil-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,02 g, 23%) como sólido blanquecino. CL-EM $(M+H)^+$ = 558,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,21 (1H, s), 8,0 (1H, s), 7,73 (1H, s), 7,42 (1H, s), 7,27 - 7,23 (2H, m), 7,16-7,12 (4H, m), 7,05 (1H, m), 4,20 (1H, m), 4,12 (1H, m), 4,05 (1H, m), 3,56 (3H, s), 3,51-3,47 (2H, m), 2,97 (3H, d, *J* = 4,0 Hz), 2,91 (3H, s).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 154A y 154B, que tuvieron idénticos datos espectrales.

Ejemplo 155

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



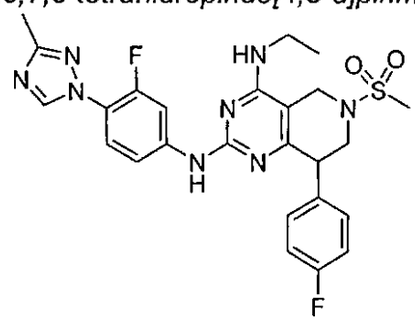
A una solución de la Preparación AGI (0,09 g, 0,018 mmol) en diclorometano se añadió trietilamina (0,037 g, 0,36 mmol) seguido por cloruro de metanosulfonilo (0,021 g, 0,182 mmol) a 0ºC. La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con

diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,04 g, 39%) como sólido blanquecino. CL-EM $(M-H)^+$ = 572,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,18 (1H, s), 7,95 (1H, s), 7,73 (1H, s), 7,42 (1H, s), 7,27 - 7,23 (2H, m), 7,17-7,12 (4H, m), 6,99 (1H, m), 4,24 (1H, d, *J* = 14,0 Hz), 4,12 (1H, m), 4,04 (1H, d, *J* = 14,0 Hz), 3,56 (3H, s), 3,55-3,47 (4H, m), 2,92 (3H, s), 1,22 (3H, t, *J* = 7,2 Hz).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 155A y 155B, que tuvieron idénticos datos espectrales.

Ejemplo 156

N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-(4-fluorofenil)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



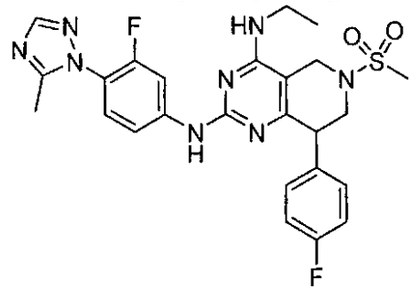
A una solución de la Preparación AGm (0,30 g, 0,649 mmol) en diclorometano se añadió diisopropiletilamina (0,168 g, 0,29 mmol) seguido por cloruro de metanosulfonilo (0,07 g, 0,649 mmol) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó

con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6-(metilsulfonil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,250 g, 71%) como sólido blanquecino. CL-EM $(M+H)^+$ = 541,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,45 (1H, s), 8,69 (1H, s), 8,01 (1H, m), 7,47-7,40 (2H, m), 7,39-7,26 (2H, m), 7,15-7,07 (3H, m), 4,20 (1H, m), 4,12-4,06 (2H, m), 3,63 (1H, m), 3,54-3,48 (3H, m), 2,94 (3H, s), 2,34 (3H, s), 1,22 (3H, t, *J* = 7,2 Hz).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 156A y 156B, que tuvieron idénticos datos espectrales.

Ejemplo 157

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-6-(metilsulfonil)-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



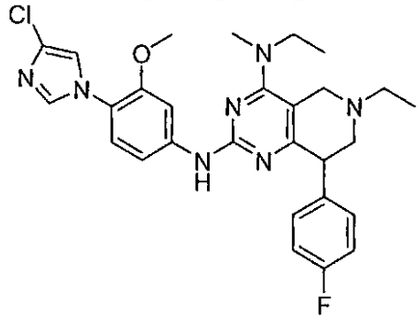
A una solución de la Preparación AGn (0,25 g, 0,540 mmol) en diclorometano se añadió diisopropiletilamina (0,139 g, 1,080 mmol) seguido por cloruro de metanosulfonilo (0,06 g, 0,540 mmol) a 0ºC. La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida

obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-6-(metilsulfonil)-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,19 g, 73%) como sólido blanquecino. CL-EM $(M-H)^+$ = 541,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,48 (1H, s), 8,01 (1H, m), 7,97 (1H, 1H), 7,43 (1H, m), 7,34-7,27 (3H, m), 7,15-7,11 (2H, m), 7,05 (1H, m), 4,23-4,07 (3H, m), 3,63 (1H, m), 3,55-3,48 (3H, m), 2,94 (3H, s), 2,28 (3H, s), 1,24 (3H, t, *J* = 7,2 Hz).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 157A y 157B, que tuvieron idénticos datos espectrales.

Ejemplo 158

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4,6-dietil-8-(4-fluorofenil)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

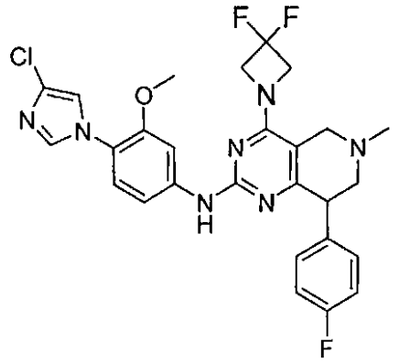


A una solución de la Preparación AGo (0,010 g, 0,019 mmol) en etanol se añadió trietilamina (0,004 g, 0,039 mmol) a 0°C seguido por yoduro de etilo (0,030 g, 0,019 mmol). La mezcla de reacción se calentó a 80 °C durante 18 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (10 ml x 3). La fase orgánica reunida se lavó con agua, se secó sobre Na_2SO_4 anhidro y se evaporó a

presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en metanol) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4,6-dietil-8-(4-fluorofenil)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,04 g, 40%) como sólido blanquecino. CL-EM $(M+H)^+$ = 536,2. RMN de ^1H (400 MHz, metanol-*d4*): δ ppm 7,80 (1H, s), 7,67 (1H, s), 7,26-7,22 (3H, m), 7,13 (1H, m), 7,07-7,00 (2H, m), 6,98 (1H, m), 4,23 (1H, m), 3,75 (1H, m), 3,56-3,48 (6H, m), 3,33 (1H, m), 3,28 (3H, s), 2,69-2,64 (2H, m), 2,53 (1H, m), 1,34 (3H, m), 1,30 (3H, m).

Ejemplo 159

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina

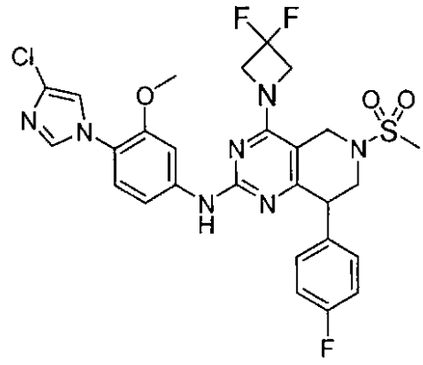


A una solución de la Preparación AGp (0,03 g, 0,055 mmol) en acetona se añadió K_2CO_3 (0,011, 0,083 mmol) seguido por yoduro de metilo (0,012 g, 0,083 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 2 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (10 ml x 3). La fase orgánica reunida se lavó con agua, se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto.

El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en metanol) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina (0,007 g, 24%). CL-EM $(M+H)^+$ = 556,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 10,50 (1H, s), 9,56 (1H, s), 7,75 (1H, s), 7,43 (1H, s), 7,33-7,30 (2H, m), 7,25-7,18 (2H, m), 7,14 (1H, m), 4,09 (1H, m), 4,82-4,76 (2H, m), 4,64 (3H, m), 4,43 (3H, m), 3,88 (1H, m), 3,51 (3H, s), 2,97 (3H, s).

Ejemplo 160

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina



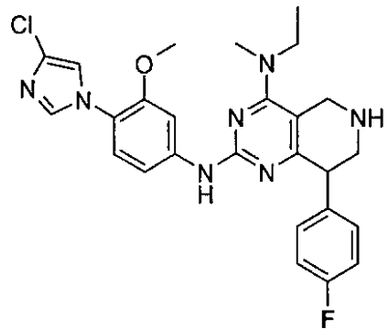
A una solución de la Preparación AGp (0,040 g, 0,073 mmol) en acetona se añadió Cs_2CO_3 (0,036 g, 0,11 mmol) seguido por cloruro de metanosulfonilo (0,012 g, 0,11 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. Se eliminó el disolvente a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (10 ml x 3). La fase orgánica reunida se lavó con agua, se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en metanol)

dando (0,005 g, 12%) como sólido blanquecino. CL-EM $(M+H)^+$ = 620,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,47 (1H, s), 7,85 (1H, s), 7,74 (1H, s), 7,43 (1H, s), 7,30-7,26 (2H, m), 7,18-7,09 (4H, m), 4,77-4,70 (4H, m), 4,36 (1H, m), 4,24 (2H, m), 3,66 (1H, m), 3,56 (3H, s), 3,44 (1H, m), 3,0 (3H, s).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros 160A y 160B, que tuvieron idénticos datos espectrales.

Ejemplo 161

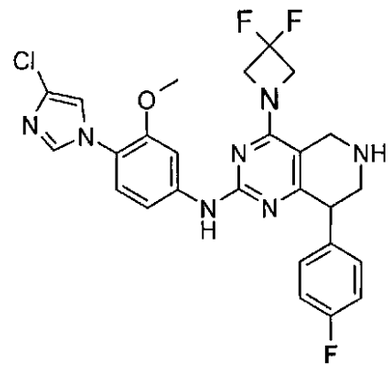
N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



Este compuesto es idéntico a la Preparación AGo (véase más arriba).

Ejemplo 162

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3,3-difluoroazetidin-1-il)-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina

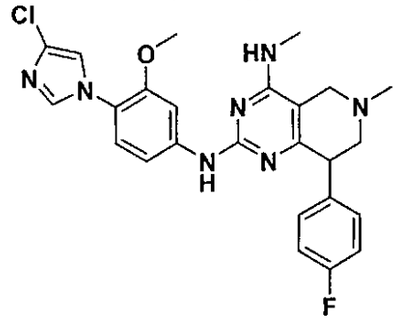


Este compuesto es idéntico a la Preparación AGp (véase más arriba).

El ejemplo se separó por cromatografía quiral proporcionando los enantiómeros individuales 162A y 162B, que tuvieron cada uno idénticos datos espectrales.

Ejemplo 163

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N4,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



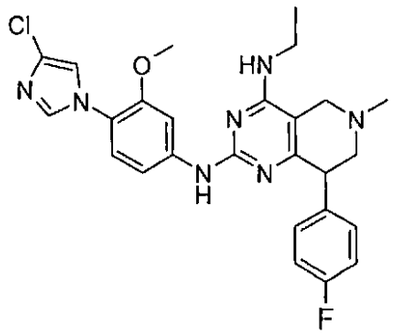
Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,109 g, 0,49 mmol), Preparación AHa (0,15 g, 0,49 mmol), Na_2CO_3 (0,103 g, 0,98 mmol) y xantphos (0,283 g, 0,49 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,253 g, 0,24 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un

lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,5% en metanol) danto N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-N4,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,035 g, 14%) como sólido blanquecino. CL-EM $(M+H)^+$ = 494,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,07 (1H, s), 8,32 (1H, s), 8,05 (1H, s), 7,72 (1H, s), 7,26 (2H, m), 7,14-7,05 (4H, m), 6,77 (1H, m), 3,96 (1H, m), 3,94 (3H, s), 3,42 (1H, m), 3,11 (1H, m), 2,92 (3H, d, *J* = 4,4 Hz), 2,82 (1H, m), 2,58 (1H, m), 2,33 (3H, s).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 163A y 163B, que tuvieron idénticos datos espectrales.

Ejemplo 164

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina



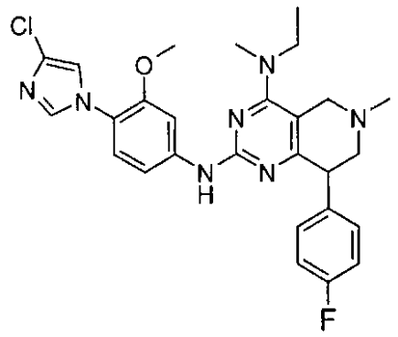
Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,146 g, 0,650 mmol), Preparación AHb (0,210 g, 0,650 mmol), Na_2CO_3 (0,139 g, 1,30 mmol) y xantphos (0,378 g, 0,650 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,338 g, 0,327 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (50 ml x 2). La fase orgánica reunida se lavó con solución de salmuera (50 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,5% en metanol) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,022 g, 22%) como sólido blanquecino. CL-EM $(M+H)^+$ = 508,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,07 (1H, s), 7,97 (1H, s), 7,73 (1H, s), 7,41 (1H, s), 7,29-7,23 (2H, m), 7,15-7,05 (4H, m), 6,73 (1H, m), 3,96 (1H, m), 3,56 (3H, s), 3,49-3,40 (3H, m), 3,13 (1H, m), 2,83 (1H, m), 2,62 (1H, m) 2,34 (3H, s), 1,21 (3H, t, *J* = 7,2 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 164A y 164B, que tuvieron idénticos datos espectrales.

Ejemplo 165

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4,6-

dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

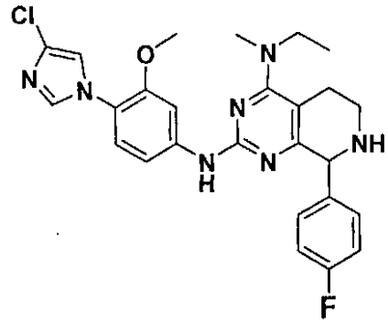


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,18 g, 0,80 mmol), Preparación AHc (0,30 g, 0,89 mmol), Na_2CO_3 (0,190 g, 1,79 mmol) y xantphos (0,519 g, 0,89 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,465 g, 0,440 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (20 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (25 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,5% en metanol) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (0,13 g, 28%) como sólido pardusco. CL-EM $(M+H)^+$ = 522,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,13 (1H, s), 7,86 (1H, s), 7,73 (1H, s), 7,42 (1H, s), 7,24 (2H, m), 7,15-7,07 (4H, m), 4,13 (1H, m), 3,55 (3H, s), 3,47-3,41 (4H, m), 3,04 (3H, s), 2,99 (1H, m), 2,48 (1H, m), 2,34 (3H, s), 1,23 (3H, t, *J* = 7,2 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 165A y 165B, que tuvieron idénticos datos espectrales.

Ejemplo 166

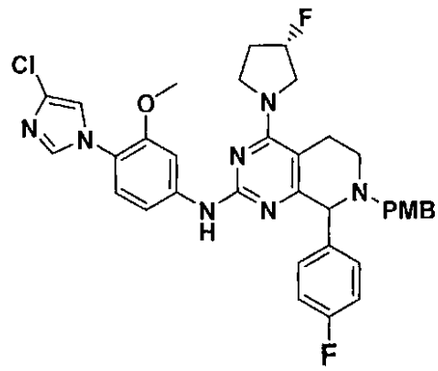
N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina



Este ejemplo es el mismo compuesto que la Preparación AII (véase más arriba).

Ejemplo 167

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina

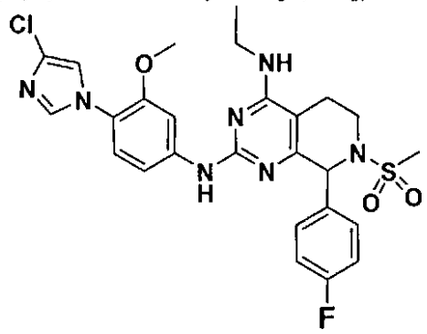


Se purgó con argon durante 1 h a temperatura ambiente una solución de la Preparación A (0,190 g, 0,851 mmol), Preparación AId (0,40 g, 0,851 mmol), Na_2CO_3 (0,180 g, 1,70 mmol) y xantphos (0,491 g, 0,851 mmol) en dioxano/agua (9:1). Se añadió $Pd(dba)_3$ (0,440 g, 0,425 mmol) a la mezcla de reacción y la solución resultante se purgó con argon durante otra 1 h. La masa de reacción se calentó a 110 °C durante 24 h. La masa de reacción se filtró a través de un lecho de tierra de diatomeas (Celite®) y se lavó con acetato de etilo. El filtrado se evaporó a presión reducida y el residuo se diluyó con agua. La solución acuosa se extrajo con acetato de etilo (25 ml x 3). La fase orgánica reunida se lavó con solución de salmuera (20 ml), se secó sobre Na_2SO_4 anhidro y se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por cromatografía en columna (malla 60-120) usando acetato de etilo al 50% en éter de petróleo como fase móvil dando una mezcla de dos diastereómeros N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((S)-3-fluoropirrolidin-1-il)-7-(4-metoxibencil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina (0,40 g, 88%, bruto) como sólido blanquecino. CL-EM $(M+H)^+$ = 658,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 8,95 (1H, s), 7,75 (1H, s), 7,74 (1H, s), 7,54 (2H, m), 7,43 (1H, s), 7,29 (1H, m), 7,22-7,14 (5H, m), 6,86 (2H, m), 5,34 (1H, m), 4,38 (1H, s), 4,03 (1H, m), 4,0 (3H, m), 3,72 (6H, s), 3,51 (1H, m), 3,33 (1H, m), 2,95 (2H, m), 2,51 (1H, m), 2,25-2,01 (3H, m).

La mezcla diastereomérica se separó por cromatografía quiral proporcionando dos diastereómeros Ejemplo 167A y 167B.

Ejemplo 168

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-7-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina



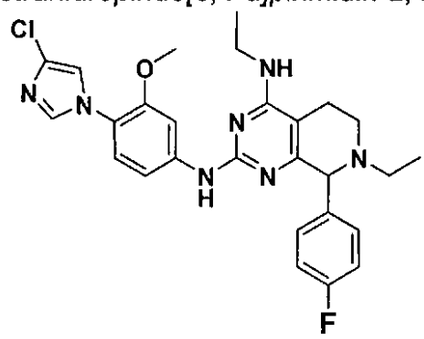
A una solución de la Preparación Alk (0,06 g, 0,121 mmol) en diclorometano se añadió diisopropiletilamina (0,041 g, 0,243 mmol) a -10 °C seguido por cloruro de metanosulfonilo (0,013 g, 0,121 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-7-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina (0,020 g, 29%) como sólido blanquecino. CL-EM $(M+H)^+$ = 572,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,23 (1H, s), 7,97 (1H, s), 7,74 (1H, s), 7,43 (1H, s), 7,35 (2H, m), 7,23-7,12 (4H, m), 7,0 (1H, m), 5,57 (1H, s), 3,85 (1H, m), 3,79 (3H, s), 3,54 (2H, m), 3,18 (1H, m), 2,88 (3H, s), 2,65 (2H, m), 1,24 (3H, t, *J* = 7,2 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando dos enantiómeros Ejemplo 168A y 168B.

Ejemplo 169

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4,7-dietil-8-(4-fluorofenil)-

5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina

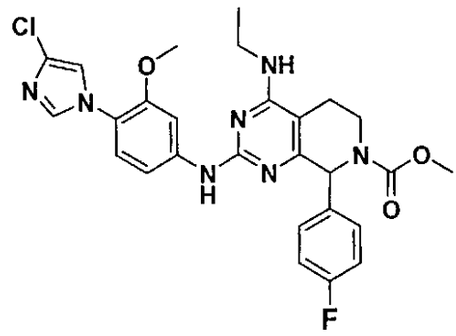


A una solución de la Preparación Alk (0,20 g, 0,405 mmol) en diclorometano se añadió diisopropiletilamina (0,104 g, 0,806 mmol) a -10 °C seguido por yoduro de etilo (0,31 g, 0,231 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4,7-dietil-8-(4-fluorofenil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina (0,110 g, 62%) como sólido blanquecino. CL-EM $(M+H)^+$ = 522,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 8,90 (1H, s), 7,70 (1H, s), 7,73 (1H, s), 7,42 (1H, s), 7,28 (2H, m), 7,17 (4H, m), 6,78 (1H, m), 4,39 (1H, s), 3,65 (3H, s), 3,48 (2H, m), 3,13 (2H, m), 3,08 (1H, m), 2,51 (1H, m), 2,39 (2H, m), 1,22-1,19 (6H, m).

La mezcla racémica se separó por cromatografía quiral proporcionando dos enantiómeros Ejemplo 169A y 169B.

Ejemplo 170

2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-(4-fluorofenil)-5,6-dihidropirido[3,4-d]pirimidin-7(8H)-carboxilato de metilo

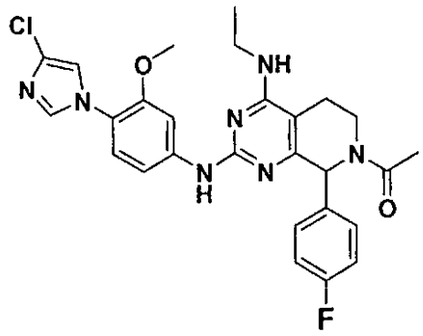


A una solución de la Preparación de Alk (0,10 g, 0,20 mmol) en diclorometano se añadió trietilamina (0,019 g, 0,20 mmol) a -10 ºC seguido por cloroformiato de metilo (0,18 g, 0,20 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando 2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-(4-fluorofenil)-5,6-dihidropirido[3,4-d]pirimidin-7(8H)-carboxilato de metilo (0,080 g, 76%) como sólido blanquecino. CL-EM $(M+H)^+$ = 552,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,22 (1H, s), 7,96 (1H, s), 7,74 (1H, s), 7,48 (1H, s), 7,33 (2H, m), 7,20-7,13 (4H, m), 6,98 (1H, m), 4,06 (1H, s), 3,82 (1H, m), 3,75 (3H, s), 3,68 (3H, s), 3,56 (2H, m), 3,02 (1H, m), 2,33 (2H, m), 1,21 (3H, t, *J* = 7,2 Hz).

La mezcla racémica se separó por cromatografía quiral proporcionando dos enantiómeros Ejemplo 170A y 170B.

Ejemplo 171

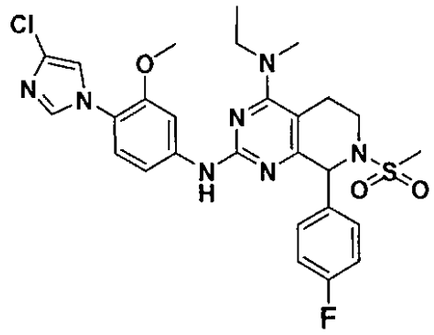
1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-(4-fluorofenil)-5,6-dihidropirido[3,4-d]pirimidin-7(8H)-il)etanona



A una solución de la Preparación Alk (0,052 g, 0,101 mmol) en diclorometano se añadió trietilamina (0,012 g, 0,126 mmol) a -10 °C seguido por cloruro de acetilo (0,007 g, 0,01 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(etilamino)-8-(4-fluorofenil)-5,6-dihidropirido[3,4-d]pirimidin-7(8H)-il)etanona (0,040 g, 72%) como sólido blanquecino. CL-EM $(M+H)^+$ = 536,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,25 (1H, s), 8,0 (1H, s), 7,75 (1H, s), 7,43 (1H, s), 7,32 (2H, m), 7,21-7,14 (4H, m), 6,99 (1H, m), 6,36 (1H, s ancho), 3,95 (1H, m), 3,90 (2H, m), 3,57 (3H, s), 3,49 (1H, m), 3,20 (1H, m), 2,34 (1H, m), 2,12 (3H, s), 1,22 (3H, t, *J* = 7,2 Hz).

Ejemplo 172

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-7-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina

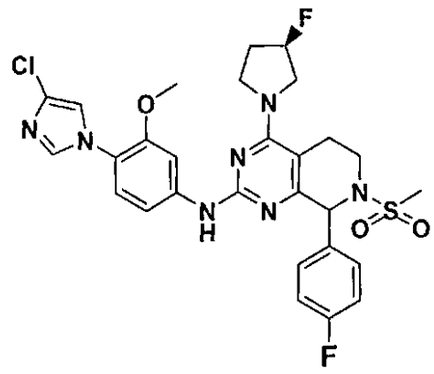


A una solución de la Preparación AII (0,070 g, 0,138 mmol) en diclorometano se añadió diisopropiletilamina (0,047 g, 0,276 mmol) a -10 °C seguido por cloruro de metanosulfonilo (0,015 g, 0,138 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-N4-metil-7-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina (0,030 g, 37%) como sólido blanquecino. CL-EM $(M+H)^+$ = 586,2. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,26 (1H, s), 7,80 (1H, s), 7,74 (1H, s), 7,43 (1H, s), 7,34 (2H, m), 7,32-7,16 (4H, m), 5,65 (1H, s), 3,55 (1H, m), 3,53 (3H, s), 3,51 (2H, m), 3,18 (1H, m), 3,08 (3H, s), 2,91 (3H, s), 2,67 (1H, m), 1,22 (3H, m).

La mezcla racémica se separó por cromatografía quiral proporcionando dos enantiómeros Ejemplo 172A y 172B.

Ejemplo 173

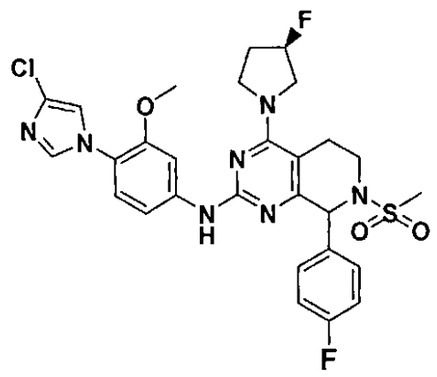
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina



A una solución de la Preparación Alm (0,041 g, 0,074 mmol) en diclorometano se añadió diisopropiletilamina (0,019 g, 0,148 mmol) a -10 °C seguido por la adición de cloruro de metanosulfonilo (0,008 g, 0,074 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina (0,010 g, 20%) como sólido blanquecino. CL-EM $(M+H)^+$ = 616,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,27 (1H, s), 7,84 (1H, s), 7,75 (1H, s), 7,43 (1H, s), 7,38 (2H, m), 7,22-7,17 (4H, m), 5,50 (1H, s), 4,11 (1H, m), 4,04 (3H, m), 3,82 (1H, m), 3,51 (3H, s), 3,23 (2H, m), 3,05 (2H, m), 2,95 (3H, s), 2,23 (2H, m).

Ejemplo 174

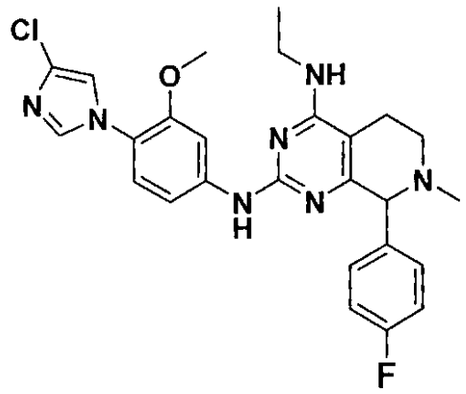
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina



A una solución de la Preparación AIn (0,041 g, 0,074 mmol) en diclorometano se añadió diisopropiletilamina (0,019 g, 0,148 mmol) a -10 °C seguido por la adición de cloruro de metanosulfonilo (0,008 g, 0,074 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano, se lavó con agua, se evaporó a presión reducida obteniendo compuesto bruto. El compuesto bruto se purificó por HPLC preparativa (acetato amónico acuoso al 0,1% en acetonitrilo) dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-8-(4-fluorofenil)-4-((R)-3-fluoropirrolidin-1-il)-7-(metilsulfonil)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina (0,012 g, 20,6%) como sólido blanquecino. CL-EM $(M+H)^+$ = 616,0. RMN de ^1H (400 MHz, DMSO-*d6*): δ ppm 9,25 (1H, s), 7,83 (1H, s), 7,74 (1H, s), 7,42 (1H, s), 7,33 (2H, m), 7,22-7,12 (4H, m), 5,76 (1H, s), 5,57 (1H, m), 4,07 (1H, m), 3,99-3,90 (3H, m), 3,88 (1H, m), 3,54 (3H, s), 3,27 (1H, m), 3,11 (1H, m), 2,93 (3H, s), 2,85 (1H, m), 2,23 (2H, m).

Ejemplo 175

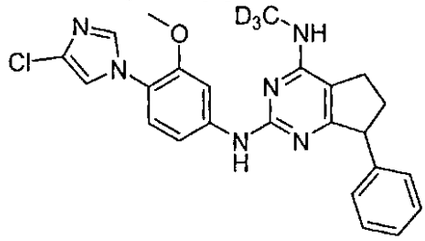
N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-7-metil-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina



La Preparación Alk se combinó con yoduro de metilo en el modo del Ejemplo 169 dando N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-etil-8-(4-fluorofenil)-7-metil-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2,4-diamina.

Ejemplo 176

N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-trideuterometil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



Se calentó a 80 °C durante la noche una solución de 2-cloro-*N*-trideuterometil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-4-amina (121,2 mg, 0,461 mmol) y 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (103 mg, 0,461 mmol) en THF (1 ml) y ácido acético (1,000 ml). La mezcla de reacción se purificó por un procedimiento de HPLC preparativa de fase inversa dando N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-trideuterometil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina, sal TFA (114,3 mg, 43%) como sólido marrón. CL-EM $(M+H)^+$ = 450,0. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 8,86 (1H,

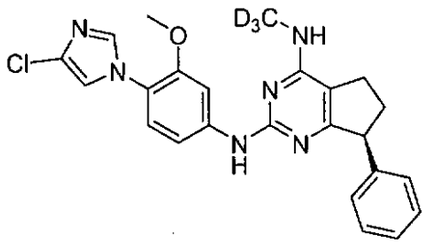
s), 7,88 (1H, t, *J*=8,4 Hz), 7,22 - 7,31 (4H, m), 7,19 (1H, d, *J*=8,9 Hz), 7,07 (3H, t, *J*=8,7 Hz), 4,27 (1H, t, *J*=8,5 Hz), 3,73 (3H, s), 2,45 - 2,59 (1H, m), 2,38 (1H, d, *J*=7,6 Hz), 2,30 (1H, d, *J*=3,7 Hz), 1,95 - 2,06 (1H, m).

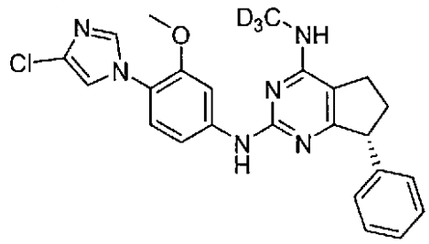
Ejemplos 176A y 176B

(S)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-trideuterometil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)-N^2-(4-(4-Cloro-1H-imidazol-1-il)-3-metoxifenil)-N^4-trideuterometil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



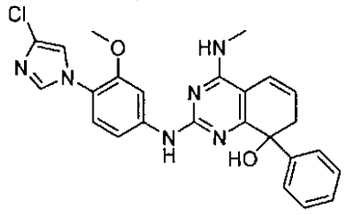


Se purificó una mezcla racémica de N^2-(4-(4-cloro-1*H*-imidazol-1-il)-3-metoxifenil)-N^4-trideuterometil-7-fenil-6,7-dihidro-5*H*-ciclopenta[*d*]pirimidin-2,4-diamina (133 mg, 0,206 mmol del *Ejemplo 176*) usando cromatografía de fluido supercrítico quiral (SFC) proporcionando 28,4 mg de pico A (*Ejemplo 176A*) y 27,4 mg de pico B (*Ejemplo 176B*). Procedimiento de SFC: Chiralpak OJ-H (30 x 250 mm, 5 µM), 40 % metanol (dietilamina al 0,1%) en CO_2, 35 ºC, caudal 70 ml/min durante 16 min, absorbancia 268 nm, inyección de 1ml de solución 22 mg/ml en metanol (varias inyecciones apiladas), t_R (pico A) = 5,0 min, t_R (pico B) 11,2 min. No se determinó la estereoquímica absoluta de enantiómeros individuales (*Ejemplos 176A y 176B*). Los datos analíticos de CL-EM y RMN de

^{1}H para los enantiómeros separados fueron idénticos a los del racemato (*Ejemplo 176*).

Ejemplo 177

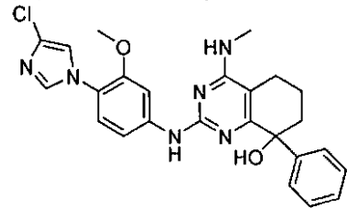
2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(metilamino)-8-fenil-7,8-dihidroquinazolin-8-ol



Se calentó a 85 °C durante 4 h una solución de 2-cloro-4-(metilamino)-8-fenil-7,8-dihidroquinazolin-8-ol (25 mg) y 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (29 mg) en dioxano (0,2 ml) y ácido acético (0,2 ml). Se eliminó el THF a vacío, y el residuo se purificó HPLC preparativa de fase inversa dando el compuesto del epígrafe (como su sal TFA) como un aceite (18 mg). CL-EM $(M+H)^+$ = 475,26. RMN de ^{1}H (sal TFA, 500 MHz, CD_3OD) δ ppm 7,2-7,9 (m), 6,56 (1H, m), 6,18 (1H, m), 3,94 (3H, s), 3,20 (3H, s), 3,10 (2H, m).

Ejemplo 178

2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(metilamino)-8-fenil-5,6,7,8-tetrahidroquinazolin-8-ol

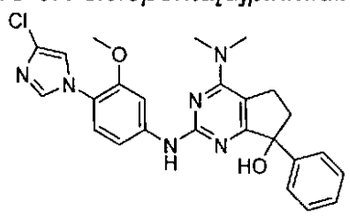


El compuesto del epígrafe como su forma de sal TFA se preparó del

mismo modo que se describe en el Ejemplo 177. CL-EM $(M+H)^+$ = 477,28. RMN de ^1H (sal TFA, 500 MHz, CD_3OD) δ ppm 7,1-8,0 (m), 3,88 (3H, s), 3,18 (3H, s), 1,2-2,5 (6H, m).

Ejemplo 179

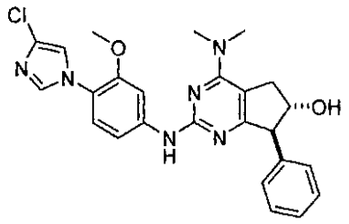
2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(dimetilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-7-ol



La mezcla de 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (37,1 mg, 0,166 mmol), 2-cloro-4-(dimetilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-7-ol (40 mg, 0,138 mmol), $Pd_2(dba)_3$ (5,06 mg, 5,52 µmol), xanphos (7,99 mg, 0,014 mmol) y Cs_2CO_3 (135 mg, 0,414 mmol) se calentó a 100 °C durante la noche. El producto bruto se purificó por HPLC preparativa (Columna: PHENOMENEX LUNA C18 30 x100 mm, Disolvente A = Acetato amónico 10 mM en H_2O / ACN 95 : 5 Disolvente B = Acetato amónico 10 mM en H_2O / ACN 5 : 95. Caudal: 40 ml / min, 35 -100% de B, 30 min) dando el compuesto del epígrafe como su sal TFA (32 mg). CL-EM $(M+H)^+$ = 477,19. RMN de ^1H (sal TFA, 500 MHz, CD_3OD) δ ppm 6,8-7,8 (m), 3,64 (3H, s), 3,30 (6H, s), 3,0-3,2 (2H, m) y 2,4 (2H, m).

Ejemplo 180

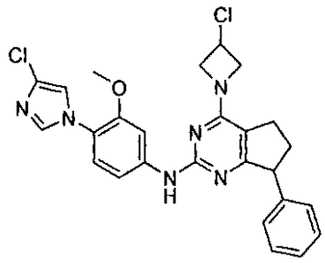
(6S,7S)-2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(dimetilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-6-ol



La reacción se llevó a cabo del mismo modo que se describe en el Ejemplo 177, pero el procedimiento de purificación fue diferente. El producto bruto se purificó por TLC preparativa eluyendo con acetona al 50%/hexanos dando el compuesto del epígrafe como un aceite. CL-EM $(M+H)^+$ = 477,13. RMN de ^1H (500 MHz, $CDCl_3$) δ ppm 6,8-7,9 (m), 4,48 (1H, m), 4,07 (1H, m), 3,58 (1H, m), 3,50 (3H, s), 3,28 (6H, s), 3,12 (1H, m).

Ejemplo 181

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-cloroazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



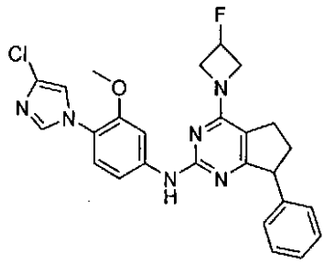
De una forma similar a la que se describe en el Ejemplo 8, se hicieron reaccionar la Preparación A y la Preparación Gi dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-cloroazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina. CL-EM $(M+H)^+$ = 507,2. RMN ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 10,71 (d, *J*=19,84 Hz, 1 H) 8,50 (d, *J*=1,53 Hz, 1 H) 7,45 (dd, *J*=8,85, 1,83 Hz, 1 H) 7,24 - 7,40 (m, 5 H) 7,18 - 7,23 (m, 2 H) 5,12 (s ancho, 1 H) 4,76 - 4,95 (m, 2 H) 4,71 (d, *J*=10,68 Hz, 1 H) 4,35 - 4,54 (m, 2 H)

3,88 (s, 3 H) 3,12 (d, *J*=14,65 Hz, 1 H) 3,01 (dd, *J*=19,99, 6,26 Hz, 1 H) 2,68 - 2,85 (m, 1 H) 2,24 - 2,42 (m, 1 H).

Los enantiómeros individuales se separaron por cromatografía quiral SFC proporcionando los Ejemplos 181A y 181B.

Ejemplo 182

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-fluoroazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

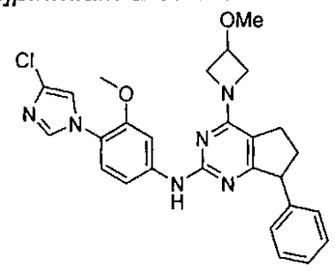


De una forma similar a la que se describe en el Ejemplo 8, se hicieron reaccionar la Preparación A y la Preparación Gj dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-fluoroazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina. CL-EM $(M+H)^+$ = 491,2. RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 11,07 (s ancho, 1 H) 8,30 (s ancho, 1 H) 7,45 (d, *J*=8,55 Hz, 2 H) 7,38 (s ancho, 3 H) 7,33 (d, *J*=4,88 Hz, 2 H) 7,13 - 7,31 (m, 1 H) 5,50 – 5,61 (m, 1 H) 4,91 (s ancho, 1 H) 4,71 (s ancho, 2 H) 4,43 (s ancho, 2 H) 3,89 (s ancho, 3 H) 3,14 (s ancho, 1 H) 3,03 (d, *J*=18,92 Hz, 1 H) 2,75 (s ancho, 1 H) 2,20 - 2,39 (m, 1 H).

Los enantiómeros individuales se separaron por cromatografía quiral SFC proporcionando los Ejemplos 182A y 182B.

Ejemplo 183

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-metoxiazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

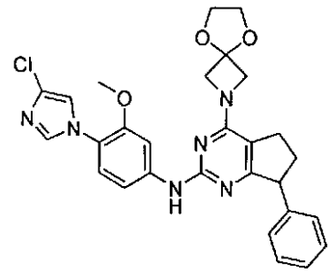


De una forma similar a la que se describe en el Ejemplo 8, se hicieron reaccionar la Preparación A y la Preparación Gk dando N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-metoxiazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina. CL-EM $(M+H)^+$ = 503,2. RMN de ^1H (500 MHz, *CLOROFORMO-d*) δ ppm 7,73 (1 H, s ancho), 7,49 (1 H, s), 7,30 - 7,35 (2 H, m), 7,22 (4 H, t, *J*=8,24 Hz), 7,04 - 7,07 (1 H, m), 7,00 (1 H, s), 6,90 (1 H, s ancho), 4,45 - 4,52 (2 H, m), 4,33 - 4,39 (1 H, m), 4,16 - 4,23 (3 H, m), 3,57 (3 H, s), 2,98 - 3,07 (1 H, m), 2,85 - 2,96 (1 H, m), 2,55 - 2,67 (1 H, m, *J*=13,28, 8,77, 8,77, 4,58 Hz), 2,06 - 2,16 (1 H, m).

Los enantiómeros individuales se separaron por cromatografía quiral SFC proporcionando los Ejemplos 183A y 183B.

Ejemplo 184

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-4-(5,8-dioxa-2-azaspiro[3,4]octan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

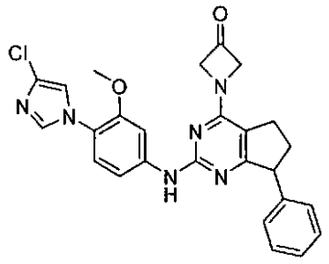


La mezcla de 2-(2-cloro-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-5,8-dioxa-2-azaspiro[3,4]octano (Preparación GI) (23 mg, 0,067 mmol), 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) (17,95 mg, 0,080 mmol), Tris(dibencilidinacetona)dipaladio(0) (3,06 mg, 3,34 µmol), (9,9-dimetil-9H-xanteno-4,5-diil)bis(difenilfosfina) (3,87 mg, 6,69 µmol) y carbonato sódico (14,18 mg, 0,134 mmol) en dioxano (319 µl) / agua (63,7 µl) se calentó a 100 °C durante la noche. El producto bruto se purificó por HPLC Prep (Disolvente A = MeOH al 10% - H20 al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H20 al 10% - TFA al 0,1%. Columna: PHENOMENEX LUNA 30 x 100mm, S10, Caudal: 40 ml / min, 30 - 100% de B, 30 min) obteniendo N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-4-(5,8-dioxa-2-azaspiro[3,4]octan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (17 mg, 0,024 mmol, 35,5 % de rendimiento).

CL-EM $(M+H)^+$ = 531,1 RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 11,39 (s, 1 H) 8,09 (s, 1 H) 7,45 (d, *J*=8,55 Hz, 1 H) 7,35 - 7,42 (m, 4 H) 7,19 - 7,34 (m, 1 H) 7,15 (s, 2 H) 4,73 (s ancho, 2 H) 4,51 (s ancho, 2 H) 4,42 (dd, *J*=8,70, 4,12 Hz, 1 H) 4,09 (d, *J*=3,66 Hz, 4 H) 3,87 (s, 3 H) 3,12 (dd, *J*=14,34, 7,02 Hz, 1 H) 2,90 - 3,05 (m, 1 H) 2,67 - 2,81 (m, 1 H) 2,29 (ddd, *J*=9,16, 4,43, 4,12 Hz, 1 H).

Ejemplo 185

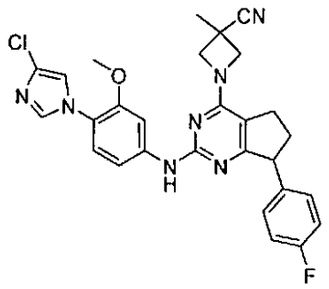
1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)azetidin-3-ona



La mezcla de N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-4-(5,8-dioxa-2-azaspiro[3,4]octan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (Ejemplo 184) (12 mg, 0,023 mmol) en acetona (161 µl) / agua (32,3 µl)/ $HClO_4$, 70% (32,3 µl) se calentó a 50 °C durante la noche. El producto bruto se purificó por HPLC Prep obteniendo 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)azetidin-3-ona (2,5 mg, 4,62 µmol, 20,5 % de rendimiento). CL-EM $(M+H)^+$ = 487,2 RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 7,57 (s, 1 H) 7,42 (t, *J*=7,63 Hz, 3 H) 7,26 - 7,38 (m, 3 H) 7,12 - 7,26 (m, 2 H) 7,00 - 7,12 (m, 1 H) 5,23 (s ancho, 4 H) 4,43 (s ancho, 1 H) 3,68 - 3,79 (m, 3 H) 3,10 - 3,27 (m, 1 H) 2,93 - 3,08 (m, 1 H) 2,71 - 2,84 (m, 1 H) 2,37 (s ancho, 1 H).

Ejemplo 186

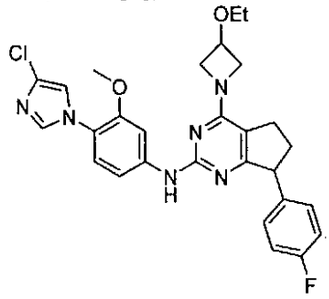
1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-metilazetidina-3-carbonitrilo



De una forma similar a la que se describe en el Ejemplo 184, se combinaron la Preparación Hac y la Preparación A obteniendo 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-metilazetidina-3-carbonitrilo. CL-EM $(M+H)^+$ = 530,1 RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 11,50 (s ancho, 1 H) 8,18 (s ancho, 1 H) 7,46 (d, *J*=7,63 Hz, 1 H) 7,12 - 7,31 (m, 3 H) 7,06 (s ancho, 3 H) 4,99 (s ancho, 1 H) 4,72 (s ancho, 1 H) 4,43 (s ancho, 2 H) 4,28 (s ancho, 1 H) 3,88 (s, 3 H) 3,11 (s ancho, 1 H) 3,00 (s ancho, 1 H) 2,76 (s ancho, 1 H) 2,28 (d, *J*=5,49 Hz, 1 H) 1,87 (s, 3 H).

Ejemplo 187

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-etoxiazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



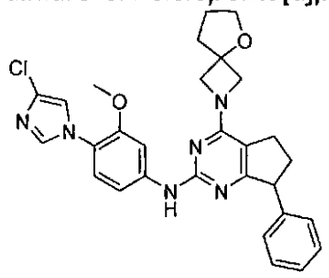
De una forma similar a la que se describe en el Ejemplo 184, se combinaron la Preparación Had y la Preparación A obteniendo N-(4-(4-cloro-

1H-imidazol-1-il)-3-metoxifenil)-4-(3-etoxiazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina. CL-EM $(M+H)^+$ = 535,1 RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 11,77 (s ancho, 1 H) 7,74 (d, *J*=4,58 Hz, 1 H) 7,52 (s ancho, 1 H) 7,34 - 7,41 (m, 1 H) 7,12 - 7,30 (m, 2 H) 7,06 - 7,12 (m, 1 H) 7,03 (s ancho, 2 H) 4,77 (s ancho, 1 H) 4,51 (s ancho, 2 H) 4,49 (d, *J*=5,49 Hz, 1 H) 4,36 (s ancho, 1 H) 4,24 (s ancho, 1 H) 3,85 (d, *J*=4,88 Hz, 3 H) 3,55 (dd, *J*=6,71, 5,49 Hz, 2 H) 3,12 (s ancho, 1 H) 2,99 (s ancho, 1 H) 2,68 (s ancho, 1 H) 2,23 (s ancho, 1 H) 1,21 - 1,37 (m, 3 H).

Los enantiómeros individuales se separaron por cromatografía quiral SFC proporcionando los Ejemplos 187A y 187B.

Ejemplo 188

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-4-(5-oxa-2-azaspiro[3,4]octan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

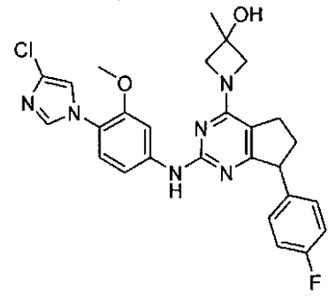


De una forma similar a la que se describe en el Ejemplo 184, se combinaron la Preparación Gm y la Preparación A obteniendo N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-4-(5-oxa-2-azaspiro[3,4]octan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina. CL-EM $(M+H)^+$ = 529,3 RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 10,85 (s ancho, 1 H) 8,36 (s ancho, 1 H) 7,49 (s ancho, 4 H) 7,20 - 7,39 (m, 4 H) 4,56 (d, *J*=9,16 Hz, 1 H) 4,41 (s ancho, 3 H) 3,92 - 4,10 (m, 3 H) 3,87 (s, 3 H) 3,11 (s ancho, 1 H) 3,00 (d, *J*=12,51 Hz,

1 H) 2,73 (s ancho, 1 H) 2,26 (t, *J*=6,87 Hz, 3 H) 2,06 (d, *J*=6,41 Hz, 2 H).

Ejemplo 189

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-metilazetidin-3-ol

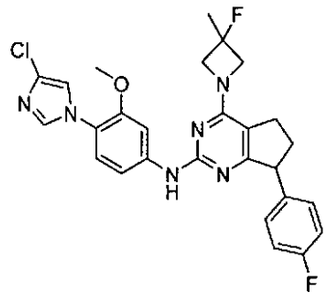


De una forma similar a la que se describe en el Ejemplo 184, se combinaron la Preparación Hae y la Preparación A obteniendo 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-metilazetidin-3-ol. CL-EM $(M+H)^+$ = 521,1 RMN de ^1H (400 MHz, MeOD) δ ppm 7,93 (d, J=1,51 Hz, 1 H) 7,65 (d, J=2,26 Hz, 1 H) 7,26 - 7,44 (m, 4 H) 7,01 - 7,26 (m, 4 H) 4,48 - 4,68 (m, 2 H) 4,44 (dd, J=9,03, 6,78 Hz, 1 H) 4,18 - 4,38 (m, 2 H) 3,90 (s, 3 H) 3,15 (dd, J=5,27, 3,76 Hz, 1 H) 2,96 - 3,06 (m, 1 H) 2,62 - 2,82 (m, 1 H) 2,12 (dddd, J=13,18, 8,85, 6,46, 6,15 Hz, 1 H) 1,55 - 1,66 (m, 3 H).

Los enantiómeros individuales se separaron por cromatografía quiral SFC proporcionando los Ejemplos 189A y 189B.

Ejemplo 190

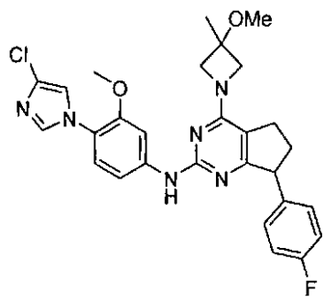
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-fluoro-3-metilazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



Se enfrió hasta -78°C una solución de 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-metilazetidin-3-ol (35 mg, 0,067 mmol) en CH_2Cl_2 (Volumen: 274 µl). A esta mezcla se añadió trifluoruro de [bis(2-metoxietil)amino]azufre (13,62 µl, 0,074 mmol) gota a gota y la solución se agitó durante 30 minutos a -78 °C y luego se calentó hasta 0 °C y se agitó durante una hora más. La reacción se inactivó con solución saturada de $NaHCO_3$ y salmuera. La fase acuosa se extrajo con CH_2Cl_2. La fase orgánica se secó sobre Na_2SO_4 y se concentró. El producto bruto se purificó por HPLC Prep obteniendo N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-fluoro-3-metilazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina, TFA (4,0 mg, 5,65 µmol). CL-EM $(M+H)^+$ = 523,1 RMN de ^1H (500 MHz, CLOROFORMO-d) δ ppm 11,38 (s ancho, 1 H) 8,14 (s, 1 H) 7,43 - 7,54 (m, 1 H) 7,30 - 7,38 (m, 1 H) 7,20 - 7,26 (m, 3 H) 7,16 (s, 1 H) 7,06 (t, J=7,78 Hz, 2 H) 4,78 (s ancho, 1 H) 4,54 (s ancho, 2 H) 4,42 (s ancho, 2 H) 3,88 (s, 3 H) 3,12 (d, J=7,93 Hz, 1 H) 3,00 (s ancho, 1 H) 2,75 (s ancho, 1 H) 2,21 - 2,34 (m, 1 H) 1,78 - 1,82 (s ancho, 3 H).

Ejemplo 191

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(3-metoxi-3-metilazetidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

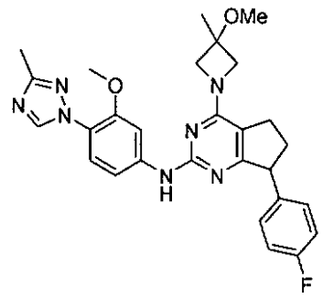


De una forma similar a la que se describe en el Ejemplo 184, se combinaron la Preparación Haf y la Preparación A obteniendo N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(3-metoxi-3-metilazetidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina. CL-EM $(M+H)^+$ = 535,1 RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 11,75 (d, *J*=4,27 Hz, 1 H) 7,83 (d, *J*=1,22 Hz, 1 H) 7,47 (d, *J*=1,83 Hz, 1 H) 7,44 (d, *J*=8,55 Hz, 1 H) 7,15 - 7,33 (m, 4 H) 7,03 (t, *J*=7,63 Hz, 2 H) 4,53 (d, *J*=8,85 Hz, 1 H) 4,24 - 4,43 (m, 3 H) 4,06 - 4,19 (m, 1 H) 3,86 (s, 3 H) 3,34 (s, 3 H) 3,13 (ddd, *J*=12,67, 6,56, 6,41 Hz, 1 H) 3,01 (ddd, *J*=15,95, 4,81, 4,58 Hz, 1 H) 2,70 (td, *J*=9,46, 3,66 Hz, 1 H) 2,24 (tt, *J*=8,96, 4,31 Hz, 1 H) 1,63 (s, 3 H).

Los enantiómeros individuales se separaron por cromatografía quiral SFC proporcionando los Ejemplos 191A y 191B.

Ejemplo 192

7-(4-fluorofenil)-4-(3-metoxi-3-metilazetidin-1-il)-N-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina

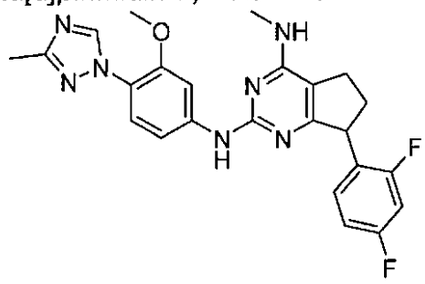


De una forma similar a la que se describe en el Ejemplo 184, se combinaron la Preparación Haf y la Preparación D obteniendo 7-(4-fluorofenil)-4-(3-metoxi-3-metilazetidin-1-il)-N-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina. CL-EM $(M+H)^+$ = 516,1 RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 11,77 (d, *J*=3,97 Hz, 1 H) 8,88 (s, 1 H) 7,69 (d, *J*=8,55 Hz, 1 H) 7,52 (dd, *J*=8,85, 2,14 Hz, 1 H) 7,47 (s, 1 H) 7,23 (t, *J*=5,49 Hz, 2 H) 7,03 (t, *J*=8,39 Hz, 2 H) 4,45 - 4,58 (m, 1 H) 4,35 (d, *J*=4,58 Hz, 2 H) 4,27 (d, *J*=7,63 Hz, 1 H) 4,10 (d, *J*=10,07 Hz, 1 H) 3,85 - 4,04 (m, 3 H) 3,33 (s, 3 H) 3,05 - 3,20 (m, 1 H) 2,92 - 3,05 (m, 1 H) 2,63 - 2,79 (m, 1 H) 2,45 - 2,59 (m, 3 H) 2,23 (td, *J*=8,39, 4,27 Hz, 1 H) 1,57 - 1,72 (m, 3 H).

Los enantiómeros individuales se separaron por cromatografía quiral SFC proporcionando los Ejemplos 192A y 192B.

Ejemplo 193

7-(2,4-difluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



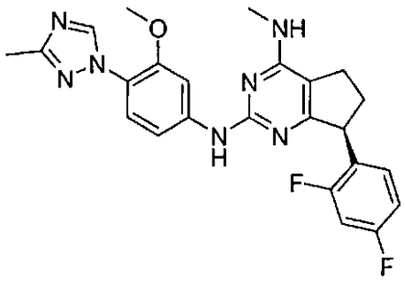
La mezcla de 2-cloro-7-(2,4-difluorofenil)-N-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (153 mg, 0,517 mmol), 3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)anilina (211 mg, 1,035 mmol) y H_2SO_4 (44,1 µl, 0,828 mmol) en N-Metil-2-pirrolidinona (Volumen: 2070 µl) se calentó a 100 °C durante la noche. Se añadió lentamente $NaHCO_3$ saturado y se extrajo con EtOAc (x3). La fase orgánica reunida se secó sobre Na_2SO_4 y se concentró. El producto bruto se purificó por HPLC Prep (Disolvente A = MeOH al 10% - H_20 al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_20 al 10% - TFA al 0,1%. Columna: PHENOMENEX LUNA 30 x 100mm, S10, Caudal: 40 ml / min, 30 - 100% B, 15 min) obteniendo 7-(2,4-difluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina, TFA (287 mg, 0,447 mmol, 86 % de rendimiento). CL-EM $(M+H)^+$ = 464,1. RMN de ^1H (500 MHz, *CLOROFORMO-d*) δ ppm 11,54 (1 H, s), 9,22 (1 H, s), 7,75 (1 H, d, *J*=8,85 Hz), 7,65 (1 H, s), 7,49 (1 H, d, *J*=8,85 Hz), 7,13 - 7,21 (1 H, m), 6,79 - 6,91 (2 H, m), 6,11 (1 H, d, *J*=4,27 Hz), 4,56 - 4,63 (1 H, m), 3,97 (3 H, s), 3,23 (3 H, d, *J*=4,27 Hz), 2,84 - 2,93 (1 H, m), 2,71 - 2,81 (2 H, m), 2,62 (3 H, s), 2,19 - 2,28 (1 H, m).

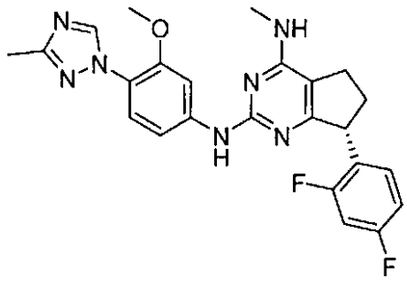
Ejemplos 193A y 193B

(S)-7-(2,4-difluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

y

(R)-7-(2,4-difluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

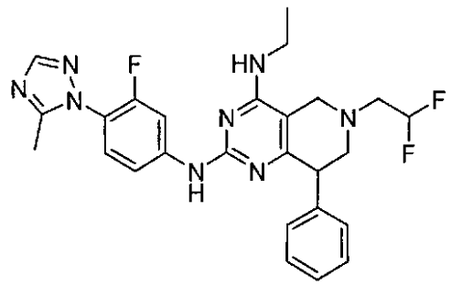




Se purificó una mezcla racémica de *7-(2,4-difluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina* (*Ejemplo 193*) usando cromatografía de fluido supercrítico (SFC) quiral proporcionando el pico A (*Ejemplo 193A*) y el pico B (*Ejemplo 193B*). Procedimiento SFC: Chiralpak OJ-H (30 x 150 mm), 30 % de metanol (0,1% dietilamina) en CO_2, 100 x 10^5 Pa, caudal 50 ml/min durante 12 min, absorbancia 268 nm, inyección 2,0 ml de solución 10 mg/ml en metanol, t_R (pico A) = 4,7 min, t_R (pico B) 9,6 min. No se determinó la estereoquímica absoluta de los enantiómeros individuales (*Ejemplos 193A y 193B*). 193A: CL-EM $(M+H)^+$ = 446,2. CL T_t 13,03 min (Waters Sunfire 4,6X150 mm 10 hasta 100% de B en A durante 15 min, 1,5 ml/min. (A es agua:MeOH:TFA 90:10:0,1; B es MeOH:agua:TFA 90:10:0,1)). RMN de ^{1}H (500 MHz, *CLOROFORMO-d*) δ ppm 8,46 (1 H, s), 8,04 (1 H, s), 7,51 (1 H, d, *J*=8,55 Hz), 7,04 - 7,13 (2 H, m), 6,78 - 6,87 (3 H, m), 4,42 - 4,50 (1 H, m), 3,68 (3 H, s), 3,13 (3 H, s), 2,62 - 2,79 (3 H, m), 2,49 (3 H, s), 1,96 - 2,08 (1 H, m).

Ejemplo 194

6-(2,2-difluoroetil)-N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

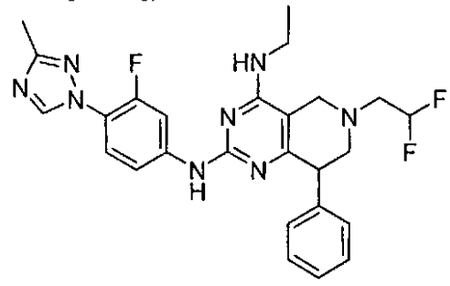


Se hizo reaccionar la Preparación AEo con difluoro-2-yodoetano, carbonato potásico y yoduro sódico en DMF a 80 °C proporcionando 6-(2,2-difluoroetil)-N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (Ejemplo 194). CL-EM $(M+H)^+$ = 509,4.

Los enantiómeros individuales se separaron por cromatografía quiral SFC proporcionando los Ejemplos 194A y 194B.

Ejemplo 195

6-(2,2-difluoroetil)-N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

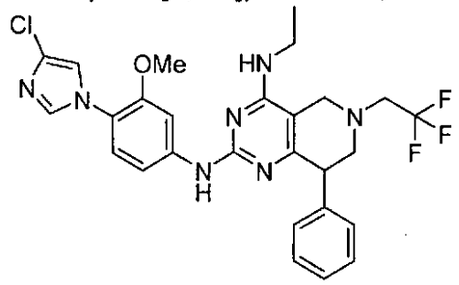


Se hizo reaccionar la Preparación AEm con difluoro-2-yodoetano, carbonato potásico y yoduro sódico en DMF a 80 °C proporcionando 6-(2,2-difluoroetil)-N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (Ejemplo 195). CL-EM $(M+H)^+$ = 509,2.

Los enantiómeros individuales se separaron por cromatografía quiral SFC proporcionando los Ejemplos 195A y 195B.

Ejemplo 196

N4-etil-N2-(3-metoxi-4-(4-cloro-1H-13-imidazol-1-il)fenil)-8-fenil-6-(2,2,2-trifluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

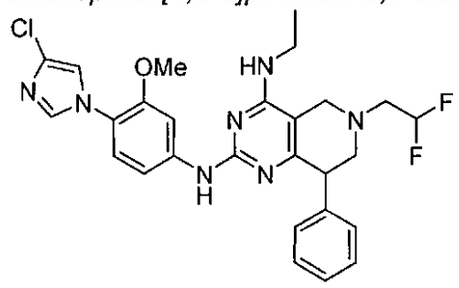


De un modo similar a la Preparación AEp y el Ejemplo 146, se transformó la Preparación AEk en N4-etil-N2-(3-metoxi-4-(4-cloro-1H-13-imidazol-1-il)fenil)-8-fenil-6-(2,2,2-trifluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (Ejemplo 196). CL-EM $(M+H)^+$ = 558,2.

Los enantiómeros individuales se separaron por cromatografía quiral SFC proporcionando los Ejemplos 196A y 196B.

Ejemplo 197

N4-etil-N2-(3-metoxi-4-(4-cloro-1H-13-imidazol-1-il)fenil)-8-fenil-6-(2,2-difluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

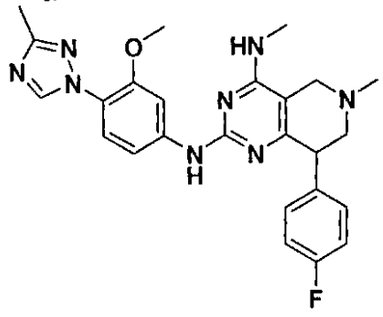


Se hizo reaccionar la Preparación AEk con difluoro-2-yodoetano, carbonato potásico y yoduro sódico en DMF a 80 °C proporcionando N4-etil-N2-(3-metoxi-4-(4-cloro-1H-13-imidazol-1-il)fenil)-8-fenil-6-(2,2-difluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina (Ejemplo 197). CL-EM $(M+H)^+$ = 540,2.

Los enantiómeros individuales se separaron por cromatografía quiral SFC proporcionando los Ejemplos 197A y 197B.

Ejemplo 198

8-(4-fluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

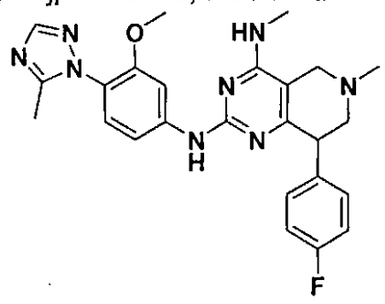


De una forma similar a la que se describe en el Ejemplo 8, se hicieron reaccionar la Preparación D y la Preparación AHa dando 8-(4-fluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina. CL-EM $(M+H)^+$ = 475,2. La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 198A y 198B.

Ejemplo 199

8-(4-fluorofenil)-N2-(3-metoxi-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4,6-dimetil-

5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina

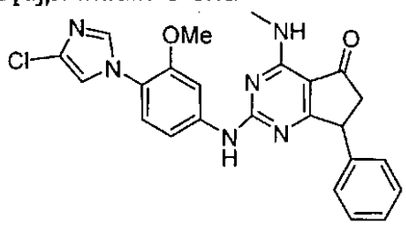


De una forma similar a la que se describe en el Ejemplo 8, se hicieron reaccionar la Preparación DD y la Preparación AHa dando 8-(4-fluorofenil)-N2-(3-metoxi-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina. CL-EM $(M+H)^+$ = 475,2.

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 199A y 199B.

Ejemplo 200

(±)-2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-5-ona



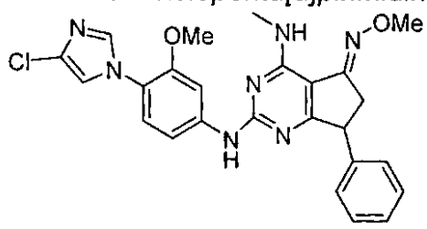
Se calentó a 85 °C durante 12 h una solución de 2-cloro-4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-5-ona (Preparación AN) (7 mg) y 4-(4-cloro-1*H*-imidazol-1-il)-3-metoxianilina (Preparación A) (7 mg) en THF (0,2 ml) y ácido sulfúrico (4 mg). Se eliminó el THF a vacío y el residuo se purificó por HPLC preparativa de fase inversa dando el compuesto del epígrafe (como

su sal TFA) como un aceite amarillento (9 mg). CL-EM $(M+H)^+$ = 461,12. RMN de ^1H (500 MHz, CD_3OD) δ ppm 7,80 (m), 7,1-7,4 (m), 4,50 (1H, m), 3,25 (1H, m), 2,56 (1H, m), 3,50 (3H, s) y 3,19 (3H, s).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 200A y 200B.

Ejemplo 201

O-metil oxima de (E)-2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-5-ona

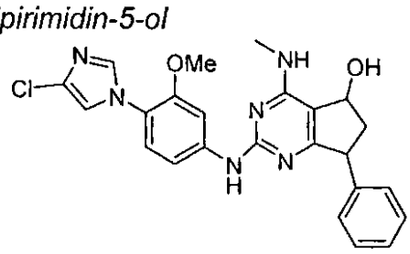


Se calentó una solución 0,15M del Ejemplo 200 en iPrOH con 4 eq de clorhidrato de metoxiamina a 85 °C durante 3h. La HPLC de fase inversa proporcionó el material deseado como una sal TFA. CL-EM $(M+H)^+$ = 490,2.

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 201A y 201B.

Ejemplo 202

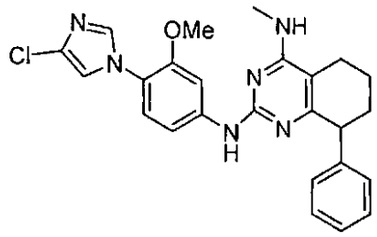
2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-5-ol



A una solución del Ejemplo 201 en metanol a ta se añadió $NaBH_4$, y la mezcla de reacción se agitó a TA durante 1 h. La reacción se trató con $EtOAc/H_2O$ dando el producto deseado como un sólido blanco. CL-EM $(M+H)^+$ = 463,1.

Ejemplo 203

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-8-fenil-5,6,7,8-tetrahidroquinazolin-2,4-diamina

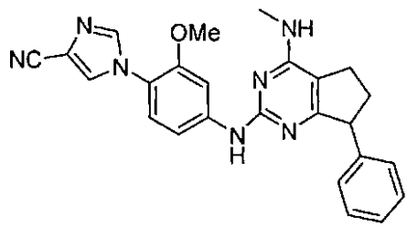


CL-EM $(M+H)^+$ = 466,0. RMN de ^1H (400 MHz, CLOROFORMO-d) δ ppm 7,86 (1 H, d, J=2,3 Hz), 7,48 (1 H, d, J=1,5 Hz), 7,24 - 7,32 (4 H, m), 7,16 - 7,23 (1 H, m), 7,08 - 7,14 (2 H, m), 7,00 (2 H, s), 6,70 (1 H, dd, J=8,3, 2,0 Hz), 4,71 (1 H, d, J=3,0 Hz), 4,03 (1 H, t, J=5,6 Hz), 3,41 (3 H, s), 3,12 (3 H, d, J=4,8 Hz), 2,30 - 2,48 (2 H, m), 2,09 - 2,22 (1H, m, J=13,0, 9,7, 6,2, 3,3, 3,1 Hz), 1,74 - 1,96 (3 H, m).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 203A y 203B.

Ejemplo 204

1-(2-metoxi-4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenil)-1H-imidazol-4-carbonitrilo

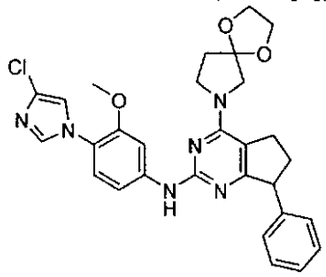


A una solución de 2-cloro-N-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (Preparación Ga) (150 mg, 0,578 mmol) en Dioxano (Relación: 1, Volumen: 1013 µl) se añadió 1-(4-amino-2-metoxifenil)-1H-imidazol-4-carbonitrilo (Preparación AA) (124 mg, 0,578 mmol), y AcOH (Relación: 1,000, Volumen: 1013 µl). La mezcla resultante se llevó hasta 100 °C en un vial herméticamente cerrado y se agitó durante la noche. La mezcla se llevó hasta pH 8 mediante la adición de hidróxido sódico acuoso 1 N. La mezcla resultante se extrajo con EtOAc(3 x 1 ml). Los extractos reunidos se secaron sobre $MgSO_4$, se filtraron y se concentraron a vacío. La purificación por HPLC prep (Waters Sunfire C18, 50 X 250mm, acetonitrilo/H_2O/acetato amónico) dio 1-(2-metoxi-4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenil)-1H-imidazol-4-carbonitrilo (57 mg, 0,130 mmol, 22,56 % de rendimiento). CL-EM $(M+H)^+$ = 438,2. RMN de ^1H (500 MHz, *MeOD*) δ ppm 8,02 - 8,08 (2 H, m), 7,90 - 7,94 (1 H, m), 7,31 (2 H, t, *J*=7,63 Hz), 7,16 - 7,24 (4 H, m), 6,99 (1 H, dd, *J*=8,55, 2,14 Hz), 4,18 (1 H, t, *J*=8,09 Hz), 3,56 (3 H, s), 3,07 (3 H, s), 2,76 - 2,84 (1 H, m), 2,59 - 2,74 (2 H, m), 1,98 - 2,05 (1 H, m).

La mezcla racémica se separó por cromatografía quiral proporcionando los enantiómeros Ejemplo 204A y 204B.

Ejemplo 205

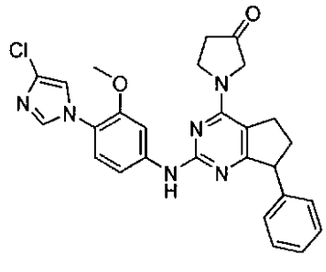
N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-4-(1,4-dioxa-7-azaspiro[4,4]nonan-7-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina



De una forma similar a la que se describe en el Ejemplo 184, se combinaron la Preparación Go y la Preparación A obteniendo N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-4-(1,4-dioxa-7-azaspiro[4,4]nonan-7-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina. CL-EM $(M+H)^+$ = 545,1. RMN de ^1H (500 MHz, *MeOD*) δ ppm 7,89 (1 H, s), 7,62 (0,5 H, s ancho), 7,53 (0,5 H, s ancho), 7,37 - 7,45 (4 H, m), 7,32 - 7,36 (1 H, m), 7,30 (2 H, d, *J*=7,63 Hz), 7,23 (0,5 H, d, *J*=7,63 Hz), 7,14 (0,5 H, d, *J*=7,32 Hz), 4,40 - 4,47 (1 H, m), 4,25 (1 H, s ancho), 3,96 - 4,14 (6 H, m), 3,88 (4 H, s ancho), 3,34 - 3,46 (1 H, m), 3,28 (1 H, s ancho), 2,69 - 2,79 (1 H, m), 2,24 - 2,32 (1 H, m), 2,09 - 2,23 (2 H, m).

Ejemplo 206

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)pirrolidin-3-ona



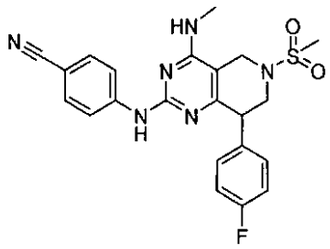
La mezcla de N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-4-(1,4-

dioxa-7-azaspiro[4,4]nonan-7-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina (Ejemplo 205) (37 mg, 0,068 mmol) y HCl (272 µl, 0,272 mmol) en THF (339 µl) se calentó a 60 °C durante la noche. Se concentró para eliminar el THF y se añadió acetona (339 µl) y HCl (272 µl, 0,272 mmol) a la mezcla. La mezcla se calentó a 60 °C durante 6 h. El producto bruto se purificó por HPLC Prep (Disolvente A = MeOH al 10% - H_20 al 90% - TFA al 0,1%, Disolvente B = MeOH al 90% - H_20 al 10% - TFA al 0,1%. Columna: PHENOMENEX LUNA 30 x 100mm, S10, Caudal: 40 ml / min, 35 - 100% de B, 40 min) y luego se purificó por HPLC Prep (Columna: PHENOMENEX LUNA C18 30 x100 mm, Disolvente A = Acetato amónico 10 mM en H_2O / ACN 95 : 5, Disolvente B = Acetato amónico 10 mM en H_2O / ACN 5 : 95. Caudal: 40 ml / min, 30 -100% de B, 35 min) obteniendo 1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)pirrolidin-3-ona (2,0 mg, 3,59 µmol, 5,29 % de rendimiento).

CL-EM $(M+H)^+$ = 501,3.

Ejemplo 207

4-(8-(4-fluorofenil)-4-(metilamino)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-ilamino)benzonitrilo

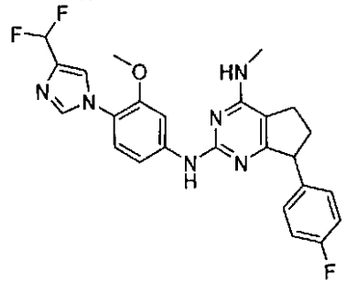


Utilizando 4-aminobenzonitrilo y Preparación AGa sucesivamente, se obtuvo el compuesto del epígrafe por los procedimientos generales descritos

en la Preparación AGj, AGk y AGp. CL-EM $(M+H)^+$ = 453,2. RMN de ^1H (400 MHz, DMSO-*d*) δ ppm 9,25 (s, 1H) 7,85 (d, *J*= 8,80 Hz, 2H) 7,55 (d, *J*= 8,80 Hz, 2H) 7,25 – 7,29 (m, 2H) 7,10 – 7,17 (m, 3H) 4,05 – 4,24 (m, 3H) 3,53 – 3,63 (m, 2H) 2,95 (d, *J*= 4,4 Hz, 3H) 2,95 (s, 3H).

Ejemplo 208

N2-(4-(4-(difluorometil)-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

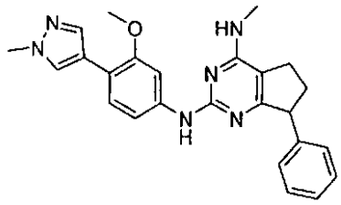


De una forma similar a la que se describe en el Ejemplo 8, se hicieron reaccionar la Preparación EE y la Preparación Hh dando N2-(4-(4-(difluorometil)-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina. CL-EM $(M+H)^+$ = 481,1 RMN de ^1H (500 MHz, MeOD) δ ppm 8,19 (s, 1 H) 7,75 (s ancho, 1 H) 7,71 (s, 1 H) 7,45 (dd, *J*=8,55, 3,05 Hz, 1 H) 7,31 (ddd, *J*=8,47, 5,26, 2,75 Hz, 2 H) 7,19 - 7,26 (m, 1 H) 7,15 (td, *J*=8,77, 2,90 Hz, 2 H) 6,83 (t, *J*=55 Hz, 1H) 4,51 (d, *J*=2,75 Hz, 1 H) 3,91 (d, *J*=3,05 Hz, 3 H) 3,18 (d, *J*=3,05 Hz, 3 H) 2,92 (d, *J*=9,16 Hz, 1 H) 2,76 - 2,85 (m, 2 H) 2,10 - 2,20 (m, 1 H).

Ejemplo 209

N2-(3-metoxi-4-(1-metil-1H-pirazol-4-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-

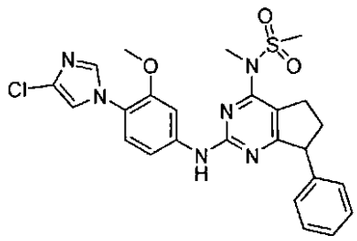
ciclopenta[d]pirimidin-2,4-diamina



De una forma similar a la que se describe en el Ejemplo 8, se hicieron reaccionar la Preparación AO y la Preparación Ga dando N2-(3-metoxi-4-(1-metil-1H-pirazol-4-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina. CL-EM $(M+H)^+$ = 425,4. RMN de ^1H (400 MHz, *CLOROFORMO-d*) δ ppm 7,84 (1 H, d, *J*=2,01 Hz), 7,81 (1 H, s), 7,74 (1 H, s), 7,32 (3 H, dd, *J*=13,55, 7,78 Hz), 7,19 - 7,26 (3 H, m), 7,07 (1 H, s), 6,78 (1 H, dd, *J*=8,28, 2,01 Hz), 4,60 (1 H, q, *J*=4,52 Hz), 4,16 - 4,23 (1 H, m), 3,91 (3 H, s), 3,64 (3 H, s), 3,11 (3 H, d, *J*=5,02 Hz), 2,58 - 2,76 (3 H, m), 2,00 - 2,11 (1 H, m).

Ejemplo 210

N-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N-metilmetanosulfonamida

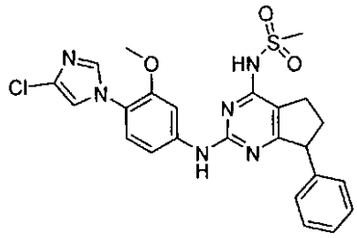


La Preparación G se hizo reaccionar con 0,9 eq de $MeSO_2NHMe$, 0,1 eq de $Pd(OAc)_2$, 0,15 eq de xanphos y Cs_2CO_3 a 110 °C. Se añadió entonces la Preparación A, dando el compuesto del epígrafe. CL-EM $(M+H)^+$ = 525,4 RMN de ^1H (400 MHz, DMSO-*d*) δ ppm 9,79 (s, 1 H) 7,75 - 7,77 (m., 2 H) 7,45 (s, 1 H) 7,32 - 7,35 (m, 2 H) 7,23 – 7,27 (m, 4 H) 7,16 – 7,18 (m, 1H) 4,35 (t, *J*=8,80

Hz, 1 H) 3,40 (s, 3 H) 3,31 (s, 3 H) 2,94 – 3,06 (m, 2 H) 2,57 - 2,61 (m, 1 H) 2,51 (s, 3 H) 2,04 – 2,08 (m, 1H).

Ejemplo 211

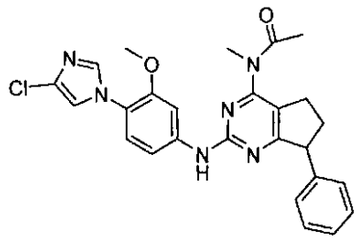
N-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N-metanosulfonamida



El compuesto del epígrafe se preparó como el Ejemplo 210, sustituyendo $MeSO_2NH_2$. CL-EM $(M+H)^+$ = 511,0 RMN de ^1H (400 MHz, DMSO-*d*) δ ppm 9,51 (s, 1 H) 7,73 – 7,76 (m., 2 H) 7,41 (s, 1 H) 7,16 - 7,31 (m, 8 H) 4,21 (t, *J*=8,40 Hz, 1 H) 3,54 (s, 3 H) 3,41 (s, 3 H) 2,88 – 2,93 (m, 2 H) 2,69 – 2,73 (m, 1 H) 1,91 – 1,97 (m, 1H).

Ejemplo 212

N-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N-metilacetamida

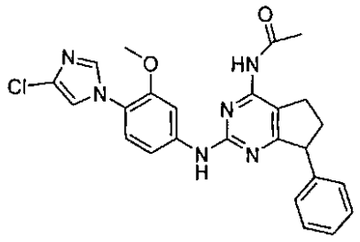


El Intermedio Ga se hizo reaccionar con *p*-metoxibencilamina en la forma de la Preparación Gd. El acoplamiento con la Preparación A en las

condiciones del Ejemplo 184, seguido por tratamiento con TFA, condujo al compuesto C4 NH2. La reacción con AcCl en dicloroetano y DIPEA a temperatura ambiente durante 4h proporcionó el compuesto del epígrafe. CL-EM $(M+H)^+$ = 489,2. RMN de ^1H (400 MHz, DMSO-*d*) δ ppm 9,89 (s, 1H), 7,92 (s, 1 H), 7,75 (s, 1 H), 7,44 (s, 1 H), 7,36 - 7,12 (m, 7H), 4,38 (t, *J*=8,6 Hz, 1 H), 3,51 (s, 3 H), 3,33 (s, 3H), 2,81 (t, *J*=7,4 Hz, 2 H), 2,59-2,55 (m, 1H), 2,17 (s, 3 H), 2,03 (dd, *J* = 8,8, 12,4 Hz, 1H).

Ejemplo 213

N-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N-acetamida

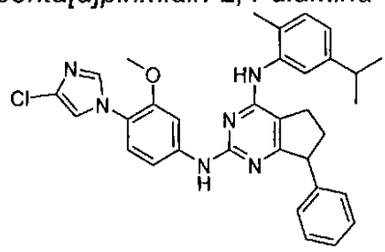


A una solución de Intermedio Ga se añadieron 1,5 eq de AcCl y 2 eq de DIPEA y se dejó hasta reflujo durante 3 días. El producto así obtenido se acopló con la Preparación A por el procedimiento del Ejemplo 184 proporcionando el compuesto del epígrafe. CL-EM $(M+H)^+$ = 475,2 RMN de ^1H (400 MHz, DMSO-*d*) δ ppm 7,86 (s, 1 H) 7,54 (s., 1 H) 7,35 (d, *J*=8,40 1 H) 7,23 - 7,30 (m, 2 H) 7,04 – 7,21 (m, 6 H) 6,73 – 6,76 (m, 1H) 4,26 (t, *J*=8,00 Hz, 1 H) 3,71 (s, 3 H) 2,58 – 2,80 (m, 3 H) 2,02 (s, 3 H) 1,96 – 2,00 (m, 1H).

Ejemplo 214

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-(5-isopropil-2-metilfenil)-7-

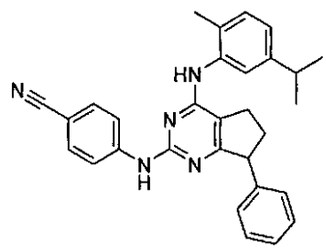
fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



A una solución de 2-cloro-N-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-amina (Preparación Gp) (26,0 mg, 100 µmol) en Dioxano (Relación: 1, Volumen: 175 µl) se añadió 4-(4-cloro-1H-imidazol-1-il)-3-metoxianilina (Preparación A) (22,37 mg, 100 µmol) y AcOH (Relación: 1,000, Volumen: 175 µl). La mezcla resultante se llevó hasta 100 °C y se agitó durante la noche. La mezcla de reacción se llevó hasta pH 10 mediante la adición de NaOH acuoso 1 N. La mezcla resultante se extrajo con EtOAc (3 x 4 ml). Los extractos orgánicos reunidos se lavaron con salmuera (4 ml), se secaron sobre $MgSO_4$, se filtraron y se concentraron a vacío. El producto se purificó por HPLC Prep proporcionando el compuesto del epígrafe. CL-EM $(M+H)^+$ = 565,2.

Ejemplo 215A y 215B

4-(4-(5-isopropil-2-metilfenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo



El procedimiento del Ejemplo 214 se usó para combinar 4-aminobenzonitrilo y la Preparación Gp proporcionando los compuestos de los

epígrafes como dos atropoisómeros diferenciados y separables. CL-EM $(M+H)^+$ = 460,3.

Ejemplos 216-256

Se usaron los siguientes procedimientos generales para unir la anilina apropiada con la Preparación Ga.

Procedimiento de acoplamiento A[a]: El procedimiento que se describe en el Ejemplo 8.

Procedimiento de acoplamiento B[a]: Los dos componentes se calentaron a 100 °C en HOAc/Dioxano 1:1.

El análisis se llevó a cabo en una de las siguientes columnas[b]:

Procedimiento de CL A[b]: Phenomenex Luna 3X50 agua/MeOH 95/5 a 5/95, TFA al 0,1%

Procedimiento de CL B[b]: Phenomenex Luna 2X50 agua/CH_3CN 95/5 a 5/95, NH_4OAc al 0,1%

Procedimiento de CL C[b]: Phenomenex Luna 2X50 agua/MeOH 95/5 a 5/95, TFA al 0,1%

Procedimiento de CL D[b]: Waters 2X50 agua/MeOH 95/5 a 5/95, NH_4OAc al 0,1%

Procedimiento de CL E[b]: Supelco Ascentis Exp agua/CH_3CN 95/5 a 5/95, NH_4OAc al 0,1%

Los tiempos de retención[c] de la CL se expresan junto con el tiempo de ejecución del gradiente (tr/grad).

Ejemplo	Nombre del compuesto	Proced. de acopla-miento[a]	Proced. de CL[b]	T de retención CL[c]	$(M+H)^+$
216	N4-metil-N2-(2-metilpiridin-4-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	B	A	1,77/3	332,2
217	N2-(3-metoxifenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	D	3,63/4	347,2
218	N2-(4-fluorofenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	D	3,68/4	335,2
219	N2-(3,5-difluorofenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	D	3,87/4	353,2
220	N2-(4-cloro-3-metoxifenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	D	3,83/4	381,2
221	N2-(4-bromo-2-metoxifenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	D	4,10/4	425,1
222	N2-(4-fluoro-3-metoxifenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	D	3,63/4	365,2

Ejemplo	Nombre del compuesto	Proced. de acopla-miento[a]	Proced. de CL[b]	T de retención CL[c]	$(M+H)^+$
223	N4-metil-7-fenil-N2-(pirimidin-5-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	D	3,12/4	319,2
224	N4-metil-7-fenil-N2-(piridin-4-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	D	2,85/4	318,2
225	4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo	A	D	3,57/4	342,2
226	4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo	A	C	2,94/4	342,1
227	4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo	A	C	2,92/4	342,1
228	2-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo	A	E	2,64/8	342,2
229	4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-1-naftonitrilo	A	E	5,73/8	392,2
230	5-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)picolinonitrilo	A	E	4,54/8	343,2

Ejemplo	Nombre del compuesto	Proced. de acopla-miento[a]	Proced. de CL[b]	T de retención CL[c]	$(M+H)^+$
231	2-(4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenil)acetonitrilo	A	E	4,65/8	356,2
232	2-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-1H-benzo[d]imidazol-5-carbonitrilo	A	E	4,57/8	382,2
233	3-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo	B	E	4,37/8	342,1
234	N2-(4-terc-butilfenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	B	E	5,47/8	373,2
235	N4-metil-N2-(4-(metilsulfonil)fenil)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	B	E	3,79/8	395,1
236	N4-metil-7-fenil-N2-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	B	E	5,13/8	400,8
237	4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)ftalonitrilo	B	E	4,47/8	367,2

Ejemplo	Nombre del compuesto	Proced. de acopla-miento[a]	Proced. de CL[b]	T de retención CL[c]	$(M+H)^+$
238	4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-2-(trifluorometil)benzonitrilo	B	E	4,90/8	410,1
239	N4-metil-7-fenil-N2-(4-(trifluorometil)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	B	E	5,13/8	385,1
240	5-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-2,3-dihidro-1H-inden-1-ona	B	E	3,89/8	371,2
241	2-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-1H-imidazol-4,5-dicarbonitrilo	B	E	4,08/8	357,2
242	2-bromo-5-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo	B	E	4,89/8	420,1
243	N,N-dimetil-4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzamida	B	E	3,50/8	388,2
244	1-(4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenil)ciclopentanocarbonitrilo	B	E	4,91/8	410,2

Ejemplo	Nombre del compuesto	Proced. de acopla-miento[a]	Proced. de CL[b]	T de retención CL[c]	$(M+H)^+$
245	N4-metil-7-fenil-N2-(1,2,3,4-tetrahidroisoquinolin-6-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	B	E	4,14/8	372,2
246	4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-2-(trifluorometoxi)benzonitrilo	B	E	5,04/8	426,1
247	1-(4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenil)ciclopropanocarbonitrilo	B	C	3,30/4	382,3
248	1-(2-metoxi-4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenilamino)ciclopropanocarbonitrilo	B	C	3,06/4	427,1
249	N4-metil-N2-(2-metil-1H-indol-5-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	B	1,75/2	370,3
250	N2-(benzofuran-5-il)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	B	1,85/2	357,2
251	N2-(1H-indol-5-il)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	B	1,68/2	356,3

Ejemplo	Nombre del compuesto	Proced. de acopla-miento[a]	Proced. de CL[b]	T de retención CL[c]	$(M+H)^+$
252	N4-metil-N2-(2-metilbenzo[d]oxazol-6-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	B	1,73/2	372,3
253	N2-(1H-benzo[d]imidazol-6-il)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	B	1,47/2	357,2
254	N4-metil-N2-(1-metil-1H-indol-5-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	B	1,82/2	370,3
255	N4-metil-N2-(2-metilbenzo[d]tiazol-6-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	B	1,78/2	388,2
256	N2-(4-bromo-3-metoxifenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina	A	A	2,63/4	425,0/ 427,0

Procedimiento de acoplamiento A[a]: El procedimiento que se describe en el Ejemplo 8.

Procedimiento de acoplamiento B[a]: Los dos componentes se calentaron a 100 °C en HOAc/Dioxano 1:1.

El análisis se llevó a cabo en una de las siguientes columnas[b]:

Procedimiento de CL A[b]: Phenomenex Luna 3X50 agua/MeOH 95/5 a 5/95, TFA al 0,1%

Procedimiento de CL B[b]: Phenomenex Luna 2X50 agua/CH3CN 95/5 a 5/95, NH4OAc al 0,1%

Procedimiento de CL C[b]: Phenomenex Luna 2X50 agua/MeOH 95/5 a 5/95, TFA al 0,1%

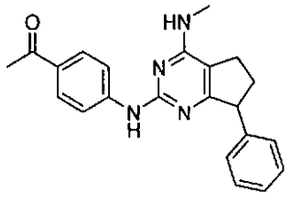
Procedimiento de CL D[b]: Waters 2X50 agua/MeOH 95/5 a 5/95, NH4OAc al 0,1%

Procedimiento de CL E[b]: Supelco Ascentis Exp agua/CH3CN 95/5 a 5/95, NH4OAc al 0,1%

Los tiempos de retención de CL[c] se expresan junto con el tiempo de ejecución del gradiente (tr/grad).

Ejemplo 257

1-(4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenil)etanona

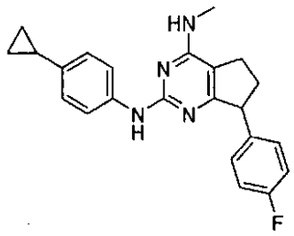


Se calentó a 80ºC durante 12 horas una mezcla del Ejemplo 256 (20 mg, 0,047 mmol), tributil(1-etoxivinil)estannano (67,9 mg, 0,188 mmol) y Tetraquis(5,43 mg, 4,70 μmol) en tolueno (188 μl). El producto bruto se purificó por HPLC prep. El producto resultante se trató con HCl (0,8 eq.) en acetona (0,285 M) y se agitó a TA durante la noche. La mezcla se concentró y se añadió EtOAc, se lavó con agua, salmuera, se secó sobre Na_2SO_4 y se

concentró obteniendo 1-(2-metoxi-4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenil)etanona (4 mg, 10,3 μmol, 22 % de rendimiento). CL-EM $(M+H)^+$ = 389,2 RMN de ^1H (500 MHz, MeOD) δ ppm 7,74 (d, *J*=8,55 Hz, 1 H) 7,66 (s, 1 H) 7,36 - 7,49 (m, 3 H) 7,19 - 7,36 (m, 2 H) 7,08 (dd, *J*=8,55, 1,83 Hz, 1 H) 4,45 (s ancho, 1 H) 3,86 - 3,98 (m, 3 H) 3,16 - 3,24 (m, 3 H) 2,93 (s ancho, 1 H) 2,73 - 2,86 (m, 2 H) 2,53 - 2,63 (m, 3 H) 2,11 - 2,23 (m, 1 H).

Ejemplo 258

N2-(4-ciclopropilfenil)-7-(4-fluorofenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

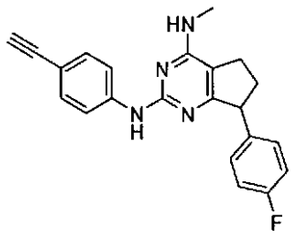


A una solución del análogo fluorado del Ejemplo 256 (150 mg, 0,338 mmol) en Tolueno (Relación: 20, Volumen: 1611 μl) se añadió ácido ciclopropilborónico (37,8 mg, 0,440 mmol), $PdOAc_2$ (3,80 mg, 0,017 mmol), triciclohexilfosfina (9,49 mg, 0,034 mmol), ortofosfato potásico (251 mg, 1,184 mmol) y agua (Relación: 1,000, Volumen: 81 μl). La mezcla resultante se llevó hasta 110 °C y se agitó durante la noche. La mezcla de reacción se diluyó con EtOAc (5 ml), se lavó con agua (2 ml), salmuera (2 ml), se secó sobre $MgSO_4$, se filtró y se concentró a vacío. La purificación por cromatografía ultrarrápida (Sílice, EtOAc/Hexanos) dio N2-(4-ciclopropil-3-metoxifenil)-7-(4-fluorofenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (15 mg, 0,037 mmol,

10,96 % de rendimiento). CL-EM $(M+H)^+$ = 405,1 RMN de ^1H (500 MHz, MeOD) δ ppm 7,60 (d, *J*=1,83 Hz, 1 H) 7,19 (dd, *J*=7,93, 5,80 Hz, 2 H) 6,97 - 7,14 (m, 3 H) 6,69 – 6,78 (m, 1H) 4,05 - 4,22 (m, 2 H) 3,62 - 3,71 (m, 3 H) 2,98 - 3,11 (m, 3 H) 2,72 - 2,85 (m, 1 H) 2,55 - 2,72 (m, 2 H) 1,90 - 2,05 (m, 2 H) 1,26 (t, *J*=7,17 Hz, 1 H) 0,73 - 0,86 (m, 1 H) 0,46 - 0,61 (m, 1 H).

Ejemplo 259

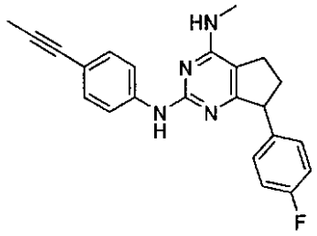
N2-(4-etinilfenil)-7-(4-fluorofenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



La mezcla de tributil(etinil)estannano (53,3 mg, 0,169 mmol), el análogo fluorado del Ejemplo 256 (50 mg, 0,113mmol) y tetraquis (10,0 mg, 0,011 mmol) en tolueno (226 µl) se calentó a 110°C durante 2 h y luego se eliminó el disolvente a vacío. El residuo se purificó por HPLC prep obteniendo N2-(4-etinil-3-metoxifenil)-7-(4-fluorofenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (1,5 mg, 3,86 µmol). CL-EM $(M+H)^+$ = 389,2 RMN de ^1H (500 MHz, CLOROFORMO-*d*) δ ppm 7,86 (s, 1 H) 7,31 (d, *J*=8,55 Hz, 2 H) 7,16 (dd, *J*=7,78, 5,65 Hz, 3 H) 7,01 (t, *J*=8,70 Hz, 2 H) 6,71 (s ancho, 1 H) 4,52 (s ancho, 1 H) 3,71 (s, 3 H) 3,15 (d, *J*=4,88 Hz, 3 H) 2,67 (d, *J*=9,77 Hz, 3 H) 1,95 - 2,14 (m, 1 H).

Ejemplo 260

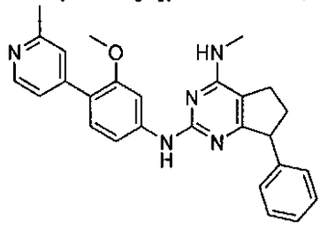
7-(4-fluorofenil)-N4-metil-N2-(4-(prop-1-inil)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



La mezcla de tributil(prop-1-inil)estannano (55,7 mg, 0,169 mmol), el análogo fluorado del Ejemplo 256 (50 mg, 0,113mmol) y tetraquis (10,0 mg, 0,011 mmol) en tolueno (226 µl) se calentó a 110°C durante 2 h y luego se eliminó el disolvente a vacío. El residuo se purificó por HPLC prep obteniendo 7-(4-fluorofenil)-N2-(3-metoxi-4-(prop-1-inil)fenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (2,0 mg, 4,97 µmol). CL-EM $(M+H)^+$ = 403,3 RMN de ^1H (400 MHz, CLOROFORMO-*d*) δ ppm 7,80 (d, *J*=1,76 Hz, 1 H) 7,10 - 7,23 (m, 3 H) 6,93 - 7,08 (m, 2 H) 6,73 (s, 1 H) 4,51 (s ancho, 1 H) 4,05 - 4,29 (m, 1 H) 3,70 (s, 3 H) 3,14 (d, *J*=4,77 Hz, 3 H) 2,56 - 2,79 (m, 3 H) 2,09 - 2,14 (m, 3 H) 1,99 - 2,09 (m, 1 H).

Ejemplo 261

N2-(3-metoxi-4-(2-metilpiridin-4-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina

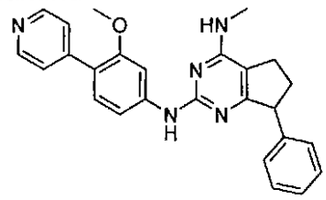


La mezcla de ácido 2-metilpiridin-4-ilborónico (25,1 mg, 0,183 mmol), Ejemplo 256 (26 mg, 0,061mmol), tetraquis (14,1 mg, 0,012 mmol) y carbonato

sódico (13,0 mg, 0,122mmol) en tolueno (255 µl)/agua (50 µl) se calentó a 150°C durante 5 h y luego se eliminó el disolvente a vacío. El residuo se purificó por HPLC prep obteniendo N2-(3-metoxi-4-(2-metilpiridin-4-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (5,0 mg, 0,011 mmol). CL-EM $(M+H)^+$ = 438,2 RMN de ^1H (500 MHz, MeOD) δ ppm 8,60 (s ancho, 1 H) 8,06 - 8,19 (m, 2 H) 7,75 (d, *J*=1,83 Hz, 1 H) 7,60 - 7,70 (m, 1 H) 7,38 - 7,49 (m, 2 H) 7,22 - 7,38 (m, 4 H) 4,43 - 4,57 (m, 1 H) 3,86 - 3,99 (m, 3 H) 3,17 - 3,26 (m, 3 H) 2,89 - 3,01 (m, 1 H) 2,73 - 2,89 (m, 5 H) 2,19 (dt, *J*=9,16, 6,87 Hz, 1 H).

Ejemplo 262

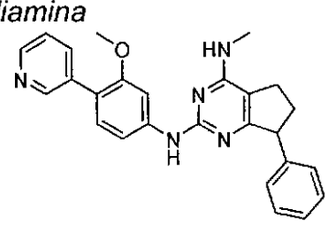
N2-(3-metoxi-4-(piridin-4-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



La mezcla de 4-(tributilestannil)piridina (69,2 mg, 0,188 mmol), Ejemplo 256 (20 mg, 0,047mmol) y tetraquis (5,43 mg, 4,70 µmol) en tolueno (196 µl)/agua (39 µl) se calentó a 100°C durante 12 h, y luego se eliminó el disolvente a vacío. El residuo se purificó por HPLC prep obteniendo N2-(3-metoxi-4-(piridin-4-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (4,0 mg, 9,44 µmol). CL-EM $(M+H)^+$ = 424,2 RMN de ^1H (500 MHz, MeOD) δ ppm 8,20 – 8,90 (m, 4H) 7,74 (d, *J*=1,83 Hz, 1 H) 7,62 - 7,70 (m, 1 H) 7,39 - 7,47 (m, 2 H) 7,23 - 7,37 (m, 4 H) 4,43 - 4,54 (m, 1 H) 3,94 (s, 3 H) 3,22 (s, 3 H) 2,89 - 3,01 (m, 1 H) 2,75 - 2,87 (m, 2 H) 2,12 - 2,29 (m, 1 H).

Ejemplo 263

N2-(3-metoxi-4-(piridin-3-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina



La mezcla de 3-(tributilestannil)piridina (55,4 mg, 0,150 mmol), Ejemplo 256 (16 mg, 0,061 mmol) y tetraquis (4,35 mg, 3,76 μmol) en tolueno (188 μl) se calentó a 100°C durante 12 h, y luego se eliminó el disolvente a vacío. El residuo se purificó por HPLC prep obteniendo N2-(3-metoxi-4-(piridin-3-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina (4,0 mg, 9,44 μmol). CL-EM $(M+H)^+$ = 424,2 RMN de ^1H (500 MHz, MeOD) δ ppm 8,52 (s ancho, 2 H) 7,67 - 7,76 (m, 2 H) 7,55 - 7,64 (m, 1 H) 7,43 - 7,50 (m, 1 H) 7,41 (d, *J*=7,32 Hz, 2 H) 7,32 - 7,37 (m, 1 H) 7,17 - 7,31 (m, 3 H) 4,41 - 4,56 (m, 1 H) 3,88 (s, 3 H) 3,16 - 3,28 (m, 3 H) 2,88 - 3,02 (m, 1 H) 2,73 - 2,88 (m, 2 H) 2,09 - 2,26 (m, 1 H).

PROCEDIMIENTOS BIOLÓGICOS

Ensayos celulares para inhibición de producción Aβ1-40 y Aβ1-42

Células H4 transfectadas establemente con APP751 conteniendo la mutación Swedish (clon H4 APP751 SWE 8.20, desarrollada a BMS) se mantuvieron en fase logarítmica a través de paso dos veces por una ranura de 1:20. Para determinaciones de CI_{50}, se plaquearon 30 μl de células (1,5 x 10^4 células/pocillo) en medios DMEM que contienen BSA al 0,0125% (Sigma

A8412) directamente en placas de compuesto de 384 pocillos (Costar 3709) conteniendo 0,1 μml de compuesto diluido en serie en DMSO. Tras incubación durante 19 horas en CO_2 al 5% a 37°C, las placas se centrifugaron brevemente (1000 rpm, 5 min). Se transfirió una alícuota de 10 mμl de cada pocillo a una segunda placa de ensayo (Costar 3709) para medidas de Aβ40. Se prepararon cócteles de anticuerpos de forma reciente mediante dilución en Tris-HCl 40 mM (pH 7,4) con BSA al 0,2% y se añadieron a placas de ensayo. Para medidas de Aβ42, los anticuerpos específicos para el neoepítopo Aβ42 (565, desarrollado en BMS; conjugado al reactivo de Wallac (Perkin Elmer)) y la secuencia N-terminal de péptido Aβ (26D6, desarrollada en SIBIA conjugada a APC (Perkin Elmer)) se mezclaron y se añadieron 20 μl de la mezcla a cada pocillo de la placa de células incubadas produciendo una concentración final de 0,8 ng de 565/pocillo y 75 ng 26D6/pocillo. Para las medidas de Aβ40, se mezclaron anticuerpos específicos para el neoepítopo Aβ40 (TSD, desarrollado a BMS Squibb; conjugado al reactivo de Wallac (Perkin Elmer)) y 26D6 como se describe anteriormente y se añadieron 20 μl de la mezcla a las alícuotas de 10 μl que se pueden retirar anteriormente de la placa de células produciendo una concentración final de 1,6 ng de TSD /pocillo y 17,5 ng de 26D6/pocillo. Se sellaron placas de ensayo que contenían anticuerpos con lámina de aluminio y se incubaron durante toda una noche a 4°C. Se determinó señal usando un contador de Viewlux (Perkin Elmer) y se determinaron valores de CI_{50} usando ajuste de curva en CurveMaster (basado en Excel Fit).

La actividad de compuestos representativos de la presente revelación, en base a valores de CI_{50} celulares de Aβ42 en clon H4 APP751 SWE 8.20, se ilustró en la Tabla 1 (más adelante).

Tabla 1

Compuesto de Ejemplo	Índice de Actividad[a]	Compuesto de Ejemplo	Índice de Actividad[a]
1	+++	85	+++
2	+++	86	++
3	++	87	60 nM
3A	+++	88	++
3B	++	88A	4,5 nM
4	+++	88B	++
4A	+++	89	++
4B	++	90A	++
5	+++	90B	270 nM
5A	+++	91A	+++
5B	++	91B	+
6	++	92	++
6A	+++	93	20 nM
6B	++	94	+++
7A	+++	94A	+++
7B	++	94B	++
8	+++	95	+++
9	8,1 nM	95A	+++
10	+++	95B	++
11	+++	96	+++
11A	3,8	96A	+++
11B	+++	96B	4,6 nM

Compuesto de Ejemplo	Índice de Actividad[a]	Compuesto de Ejemplo	Índice de Actividad[a]
12	+++	97	+++
12A	+++	97A	+++
13	-	97B	++
14	-	98	++
15	++	98A	+++
16	++	98B	++
16A	+++	99	19 nM
16B	+	99A	++
17	++	99B	190 nM
17A	120 nM	100	+++
17B	++	100A	4,7 nM
18	++	100B	++
18A	8,8 nM	101	++
18B	++	101A	+++
19	++	101B	++
19A	++	102	+++
19B	59 nM	102A	+++
20	+++	102B	++
20A	+++	103	+++
20B	++	103A	+++
21	++	103B	++
21A	++	104	++
21B	+	105	8,8 nM

Compuesto de Ejemplo	Índice de Actividad[a]	Compuesto de Ejemplo	Índice de Actividad[a]
23	++	106	++
23A	++	107	++
23B	+	107A	++
24	++	107B	+
24A	++	108	20 nM
24B	200 nM	109A	+++
25	++	109B	+++
26	+++	110A	+++
26A	++	110B	++
26B	++	111	35 nM
27	++	112	+++
28	++	112A	+++
28A	++	112B	++
29	++	113	5,7 nM
29A	++	113A	+++
29B	++	113B	++
30	++	114	+++
30A	++	114A	++
30B	230 nM	114B	+
31	+	115	+++
32	++	115A	+++
33	100 nM	115B	++
34	++	116	++

Compuesto de Ejemplo	Índice de Actividad[a]	Compuesto de Ejemplo	Índice de Actividad[a]
35	+++	116A	+++
36	++	116B	+
37	+++	117	45 nM
38	++	117A	++
38A	12 nM	117B	+
38B	++	118	++
39	++	118A	+++
39B	+	118B	+
40A	+++	119	++
40B	+	119A	7,4 nM
41	++	119B	+
41A	++	120	++
41B	++	120A	+++
41C	++	120B	+
41D	++	121	++
42	++	121A	+++
42A	+++	121B	120 nM
43	+++	122A	+++
44	13 nM	123A	++
44A	+++	123B	370 nM
45A	++	124	++
45B	2,5 nM	124A	+++
45C	++	124B	++

Compuesto de Ejemplo	Índice de Actividad[a]	Compuesto de Ejemplo	Índice de Actividad[a]
45D	+++	125	++
46	+++	126	++
46A	+++	127	++
46B	++	127A	+++
47	+++	127B	++
48	18 nM	128	+
48A	+++	129	++
48B	130 nM	129A	+++
49	+++	130	+++
49A	+++	130A	+++
49B	++	131	++
50	+++	131A	+++
50A	+++	132	++
50B	++	132A	15 nM
51	4,5 nM	133	++
51A	+++	133A	+++
51B	+++	134	+++
52	++	134A	3,6 nM
52A	+++	135	++
52B	++	135A	++
53	++	136	+++
53A	+++	136A	+++
53B	++	137	11 nM

Compuesto de Ejemplo	Índice de Actividad[a]	Compuesto de Ejemplo	Índice de Actividad[a]
54	++	137A	+++
54A	++	138	++
54B	+++	138A	+++
55	++	139	++
55B	++	139A	++
56	++	140	++
56A	+++	140A	+++
56B	++	141	++
57A	14 nM	141A	+++
57B	+	142	++
58A	+++	143	++
58B	120 nM	143B	430 nM
59	++	144	++
59A	+++	144B	540 nM
60	+++	145	++
60A	5,6 nM	146	++
60B	++	147	++
61	++	148A	+++
61A	+++	149	++
61B	++	150	++
62	++	151	+++
62A	+++	151A	+++
62B	86 nM	152	++

Compuesto de Ejemplo	Índice de Actividad[a]	Compuesto de Ejemplo	Índice de Actividad[a]
63	++	153	++
63A	++	154	++
63B	+	154A	+++
64	++	155A	+++
64A	+++	156	+++
64B	++	156A	9,8 nM
65	++	157	++
65A	5,3 nM	157A	++
65B	160 nM	158	++
66	++	159	++
66A	+	160	++
66B	+++	161	+
67	++	162	++
67A	++	162A	++
67B	540 nM	163A	+++
68	++	164A	++
69	++	165	++
69A	+++	165A	++
69B	+	165B	180 nM
70	+++	166	+
70A	+++	167A	26 nM
70B	++	168A	+++
71	++	169	++

Compuesto de Ejemplo	Índice de Actividad[a]	Compuesto de Ejemplo	Índice de Actividad[a]
71A	+++	169A	+++
71B	++	170	++
72	+++	170A	+++
73	3,8 nM	171	16 nM
74A	++	171A	++
75	++	172A	+++
75A	+++	172B	+
75B	++	173	490 nM
76	++	174	++
77	++	175	++
78	++	175A	+++
78A	19 nM	176	+++
78B	++	176A	+++
79A	5,8 nM	176B	+++
79B	++	177	++
80	++	178	+++
80A	++	179	++
81	++	180	++
82	++	181	++
82A	+++	181A	+++
82B	++	181B	50 nM
83	++	182	++
83A	+++	182A	+++

Compuesto de Ejemplo	Índice de Actividad[a]	Compuesto de Ejemplo	Índice de Actividad[a]
83B	++	182B	++
84	++	183	11 nM
84A	++	183A	+++
84B	290 nM	183B	++
184	++	211	+++
185	++	212	33 nM
186	++	213	insol
187	++	214	77 nM
187A	++	215A	^
187B	++	215B	173 nM
188	19 nM	216	^
189	+++	217	^
189A	+++	218	3700 nM
189B	++	219	^
190	37 nM	220	550 nM
191	++	221	^
191A	++	222	^
191B	96 nM	223	11000 nM
192	64 nM	224	^
192A	170 nM	225	18 nM
192B	16 nM	226	+
193	++	193B	++
193A	+	227	12 nM

Compuesto de Ejemplo	Índice de Actividad[a]	Compuesto de Ejemplo	Índice de Actividad[a]
194	++	228	^
194A	++	229	^
194B	175 nM	230	42 nM
195	17 nM	231	+
195A	26 nM	232	^
195B	+	233	^
196	++	234	^
196A	+++	235	+
196B	54 nM	236	^
197	16 nM	237	29 nM
197A	60 nM	238	+
197B	+++	239	+
198	++	240	Insol
198A	+	241	Insol
198B	15 nM	242	67 nM
199	++	243	+
199A	+	244	^
199B	+++	245	^
200	++	246	31 nM
200A	++	247	+
200B	++	248	^
201	5,3 nM	249	^
201A	10 nM	250	^

Compuesto de Ejemplo	Índice de Actividad[a]	Compuesto de Ejemplo	Índice de Actividad[a]
201B	++	251	^
202	+++	252	^
203	19 nM	253	5900 nM
203A	+++	254	1000 nM
203B	++	255	^
204	19 nM	256	97 nM
204A	19 nM	257	++
204B	+	258	^
205	++	259	940 nM
206	15 nM	260	860 nM
207	+	261	+++
208	++	262	+++
209	+++	263	32 nM
210	61 nM		

[a]Actividad en base a valores de CI_{50} celular de Aβ42 en clon H4 APP751 SWE 8.20.

+++ = 1,5 nM - 0,0099 M

++ = 0,010 – 0,100 μM

+ = 0,100 – 1,0 μM

^ = > 1,0 μM

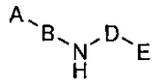
Será evidente para un experto en la técnica que la presente revelación no se limita a los ejemplos precedentes, y que puede realizarse en otras formas

específicas sin apartarse de los atributos esenciales de la misma. Se desea por lo tanto que los ejemplos se consideren a todos los respectos como ilustrativos y no restrictivos, haciéndose referencia a las reivindicaciones adjuntas, más que a los ejemplos precedentes, y todos los cambios que estén dentro del significado y el alcance de las reivindicaciones se desea por lo tanto que estén abarcados en las mismas.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un compuesto de fórmula (I)



(I),

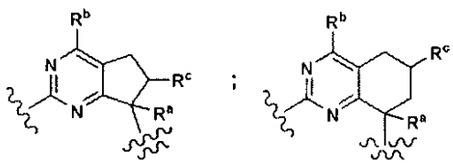
o una sal farmacéuticamente aceptable del mismo; en la que

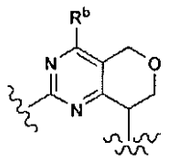
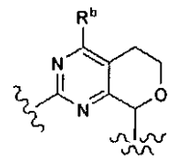
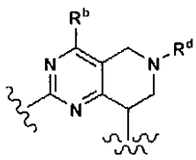
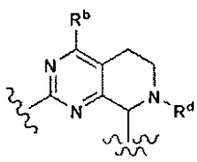
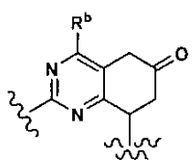
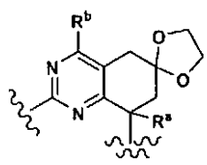
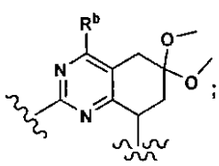
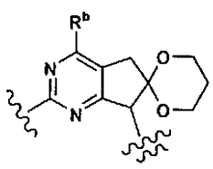
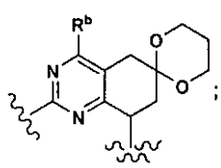
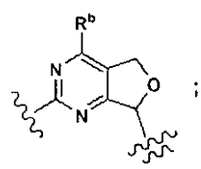
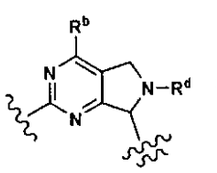
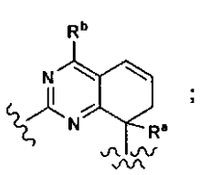
A es un anillo heteroaromático de cinco o seis miembros que contiene de uno a tres heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre; en el que dicho anillo heteroaromático está opcionalmente sustituido con uno o dos grupos seleccionados de halo, haloalquilo C_{1-6}, hidroxi, amino, alcoxi C_{1-6} y alquilo C_{1-6};

B se selecciona de fenilo y piridinilo, en el que el fenilo y el piridinilo están opcionalmente sustituidos con uno o dos sustituyentes seleccionados independientemente de

alcoxi C_{1-6}, alquilo C_{1-6}, alquilamino C_{1-3}alcoxi-C_{1-6}, ciano, dialquilamino C_{1-3}-alcoxi C_{1-6}, halo, haloalcoxi C_{1-6}, haloalquilo C_{1-6}, hidroxi, metilamino y amino;

D se selecciona de


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" indica el punto de unión del átomo de nitrógeno a la molécula parental;


" indica el punto de unión al resto 'E';

R^a se selecciona de hidrógeno, alquilo C_{1-6}, alquenilo C_{2-6} e hidroxi;

R^b es $-NR^xR^y$, en el que R^x y R^y están independientemente seleccionados de hidrógeno, alcoxi C_{1-4}, alcoxi C_{1-4}-alquilo C_{1-4}, alcoxicarbonilo C_{1-4}, alquilo C_{1-6}, cicloalquilo C_{3-7}, (cicloalquilo C_{3-7})alquilo C_{1-4}, hidroxialquilo C_{1-4} y trideuterometilo, en los que la parte alquilo del (cicloalquilo C_{3-7})alquilo C_{1-4} puede estar opcionalmente sustituida con grupo alcoxi C_{1-4}; o, R^x y R^y, conjuntamente con el átomo de nitrógeno al que están unidos, forman un anillo monocíclico o bicíclico de cuatro a siete miembros que contiene opcionalmente un enlace doble y que contiene opcionalmente un heteroátomo adicional

seleccionado de O, NR^z y S; en el que R^z se selecciona de hidrógeno, alquilo C_{1-6} y alcoxicarbonilo C_{1-4}; y en el que el anillo está opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente de alcoxi C_{1-6}, alquilo C_{1-6}, halo, haloalquilo C_{1-4}, hidroxi, $-NR^fR^g$, oxo, dioxolanilo espirocíclico; en el que R^f y R^g están independientemente seleccionados a partir de hidrógeno, alcoxicarbonilo C_{1-4} y alquilo C_{1-6};

R^c se selecciona de hidrógeno, alquilsulfonilo C_{1-4}, alquilsulfonilamido C_{1-4}, amino, alquilamino C_{1-6}, dialquilamino C_{1-6}, cicloalquilamino C_{3-7}, hidroxi y alcoxi C_{1-4};

R^d se selecciona de hidrógeno, alquilo C_{1-6}, alcoxi C_{1-4}alquilcarbonilo C_{1-4}, alcoxicarbonilo C_{1-6}, alquilcarbonilo C_{1-6}, alquilsulfonilo C_{1-6}, cicloalquilsulfonilo C_{3-7}, cicloalquilcarbonilo C_{3-7}, dialquilamino C_{1-6}-alquilcarbonilo C_{1-4} y haloalquilo C_{1-4}, en los que la parte alquilo del alcoxicarbonilo, el alquilcarbonilo y el alquilsulfonilo están opcionalmente sustituidos con un sustituyente seleccionado de dialquilamino C_{1-4} y alcoxi C_{1-4}; y

E se selecciona de alquilo C_{1-6}, cicloalquilo C_{4-6}, (cicloalquilo C_{4-7})alquilo C_{1-4}, bencilo, fenilo y un anillo heteroaromático de cinco- a seis-miembros que contiene uno o dos átomos de nitrógeno, en los que el fenilo, la parte fenilo del bencilo y el anillo heteroaromático están cada uno opcionalmente sustituidos con uno, dos, o tres sustituyentes independientemente seleccionados de alquilo C_{1-6}, alcoxi C_{1-6}, ciano, halo, haloalcoxi C_{1-6} y haloalquilo C_{1-6}.

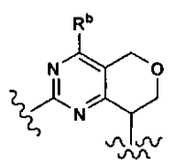
2. Un compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en el que A es un anillo heteroaromático de cinco

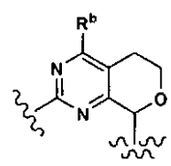
miembros que contiene de uno a tres átomos de nitrógeno; en los que dicho anillo heteroaromático está opcionalmente sustituido con un grupo seleccionado de halo y alquilo C_{1-6}.

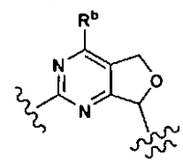
3. Un compuesto de la reivindicación 2, o una sal farmacéuticamente aceptable del mismo, en el que B se selecciona de fenilo y piridinilo, en el que el fenilo y el piridinilo están opcionalmente sustituidos con uno o dos sustituyentes independientemente seleccionados de alcoxi C_{1-6} y halo.

4. Un compuesto de la reivindicación 3, o una sal farmacéuticamente aceptable del mismo, en el que E es fenilo opcionalmente sustituido con uno, dos, o tres sustituyentes independientemente seleccionados de alquilo C_{1-6}, alcoxi C_{1-6}, ciano, halo, haloalcoxi C_{1-6} y haloalquilo C_{1-6}.

5. Un compuesto de la reivindicación 4, o una sal farmacéuticamente aceptable del mismo, en el que D está seleccionado de



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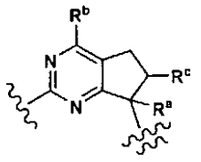
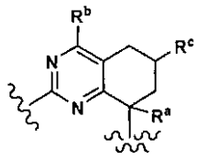
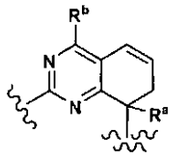
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6. Un compuesto de la reivindicación 5, o una sal farmacéuticamente aceptable del mismo, en el que R^b es $-NR^xR^y$, en el que R^x y R^y se seleccionan independientemente de hidrógeno, alcoxi C_{1-4}alquilo C_{1-4}, alquilo C_{1-6}, cicloalquilo C_{3-7}, hidroxialquilo C_{1-4} y trideuterometilo, en el que la parte alquilo del (cicloalquilo C_{3-7})alquilo C_{1-4} puede estar opcionalmente sustituida con un

grupo alcoxi C_{1-4}.

7. Un compuesto de la reivindicación 5, o una sal farmacéuticamente aceptable del mismo, en el que R^b es $-NR^xR^y$, en el que R^x y R^y, conjuntamente con el átomo de nitrógeno al que están unidos, forman un anillo monocíclico o bicíclico de cuatro a siete miembros que contiene opcionalmente un heteroátomo adicional seleccionado de O y NR^z; en el que R^z se selecciona de alquilo C_{1-6} y alcoxicarbonilo C_{1-4}; y en el que el anillo está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados de alcoxi C_{1-6}, alquilo C_{1-6}, halo, haloalquilo C_{1-4}, hidroxi, $-NR^fR^g$, oxo y dioxolanilo espirocíclico; en los que R^f y R^g están independientemente seleccionados de hidrógeno, alcoxicarbonilo C_{1-4} y alquilo C_{1-6}.

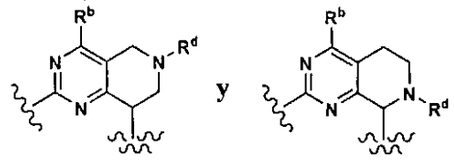
8. Un compuesto de la reivindicación 4, o una sal farmacéuticamente aceptable del mismo, en el que D está seleccionado de


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; y

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9. Un compuesto de la reivindicación 8, o una sal farmacéuticamente aceptable del mismo, en el que R^b es $-NR^xR^y$, en el que R^x y R^y se seleccionan independientemente de hidrógeno, alcoxi C_{1-4}alquilo C_{1-4}, alquilo C_{1-6}, cicloalquilo C_{3-7}, hidroxialquilo C_{1-4} y trideuterometilo, en los que la parte alquilo del (cicloalquilo C_{3-7})alquilo C_{1-4} puede estar opcionalmente sustituida con un grupo alcoxi C_{1-4}.

10. Un compuesto de la reivindicación 8, o una sal farmacéuticamente aceptable del mismo, en el que R^b es $-NR^xR^y$, en el que R^x y R^y, conjuntamente con el átomo de nitrógeno al que están unidos, forman un anillo monocíclico o bicíclico de cuatro a siete miembros que contiene opcionalmente un heteroátomo adicional seleccionado de O y NR^z; en el que R^z se selecciona de alquilo C_{1-6} y alcoxicarbonilo C_{1-4}; y en el que el anillo está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados de alcoxi C_{1-6}, alquilo C_{1-6}, halo, haloalquilo C_{1-4}, hidroxi, $-NR^fR^g$, oxo y dioxolanilo espirocíclico; en los que R^f y R^g están independientemente seleccionados de hidrógeno, alcoxicarbonilo C_{1-4} y alquilo C_{1-6}.

11. Un compuesto de la reivindicación 4, o una sal farmacéuticamente aceptable del mismo, en el que D está seleccionado de



y

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12. Un compuesto de la reivindicación 11, o una sal farmacéuticamente aceptable del mismo, en el que R^b es $-NR^xR^y$, en el que R^x y R^y se seleccionan independientemente de hidrógeno, alcoxi C_{1-4}alquilo C_{1-4}, alquilo C_{1-6}, cicloalquilo C_{3-7}, hidroxialquilo C_{1-4} y trideuterometilo, en el que la parte alquilo del (cicloalquilo C_{3-7})alquilo C_{1-4} puede estar opcionalmente sustituida con un grupo alcoxi C_{1-4}.

13. Un compuesto de la reivindicación 11, o una sal farmacéuticamente aceptable del mismo, en el que R^b es $-NR^xR^y$, en el que R^x y R^y, conjuntamente con el átomo de nitrógeno al que están unidos, forman un anillo monocíclico o bicíclico de cuatro a siete miembros que contiene opcionalmente un heteroátomo adicional seleccionado de O y NR^z; en el que R^z se selecciona de alquilo C_{1-6} y alcoxicarbonilo C_{1-4}; y en el que el anillo está opcionalmente sustituido con uno o dos sustituyentes independientemente seleccionados de alcoxi C_{1-6}, alquilo C_{1-6}, halo, haloalquilo C_{1-4}, hidroxi, $-NR^fR^g$, oxo y dioxolanilo espirocíclico; en los que R^f y R^g están independientemente seleccionados de hidrógeno, alcoxicarbonilo C_{1-4} y alquilo C_{1-6}.

14. Un compuesto seleccionado de

N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4,N^4-dimetil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4,N^4-dimetil-7-fenil-

6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4,N^4-dimetil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

4-(azetidin-1-ilo)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

(S)-4-(azetidin-1-ilo)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

(R)-4-(azetidin-1-ilo)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-ciclopropil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-ciclobutil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-isopropil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(2-fluoro-5-metoxi-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(6-(4-cloro-1H-imidazol-1-ilo)-5-metoxipiridin-3-ilo)-7-(4-fluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

4-(3,3-difluoroazetidin-1-ilo)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

4-(3,3-difluoroazetidin-1-ilo)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

4-(3,3-difluoroazetidin-1-ilo)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(3-cloro-1H-1,2,4-triazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(3-cloro-1H-1,2,4-triazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(3-cloro-1H-1,2,4-triazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

4-((1S,4S)-2-oxa-5-azabiciclo[2.2.1]heptan-5-ilo)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

4-((1S,4S)-2-oxa-5-azabiciclo[2.2.1]heptan-5-ilo)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

4-((1S,4S)-2-oxa-5-azabiciclo[2.2.1]heptan-5-ilo)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(2-metilpirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(2-metilpirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(2-metilpirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(2-metilpirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(2-metilpirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(2-metilpirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

1-(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-ilo)-4-metilpiperidin-4-ol;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(2-etilpirrolidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(2-etilpirrolidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(2-etilpirrolidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(2-etilpirrolidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(2-etilpirrolidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(2-etilpirrolidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

4-(4-amino-4-metilpiperidin-1-ilo)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

1-(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-ilo)-3-(trifluorometil)pirrolidin-3-ol;

1-(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-ilo)-3-(trifluorometil)pirrolidin-3-ol;

1-(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-ilo)-3-(trifluorometil)pirrolidin-3-ol;

1-(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-ilo)-3-(trifluorometil)pirrolidin-3-ol;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3-(dimetilamino)pirrolidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3-(dimetilamino)pirrolidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3-(dimetilamino)pirrolidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(4-metilpiperazin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(4-metilpiperazin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(4-metilpiperazin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(piperazin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(3-(metilamino)pirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(3-(metilamino)azetidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3-(dimetilamino)azetidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N^2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-((S)-3-fluoropirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-((S)-3-fluoropirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-((R)-3-fluoropirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-((R)-3-fluoropirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina);

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(4,4-difluoropiperidin-1-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(4-fluoro-5,6-dihidropiridin-1(2H)-ilo)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-(3-(trifluorometil)pirrolidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-(3-etoxipropil)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

3-(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-ilamino)propan-1-ol;

7-(4-fluorofenilo)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-(1-ciclopropil-2-metoxietil)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-N^4-trideuterometil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-N4-((R)-1-metoxibutan-2-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-((R)-1-ciclopropiletil)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-((S)-1-ciclopropiletil)-7-(4-fluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-N^4-metil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4,N^4-dimetil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4,N^4-dimetil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4,N^4-dimetil-8-fenil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-fluorofenilo)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N4-

metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N4-etil-8-(4-fluorofenilo)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-4-((R)-3-fluoropirrolidin-1-ilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-4-((R)-3-fluoropirrolidin-1-ilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-4-((S)-3-fluoropirrolidin-1-ilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-4-((S)-3-fluoropirrolidin-1-ilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina;

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-8-(4-fluorofenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-N4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-N4,N4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-N4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-8-(4-fluorofenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-clorofenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-clorofenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-clorofenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-clorofenilo)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-clorofenilo)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-clorofenilo)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-clorofenilo)-4-(3,3-difluoroazetidin-1-ilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-clorofenilo)-4-(3,3-difluoroazetidin-1-ilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-clorofenilo)-4-(3,3-difluoroazetidin-1-ilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina;

8-(4-clorofenilo)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-clorofenilo)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-clorofenilo)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4,N^4-dimetil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-clorofenilo)-4-(3,3-difluoroazetidin-1-ilo)-N-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina;

8-(4-clorofenilo)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4-

metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-clorofenilo)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-clorofenilo)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-clorofenilo)-N^2-(3-metoxi-4-(4-metil-1H-imidazol-1-ilo)fenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-clorofenilo)-N^2-(3-metoxi-4-(4-metil-1H-imidazol-1-ilo)fenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-clorofenilo)-N^2-(3-metoxi-4-(4-metil-1H-imidazol-1-ilo)fenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-clorofenilo)-N^2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-clorofenilo)-N^2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-clorofenilo)-N^2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-bromofenilo)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(4-bromofenilo)-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-((S)-2-metilpirrolidin-1-ilo)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina ;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-7-(4-fluorofenilo)-5,7-dihidrofuro[3,4-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-7-(4-fluorofenilo)-5,7-dihidrofuro[3,4-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-7-(4-fluorofenilo)-5,7-dihidrofuro[3,4-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-((S)-3-fluoropirrolidin-1-ilo)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-((S)-3-fluoropirrolidin-1-ilo)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina;

N^4-etil-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-5,7-dihidrofuro[3,4-d]pirimidina-2,4-diamina;

N^4-etil-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-5,7-dihidrofuro[3,4-d]pirimidina-2,4-diamina;

N^4-etil-N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-5,7-dihidrofuro[3,4-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-N^4-metil-5,7-dihidrofuro[3,4-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-N^4-metil-5,7-dihidrofuro[3,4-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-7-(4-fluorofenilo)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-((R)-1-ciclopropiletil)-7-(4-fluorofenilo)-5,7-dihidrofuro[3,4-d]pirimidina-2,4-diamina;

N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7-(4-fluorofenilo)-N4-metil-5,7-dihidrofuro[3,4-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-fluorofenilo)-4-((R)-

3-fluoropirrolidin-1-ilo)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-((2S,6R)-2,6-dimetilmorfolino)-7-(4-fluorofenilo)-5,7-dihidrofuro[3,4-d]pirimidin-2-amina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-metil-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidina-2,4-diamina;

N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N4-metil-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidina-2,4-diamina;

N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N4-metil-8-fenil-6,8-dihidro-5H-pirano[3,4-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-6,8-dihidro-5H-pirano[3,4-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-N4-metil-6,8-dihidro-5H-pirano[3,4-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-4-((R)-3-fluoropirrolidin-1-ilo)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-4-((R)-3-fluoropirrolidin-1-ilo)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-4-((S)-3-fluoropirrolidin-1-ilo)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-4-((S)-3-fluoropirrolidin-1-ilo)-6,8-dihidro-5H-pirano[3,4-d]pirimidin-2-amina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-clorofenilo)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-clorofenilo)-4-(3,3-difluoroazetidin-1-ilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-clorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-clorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-clorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(3,4-difluorofenilo)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(3,4-difluorofenilo)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(3,4-difluorofenilo)-N^4,N^4-dimetil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(3,4-difluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(3,4-difluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(3,4-difluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-7-(4-

(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

(S)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

(R)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4,N^4-dimetil-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4,N^4-dimetil-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4,N^4-dimetil-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

4-(azetidin-1-ilo)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

(S)-4-(azetidin-1-ilo)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

(R)-4-(azetidin-1-ilo)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(4-(trifluorometoxi)fenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(3,5-difluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-7-(3,4,5-trifluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-7-(3,4,5-trifluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-metil-7-(3,4,5-trifluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N^4-metil-7-(3,4,5-trifluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(6-(4-cloro-1H-imidazol-1-ilo)-5-metoxipiridin-3-ilo)-N^4-metil-7-(3,4,5-trifluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N^2-(4-(3-cloro-1H-1,2,4-triazol-1-ilo)-3-metoxifenilo)-N^4-metil-7-(3,4,5-trifluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoropirrolidin-1-ilo)-7-(3,4,5-trifluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

(S)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoropirrolidin-1-ilo)-7-(3,4,5-trifluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

(R)-N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoropirrolidin-1-ilo)-7-(3,4,5-trifluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-7-(3,4,5-trifluorofenilo)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(2,4-difluorofenilo)-N^4-

metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(2,4-difluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-7-(2,4-difluorofenilo)-N^4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-7-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-7-alil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(3,5-difluorofenilo)-N4-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(3,4-difluorofenilo)-N4-etil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-8- (3,4-difluorofenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(3,4-difluorofenilo)-N4-metil-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

8-(3,4-difluorofenilo)-N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-((R)-1-ciclopropiletil)-8-(4-(trifluorometil)fenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-(trifluorometil)fenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-8-(4-

(trifluorometil)fenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-metil-8-(4-(trifluorometil)fenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

4-(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-4-(etilamino)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-8-ilo)benzonitrilo;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-metil-8-(4-(trifluorometoxi)fenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-((R)-3-fluoropirrolidin-1-ilo)-8-(4-(trifluorometoxi)fenilo)-7,8-dihidro-5H-pirano[4,3-d]pirimidin-2-amina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-N^4-metil-8-fenil-5,6,7,8-tetrahidroquinazolina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-N^4-metil-8-fenil-5,6,7,8-tetrahidroquinazolina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-N^4-metil-8-fenil-5,6,7,8-tetrahidroquinazolina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-fenil-5,6,7,8-tetrahidroquinazolin-2-amina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-etil-8-(4-fluorofenilo)-N^4-metil-5,6,7,8-tetrahidroquinazolina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-N^4,N^4-dimetil-5,6,7,8-tetrahidroquinazolina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-N^4,N^4-dimetil-5,6,7,8-tetrahidroquinazoline-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-N^4,N^4-dimetil-5,6,7,8-tetrahidroquinazolina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-5,6,7,8-tetrahidroquinazolin-2-amina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-metil-6-(metilsulfonilo)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-6-(ciclopropilsulfonilo)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenolamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidina-6(5H)-carboxilato de metilo;

(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-ilo)(ciclopropil)metanona;

1-(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-ilo)-2-metoxietanona;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-6-(metilsulfonilo)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

1-(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-ilo)-2-(dimetilamino)etanona;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-6-(ciclopropilsulfonilo)-N4-etil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

1-(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-4-(etilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-ilo)etanona;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-6-(etilsulfonilo)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-6-(metilsulfonilo)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-6-

(metilsulfonilo)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

6-(ciclopropilsulfonilo)-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

6-(ciclopropilsulfonilo)-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N4-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

ciclopropil(4-(etilamino)-2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-ilo)metanona;

ciclopropil(4-(etilamino)-2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilamino)-8-fenil-7,8-dihidropirido[4,3-d]pirimidin-6(5H)-ilo)metanona;

N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-8-fenil-6-(2,2,2-trifluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-8-fenil-6-(2,2,2-trifluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4,N4-dimetil-6-(metilsulfonilo)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4,6-dimetil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N4,6-dimetil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-N4,6-dimetil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-6-metil-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-N4-metil-6-(metilsulfonilo)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-6-(metilsulfonilo)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-ilo)fenilo)-8-(4-fluorofenilo)-6-(metilsulfonilo)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-ilo)fenilo)-6-(metilsulfonilo)-8-(4-fluorofenilo)-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4,6-dietil-8-(4-fluorofenilo)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-8-(4-fluorofenilo)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-8-(4-fluorofenilo)-6-(metilsulfonilo)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-N4-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-4-(3,3-difluoroazetidin-1-ilo)-8-(4-fluorofenilo)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-amina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-N4,6-

dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-6-metil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-N4,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-N4-metil-5,6,7,8-tetrahidropirido[3,4-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-4-((S)-3-fluoropirrolidin-1-ilo)-7-(4-metoxibencilo)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-7-(metilsulfonilo)-5,6,7,8-tetrahidropirido[3,4-d]pirimidina-2,4-diamina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4,7-dietil-8-(4-fluorofenilo)-5,6,7,8-tetrahidropirido[3,4-d]pirimidina-2,4-diamina;

2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-4-(etilamino)-8-(4-fluorofenilo)-5,6-dihidropirido[3,4-d]pirimidina-7(8H)-carboxilato de metilo;

1-(2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-4-(etilamino)-8-(4-fluorofenilo)-5,6-dihidropirido[3,4-d]pirimidin-7(8H)-ilo)etanona;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-N4-metil-7-(metilsulfonilo)-5,6,7,8-tetrahidropirido[3,4-d]pirimidina-2,4-diamina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-4-((R)-3-fluoropirrolidin-1-ilo)-7-(metilsulfonilo)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-8-(4-fluorofenilo)-4-((R)-3-fluoropirrolidin-1-ilo)-7-(metilsulfonilo)-5,6,7,8-tetrahidropirido[3,4-d]pirimidin-2-amina;

N2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N4-etil-8-(4-fluorofenilo)-7-metil-5,6,7,8-tetrahidropirido[3,4-d]pirimidina-2,4-diamina;

N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-trideuterometil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(S)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-trideuterometil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

(R)-N^2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilo)-N^4-trideuterometil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidina-2,4-diamina;

2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-4-(metilamino)-8-fenil-7,8-dihidroquinazolin-8-ol;

2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-4-(metilamino)-8-fenil-5,6,7,8-tetrahidroquinazolin-8-ol;

2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-4-(dimetilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-7-ol;

(6S,7S)-2-(4-(4-cloro-1H-imidazol-1-ilo)-3-metoxifenilamino)-4-(dimetilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-6-ol;

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-cloroazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-fluoroazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-metoxiazetidin-1-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-4-(5,8-dioxa-2-azaspiro[3,4]octan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)azetidin-3-ona;

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-metilazetidina-3-carbonitrilo;

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-etoxiazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-4-(5-oxa-2-azaspiro[3,4]octan-2-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-3-metilazetidin-3-ol;

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-4-(3-fluoro-3-metilazetidin-1-il)-7-(4-fluorofenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-4-(3-metoxi-3-metilazetidin-1-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

7-(4-fluorofenil)-4-(3-metoxi-3-metilazetidin-1-il)-N-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

7-(2,4-difluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

(S)-7-(2,4-difluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

(R)-7-(2,4-difluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

6-(2,2-difluoroetil)-N4-etil-N2-(3-fluoro-4-(5-metil-1H-1,2,4-triazol-1-

il)fenil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina;

6-(2,2-difluoroetil)-N4-etil-N2-(3-fluoro-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-8-fenil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina;

N4-etil-N2-(3-metoxi-4-(4-cloro-1H-13-imidazol-1-il)fenil)-8-fenil-6-(2,2,2-trifluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina;

N4-etil-N2-(3-metoxi-4-(4-cloro-1H-13-imidazol-1-il)fenil)-8-fenil-6-(2,2-difluoroetil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina;

8-(4-fluorofenil)-N2-(3-metoxi-4-(3-metil-1H-1,2,4-triazol-1-il)fenil)-N4,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina;

8-(4-fluorofenil)-N2-(3-metoxi-4-(5-metil-1H-1,2,4-triazol-1-il)fenil)-N4,6-dimetil-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2,4-diamina;

(±)-2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-5-ona;

O-metil oxima de (E)-2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-5-ona;

2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-5-ol;

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-metil-8-fenil-5,6,7,8-tetrahidroquinazolin-2,4-diamina;

1-(2-metoxi-4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenil)-1H-imidazol-4-carbonitrilo;

N-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-7-fenil-4-(1,4-dioxa-7-azaspiro[4,4]nonan-7-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-amina;

1-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)pirrolidin-3-ona;

4-(8-(4-fluorofenil)-4-(metilamino)-6-(metilsulfonil)-5,6,7,8-tetrahidropirido[4,3-d]pirimidin-2-ilamino)benzonitrilo;

N2-(4-(4-(difluorometil)-1H-imidazol-1-il)-3-metoxifenil)-7-(4-fluorofenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(3-metoxi-4-(1-metil-1H-pirazol-4-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N-metilmetanosulfonamida;

N-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N-metanosulfonamida;

N-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N-metilacetamida;

N-(2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-4-il)-N-acetamida;

N2-(4-(4-cloro-1H-imidazol-1-il)-3-metoxifenil)-N4-(5-isopropil-2-metilfenil)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

4-(4-(5-isopropil-2-metilfenilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo;

N4-metil-N2-(2-metilpiridin-4-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(3-metoxifenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(4-fluorofenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(3,5-difluorofenil)-N4-metil-7-fenil-6,7-dihidro-5H-

ciclopenta[d]pirimidin-2,4-diamina;

N2-(4-cloro-3-metoxifenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(4-bromo-2-metoxifenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(4-fluoro-3-metoxifenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N4-metil-7-fenil-N2-(pirimidin-5-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N4-metil-7-fenil-N2-(piridin-4-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo;

4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo;

4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo;

2-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo;

4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-1-naftonitrilo;

5-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)picolinonitrilo;

2-(4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenil)acetonitrilo;

2-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-1H-benzo[d]imidazol-5-carbonitrilo;

3-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo;

N2-(4-terc-butilfenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N4-metil-N2-(4-(metilsulfonil)fenil)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N4-metil-7-fenil-N2-(4-(trifluorometoxi)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)ftalonitrilo;

4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-2-(trifluorometil)benzonitrilo;

N4-metil-7-fenil-N2-(4-(trifluorometil)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

5-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-2,3-dihidro-1H-inden-1-ona;

2-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-1H-imidazol-4,5-dicarbonitrilo;

2-bromo-5-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzonitrilo;

N,N-dimetil-4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)benzamida;

1-(4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-

ilamino)fenil)ciclopentanocarbonitrilo;

N4-metil-7-fenil-N2-(1,2,3,4-tetrahidroisoquinolin-6-il)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)-2-(trifluorometoxi)benzonitrilo;

1-(4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenil)ciclopropanocarbonitrilo;

1-(2-metoxi-4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenilamino)ciclopropanocarbonitrilo;

N4-metil-N2-(2-metil-1H-indol-5-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(benzofuran-5-il)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(1H-indol-5-il)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N4-metil-N2-(2-metilbenzo[d]oxazol-6-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(1H-benzo[d]imidazol-6-il)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N4-metil-N2-(1-metil-1H-indol-5-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N4-metil-N2-(2-metilbenzo[d]tiazol-6-il)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(4-bromo-3-metoxifenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

1-(4-(4-(metilamino)-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2-ilamino)fenil)etanona;

N2-(4-ciclopropilfenil)-7-(4-fluorofenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(4-etinilfenil)-7-(4-fluorofenil)-N4-metil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

7-(4-fluorofenil)-N4-metil-N2-(4-(prop-1-inil)fenil)-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(3-metoxi-4-(2-metilpiridin-4-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina;

N2-(3-metoxi-4-(piridin-4-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina y

N2-(3-metoxi-4-(piridin-3-il)fenil)-N4-metil-7-fenil-6,7-dihidro-5H-ciclopenta[d]pirimidin-2,4-diamina; o una de sus sales sal farmacéuticamente aceptables.

15. Una composición farmacéutica para el tratamiento de trastornos que responden a la reducción de producción de péptido β-amiloide que comprende una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en asociación con un vehículo o diluyente farmacéuticamente aceptable.

16. Un procedimiento para el tratamiento de trastornos que responden a la reducción de péptido β-amiloide en un mamífero en necesidad del mismo, que comprende administrar a dicho mamífero una cantidad terapéuticamente

efectiva de un compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo.

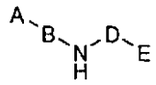
17. Un procedimiento de la reivindicación 16 en el que dicho trastorno se selecciona de Enfermedad de Alzheimer (AD), Síndrome de Down, alteración cognitiva débil (MCI), angiopatía amiloide cerebral (CAA), demencia con cuerpos de Lewy (DLB), esclerosis lateral amiotrófica (ALS-D), miositis de cuerpos de inclusión (IBM), degeneración macular relacionada con la edad y cáncer.

18. Un procedimiento de la reivindicación 17 en el que dicho trastorno se selecciona de Enfermedad de Alzheimer y Síndrome de Down.

19. Un procedimientos de la reivindicación 18 en el que dicho trastorno es Enfermedad de Alzheimer.

RESUMEN

La presente revelación proporciona una serie de compuestos de fórmula (I)



(I),

que modulan producción de péptido β-amiloide (β-AP) y son útiles en el tratamiento de Enfermedad de Alzheimer y de otras afecciones afectadas por la producción de péptido β-amiloide (β-AP).

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from BOY, Kenneth M. to BRISTOL-MYERS SQUIBB COMPANY, dated 15 April 2010 (15.04.2010)
VIII-2-1(iv)		an assignment from GUERNON, Jason M. to BRISTOL-MYERS SQUIBB COMPANY, dated 16 April 2010 (16.04.2010)
VIII-2-1(iv)		an assignment from MACOR, John E. to BRISTOL-MYERS SQUIBB COMPANY, dated 28 April 2010 (28.04.2010)
VIII-2-1(iv)		an assignment from OLSON, Richard E. to BRISTOL-MYERS SQUIBB COMPANY, dated 15 April 2010 (15.04.2010)
VIII-2-1(iv)		an assignment from SHI, Jianliang to BRISTOL-MYERS SQUIBB COMPANY, dated 20 April 2010 (20.04.2010)
VIII-2-1(iv)		an assignment from THOMPSON, III, Lorin A. to BRISTOL-MYERS SQUIBB COMPANY, dated 27 April 2010 (27.04.2010)
VIII-2-1(iv)		an assignment from WU, Yong-Jin to BRISTOL-MYERS SQUIBB COMPANY, dated 16 April 2010 (16.04.2010)
VIII-2-1(iv)		an assignment from XU, Li to BRISTOL-MYERS SQUIBB COMPANY, dated 15 April 2010 (15.04.2010)
VIII-2-1(iv)		an assignment from ZHANG, Yunhui to BRISTOL-MYERS SQUIBB COMPANY, dated 20 April 2010 (20.04.2010)
VIII-2-1(iv)		an assignment from ZUEV, Dmitry S. to BRISTOL-MYERS SQUIBB COMPANY, dated 15 April 2010 (15.04.2010)

VIII-3-1	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	In relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to claim priority of earlier application No. 61/230,202 by virtue of the following:
VIII-3-1(iv)		an assignment from ZUEV, Dmitry S. to BRISTOL-MYERS SQUIBB COMPANY, dated 12 August 2009 (12.08.2009)

Hayden 1161

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
SALLY B. HANSEN

3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY

4. LLEVA EL SELLO DE:
SALLY B. HANSEN, NOTARIO

AUTENTICACION DE COPIA DE ORIGINAL
EL SUSCRITO NOTARIO TREINTA Y OCHO(38)(E) CERTIFICA QUE LA PRESENTE COPIA COINCIDE EXACTAMENTE CON EL DOCUMENTO ORIGINAL QUE HE TENIDO A LA VISTA.
04 ENE 2012
38
ROBERTO FOREY BERMUDEZ
Notario 38(E) DEL CIRCULO DE BOGOTÁ D.C.

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL 28 DE JUNIO DE 2007

7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY

8. N° A295716

9. SELLO (APARECE ADHERIDO SELLO DORADO)

10. FIRMA (FIRMADO) BRADLEY ABELOW

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior)

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

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04 ENE 2012
NOTARIA ... Y BERMUDEZ
BOGOTÁ D.C.

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 82106

JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A295716

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow

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04 ENE 2012
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RODOLFO BERMUDEZ
Notario 38 (E) DEL CIRCULO DE BOGOTA D.C.

BAKER & MCKENZIE

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.068.640-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned.

BRISTOL-MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL-MYERS SQUIBB COMPANY

domiciliada en

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

AUTENTICACION DE COPIA DE ORIGINAL
EL SUSCRITO NOTARIO ENCARGADO CERTIFICA
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04 ENE 2012
38
RODOLFO [illegible] BERMUDEZ
Notario 38(E) del CIRCULO DE BOGOTA D.C.

NOTARIAL CERTIFICATION

On this 30 day of May

2007 , the undersigned Notary

CERTIFIES

1. That **Name of the person issuing the power**
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
Address, city, state, country

set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as
Senior Patent Counsel
Position of the person issuing the Power
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

having its home office in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public

SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo

de 2007 , el suscrito Notario

DA FE

1 Que Anastasia P. Winslow

mayor y domiciliado en Princeton, NJ
Estados Unidos de América

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de
Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

con sede en

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

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04 ENE 2012
38
RODOLFO REY BERMÚDEZ
NOTARIO (38) DEL CIRCULO DE BOGOTÁ D.C.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-001857- -00000-0000
Fecha: 2012-01-05 16:55:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1164

PATENTE DE INVENCIÓN ☐ MODELO

- ☐ Indicación que se solicita una paten
- ☐ 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 ☐